

# Lewis Base Directed Cycloaddition Reactions of 2-Pyrones and Alkynylaluminum Reagents

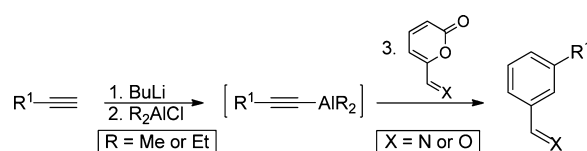
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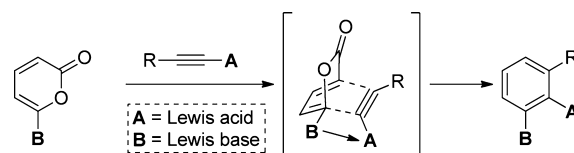
## ABSTRACT



In situ generated alkynylaluminum reagents have been utilized in a [4 + 2] cycloaddition with 2-pyrones bearing a Lewis basic donor. The reactions proceed at or below room temperature and with complete regiocontrol. This one-pot method affords diversely substituted aromatic compounds under very mild conditions.

The selective formation of aromatic compounds has attracted considerable interest in synthetic chemistry due to their importance in diverse areas of the chemical industry. Various methods have been developed for their synthesis, mainly including electrophilic or nucleophilic substitution reactions, transition-metal-catalyzed cross-coupling, or C–H bond functionalization of preformed aromatic compounds.<sup>1</sup> Another strategy relies on regioselective benzannulation reactions that obviate the need for specific directing groups when incorporating substituents, and a range of such methods have been reported that employ metal promoted or pericyclic reactions.<sup>2</sup> As outlined in Figure 1, we have become interested in the potential of the substrate directing group concept<sup>3</sup> for promoting such cycloadditions and have reported the implementation of in situ generated alkynylaluminum reagents toward this end.<sup>4</sup> This mild method allows for the formation of diversely substituted aromatic compounds

which can easily undergo further functionalization. We envisaged that this method could allow access to other arene-based organometallics by the cycloaddition of alkynes bearing other Lewis acids. In this context, we report herein the use of alkynylaluminum derivatives as new 2π components in a directed [4 + 2] cycloaddition with 2-pyrones.



**Figure 1.** Lewis base directed cycloaddition of 2-pyrones and alkynes.

Preliminary investigations into the cycloaddition of 2-pyrones and alkynylaluminum reagents<sup>5</sup> proved to be disappointing. These alkynes appeared to be unreactive at low temperature (−78 °C) and served to decompose the pyrones at more elevated temperatures. In contrast however, in situ generated diethyl(phenylethynyl)aluminum **2a** reacted with 2-pyrone **3a** at ambient temperature to provide

(1) (a) Miura, M.; Momura, M. *Top. Curr. Chem.* **2002**, *219*, 212. (b) Culkun, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) (a) Saito, S.; Yao, Y. *Chem. Rev.* **2000**, *100*, 2901. (b) D'Souza, D. M.; Müller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095.

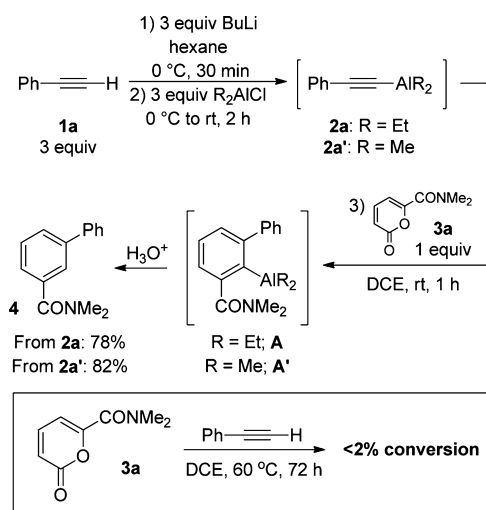
(3) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(4) (a) Vivat, J. F.; Adams, H.; Harrity, J. P. A. *Org. Lett.* **2010**, *12*, 160. (b) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6402. For cycloadditions of 2-pyrones and alkynylboronic esters, see: (c) Kirkham, J. D.; Leach, A. G.; Row, E. C.; Harrity, J. P. A. *Synthesis* **2012**, *44*, 1964. (d) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866.

(5) For examples of synthesis and use of alkynylaluminum reagents, see: (a) Leung, S.-W.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 1955. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879.

biaryl **4** in high yield. We presume that **4** results from the hydrolysis of intermediate **A** (vide infra).<sup>6</sup> Similarly, dimethyl(phenylethynyl)aluminum **2a'** can also be prepared in situ and employed in the cycloaddition with pyrone **3a**, affording compound **4** in 82% yield.<sup>7</sup> The importance of the Al-moiety in this reaction was confirmed by reacting **3a** with phenylacetylene; we were unable to detect any cycloadduct after heating the substrates at 60 °C over an extended time period.

### Scheme 1. Initial Conditions of Cycloaddition



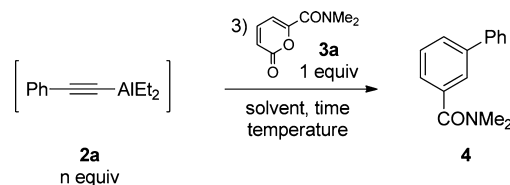
The optimization of the initial conditions (Table 1, entry 1) was carried out using diethyl(phenylethynyl)aluminum **2a** due to the less pyrophoric nature of diethylaluminum chloride relative to the dimethyl- analog. We observed no reactivity upon changing the reaction solvent for THF, or reducing the reaction temperature to  $-78\text{ }^{\circ}\text{C}$  (entries 2 and 3). However, conducting the reaction in DCE at  $0\text{ }^{\circ}\text{C}$  resulted in full conversion after 2 h and **4** was isolated in 59% yield. Moreover, we found that the stoichiometry of diethyl(phenylethynyl)aluminum reagent **2a** could be reduced to 1.5 equiv, affording biphenyl **4** in 73% yield when the reaction was conducted at rt (entry 5). Decreasing the temperature to  $0\text{ }^{\circ}\text{C}$  gave **4** in a similar yield (entry 6). Finally, we found that pyrone **3a** also undergoes the cycloaddition when treated with only 1.1 equiv of alkynylaluminum **2a** (entry 7). Under these conditions, **4** was isolated in 69% yield.

We next investigated the scope of the reaction, using 3 equiv of alkynyldiethylaluminum compounds **2a–d** throughout to ensure complete conversion (Table 2). We

(6) For examples of the use of dialkyl(aryl)aluminum intermediates in synthesis, see: (a) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211. (b) Gao, H.; Knochel, P. *Synlett* **2009**, 1321.

(7) For examples of synthesis and use of alkynyl(dialkyl)aluminum species in cycloaddition reactions, see: (a) Tirado, R.; Torres, G.; Torres, W.; Prieto, J. A. *Tetrahedron Lett.* **2005**, *46*, 797. (b) von Zezschwitz, P. *Synthesis* **2008**, 1809. (c) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664. (d) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2607.

**Table 1.** Optimization of the [4 + 2] Cycloaddition

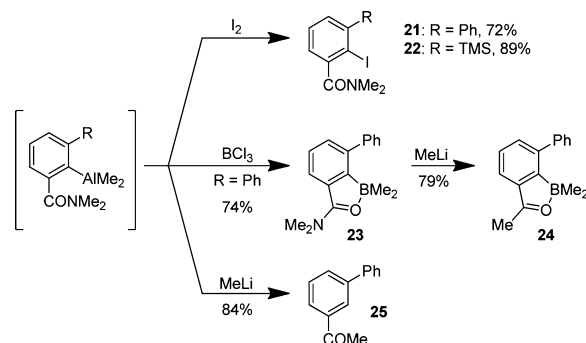


| entry | <i>n</i> equiv of <b>2a</b> <sup>a</sup> | solvent | temp                          | time  | isolated yield of <b>4</b> |
|-------|--|---------|-------------------------------|-------|----------------------------|
| 1     | 3  | DCE     | rt                            | 1 h   | 78%                        |
| 2     | 3  | THF     | rt                            | 1 h   | –                          |
| 3     | 3  | DCE     | $-78\text{ }^{\circ}\text{C}$ | 1 h   | –                          |
| 4     | 3  | DCE     | $0\text{ }^{\circ}\text{C}$   | 2 h   | 59%                        |
| 5     | 1.5                                      | DCE     | rt                            | 1 h   | 73%                        |
| 6     | 1.5                                      | DCE     | $0\text{ }^{\circ}\text{C}$   | 1.5 h | 72%                        |
| 7     | 1.1                                      | DCE     | rt                            | 2.5 h | 69%                        |

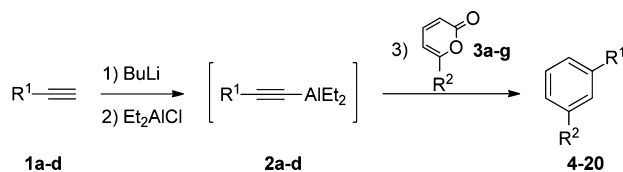
<sup>a</sup> Alkyne **2a** was prepared in situ following the conditions shown in Scheme 1.

found that pyrones **3b** and **3c**, respectively substituted by a thioamide and an ester group, did not undergo the cycloaddition; instead the starting material was recovered in each case (entries 2 and 3). In contrast, pyrones that incorporated various amide groups **3d–f** afforded the corresponding cycloadducts **7–9** in good yields (entries 4–6), including substrate **3f** that bears a free N–H group. We next looked at a range of *N*-heteroaromatics in order to establish their potential as directing groups for the cycloaddition of **2a**. While pyridine-substituted pyrone **3g** gave product **10** in 78% yield (entry 7), we were surprised to recover oxazole and thiazole substituted pyrones **3h** and **3i** unreacted (entries 8 and 9). Interestingly, when the pyrone is branched at the C2 position of the thiazole instead of position C4 (**3j** versus **3i**), cycloadduct **13** was produced in 70% yield (entry 10). Moreover, imidazole-substituted pyrone **3k** was also reactive, affording **14** in 69% yield (entry 11). Finally, we discovered that different

### Scheme 2. Functionalization of Aryl(dimethyl)aluminum Intermediates<sup>a</sup>



<sup>a</sup> The aryl(dimethyl)aluminum intermediates were prepared according to the optimized conditions, using  $\text{Me}_2\text{AlCl}$ .

**Table 2.** Scope of the Cycloaddition<sup>a</sup>


| entry          | R <sup>1</sup>   | R <sup>2</sup>                             | product 4-19 | isolated yield of 4-19  | entry           | R <sup>1</sup>                | R <sup>2</sup>                               | product 4-19 | isolated yield of 4-19     |
|----------------|------------------|--|--------------|-------------------------|-----------------|-------------------------------|--|--------------|----------------------------|
| 1              | Ph ( <b>1a</b> ) |  |              | X = O; 78% ( <b>4</b> ) | 10 <sup>d</sup> | Ph ( <b>1a</b> )              |  |              | X = S; 70% ( <b>13</b> )   |
| 2 <sup>b</sup> |                  | X = O ( <b>3a</b> )<br>X = S ( <b>3b</b> ) |              | X = S; 0% ( <b>5</b> )  | 11 <sup>d</sup> |                               | X = S ( <b>3j</b> )<br>X = NMe ( <b>3k</b> ) |              | X = NMe; 69% ( <b>14</b> ) |
| 3 <sup>b</sup> | Ph ( <b>1a</b> ) |  |              | 0% ( <b>6</b> )         | 12              | TMS ( <b>1b</b> )             |  |              | 80% ( <b>15</b> )          |
| 4              |                  |  |              | 76% ( <b>7</b> )        | 13              | TMS ( <b>1b</b> )             |  |              | 41% ( <b>16</b> )          |
| 5 <sup>c</sup> | Ph ( <b>1a</b> ) |  |              | 72% ( <b>8</b> )        | 14              | Bu <sup>n</sup> ( <b>1c</b> ) |  |              | 73% ( <b>17</b> )          |
| 6              |                  |  |              | 67% ( <b>9</b> )        | 15              |                               | Bu <sup>n</sup> ( <b>1c</b> )                |              |                            |
| 7              | Ph ( <b>1a</b> ) |  |              | 78% ( <b>10</b> )       | 16              | Bu <sup>n</sup> ( <b>1c</b> ) |  |              | 82% ( <b>19</b> )          |
| 8 <sup>b</sup> |                  |  |              | X = O; 0% ( <b>11</b> ) | 17              |                               | 1-Cyclohexenyl ( <b>1d</b> )                 |              |                            |
| 9 <sup>b</sup> | Ph ( <b>1a</b> ) | X = O ( <b>3h</b> )<br>X = S ( <b>3i</b> ) |              | X = S; 0% ( <b>12</b> ) |                 |                               |  |              |                            |

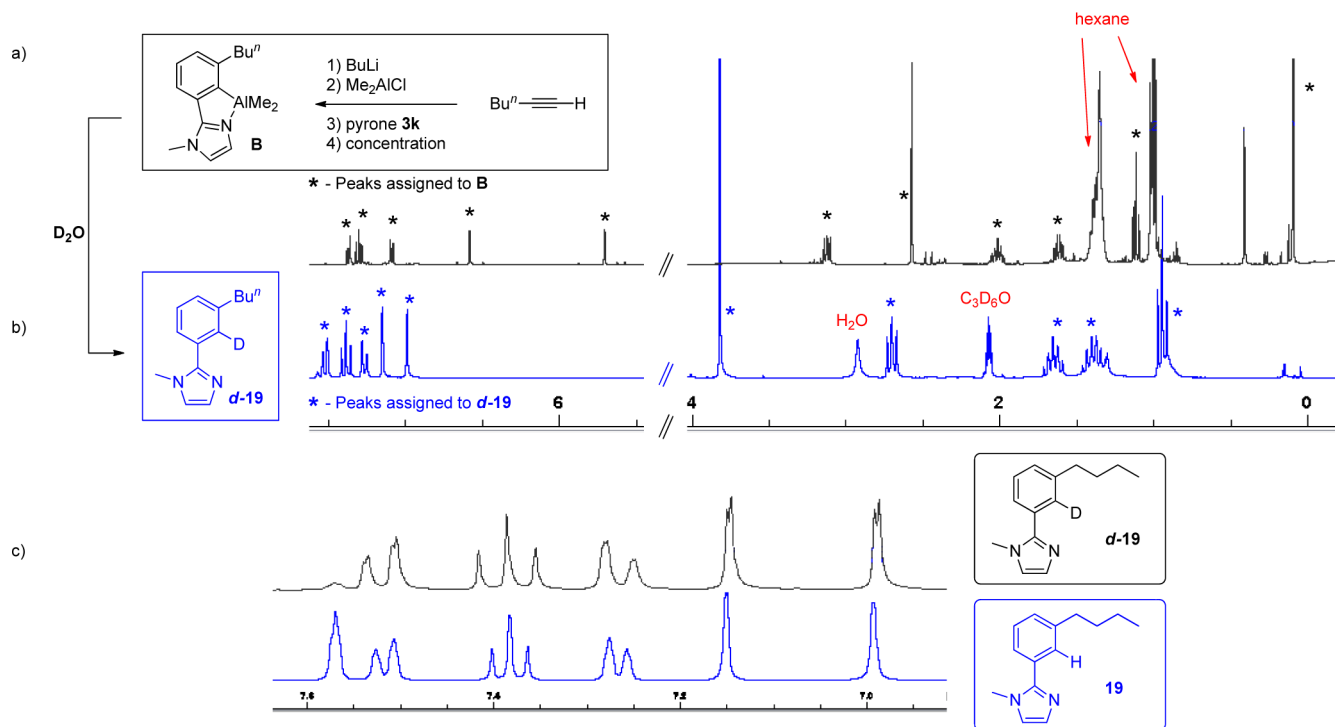
<sup>a</sup> Alkyne (**1a–d**) (3 equiv), BuLi (3 equiv), Et<sub>2</sub>AlCl (3 equiv); pyrone (**3a–k**) (1 equiv), rt, 1 h. <sup>b</sup> Pyrone substrate was recovered. <sup>c</sup> Reaction conducted for 3 h. <sup>d</sup> Reaction conducted for 12 h.

terminal alkynes can be employed. Hence, trimethylsilylacetylene **1b** and 1-hexyne **1c** reacted with pyrones **3a**, **3g**, and **3k**, affording aromatic compounds **15–19** (entries 12–16). Finally, 1-ethynylcyclohexene **1d** was also employed, giving **20** in moderate yield (entry 17).

The role played by the Al-group in promoting the reaction together with the consistent *meta*-substitution pattern observed in products generated by this process provided circumstantial evidence for the operation of a directed cycloaddition process (along the lines depicted in Figure 1). In order to gather further evidence however, we attempted to identify and characterize an intermediate arylaluminum cycloadduct. Although we found these intermediates to be hydrolytically unstable, careful concentration of the reaction mixture derived from the

dimethylaluminum promoted cycloaddition of **1c** and **3k** allowed us to record a <sup>1</sup>H NMR spectrum of the crude material (Figure 2a). We were able to identify a signal at 0.09 ppm that was consistent with the Me-Al group.<sup>8</sup> Furthermore, quenching this reaction mixture with D<sub>2</sub>O resulted in the formation of compound **d-19** after work-up (Figure 2b). The <sup>1</sup>H NMR spectrum shows approximately 90% incorporation of the deuterium label occurred in this case (Figure 2c).<sup>8</sup>

(8) Although we have been unable to gather clear evidence for the formation of a Lewis acid–base complex in these products (e.g. **B** in Figure 2) Blum and co-workers have reported similar intramolecularly stabilized dialkyl(aryl)aluminum complexes; see: Blum, J.; Gelman, D.; Baidossi, W.; Sharkh, E.; Rosenfeld, A.; Aizenshtat, Z. *J. Org. Chem.* **1997**, *62*, 8681.



**Figure 2.** (a) <sup>1</sup>H NMR in C<sub>6</sub>D<sub>6</sub> of crude intermediate **B**. (b) <sup>1</sup>H NMR in C<sub>3</sub>D<sub>8</sub>O after quench of intermediate **B** with D<sub>2</sub>O followed by standard workup. (c) Comparison of the aromatic region of **d-19** and **19**.

Finally, we wanted to investigate the synthetic potential of the aryl(dimethyl)aluminum intermediates, and some illustrative examples are shown in Scheme 2. First, we found that the intermediate arylaluminum compounds reacted smoothly with iodine, affording iodobenzene derivative **21** and **22** in high yield. Moreover, when the intermediate was treated with boron trichloride, dimethylboryl product **23** was obtained in 74% yield.<sup>9</sup> The latter could be transformed into methylketone **24** upon exposure to methyl lithium; a similar transformation could be accomplished directly from the intermediate aluminum species to afford methylketone **25** in 84% yield. Overall, this technique complements our recent cycloaddition chemistry of alkynyldifluoroboranes,<sup>4b</sup> as it offers a one-pot

(9) The structure of this compound, including evidence for coordination of the amide oxygen atom, was obtained by X-ray crystallography. The similarity of <sup>11</sup>B NMR data in **23** and **24** suggests that **24** has a similar Lewis acid–base interaction. See Supporting Information for details.

benzannulation of terminal alkynes, with the option of generating arylhalides or boranes depending on the work-up employed.

In conclusion, we have demonstrated that in situ generated alkynylaluminum reagents undergo rapid cycloaddition reactions with 2-pyrones bearing proximal Lewis bases. This method provides an effective route to functionalized benzene derivatives with predictable substitution patterns and complete regiocontrol.

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**Supporting Information Available.** Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.