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Dichlorination of (Hexadehydro-Diels–Alder Generated) Benzynes and a Protocol for Interrogating the Kinetic Order of Bimolecular Aryne Trapping Reactions

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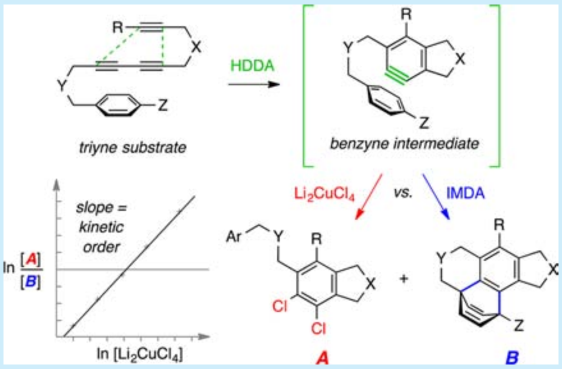
Supporting Information

ABSTRACT: The efficient dichlorination of benzynes prepared by the hexadehydro-Diels–Alder (HDDA) reaction is reported. Cycloisomerization of a triyne substrate in the presence of dilithium tetrachlorocuprate is shown to provide dichlorinated products *A* by capture of the benzyne intermediate. A general strategy for discerning the kinetic order of an external aryne trapping agent is presented. It merely requires measurement of the competition between bimolecular vs unimolecular trapping events (here, dichlorination vs intramolecular Diels–Alder (IMDA) reaction to give *A* vs *B*, respectively) as a function of the concentration of the trapping agent.

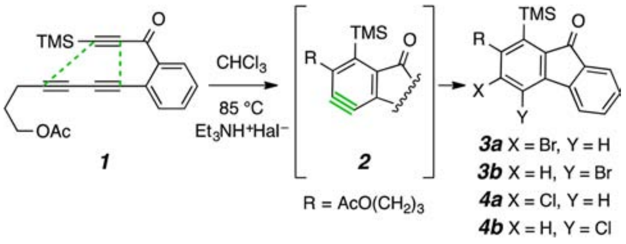


Arynes represent a very old and well-studied class of reactive intermediates in organic chemistry. Since the report over a century ago of what is now recognized as the first example of a transformation consistent with a benzyne species,[1] many methods for aryne generation have been developed.[2] Most commonly used is the strategy introduced by Kobayashi in 1983, in which *ortho*-TMSPhOTf (or a substituted variant) is treated with a fluoride ion to generate the aryne under mildly basic conditions.[3] This method, because of its operational ease and broad functional group compatibility, spurred renewed interest in aryne trapping chemistry.[4] Recently, we reported the generality of a transformation we call the hexadehydro-Diels–Alder (HDDA) reaction. This thermal cycloisomerization of a triyne precursor (e.g., **1**) constitutes a reagent- and byproduct-free method for making benzyne intermediates of considerable structural complexity (e.g., **2**). This convenient conversion of a triyne substrate to aryne intermediate has enabled us and others to explore aspects of intrinsic aryne reactivity,[5,6] including the discovery of entirely new modes of trapping reactions.[5b,6a] However, despite the numerous (and multifaceted) aryne trapping reactions that have been developed to date, rarely has it been possible to probe kinetic aspects of these powerful transformations. This is not a trivial problem because the benzyne forming reaction rather than its subsequent trapping is nearly always the rate-limiting event. Certainly there is no report of a general strategy for studying the kinetics of aryne trapping [e.g., for deducing the kinetic order of the trapping reactant(s)].

Aryl chlorides are commonly encountered in, for example, agrochemicals, pharmaceuticals, natural products, and photonic materials. Aryl chlorides have also grown in importance as synthetic intermediates in light of improved methodologies capable of activating the relatively inert C_{sp2}–Cl bonds.[7] Classically, aryl chlorides are made from the Sandmeyer reaction or electrophilic aromatic halogenation. One of the benzyne trapping reactions we have reported[5a] is that with an HBr source to produce the monobromoarenes **3a** and **3b** (Scheme 1). Since then, we have observed that treatment with various ammonium chlorides gives a similar outcome, namely the formation of monochlorides **4a** and **4b**.

1,2-Dichlorobenzene derivatives, the principal subject of the investigations reported here, are seen in target compounds of interest, as represented by the structures **5a–d** (Figure 1). The preparation of *ortho*-dichlorinated arenes is more challenging than that of monochloroarenes. There are only a few reports of direct 1,2-dihalogenation of arynes. These are limited to (i)

Scheme 1[a]



[a]Monohalo arene formation [**3** or **4**; 70–80% yield (**3a**:**3b** = 13:1; **4a**:**4b** = 6:1)] through net hydrogen halide addition to the benzyne **2** formed via the HDDA reaction of the triyne **1**.

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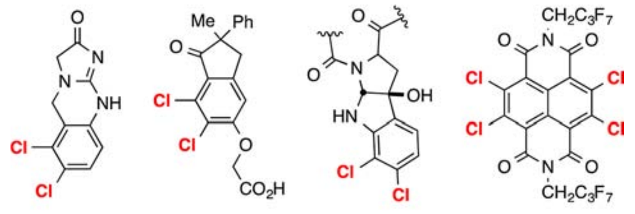
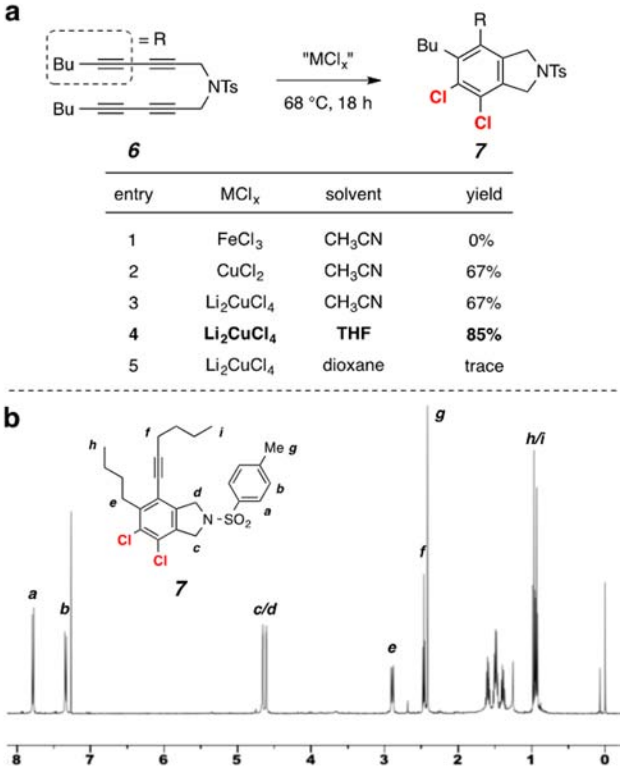


5a **5b** **5c** **5d**

Figure 1. Examples of 1,2-dichlorinated target compounds (**5a**, Agrylin, platelet reducing agent for treatment of thrombocytosis; **5b**, indacrinone, diuretic developed for treatment of gout and hypertension; **5c**, kutznerides, antimicrobial cyclic peptides; and **5d**, for organoelectronic applications).



entry	MCl$_x$	solvent	yield
1	FeCl$_3$	CH$_3$CN	0%
2	CuCl$_2$	CH$_3$CN	67%
3	Li$_2$CuCl$_4$	CH$_3$CN	67%
4	**Li$_2$CuCl$_4$**	**THF**	**85%**
5	Li$_2$CuCl$_4$	dioxane	trace

Figure 2. (a) Identification of Li$_2$CuCl$_4$ as an effective reagent for dichlorination of the benzyne derived from tetrayne **6**. (b) ^{1}H NMR spectrum of the *crude product mixture* following simple extractive workup of the entry 4 experiment.

diiodination[8,9] (with I$_2$) or dibromination[8a] (with Br$_2$), in which the reactions tend to proceed less effectively for arynes more elaborate than those of benzyne itself (from anthranilic acid or *ortho*-TMSPhOTf)[8c] and (ii) vicinal, mixed fluorohalogenation via silver(I)-promoted, net addition of FCl, FBr, or FI to HDDA-generated benzynes.[6b] We are not aware of any examples of aryne dichlorination. A strategy to make 1,2-dichlorinated arenes from triynes via the intermediate benzynes is reported here. It is additionally important that, in the course of these studies, a simple but general protocol that can be used to gain insight to various kinetic aspects of aryne trapping events has also been developed.

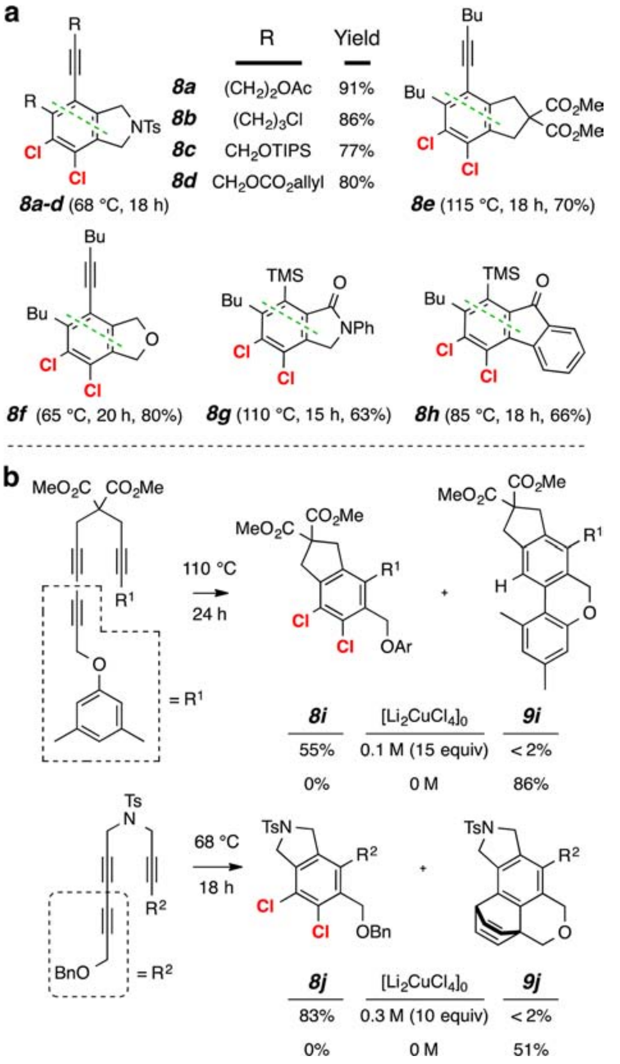
We initially explored the possibility of trapping the HDDA-generated benzyne **2** with either I$_2$ or Br$_2$. We were not surprised that this experiment did not produce observable amounts of the desired dihalobenzenes (i.e., **3**/**4** where X = Y = I or Br). In general, one practical feature of HDDA chemistry is that the alkynes in the triyne reactant need to be compatible with the agents intended to trap the intermediate benzynes under the conditions required to generate the benzyne. For example, addition of Cl$_2$ (and Br$_2$) to alkynes is relatively fast and is not expected to be compatible with most HDDA substrates. However, various metal halides are known to act as milder dihalogen surrogates for some dihalogen addition reactions.[10] We have learned that dilithium tetrachlorocuprate (Li$_2$CuCl$_4$) functions as an effective dichlorinating agent of HDDA-generated benzynes and report those observations here.

We used the symmetrical tetrayne **6** for our initial explorations; it is both quite easy to prepare and has relatively high reactivity as an HDDA substrate. When a solution of **6** in CH$_3$CN was heated in the presence of FeCl$_3$, no desired dichlorination product **7** was formed, as judged by GC or TLC analysis (entry 1, Figure 2a). The first indication of a successful outcome was seen with the use of CuCl$_2$ in acetonitrile. Addition of **6** and warming the resulting solution to 68 °C led to the formation of **7** in 67% yield following purification. Use of Li$_2$CuCl$_4$, formed in situ by mixing CuCl$_2$ with solid LiCl, in acetonitrile gave the desired dichlorination product in a similar yield. The efficiency of the reaction was increased when the solvent was changed to THF; **7** was isolated in 85% yield. Under these conditions, no noticeable amount of dihydrogenation (by THF)[5b] or HCl addition products derived from competitive trapping of the intermediate benzyne was observed. Notably, dioxane was an ineffective solvent for this transformation, presumably due to the low solubility of Li$_2$CuCl$_4$, a feature that stands in contrast to its high solubility in THF.

We next probed some of the scope of this Li$_2$CuCl$_4$-mediated dichlorination reaction. Products **8a**–**h** (Figure 3a) encompass dichlorinated isoindoline, isoindolone, isobenzofuran, indane, and fluorenone skeletons. These results show that a variety of functional groups are tolerated in the triyne precursors and/or the benzenoid products. They include toluenesulfonamide, ketone, ester, amide, carbonate, alkyl or aryl chloride, silyl ether, silyl alkyne, alkene, and an (electron rich) aromatic ring. However, we have observed that triyne substrates containing a free alcohol or terminal alkyne are not compatible with the reaction conditions.

Notably, each of the benzyne precursors to **8i** and **8j** bears an intramolecular trap. In the absence of an external trapping agent, an efficient aromatic Diels–Alder[5a] or aromatic ene[5c] reaction within the intermediate benzyne occurs to give **9i** or **9j**, respectively (Figure 3b). However, in the presence of Li$_2$CuCl$_4$ these intramolecular trapping modes were largely if not completely superseded by chlorination to instead produce **8i** or **8j**.

In the course of sorting out some of the details of these competition reactions, we noticed that, for the case of products **8k** vs **9k**, the extent of formation of the latter could not be entirely suppressed (Figure 4). Moreover, the amount of **9k** formed was dependent on the concentration of the Li$_2$CuCl$_4$ used in any given experiment. This led us to consider in further detail the factors that are relevant to this pair of competing events. The Diels–Alder adduct **9k** results from unimolecular cycloaddition within the benzyne **11**.[11] On the other hand, reaction between **11** and the chlorination agent is intermolecular and the rate of that trapping event should be, therefore, dependent on the concentration of Li$_2$CuCl$_4$. The ratio of rate equations for the formation of **8k** and **9k** can be expressed as shown in eq 1 which, rewritten, is eq 2. When Li$_2$CuCl$_4$ is

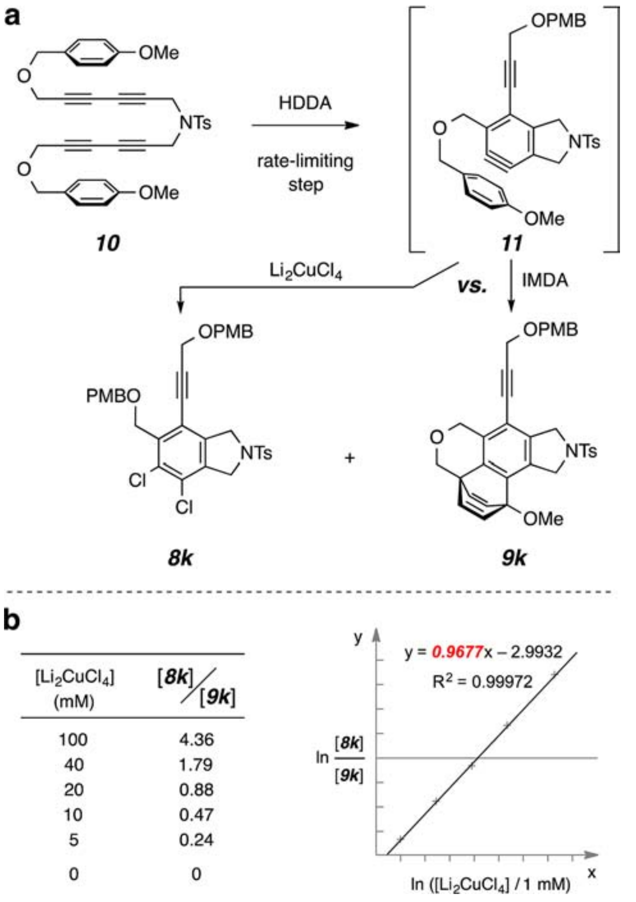


	R	Yield
8a	$(CH_2)_2OAc$	91%
8b	$(CH_2)_3Cl$	86%
8c	CH_2OTIPS	77%
8d	CH_2OCO_2allyl	80%

8i	$[Li_2CuCl_4]_0$	**9i**
55%	0.1 M (15 equiv)	< 2%
0%	0 M	86%

8j	$[Li_2CuCl_4]_0$	**9j**
83%	0.3 M (10 equiv)	< 2%
0%	0 M	51%

Figure 3. (a) Products (**8a**−**h**) of dichlorination (10 equiv of Li_2CuCl_4, $[substrate]_0 = 0.03$ M in THF) of various HDDA-derived arynes. The green dashed line indicates the C−C bonds formed in the HDDA reaction. (b) Competitive dichlorination (to **8i** or **8j**) vs intramolecular benzyne trapping by aromatic ene (to **9i**)[5c] or Diels−Alder (to **9j**)[5a] reaction, respectively.



$[Li_2CuCl_4]$ (mM)	[8k]/[9k]
100	4.36
40	1.79
20	0.88
10	0.47
5	0.24
0	0

Figure 4. (a) Competition experiment involving the intramolecular Diels−Alder (IMDA) reaction of benzyne **11** vs the bimolecular trapping by Li_2CuCl_4 to give **9k** vs **8k**. (b) Product ratios at varying concentrations of Li_2CuCl_4 (20 equiv in each case) and the log−log plot from which the kinetic order was obtained.

present in excess, eq 2 can be approximated by eq 3, which can also be expressed as eq 4.

$$\frac{d[\mathbf{8k}]}{d[\mathbf{9k}]} = \frac{k_2\cdot[\mathbf{11}]\cdot[Li_2CuCl_4]^n\cdot dt}{k_1\cdot[\mathbf{11}]\cdot dt} \quad (1)$$

$$\frac{[\mathbf{8k}]}{[\mathbf{9k}]} = \frac{\int k_2\cdot[\mathbf{11}]\cdot[Li_2CuCl_4]^n\cdot dt}{\int k_1\cdot[\mathbf{11}]\cdot dt} \quad (2)$$

$$\frac{[\mathbf{8k}]}{[\mathbf{9k}]} \approx \frac{k_2}{k_1}\cdot[Li_2CuCl_4]^n \quad (3)$$

$$\ln\frac{[\mathbf{8k}]}{[\mathbf{9k}]} \approx n\cdot\ln[Li_2CuCl_4] + \ln\frac{k_2}{k_1} \quad (4)$$

The product ratio of **8k** to **9k** was measured at a series of different concentrations of Li_2CuCl_4, and the results are given in Figure 4b. The slope of the plot of ln[**8k**]/[**9k**] vs ln[Li_2CuCl_4] shows that formation of **8k** has a first-order dependence on [Li_2CuCl_4], indicating that only one copper species is involved up through the rate-limiting step in the product-forming phase of the reaction.

In conclusion, we have developed a new and efficient benzyne dichlorination reaction using the mild oxidizing agent, dilithium tetrachlorocuprate. We have shown that various types of 1,2-dichlorinated products can be accessed. The conditions are compatible with a considerable variety of functional groups in the benzyne precursor and resultant benzenoid product. In the course of the studies, we have also developed a strategy for probing some important kinetic aspects of benzyne trapping reactions. In particular, we made use of the competitive intramolecular Diels−Alder (IMDA) reaction of benzyne **11** as an internal clock reaction and observed the change in ratio of the dichlorination to IMDA products as a function of the concentration of the dichlorinating agent. Thereby, we have shown that the dichlorination of benzyne **11** has a first order dependence on the concentration of Li_2CuCl_4. This protocol is noteworthy because kinetic studies of the reactions of arynes are challenging, given that the formation, not the trapping, of these highly reactive intermediates is virtually always the rate limiting event. This protocol, determining the change in product ratios arising from a bimolecular vs an intramolecular trapping reaction as a function of concentration of the trapping agent, represents an approach we believe applicable for studying the molecularity of many other classes of intermolecular aryne trapping reactions. Such studies are in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) We presume that the presence of Li_2CuCl_4 does not affect the rate of formation of **9k**. If this reagent were acting to catalyze (or inhibit) the net Diels–Alder cycloaddition, then it would be highly improbable that the order of the dependence of formation of dichloride product **8k** would be so close to a whole integer value.