



# *ortho*-Difunctionalization of arynes by LiZnEt<sub>2</sub>(TMP)-mediated deprotonative zincation/elimination of aryl triflates

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## ABSTRACT

Generation of arynes from aryl triflates has been achieved using lithium diethyl(tetramethylpiperidyl)-zincate base LiZnEt<sub>2</sub>(TMP), via a directed *ortho*-deprotonative zincation and subsequent elimination of the triflate group. The aryne formation has been demonstrated by the cycloaddition reaction with diene and insertion reactions with ureas. Furthermore, the nucleophilic addition of LiZnEt<sub>2</sub>(TMP) to arynes was observed in the absence of external aryne partners, offering a new cascade strategy for diverse difunctionalization of arynes.

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## 1. Introduction

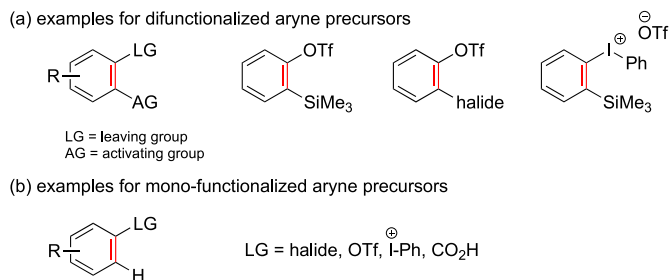
Aryne chemistry has received great attention in organic chemistry, mechanistic studies, and synthesis of versatile functionalized arene derivatives, such as natural products and functional materials.<sup>1</sup> Aryne is a highly reactive intermediate<sup>2</sup> and its synthesis<sup>3,4</sup> commonly starts from difunctionalized arene precursors,<sup>5</sup> including commonly used 2-(trimethylsilyl)phenyl triflates (Scheme 1, a).<sup>5a</sup> However, access to highly functionalized and elaborate arynes remains limited due to the lengthy synthesis required to introduce bis-functional groups onto their precursors. Alternatively, *ortho*-C–H deprotonative metalation/elimination has been reported for aryne formation from arenes bearing a leaving group, such as halides,<sup>6</sup> triflates,<sup>6d</sup> iodonium salts,<sup>7</sup> and carboxylic acids<sup>8</sup> (Scheme 1, b). Thus, from the aspects of the availability of precursors and general applicability, the preparation of arynes from mono-functionalized arene precursors is attractive and advantageous. Yet in most cases, a strong base (e.g., LiR) is required for the deprotonative metalation step, which would limit the substrate scope, and result in side reactions (e.g., thia-Fries rearrangement).<sup>9</sup> When multiple functionalities or leaving groups are present, chemoselectivity arises for both C–H deprotonation and the selective

elimination of the leaving group. In 2002, Uchiyama reported the use of lithium dimethyl(tetramethylpiperidyl)-zincate to promote the *ortho*-C–H zincation/elimination of aryl halides toward the aryne formation.<sup>10</sup> Encouragingly, the arylzincate intermediates were found to be compatible with sensitive substituents such as ester, amide, and cyano groups.

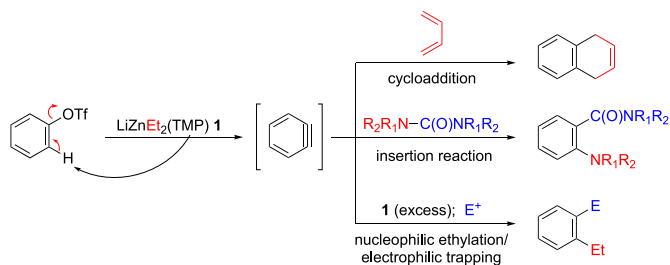
Recently, we have investigated the use of a related zincate base LiZnEt<sub>2</sub>(TMP) **1** to achieve selective C–H zincation for an extensive scope of functionalized arenes.<sup>11</sup> During our studies, no aryne formation was detected from fluoro-, bromo- or chloro-substituted arenes when LiZnEt<sub>2</sub>(TMP) was used, in contrast to the aryne formation from aryl halides reported in Uchiyama's studies where LiZnMe<sub>2</sub>(TMP) was used.<sup>10</sup> Furthermore, the analogous LiZn(tBu)<sub>2</sub>(TMP) in Uchiyama's studies was effective for promoting the C–H zincation similar to LiZnMe<sub>2</sub>(TMP) for aryl halides, but without forming the aryne intermediates from the resulting arylzincate intermediate. As both the nature of alkyl ligands in the arylzincate intermediates and the leaving group strongly influence the aryne formation, we became interested whether the zincate base LiZnEt<sub>2</sub>(TMP) **1** may promote the formation of aryne intermediates via deprotonative zincation/elimination starting from aryl triflates. Note the triflate group (OTf) is expected to be a better leaving group than halides to facilitate the aryne formation, while aryl triflates were much less explored than aryl halides due to common side reactions of thia-Fries rearrangement. Herein, we report our findings regarding LiZnEt<sub>2</sub>(TMP)-mediated aryne

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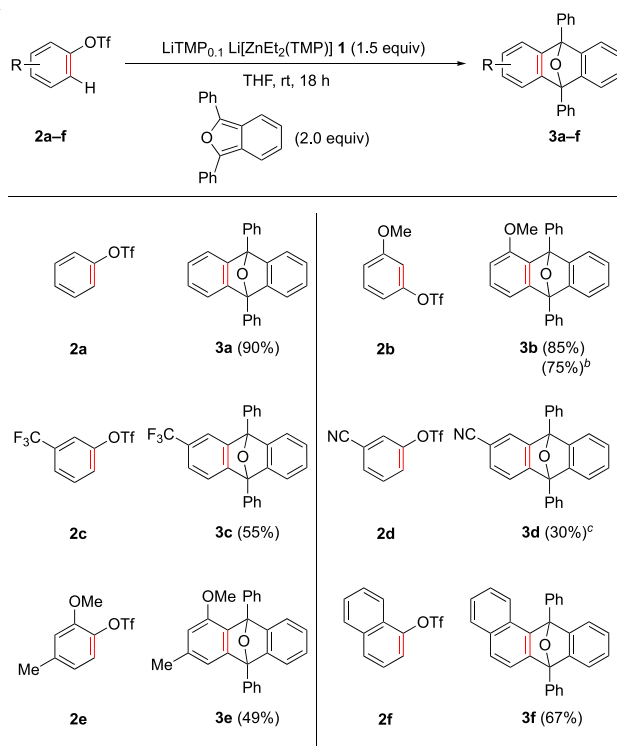
**Scheme 1.** Representative aryne precursors.



**Scheme 2.** Aryne formation and transformations via deprotonative zincation/elimination of ArOTf. **1** = (LiTMP<sub>0.1</sub>)LiZnEt<sub>2</sub>(TMP), TMP = tetramethylpiperidine.

formation and its application in versatile aryne transformations for rapid access to diverse functionalized arenes (**Scheme 2**).

**Table 1**  
Aryne formation via LiZnEt<sub>2</sub>(TMP)-mediated deprotonative zincation of aryl triflates and subsequent [4+2] cycloaddition reactions.<sup>a</sup>



Isolation yields shown. <sup>a</sup>Reactions on 0.2-mmol scale. <sup>b</sup>Reaction on 4.0-mmol scale. <sup>c</sup>Major product. <sup>1</sup>H-NMR spectrum of the crude mixture shows a 3:1 product mixture of two isomers.

## 2. Results and discussion

### 2.1. Aryne formation and cycloaddition chemistry

We examined lithium diethyl(tetramethylpiperidyl)-zincate base LiZnEt<sub>2</sub>(TMP) **1** for its ability to generate arynes from aryl triflates via an *ortho*-deprotonative zincation/elimination pathway, in the presence of 1,3-diphenylisobenzofuran (**Table 1**). The generation of arynes was confirmed by the formation of corresponding [4+2] cycloaddition products. First, the treatment of phenyl triflate **2** under standard conditions successfully provided cycloadduct **3a** in 90% yield. Next, aryne precursors **2b–2e** bearing different substituents were tested; the formation of **3b–3e** suggested good tolerance of both electron-rich and electron-deficient groups under these conditions. Similarly, naphthalenyl triflate **2f** formed cycloadduct **3f**. Interestingly, we found that the position of the arylne could vary depending on the substitution *meta* to the triflate group: the methoxy group of **2b** directed the *ortho*-zincation to form 2,3-aryne, while trifluoromethyl group of **2c** directed the generation of 3,4-aryne. For the cyano group of **2d**, a 3:1 regioselectivity was observed for cycloadduct **3d**, indicating the preferred formation of the 3,4-aryne intermediate. These representative examples have established that zincate base **1** is capable of promoting the *ortho*-deprotonative zincation and elimination reaction of aryl triflates and generating diverse aryne intermediates. A comparable efficacy was observed on a scale-up reaction of **2b** (i.e., 75% and 85% yields on 4.0-mmol and 0.2-mmol scales, respectively), further demonstrating the scalability and reliability of this method.

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