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Amination of Arenes through Electron-Deficient Reaction Cascades of Aryl Epoxyazides

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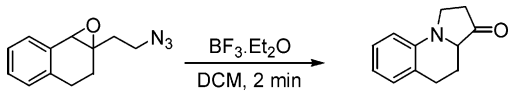
ABSTRACT



94%

Aryl epoxyazides undergo efficient electron-deficient reaction cascades mediated by Lewis acids, leading to regiospecific amination of the aromatic ring.

Sequencing organic reactions in a single-pot process is a powerful way of designing complex molecular architectures from relatively simple starting materials. This is beautifully exemplified in the use of cascade reactions in free radical[1] chemistry and organopalladium chemistry[2] for organic synthesis. Our background in cascade reactions[3] includes the TTF-mediated radical−polar crossover sequence[3b] and nitration sequences that highlight cationic chemistry,[4] and this focused our attention on the fact that reaction cascades involving cations or incipient cations are less well explored. Cascade reactions of cations are well-known in nature in the biogenetic [and biomimetic] synthesis of steroids and terpenes;[5] however, these involve cationic cascades on hydrocarbon skeletons, and heteroatoms are very poorly represented. Recent elegant developments of the Schmidt reaction, particularly by the research groups of Aubé[6] and Pearson,[7] have shown how useful azide groups can be in intercepting cations and incipient cations. Our aim in this program is to bring together Schmidt-type azide interceptions with other types of electron-deficient rearrangement−epoxide-opening, aryl, alkyl, and hydride migrations, as well as fragmentations, to test for compatibility and to come to an understanding of the ground-rules for sequencing the reactions. The first epoxide-based Schmidt reactions were very recently reported by Baskaran and co-workers.[8] The very different types of

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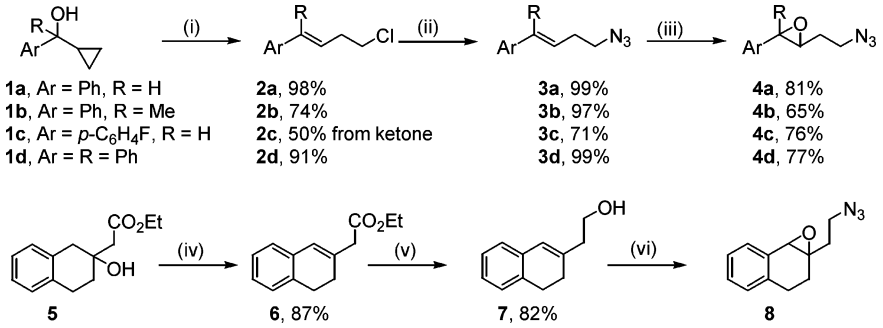
Scheme 1[a]



[a] Reagents and conditions: (i) Hydrochloric acid (concentrated), 5 min, rt. (ii) NaN_3 (5 equiv), DMF, 60 °C, 18 h. (iii) *m*CPBA (2 equiv), DCM, 16h, 0 °C to rt. (iv) *p*-TsOH (1 equiv), toluene, Δ, 64 h. (v) $LiAlH_4$ (1 equiv), THF, 0 °C to rt, 2 h, 82%. (vi) DPPA (1.2 equiv), PPh_3 (1.2 equiv), DIAD (1.2 equiv), THF, 0 °C to rt, 24 h, 78%, then *m*CPBA (2 equiv), DCM 16 h, 0 °C, 4 h, 66%.

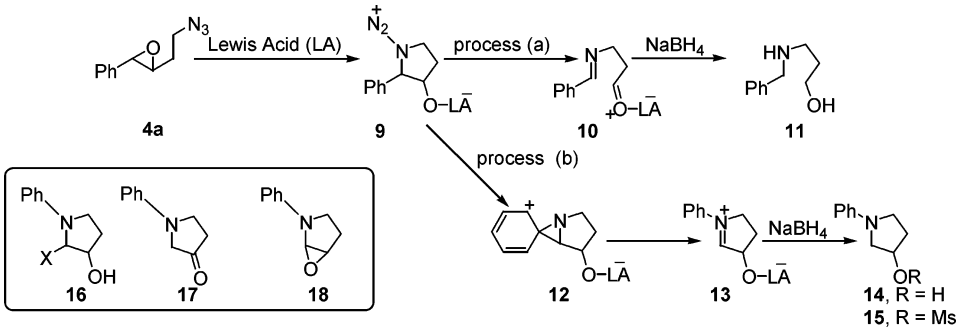
chemistry seen in their paper compared to this one clearly illustrate the extensive scope of this area of chemistry for molecular design.

Our plans bring together, in one molecule, three reactive entities (an arene, an epoxide, and an azide), and so substrates **4a**−**d** and **8** were prepared as shown in Scheme 1. We predicted that opening of these epoxides in the presence of Lewis acids would lead to attack by the azide group at the benzylic position to give a five-membered ring; attack at the alternate epoxide carbon would lead to a strained four-membered ring. Compounds **4a**,**b**,**d** were prepared from the commercially available cyclopropanes **1a**,**b**,**d**, while **4c** was prepared from **1c**; in turn, this was prepared by reduction of the corresponding commercially available ketone. Compounds **5**−**7** were prepared by the route of Ferraz and Silva.[9] Turning to the simplest substrate, **4a**, we gave some thought in advance to the possible outcomes of the experiment before choosing the conditions for the workup of the reaction. Lewis acid-induced opening of the epoxide should lead to attack by the azide at the benzylic position to form **9** (Scheme 2), and then two potentially competing processes come into play: (a) ring-fragmentation driven by the Lewis acid-linked alkoxide **9** or (b) aryl-group migration via aziridine **12**. Looking at process a, the imine **10** would be rather sensitive; therefore, to facilitate isolation, a reduction step was introduced in situ to trap this compound, if it formed, as the corresponding amine **11**. The alternate process b, would result in a rare example of electrophilic amination of the arene.[10,11] This route comprises an electron-deficient cascade featuring epoxide-opening and 1,2-shift of the aryl ring to give **13** followed by reduction to **14**. Either route would afford attractive applications to synthesis, providing that the outcome could be tuned so that only one of the processes predominated and, hence, that complex mixtures were not formed.

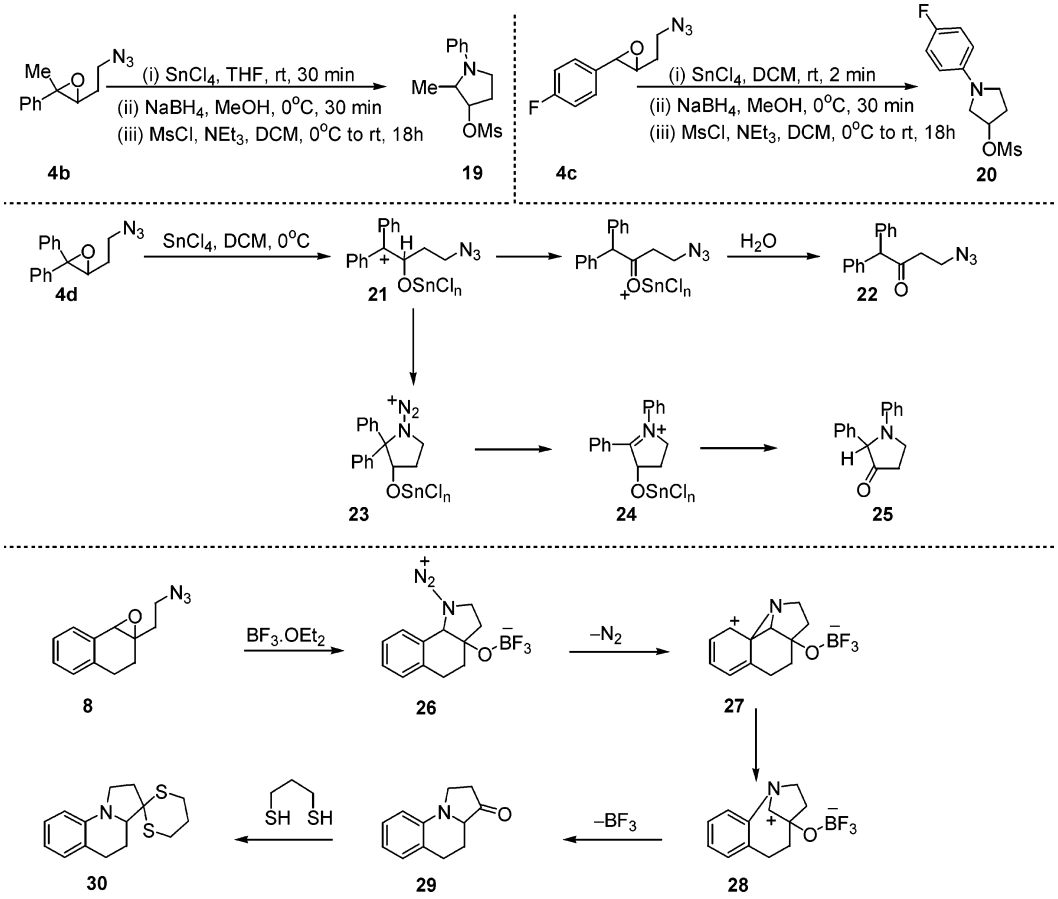
Epoxyazide **4a** was treated with stannic chloride (1.5 equiv) in DCM at 0 °C for 5 min followed by reduction with $NaBH_4$ (3 equiv) in methanol at 0 °C, affording a single product, **14**, cleanly in 88% yield. The ^1H NMR spectrum of the product showed three upfield protons in the aromatic region (2H, δ 6.6, and 1H, δ 6.7), suggesting that they occupied ortho and para positions, respectively, on an aniline ring. Although the compound was crystalline, the structure of this solid compound could not be confirmed by X-ray crystallography due to the poor quality of the crystals. Moreover, the compound appeared to be rather unstable on storage.

However, in efforts to transform alcohol **14** into other compounds, the crystalline and surprisingly stable mesylate **15** was prepared, which on X-ray structure analysis confirmed the structure.

Scheme 2



Scheme 3



A question arises over the origin of alcohol **14**; it could arise from direct reduction of the iminium salt **13** or from reduction of either the adduct **16** (where X^- comes from the Lewis acid) or ketone **17**. We also considered that an epoxide, **18**, might be the intermediate, resulting from ring-closure of **13**, although this compound should be very labile. Detailed information on the nature of the intermediates was obtained by conducting the reaction without the borohydride reduction step. Workup established that the ketone, **17**, was definitely not an intermediate. Rather, the isolated product was a 3:1 mixture of diastereomers of the diol **16** (X = OH) with N−CH−O doublets at δ 4.99 (major, J 5.1 Hz) and 5.32 (minor, J 5.1 Hz) (1H) and a CH_2−C*H*−O multiplet at δ 4.35 (1H).

The related aryl epoxy-azide substrate **4b** was next subjected to the rearrangement in the presence of stannic chloride. This reaction proceeded most efficiently in THF as the solvent. Reduction and mesylation gave a remarkable 94% yield of the pair of diastereomers **19** (51 and 43% yields of the separate isomers) (Scheme 3).

It is clear from the above examples that neighboring-group participation by the aryl group occurs very readily; the extent of participation should depend on the electron-richness of the arene. The *p*-fluoro derivative **4c** was prepared to see if the fluorine substituent would inhibit this reaction. However, the corresponding pyrrolidine mesylate **20** was formed as the exclusive product (64% yield) (see Scheme 3). Hence, this substrate behaved exactly as its analogue, **4a**, and a fluorine atom had no apparent effect in diverting the course of the reaction. Thus, electrophilic amination of the arene results even with an electron-withdrawing group in the para position.

Anomalous results occurred, however, when the epoxide **4d** reacted in DCM; two products were furnished in a 1.6:1 ratio, namely, the acyclic ketoazide **22** and the pyrrolidinone **25**. Compound **22** could arise by 1,2-hydride migration in cation **21** or by proton loss from **21** to give a stannylenolate that breaks down to ketone **22** on workup. Similarly, a ketone **25** was formed from the cyclized intermediate **24**. The appearance of two products **22** and **25** on workup led us to investigate whether changing the solvent might alter the ratio in the rearrangement reaction. Happily, in THF as the solvent, essentially only the 3-ketoypyrrolidone **25** is formed (48%), while in toluene, the acyclic ketone **22** is the dominant

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(11) For other reactions of azides that lead to migration of aryl groups to nitrogen, see ref 6f and: Wrobleski, A.; Aubé, J. *J. Org. Chem.* **2001**, *66*, 886.

product (83%). Although the isolated yield of **25** is not very high, this reflects difficulties in handling the compound; a notable feature of the ketone **25** was its instability in air.[12]

All of the examples so far presented feature epoxides with C−O bonds to a (secondary or tertiary) benzylic carbon and to an aliphatic (secondary) carbon. The attack of azide was seen exclusively at the benzylic site. In substrate **8**, a secondary benzylic carbon competes with a tertiary aliphatic carbon for attack by the azide group. Reaction with $SnCl_4$ led to tricyclic amine **29** in 74% yield, and no other product was isolated, implying that the benzylic carbon is still the site of interception by the azide group. Despite the strain inherent in **27**, neighboring group participation by the aryl ring still occurs. Cleavage of the aziridine gives the bridged intermediate **28**. Unlike in previous examples, hydride shift/deprotonation is not possible here; so instead, a regiospecific ring-contraction occurs with assistance from the oxygen atom to afford ketone **29**. This substrate was then used to analyze the effect of changing the acid used for the reaction.

As seen in Table 1, the reaction works fairly well for all of the Lewis acids except $TiCl_4$, which led to decomposition. Importantly, protic acid also works fairly well, but the best conditions (94% yield) are seen when $BF_3{\cdot}OEt_2$ is used.

The structure of the final product was confirmed by in situ conversion of the product ketone to its dithiane, **30**, which was subjected to crystal structure determination.

In summary, in the presence of acid stimulus, aryl epoxyazides afford high yields of products deriving from cascades of electron-deficient reactions such as epoxide-opening, electrophilic amination of an arene, and hydride or alkyl shifts. The reactions are generally highly efficient and can be tuned by varying the acid used or the reaction solvent. We are currently applying these reactions to the synthesis of more complex natural compounds.

Table 1. Effect of Variation of Acid on Yield of **29**

entry	conditions	yield **29** (%)
1	$SnCl_4$, DCM, 0 °C, 40 s	74
2	$BF_3{\cdot}OEt_2$, DCM, 0 °C, 3 min	92
3	$BF_3{\cdot}OEt_2$, DCM, rt, 2 min	94
4	$TiCl_4$, DCM, 0 °C, 10 s	0
5	TfOH, DCM, 0 °C, 5 s	53

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Supporting Information Available: X-ray crystal structures for **15** and **30**, as well as spectroscopic data for compounds **2**-**8**, **14**, **15**, **19**, **20**, **22**, **25**, **29**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035319D

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