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Magnesium chloride ($MgCl_2$) catalyzed highly regioselective C-3 ring opening of 2,3 epoxy alcohols by *N*-nucleophile

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ABSTRACT

We herein report Magnesium chloride ($MgCl_2$) catalyzed first highly C3-selective ring-opening reaction of various 2,3-epoxy alcohols with assorted *N*-Nucleophiles and sodium azide to furnish 3-amino-1,2 diols and 3-azido-1,2 diols respectively in high yields under mild reaction conditions. This protocol attributes the use of catalytic amount of Magnesium chloride ($MgCl_2$), simple reaction conditions, practical operation and broad functional group tolerance.

Introduction

Seebach [1] once expressed his opinion as "If carbonyl compounds have been said to be 'virtually the backbone of organic synthesis', the epoxides correspond to at least 'one of the main muscles'." This message can be very effective for researchers to understand the importance of epoxides in chemical synthesis [2]. Regioselective and stereospecific ring opening of 2,3-epoxy compounds with various nucleophiles [3] provide a direct access to versatile chiral building blocks for the synthesis of natural products and synthetic analogues with promising biological activities. Nucleophilic addition at the C-3 position of 2,3- epoxy alcohols by amines and azides affords 3-amino 1,2-diols and 3-azido-1,2 diols respectively. 3-amino 1,2-diols can be observed in cardiovascular [4], antibacterial [5], and sedative agents [6] as synthetic intermediates. However, 3-azido-1,2 diols are used as key intermediate for bioactive Dapoxetine [7]. Very less approaches have been reported for the C-3 regioselective ring opening of 2,3-epoxy alcohols using amines [8–12]and azides [13–18] as nucleophiles. Very recently, Chen J. *et al.* reported a metal and solvent-free acetic acid-mediated ring-opening reaction of epoxides with amines [19]. Despite the significant progress achieved in the area of C-3 regioselective ring opening of 2,3-epoxy alcohols with amines or azide, however many of the reported protocols used stoichiometric amount of promoters, high temperature and excess use of nucleophiles. Therefore, the development of a catalytic version of this type of reaction is still highly desirable [20]. Yamamoto H. *et al.* reported the first catalytic, highly C3-selective, stereospecific ring-opening reaction of 2,3-epoxy alcohols with diverse *N*-nucleophiles using W-salts providing various 3-amino-1,2 diols [21]. Surendra K *et al.* reported the C-3 selective ring-opening of 2,3-epoxy alcohols with aromatic amines catalysed by β-cyclodextrin in water at room temperature to afford the corresponding β-aminoalcohols in excellent yields with high regioselectivity [22]. Even though, few reports have been published dealing with very expensive catalyst like W-salts, Et_2AlF, and $Ti(O\text{-}^iPr)_4$) for aminolysis with the amines and azidolysis using azides of 2,3-epoxy alcohols. However, to the best of our knowledge, Magnesium chloride ($MgCl_2$) promoted C-3 ring opening of 2,3 epoxy alcohols with *N*-nucleophiles has not been reported so far. Inspired by these well developed strategies, we sought to investigate whether the less expensive and easily available Magnesium chloride ($MgCl_2$) reagent in catalytic amount could be used for the *N*-nucleophile addition reaction on 2,3 epoxy alcohols to generate 3-amino-1,2 diols and 3-azido-1,2 diols. Herein, we describe highly efficient regioselective aminolysis of 2,3-epoxy alcohols with diverse aromatic as well as aliphatic amines and azidolysis of 2,3-epoxy alcohols azides using catalytic amount of Magnesium chloride ($MgCl_2$).Scheme 1.

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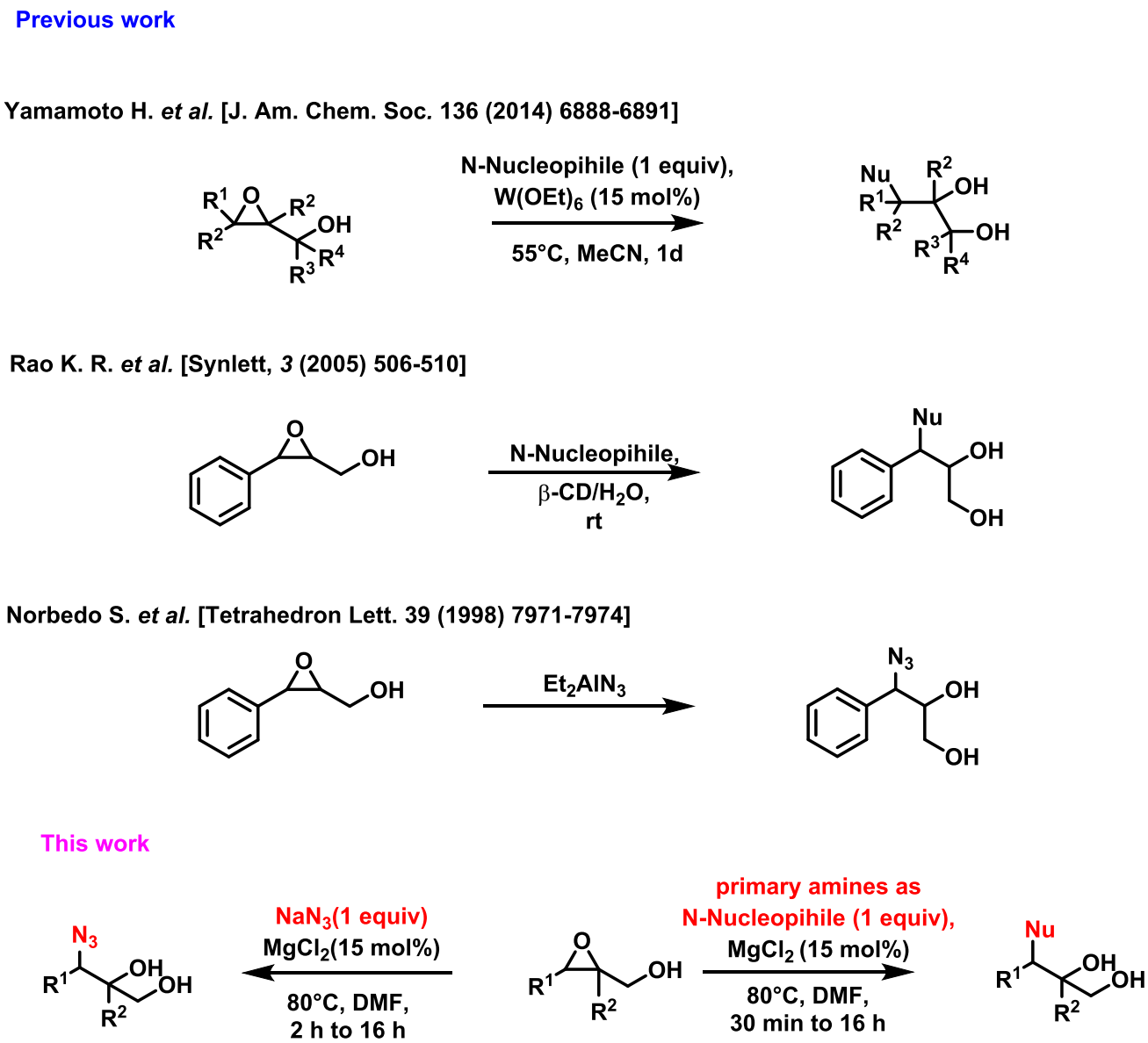


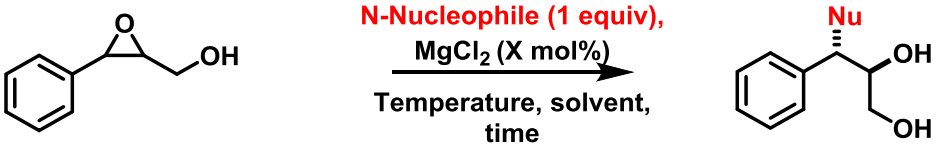
Scheme 1. Ring opening of 2,3 epoxy alchohol.

Results and discussion

In order to accomplish our deliberate approach for ring opening of 2,3-epoxy alcohols with both diverse organic *N*-Nucleophiles and sodium azide, we began our investigation using racemic trans (3-phenyloxiran-2-yl)methanol (**1a**) and aniline as standard substrates. Initially, the reaction of **1a** and aniline in the absence of $MgCl_2$ was carried out at room temperature for 8 h followed by heating at 80 °C for another 8 h in DMF as solvent but no ring-opening reaction occurred. Similarly, azidolysis of racemic *trans* (3-phenyloxiran-2-yl)methanol (**1a**) with sodium azide in absence of $MgCl_2$ was also not observed. Delightfully, when the reaction was performed with 10 mol% $MgCl_2$ at room temperature, *trans* (3-phenyloxiran-2-yl)methanol (**1a**) afforded 3-amino-1,2 diol (50% yield) and 3-azido-1,2 diol (45% yield) with Aniline and Sodium azide respectively as confirmed by ^1H and ^{13}C NMR. In order to enhance the product yield and rate of reaction, the reaction of *trans* (3-phenyloxiran-2-yl)methanol (**1a**) was performed at 80 °C with 15 mol% of $MgCl_2$ with Aniline and sodium azide separately which results in drastic change in conversion to desired product (entry 8 and 20 of table 1). Moreover, product yield was slightly reduced when amount of $MgCl_2$ increased from 15 mol% to 20 mol%. It indicated that 15 mol% of $MgCl_2$ was found to be sufficient for aminolysis and azidolysis. Next, a brief solvent screening was undertaken to explore the possibility of using various organic solvents for the reaction. Thus, the optimization studies were carried out using different organic solvents such as Acetonitrile (ACN), Dimethyl sulfoxide (DMSO) and Toluene. Among them, except DMSO, almost all the solvents were found to be admissible. Notably, the reaction in the presence of toluene and DMF were found to be most efficient solvents. Moreover, 15 mol% of $MgCl_2$ was found superior in Azidolysis of *trans* (3-phenyloxiran-2-yl)methanol (**1a**) as compared to known NH_4Cl reagent for Azidolysis (entry-19 of Table 1).

Using the set of optimized reaction conditions, the scope of this $MgCl_2$ catalyzed ring-opening reaction of various 2,3-epoxy alcohols with respect to different kinds of N- nucleophiles was explored as shown in Table 2. Firstly, disubstituted 2,3-epoxy alcohol was introduced with divergent N- nucleophiles under the optimized reaction conditions, and afforded the desired products in

Table 1
Optimization of the Reaction Conditions.



Entry	*N*-Nucleophile	X	solvent	Temperature[a]	Time (h)	Yield (%)[b]
1	Aniline	–	DMF	rt	8	NR
2	Aniline	–	DMF	**80**	8	NR
3	Sodium azide	–	DMF	rt	8	NR
4	Sodium azide	–	DMF	**80**	8	NR
5	Aniline	10	DMF	rt	3	50
6	Aniline	15	DMF	rt	3	65
7	Aniline	15	DMF	rt	16	71
8	**Aniline**	**15**	**DMF**	**80**	**0.5**	**93**
9	Aniline	20	DMF	80	0.5	89
10	Sodium azide	10	DMF	rt	4	45
11	**Sodium azide**	**15**	**DMF**	**80**	**2**	**90**
12	Sodium azide	20	DMF	80	2	85
13	Aniline	15	Toluene	80	0.5	88
14	Sodium azide	15	Toluene	80	2	84
15	Aniline	15	Acetonitrile	80	4	61
16	Sodium azide	15	Acetonitrile	80	4	58
17	Aniline	15	DMSO	80	4	35
18	Sodium azide	15	DMSO	80	4	30
19	Sodium azide	NH_4Cl (15 mol%)	DMF	80	16	70

[a]Temperature in Degree Celsius; [b]isolated yield as separated from PTLC; NR = No Reaction.

excellent yields (**2aa-2al**, **2b** and **2c**). Notably, the reaction with 4-(methylthio)aniline, 4-Aminobiphenyl, 3,4-(Methylenedioxy)aniline, and aniline provided the respective 3-amino-1,2 diols very smoothly. Additionally, the reaction was also carried out with 3,4-dimethoxyaniline, 2,6-dimethoxyaniline, 2,5-dimethylaniline, and benzyl amine to afford the corresponding product in excellent yields. Pleasingly, the reaction worked well with aniline having electron withdrawing at *para*- position and the desired product (**2ag**) was isolated in 70% yield. It is worth noting that, the heteroaryl 5-bromopyridin-2-amine underwent smooth transformation leading to product (**2ah**) in admirable yield (**68%**). The ring opening was smoothly carried out with most interesting 2-aminophenol as nucleophile and free hydroxyl group of 2-aminophenol was not interfering the epxide ring opening. Additionally, Regioselective C-3 ring opening for resulted compound **2al** was confirmed by ^{13}C–^{1}H heteronuclear long-range correlations (Fig. 1). Long-range correlation between H^a (δ = 3.24 ppm), H^b (δ = 4.68 ppm), H^c (δ = 5.06 ppm), H^e (δ = 4.48 ppm), H^f (δ = 5.48 ppm), and C_2 (δ = 74.13 ppm) along with the long-range correlation between H^b (δ = 4.68 ppm), H^c (δ = 5.06 ppm), H^d (δ = 3.88 ppm), and C_1 (δ = 63.30 ppm) supports the C-3 ring opening of epoxide. Here the possibility of regioselctive C-2 ring opening could be ignored because of observed long-range correlation between H^c (δ = 5.06 ppm), and C_1 (δ = 63.30 ppm) which would be feasible only in C-3 ring opening.

Interestingly, electron withdrawing group containing disubstited 2,3-epoxy alcohol (**1b**) was also reacted efficiently with sodium azide in presence of catalytic amount of $MgCl_2$ to afford the corresponding 3-azido-1,2 diol (**2b**) in 84% yield. Moreover, disubstited 2,3-epoxy alcohol with long aliphatic side chain (**1c**) was cleanly reacted with 4-(methylthio)aniline to furnish **2c** in 82% of yield.

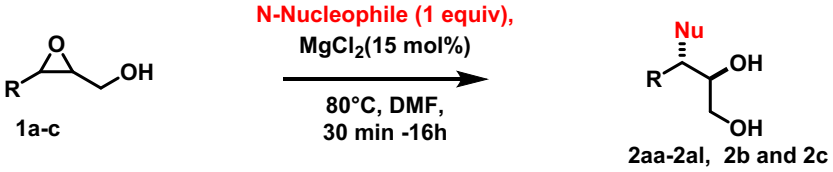
In the next phase of our investigation, more sterically hindered multifarious trisubstituted 2,3 epoxy alcohols were introduced and examined the scope of various N- nucleophiles under the optimized reaction conditions. It was observed that trisubstituted 2,3 epoxy alcohols (**1d-i**) underwent smoothly to Azidolysis for 3-azido-1,2 diols (**2d**, **2ec**, **2fa**, **2 g**, **2 h** and **2i**) and Aminolysis for the 3-azido-1,2 diols (**2ea, 2eb** and **2fb**) in reasonably good to excellent yields (Table 3). Epoxy ring of (2,3-diphenyloxiran-2-yl) methanol (**1e**) was successfully opened with aniline and benzyl amine as nucleophile through the optimized reaction to furnish 3-amino-1,2 diols (**2ea** and **2eb**) in admirable yields. Similarly, aniline opened the ring of more crowded (2-(naphthalen-1-yl)-3-(p-tolyl)oxiran-2-yl)methanol (**1f**) very gently to accomplish **2fb** in 72% yield.

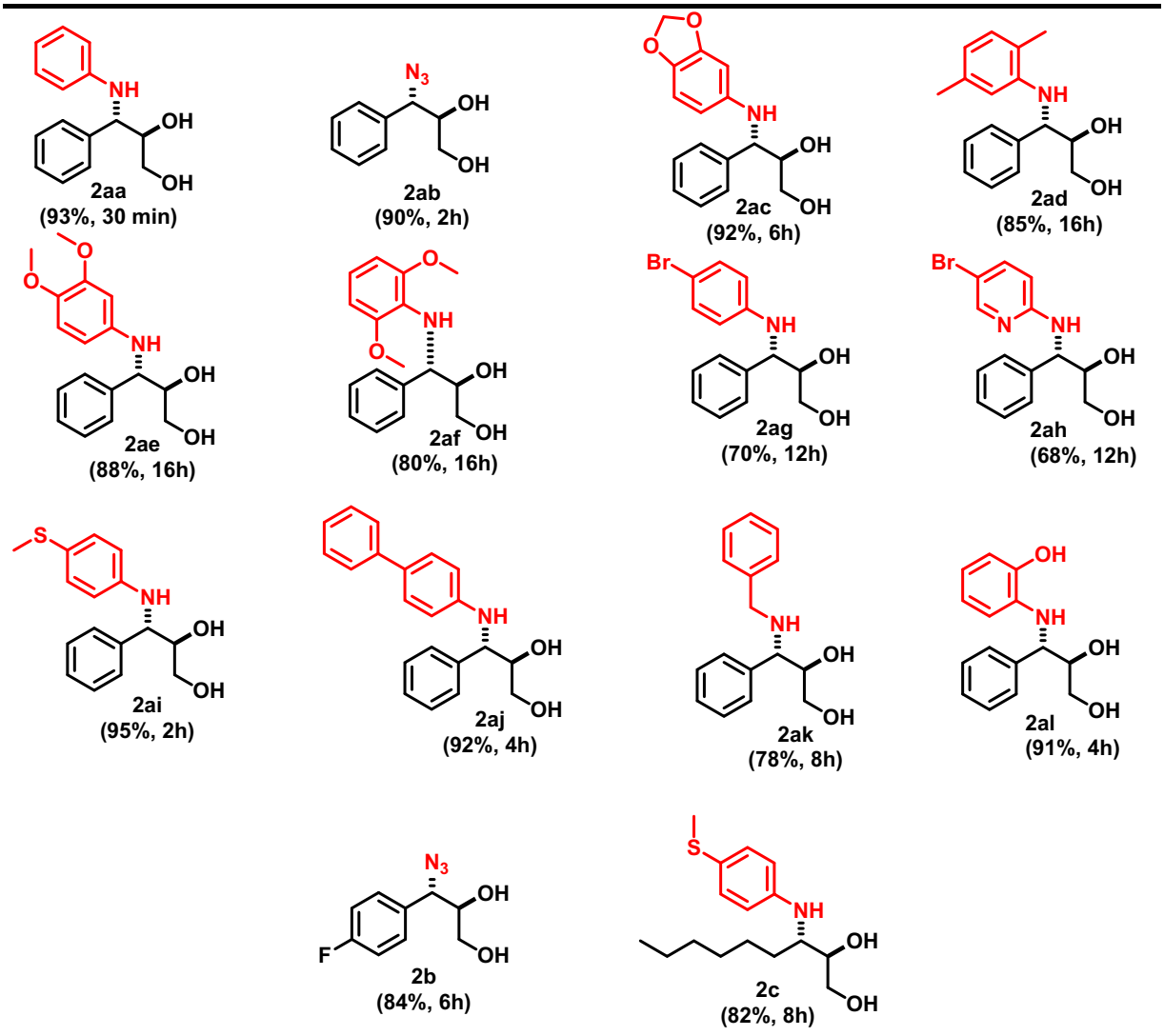
Finally, the optimized reaction was applied over commercially available enantiomerically pure (*S*)-(-) Glycidol. As a result, compounds **3** (89%) and **4** (85%) were synthesized successfully by using sodium azide and Aniline as *N*-nucleophile respectively (table 4).

Plausible Mechanism:

In general, when Lewis acid coordinates with oxirane oxygen, it was found that Lewis acid induces polarization of the oxirane C–C bond and enhances the electrophilicity of these two carbon atoms. In the consequence, nucleophilic [23,24] attack at epoxide ring was more accessible. In this study, the Mg coordinated with the epoxide oxygen [25] and the oxygen of hydroxyl group at C-1 carbon in a rigid, bidentate manner, which facilitated the ring opening of 2,3-epoxy alcohols with diverse N- Nucleophile (Scheme 2).

Table 2
Substrate scope for disubstituted 2,3-epoxy alcohols.[a,b,c]





[a]Reactions were performed on racemic 2,3-epoxy alcohols 1.0 equiv, anilines/sodium azide 1.0 equiv and 15 mol% $MgCl_2$ at 80 °C in DMF MeCN. [b]Yields were calculated after separation through manual column chromatography. [c] One regioisomer could be detected by ^1H NMR spectroscopy analysis.

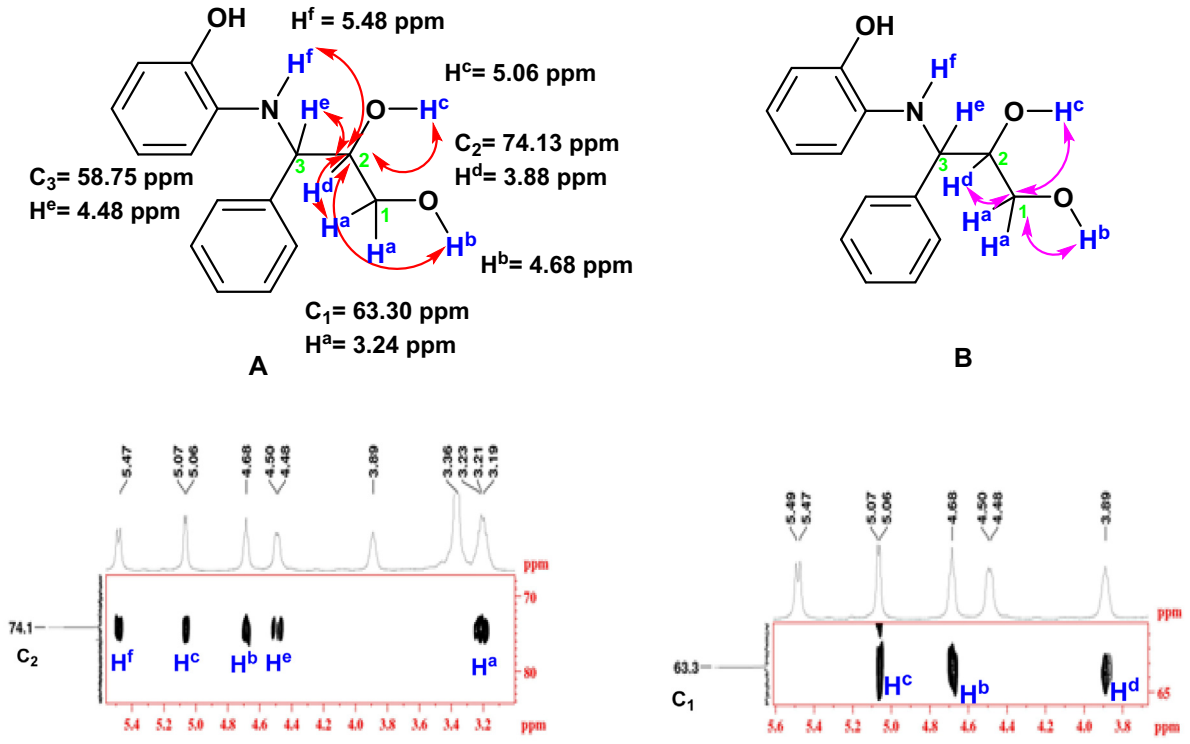
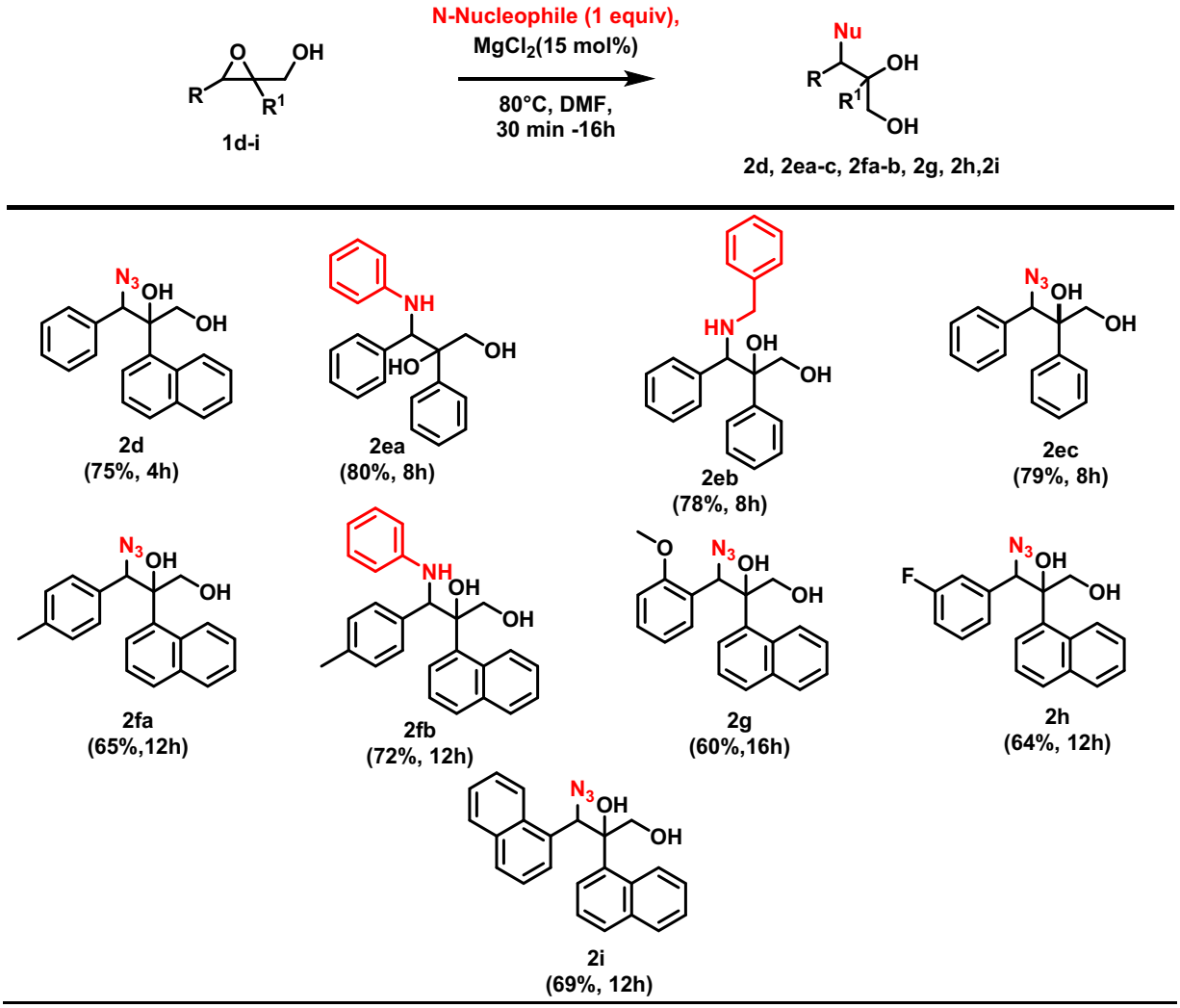


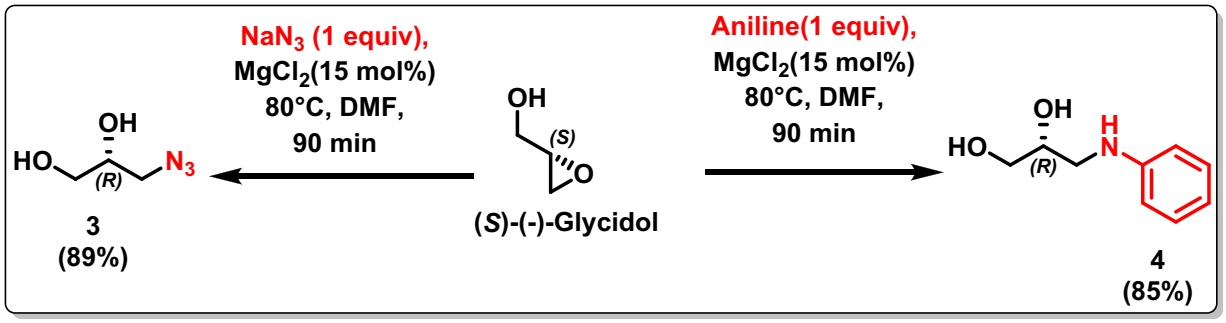
Fig. 1. (**A**) $^{13}C–^{1}H$ HMBC correlations of **2al** are shown between H^f, H^c, H^b, H^e and H^a with C_2; (**B**) $^{13}C–^{1}H$ HMBC correlations of **2al** are shown between H^c, H^b and H^d, with C_1.

Table 3
Substrate scope for disubstituted 2,3-epoxy alcohols.[a,b,c]



[a]Reactions were performed on Mixture of Cis/Trans racemic 2,3-epoxy alcohols 1.0 equiv, anilines/sodium azide 1.0 equiv and 15 mol% $MgCl_2$ at 80 °C in DMF MeCN. [b]Yields were calculated after separation through manual column chromatography. [c]One regioisomer could be detected by ^{1}H NMR spectroscopy analysis.

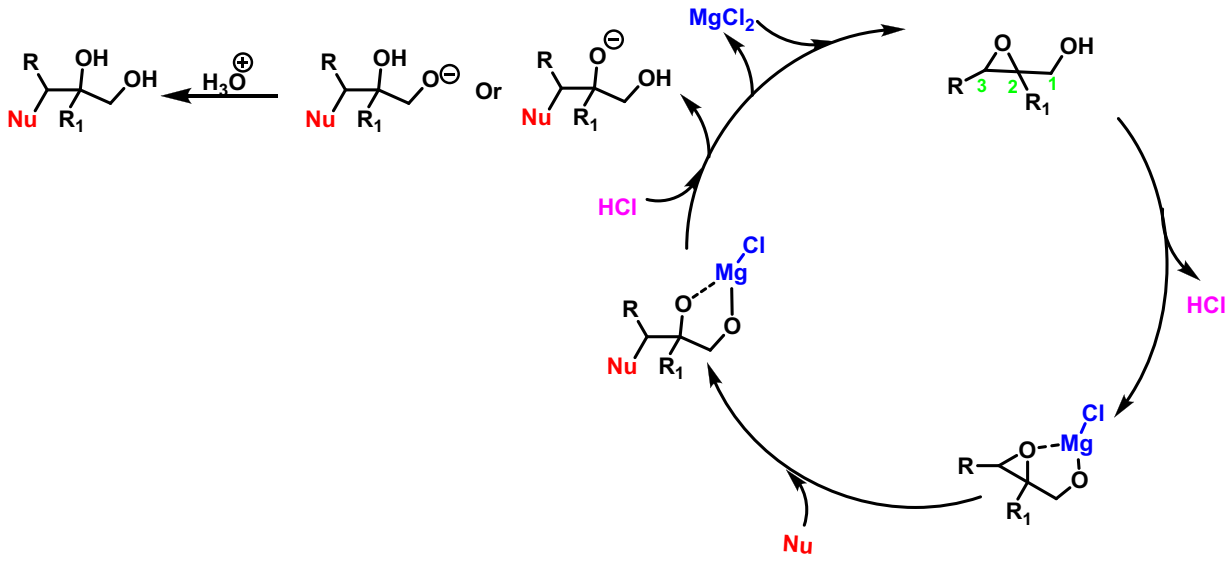
Table 4
Epoxide ring opening (*S*)-(-) Glycidol by NaN_3 and aniline[a].



[a]One regioisomer could be detected by ^{1}H NMR spectroscopy analysis.

Conclusion

In conclusion, we systematically studied the $MgCl_2$ catalyzed regioselective C-3 ring-opening reactions of various 2,3 epoxy alcohols. Only $MgCl_2$ in catalytic amount provides epoxide ring opening by both organic amines and sodium azide for facile access to 3-amino-1,2 diols and 3-azido-1,2 diols in good to excellent yields. Interestingly, this strategy was also found suitable for trisubstituted 2,3 epoxy alcohols to generate quaternary carbon containing 3-amino-1,2 diols. Application of this methodology towards synthesis of natural products having quaternary carbon is underway and will be reported elsewhere.



Scheme 2. Plausible Mechanism of Epoxide ring opening by N- Nucleophile.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153013.

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