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Communication

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The aza-hexadehydro-Diels-Alder (aza-HDDA) reaction

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Supporting Information Placeholder

ABSTRACT: The generation of pyridynes from diyne nitriles is reported. These cyano-containing precursors are analogs of the triyne substrates typically used for the hexadehydro-Diels-Alder (HDDA) cycloisomerization reactions that produce ring-fused benzynes. Hence, the new processes described represent aza-HDDA reactions. Depending on the location of the nitrile, either 3,4-pyridynes (from 1,3-diynes containing a tethered cyano group) or 2,3-pyridynes (from 1-cyanoethyne derivatives containing a tethered alkyne) are produced. In situ trapping of these reactive intermediates leads to highly substituted and functionalized pyridine derivatives. In several instances, unprecedented pyridyne trapping reactions are seen. Differences in reaction energetics between the aza-HDDA substrates and that of their analogous HDDA (triyne) substrates are discussed.

The cycloisomerization reaction of substrates containing a conjugated 1,3-diyne and a remotely tethered alkyne (the diynophile) (cf. **1**, Figure 1a) to give benzyne intermediates[1] has proven to be quite general and fairly robust.[2] This so-called hexadehydro-Diels-Alder reaction,[3] when carried out in the presence of suitable trapping partners (T^2-T^1), provides a platform for (i) discovering new modes of reactivity, (ii) uncovering fundamental mechanistic details about aryne reactivity, and (iii) accessing complex benzenoid products (cf. **1**-**Ar**). Notably, the core benzene ring is created in a de novo fashion.

It is natural to ask what might result upon replacing the remote carbon atom of the monoyne or of the 1,3-diyne in **1** with a nitrogen atom—that is, would the nitrile analogs **2** (nitrile as diynophile) or **3** (nitrile as an element of a cyanoalkyne) enter into analogous transformations (Figure 1b) to produce highly substituted pyridine products such as **2**-**Ar** or **3**-**Ar** by way of pyridyne[4] intermediates? This would comprise an aza-hexadehydro-Diels-Alder reaction (aza-HDDA). We distinguish these two variants, arbitrarily, as class 1 vs. class 2 processes, respectively (Figure 1b).

A potentially mitigating challenge for the success of an aza-HDDA process is the fact that thermal cycloaddition reactions of nitriles are much more rare than those of alkynes. In part, this stems from the fact that a C≡N triple bond is inherently stronger than that of a C≡C bond.[5] Nitriles do engage in metal-catalyzed net cycloadditions. Notable are nitrile plus azide (3+2)-cycloadditions to give tetrazoles[6] and nitrile + alkyne + alkyne, net [2+2+2]-cycloisomerizations to give pyridines.[7] Nitriles also can serve as a dienophile, either as activated species such as a sulfonylcyanide[8] or in high-temperature hetera-Diels-Alder reactions,[9] as well as with certain more reactive alkenylallenes[10] or alkynylallenes as the 4-atom partner in (4+2) net cycloisomerization reactions. The latter

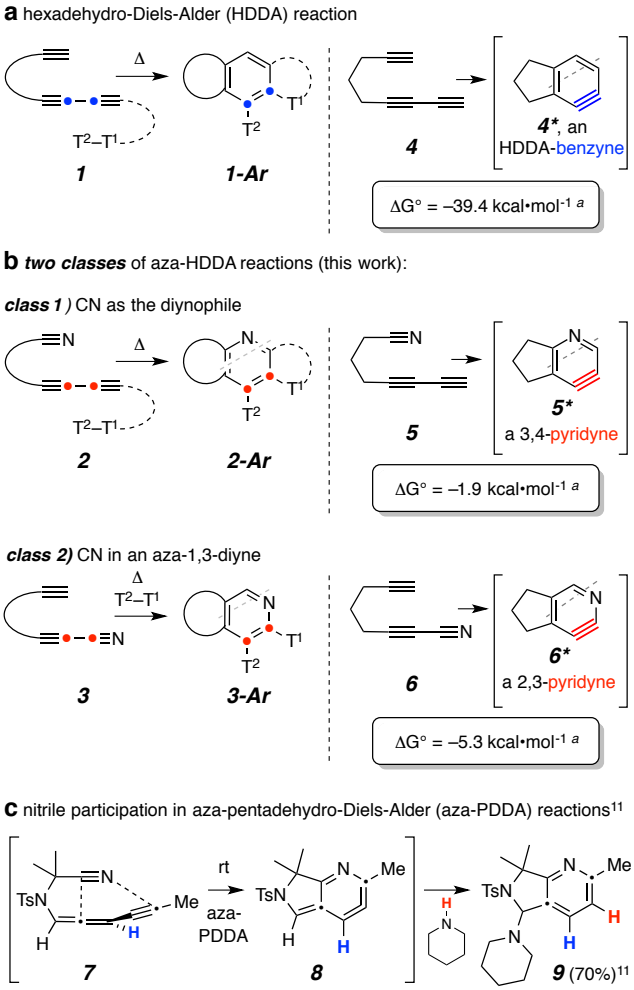

Figure 1. a), **b**) Trimethylene-linked cycloisomerizations to the reactive aryne intermediate for **a**) the all-carbon HDDA reaction and **b**) each of two classes of aza-HDDA reactions with a nitrogen atom at either terminus of the 1,3,8-nonatriyne substrate. **c**) Engagement of a nitrile with a tethered alkynylallene moiety in an aza-PDDA reaction.[11]

[a]Calculated free energy change for the conversion of a prototypical HDDA substrate to its corresponding benzyne or pyridyne {DFT [M06-2X/6-31+G(d,p) with SMD($CHCl_3$)]}.

of these last two examples constitutes an aza-pentadehydro-Diels-Alder (aza-PDDA) cyclization,[11] an example of which is shown in the cycloaromatization of nitrile **7** to give pyridine **9** via the reactive intermediate **8** (Figure 1c). This previously reported process is mechanistically quite distinct from the aza-HDDA reactions described here.

Some of the energetic challenge posed by a potential aza-HDDA reaction can be discerned from the relative free energy changes computed for the all-carbon HDDA reaction of 1,3,8-nonatriyne (**4** to **4***, Figure 1a) vs. each of the class 1 and class 2 aza-HDDA cyclizations (**5** to **5*** and **6** to **6***, respectively; Figure 1b). The all-carbon HDDA is substantially more exergonic than for either of the aza-HDDA cyclizations, suggestive of higher activation energies for the cyclizations of the aza-substrates.

We first examined the feasibility of an aza-HDDA reaction with the nitrile-diyne **10a** [from a four linear-step sequence; see Supporting Information (SI)]. This substrate contains a pendant TBS-ether, a moiety known to efficiently trap HDDA benzynes.[12] Heating nitrile **10a** at 225 °C [in *o*-dichlorobenzene (DCB)] for 16 hours resulted in its nearly complete consumption. The tricyclic pyridine derivative **11a** was isolated (36%) along with its desilylated analog **11a-H** (10%). Even though modest yielding, this transformation clearly established the viability of an aza-HDDA process, at least for a class 1 variant (nitrile as diynophile).

We then scouted a number of related substrates, **10b-f** (Figure 2), each bearing the tethered OTBS trap but differing in the nature of the nitrile-to-diyne linker. Several of these substrates contain geminal dimethyl substituents, which likely facilitates the cycloaromatization step through the Thorpe–Ingold effect, [13] although this point was not explicitly explored. Several benefit from the restricted rotation imposed by the alkene or arene within the tether, although the successful cyclization of **10a** shows that this constraint is not an absolute requirement. Each of pyridines **11b-f** was the predominant product in each crude product mixture. Based upon evaluation of a combination of the cleanliness of this mixture (^{1}H NMR analysis), the isolated yield of products **11a-f**,[14] the substrate stability (an issue with **10d**), and the reaction rate, we elected to use analogs of **10e** and **10f** to study a variety intermolecular trapping reactions. In particular, for this purpose we synthesized substrates **12** and **13** (Figure 3), each bearing a simple methyl substituent in place of the siloxypropyl group at the diyne terminus.

Nitriles **12** and **13** gave rise to the pyridynes **12*** and **13*** in *o*-DCB at 175 °C. For comparison, the close structural analogs of **12** in which the CN is replaced by an alkyl group (cf. **ia**/**b** to **iia**/**b**[15]) cyclize to their respective benzyne analogs via a HDDA reaction with a half-life of ca. 4 hours at 85 °C. Several different bimolecular trapping reagents were used to capture the aryne **12***, giving rise to products **14a-d** (Figure 3). The electrophilicity of the acyl nitrile in **12** imposed a limitation on the types of nucleophilic traps that could be used as trapping agents; the substrate needs, of course, to be compatible with the trapping agents under the thermal conditions required to promote the aza-HDDA cycloisomerization event. Furan and cyclooctane, a 4π-diene and a dihydrogen donor molecule,[16] respectively, meet that requirement and gave rise to products **14a** and **14b**, respectively. Acetic acid was also a viable trapping agent, leading to adduct **14c**. Now, and in contrast to furan and cyclooctane, the trapping event can lead to two different isomeric acetate products. The ester **14c** was produced as the major adduct along with a minor amount of the adduct arising from trapping at C4 (not shown[17]). The three-component adduct **14d**[18] was produced when tetrahydrothiophene (THT) and acetic acid were both present during pyridyne generation. This demonstrates the greater proclivity of a softer, more polarizable nucleophile to engage the electrophilic pyridyne, as has been observed[19] for other three-component reactions involving benzynes.

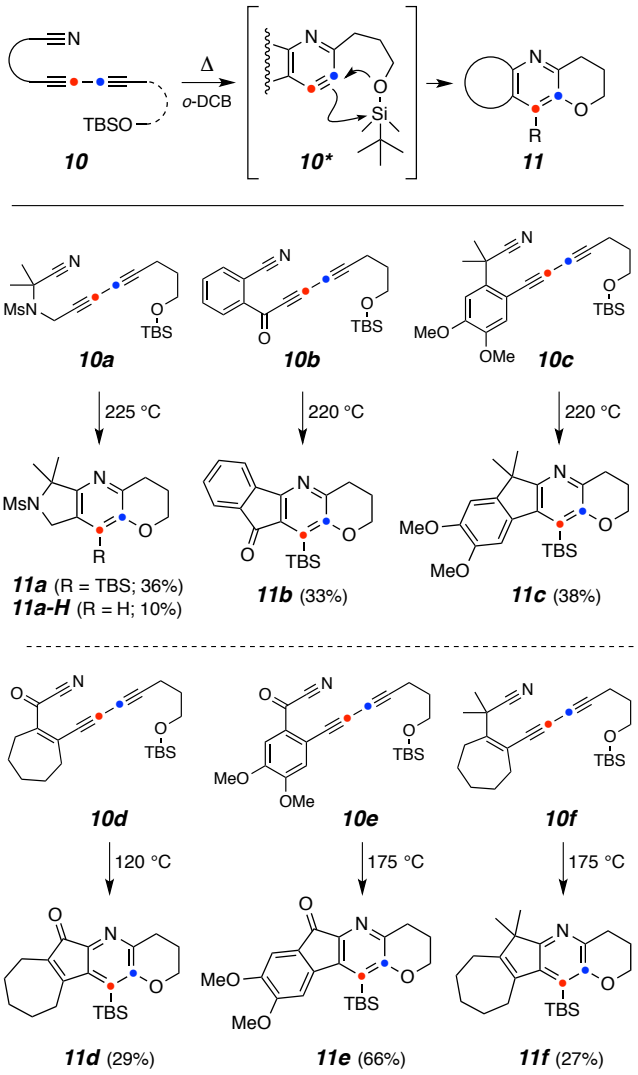

Figure 2. Class 1 aza-HDDA nitrile diyne substrates preliminarily explored. Reaction temperatures reflect the relative reactivities.

Under identical reaction conditions, the analogous pyridine products **15a-15d** were formed from substrate **13** using the same pyridyne-trapping reagents as for **12**. Additional traps yielded the pyridine products **15e-15i**: The reaction of pyridine **13*** with tetraphenylcyclopentadienone (TPCPD) in a [4+2] addition, followed by the thermal cheletropic extrusion of carbon monoxide, yielded the isoquinoline **15e**. The absence of a highly electrophilic acyl nitrile moiety in substrate **13** further allowed for the use of nucleophilic pyridyne traps such as *n*-butylamine and 2,4,6-trimethylphenol to give **15f** and **15g**, respectively. Finally, the pericyclic reactions of **13*** with trimethylsilyl azide (in a 1,3-dipolar cycloaddition) and p-xylene (in a [4+2] cycloaddition) gave the respective pyridine products **15h** and **15i**.

The sense of regioselectivity of nucleophilic addition to unsymmetrical arynes often correlates with the extent (and direction) of geometric distortion, as computed for the aryne structure.[4d, 20] In the case of **12*** and **13*** (Figure 3), DFT calculations show only a slight degree of distortion in these 3,4-pyridynes, as indicated by the denoted internal bond angles. Accordingly, mixtures of regioisomers were observed for those trapping reactions capable of leading to constitutionally isomeric

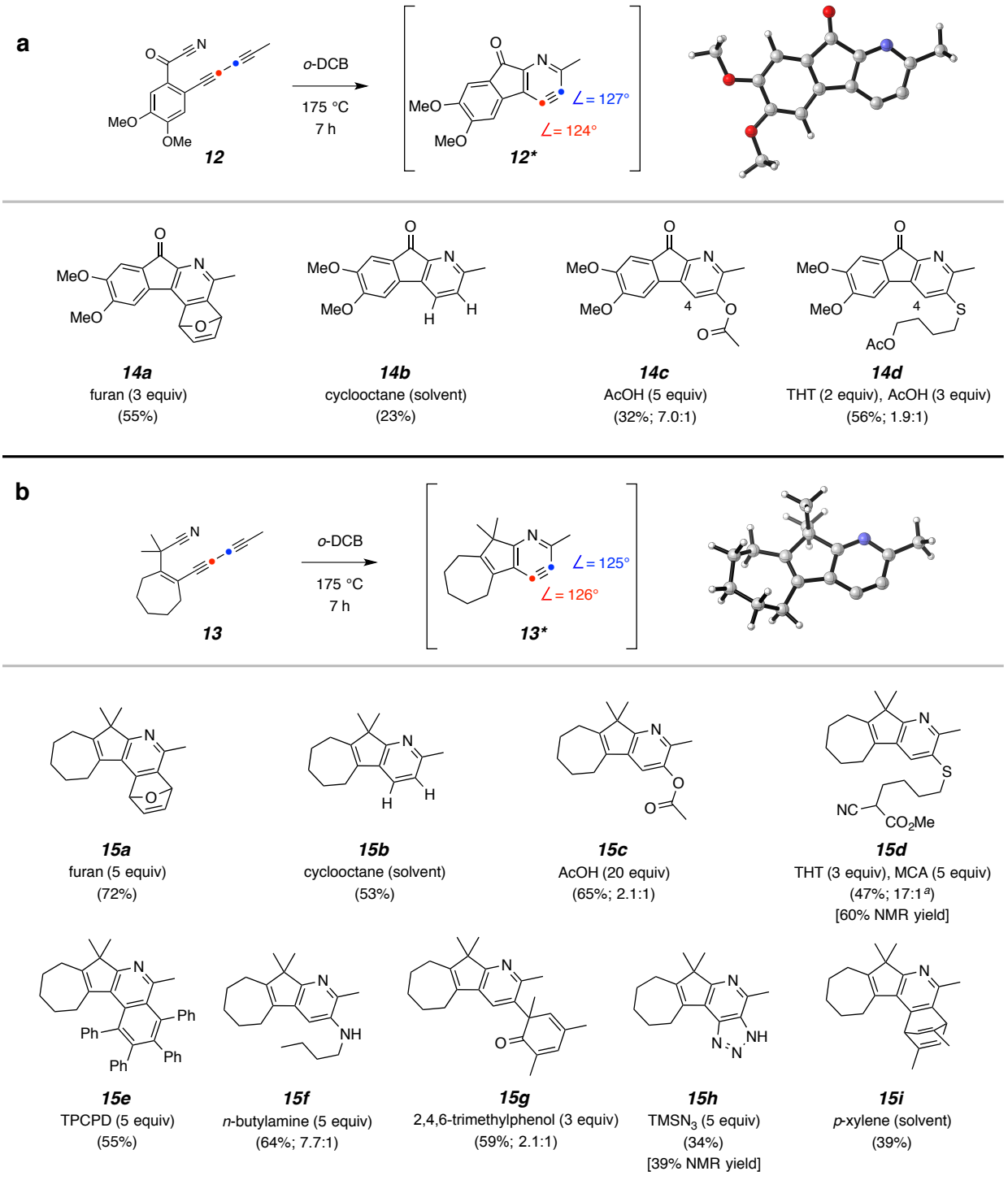

Figure 3. Reactions of the class 1 substrates **12** and **13** (methyl-bearing analogs of **10e** and **10f**, respectively) involving trapping of pyridynes **12*** and **13***to give products **14a-d** and **15a-i**, respectively.

[a]The minor isomer was not isolated; this ratio reflects integration of an HPLC/MS chromatogram that verifies the mass of the minor component.

adducts. However, the product ratios vary considerably, suggesting that steric differences for the approach of the trapping agent also impact the regioselectivities.[21]

In contrast, 2,3-pyridynes are recognized as being much more distorted and, accordingly, more discriminating in their site-selectivity for nucleophilic addition.[4c,e] The computed structures for **16*** and **18*** (Figure 4) are well in line with this expectation. This further incentivized our exploration of class 2 aza-HDDA reactions [conjugated cyanoalkyne as the 4π-component (cf. **3**, Figure 1)]. We first examined substrate **16** (preparation in SI). The lack on an open valency on the nitrogen terminus of the 4π-unit precluded the use of a tethered OTBS trapping group analogous to those used to explore the class 1 substrates (Figure 2).

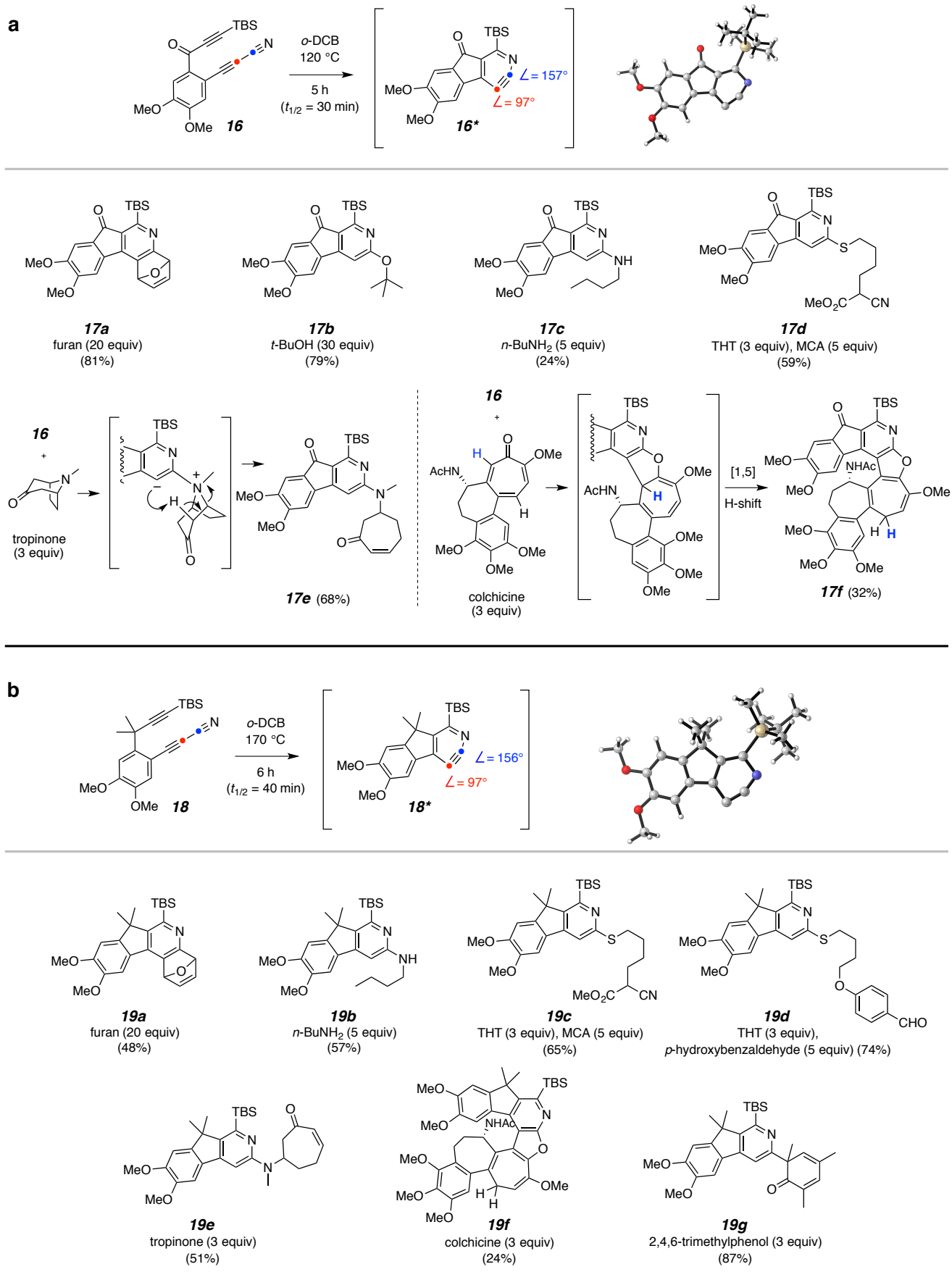

Figure 4. (**a**) Reactions of the class 2 substrate **16** to give products **17a-f.** (**b**) Reactions of the class 2 substrate **18** to give products **19a-g.**

When heated to, now, just 120 °C for five hours in a solution containing furan, the ynone **16** was smoothly transformed into the furan adduct **17a** in excellent yield (81%). The half-life for disappearance of **16** to give the pyridyne **16*** was ca. 25 min.

We proceeded to test a number of other trapping reactions known to be effective for HDDA-benzynes. These gave rise to products **17b-f**. In no instance was a second isomer isolated nor even definitively identified as a minor constituent in the crude product mixture, and in most cases its presence in as little as 1% would have been detectable by HPLC/MS. This high level of selectivity is consistent with the highly distorted nature of the computed structure of the 2,3-pyridyne **16***. The assignment of structure to the products rests, on i) NOE experiments for adducts **17b-f** and ii) NMR chemical shift similarities (both ^{1}H and ^{13}C) throughout the series of six compounds. Capture by protic nucleophiles, exemplified by products **17b** and **17c**, are noteworthy, given the potentially electrophilic ynone and cyanoalkyne moities present in substrate **16**. However, we surmise that the low yield of **17c** is a reflection of competitive consumption of the substrate prior to its cyclization. The three-component adduct[18,19] **17d** arises from trapping of the pyridyne by, first, the sulfur atom in THT followed by the conjugate base of methyl cyanoacetate (MCA). Formation of products **17e** and **17f** demonstrates that pyridyne **16*** is capable of providing complex structures upon engaging natural products.[22] The tropinone and colchicine adducts, respectively, can be viewed as arising via the species indicated in brackets in the second row of Figure 4a.

A complementary set of experiments was performed with the class 2 substrate **18**, in which the carbonyl oxygen in **16** has been replaced by a ***gem***-dimethyl moiety. This compound cyclized considerably more slowly than did the ynone **16** (comparable $t_{1/2}$ values at 170 vs. 120 °C, respectively). We have previously observed this type of rate difference in triyne-to-benzyne transformations,[23] but attribute it not to an electronic effect but, instead, to a difference in the distance between the two closest sp-hybridized carbons attainable in the reactive conformer of the substrate.

Cyclization of **18** in the presence of furan led to **19a** in a more modest yield than for the case of **17a**—a reflection of that fact that at higher reaction temperatures adducts like **19a** undergo further [4+2] cycloaddition with an additional molecule of furan.[24] Products **19b-f** demonstrate reactivity analogous to that giving **17c-f**. Finally, trapping **18*** with 2,4,6-trimethylphenol led to formation of **19g** in high yield, a process we have described as a phenolic ene reaction.[25]

In conclusion, we have demonstrated that two different types of nitrile analogs of HDDA triyne substrates can be thermally cyclized to produce either 3,4- or 2,3-pyridynes. These reactive intermediates are captured in situ by a variety of different trapping reagents. The 3,4-pyridynes (from what we call class 1 aza-HDDA reactions) show (by DFT) only a minimal amount of distortion and often give rise to two isomeric products wherein the nucleophilic portion of the trapping agent has competitively attacked the C3- vs. the C4-pyridyne carbons. In contrast, 2,3-pyridynes (from class 2 aza-HDDA reactions) are considerably more distorted and, accordingly, lead to the isolation of only a single regioisomeric product. Reflecting the inherently higher bond enthalpy of a C≡N vs. a C≡C bond, the aza-HDDA reaction proceeds more slowly (i.e., with a higher activation barrier) than HDDA reactions of analogous triyne substrates. Several of the products arise from reactions in which the aryne has been captured by a process that is, to our knowledge, unprecedented for pyridyne; these include reduction by dihydrogen transfer (**14b**/**15b**), carboxylic acid addition (**14c**/**15c**), three-component trapping initiated by sulfide (**14d**/**15d**/**17d**/**19c**/**19d**), phenol ene reaction (**15g**/**19g**/**19h**), and capture by a tertiary amine (**17e**/**19e**). Overall, the aza-HDDA reaction represents a new way to assemble substituted pyridine compounds and do so in a fashion that is complementary to more classical approaches for construction of this long-revered heterocycle.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures for all reactions; spectroscopic characterization data for all new compounds; details of computational methods; copies of ^{1}H and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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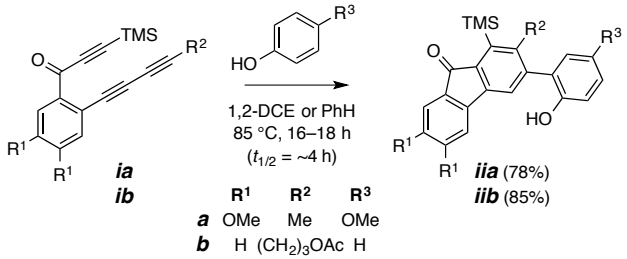
(14) Although the isolated yield of product **11f** was low (27% in *o*-DCB, see SI), when the reaction was performed in the presence of furan (6 equiv), an excellent external trapping agent for arynes, the furan adduct (cf. **15a**) was isolated in 52% along with **11f** (13%) (see SI). The overall yield of pyridyne-derived adducts encouraged us to pursue this type of substrate further.

(15) Rates of HDDA cyclization of, for example, **ia**[24] and **ib**[3] for comparison with that of **12** (Figure 3).



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(17) Throughout the manuscript only the major product is shown along with the ratio of major to minor adducts in instances where constitutional isomers are formed. The characterization data for both are provided in the Supporting Information (SI).The structure assignment was made on the basis of both NOE experiments as well as the significant chemical shift differences between H3 and H4 in the ^{1}H NMR spectrum each of pyridine product.

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