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Reactions of Cyclopropanone Acetals with Alkyl Azides: Carbonyl Addition versus Ring-Opening Pathways

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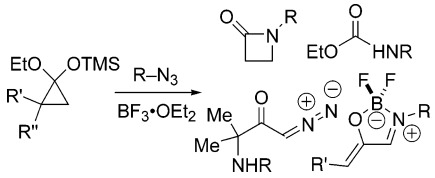
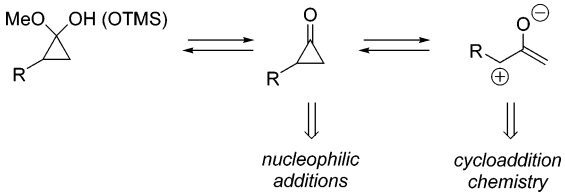


The Lewis acid-mediated reactions of substituted cyclopropanone acetals with alkyl azides were found to strongly depend on the structure of the ketone component. When cyclopropanone acetal was treated with alkyl azides, *N*-substituted 2-azetidinones and ethyl carbamate products were obtained, arising from azide addition to the carbonyl, followed by ring expansion or rearrangement, respectively. When 2,2-dimethylcyclopropanone acetals were reacted with azides in the presence of $BF_3{\cdot}OEt_2$, the products obtained were α-amino-α′-diazomethyl ketones, which arose from C2−C3 bond cleavage of the corresponding cyclopropanone, giving oxyallyl cations that were captured by azides. Aryl-substituted cyclopropanone acetals, when subjected to these conditions, afforded [1,2,3]oxaborazoles exclusively, which were also the result of C2−C3 bond rupture, azide capture, and then loss of nitrogen. In the reactions of *n*-hexyl-substituted cyclopropanone acetals with alkyl azides, a mixture of 2-azetidinones and regioisomeric [1,2,3]-oxaborazoles was obtained. The reasons for the different behavior of the various systems are discussed.

Cyclopropanones display unusual properties arising from the incorporation of the carbonyl group into a strained three-membered ring.[1] Initially, cyclopropanones attracted interest due to their role as intermediates in Favorskii rearrangements.[2] Since then, there have been numerous experimental and theoretical studies aimed at understanding the nature of cyclopropanone reactivity.[3] Inherently reactive, cyclopropanones are usually generated in situ from the corresponding hemiketals (or their derivatives), which are readily synthesized and easily handled (Scheme 1).[4] In general, the chemistry of cyclopropanones is dominated by ketone addition or ring-opening to form oxyallyl cations.[5] The latter species can be trapped with a nucleophile[6] or cyclized with a dipolarophile to give bicyclic ketones.[7]

SCHEME 1



In the 1970s, Wasserman et al. showed that cyclopropanones react with sodium azide to afford *β*-lactams (Scheme 2).[8] This reaction presumably proceeds due to the release of strain upon ring expansion coupled with the generation of nitrogen as the byproduct. Our group has previously studied the intermolecular

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(1) (a) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25−23. (b) Turro, N. J.; Gagosian, R. B.; Edelson, S. E.; Darling, T. R.; Williams, J. R.; Hammond, W. B. T. *Ann. N. Y. Acad. Sci.* **1971**, *33*, 396−404. (c) Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Top. Curr. Chem.* **1974**, *47*, 73−156. (d) Salaun, J. *Chem. Rev.* **1983**, *83*, 619−632.

(2) (a) Baretta, A.; Waegell, B. In *Reactive Intermediates*; Abromovich, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, pp. 527−585. (b) Moulay, S. *Chem. Educ.*: *Res. Pract. Eur.* **2002**, *3*, 33−64.

(3) (a) Turro, N. J.; Edelson, S. S.; Williams, J. R.; Darling, T. R.; Hammond, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 2283−2292. (b) Liberles, A.; Greenberg, A.; Lesk, A. *J. Am. Chem. Soc.* **1972**, *94*, 8685−8688. (c) Zandler, M. E.; Choc, C. E.; Johnson, C. K. *J. Am. Chem. Soc.* **1974**, *96*, 3317−3319. (d) Turecek, F.; Drinkwater, D. E.; McLafferty, F. W. *J. Am. Chem. Soc.* **1991**, *113*, 5950−5958. (e) Hess, B. A., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310−12315. (f) Hess, B. A., Jr.; Smentek, L. *Eur. J. Org. Chem.* **1999**, 3363−3367. (g) Lim, D.; Hrovat, D. A.; Borden, W. T.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 3494−3499.

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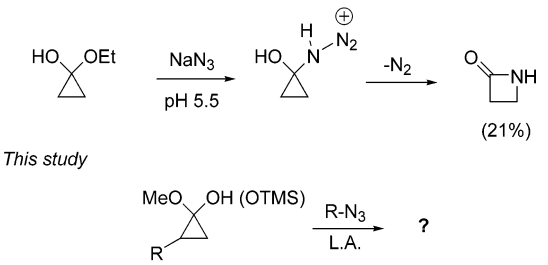
SCHEME 2



reaction of alkyl azides with cyclic ketones, which generally leads to ring-expanded lactams in a process reminiscent of the Schmidt reaction.[9] Following Wasserman, we were initially interested in reacting cyclopropanones with alkyl azides under Lewis acidic conditions as a means of synthesizing *N*-substituted β-lactams. In the course of this study, we discovered that the Lewis acid promoted reactions of azides and cyclopropanones provide a rich array of products that depend on the nature of the cyclopropanone substitution. Previously, we disclosed that the reactions of 2,2-dimethylcyclopropanone equivalents with azides provide α-amino-α′-diazomethyl ketones.[10] Herein, we describe the results of a broader investigation on the reactions of substituted cyclopropanones with alkyl azides. In so doing, we describe several previously unknown reaction pathways that result from both C_1/C_2 and C_2/C_3 bond rupture of the cyclopropanone reactant. The mechanisms of the various reactions will also be discussed.

Results

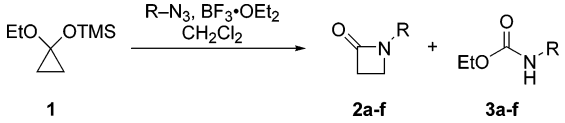
Cyclopropanone Proper. As noted above, the present study began as an attempt to make *N*-substituted β-lactams through azide-mediated ring-expansion processes.[9] To this end, a mixture of cyclopropanone hemiketal and alkyl azide were allowed to react in the presence of $BF_3{\cdot}OEt_2$. Although the expected ring-expanded β-lactams **2** were consistently formed in 27−58% yield, a significant amount of ethyl carbamate product of type **3** was also observed in every case (Table 1).

In an effort to increase the β-lactam yield, a variety of acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, TfOH, and TFA were surveyed. Only $BF_3{\cdot}OEt_2$ was found to reproducibly provide the desired products, although TFA also gave very low yields of β-lactam and ethyl carbamate. The highest yields were obtained when 2.5 equiv of $BF_3{\cdot}OEt_2$ was used. Although the combined yield of β-lactam and carbamates was good to excellent for the series of alkyl azides examined (51−98% combined), we were unable to obtain β-lactam products to the exclusion of carbamate products, which in several cases were the major products.

In the case of β-lactam formation, typical azido-Schmidt chemistry is at work: the azide attacks the ketone and the ensuing azidohydrin collapses with the loss of nitrogen and concomitant ring expansion to give β-lactams **2** (Scheme 3).[9]

The ethyl carbamates **3** could arise from an azidohydrin intermediate that, instead of bond migration, undergoes ring-opening to give a carbocation. This step is analogous to the well-known cyclopropylcarbinyl cation homoallylic rearrangement.[11] Pirrung's work in the study of ethylene biosynthesis invokes a similar carbocation intermediate derived from 1-aminocyclopropanecarboxylic acid, which fragments to produce ethylene.[12] Loss of ethylene provides an isocyanate that reacts

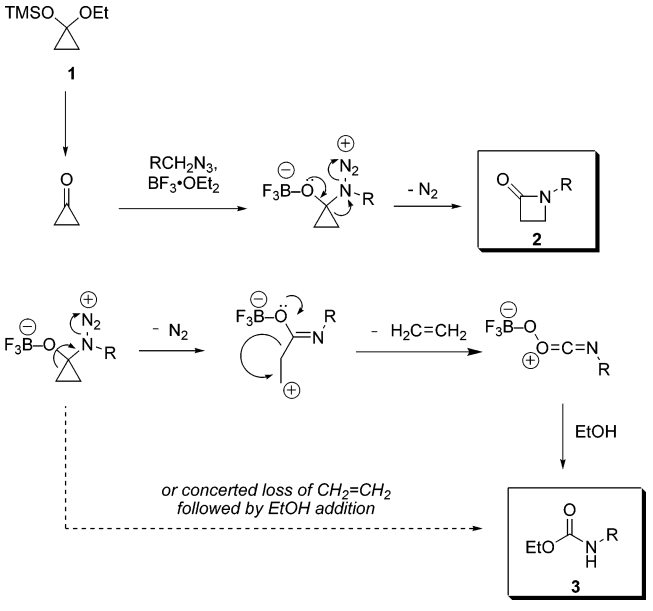
TABLE 1. Reactions of Cyclopropanone Acetal 1 with Azides



1 **2a-f** **3a-f**

entry	R	product (yield, %)	
a	$C_6H_5CH_2$	**2a** (45)	**3a** (13)
b	*n*-C_6H_{14}	**2b** (58)	**3b** (40)
c	3-MeO(C_6H_4)CH_2	**2c** (36)	**3c** (60)
d	4-MeO(C_6H_4)CH_2	**2d** (27)	**3d** (35)
e	4-MeO_2C(C_6H_4)CH_2	**2e** (38)	**3e** (43)
f	4-Br(C_6H_4)CH_2	**2f** (45)	**3f** (34)

SCHEME 3



(4) (a) McElvain, S. M.; Weyna, P. L. *J. Am. Chem. Soc.* **1959**, *81*, 2579−2588. Dull, M. F.; Abend, P. G. *J. Am. Chem. Soc.* **1959**, *81*, 2588−2591. (b) Giusti, G.; Morales, C. *Bull. Soc. Chim. Fr.* **1973**, 382−387. (c) Rousseau, G.; Slougui, N. *Tetrahedron Lett.* **1983**, *24*, 1251−1254. (d) Salaun, J.; Marguerite, J. *Org. Synth.*; Wiley: New York, 1989; Collect. Vol. VII, pp 131−134.

(5) (a) Wasserman, H. H.; Clagett, D. C. *J. Am. Chem. Soc.* **1966**, *88*, 5368−5369. (b) Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375−2376. (c) Wasserman, H. H.; Baird, M. S. *Tetrahedron Lett.* **1971**, 3721−3724. (d) Van Tilborg, W. J. M.; Steinberg, H.; De Boer, T. J. *Synth. Commun.* **1973**, *3*, 189−196. (e) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505−1506.

(6) Turro, N. J.; Hammond, W. B. *Tetrahedron* **1968**, *24*, 6017−6028.

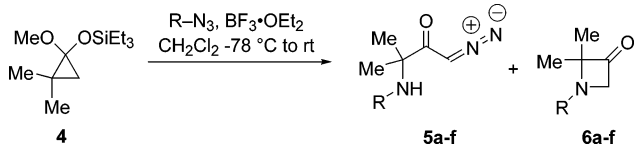
(7) (a) Turro, N. J.; Hammond, W. B. *J. Am. Chem. Soc.* **1967**, *89*, 1028−1029. (b) Hess, B. A., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310−12315. (c) Cho, S. Y.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2891−2893.

(8) (a) Wasserman, H. H.; Adickes, H. W.; Espejo de Ochoa, O. *J. Am. Chem. Soc.* **1971**, *93*, 5586−5587. (b) Wasserman, H. H.; Baird, M. S. *Tetrahedron Lett.* **1971**, 3721−3724. (c) Wasserman, H. H.; Glazer, E. A.; Hearn, M. J. *Tetrahedron Lett.* **1973**, 4855−4858. (d) Wasserman, H. H.; Glazer, E. *J. Org. Chem.* **1975**, *40*, 1505−1506.

(9) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (c) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147. (d) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459. (e) Mossman, C. J.; Aubé, J. *Tetrahedron* **1995**, *52*, 3403−3408. (f) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (g) Forsee, J. E.; Smith, B. T.; Frank, K. E.; Aubé, J. *Synlett* **1998**, 1258−1260. (h) Schildknegt, K.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1998**, *39*, 7687−7690. (i) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232.

(10) Desai, P.; Aubé, J. *Org. Lett.* **2000**, *2*, 1657−1659.

TABLE 2. Reactions of Azides with Cyclopropanone Acetal 4



4 5a-f 6a-f

entry	R	product (yield, %)	
a	$C_6H_5CH_2$	**5a** (47)	**6a** (4)
b	4-Br(C_6H_4)CH_2	**5b** (41)	
c	4-MeO_2C(C_6H_4)CH_2	**5c** (46)	
d	2-naphthyl	**5d** (38)	**6d** (5)
e	9-anthracenyl	**5e** (54)	
f	*n*-C_6H_{14}	**5f** (44)	

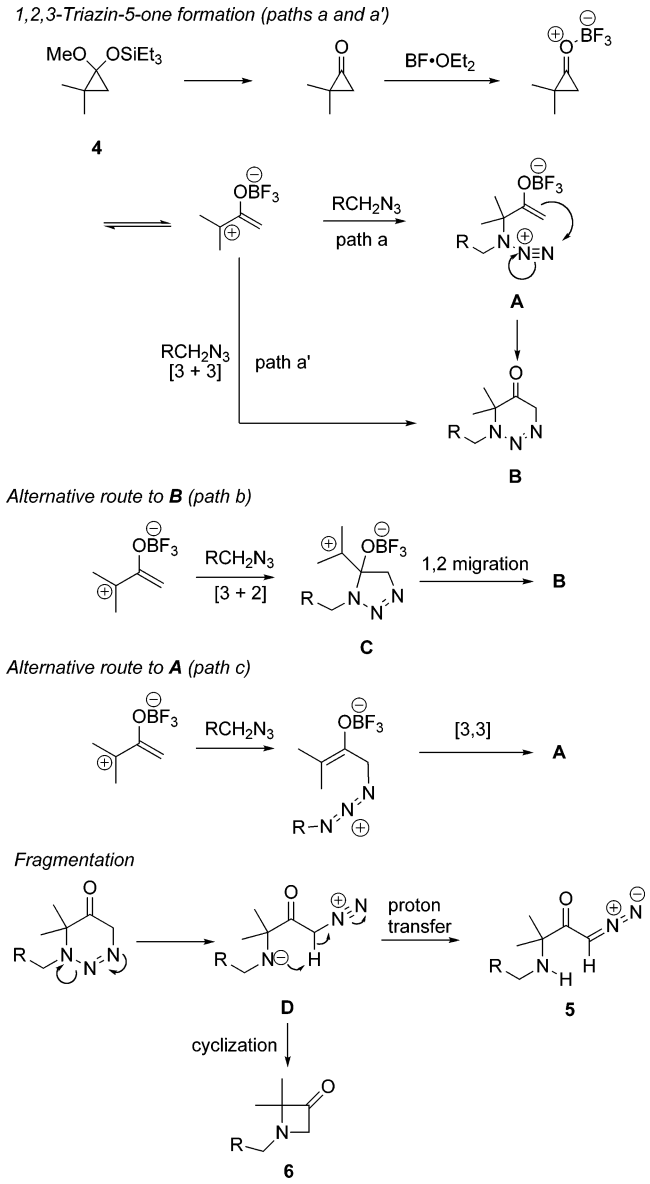
with ethanol to give the product. Other mechanisms that include concerted cheletropic elimination of ethylene could also be envisioned. We did not pursue extensive mechanistic study of this interesting, if not especially useful, process.

2,2-Dimethylcyclopropanone. To extend the above study to encompass differently substituted cyclopropanones, we treated triethyl(1′-methoxy-2′,2′-dimethylcyclopropoxy)silane **4** with 2.0 equiv of benzyl azide and 1.0 equiv of BF_3•OEt_2 in CH_2Cl_2 (−78 °C to rt, 12 h).[10] Workup followed by chromatography provided two products, neither of which was the β-lactam or carbamate anticipated from the previous study. Specifically, the IR spectra lacked the characteristic carbonyl β-lactam stretching frequency at ca. 1740 cm^{-1}, but instead had two strong absorbances at 2099 and 1633 cm^{-1}. In addition, the ^{13}C NMR spectrum contained a ketone signal at 201 ppm and the mass spectrum indicated the retention of all three nitrogen atoms in the major product. Unfortunately, the ^1H NMR spectrum provided almost no connectivity information, consisting mainly of singlets at 1.3, 3.7, and 6.0 ppm. In contrast, the minor product, (in 4% yield) was readily identified as the known *N*-benzyl-2,2-dimethyl-3-azetidinone[13] by NMR and IR spectroscopy. In particular, the IR spectrum contained a prominent absorption at 1840 cm^{-1}, while the ^{13}C NMR spectrum contained a carbonyl resonance at 209.1 ppm. After some experimentation, the identity of the major product was confirmed through X-ray crystallographic analysis of the product isolated from the reaction of cyclopropanone acetal **4** with *p*-carbomethoxybenzyl bromide (**5c**, Table 2).

We surveyed a variety of alkyl azides in this reaction. The α-amino-α′-diazomethyl ketones were obtained in ca. 40−50%, but the 3-azetidinone was formed only occasionally and in low yield (Table 2). After a brief survey of acids and various conditions, we found that our initial conditions gave the highest yields and that BF_3•OEt_2 was the only acid that led to these products, while other conditions resulted only in decomposition of the starting materials.

The retention of all three nitrogen atoms of the alkyl azide in products **5** suggested that this conversion involved the acid-promoted C2−C3 bond cleavage of 2,2-dimethylcyclopropanone

SCHEME 4



to yield the corresponding oxyallyl cation.[7,14] We propose that the cation-stabilizing character of the two methyl groups allowed this pathway to predominate over azide addition to the carbonyl.[15] The oxyallyl cation could then react with the alkyl azide in several ways (Scheme 4). A stepwise pathway involving nucleophilic attack of the azide on the most-substituted carbon of the oxyallyl cation providing **A**, followed by electrophilic capture by the azide of the resulting anion, could give rise to the 1,2,3-triazin-5-one intermediate **B**. In principle, this order of events could also be reversed as azides have both nucleophilic and electrophilic tendencies.[16] Intermediate **B** could also result from a concerted [3 + 3] cycloaddition (path a′) or from a [3 + 2] cycloaddition of azide with the oxyallyl cation, followed

(11) (a) Olah, G. A.; Kelly, D. P.; Jeuell, C. L.; Porter, R. D. *J. Am. Chem. Soc.* **1970**, *92*, 2544−2546. (b) Mayr, H.; Olah, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 510−513. (c) Olah, G. A.; Liang, G.; Ledlie, D. B.; Costopoulos, M. G. *J. Am. Chem. Soc.* **1977**, *99*, 4196−4198. (d) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69−95.

(12) (a) Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207−7209. (b) Pirrung, M. C. *Acc. Chem. Res.* **1999**, *32*, 711−718.

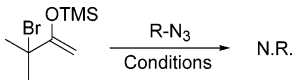
(13) Katritzky, A. R.; Cundy, D. J.; Chen, J. *J. Heterocycl. Chem.* **1994**, *31*, 271−275.

(14) Bakker, B. H.; van Ramesdonk, H. J.; Steinberg, H.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 64−69.

(15) (a) Deno, N. C.; Jaruzelski, J. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044−3051. (b) Arnett, E. M.; Hofelich, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2889−2895.

(16) For an outstanding recent review of alkyl azide chemistry, see: Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

SCHEME 5

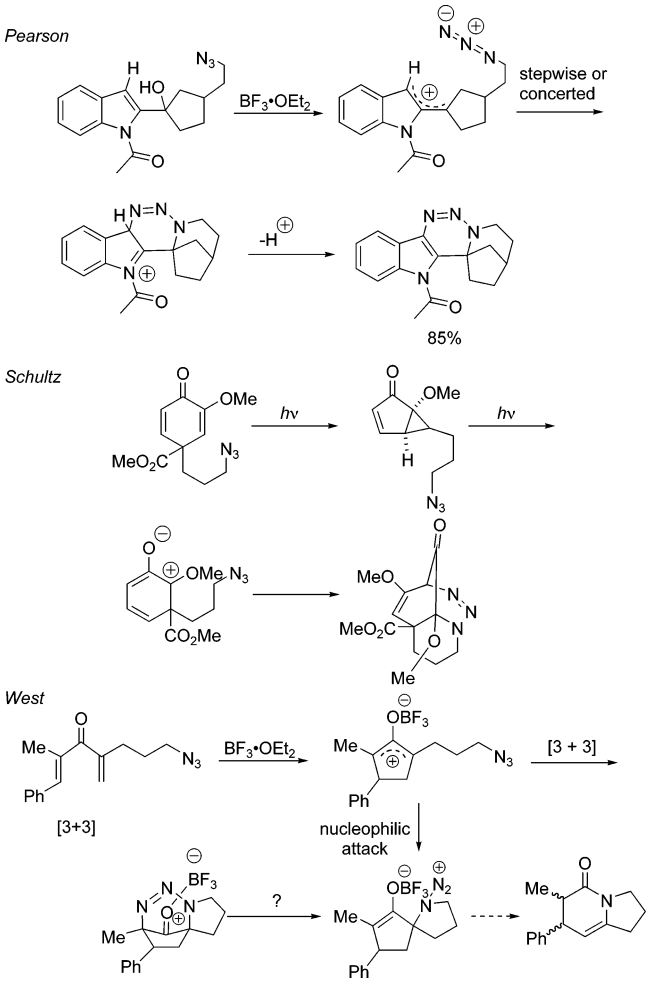


by 1,2-migration of the resulting triazole cation **C** (path b). Another possibility is that azide attacks at the unsubstituted terminus of the oxyallyl cation followed by allylic transposition, giving rise to **A** (path c).[17] We do not currently have strong evidence to rule out any of these possibilities, although we did attempt to react the bromo silyl enol ether shown in Scheme 5 with benzyl azide under a variety of conditions.[18] We were unable to isolate any product from these reactions. Although the intermediacy of **C** cannot be completely ruled out, we favor the stepwise or concerted formation of **B** via paths a/a′ due to the observation of similar intermediates under other conditions (Scheme 6). Thus, in work reported by Pearson, azido-tethered indoles were submitted to acidic conditions to afford triazines incorporated into a complex indole-containing framework.[19a] Schultz et al. also reported tetracyclic triazines arising from a photoinduced cycloaddition of an azido-tethered quinone.[19b,c] Recently, West and co-workers found that Nazarov intermediates derived from dienones could be trapped with pendant azides when treated with BF_3·OEt_2 leading to a variety of products.[19d,e] They propose two possible mechanisms to account for their observations: (1) direct attack of the proximal nitrogen of this azide onto the oxyallyl cation to give a boron enolate/diazo cation species or (2) [3 + 3] cycloaddition of the tethered azide with the oxyallyl cation followed by ring opening of the 1,2,3-triazin-5-one to provide the same enolate cation.

We neither observed nor isolated 1,2,3-triazin-5-ones in any of our experiments. However, their involvement is strongly suggested by the observation of products **5** and **6**. We propose that fragmentation of the 1,2,3-triazin-5-one followed by proton transfer gives products **5** (Scheme 4, above). The difference in reactivity between the triazines formed in the present project and those reported by Schultz and Pearson may be ascribed to stabilization of the latter through electronic means or by virtue of their presence in more complex ring systems. We also note that the Schultz experiment was done under photochemical, not Lewis acid-mediated, conditions.

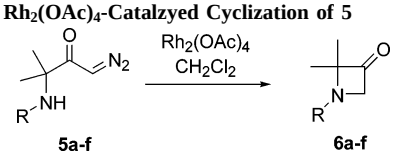
The small amount of 3-azetidinones **6** isolated in two of these reactions could conceivably arise from the direct cyclization reaction of intermediate **D** or from the acid-promoted decomposition of **5** (Scheme 4). We did not observe formation of 3-azetidinone after isolating ketone **5a** and resubmitting it to the acidic reaction conditions for several days, which suggests that **6a** and **6d** arise directly from **D** as shown. α-Amino-α′-diazomethyl ketones are known precursors to 3-azetidinones by metallocarbene-mediated NH insertion reactions.[20] Therefore, we treated α-amino-α′-diazomethyl ketones **5** with $Rh_2(OAc)_4$, which afforded the cyclized products **6** in high yield (Table 3).

SCHEME 6



Aryl-Substituted Cyclopropanones. The observation of ring-opening products from 2,2-dimethyl-substituted cyclopropanone, but not from the parent ring system suggested that the former pathway was favored by the ability of the methyl groups to stabilize the oxyallyl cation intermediate. If so, we reasoned that a phenyl group might be able to play a similar role. Thus, triethyl(1-methoxy-2-phenylcyclopropoxy)silane[21] **7** was treated with 2.0 equiv of benzyl azide and 1.0 equiv of BF_3·OEt_2 in CH_2Cl_2 (−78 °C to rt, 12 h). After $NaHCO_3$ workup and silica

TABLE 3. $Rh_2(OAc)_4$-Catalzyed Cyclization of 5



entry	R	product (yield %)
a	$C_6H_5CH_2$	**6a** (90)
b	4-Br(C_6H_4)CH_2	**6b** (87)
c	4-MeO_2C(C_6H_4)CH_2	**6c** (77)
d	2-naphthyl	**6d** (95)
e	9-anthracenyl	**6e** (100)
f	*n*-C_6H_{14}	**6f** (72)

(17) Attack of nucleophiles at the terminal end of an azide, i.e., as seen in the Staudinger reaction, is known: Nyffeler, P. T.; Liang, C. H.; Koeller, K. M.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778 and references cited therein.

(18) Sakurai, H.; Shirahata, A.; Hosomi, A. *Angew. Chem., Int. Ed.* **1979**, *91*, 178−179.

(19) (a) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684. (b) Schultz, A. G.; Myong, S. O.; Puig, S. *Tetrahedron Lett.* **1984**, *25*, 1011−1014. (c) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391−395. (d) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703−706. (e) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019−12022.

(20) (a) Regitz, M.; Maas, G. *Diazo Compounds*: *Properties and Synthesis*; Academic: Orlando, FL, 1986; p 596. (b) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1035−1041. (c) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238−1246. (d) Axenrod, T.; Watnick, C.; Yazdekhasti, H.; Dave, P. R. *J. Org. Chem.* **1995**, *60*, 1959−1964.

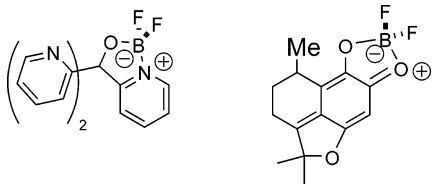


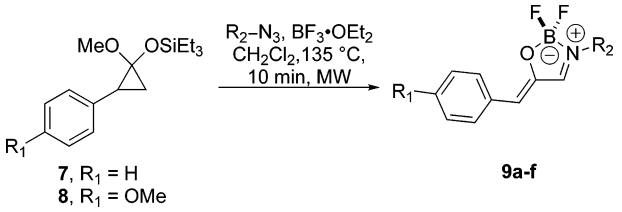
FIGURE 1. Examples of known [1,2,3]oxaborazole analogues.

gel chromatography, a light yellow solid was obtained. In light of the previously described experiments, we had expected to obtain an α-amino-α′-diazomethyl ketone or a 2- or 3-azetidinone from this experiment. However, the spectral data obtained for the reaction product ruled out all of these possibilities. Both IR and ^{13}C NMR spectra indicated the lack of a carbonyl group. Additionally, the absorbance corresponding to the diazoalkane group at ca. 2100 cm^{-1} was lacking. Interestingly, the product from this reaction fluoresced strongly under ultraviolet radiation, giving a bright blue spot when irradiated. As before, only reactions promoted by BF_3•OEt_2 gave the observed products. In particular, other boron-containing Lewis acids including BBr_3 and BCl_3 did not lead to the formation of any tractable products.

An X-ray crystallographic analysis of the product resulting from reaction of cyclopropanone acetal **8** with phenylethyl azide was performed following recrystallization from Et_2O/CH_2Cl_2. The product obtained was a [1,2,3]oxaborazole in which oxygen and boron form a complex and nitrogen and boron share a coordinate covalent bond (Table 4). This unusual heterocycle **9** had incorporated a stoichiometric quantity of BF_2, readily explaining why using more than 1 equiv of BF_3•OEt_2 gave better yields and why only boron-based Lewis acids led to formation of this product. These 1,2,3-oxaborazoles proved remarkably stable, surviving chromatography, extended heating, and strongly basic conditions.[22] Related heterocycles have been used as fluorescent probes and participate in phototriggered [2 + 2] cycloadditions (Figure 1).[23]

A series of these products was generated in yields ranging from 32% to 50% when 1.5 equiv of BF_3•OEt_2 was used. We also noted that both phenyl- and *p*-methoxyphenyl-substituted cyclopropanone acetals gave comparable yields, suggesting that the electronic differences between these two cyclopropanones did not significantly affect reaction outcome (Table 4). These reactions could be conveniently performed in a microwave reactor (135 °C, CH_2Cl_2, 10 min) to give the same products in comparable or slightly higher yield in much less time.[24] Last,

TABLE 4. Reactions of Azides with Cyclopropanone Acetals 7 and 8

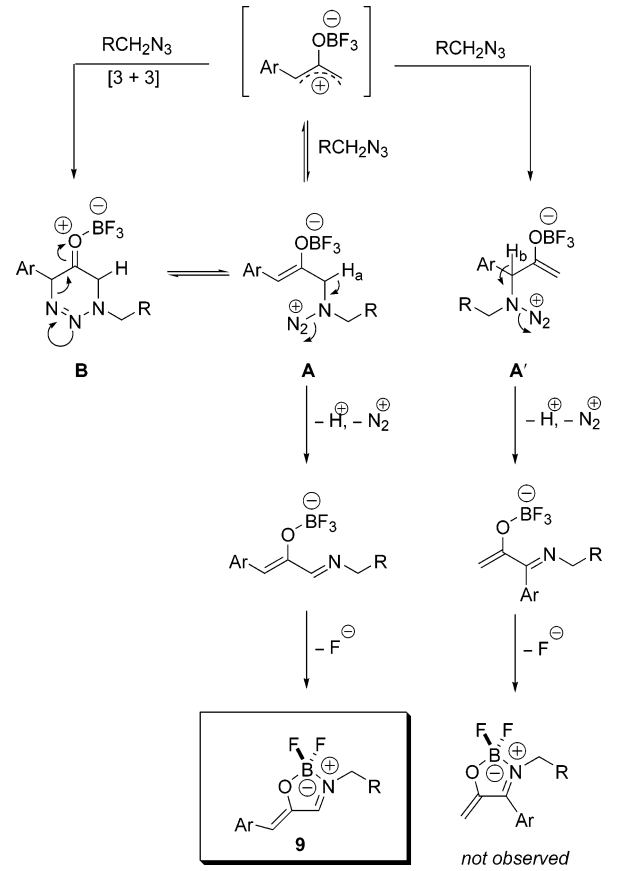


7, R_1 = H
8, R_1 = OMe

9a-f

entry	cyclopropanone	R_2	product (yield %)
a	**7**	$C_6H_5CH_2$	**9a** (50)
b	**7**	4-Br(C_6H_4)CH_2	**9b** (40)
c	**7**	$C_6H_5CH_2CH_2$	**9c** (44)
d	**7**	*n*-C_6H_{14}	**9d** (50)
e	**8**	$C_6H_5CH_2$	**9e** (40)
f	**8**	4-Br(C_6H_4)CH_2	**9f** (32)
g	**8**	$C_6H_5CH_2CH_2$	**9g** (30)

SCHEME 7

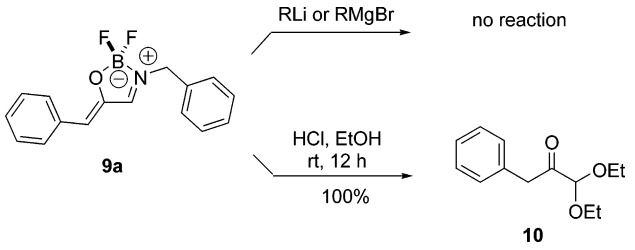


variation of the acetal function did not appreciably affect the reaction. Reactions in which the trimethylsilyl acetal or the hemiketal of **7** were used provided the corresponding 1,2,3-oxaborazoles **9** in yields comparable to those employing triethylsilyl acetals (±5% in each case).

The observation of oxaborazoles is consistent with either a 1,2,3-triazin-5-one intermediate **B** or nucleophilic attack with azide onto the oxyallyl cation, the latter of which directly affords a boron enolate diazonium cation **A** (Scheme 7). The 1,2,3-triazin-5-one, if formed, may then undergo ring opening to form **A** as well. Although azide may add to either terminus of the oxyallyl cation, only oxaborazoles **9** corresponding to azide addition to the unsubstituted terminus were

(21) Rousseau, G.; Slougui, N. *Tetrahedron Lett.* **1983**, *24*, 1251−1254.
(22) (a) White, D. L.; Faller, J. W. *Inorg. Chem.* **1982**, *21*, 3119−3122. (b) Joseph-Nathan, P.; Garibay, M. E.; Santillan, R. L. *J. Org. Chem.* **1987**, *52*, 759−763. (c) Yuan, G.; Jiang, M.; Zhang, G. *Wuji Huaxue Xuebao* **1990**, *6*, 314−318. (d) Joseph-Nathan, P.; Burgueno-Tapia, E.; Santillan, R. L. *J. Nat. Prod.* **1993**, *56*, 1758−1765. (e) Patel, B. P. U.S. Patent 5348948, 1994. (f) Agustin, D.; Rima, G.; Gornitzka, H.; Barrau, J. *Organometallics* **2000**, *19*, 4276−4282. (g) Hopfl, H.; Barba, V.; Vargas, G.; Farfan, N.; Santillan, R.; Castillo, D. *Chemistry of Heterocyclic Compounds*; Wiley: New York, 2000; Vol. 35, pp 912−927. (h) Ramos, J.; Soderquist, J. A. *ARKIVOC* **2001**, 43−58. (i) Tavassoli, A.; Benkovic, S J. WO Patent 2003059916, 2003.
(23) (a) Chow, Y. L.; Cheng, X. *Chem. Commun.* **1990**, 1043−1045. (b) Chow, Y. L.; Cheng, X. *Can. J. Chem.* **1991**, *69*, 1575−1583. (c) Cogne-Laage, E.; Allemand, J.-F.; Ruel, O.; Baudin, J.-B.; Croquette, V.; Blanchard-Desce, M.; Jullien, L. *Chem. Eur. J.* **2004**, *10*, 1445−1455.
(24) (a) Kingston, H. M.; Haswell, S. J., Eds. *Microwave-Enhanced Chemistry*: *Fundamentals, Sample Preparation, and Applications*; American Chemical Society: Washington, DC, 1997. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (c) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

SCHEME 8



observed. It appears that only one mode of addition is favored (kinetically or thermodynamically) or the azide addition step is reversible and elimination of H_a is faster than elimination of H_b. This regiochemistry issue and the comparison of these results with those obtained from 2,2-dimethylcyclopropanone **4** will be discussed below.

The 1,2,3-oxaborazoles are formal equivalents of an activated iminium ion and an enolate coordinated by a Lewis acid. We wondered if these compounds might display reactivity characteristic of either species, or conceivably of an amine-stabilized oxyallyl cation.[25] With approximately a gram of 1,2,3-oxaborazole **9a** at our disposal, a variety of reaction types were surveyed, including reactions with alkyl lithiums, Grignards, carbenes, and dipolarophiles. In only one case was reaction with this heterocycle observed. Thus, subjecting the 1,2,3-oxaborazole **9a** to acidic ethanolic conditions furnished the 1,2 keto acetal **10** in ca. 100% yield (Scheme 8).

Monoalkyl Cyclopropanones. We also examined the analogous reactions of singly substituted cyclopropanone acetals. Thus, we treated trimethyl(1-methoxy-2-heptylcyclopropoxy)-silane[21] **11** with 2.0 equiv of benzyl azide and 1.5 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (−78 °C to rt, 12 h). These conditions did not result in any isolable product or recovery of the starting material. In contrast, heating the components with $BF_3{\cdot}OEt_2$ at 135 °C for 30 min afforded small amounts of β-lactam **12** and 1,2,3-oxaborazole **13**. Extensive optimization attempts did not result in greater than ca. 15% total yields (Scheme 9). The reaction products from phenylethyl azide were constitutionally isomeric adducts of the 1,2,3-oxaborazoles **14a** (ca. 4:1 *Z*:*E*) and **14b**, which were obtained in 6% and 5% yields, respectively. However, no β-lactam was obtained from this particular reaction. Due to the poor yields, we opted not to study this cyclopropanone further.

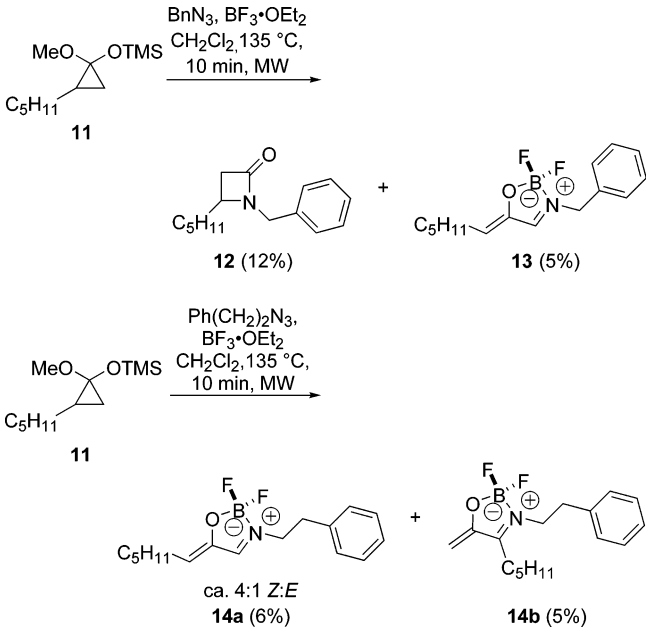
It appears that a bifurcation between two poorly productive mechanistic pathways occurs in these examples (Scheme 10). Thus, Schmidt ring-expansion chemistry leading to β-lactam **12**, as well as ring-opening processes leading to constitutionally isomeric 1,2,3-oxaborazoles **13**, **14a**, and **14b** were noted. The observation of two regioisomeric 1,2,3-oxaborazoles obtained from the reaction of **11** and phenylethyl azide can be ascribed to the nonspecific formation of boron enolate diazo cation intermediates, each having a proton adjacent to the *N*−*N* bond. As before, triazinone involvement is possible here but not necessary (and not depicted in Scheme 10).

Discussion

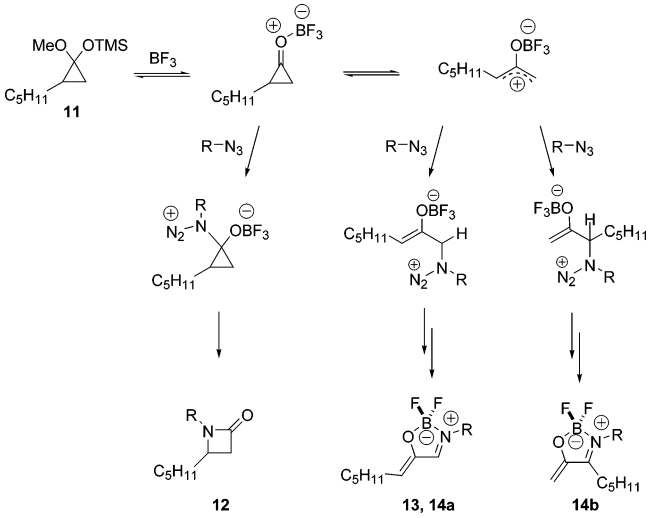
Five chemotypes of products were observed from the Lewis acid-promoted reactions of azides with cyclopropanones (β-lactams, carbamates, α-amino-α′-diazomethyl ketones, 3-azetidinones, and [1,2,3]oxaborazoles). The first two of these were only observed in reasonable yields when cyclopropanone itself was used as the ketone substrate. On the other hand, substituted cyclopropanone acetals underwent ring-opening and provided α-amino-α′-diazomethyl ketones, 3-azetidinones, and [1,2,3]oxaborazoles. In these cases, ring opening to afford an oxyallyl cation is favored by stabilization of the oxyallyl cation by the attachment of alkyl or aryl groups. Additionally, the increased steric bulk provided by the cyclopropaneone substitutents may disfavor the direct nucleophilic addition of azide to the ketone.

Whether the oxyallyl cation affords α-amino-α′-diazomethyl ketones or 1,2,3-oxaborazoles depends on whether there is a proton α to the ketone and upon the regiochemistry of azide addition to the oxyallyl cation. Consider the example of 2,2-dimethylcyclopropanone, which affords α-amino-α′-diazomethyl ketones **5** along with small amounts of 3-azetidinones **6** (Scheme 11). The dimethyl-substituted oxyallyl cation is able to undergo attack by azide to afford two sets of regioisomeric products. One set consists of azide addition product **A** along with the

SCHEME 9

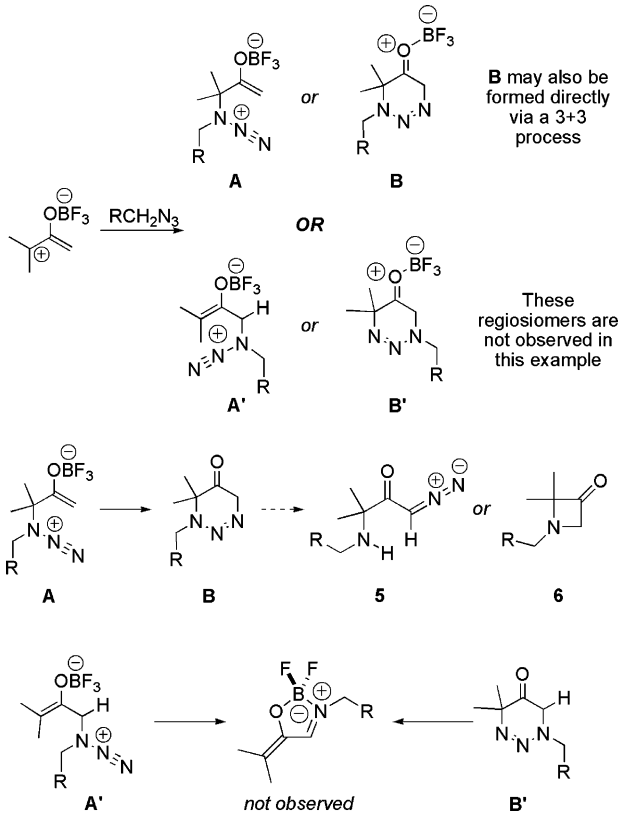


SCHEME 10



(25) (a) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694−12695. (b) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615−618.

SCHEME 11



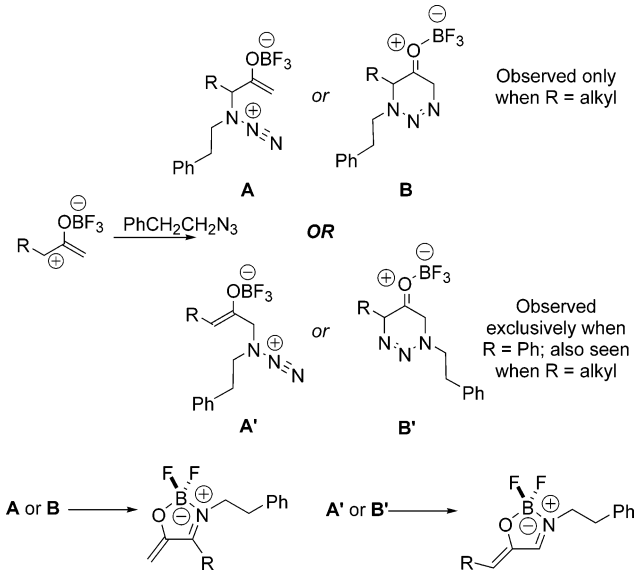
analogous product of concerted [3 + 3] addition **B**; note that exclusive attack of electrophiles on the proximal nitrogen of the azide is well-precedented and also supported by theory (see below). The alternative regioisomeric products **A′** and **B′** are also possible, in principle. In this set of reactions, the formation of the observed products **5** and **6** requires the intermediacy of **B**, which can break down as indicated in Scheme 4. However, note that the alternative regioisomer **B′** cannot afford an isomeric α-amino-α′-diazomethyl ketone because doing so would require the cleavage of a C−Me bond. Furthermore, either **A′** or **B′** could lead to an alternative 1,2,3-oxazaboroline product as shown at the bottom of Scheme 11. Thus, a key factor that determines the product profile in this reaction is the apparently exclusive formation or preferred reaction of regioisomers **A** or **B** in lieu of **A′** or **B′**.

The aryl- or alkyl-monosubstituted examples could in principle lead to any of the observed products because of the presence of at least one proton at either side of the ketone (Scheme 12). However, the lack of any α-amino-α′-diazomethyl ketone products analogous to **5** suggests that this pathway is intrinsically less favorable than the alternative loss of a proton and formation of 1,2,3-oxaborazole. For the observed products **9**, **13**, or **14**, the intermediacy of a 1,2,3-triazin-5-one intermediate (**B** in Scheme 7) is permitted but not required, while the intermediacy of **A** or **A′** is essential.

Taken together, these results suggested that we address the source of the apparent regiochemical differences between cyclopropanones bearing 2,2-dimethyl vs 2-aryl vs 2-alkyl substitution. To this end, we carried out preliminary ab initio calculations to determine whether the regiochemical trends might

(26) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478−1486.

SCHEME 12



be understood on the basis of frontier orbital considerations.[26,27] Thus, B3LYP/6-31+G(d) calculations were performed on the three oxyallyl cations shown in Figure 2 and methyl azide (Figure 3).[28] For oxyallyl cation **a**, the structure shown in Figure 2 was the only conformer that could be located at this level of theory. At the RHF/6-31G(d) level of theory, a second conformer had been located, while no conformers could be found at the MP2/6-31G(d) level of theory. For **b**, only one conformer could be located at all levels of theory. Three conformers were found for oxyallyl cation **c** at all levels of theory. The lowest energy conformer for the phenyl-substituted oxyallyl cation **c** is depicted in Figure 2. This could mean that dimethyl- and phenyl-substituted analogues **a** and **c** are more stable than the methyl oxyallyl cation **b**. All structures were confirmed to be ground state structures via frequency calculations. For a particular molecular orbital, the coefficients for each atom were calculated by summing the squares of the coefficients for each basis set orbital on that atom.

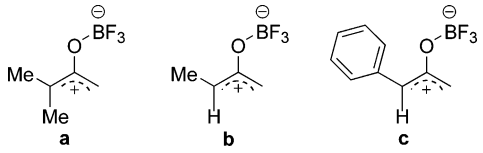
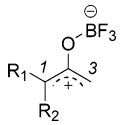


FIGURE 2. Low-energy conformations used for the calculation of oxyallyl LUMO coefficients.

In all cases, the energy gap between the HOMO of the methyl azide and the LUMO of the oxyallyl cation was much smaller

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, M.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.11; Gaussian, Inc.: Pittsburgh, PA, 2001.

TABLE 5. B3LYP/6-31+G* Molecular Orbital Coefficients for the LUMOs of Oxyallyl Cations



entry	oxyallyl cation	R_1	R_2	LUMO coefficients C(1)	LUMO coefficients C(3)
1	**a**	CH_3	CH_3	0.51	0.23
2	**b**	CH_3	H	0.38	0.30
3	**c**	C_6H_5	H	0.26	0.23

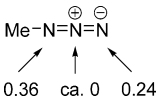


FIGURE 3. B3LYP/6-31+G* molecular orbital coefficients for the HOMOs of methyl azide.

than the energy gap between the LUMO of the methyl azide and the HOMO of the oxyallyl cation.[29] The coefficients of the HOMO of methyl azide and the LUMO of the oxyallyl cation, reported in Table 5, suggest that both orbitals are similar to the allyl nonbonding orbital.[30] For methyl azide, the proximal nitrogen has a larger coefficient than the distal nitrogen (Figure 3).[31] It is likely that the same regioisomeric preferences would be observed regardless of stepwise nucleophilic attack of azide upon oxyallyl cation or in a $HOMO_{azide}-LUMO_{oxyallyl\ cation}$ controlled [3 + 3] concerted reaction.

The calculated LUMO coefficients for oxyallyl cation **a** are in line with the results obtained with this substrate: α-amino-α′-diazomethyl ketones, which result from proximal azide attack at C_1, were exclusively observed. The small difference in the calculated LUMO cofficients at C_1 and C_3 for oxyallyl cation **b** is likewise consistent with nonspecific formation of a mixture of constitutionally isomeric 1,2,3-oxaborazoles **13** and **14**. Furthermore, the apparent lack of stability of the oxyallyl cation **b** may be reflected in the poor efficiency of these reactions. This same effect could also contribute to the small amount of 3-azetidone **12** observed by making the ring opening to the oxyallyl cation less favorable in comparison to ketone addition.

The most difficult case to understand is that of the oxyallyl cation **c** derived from phenylcyclopropanone. This species has comparable LUMO coefficients at C_1 and C_3, yet a single 1,2,3-oxaborazole consistent with proximal bond formation of the azide onto the oxyallyl cation at C-3 was formed in its reactions with alkyl azides. There are several possible explanations for this outcome. Since the LUMO coefficients at C_1 and C_3 are of comparable magnitude, a simple steric bias may override any small electronic preference for attack at C_1. On the other hand, it is possible that the initial addition reaction or even the [3 + 3] reaction is reversible and that the elimination of a proton H_b from intermediate **A′** is favored over the alternative loss of H_a (Scheme 7). However, the present studies do not address the likelihood of this possibility. The presence of the phenyl group could also stabilize the oxyallyl cation and contribute to the reversibility of the initial reaction.

Summary

The Lewis acid-mediated reactions of cyclopropanones with alkyl azides provide access to a variety of distinct products. Marked differences in reaction course and regiochemistry were encountered depending on the substitution pattern of the starting cyclopropanone acetal. We believe that the products obtained from the reactions described in this paper are the result of divergent reaction pathways (1) exploiting the "traditional" ketone behavior for unsubstituted cyclopropanone, providing 2-azetidinone and carbamates, and (2) the oxyallyl cationic behavior of substituted cyclopropanones. In these cases, the nature of the oxyallyl cation appears to affect the regiochemistry of azide addition and whether the products are α-amino-α′-diazomethyl ketones or 1,2,3-oxaborazoles. The regiochemistry of azide addition appears to be in accordance with simple FMO theory, although that method does not fully address the situation with the phenyl case. To that end, future studies will include a full ab initio study of the various pathways in hopes of understanding the mechanisms of this suite of reactions and how they are modulated by substitution.

Experimental Section

General Procedure for the Preparation of *β*-Lactam and Ethyl Carbamate Products. To a solution of alkyl azide (2.0 equiv) in 8 mL of CH_2Cl_2 at 0 °C was added [(1-ethoxycyclopropyl)oxy]trimethylsilane (1.0 equiv). The mixture was stirred for 10 min and $BF_3{\cdot}OEt_2$ (2.5 equiv) was added dropwise; gas evolution was observed. The reaction was allowed to warm to room temperature and stirred for 20 h at which time 10 mL of saturated $NaHCO_3$ and 10 mL of CH_2Cl_2 were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Concentration followed by chromatography (20% EtOAc/hex) afforded the *β*-lactam and ethyl carbamate products.

***N*-Phenylmethylazetidin-2-one (2a).** Clear oil (45%). Known compound.[32]

***N*-Phenylmethylcarbamic Acid Ethyl Ester (3a).** Clear oil (13%). Known compound.[33]

General Procedure for the Reaction of Triethyl(1-methoxy-2,2-dimethylcyclopropoxy)silane with Alkyl Azides. Triethyl(1-methoxy-2,2-dimethylcyclopropoxy)silane (1.0 equiv) was added to a solution of alkyl azide (2.0 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (1.0 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight, at which time it was poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was then dried with $MgSO_4$ and evaporated to provide a residue that was purified by flash chromatography (20% EtOAc/hex).

1-Diazo-3-methyl-3-phenylaminobutan-2-one (5a): yellow oil (47%); R_f 0.06 (20% EtOAc/hex); IR (neat) 3326, 2099, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37−7.26 (m, 5H), 5.96 (br s, 1H), 3.66 (s, 2H), 1.60 (br s, 1H), 1.34 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) 201.3, 140.7, 128.9, 128.4, 127.5, 62.6, 52.2, 48.6, 25.8; CIMS *m*/*z* (rel intensity) 218 (MH^+, 100), 190 (97); HRMS calcd for $C_{12}H_{16}N_3O$ 218.1293, found 218.1268.

(28) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176−186.

(29) Noyori, R.; Shimizu, F.; Fukuta, K.; Takaya, H.; Hayakawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5196−5198.

(30) Inclusion of solvent (dichloromethane) via the IEFPCM algorithm in Gaussian03 gave a similar trend with the differences in coefficients being 0.12 for methyl azide, 0.21 for **a**, 0.08 for **b**, and 0.07 for **c**.

(31) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287−7301.

(32) Holley, R. W.; Holley, A. D. *J. Am. Chem. Soc.* **1949**, *71*, 2124−2129.

(33) Reimer, M. *J. Am. Chem. Soc.* **1926**, *48*, 2454−2462.

1-Benzyl-2,2-dimethylazetidin-3-one (6a): yellow oil (4%); R_f 0.14 (20% ethyl acetate/hexanes); IR (neat) 2970, 1804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.25−7.39 (m, 5H), 4.03 (s, 2H), 3.84 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) 209.1, 139.3, 128.8, 128.7, 127.5, 83.8, 71.0, 55.4, 20.3; CIMS *m*/*z* (rel intensity) 190 (MH^+, 76), 160(11), 148(23), 91 (100), 70 (81); HRMS calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1221.

General Procedure for the Reaction of Aryl- and Monalkyl-Substituted Cylopropanone Silyl Acetals with Alkyl Azides. To a solution of cyclopropanone acetal (1.0 equiv) and alkyl azide (2.0 equiv) was added $BF_3{\cdot}OEt_2$ (2.0 equiv). The reaction vial was immediately sealed and placed in a microwave and heated at 135 °C for 10 min. The reaction mixture was then diluted in CH_2Cl_2 (15 mL) and washed with a saturated solution of $NaHCO_3$ (50 mL). The mixture was extracted twice with CH_2Cl_2 (25 mL). The combined extracts were then dried with $MgSO_4$, filtered, and concentrated. The remaining residue was then purified by column chromatography, using 5−20% EtOAc/hexanes as eluent.

3-Benzyl-5-benzylidene-2,2-difluoro-2,5-dihydro[1,2,3]-oxaborazole (9a): white solid (51 mg, 50%); R_f 0.13 (20% EtOAc/hex); mp 153−156 °C; IR (KBr pellet) 3450, 1644, 1629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.3 Hz, 2H), 7.59 (br s, 1H), 7.41 (m, 8H), 5.98 (s, 1H), 4.86 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 149.1, 133.6, 132.3, 130.6, 129.7, 129.5, 129.4, 129.3, 128.7, 128.6, 119.0, 52.0; MS (FAB) *m*/*z* 285 (M^+), 266; HRMS calcd for $C_{16}H_{14}BF_2NO$ 285.1137, found 285.1136.

General Procedure for the $Rh_2(OAc)_2$-Catalyzed Cyclization of α-Amino-α′-diazomethyl Ketones. Compounds **5** (0.138 mmol) in 2 mL of CH_2Cl_2 were added to a solution of $Rh_2(OAc)_4$ (3 mg, 0.007 mmol) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was allowed to warm to room temperature and stirred for 20 h at which time 10 mL of water was added. The aqueous layer was partitioned between CH_2Cl_2 and brine and dried over anhydrous $MgSO_4$ and evaporated to provide a yellow oil, which was purified by flash chromatography (20% EtOAc/hex).

1-Benzyl-2,2-dimethylazetidin-3-one (6a): yellow oil (90%); R_f 0.14 (20% ethyl acetate/hexanes); IR (neat) 2970, 1804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.25−7.39 (m, 5H), 4.03 (s, 2H), 3.84 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) 209.1, 139.3, 128.8, 128.7, 127.5, 83.8, 71.0, 55.4, 20.3; CIMS *m*/*z* (rel intensity) 190 (MH^+, 76), 160(11), 148(23), 91 (100), 70 (81); HRMS calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1221.

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Supporting Information Available: Experimental procedure for the preparation of substituted cyclopropanone acetals, and acidic ethanolysis of **9a**, characterization data for compounds **2b**−**4**, **5b**−**8**, and **9b**−**14b**, and ^1H and ^{13}C NMR spectra for compounds **2b**, **2c**, **2d**−**9g** and **12**−**14b**; CIF file for compound **9g**; and details of calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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