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A Facile Epoxide Aminolysis Promoted by $(t\text{-BuO})_2Mg$ and Its Application to the Synthesis of Efinaconazole

Fuqiang Zhu,[†,⊥,‖] Yuanchao Xie,[‡,‖] Jian Zhang,[§] Guanghui Tian,[§] Hongjian Qin,[§] Xiaojun Yang,[§] Tianwen Hu,[§] Yang He,[‡] Haji A. Aisa,[*,†] and Jingshan Shen[*,‡]

†Key Laboratory of Plant Resources and Chemistry in Arid Regions, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, South Beijing Road 40–1, Urumqi, Xinjiang 830011, P. R. China.

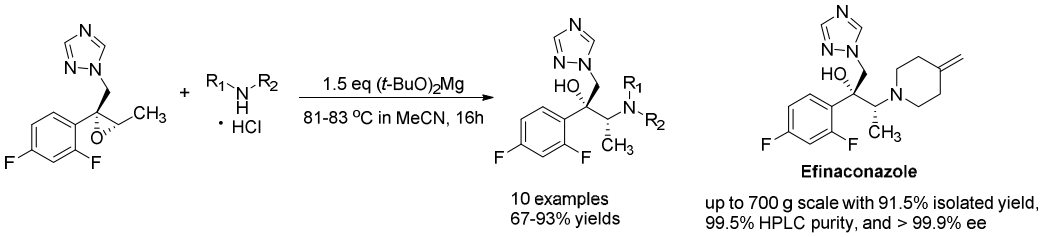
⊥University of Chinese Academy of Sciences，No.19A Yuquan Road, Beijing 100049, P. R. China.

§Topharman Shanghai Co., Ltd., Building 1, No.388 Jialilue Road, Zhangjiang Hitech Park, Shanghai 201209, P. R. China.

‡CAS Key Laboratory for Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China.

‖The first two authors contribute equally to this paper.

TOC:


1.5 eq (t-BuO)2Mg
81-83 °C in MeCN, 16h
10 examples
67-93% yields
Efinaconazole
up to 700 g scale with 91.5% isolated yield,
99.5% HPLC purity, and > 99.9% ee

ABSTRACT

A novel and efficient method for the aminolysis of trizole epoxide is described. This method consists of a facile ring opening of epoxides mediated by *t*-BuOMgCl generated in situ from hydrochloride of amines and $(t\text{-BuO})_2Mg$. The desired β-amino alcohol molecules were obtained in good yields without employing other heavy metals or precious catalysts. The optimized conditions were successfully applied to the synthesis of a number of potential triazole antifungal compounds, as well as efinaconazole up to 700 g scale.

Keywords: Epoxide aminolysis, Triazole, Magnesium *tert*-butoxide

INTRODUCTION

The β-amino alcohol moiety, is a popular structural component widely present in a variety of biologically active natural products,[1] active pharmaceutical ingredients (APIs)[2] and chiral auxiliaries or ligands used in asymmetric synthesis.[3] Since its versatile functionality and potential applications, a number of synthetic pathways have been well established to provide β-amino alcohol group in the past decades.[4] One of the best known and straight-forward method is the ring-opening reaction of epoxides with various amines.[5] However, in many cases, it would not proceed smoothly or even fail in the preparation of hindered β-amino alcohols. Large excess of materials and elevated temperature are frequently required, which likely resulted in undesired side reactions such as rearrangement or polymerization.

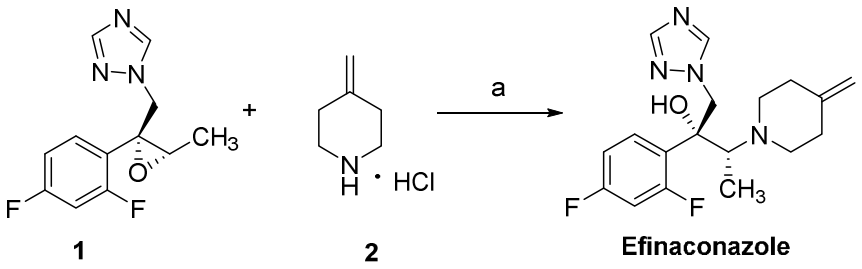
To address these issues, a lot of methods have been developed to promote epoxide aminolysis, such as the employment of Lewis acids,[6] microwave-assisted synthesis,[7] and performing these reactions in continuous-flow microreactors.[8] However, some of these methods are still associated with shortcomings like the use of dangerous perchlorate, toxic heavy metals and costly catalyst which greatly limited their practical application in pharmaceutical manufacturing. Therefore, developing a safe, efficient and inexpensive epoxide ammonolysis method is still highly desirable.

RESULTS AND DISCUSSION

Efinaconazole (trade name Jublia (R)), a new triazole antifungal drug, was

approved by FDA in 2014 for the topical treatment of mild to moderate toenail onychomycosis.[9] It has shown significant antifungal activity against dermatophytes, *Candida spp*. and nondermatophyte molds in a mechanism of inhibiting fungal lanosterol 14α-demethylase.[10] There are several routes established for the synthesis of efinaconazole,[11] but from an application perspective, the ring-opening reaction of epoxide **1** with piperidine hydrochloride **2** was believed to be the most efficient method, and also a suitable case for studying the reaction conditions for epoxide aminolysis (Scheme 1).

Scheme 1. Synthetic Route of Efinaconazole



1 **2**

Reagents and conditions: a. Additives, solvent, heating.

With the trisubstituted epoxide **1** and hindered piperdine **2,** it was estimated that the reaction would not go well if only classical procedure was utilized. This assumption was proved in our lab by performing the ring-opening reaction in the presence of stoichiometric amounts of bases. As shown in Table 1, the reactions generally proceeded sluggishly in most of entries, and satisfactory results did not arise with varying types of bases and equivalents of piperidine **2**. A 44% isolated yield of this reaction was reported using similar conditions in a literature, in which microwave irradiation was employed to solve this problem, affording 90% yield.[11b] The adjacent trizole group, a electron-withdrawing group, facilitated the arrangement of epoxide **1** under basic conditions, leading to the formation of the main side product **3.**[12] The initial reaction results confirmed that this transformation was troublesome due to the low activity of the two substrates.

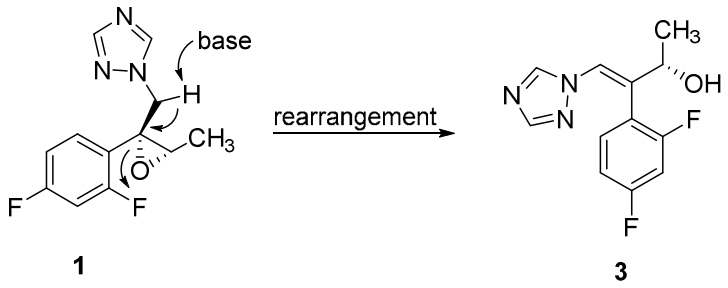
Table 1 Initial Screening Results of the Aminolysis of Epoxide 1[a]

Entry	Equiv of **2**	Base (equiv)	Conversion [b] (%)	Yield [c] (%)

1	1.5	LiOH (2.0)	76.5	63.8
2	1.5	NaOH (2.0)	46.8	30.5
3	1.5	KOH (2.0)	54.2	32.9
4	3.0	K_2CO_3 (3.0)	26.1	18.7
5	3.0	*t*-BuONa (3.5)	66.2	40.8
6	2.0	TEA (2.5)	< 10	< 10

[a]Conditions: Epoxide **1** at 5 g scale. All reactions were performed by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] Conversion was calculated from the HPLC area. [c] The yield of efinaconazole was determined by HPLC area in reaction mixture.

Scheme 2. Formation of Impurity 3



1 **3**

Many studies have showed that the ring opening reaction of epoxides could be promoted by various lithium salts, such as LiOH,[13a, b] LiBr,[11f, 13c] Li_2CO_3[11d] and $LiClO_4$.[13d] In Table 1, we also noted that moderate conversion and yield was achieved in the presence of lithium hydroxide (entry 1), which was the present perfect conditions. This improvement may be rationalized by coordination of the epoxy oxygen with the metal center, and thereby greatly facilitating the epoxide aminolysis with 4-methylenepiperidine. Accordingly, we considered other metal salts would also promote this reaction by the way of coordination.

For the purpose of seeking better catalysts, a broad screen of possible alternatives was initiated from economical and readily available metal salts, including series of Li, Fe, Cu, Mg, Co, Mn, Zn, most of which have been well documented in the literature to promote ring-opening reactions.[6] The screening results were illustrated in Table 2,

showing the conversion rate of triazole epoxide **1** and the yield of efinaconazol. Notably, all the reactions proceeded in favor of forming C-3-regioisomer of the epoxy triazole, rather than C-2-regioisomer.

A survey of 11 catalysts revealed that the reactions were significantly influenced by the nature of Lewis acidic metal salt. As shown in Table 2, except Li and Mg salts (Entries 1-4), most of the others gave poor conversion or significantly resulted in the byproduct of allylic alcohol **3**. For $FeCl_3$ (Entry 6), $ZnCl_2$ (Entry 9) and $MnCl_2$ (Entry 10), only trace product was observed. The use of $Al(OTf)_3$ (Entry 5), $Cu(OTf)_2$ (Entry 7), $CoCl_2$ (Entry 8) and Ti(O-*i*-Pr)$_4$ (Entry 11) gave low conversion. Moderate conversion and yields were obtained with Li-series (Entry 1 and 2). To our delight, the combination of $MgCl_2$ and DIPEA gave better results with 85.3% conversion and 78.8% yield (Entry 3 and 4).[14] Indeed, some magnesium salts, such as $Mg(ClO_4)_2$, EtMgBr, and $MgBr_2$ have also been reported to catalyze the epoxide aminolysis.[15] As a readily available inorganic salt, $MgCl_2$ remarkably improve the reaction, so we were encouraged to search for more effective and selective magnesium salts.

Table 2. Lewis Acids Promoted Ring Opening of Epoxide 1 with 4-Methylenepiperidine Hydrochloride 2[a]

Entry	Base (equiv)	Lewis acid (equiv)	Conversion [b] (%)	Yield [c] (%)
1	TEA (2.5)	LiCl (2.0)	68.5	62.7
2	*t*-BuONa (2.0)	LiBr (1.5)	75.4	63.5
3	Py (2.5)	$MgCl_2$ (2.0)	77.5	72.2
4	DIPEA (2.0)	$MgCl_2$ (1.5)	85.3	78.8
5	TEA (2.5)	$Al(OTf)_3$ (0.2)	20.3	15.5
6	TEA (2.0)	$FeCl_3$ (1.0)	< 10	–
7	$NaHCO_3$ (1.5)	$Cu(OTf)_2$ (0.2)	45.6	30.6
8	TEA (2.0)	$CoCl_2$ (1.5)	38.1	32.7
9	TEA (2.0)	$ZnCl_2$ (1.5)	< 10	–
10	$NaHCO_3$ (1.5)	$MnCl_2$ (0.5)	< 10	–
11	TEA (2.0)	Ti(O-*i*-Pr)$_4$ (0.2)	56.9	38.3

[a] Conditions: All reactions were performed as a molar ratios of **1** and **2** with 1:1.5 at 5 g scale by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] Conversion was calculated from the HPLC area. [c] The yield of efinaconazole was determined by HPLC area in reaction mixture.

Based on above reaction result, magnesium cation was thought to be favorable to promote the reaction by coordinating with the epoxide oxgen, and thereafter, various magnesium compounds were attempted for studying the reaction (Table 3). The use of $Mg(OH)_2$ or $MgCO_3$ gave disappointing results due to their poor solubility (Entry 1 and 2). Combination of $MgCl_2$ with various alkaline metals did not display beneficial effect too (Entry 3–8), compared with the above mentioned condition, DIPEA/$MgCl_2$ (Entry 4, Table 2). The addition of *t*-BuOK provided high conversion, but a large amount of allylic alcohol **3** was formed. A slight increase in yield was observed in the presence of $(MeO)_2Mg$ and $(EtO)_2Mg$ (Entry 9 and 10). To our delight, the use of $(t\text{-BuO})_2Mg$ afforded a 99.4% conversion and 96.1% yield, with no formation of byproduct **3** (Entry 11). However, when in conjunction with LiCl, the yield was reduced to 76.8% (Entry 12). In a recent example, $(t\text{-BuO})_2Mg$ was utilized as a weak Lewis acid to participate intramolecular ring-opening reaction of 2,3-epoxy alcohols with high regioselectivity.[16] .

Table 3. Mg-salts Promoted Aminolysis of Epoxide 1 with 4-Methylenepiperidine Hydrochloride 2[a]

Entry	Base (equiv)	Additives (equiv)	Conversion [b] (%)	Yield [c] (%)
1	$Mg(OH)_2$ (2.0)	/	< 10	–
2	$MgCO_3$ (2.0)	/	< 10	–
3	NaOH (1.5)	$MgCl_2$ (1.0)	59.3	33.5
4	K_2CO_3 (1.0)	$MgCl_2$ (1.0)	49.7	38.9
5	Na_2CO_3 (1.0)	$MgCl_2$(1.0)	32.7	26.8
6	*t*-BuOK (1.5)	$MgCl_2$ (1.5)	96.4	22.7
7	*t*-BuONa (1.5)	$MgCl_2$ (1.5)	82.3	59.1

8	*t*-BuOLi (1.5)	$MgCl_2$ (1.5)	79.6	25.3
9	$(MeO)_2Mg$ (2.0)	/	68.2	59.3
10	$(EtO)_2Mg$ (2.0)	/	72.1	62.5
11	$(t\text{-BuO})_2Mg$ (2.0)	/	99.7	96.1
12	$(t\text{-BuO})_2Mg$ (2.0)	LiCl (1.0)	86.6	76.8

[a] Conditions: All reactions were performed as a molar ratio of **1** and **2** with 1:1.5 at 5 g scale by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] Conversion was calculated from the HPLC area. [c] The yield of efinaconazole was determined by HPLC area in reaction mixture.

The high yield of the reaction using $(t\text{-BuO})_2Mg$ led us to investigate the other reaction parameters. A solvent survey (MeCN, THF, *t*-BuOH and toluene) indicated that MeCN was optimal in aspects of the yield and impurities (Table 4). With THF in place of MeCN, the reaction gave poor conversion. For *t*-BuOH, the triazole epoxide **1** disappeared almost completely, but, about 10% of byproduct **3** was formed. The sluggish reaction in toluene might be explained by the low solubility of $(t\text{-BuO})_2Mg$.

Table 4. The Results of Solvents Screening[a]

Entry	Solvents	Conversion [b] (%)	By-product **3** [b] (%)	Yield [c] (%)
1	MeCN	99.5	< 0.1	96.2
2	THF	35.2	3.6	30.8
3	*t*-BuOH	99.2	10.3	86.2
4	Toluene	< 10	–	–

[a] Conditions: All reactions were performed as a molar ratio of **1, 2** and $(t\text{-BuO})_2Mg$ with 1:1.5:1.5 at 5 g scale by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] Conversion was calculated from the HPLC area. [c] The yield of efinaconazole was determined by HPLC area in reaction mixture.

While the equivalent of $(t\text{-BuO})_2Mg$ was decreased to 1.5 equiv from 2.0 equiv, a 99.5% conversion was still achieved without the need of extending reaction time. A further reduction to 1.2 equiv led to incomplete reaction, even though the aging time

was extended 24 h. Therefore, 1.5 equiv was thought to be the optimal equivalent. Using the optimized conditions, efinaconazol was synthesized from epoxide **1** and piperidine **2** in 88.5% isolated yield, 99.5% HPLC purity, and > 99.9% ee at a 700 g scale. Compared with the existing epoxide ring–opening regents, such as LiOH,[13a, b] $MgCl_2$/DIPEA[14] and $LiClO_4$, [13d] the choice of $(t\text{-BuO})_2Mg$ gave a higher yield and dispelled safety concern.

Remarkably, the using of $(t\text{-BuO})_2Mg$ for epoxide aminolysis has not been previously reported to our knowledge. To understand the detailed process, several control experiments were performed and the results were summarized in Table 5. When the free base of 4-methylenepiperidine was used in place of the hydrochloride (entries 1-4), incomplete conversion and low yield were observed in the presence of $(t\text{-BuO})_2Mg$, $MgCl_2$, $MgBr_2$ or $(t\text{-BuO})_2Mg/MgCl_2$,. These results indicated that the actually optimal activator was not likely the $(t\text{-BuO})_2Mg$ or $MgCl_2$. It was also notable that reduction of $(t\text{-BuO})_2Mg$ equivalent from 1.5 equiv to 0.75 equiv resulted in significant lower conversion. This visible difference related to the quantity of $(t\text{-BuO})_2Mg$ was probably attributed to the different components of magnesium salts existing in the reaction system. With the same equivalent of compound 2 and $(t\text{-BuO})_2Mg$ (Entry 4), *t*-BuOMgCl was mainly formed; however, the main product was changed to $MgCl_2$ while a 2:1 molar ratio of **2** and $(t\text{-BuO})_2Mg$ was employed (Scheme 3). Therefore, we concluded that *t*-BuOMgCl generated in situ was the real mediator that contributed to the efficient aminolysis.

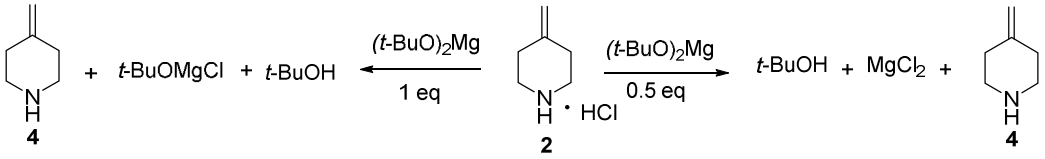
Table 5. Control Epoxide Aminolysis of 1 Promoted by Mg-salts

Entry	Form of **2**	Additive (equiv)	Conversion [b] (%)	Yield [c] (%)
1	base	$(t\text{-BuO})_2Mg$ (1.5)	52.2	45.2
2	base	$MgCl_2$ (1.5)	89.2	61.4
3	base	$MgBr_2$ (1.5)	83.5	58.7
4	base	$(t\text{-BuO})_2Mg$ (1.0) and $MgCl_2$ (0.5)	79.4	76.8
5	hydrochloride	$(t\text{-BuO})_2Mg$ (1.5)	99.5	96.3

6	hydrochloride	$(t\text{-BuO})_2Mg$ (0.75)	81.8	76.4

[a] Conditions: All reactions were performed as a molar ratio of **1** and **2** with 1:1.5 at 5 g scale by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] Conversion was calculated from the HPLC area. [c] The yield of efinaconazole was determined by HPLC area in reaction mixture.

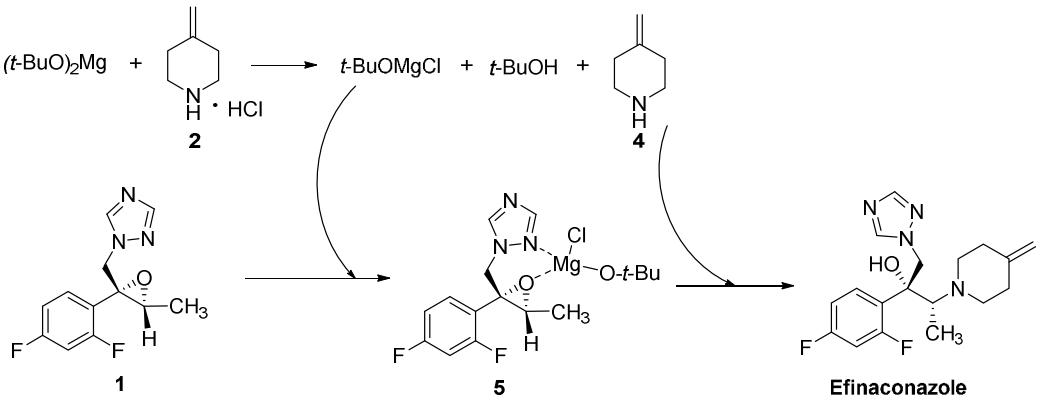
Scheme 3. Different Magnesium Salts Generated by $(t\text{-BuO})_2Mg$



To the best of our knowledge, this is the first report on the chemistry of *t*-BuOMgCl, which greatly facilitated the epoxide aminolysis. Despite the deficiency of physicochemical data of *t*-BuOMgCl, it would be defined as a weaker Lewis acid than $MgCl_2$, yet stronger than $(t\text{-BuO})_2Mg$ through the judgment of electronegativity of oxygen and chlorine. The overall catalytic activity of these three magnesium reagents were found to be in the order *t*-BuOMgCl > $MgCl_2$ > $(t\text{-BuO})_2Mg$ (Entry 1, 2 and 5, Table 4) that was not parallel with their acidity.

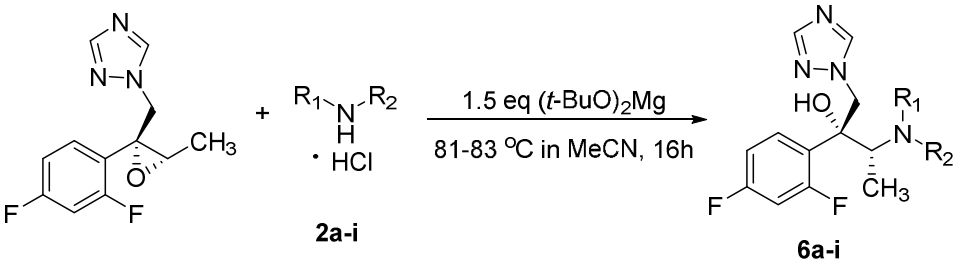
It was generally thought that the coordination of a Lewis acid with the oxirane oxygen would induce polarization of the oxirane C−C bond and increase the electrophilicity of these two carbon atoms. As a result, the epoxide ring was more accessible to be attacked by a nucleophile.[17] In the present study, the Mg cation coordinated with the epoxide oxygen and the trizole nitrogen in a rigid, bidentate manner, which facilitated the ring opening with 4-methylenepiperidine. The suggested role of magnesium *t*-butoxide chloride in the process was depicted in Schemes 4.

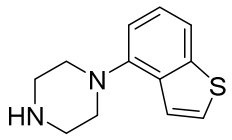
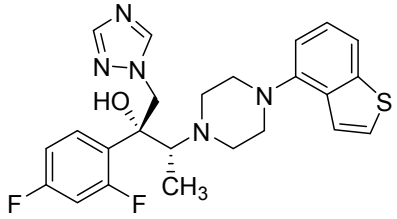
Scheme 4. Plausible Mechanism of the Epoxide 1 Aminolysis

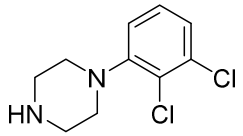
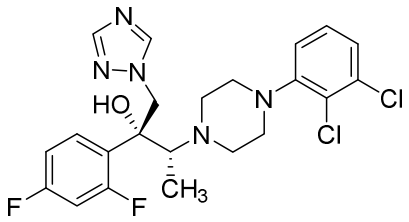
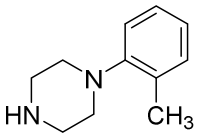
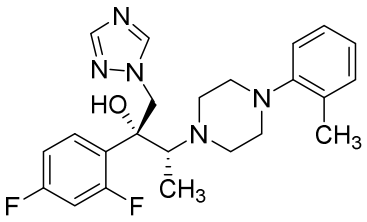
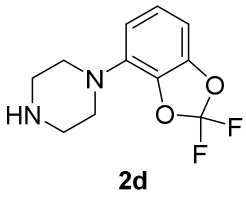
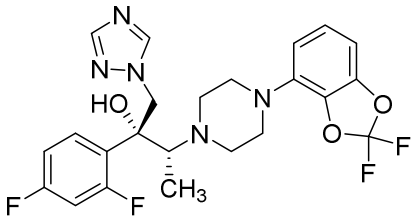
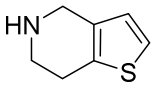
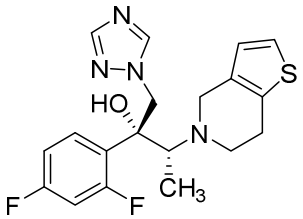
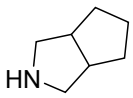
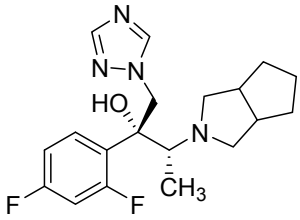
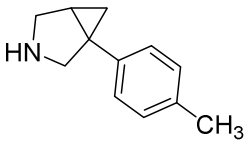
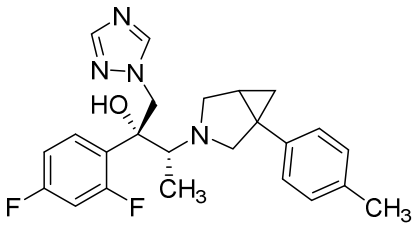


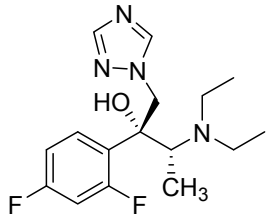
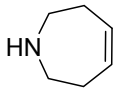
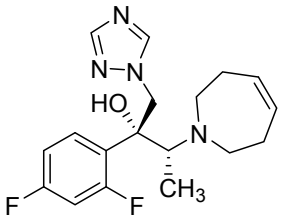
Further, we examined the scope of this method by reacting epoxide **1** with different aliphatic amines. As was showed in Table 6, *N*-aryl substituted piperazines afforded the 2-amino alcohols in good yields (entry 1−4), as well as the piperidine fused thiophene (entry 5). Similar results were observed for the pyrrole 2f (entry 6), diethylamine 2h (entry 8) or azepine 2i (entry 9), but 2g (entry 7) resulted in a relative lower yield.

Table 6. (*t*-BuO)$_2$Mg-Promoted Epoxide Ring-Opening Reaction of 1 with Various Aliphatic Amine Hydrochloride [a]



Entry	Amine	Product[b]	Yield[c] (%)
1	 **2a**	 **6a**	86

2	 **2b**	 **6b**	73
3	 **2c**	 **6c**	79
4	 **2d**	 **6d**	81
5	 **2e**	 **6e**	93
6	 **2f**	 **6f**	91
7	 **2g**	 **6g**	77

8	 **2h**	 **6h**	88
9	 **2i**	 **6i**	90

[a] Conditions: All reactions were performed as a molar ratio of **1** and amines hydrochloride with 1:1.5 at 200 mg scale by refluxing for 16 h in acetonitrile under a nitrogen atmosphere. [b] The products were characterized by ^{1}H, ^{13}C NMR, and ESI-MS. [c] Isolated yield of the corresponding epoxide aminolysis.

CONCLUSION

The development of a novel and efficient method of triazole epoxide ring opening with amines to form β-amino alcohols has been described, and $(t\text{-BuO})_2Mg$ was found to be a highly efficient reagent with the advantage of high yields, readily commercially available and low toxicit.[18] This method was demonstrated by applying it to the ring opening with a number of amines, including the synthesis of efinaconazole. Moreover, the method will be contributed to synthesize new triazole compounds with potential antifungal activity. Meanwhile, the expanding to other types of epoxides will also be studied.

EXPERIMENTAL SECTION

General Method. All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise noted. All commercially available material and solvents were used directly without further purification. Yields reported are for isolated, spectroscopically pure compounds. ^{1}H NMR (400 MHz), ^{13}C NMR (100

MHz) were recorded with a Bruker spectrometer using TMS as internal standard. The ESI mass spectra were determined on a THERMO LTQ spectrometer. HPLC conditions for efinaconazole: column: C18 (3.5 μm, 100 mm × 4.6 mm); flow rate: 1.0 mL/min; and detection at 210 nm; injection vol: 20 μL; gradient elution from 83:17 A/B to 30:70 A/B over 50 min. Mobile phase A: 0.01 mol/L KH_2PO_4-K_3PO_4/MeOH, 92:8. Mobile phase B: acetonitrile. Run time: 55 min. Temperature: 30 °C.

Representative Experimental Procedure for (t-BuO)$_2$Mg-Promoted Epoxide Aminolysis To a 25 mL round-bottom flask with a magnetic stir bar were charged epoxide **1** (500 mg), acetonitrile (10 mL), amine hydrochloride and (t-BuO)$_2$Mg (1.5 mol equiv to epoxide **1**) under nitrogen. The reaction mixture was heated and stirred under reflux for 16 h. Then the mixture was concentrated under vacuum and the residual was poured into water and extracted with dichloromethane. The organic phase was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give the crude material. The amino alcohols 6a to 6k were isolated by column chromatography on silica gel using *n*-heptane/acetone (5:1–10:1, v/v) or dichloromethane/methanol (50:1–20:1, v/v) as eluents.

6a. White solid, 256 mg, 86% yield. Mp: 74.9−75.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01 (s, 1 H), 7.81 (s, 1 H), 7.59–7.49 (m, 2 H), 7.40 (s, 2 H), 7.32–7.30 (m, 1 H), 6.92 (d, J = 7.6 Hz, 1 H), 6.81–6.74 (m, 2 H), 5.38 (brs, 1 H), 5.00 (d, J = 14.4 Hz, 1 H), 4.90 (d, J = 14.4 Hz, 1 H), 3.19 (brs, 4H), 3.07–3.04 (m, 3 H), 2.71–2.65 (m, 2 H), 1.08 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.66, 161.67 (dd, J = 199.2, 9.8 Hz), 159.49, 157.46 (dd, J = 194.7, 8.8 Hz), 151.55, 148.31, 144.35, 141.16, 134.05, 130.86–130.74 (m), 125.06, 125.01, 124.79–124.68 (m), 121.82, 117.13, 112.18, 111.66–111.47 (m), 104.37–103.94 (m), 78.46 (d, J = 4.4 Hz), 64.17, 55.96 (d, J = 6.6 Hz), 52.66 (d, J = 12.8 Hz), 30.95, 7.44; MS (ESI): m/z = 470.4 $[M + H]^+$; HRMS (ESI): Calcd for $C_{24}H_{25}F_2N_5OS$ $[M + H]^+$ 470.1826, Found 470.1830.

6b. Isolated as an oil, 280 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):7.98 (s, 1 H), 7.80 (s, 1 H), 7.50–7.48 (m, 1 H), 7.17–7.15 (m, 2 H), 6.97–6.95 (m, 1 H), 6.80–6.73 (m, 2 H), 5.22 (s, 1 H), 4.97 (d, J = 14.8 Hz, 1 H), 4.88 (d, J = 14.8 Hz, 1

H), 3.06–2.98 (m, 7 H), 2.64–2.61 (m, 2 H), 1.03–1.01 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.64, 161.65 (dd, J = 198.7, 10.7 Hz), 159.37, 157.42 (dd, J = 195.2, 9.0 Hz), 151.59, 151.15, 144.30, 134.06, 130.83–130.70 (m), 127.50, 127.45, 124.81–124.70 (m), 124.65, 111.64–111.45 (m), 104.35–103.93 (m), 78.53 (d, J = 4.5 Hz), 64.13, 55.97 (d, J = 5.9 Hz), 51.88, 30.94, 7.43; MS (ESI): m/z = 482.3 $[M + H]^+$; HRMS (ESI): Calcd for $C_{22}H_{23}Cl_2F_2N_5O$ $[M + H]^+$ 482.1326, Found 482.1332.

6c: Isolated as an oil, 268 mg, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1 H), 7.85 (s, 1 H), 7.54–7.50 (m, 1 H), 7.20–7.17 (m, 2 H), 7.05–6.98 (m, 2 H), 6.82–6.73 (m, 2 H), 5.37 (s, 1 H), 4.98 (d, J = 14.4 Hz, 1 H), 4.88 (d, J = 14.8 Hz, 1 H), 3.01–2.94 (m, 7 H), 2.59–2.56 (m, 2 H), 2.30 (s, 3 H), 1.06–1.04 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.63, 161.65 (dd, J = 198.3, 9.2 Hz), 159.49, 157.53 (dd, J = 196.4, 9.6 Hz), 151.49, 151.36, 144.39, 132.56, 131.10, 130.90–130.78 (m), 126.59, 124.84–124.70 (m), 123.20, 118.94, 111.61–111.43 (m), 104.35–103.92 (m), 78.25 (d, J = 4.4 Hz), 64.18, 55.97 (d, J = 5.9 Hz), 52.28, 30.94, 17.90, 7.52; MS (ESI): m/z = 428.4 $[M + H]^+$; HRMS (ESI): Calcd for $C_{23}H_{27}F_2N_5O$ $[M + H]^+$ 428.2262, Found 428.2264.

6d. Isolated as an oil, 318 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (s, 1H), 7.81 (s, 1H), 7.52–7.46 (m, 1H), 7.02 (t, J = 8.3 Hz, 1H), 6.83–6.75 (m, 2H), 6.69 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 5.20 (s, 1H), 4.95–6.86 (m, 2H), 3.11–3.14 (m, 4H), 3.03–2.98 (m, 3H), 2.65–2.63 (m, 2H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.68, 161.69 (dd, J = 198.5, 9.4 Hz), 159.37, 157.36 (dd, J = 195.1, 8.5 Hz), 151.55, 144.54, 144.35, 135.79, 133.66, 131.14, 130.79–130.66 (m), 124.69 (d, J = 12.6 Hz), 124.06, 111.70–111.52 (m), 104.39–103.96 (m), 102.00, 78.62 (d, J = 4.4 Hz), 64.22, 56.01 (d, J = 4.9 Hz), 49.44, 29.28, 7.22; MS (ESI): m/z = 494.4 $[M + H]^+$; HRMS (ESI): Calcd for $C_{23}H_{23}F_4N_5O_3$ $[M + H]^+$ 494.1815, Found 494.1820.

6e. Isolated as an oil, 287 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):7.98 (s, 1 H), 7.79 (s, 1 H), 7.55–7.49 (m, 1 H), 7.11 (d, J = 5.1 Hz, 1 H), 6.83–6.74 (m, 3 H), 5.29 (brs, 1 H), 4.96 (d, J = 14.4 Hz, 1 H), 4.87 (d, J = 14.8 Hz, 1 H), 3.89 (d, J = 14.4 Hz, 1 H), 3.64 (d, J = 14.0 Hz, 1 H), 3.20–3.13 (m, 2 H), 2.90–2.83 (m, 2 H),

2.61 (br. s., 1 H), 1.05 (m, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.13, 161.17 (dd, J = 195.6, 9.8 Hz), 159.91, 157.96 (dd, J = 195.0, 9.2 Hz), 150.93, 145.16, 135.28, 133.62, 130.74–130.61 (m), 126.27, 126.25–126.01 (m), 123.11, 111.30–111.13 (m), 104.54–104.10 (m), 79.25 (d, J = 5.6 Hz), 63.11 (d, J = 2.7 Hz), 56.23 (d, J = 4.3 Hz), 51.46, 47.80 (d, J = 9.9 Hz), 26.13, 7.71; MS (ESI): m/z = 391.3 $[M + H]^+$; HRMS (ESI): Calcd for $C_{19}H_{20}F_2N_4OS$ $[M + H]^+$ 391.1404, Found 391.1397.

6f. White solid as a mixture of diastereoisomer at cyclopropyl position, 262 mg, 91% yield. Mp: 72.5−73.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1 H), 7.78 (s, 1 H), 7.51–7.47 (m, 1 H), 6.82–6.72 (m, 2 H), 5.51 (s, 1 H), 4.86–4.77 (m, 2 H), 3.14–3.12 (m, 1 H), 2.74–2.70 (m, 1 H), 2.57–2.42 (m, 3 H), 2.32–2.26 (m, 2 H), 1.80–1.62 (m, 3 H), 1.49–1.32 (m, 3 H), 0.93–0.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.57, 161.59, (dd, J = 198.4, 9.9Hz), 159.69, 157.73 (dd, J = 195.7, 9.5 Hz), 151.24, 144.37, 131.05–130.93 (m), 124.51–124.38 (m), 111.46–111.28 (m), 104.18–103.75 (m), 77.84 (d, J = 4.5 Hz), 59.01, 58.48, 55.99 (d, J = 6.0 Hz), 55.75, 41.91, 41.33, 33.85, 33.62, 26.84, 7.18 (d, J = 2.7 Hz); MS (ESI): m/z = 363.3 $[M + H]^+$; HRMS (ESI): Calcd for $C_{19}H_{24}F_2N_4O$ $[M + H]^+$ 363.1996, Found 363.1997.

6g. White solid, 266 mg, 77% yield. Mp: 49.6−54.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94 (s, 1 H), 7.79 (s, 1 H), 7.47–7.44 (m, 1 H), 7.13–7.05 (m, 4 H), 6.80–6.71 (m, 2 H), 4.95 (brs, 1 H), 4.85 (m, 2 H), 3.32–3.20 (m, 2 H), 3.12–2.93 (m, 3 H), 2.34 (s, 3 H), 1.71–1.70 (m, 1 H), 1.37–1.35 (m, 1 H), 0.91–0.90 (m, 3 H), 0.86–0.83 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.56–161.49 (m), 159.32–157.24 (m), 151.64 (d, J = 3.2 Hz), 144.13, (d, J = 2.6 Hz), 139.81, 139.57, 135.44, 130.78 (d, J = 5.3 Hz), 129.02 (d, J = 3.5 Hz), 126.43 (d, J = 7.3 Hz), 124.84–124.73 (m), 111.57 (d, J = 15.9 Hz), 104.20–103.77 (m), 79.25 (d, J = 4.3 Hz), 79.11 (d, J = 4.3 Hz), 58.83–58.34 (m), 56.07–55.15 (m), 51.18, 47.33, 31.02, 29.03, 24.99, 24.38–23.07 (m), 20.98, 17.03, 16.96, 7.27 (d, J = 3.2 Hz); MS (ESI): m/z = 425.4 $[M + H]^+$. HRMS (ESI): Calcd for $C_{24}H_{26}F_2N_4O$ $[M + H]^+$ 425.2153, Found 425.2154.

6h. White solid, 227 mg, 88% yield. Mp: 61.0−62.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H), 7.82 (s, 1H), 7.61–7.55 (m, 1H), 6.85–6.74 (m, 2H), 5.87 (brs, 1H), 4.93 (d, J = 14.4 Hz, 1H), 4.67 (d, J = 14.4 Hz, 1H), 2.94–2.89 (m, 1H), 2.28–2.22 (m, 4H), 1.03–0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.63, 161.65 (dd, J = 197.4, 8.9 Hz), 161.55,157.86 (dd, J = 195.9, 9.3 Hz), 151.17, 144.86, 130.93–130.80 (m), 124.90 (dd, J = 8.1 Hz), 111.44–111.26 (m), 104.33–103.90 (m), 76.26 (d, J = 4.2 Hz), 59.28, 55.61 (d, J = 6.1 Hz), 44.41 (d, J = 8.4 Hz), 13.81, 7.98 (d, J = 4.5 Hz); MS (ESI): m/z = 325.3 $[M + H]^+$; HRMS (ESI): Calcd for $C_{16}H_{22}F_2N_4O$ $[M + H]^+$ 325.1840, Found 325.1827.

6i. Isolated as an oil, 249 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (s, 1H), 7.80 (s, 1H), 7.59–7.53 (m, 1H), 6.84–6.74 (m, 2H), 5.79 (brs, 2H), 4.98–4.80(m, 2H), 2.95–2.92 (m, 2H), 2.68–2.65 (m, 1H), 2.36–2.20 (m, 4H), 1.77–1.63 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.61, 161.63 (dd, J = 198.3, 9.8 Hz), 159.59, 157.63 (dd, J = 195.2, 9.1 Hz), 151.09 (d, J = 6.3 Hz), 144.55, 132.51, 131.20–130.86 (m), 129.03, 124.59 (d, J = 2.7 Hz), 111.48–111.20 (m), 104.24–103.89 (m), 77.27 (d, J = 4.2 Hz), 67.38, 56.03–55.76 (m), 30.56, 27.19, 8.56 (d, J = 3.2 Hz); MS (ESI): m/z = 349.4 $[M + H]^+$; HRMS (ESI): Calcd for $C_{18}H_{22}F_2N_4O$ $[M + H]^+$ 349.1840, Found 349.1838.

Procedure for the Scalable Synthesis of Efinaconazole: (t-BuO)$_2$Mg (712.8 g, 4.18 mol) was added to a mixture of epoxide **1** (700 g, 2.79 mol), piperidine **2** (558.4 g, 4.18 mol), and CH_3CN (5.6 L) in three portions while maintaining the temperature below 35 °C. The resulting mixture was heated to 82-86 °C for 16 h and monitored by HPLC. Upon completion (residual lactate: 1.0 HPLC area %), the reaction mixture was cooled to 35–45 °C. Most of solvent was distilled off by concentration under reduced pressure to give a semisolid mass. After the addition of EtOH (4 L) was charged, followed by the addition of 20% NaOH solution (850 g) was added at < 20 °C. The precipitated solid (magnesium salt) was filtered and washed with EtOH (1 L). Water (4 L) and charcoal (25 g) were added to the combined filtrate and the resulting mixture was then heated to 75–80 °C for 30 min. The charcoal was removed by filtration at this temperature and was rinsed with a solution of EtOH (200 mL) and

H_2O (200 mL). The solution was cooled to 0–10 °C within 3 h and held for 2 h to make efinaconazole crystallized completely. The solid was filtered and dried in vacuum to give efinaconazole as off-white powder (860 g) in 88.5% isolated yield, 99.5% HPLC purity, and > 99.9% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (s, 1H), 7.68 (s, 1H), 7.37–7.30 (m, 1H), 7.14–7.08 (m, 1H), 6.93–6.88 (m, 1H), 5.50 (s, 1H), 4.89 (d, J = 14.4 Hz, 1 H), 4.83 (d, J = 15.2 Hz, 1 H), 4.63 (s, 2H), 3.15–3.11 (m, 1H), 2.86–2.82 (m, 2H), 2.43–2.40 (m, 2H), 2.25–2.22 (m, 4H), 0.75 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.36,160.91, (dd, J = 244.7, 12.7Hz), 160.15,157.71 (dd, J = 244.4, 11.3 Hz), 150.94, 147.10, 145.15, 130.80–130.65 (m), 126.28–126.14 (m), 111.27 (d, J = 18.5 Hz), 108.10, 104.56–104.02 (m), 79.02 (d, J = 6.6 Hz), 63.82 (d, J = 3.1 Hz), 56.19 (d, J = 5.5 Hz), 52.72, 35.37, 7.63; MS (ESI): m/z = 349.2 $[M + H]^+$.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for the compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Address: Tel: +86–0991–3835679. Fax: +86–0991–3835679. E–mail: haji@ms.xjb.ac.cn.

*Address: Tel: +86–21–20231000–2407. Fax: +86–21–20231000–2407. E–mail: shenjingshan@simm.ac.cn

Notes

The authors declare no competing financial interest.

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