Ytterbium Triisopropoxide Catalysed Ring Opening of Epoxides with Trimethylsilyl Azide

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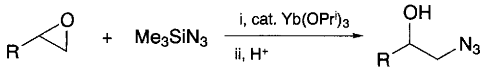
Ring opening of epoxides with trimethylsilyl azide is catalysed by ytterbium triisopropoxide at room temperature in THF, giving the corresponding vicinal azide alcohols in very high yields.

Vicinal azidohydrins,[1] potential precursors for 1,2-aminoalcohols and often used in carbohydrate chemistry or in the chemistry of carbocyclic nucleosides,[1,2] are generally synthesized from epoxides by reaction with an alkali azide under alkaline or acidic conditions. The reaction usually requires high temperatures and long reaction times. Furthermore, this classical method is often accompanied by side reactions such as isomerization, epimerization, and rearrangement induced by the acidic or alkaline conditions.[1,2] More recently, it has been reported that the use of stoichiometric (or excess) amounts of organometallic (including metallic salt or solid) reagents facilitates the azidolysis of epoxides; $Et_3Al–HN_3$,[3a] $Et_2AlF–Me_3SiN_3$,[3b] $Al_2O_3–NaN_3$,[4] $LiClO_4–NaN_3$,[5] $(Pr^iO)_nTi(N_3)_{4-n}$,[6] $Bu_2Sn(N_3)_2$[7] and Me_3SiN_3 itself[8] (only for heteroaryl substituted epoxides). Furthermore, the azidolysis of epoxides proceeds even in the presence of a catalytic amount of organometallic and related reagents; cat. $VO(OPr^i)_3$, $(C_5H_5)_2VCl_2$, or $Ti(OPr^i)_4–Me_3SiN_3$,[9] cat. $Al(OPr^i)_3–Me_3SiN_3$,[10] cat. $BF_3·OEt_2–Me_3SiN_3$,[11] cat. $Cr(NBu^t)_2Cl_2–Me_3SiN_3$,[12] cat. zinc tartrate–Me_3SiN_3[13] and cat. $Zr(OBu^t)_4–Me_3SiN_3$.[14] In spite of the development of these catalytic procedures,[9–14] we needed a much milder, more efficient, and widely applicable procedure for the azidolysis of epoxides.

We report herein that ytterbium triisopropoxide is an effective catalyst for the azidolysis of epoxides [eqn. (1)].

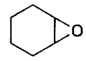
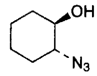
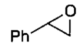
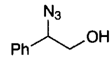
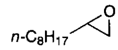
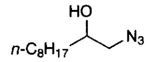
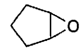
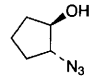
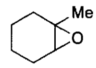
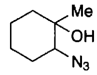
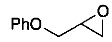
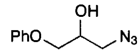
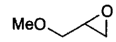
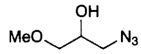
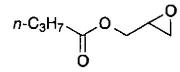
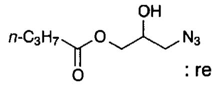
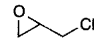
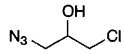
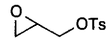
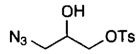
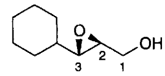
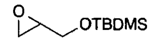
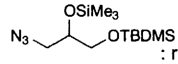


(1)

Recently, Crotti *et al.* and our group have found that $Yb(OTf)_3$ catalyses very efficiently the ring opening of epoxides with amines.[15] Furthermore, ring opening of aziridines with amines takes place readily in the presence of a catalytic amount of $Yb(OTf)_3$.[16] It occurred to us that an f-block metallic reagent such as Yb, La or Y might act as an efficient catalyst for the azidolysis of small ring heterocycles. The $Yb(OPr^i)_3$ catalysed reactions of Me_3SiN_3 with various epoxides are summarized in Table 1.

Initially, the reaction of cyclohexene oxide with Me_3SiN_3 was examined in the presence of 10 mol% $Yb(OTf)_3$ in THF at room temperature. However, the desired azidohydrin was not obtained and the starting materials were decomposed, perhaps owing to the relatively high Lewis acidity of the triflate. After several attempts, we found that $Yb(OPr^i)_3·3LiOTf$, prepared *in situ* from $Yb(OTf)_3$ (1 equiv.) and $LiOPr^i$ (3 equiv.) in THF (procedure A), gave the best result among the catalysts examined (entry 1). The reaction of cyclohexene oxide with Me_3SiN_3 using 10 mol% $La(OPr^i)_3$ or $Y(OPr^i)_3$ under similar conditions gave the corresponding azidohydrin in 84 or 74% yield, respectively. No reaction took place in the absence of the catalysts or in the presence of LiOTf (1 equiv.) alone, even after 9 d. Salt-free $Yb(OPr^i)_3$,[17] prepared by Kagan's procedure, exhibited a similar catalytic activity (procedure B) (entry 2). Mono- (entries 3,5), di- (entries 1,2,6 and 7), and tri-substituted epoxides (entry 8) smoothly underwent azidolysis at room temperature in the presence of catalytic amounts of $Yb(OPr^i)_3·3LiOTf$ or $Yb(OPr^i)_3$, giving the corresponding azidohydrins in very high yields.

Table 1 $Yb(OPr^i)_3$ catalysed ring opening of epoxides with Me_3SiN_3

Entry	Epoxide	Reaction time / h	Product and isolated yield (%)	
1[a]		12		95
2[b]		12		83
3[a]		13	 : regioisomer 86 : 14	83
4[b]		12	82 : 18	92
5[c]		36	 : regioisomer 90 : 10	94
6[a]		12		95
7[b]		13		93
8[d]		24	 : regioisomer 74 : 26	95
9[a]		12	 : regioisomer 95 : 5	94
10[a]		12	 : regioisomer >99 : 1	75[e]
11[a]		17	 : regioisomer 96 : 4	*ca.* 100
12[a]		24	 : regioisomer >99 : 1	94
13[a]		12	 : regioisomer 88 : 12	80
14[b]		36	C-3 : C-2 93 : 7	92[f]
15[b]		12	 : regioisomer 80 : 20	88[g]

Catalysts used: [a] 10 mol% A. [b] 10 mol% B. [c] 20 mol% A. [d] 20 mol% B. A = $Yb(OPr^i)_3$ prepared from 1 equiv. $Yb(OTf)_3$ and 3 equiv. $LiOPr^i$ in THF; B = $Yb(OPr^i)_3$ prepared by Kagan's procedure (LiCl free). [e] Isolated as benzoate. [f] Isolated as diacetate. [g] This entry was conducted without acidic work-up.

These new methods are also applicable to epoxides bearing a functional group. The catalytic system tolerated phenoxy (entry 9), methoxy (entry 10) and ester (entry 11) groups. Furthermore, selective ring opening took place even in the presence of a leaving group, such as Cl or OTs, which could be substituted readily by N_3^- (entries 12, 13). In entry 14, the azide reacted predominantly at the C-3 position bearing a sterically demanding group, suggesting that Yb forms a five-membered chelate including the epoxide oxygen and alcohol oxygen.[6] To the best of our knowledge, all the previous methods using Me_3SiN_3 afford azidohydrins in their alcohol form. However, we have found that the product can be isolated as its Me_3Si ether form (entry 15) if the work-up process is carried out under non-acidic conditions: diethyl ether and distilled water were added after the reaction was over, and ether extraction followed by distillation gave the Me_3Si ether derivative.

The reaction of cyclohexene oxide with Me_3SiN_3 is representative. To a solution of $Yb(OTf)_3$ (57 mg, 0.10 mmol) and $LiOPr^i$ (20 mg, 0.30 mmol) in dry THF (1.0 ml) (procedure A), or to a solution of $Yb(OPr^i)_3$ (35 mg, 0.10 mmol) in dry THF (1.0 ml) (procedure B), were added cyclohexene oxide (0.10 ml, 1.0 mmol) and Me_3SiN_3 (0.20 ml, 1.5 mmol) and the mixture was stirred at room temperature. The reaction was monitored by TLC. After consumption of the starting material, aqueous 1 mol dm^{-3} HCl was added. The organic layer was extracted with three portions of diethyl ether, washed with brine and dried with anhydrous Na_2SO_4. Filtration and removal of the solvents under reduced pressure gave the crude product which was purified by silica-gel column chromatography using hexane–AcOEt (7 : 1) as eluent to give *trans*-2-azidocyclohexan-1-ol (134 mg) in 95% yield.

It seems to us that the $Yb(OPr^i)_3$ catalysed azidolysis is an effective and widely applicable method for the synthesis of vicinal azidohydrins in comparison with the previously known procedures. The mechanism of the f-block metal catalysed reaction is under investigation.

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