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Mechanistic Duality in Tertiary Amine Additions to Thermally Generated (HDDA) Benzynes

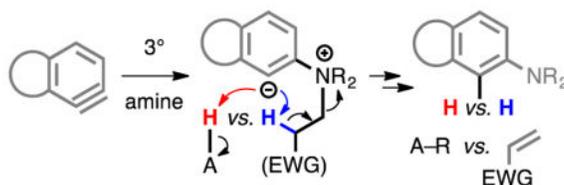
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Abstract

Reported here are studies directed at understanding the mechanism of tertiary amine addition to hexade-hydro-Diels-Alder (HDDA)-generated benzynes. Tertiary amines are presumed to engage benzynes by generation of a zwitterionic intermediate. Simple trialkylamines undergo intermolecular protonation by a protic nucleophile to give an aryl ammonium intermediate that is then dealkylated. Amines containing acidified β -protons undergo an intramolecular elimination to give the aniline and an alkene. Finally, aminoalcohols react at either of their N- or O-atoms, depending upon the extent of internal hydrogen bonding.

Graphical Abstract



Benzynes are versatile reactive intermediates, due in part to the variety of trapping reactions by which they can be captured.¹ Most of the trapping agents are nucleophilic species that are well-suited for engaging the elec-trophilic aryne. Among these are myriad secondary and primary amines (or their conjugate bases²) that readily afford aminoarene products. Fewer examples are known in which tertiary aliphatic amines (R_3N) have trapped benzyne and its derivatives.³ In many cases such a reaction results in loss of one of the alkyl groups from R_3N to produce the same dialkylamino adduct as would arise from using R_2NH (secondary amine) instead.

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Notes

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Supporting Information

Experimental procedures, characterization data, and copies of all 1H - and ^{13}C -NMR spectra for all isolated compounds (single PDF). The Supporting Information is available free of charge on the ACS Publications website.

The earliest example of this type of process comes from a study by Wittig^{3a} in which *N,N*-diethylaniline was produced when *o*-benzyne (**1**) was generated in the presence of Et₃N (Scheme 1a). The mechanistic explanations for this reaction invoked the fragmentation of the 1,3-zwitterion (or betaine) **2** to eject ethylene and release the observed benzyne-derived product.^{3a,b,h,k-o,s} Alternative proposals have been made for similar transformations in light of the fact that amines lacking a β -hydrogen give rise to similar aniline derivatives.^{3c,d,f,h,i,k-n,p,q,r} For example, Biju and coworkers^{3q} have reported that *N*-methyl-*N*-phenylaniline is produced when **1** is generated in the presence of *N,N*-dimethylaniline (Scheme 1b). This is proposed to proceed through the quaternary ammonium triflate **3**, which is then demethylated, presumably *via* nucleophilic displacement. In all of these previous studies, the benzyne has been generated under basic conditions, which could influence the mechanistic path by which the intermediates **2** or **3** proceed to the product.

The thermal cycloisomerization of triynes and tetraynes connected by a three-atom tether produces fused bicyclic benzyne derivatives.⁴ The benzynes generated by this hexadehydro-Diels-Alder (HDDA) reaction⁵ are produced in the absence of the reagents and byproducts that necessarily accompany many of the now-classical methods of aryne generation. This has provided the opportunity to gain new mechanistic understanding of the inherent reaction pathways of certain aryne trapping reactions.⁶ Capitalizing on this feature, we have studied and report here mechanistic details concerning the reactions of tertiary amines with HDDA benzynes. We show that the nature of the amine dictates the fate of the initially formed 1,3-zwitterion.

Tetrayne **4** undergoes a HDDA cycloisomerization to form the electrophilic benzyne **6**, which then engages tertiary amines like Et₃N to produce the aniline derivatives **5-maj** and **5-min** (Scheme 2a).⁷ The initially formed 1,3-zwitterion **7** could give rise to aniline **5-maj** by two distinct pathways, similar to those discussed above for traditionally generated benzynes. Spontaneous ejection of ethylene (path i) would lead directly to **5-maj**, whereas protonation of **7** at carbon by a Brønsted acid present in the reaction mixture (path ii) would give ion pair **8**, which could give **5-maj** by either E2 elimination (to give ethylene) or by substitution (to give the ethylated analogue of A⁻).

When tetrayne **4** and triethylamine were heated in deuteriochloroform, a 1.1:1 ratio of **5-maj-d**:**5-min-d** was observed; each was ca. 98% isotopically labeled (¹H NMR and GC-MS). These presumably arose by deuteration of **7** by solvent followed by deethylation. This implied that path ii (Scheme 2a) was the operative mode. To determine the fate of the alkyl group, trioctylamine and **4** were heated in chloroform (Scheme 2b). This resulted predominantly in the formation of the dioctylaniline derivative **9** and 1-chlorooctane (**10a**) as the only observed product of loss of the octyl moiety. No 1-octene was seen, suggesting that path i is not operative. We have previously observed alkyl chloride formation in a different benzyne trapping reaction in chloroform;⁸ the chloride nucleophile could be generated by loss/delivery of chloride ion from Cl₃C⁻. An attempt to trap Cl₂C: with cyclohexene did not lead to an observable amount of the cyclopropane derivative. α -Elimination of chloride from Cl₃C⁻ is slow in the absence of a metal counterion.⁹ When this reaction was performed in CDCl₃, nearly complete deuteration of the aromatic site in both the major and minor isomers of **9** was seen.

An analogous experiment was performed in ethyl acetate solution to remove the proton donation event that chloroform provided. Adducts **9** were formed, now accompanied by octyl acetate (**10b**, 77% relative to **9**) as the only identifiable octyl related byproduct (Scheme 2c). Assuming that the presence of a small amount of water in the ethyl acetate was responsible for the acetate byproduct, we repeated the experiment in water-saturated EtOAc. If D₂O was used instead, ring deuteration levels were, again, very high, consistent with rapid hydrogen donation by water to the initial 1,3-zwitterion (cf. **7**).

The Et₃N trapping experiment was next repeated in carefully dried benzene (azeotropic predistillation and treatment with activated molecular sieves). This resulted in a very complex product mixture with formation of only a trace amount of products **5**. This argues against the viability of path i. However, when acetic acid (1.5 equiv) was used as a proton source and Et₃N and **4** were heated in benzene-*d*₆, extremely clean formation of **5-maj** and **5-min** was observed. The ¹H NMR spectrum of this reaction mixture (Figure 1a) shows the (i) formation of an equivalent of ethyl acetate, formed almost assuredly by dealkylation of **8** (A = AcO, Scheme 2a) by the acetate counterion and (ii) the overall cleanliness of the reaction. These results suggest the possibility of multicomponent coupling if a cyclic tertiary amine were to be used, a process known for both traditional^{3r,t-w,10 a} as well as HDDA-generated benzyne^{10b}.

We next surmised that use of triflic instead of acetic acid might allow for formation of the stable ion pair **8** (A = TfO). Indeed and as shown by the NMR spectrum in Scheme 3b, very clean formation of the ammonium triflates **8-maj** and **8-min** was observed. Formation of similar ammonium triflate salts has been seen for R₃N trapping of 1,2-dehydrobenzene itself, generated from 2-(trimethylsilyl)phenyltriflate.^{3p,q, 11}

We have also explored a tertiary amine having β-aminoester moieties, which bear more acidic protons beta to the nitrogen atom. Specifically, the β-aminodiester **12** was used to capture the unsymmetrical benzyne **13**, formed upon heating **11** (Scheme 3a). Adduct **14** (now as essentially a single constitution because of the nature of the reactivity of benzyne **13**)¹² and acrylic acid ethyl ester were formed in a nearly 1:1 ratio (in-situ ¹H-NMR). This shows that the presence of an electron-withdrawing group beta to the amine activates an elimination pathway. This could occur either by direct deprotonation of the proton alpha to the ester by the phenyl anion (cf. path i, Scheme 2a) or by sequential protonation and deprotonation by an external acid (e.g., adventitious water). When **11** and **12** were heated in CDCl₃, **14** was formed with no detectable deuterium incorporation, ruling out bimolecular protonation by solvent, an efficient process in the case of formation of deuterated **5** and **9** (Scheme 2).

A series of labeling studies was designed to assess the origin of the aromatic proton in **14**. The deuterated diester **12-d₄** [from **12** and DBU in MeOD; 95%-*d* (GC-MS)] and **11**, when heated, showed partial deuterium incorporation at the C7 position of **14**, presumably via the elimination shown in **16a**. Careful examination indicated that deuterium had also been partially incorporated at the benzylic position in product **14**. This likely occurs through an initial deprotonation of the benzylic proton in conformer **16b** to give the benzylic nitrogen ylide **17**,^{13,14} which then abstracts a deuterium alpha to the ester (Scheme 3b). When the *N*-

n-butyl analog **18** was used (in CHCl₃), adduct **19** (63%) was cleanly formed; when this experiment was repeated in deuteriochloroform, there was no sign of deuterium incorporation. When tetrayne **11** was heated in the presence of the deuterated diester **18-d₄**, deuterium was incorporated at the aryl position to give **19-d₃** (71%). We presume that the less than complete deuteration seen at C7 in the arene is arising from the small levels of water likely present in these NMR experiments. Regardless, these results clearly point to intramolecular protonation of the carbanionic center by the protons alpha to the methyl ester; in other words, path i is viable when the protons have enhanced acidity.

We also explored reactions of amino alcohols in which competitive *O*-^{6b} vs. *N*-addition modes of reaction could occur. In-deed, the reaction of **11** with 2-(*N,N*-dimethylamino)ethanol gave both the 2-(dimethylamino)ethyl aryl ether **20** and tertiary anilines **21** and **22** (Scheme 4a). The latter pair presumably arise from competitive demethylation vs. de-hydroxyethylation (oxirane formation?). In contrast, the homolog 3-(*N,N*-dimethylamino)-1-propanol gave, at most, only a trace of the ether analog **23**; the amines **24** and **22** were the predominate products. Now a greater amount of the latter was formed, perhaps reflecting a slower loss of oxetane vs. oxirane. An explanation for preferential formation of ether **20** is offered in Scheme 4b. The intramolecularly hydrogen bonded aminoethanol¹⁵ **25** adds to the benzyne to produce the 1,6-zwitterion **26** directly. This would require only slight reorganization of the O–H and N–H bond lengths along the reaction coordinate.

Finally, when the tropane alkaloid^{10b} scopoline (**27**), the *N*-(β-hydroxyalkyl)amine of which exists nearly exclusively in a hydrogen bonded array,¹⁶ was used (10 equiv), the 1:1 ether adduct **28** was cleanly formed. The use of only 1.5 equivalents of this more exotic aminoalcohol produced not only **28** but the 2:1 adduct **29** in a similarly clean overall reaction. The no-longer hydrogen bonded amine in primary product **28** reacted further with a second copy of the benzyne at a rate competitive with the initial addition by the alcohol in **27**. Consistent with this behavior, when the reaction of **11** was reexamined using reduced amounts of 2-(*N,N*-dimethylamino)ethanol, increasing levels of an analogous 2:1 adduct were observed [see Supporting Information (SI)].

In conclusion, we have shown that the reaction of HDDA-generated benzynes with tertiary amines can follow two distinct mechanistic paths originating from the 1,3-zwitterion (e.g., **7**) depending on the nature of the amine. If the amine contains only unactivated β-protons in its alkyl groups, intermolecular protonation by a protic nucleophile followed by substitution is the predominant event (Scheme 2, path ii; and Figure 1a). If the counterion of the HA proton donor is a weak nucleophile (i.e., HA is a strong acid), quaternary ammonium ions are formed (Figure 1b). If acidified protons are present in the position beta to the amine nitrogen atom, an intramolecular proton transfer and elimination predominates (Scheme 3). *N*-(β- and γ-Hydroxyalkyl)amines can undergo reaction at either the oxygen or nitrogen atom, depending on the presence and strength of intramolecular hydrogen bonding (Scheme 4). Collectively, these results show that tertiary amines can be efficient traps for HDDA-generated benzynes and, when paired with a protic nucleophile, have the potential to be used in multicomponent coupling reactions,¹⁰ a topic that is currently being explored in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

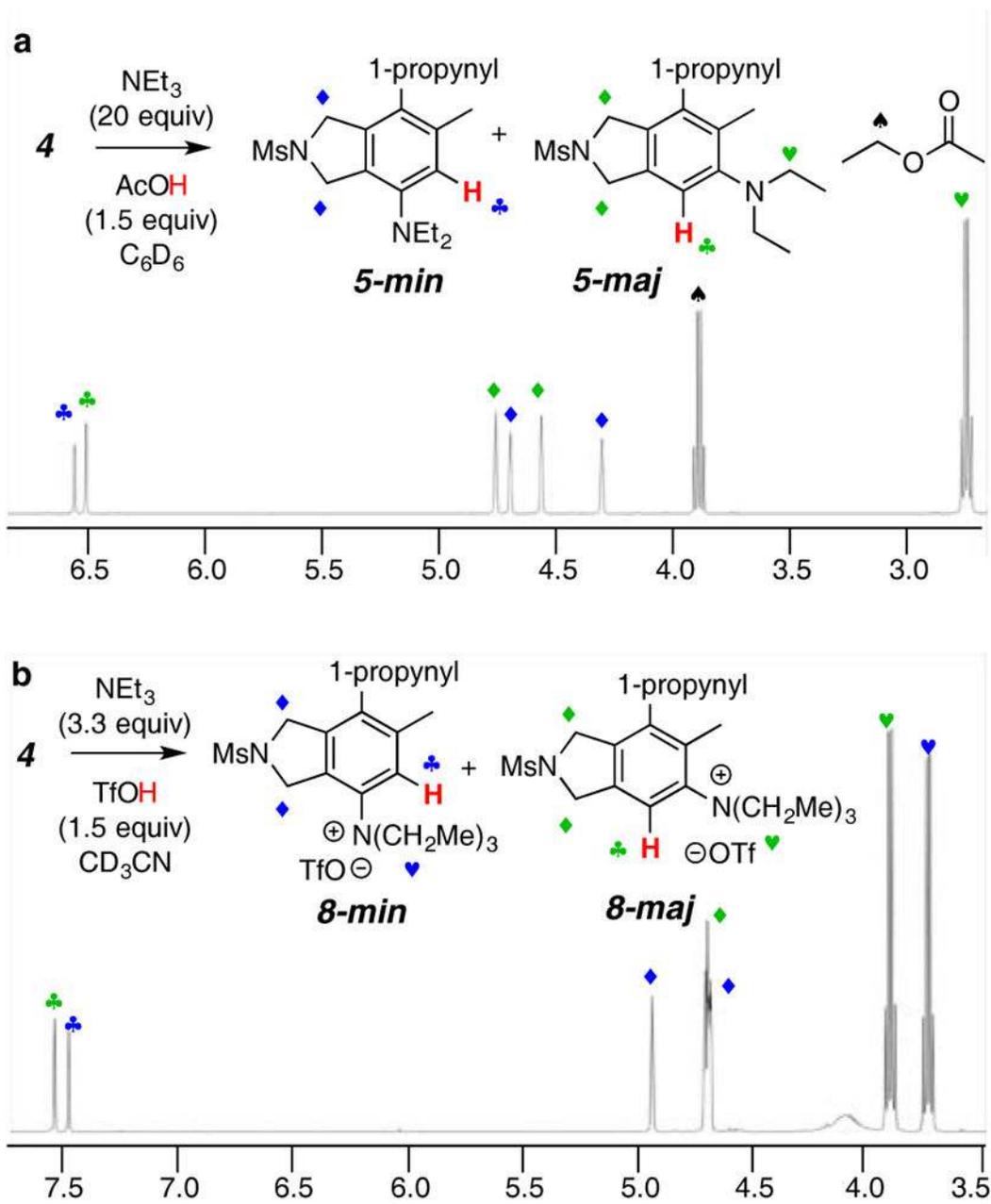
Acknowledgments

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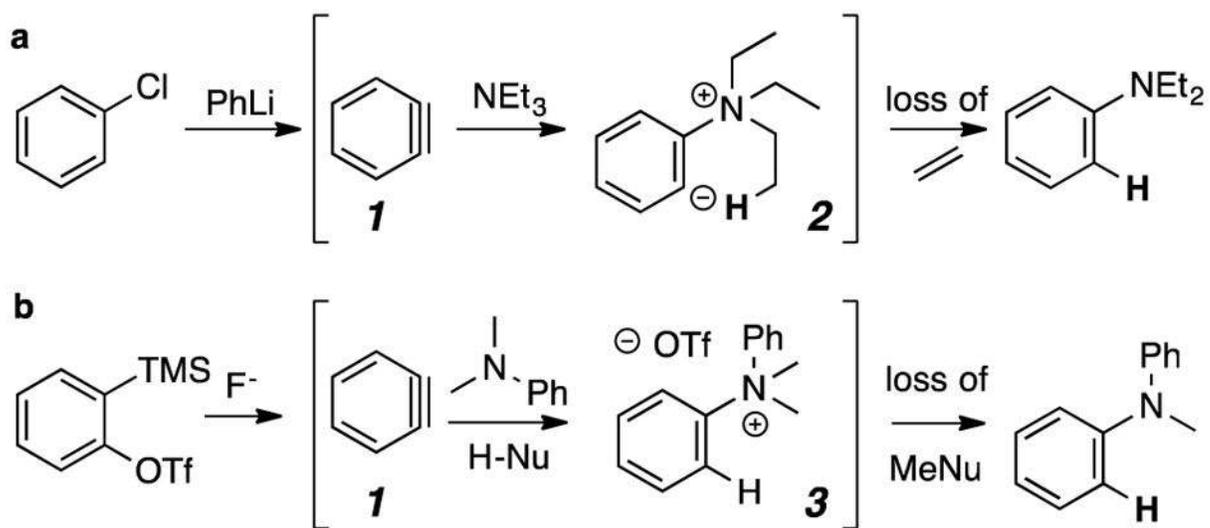
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7. a) Benzyne 6 often gives significant amounts of products arising from competitive attack at both of its sp-carbons^{10b,3s} whereas most other HDDA benzyne (cf. that from 11) undergo nucleophilic attack with much higher selectivities.^{7c-e} b) For the sake of simplicity only the major isomer is shown for all products (other than 5-maj and 5-min) arising from benzyne 6. Yield data and

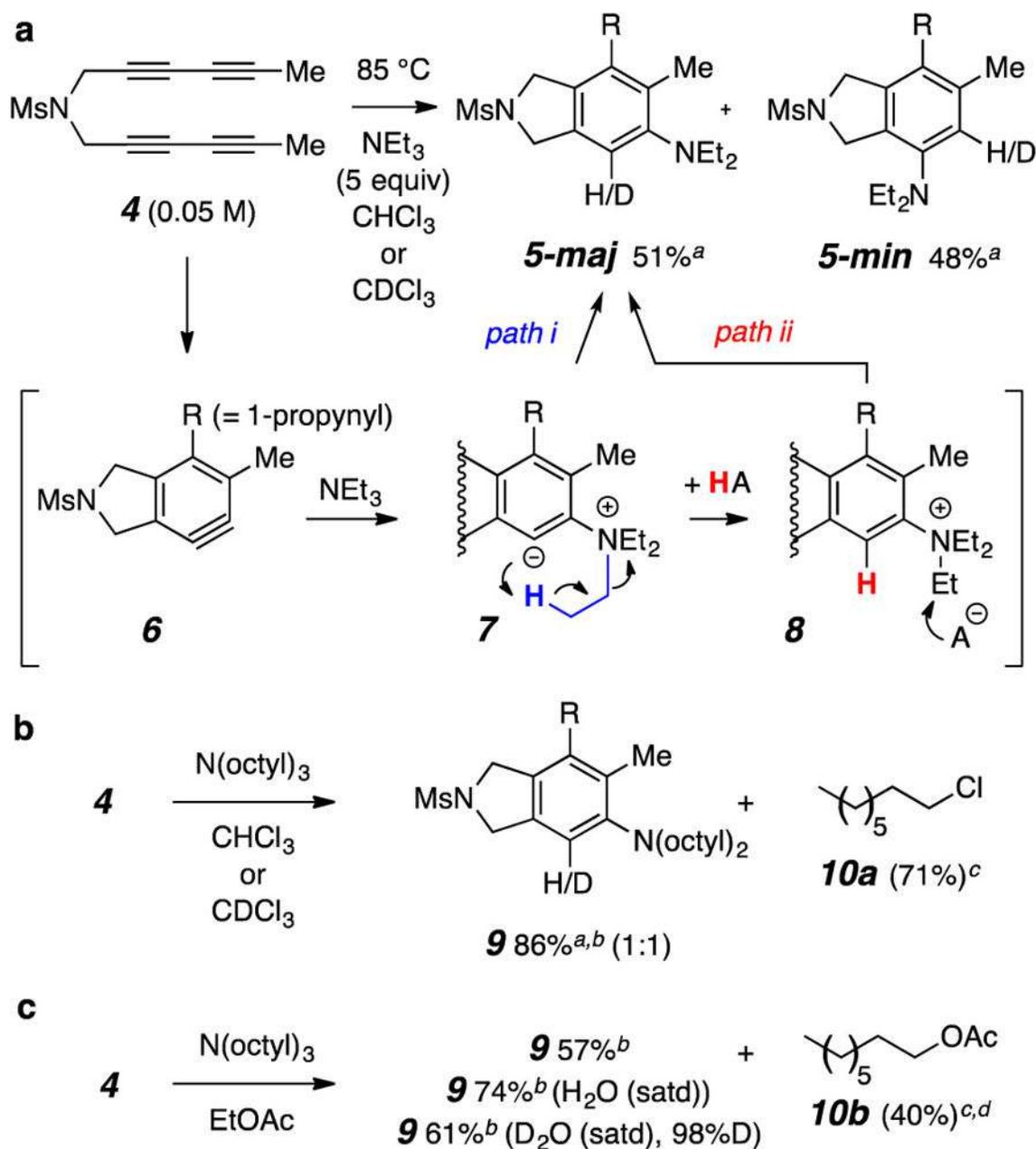
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**Figure 1.**

^1H NMR spectra (downfield portions) of reaction mixtures in which diethylaniline and triethylanilinium derivatives **5** and **8** were formed (85 °C, 14 h).

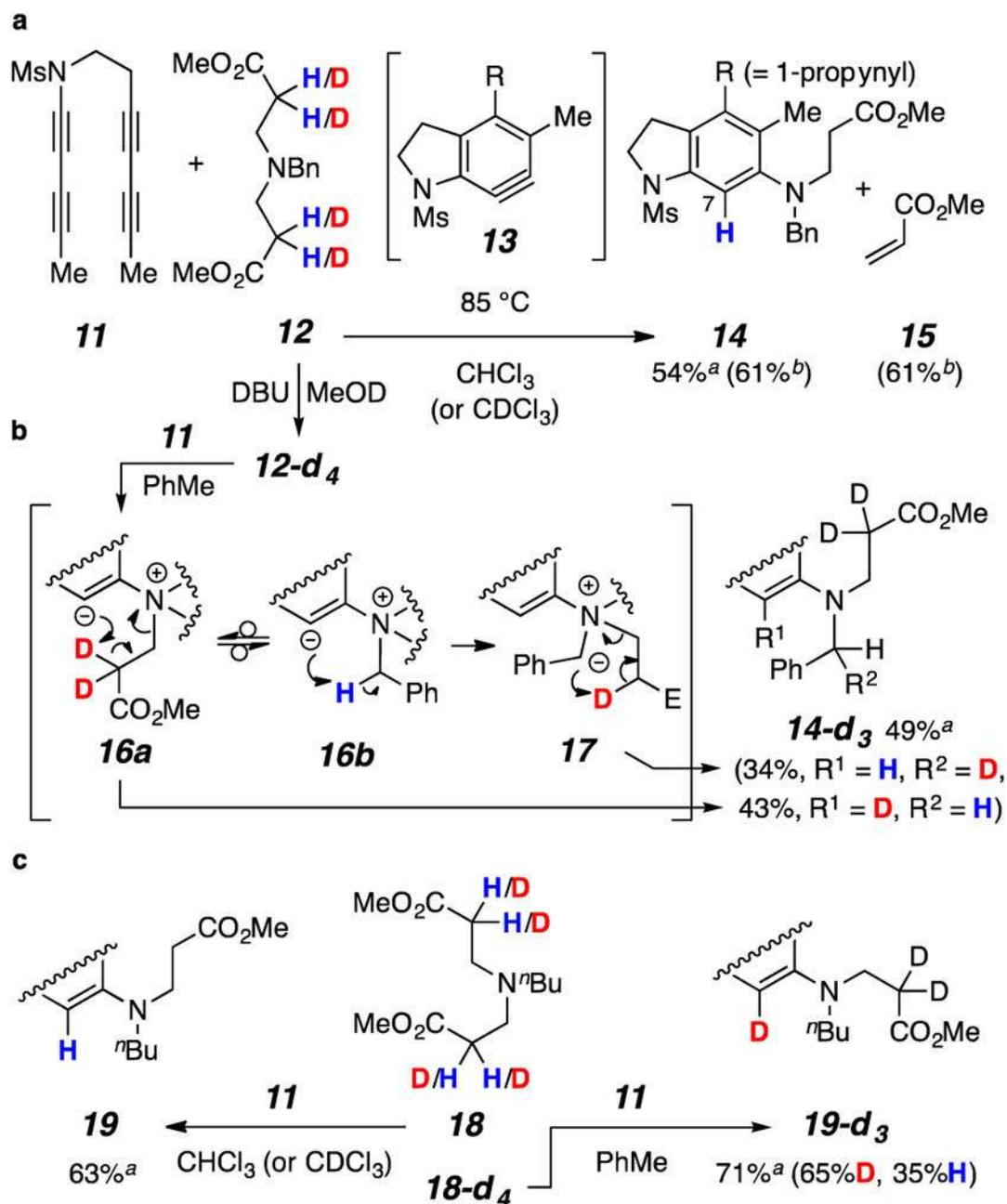
**Scheme 1.**

Mechanistic proposals for the reaction of tertiary amines with benzyne generated using (a) a strong base or (b) fluoride ion



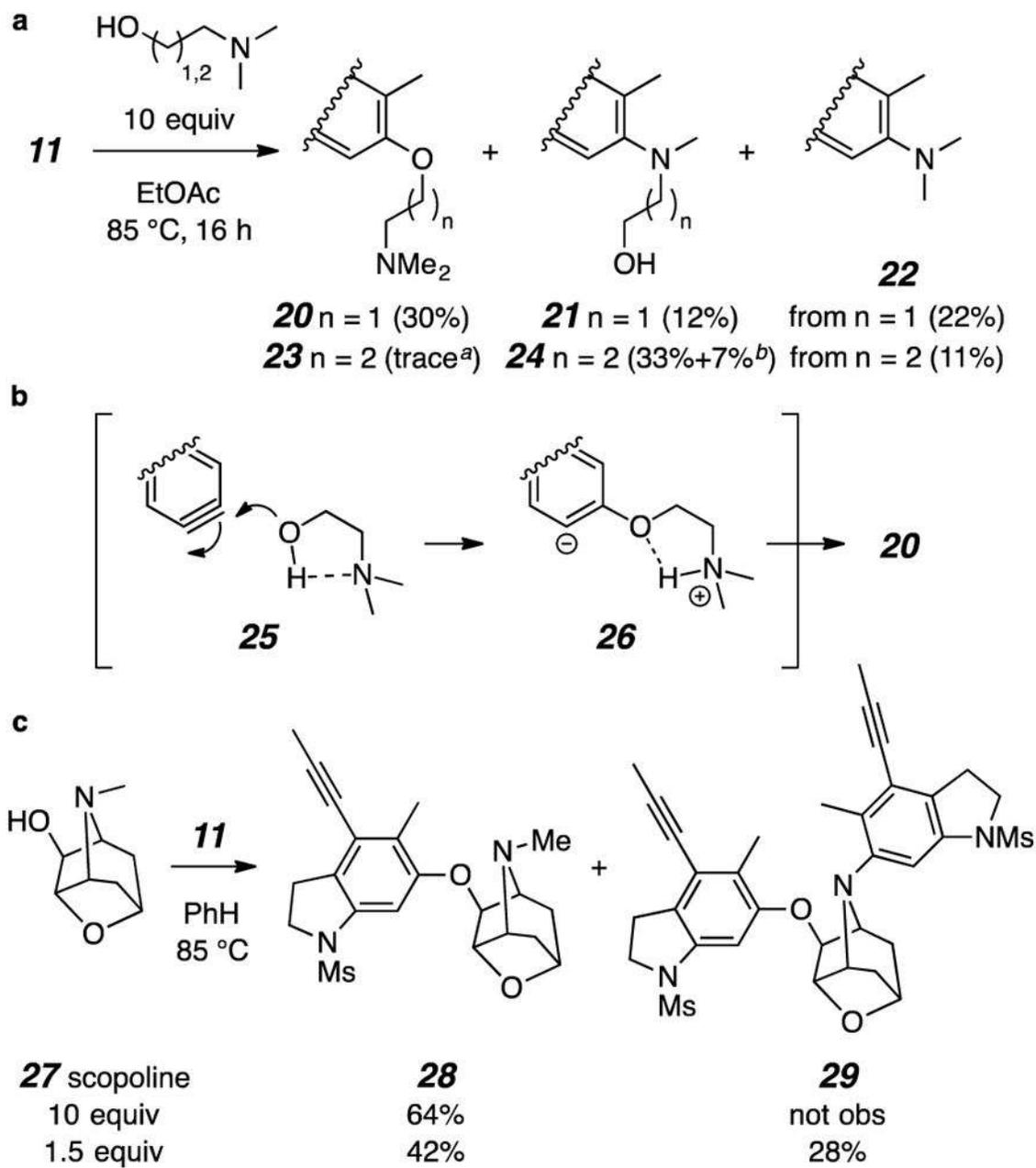
Scheme 2. Source of the proton in the arene product and fate of the alkyl moiety for amine trapping reactions performed in chloroform and ethyl acetate

^aWhen this experiment was performed in $CDCl_3$, each product showed >98% deuterium incorporation. ^bYield (and ratio) of isolated material; for simplicity, only the major constitutional isomer is shown. ^cYield based on NMR integration (vs. added 4-nitrotoluene) of the crude reaction mixture. ^d77% relative to **9**.



Scheme 3. Use of β -aminoesters results in in-tramolecular protonation of the benzyne and elimination of an enoate

^aYield of isolated material (a single constitutional isomer). ^bYield based on NMR integration (vs. added 4-nitrotoluene) of the crude reaction mixture.



Scheme 4. *N*-(β - and γ -Hydroxyalkyl)amines react, competitively, at the *N*- vs. *O*-nucleophilic atom

^aCa. 1% of a species with key chemical shifts analogous to **20** detectable by ¹H-NMR. ^bThe OAc ester derivative was also formed (**24-OAc**, SI).