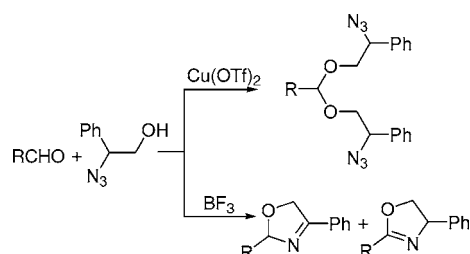# Some New Aspects of the Boyer Reaction

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ABSTRACT

The reaction outcome of 2-azidoethanol and aliphatic aldehyde is found to be dependent on the catalyst and the structure of the azido alcohol. Under the catalysis of Cu(II) triflate, the corresponding acetal is obtained. A similar reaction between 2-aryl-2-azidoethanol and aldehyde catalyzed by BF₃ yields a mixture of 3-oxazoline and 2-oxazoline. The latter reaction has been used for the preparation of 3-oxazolines in good enantioselectivity.

The reaction of an azido compound with an aldehyde or ketone catalyzed by a Brønsted acid or a Lewis acid, which is generally known as the Schmidt reaction,[1] may yield an amide, a lactam, or a heterocyclic product, depending on the structure of the azido compound and the carbonyl compound. Through recent efforts in developing an asymmetric version of this reaction, the Schmidt reaction has become a new strategy for the synthesis of optically active lactams and nitrogen-containing heterocyclic compounds.[2] For example, Aubé and co-workers have synthesized potential peptide β- and γ-turn mimics by using this method.[3]

Mechanistically akin to the Schmidt reaction, the Boyer reaction refers to the reaction of 2-azidoethanol or 3-azidopropanol and an aldehyde, where 2-oxazoline or dihydrooxazine form as the product (eq 1). This reaction was
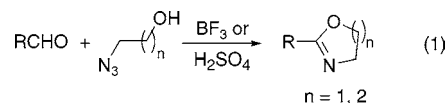
originally studied by Boyer with H_2SO_4 as the catalyst, with a very limited substrate scope;[4] however, Aubé and co-workers demonstrated that this can be much improved by using Lewis acids, such as $BF_3 \cdot Et_2O$, as the catalyst.[5] Recently, we accidentally found some new pathways of this reaction when we studied the Lewis acid catalyzed ring-

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(1) For reviews, see: (a) Wolff, H. *Org. React.* **1946**, *3*, 307–336. (b) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279–1300. (c) Krow, G. R. *Tetrahedron* **1981**, *37*, 1283–1307.

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(3) (a) Reddy, D. S.; Vander Velde, D.; Aubé, J. *J. Org. Chem.* **2004**, *69*, 1716–1719. (b) Ramanathan, S. K.; Keeler, J.; Lee, H.-L.; Reddy, D. S.; Lushinton, G.; Aubé, J. *Org. Lett.* **2005**, *7*, 1059–1062.

(4) (a) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954. (b) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325–327. (c) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561–562.

(5) (a) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484–2487. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241–16252.

opening reaction of epoxides.[6] Herein, we wish to report our preliminary results.

Although most Lewis acids catalyze the reaction 2-azidoethanols and aliphatic aldehydes to give the reported 2-oxazoline products, we found that Cu(II) triflate behaves totally differently. Instead of the normal 2-oxazoline, this reaction gives an acetal as the product (eq 2).[7] The results are summarized in Table 1 (**Caution:** Although we did not

Table 1. Formation of Acetals between Aliphatic Aldehydes and Azido Alcohols[a]

entry	R^1	R^2	yield[b] (%)
1	n-C_5H_{11}	Ph	68
2	n-C_6H_{13}	Ph	64
3	n-C_8H_{17}	Ph	75
4	$PhCH_2CH_2$	Ph	87
5	cyclohexyl	Ph	66
6	Me_3C	Ph	42
7	n-C_5H_{11}	H	81
8	n-C_6H_{13}	H	65
9	$PhCH_2CH_2$	H	66
10	cyclohexyl	H	65

[a] Carried out with the aldehyde (1.0 mmol), the azido alcohol (1.0 mmol), and 5 mol % of Cu(OTf)$_2$ in dry CH$_2$Cl$_2$ (5 mL) under reflux overnight. [b] Yield of isolated product after chromatography.

encounter any problem with these products, diazides are potential explosives and should be handled with care and all necessary protective measures should be taken during the reaction). Aldehydes with straight alkyl chain, such as hexanal (entry 1), heptanal (entry 2), nonanal (entry 3), and hydrocinnamaldehyde (entry 4), all gave good yields of the acetal products when 2-azido-2-phenylethanol was used. Aldehydes with branching at the α position also participate in this reaction. For example, cyclohexanecarbaldehyde gave 66% yield of the desired acetal (entry 5). A sterically hindered 2,2-dimethylpropionaldehyde also gave a 42% yield of the expected acetal (entry 6). When 2-azidoethanol was used as the substrate, similar results were obtained (Table 1, entries 7−10). However, when aromatic aldehydes or ketones were used, no acetal could be obtained (data not shown).

Formation of an acetal from aldehyde and azido alcohol under acid catalysis is unprecedented in the literature. Even though the acid-catalyzed formation of acetal from aldehyde and alcohol is well-known, the present reaction is apparently different from such a reaction, since ethanol *does not* form

(6) Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991−4993.
(7) A mixture of *d,l* and meso compounds was obtained when a racemic azido alcohol was used.

acetal with hexanal under the catalysis of Cu(OTf)$_2$ (data not shown).

To demonstrate the usefulness of this new reaction, acetal **1a** was reduced to diamine **2** (Scheme 1). Reaction of **2** with

Scheme 1. Synthesis of Ligand **3**
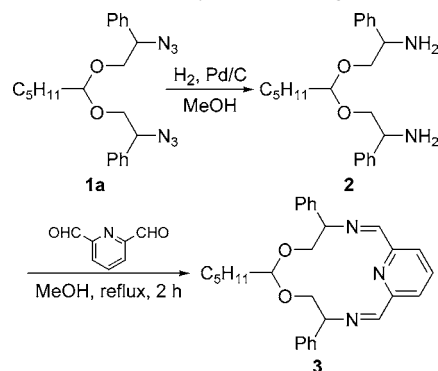
pyridine-2,6-dicarbaldehyde produced a macrocyclic compound **3**, which may be used as a ligand in the Cu(OTf)-catalyzed addition of phenylacetylene to *N*-benzylideneaniline to yield the propargylamine in 75% yield (eq 3, no yield without **3**).[8] Moreover, since the azido group is a masked amino group, the present acetal formation reaction may be viewed as a selective protection method for the hydroxyl group of an amino alcohol, which is usually difficult to achieve.
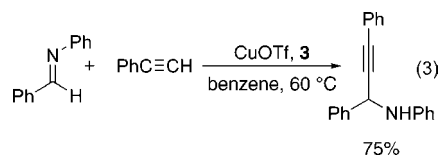
When BF$_3$·Et$_2$O was used as the catalyst, the reaction of aldehydes with 2-aryl-2-azido alcohol was found to be more complicated than expected: Besides the expected 2-oxazolines (**5**), 3-oxazoline (**4**) and a third product, which we tentatively assigned the structure **6**, were also isolated (eq 4). The results are summarized in Table 2.

As shown in Table 2, 3-oxazoline (**4**) is always formed except for 4-nitro-substituted azido alcohol, while the formation of the other two products is dependent on the substrates. Again, different types of aliphatic aldehydes (entries 1−6) can be used as substrates for this reaction. As in the aforementioned acetal formation reaction, aromatic aldehydes do not react (data not shown). Since multiple products are formed in this reaction, the yield of each of the individual products is low. The best yields of the 3-oxazoline product were achieved with aldehydes with two phenyl substituents at the α position (entries 4 and 6). Similarly, azido alcohols

(8) For recent examples of transition-metal-catalyzed addition of acetylene to imines, see: (a) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268−269. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319−4321. (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639.

**Table 2.** Boyer Reaction of Aliphatic Aldehyde with 2-Aryl-2-azidoethanol[a]
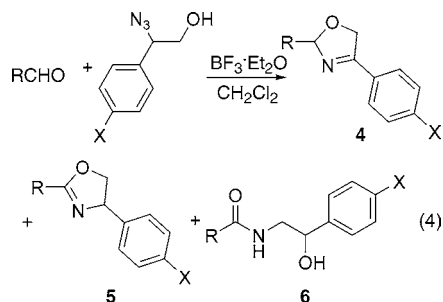
entry	R	X	yield[b] (%) 4	5	6
1	n-C$_6$H$_{13}$	H	24[c]		
2	n-C$_8$H$_{17}$	H	20	14	
3	n-C$_9$H$_{19}$	H	18	38	
4	Ph$_2$CH	H	47[d,e]		
5	PhMeCH	H	17[d,f]	41	
6	Ph$_2$MeC	H	40	21	
7	n-C$_8$H$_{17}$	Me	23	28	
8	n-C$_8$H$_{17}$	MeO	24		
9	n-C$_8$H$_{17}$	Cl	15	trace	20
10	n-C$_8$H$_{17}$	F	17	26	11
11	n-C$_8$H$_{17}$	NO$_2$		29	38

[a] Carried out with the aldehyde (0.3 mmol) and 2-aryl-2-azidoethanol (0.3 mmol) in dry CH$_2$Cl$_2$ with BF$_3$·Et$_2$O (2 equiv) as the catalyst at room temperature (25 °C) for 3 h, unless otherwise indicated. [b] Yields of isolated products after column chromatography. [c] With 1.0 equiv of BF$_3$·Et$_2$O and overnight reaction. [d] At 40 °C. [e] With 2.5 equiv of BF$_3$·Et$_2$O for 6 h. [f] With 1.66 equiv of BF$_3$·Et$_2$O for 5 h.

with different aryl substituents also participate in the reaction to give these products (entries 2, 7−11). The data indicate that the electronic effects of the substituent on the para position of the phenyl ring have some influence on the product distribution: An electron-withdrawing group favors the formation of product **6** (entries 9−11), while the strong electron-withdrawing nitro group totally inhibits the formation of the 3-oxazoline product (entry 11).

The formation of 3-oxazoline product may be rationalized by a modified reaction mechanism proposed originally by Aubé and co-workers.[5a] As shown in Scheme 2, the addition

Scheme 2. Mechanism for the Formation of 3-Oxazoline
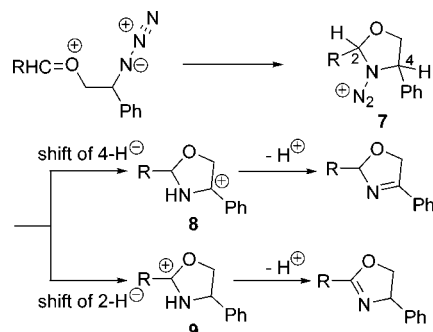
of the azido group to the oxonium ion forms the intermediate **7**,[5a] The hydrides at 4- or 2-position of this intermediate migrate followed by N$_2$ loss to form two new cationic intermediates **8** and **9**, stabilized by phenyl and oxygen groups, respectively. The relative energy of these two cationic intermediates would affect the rate of hydride migration. Our results and those of Aubé[5] and Boyer[4] indicate that, without a phenyl group at 4-position, the formation of intermediate **8** is unfavorable and the normal 2-oxazoline product is observed,[4,5] while the formation of **8** becomes important when such a phenyl group is present, since its energy is now lowered through conjugation. This mechanism explains better why arene with a strong electron-withdrawing para substituent (NO$_2$) totally inhibits the formation of 3-oxazoline.

3-Oxazolines are very useful compounds. Their derivatives have been isolated and characterized as volatile flavor compounds in food.[9] Some of these compounds have shown important organoleptic properties.[10] Reported synthetic methods of 3-oxazolines include photochemically induced[11] or base-catalyzed[12] ring opening of substituted 2H-azirines and oxidative elimination of 1,3-oxazolidines with t-BuOCl/KO$_2$[13] or with NaOCl/KOH.[14] However, none of these methods may be used to synthesize 3-oxazoline *enantioselectively*.

During the formation of 3-oxazoline in our reaction, a new chiral center at the 2-position is created (Scheme 2). Although the yield of this reaction is not satisfactory, it is possible to control the stereo outcome of the 2-position based on the proposed mechanism. Thus, we tried the asymmetric induction in this reaction, and the preliminary results are summarized in Table 3. When enantiomerically pure (*S*)-2-azido-

Table 3. Asymmetric Induction in Reaction of Nonanal with (*S*)-2-Aryl-2-azidoethanol[a]

entry	Ar	t (h)	T (°C)	yield[b] (%)	ee[c] (%)
1	Ph	3	25	16	45[d]
2	Ph	9	0−5	15	65[d]
3	Ph	9	−23	15	74[d]
4	4-Cl-Ph	9	−23	14	67[e]

[a] Carried out with a mixture of nonanal (0.3 mmol), (*S*)-2-aryl-2-azidoethanol (0.3 mmol), and BF$_3$·Et$_2$O (2 equiv) in dry CH$_2$Cl$_2$ at the specified temperature. [b] Yield of isolated product after column chromatography. [c] Absolute configuration of the major enantiomer not determined. [d] Determined by HPLC analysis using a Chiralcel OD-H column. [e] Determined by HPLC analysis using a Chiralcel AS column.

2-phenylethanol[2d] was used, the product of nonanal gives an ee value of 45% at room temperature (entry 1). When

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the temperature was lowered to ca. 0 °C, the ee value was improved to 65% (entry 2). The enantioselectivity of this reaction may be further improved to 74% ee by carrying out the reaction at −23 °C (entry 3). A similar result was also obtained with (S)-2-azido-2-(4-chlorophenyl)ethanol[15] (entry 4).

Optically active 3-oxazolines, although unexplored previously, have the potential to be used as chiral ligands for asymmetric catalysis, since their structural isomers, 2-oxazolines, have been widely utilized for this purpose.[16]

In summary, we have found some new pathways in the Lewis acid catalyzed reaction of aldehyde and 2-azido

alcohol. When $Cu(OTf)_2$ is used as the catalyst, an acetal is formed, while when 2-aryl-2-azidoethanol is used with BF_3 as the catalyst, formation of 3-oxazoline is observed. The latter reaction has been used for the enantioselective synthesis of 3-oxazolines in good ee values for the first time.

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(15) Synthesized in a similar way as (S)-2-azido-2-phenylethanol.

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