# Substituent Effects in Carboni–Lindsey Reactions of 1,2,4,5-Tetrazines and Aryl-Substituted Alkynylboronates

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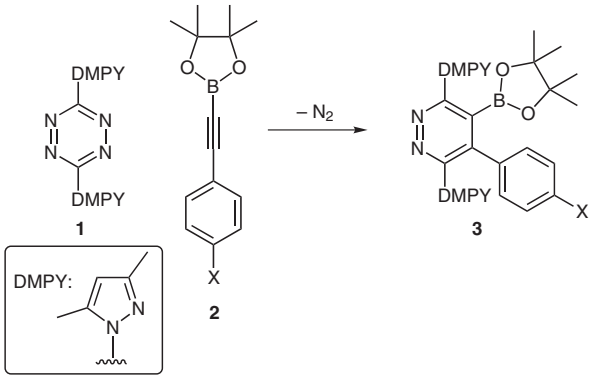
**Abstract:** Evidence for an inverse-electron-demand cycloaddition of tetrazines with alkynylboronates is presented by the reaction of 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine with aryl-alkynylboronate substrates bearing various *para* substituents.

**Key words:** cycloaddition, Carboni–Lindsey reaction, 1,2,4,5-tetrazine, pyridazine, boronic ester

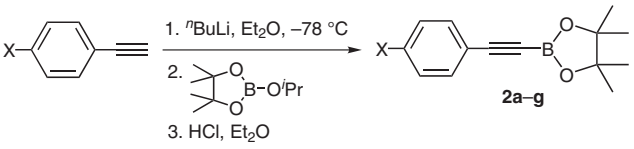
The widespread employment of aromatic and heteroaromatic boronic acid derivatives in organic synthesis has resulted in the development of a range of methods for the synthesis of these extremely useful compounds.[1] In this context, recent studies in our laboratories have focused on the cycloaddition of alkynylboronates,[2] and a number of metal-mediated[3] and metal-free[4] strategies have been reported. During our studies on [4+2] approaches, we noted that alkynylboronates showed a tendency to react with electron-deficient dienes rather than electron-rich dienes. This observation led us to carry out kinetic and computational studies on the reaction of alkynylboronates with tetrazines and these studies provided evidence for an inverse-electron-demand [4+2]-cycloaddition process.[5] In an effort to confirm that these processes do proceed in this manner, we opted to study the relative reaction rates of cycloadditions of aryl alkyne substrates **2** bearing electron-donating/-withdrawing groups with tetrazine **1** and report our findings herein (Scheme 1).[6,7]




**Scheme 1**

In order to conduct the relative rate experiments, alkynylboronates of similar steric size but of varying electronic nature were needed. Accordingly, we set out to prepare a series of these substrates from readily available terminal alkynes using Brown's procedure (Table 1).[8] Deprotonation of phenylacetylene and *para*-substituted arylacetylenes bearing OMe, F, Cl, CN groups proceeded smoothly and successfully generated alkynylboronates **2a–e** in modest to high yields. Unfortunately, however, this method was unsuccessful in producing electron-deficient alkynes **2f**,**g** due to decomposition during deprotonation. Although we were unable to prepare all the desired alkyne substrates, we felt that compounds **2a–e** provided sufficient electronic variation to get useful information from the relative rate studies.

**Table 1** Preparation of Alkynylboronates from Terminal Alkynes Using Brown's Procedure




| X | H **2a** | MeO **2b** | F **2c** | Cl **2d** | CN **2e** | $CO_2Me$ **2f** | $NO_2$ **2g** |
|---|---|---|---|---|---|---|---|
| Yield | 64% | 76% | 33% | 44% | 39% | 0% | 0% |

We began our cycloaddition experiments by investigating the reactions of alkynes **2a–e** with tetrazine **1** to confirm their participation in the Carboni–Lindsey[9] reaction. As outlined in Table 2, we were pleased to find that all cycloadditions proceeded smoothly when conducted in nitrobenzene to provide the corresponding cycloadducts in good to high yield.[10,11]

In order to establish the relative rates of cycloaddition of alkynes **2a–e** with tetrazine **1**, we ran a series of competition experiments. Specifically, we decided to run the cycloadditions of each of the alkynes **2b–e** against **2a** and our results are depicted in Table 3. We opted to employ an excess of alkyne (5 equiv each) so as to maintain an approximately equal concentration of each alkyne as the cycloaddition proceeded. Moreover, each cycloaddition was run until complete conversion of the tetrazine and the product ratios were determined by 250 MHz $^1$H NMR spectroscopy of the crude reaction mixtures. Reaction of

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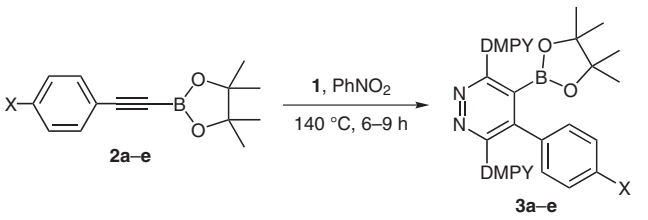
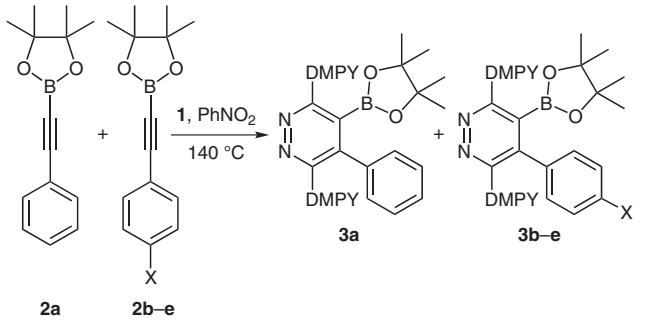
**Table 2** Reactions of Alkynes **2a–e** with Tetrazine **1** in Nitrobenzene



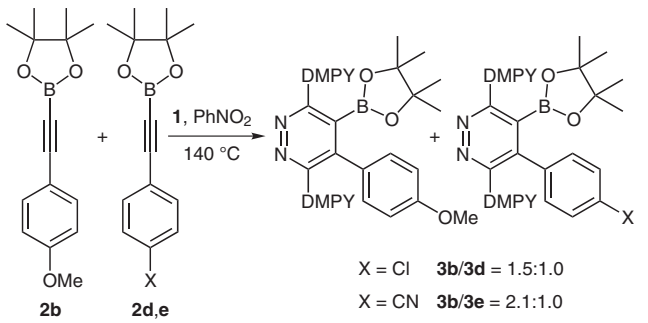

| X | H; **3a** | MeO; **3b** | F; **3c** | Cl; **3d** | CN; **3e** |
|---|---|---|---|---|---|
| Yield | 84% | 83% | 77% | 61% | 59% |

**1** with a mixture of alkynes **2a** and **2b** gave a 1.8:1 ratio of products in favour of pyridazine **3b** (entry 1). Cycloaddition of *p*-F- and *p*-Cl-substituted arylalkynes **2c** and **2d** showed a slight preference for the corresponding boronic esters **3c** and **3d** (entries 2 and 3). Finally, nitrile-substituted alkyne **2e** was found to react more slowly than the parent phenylacetylene **2a** resulting in formation of **3a** as the major product (entry 4).

**Table 3** Cycloaddition Reactions of Alkynes **2b–e** with Tetrazine **1** vs. Reaction of **2a** with Tetrazine **1**




| Entry | Alkyne substrates | Product ratios |
|---|---|---|
| 1 | **2a/2b** | **3a**:**3b**; 1.0:1.8 |
| 2 | **2a/2c** | **3a**:**3c**; 1.0:1.1 |
| 3 | **2a/2d** | **3a**:**3d**; 1.0:1.1 |
| 4 | **2a/2e** | **3a**:**3e**; 1.2:1.0 |




**Scheme 2**

In an effort to validate the competition experiments described in Table 3, we also carried out competition experiments between **2b** and **2d**,**e** (Scheme 2). We were pleased to find that the product ratios observed in these cases were in line with the relative rates calculated in Table 3.

The data outlined in Table 3 and Scheme 1 allowed us to calculate relative rate values ($k_{rel}$) for the cycloaddition of tetrazine **1** with alkynes **2a–e**; these are summarized in Table 4. Overall, these values indicate that increased reactivity is observed with electron-rich alkynes (e.g. **2b**) over electron-deficient alkynes (e.g. **2e**) and this supports our proposed inverse-electron-demand nature of the Carboni–Lindsey reaction of alkynylboronates.[12] Moreover, the small differences in relative rates observed are indicative of little to no charge separation in the rate-determining transition state. This result is in agreement with our computational studies that suggest a highly synchronous transition state in this reaction.[5]

**Table 4** Relative Rate Values ($k_{rel}$) for the Cycloaddition of Tetrazine **1** with Alkynes **2a–e**

| R | H; **2a** | OMe; **2b** | F; **2c** | Cl; **2d** | CN; **2e** |
|---|---|---|---|---|---|
| $k_{rel}$ | 1.0 | 1.8 | 1.1 | 1.1 | 0.9 |

In conclusion, we have studied the cycloaddition of tetrazine **1** with a series of aryl-substituted alkynylboronates. We have observed a trend whereby electron-rich alkynes undergo cycloaddition with higher rates than the corresponding electron-deficient analogues suggesting an inverse-electron-demand [4+2] process.

## Acknowledgment

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(10) **Representative Experimental Procedure for Alkynylboronate Cycloaddition Reactions; Synthesis of 3,6-Bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (3b)**: 3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**1**; 131 mg, 0.486 mmol) and **2b** (125 mg, 0.486 mmol) were dissolved in nitrobenzene (2 mL) and heated at 140 °C until the red colour of the tetrazine had faded. The nitrobenzene was then removed by bulb-to-bulb distillation under reduced pressure and the residue was purified by chromatography on silica gel to give the title compound as a light yellow solid (202 mg, yield: 83%); mp 169.3–170.2 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.03 (s, 12 H, Me), 1.92 (s, 3 H, Me), 2.09 (s, 3 H, Me), 2.29 (s, 3 H, Me), 2.72 (s, 3 H, Me), 3.74 (s, 3 H, Me), 5.72 (s, 1 H, CH), 6.04 (s, 1 H, CH), 6.71–6.80 (m, 2 H, CH), 7.10–7.20 (m, 2 H, CH). $^{13}$C NMR (69.2 MHz, $CDCl_3$): δ = 11.2, 13.4, 13.9, 14.8, 25.2, 55.3, 84.3, 106.0, 111.1, 113.0, 126.0, 130.9, 141.0, 142.4, 145.5, 149.5, 150.4, 152.6, 157.7, 160.0. FTIR: 2977 (m), 2930 (m), 2837 (w), 1611 (m), 1576 (m), 1536 (w), 1507 (s), 1498 (s), 1421 (s), 1402 (s), 1370 (s), 1302 (m), 1251 (s), 1179 (m), 1140 (m), 1124 (m) cm$^{-1}$. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{27}H_{34}BN_6O_3$: 501.2785; found: 501.2800.

(11) **Characterisation Data for Compounds 3c–e**: **3c**: isolated as a light yellow solid; mp >184 °C (dec.). $^1$H NMR (250 MHz, $CDCl_3$): δ = 0.99 (s, 12 H, Me), 1.97 (s, 3 H, Me), 2.01 (s, 3 H, Me), 2.27 (s, 3 H, Me), 2.70 (s, 3 H, Me), 5.70 (s, 1 H, CH), 6.02 (s, 1 H, CH), 6.85–6.95 (m, 2 H, CH), 7.12–7.22 (m, 2 H, CH). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 11.3, 13.3, 13.9, 14.9, 25.3, 84.3, 106.2, 111.3, 114.6 (d, *J* = 22.0 Hz), 129.8, 131.4 (d, *J* = 8.5 Hz), 141.2, 142.5, 144.7, 149.7, 150.5, 152.4, 157.6, 162.9 (d, *J* = 249.0 Hz). FTIR: 2980 (m), 2922 (w), 1604 (w), 1579 (m), 1535 (w), 1505 (s), 1475 (s), 1422 (s), 1402 (s), 1341 (s), 1234 (m), 1162 (w), 1142 (m), 1123 (m) cm$^{-1}$. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{26}H_{31}BN_6O_2F$: 489.2586; found: 489.2581. **3d**: isolated as a light yellow solid; mp 191.9–193.4 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ = 0.98 (s, 12 H, Me), 1.98 (s, 3 H, Me), 2.01 (s, 3 H, Me), 2.26 (s, 3 H, Me), 2.70 (s, 3 H, Me), 5.71 (s, 1 H, CH), 6.01 (s, 1 H, CH), 7.09–7.22 (m, 4 H, CH). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 11.3, 13.3, 13.9, 14.9, 25.3, 84.4, 106.3, 111.3, 127.7, 130.9, 132.3, 134.8, 141.2, 142.5, 144.5, 149.8, 150.6, 152.1, 157.5. FTIR: 2980 (m), 2929 (m), 1600 (w), 1579 (m), 1560 (m), 1532 (m), 1493 (s), 1475 (s), 1448 (m), 1421 (s), 1356 (s), 1140 (s) cm$^{-1}$. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{26}H_{31}BN_6O_2Cl$: 505.2290; found: 505.2310. **3e**: isolated as a light yellow solid; mp 215.3–217.0 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.00 (s, 12 H, Me), 1.97 (s, 3 H, Me), 2.14 (s, 3 H, Me), 2.32 (s, 3 H, Me), 2.76 (s, 3 H, Me), 5.77 (s, 1 H, CH), 6.08 (s, 1 H, CH), 7.30–7.38 (m, 2 H, CH), 7.52–7.61 (m, 2 H, CH). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 11.5, 13.2, 13.9, 14.9, 25.3, 84.4, 106.6, 111.6, 112.2, 118.4, 130.3, 131.2, 138.9, 141.4, 142.5, 143.4, 149.9, 150.7, 151.5, 157.4. FTIR: 2992 (m), 2925 (w), 1857 (w), 2232 (m), 1579 (m), 1534 (m), 1503 (m), 1469 (s), 1419 (s), 1369 (m), 1141 (m) cm$^{-1}$. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{27}H_{31}N_7O_2B$: 496.2632; found: 496.2608.

(12) Unfortunately, the relative rates depicted in Table 4 did not provide a good linear slope when a Hammett plot was drawn up.