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A Novel Effective Transition Metal Based Salt-Catalyzed Azidolysis of 1,2-Epoxides

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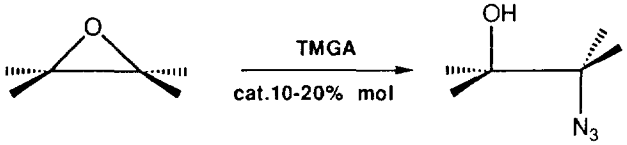
Abstract: A simple, efficient, stereoselective, and in some cases usefully non-regioselective method for the synthesis of β-azido alcohols by the direct opening of 1,2-epoxides with 1,1,3,3-tetramethylguanidinium azide (TMGA) in CH_3CN, catalyzed by simple transition metal-based salts [$Hf(OTf)_4$, $Zr(OTf)_4$, $Yb(OTf)_3$], is described. Also $TMSN_3$ may be used in some reactions as a source of N_3^-. This new method appears to be competitive with other methods previously reported.

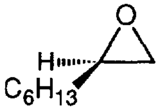
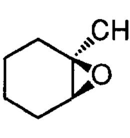
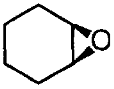
We have recently shown that lanthanide(III) triflates can be utilized as efficient catalysts for the aminolysis of 1,2-epoxides[1] and for oxirane ring opening by lithium enolates derived from simple ketones.[2] In these reactions, high yields of the corresponding 1,2-addition products were obtained, showing almost complete (except for styrene oxide) contra-Markovnikov[3] regioselectivity.[1,2]

β-Azido alcohols are compounds of undoubted interest in organic synthesis.[4] Recently, we found that common metal salts, such as $LiClO_4$, promote in an efficient way the direct azidolysis of several 1,2-epoxides with NaN_3 in anhydrous CH_3CN, and this protocol turned out to be effective also with hindered epoxides. However, more than an equimolar amount (150% mol) of the catalyst had to be used and the reaction temperature was relatively high (80°C).[5] Moreover, quite recently, an $SmI_2(THF)_2$-catalyzed azidolysis of simple epoxides with Me_3SiN_3 has been reported.[6] Searching for new, even more efficient catalysts for this reaction, we have now found that various metal salts [$Hf(OTf)_4$, $Zr(OTf)_4$, $Yb(OTf)_3$][1,7], catalyze (10-20% mol) the azidolysis of 1,2-epoxides with 1,1,3,3-tetramethylguanidinium azide (TMGA)[8] in CH_3CN[9] at room temperature (see Table, where, for comparison, some results previously obtained in the corresponding $LiClO_4$-promoted reactions[5] are reported, too). Attempts to diminish the amounts of the catalyst markedly reduced the yields of the azido alcohols, even after much longer reaction times (several days, results not shown in the Table); only after the successive addition of additional catalyst does the reaction proceed and an increase in the yields of the addition product is observed.



TMGA is easy to prepare,[10] stable, and soluble in organic solvents such as CH_3CN and CH_3NO_2. The work-up procedure is very simple (see experimental section) and the azido alcohol is easily obtained in an almost pure state: in fact, the addition of ether to the reaction mixture solubilizes the azido alcohol, while the excess of TMGA, insoluble in ether, may be removed by water washings. To our knowledge, TMGA has not been previously employed for oxirane ring cleavage. Also Me_3SiN_3 may be used in this reaction as source of N_3^-:[6,11] in this case, the amount of the metal salt may be markedly lowered [only 2% mol in the case of cyclohexene oxide (**3**), entry 16, Table] indicating a considerably increased reactivity for this reagent compared with TMGA.[12] However, with Me_3SiN_3 as the nucleophile, mixtures of *O*-protected (*O*-TMS) and

Table. Azidolysis of Epoxides 1-4 with TMGA in Anhydrous CH_3CN, or Me_3SiN_3 in CH_2Cl_2, Catalyzed by Transition Metal-Based Salts.

entry	epoxide[a]	nucleophile	catalyst	reaction time and temp. (°C)	α attack[b]	β attack[c]	yield %[d]
1	 **1**	TMGA	$Zr(OTf)_4$ 20%	4d (r.t.)	18	82	75
2		TMGA	$Hf(OTf)_4$ 20%	4d (r.t.)	18	82	74
3		TMGA	$Yb(OTf)_3$ 20%	4d (r.t.)	7	93	54
4		Me_3SiN_3	$Hf(OTf)_4$ 10%	18h (r.t.)	51[e]	49[e]	80
5		Me_3SiN_3	$Zr(OTf)_4$ 10%	18h (r.t.)	45[e]	55[e]	76
6		NaN_3	$LiClO_4$ 150%	24h (80°C)[f]	8	92	96
7	 **2**	TMGA	$Zr(OTf)_4$ 20%	3d (r.t.)	55	45	60
8		TMGA	$Hf(OTf)_4$ 20%	3d (r.t.)	58	42	72
9		TMGA	$Yb(OTf)_3$ 20%	3d (r.t.)	20	80	51
10		TMGA	no catalyst	3d (r.t.)	16	84	7
11		Me_3SiN_3	no catalyst	42h (r.t.)	complex	mixture	
12		NaN_3	$LiClO_4$ 150%	48h (80°C)[f]	27	73	94
13	 **3**	TMGA	$Zr(OTf)_4$ 20%	42h (r.t.)			84
14		TMGA	$Hf(OTf)_4$ 20%	42h (r.t.)			82
15		TMGA	$Yb(OTf)_3$ 20%	42h (r.t.)			78
16		Me_3SiN_3	$Zr(OTf)_4$ 2%	3d (r.t.)			80
17		Me_3SiN_3	$Zr(OTf)_4$ 10%	4h (r.t.)			80
18		Me_3SiN_3	$Yb(OTf)_3$ 10%	4h (r.t.)			35
19		NaN_3	$LiClO_4$ 150%	18h (80°C)[f]			94
20	 **4**	TMGA	$Zr(OTf)_4$ 10%	42h (r.t.)	74	26	67
21		TMGA	$Hf(OTf)_4$ 10%	42h (r.t.)	78	22	65
22		TMGA	$Yb(OTf)_3$ 10%	4d (r.t.)	72	28	82
23		Me_3SiN_3	$Zr(OTf)_4$ 10%	18h (r.t.)	>99[e]	<1[e]	30[g]
24		NaN_3	$LiClO_4$ 150%	5h (80°C)[f]	82	18	92

[a] All the reactions were carried out on racemic material. [b] Attack of the nucleophile on the more substituted oxirane carbon. [c] Attack of the nucleophile on the less substituted oxirane carbon .[d] Yields based on weight and ^1H NMR examination of the isolated crude reaction product. All compounds were fully characterized by ^1H and ^{13}C NMR, GC/MS, and IR. [e] α-Attack/β-attack ratio determined after complete deprotection (TBAF in THF) of the crude reaction product.[f] Also this reaction was carried out in MeCN (see ref. 5). [g] A complex reaction mixture was obtained.

O-deprotected azido alcohols are commonly obtained depending on the type of the metal salt used; for example, only *O*-protected azido alcohols are obtained when 2% mol of $Zr(OTf)_4$ is used as the promoting metal salt (entry 16, Table). Moreover, the use of Me_3SiN_3 as the reagent in the corresponding reactions of a phenyl-substituted epoxide, such as styrene oxide (**4**) and of a more substituted epoxide such as 1-methylcyclohexene oxide (**2**), affords quite complex reaction mixtures, probably as a consequence of the lack of free N_3^- in the reaction mixture with this reagent. Under these conditions, the reactive complexing species formed between the oxirane and the metal (see later) can partially evolve to non-addition products, when readily available N_3^- is not sufficiently present in the reaction medium. With TMGA as the reagent, only *O*-deprotected azido alcohols are obtained, in a moderate to good yield (51-84 %), thus avoiding the deprotection stage necessary when Me_3SiN_3 is used. The reactions carried out with these new methodologies are completely anti stereoselective, as shown by the exclusive presence of the anti adduct in the reactions of cyclic epoxides **2** and **3**. As for the regioselectivity, this largely depends on the type of the 1,2-epoxide, on the metal salt, and on the reagent (TMGA or $TMSN_3$) used. For example, while the reaction of 1,2-epoxyoctane (**1**) with TMGA in the presence of $Yb(OTf)_3$ is highly regioselective, with the attack of the nucleophile on the less substituted oxirane carbon (β-attack in the Table), the use of Me_3SiN_3 in the presence of $Hf(OTf)_4$ or $Zr(OTf)_4$ affords an almost 1:1 mixture of both the regioisomers (entries 4 and 5, Table). This makes the latter procedure very useful for the synthesis of Markovnikov-type 1,2-azido alcohols which are not easily prepared from typical aliphatic 1,2-epoxides such as **1**, considering that the best results previously reported for the preparation of the same regioisomer are not superior to 13-15%.[6,11,13] In the case of epoxide **2**, and particularly of epoxide **4**, a considerable prevalence of the Markovnikov-type regioisomer is obtained also using TMGA. It should be noted that general catalytic methods previously effective for the azidolysis of 1,2-epoxides,[6,11] when applied to epoxide **2**, were somewhat ineffective or gave the contra-Markovnikov-type regioisomer,[3] as the major reaction product.[11,14] According to previous hypotheses,[1,2] the catalytic effects of these transition metal based triflates can be ascribed to the strong oxophilicity of the metal in these compounds, which allows the metal to coordinate the oxirane oxygen tightly, thus favoring the nucleophilic ring opening process. The clear tendency of $Hf(OTf)_4$ and $Zr(OTf)_4$, in particular, to afford considerable amounts of Markovnikov-type regioisomers in the azidolysis of 1,2-epoxides, could be ascribed to the decidedly high Lewis acidity of these salts, which makes possible a transition state with a more pronounced carbocationic character. In this case, the nucleophilic attack on the more substituted oxirane carbon appears to be favored.

In conclusion, this new procedure, which is the first example of the use of TMGA as a source of N_3^- for the azidolysis of 1,2-epoxides, appears to be highly competitive with the other catalytic methods reported in literature.[6,11] The operating conditions are decidedly mild, and the yields moderate to good. No supplementary deprotection stage is necessary to obtain the free reaction product (the azido alcohol) when TMGA is used. Moreover the appropriate coupling of the reagents (TMGA or Me_3SiN_3 and metal salt) makes it possible to achieve different and, as shown in the case of entries 4 and 5 (Table), unusual non-regioselectivity which can be advantageously utilized for the synthesis of both regioisomeric β-azido alcohols.

General Procedure and Identification of β-Azido Alcohols.

A solution of the epoxide (1.0 mmol) in anhydrous CH_3CN (CH_2Cl_2 in the case of Me_3SiN_3) (2 ml) was treated with TMGA (1.8 mmol) or Me_3SiN_3(1.5 mmol) and the required amount of anhydrous metal salt (2-20%mol) (see Table). The reaction mixture was stirred for the time shown in the Table and then diluted with ether. Evaporation of the washed (water) organic solution afforded a crude reaction product consisting of the corresponding β-azido alcohols, which were analyzed by GC/MS and by ^1H NMR examination. The two regioisomers (α-attack and β-attack) obtained in the reaction of epoxide **1** (entry 4 or 5, Table) were separated by flash chromatography using an 8:2 mixture of hexane and ethyl acetate: **1-azido-2-octanol**[13] (β-attack, Table), ^{13}C NMR ($CDCl_3$) δ 71.46, 57.70, 34.93, 32.33, 29.80, 26.04, 23.18, 14.65; **2-azido-1-octanol**[13] (α-attack, Table), ^{13}C NMR ($CDCl_3$) δ 65.95, 65.20, 32.33, 31.28, 29.78, 26.67, 23.24, 14.74.

The structures of all the azido alcohols were confirmed by comparison with authentic samples prepared in accordance with literature procedures.[5] When Me_3SiN_3 was used as the nucleophile, the α-attack/β-attack ratio was determined after treatment of the reaction product with TBAF in THF.

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(2) Crotti,P.;Di Bussolo,V.;Favero, L.;Macchia, F.;Pineschi, M.*Tetrahedron Lett.* **1994,** *35*, 6537-6540.

(3) The term "contra-Markovnikov" is preferred to "anti-Markovnikov" in order to avoid confusion with the stereochemical use of the prefix "anti" (De La Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems* ; Elsevier Scientific: Amsterdam, 1982).

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(8) Li, C.; Arasappan, A.; Fuchs, P.L. *Tetrahedron Lett.* **1993,** *34*, 3535-3538.

(9) The present addition reaction with TMGA occurs also in CH_2Cl_2. However, as the use of sodium azide in this solvent has been reported to cause explosions, we thought it better to discard CH_2Cl_2 as a solvent for this reaction (Li, C.; Shih, T-L.; Jeong, J.U.; Arasappan, A.; Fuchs P.L. *Tetrahedron Lett.* **1994,** *35*, 2645-2646, and references therein). Even if the addition reaction occurs also in CH_3NO_2, CH_3CN was preferred, due to the better chemical yields generally obtained with this latter solvent.

(10) Papa, A.J. *J.Org.Chem.* **1966,** *31*, 1426-1430.

(11) While this work was in progress, two new papers appeared on the ring opening of epoxides with Me_3SiN_3 catalyzed by ytterbium (III) isopropoxide (Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc. Chem. Comm.* **1995**, 1021-1022) and by tetraphenylstibonium hydroxide (Fujiwara, M.; Tanaka, M.; Baba, A.; Ando, H.; Souma, Y. *Tetrahedron Lett.* **1995,** *36*, 4849-4852).

(12) The lower efficiency of the reactions carried out with TMGA and the need for larger amounts of the catalyst with this reagent could be explained by proposing that the free N_3^- nucleophile present in the reaction medium can substitute one or more triflate groups of the catalyst, thus deactivating it.

(13) Onaka, M.; Sugita, K.; Izumi, Y. *J. Org. Chem.* **1989,** *54*, 1116-1123.

(14) The reaction of epoxide **2** with Me_3SiN_3 and 10%mol $SmI_2(THF)_2$ under the conditions of ref.6 was repeated by us to give the corresponding azido alcohols (16% yield) in the α:β-attack ratio =37:63.

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