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Greener aminolysis of epoxides on $BiCl_3/SiO_2$

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The remarkable catalytic activity of $BiCl_3/SiO_2$ for the ring-opening of epoxides with aromatic and aliphatic amines under microwave and thermal heating was observed. This eco-friendly heterogeneous catalyst displayed high to excellent regioselectivity in the synthesis of β-amino alcohols under solvent-free conditions. High turnover frequency (TOF) values under microwave heating and excellent reusability of the catalyst may significantly contribute to applied chemistry.

1. Introduction

Bismuth(III) salts such as $BiCl_3$, $Bi(NO_3)_3$, and $Bi(OTf)_3$ have low toxicity and are widely used as homogeneous catalysts in a great number of organic reactions [1–5]. However, catalyst deactivation and bismuth ion leaching are the main problems when applied in chemical reactions [6]. To make waste-free processes, the immobilization of bismuth(III) salts on solid supports gives eco-friendly heterogeneous catalysts [7–10]. The main advantages of these heterogeneous catalysts are the uniformity and accessibility of active sites, chemical and thermal stability, ease of separation, reusability, and environmental acceptability.

β-Amino alcohols are compounds of interest in organic synthesis due to their wide existence in a vast number of natural compounds and pharmaceutical drugs [11]. They are prepared by the ring-opening reaction of an epoxide with amines under mild conditions in the presence of a number of Lewis acids, such as metal chlorides [12–15] and metal triflates [16–20], which are easily deactivated. Therefore, there is a need to develop greener catalysts for the synthesis of β-amino alcohols.

Recently, we have reported the remarkable catalytic activity of $BiCl_3/SiO_2$ for the Paal–Knorr pyrrole synthesis [7] and benzo[*N*,*N*]-heterocyclic condensation [8]. Considering the importance of environmentally friendly protocols in organic transformations, the aim of this study is to explore the viability of this catalyst for the ring-opening of epoxides with aromatic and aliphatic amines under microwave and classical conditions.

2. Experimental

2.1. Materials and methods

Melting points were measured on a Büchi B-545 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker-500. All NMR samples were run in $CDCl_3$ and chemical shifts are expressed as ppm relative to internal Me_4Si. Single crystal X-Ray data were collected on a diffractometer equipped with a STOE IPDS/2T imaging plate detector, a graphite monochromator, $T = 298(2)$ K and Mo Kα radiation ($\lambda_{Mo\ K\alpha} = 0.71073$ Å). Mass spectra were obtained on a Fisons instrument. Substrates are commercially available and used without further

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purification. A laboratory microwave oven MW 3100 (Landgraf Laborsysteme HLL GmbH, Langenhagen, Germany) equipped with a magnetic stirrer operating at 2450 MHz was used for syntheses of β-amino alcohols. All microwave assisted reactions were performed at 420 W (70% of maximum power) while stirring.

2.2. Preparation of the $BiCl_3/SiO_2$ catalyst

To activate the silica gel surfaces, 30 g of silica gel (300–400 mesh) was refluxed under stirring with 150 mL of 6 M hydrochloric acid for 24 h. The resulting silica was then filtered off and washed with doubly distilled water to neutral and dried under vacuum at 70 °C for 24 h.

Bismuth(III) chloride (1.575 g, 5 mmol) was added to a suspension of activated silica gel (17.5 g) in toluene (30 mL). The mixture was stirred at room temperature overnight and filtered off. The solid was washed with ethanol and filtered off. The obtained solid was dried at 120 °C under vacuum for 5 h to furnish $BiCl_3/SiO_2$ as a white free-flowing powder (6.1 wt% of –O–BiOCl species as determined by TGA and 5.0 mol% of Bi as determined by atomic absorption spectrophotometry). Characterization details of the catalyst are given in our previous work [7].

2.3. General procedure for the preparation of β-amino alcohols

In a typical reaction, aniline (1.0 mmol), styrene oxide (1.2 mmol) and $BiCl_3/SiO_2$ (0.05 g, 0.0125 mmol) were mixed thoroughly for 5 min. The mixture was taken in an open vessel and irradiated at 420 W for 15 min and the progress was monitored by TLC. The reaction mixture was filtered and washed with 2 mL of ethanol. The organic medium was subjected to GC analysis in order to find out the conversion. The products were then analyzed by GC–MS. The crude product was purified by short column chromatography [eluted with ethyl acetate–hexane (3:7)] to give the pure product. The product was recrystallized from ethanol to obtain the single crystal.

In the case of classical reactions, the typical reaction was carried out at 50 °C for 1 h.

2.4. Selected spectroscopic data

2.4.1. 2-(2,5-Dichlorophenylamino)-2-phenylethanol

Mp 90–91 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 13H), 7.15 (d, 1H, $J = 8.4$ Hz), 6.57–6.55 (dd, 2H, $J = 2.3$, 8.4 Hz), 6.39 (d, 1H, $J = 2.3$ Hz), 5.24 (d, 1H, $J = 5.4$ Hz), 4.49 (AB quartet, 1H, $J = 6.0$ Hz), 3.96 (m, 1H), 3.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.81, 160.96, 140.85, 138.76, 133.32, 129.69, 128.98 (2C), 127.96, 126.53 (2C), 117.80, 117.50, 112.49, 67.05, 59.36.

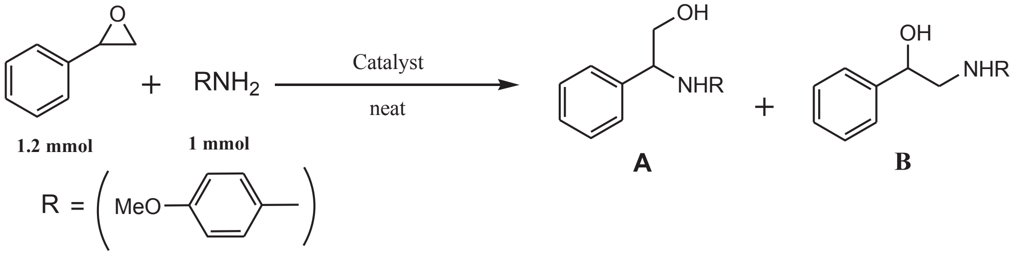
3. Results and discussion

3.1. Optimization of the model reaction

Initially, the aminolysis of styrene oxide (1.2 mmol) with 4-methoxyaniline (1 mmol) was chosen as a model reaction. First, the catalytic effect of $BiCl_3/SiO_2$ and the reaction time under microwave-induced conditions were investigated (Table 1, entries 1–5). Under the optimum conditions, the aminolysis of styrene oxide in the presence of 0.05 g of

Table 1

Catalyzed aminolysis of styrene oxide by 4-methoxyaniline under various conditions.



Entry	Catalyst (g)	Conditions	Time (min)	Conversion (%)[b]	Product selectivity[c]	
					A	B
1	$BiCl_3/SiO_2$ (0.05)	MWI[a]	5	52	96	4
2	$BiCl_3/SiO_2$ (0.05)	MWI	10	89	96	4
3	$BiCl_3/SiO_2$ (0.05)	MWI	15	100	95	5
4	$BiCl_3/SiO_2$ (0.03)	MWI	15	89	95	5
5	$BiCl_3/SiO_2$ (0.07)	MWI	15	100	93	7
6	$BiCl_3$ (0.03)	MWI	15	85	96	4
7	SiO_2 (0.05)	MWI	15	32	91	9
8	–	MWI	15	25	82	18
9	$BiCl_3/SiO_2$ (0.05)	25 °C	60	69	84	16
10	$BiCl_3/SiO_2$ (0.05)	50 °C	60	100	95	5

[a] Microwave irradiation: 420 W.

[b] Conversions were determined by GC.

[c] Selectivities were determined by GC–MS.

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$BiCl_3/SiO_2$ (1.25 mol%) under 15 min irradiation led to quantitative conversion and excellent regioselectivity (Table 1, entry 3).

Further work showed that SiO_2 has poor catalytic activity, whereas the yield of the desired product sharply increased in the presence of $BiCl_3$ to highlight its important role in catalyzing the reaction (Table 1, entries 6–8). Nevertheless, the efficiency of $BiCl_3/SiO_2$ over $BiCl_3$ itself in the reaction is clear (Table 1, entries 3, 6).

The classical reaction was also studied in the presence of $BiCl_3/SiO_2$ at 25 and 50 °C for 1 h (Table 1, entries 9, 10). The same results were obtained under microwave irradiation and classical heating at 50 °C (Table 1, entries 3, 10) to highlight the role of the catalyst.

The higher catalytic activity of $BiCl_3/SiO_2$ is due to good dispersion of $BiCl_3$ over high surface area of silica and may be attributed to −O−BiOCl catalytic sites.

3.2. *Recycling of the catalyst*

The feasibility of repeated use of $BiCl_3/SiO_2$ was also examined (Table 2). The catalyst was readily isolated from the reaction mixture. After completion of the reaction, ethanol (2 mL) was added to the reaction mixture. The catalyst is insoluble in ethanol and was simply filtered from the resulting mixture. The recycled catalyst was washed with ethanol twice more, filtered off and dried at 100 °C under reduced pressure for 2 h and then reused in the subsequent run without adding any fresh catalyst. The reused catalyst is stable under the reaction conditions, and remains active even in fifth run with no decrease in activity while high regioselectivity is maintained.

3.3. *Evaluation of the reaction scope*

The excellent preliminary results of the model reaction led us to expand the generality of this catalyst ($BiCl_3/SiO_2$) to a series of amines and epoxides under solvent-free microwave and thermal conditions. The results are summarized in Table 3.

It was found that aniline derivatives bearing either electron-donating (such as methoxy, methyl, and dimethyl) or electron-withdrawing (such as bromo, chloro, and dichloro) substituents reacted smoothly to give the corresponding β-amino alcohols (Table 3, entries 1–13) in quantitative yields with high to excellent regioselectivities (from 90:10 to 100:0). Moreover, the selectivity of products is almost comparable under microwave and classical heating, when aniline derivatives are used as substrates (Table 3, entries 2, 5–9).

Table 2
Recyclability of $BiCl_3/SiO_2$ (0.25 g) for aminolysis of styrene oxide (6 mmol) with 4-methoxyaniline (5 mmol).

Run	Conversion (%)	Product selectivity	
		A	B
1st	100	95	5
2nd	100	95	5
3rd	100	95	5
4th	100	92	8
5th	100	92	8

In contrast to styrene oxide, epoxides such as epichlorohydrin and isopropyl glycidyl ether showed lower activity (Table 3, entries 2, 7, 8).

The reaction was also carried out with aliphatic amines, e.g., *n*-hexylamine, benzylamine, cyclohexylamine and morpholine (Table 3, entries 14–17). Except cyclohexylamine (91%), the other aliphatic amines exhibited moderate selectivity (70%) under microwave heating. When the same reaction was conducted under thermal heating, both products **A** and **B** were obtained in a ratio of 1:1 (Table 3, entry 17).

The turnover frequencies (TOF) of all reactions were calculated to measure the catalyst activity. It was found that TOF values are in the range of 256–320 h^{-1} and 58–80 h^{-1} under microwave and classical conditions, respectively (Table 3).

In general, the reaction of epoxide with aromatic and aliphatic amines is regioselective. A tentative reaction route for the $BiCl_3/SiO_2$ catalyzed ring-opening of styrene oxide with aniline and cyclohexylamine is depicted in Scheme 1. It is well known that the nature and type of the amine molecule influence the selective ring-opening of the styrene oxide [11]. Cyclohexylamine as a stronger nucleophile, attacks on the carbon atom of the epoxide ring with a more positive charge and less steric hindrance, whereas in the case of aniline, steric factors predominate over electronic factors [21,22].

On the other hand, the Lewis acidic sites on the surface of the $BiCl_3/SiO_2$ catalyst are responsible for the activation of epoxide to enhance the reaction rate.

3.4. *Crystal structure of 2-(2,5-dichlorophenylamino)-2-phenylethanol*

Single crystals of compound **13** (Table 3, entry 13) suitable for SCXRD measurement were grown by slow evaporation of an ethanol solution. The unit cell dimensions were determined from 2000 reflections. The structure was solved by the direct method and refined by full matrix least-squares calculations based on F^2 to final $R_1 = 0.0793$ and wR_2 (all data) $= 0.2262$, using SHELXL-2014 and WinGX-2013.3 programs [23–29]. The compound crystallizes in the triclinic system and $P\bar{1}$ space group. Two independent molecules with a molecular formula of $C_{14}H_{14}Cl_2NO$ were found in the asymmetric unit giving a total $Z = 4$ for the unit cell; $a = 8.8614(18)$, $b = 10.969(2)$, $c = 15.914(3)$, $\alpha = 70.44(3)$, $\beta = 78.16(3)$, $\gamma = 88.87(3)$, cell volume $V = 1424.6(6)$ Å^3, crystal dimensions: 0.64 × 0.34 × 0.15 mm, measurement range: $5.4 < 2\theta < 50$, 4819 independent reflections and max/min residual electron density [e Å^3]: 0.403/−0.426. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. A view of the structure is depicted in Fig. 1. As revealed by X-ray crystallography [30], the solid state structure of compound **13** exhibits an unprecedented fourfold R4,4(8) intermolecular hydrogen-bonding motif [O1−H1O1···O2_$2 d(H···A = 2.724(5)Å

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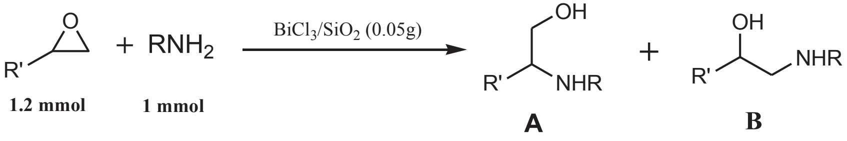
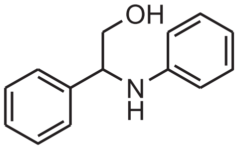
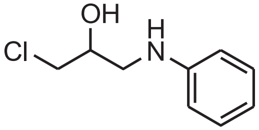
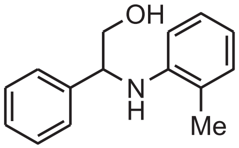
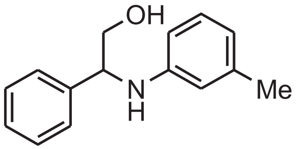
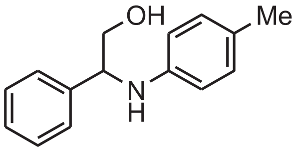
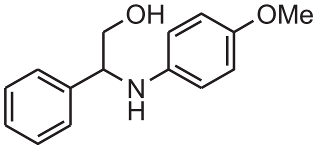
Table 3

Synthesis of β-amino alcohols catalyzed by $BiCl_3/SiO_2$ (1.25 mol%) under microwave and classical heating.



Entry	R′	R	Major regioisomer	Method[a]	Conversion (%)[b]	TOF (h^{-1})[c]	Product selectivity[d]	
							A	B
1	Phenyl	Phenyl		M	100	320	97	3
2	2-Chloromethyl	Phenyl		M	94	301	10	90
				C	90	72	2	98
3	Phenyl	2-Methylphenyl		M	100	320	95	5
4	Phenyl	3-Methylphenyl		M	100	320	93	7
5	Phenyl	4-Methylphenyl		M	100	320	94	6
				C	100	80	97	3
6	Phenyl	4-Methoxyphenyl		M	100	320	95	5
				C	100	80	95	5

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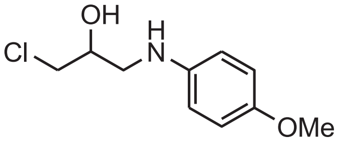
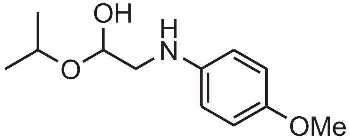
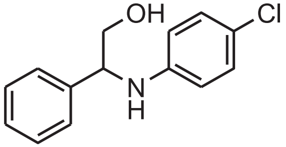
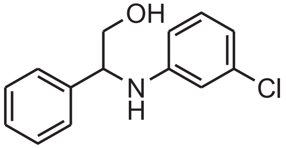
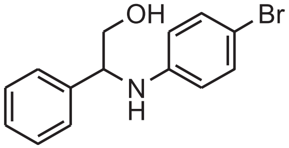
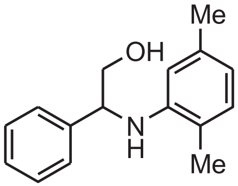
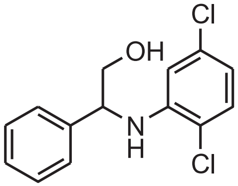
7	2-Chloromethyl	4-Methoxyphenyl		M	100	320	0	100
				C	91	73	0	100
8	2-Isopropoxymethyl	4-Methoxyphenyl		M	80	256	0	100
				C	72	58	0	100
9	Phenyl	4-Chlorophenyl		M	100	320	100	0
				C	100	80	100	0
10	Phenyl	3-Chlorophenyl		M	100	320	100	0
11	Phenyl	4-Bromophenyl		M	100	320	99	1
12	Phenyl	2,5-Dimethylphenyl		M	100	320	95	5
13	Phenyl	2,5-Dichlorophenyl		M	84	269	99	1

(*continued on next page*)

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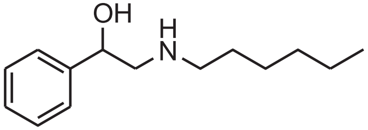
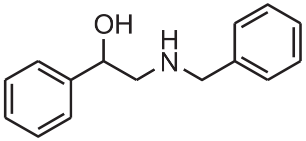
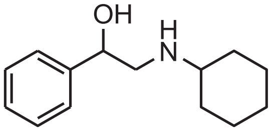
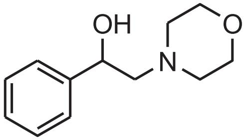
Table 3 (*continued*)

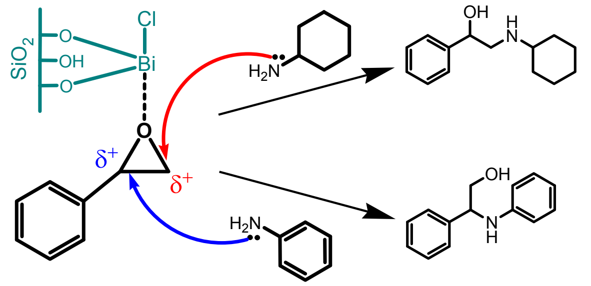
Entry	R′	R	Major regioisomer	Method[a]	Conversion (%)[b]	TOF (h^{-1})[c]	Product selectivity[d]	
							A	B
14	Phenyl	*n*-Hexyl		M	40	128	30	70
15	Phenyl	Benzyl		M	84	269	26	74
16	Phenyl	Cyclohexyl		M	100	320	9	91
17	Phenyl	Morpholine		M C	100 100	320 80	30 49	70 51

[a] Method M: microwave heating/420 W/15 min. Method C: 50 °C/1 h.

[b] Conversions were determined by GC.

[c] TOF: turnover frequency = moles of converted substrate (amine)/(moles of catalyst × reaction time in h).

[d] Selectivities were determined by GC−MS.



Scheme 1. $BiCl_3/SiO_2$ catalyzed regioselective ring-opening of styrene oxide with aniline and cyclohexylamine.

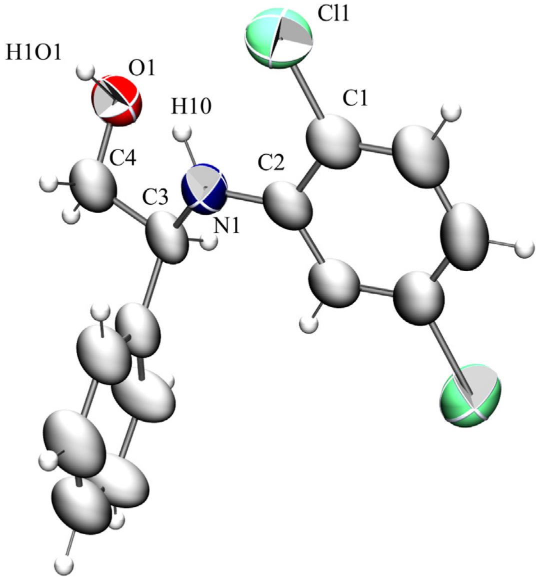


Fig. 1. Structure of the formula unit of **13** (thermal ellipsoids set at the 40% probability level). Selected bond lengths [Å] and angles [°]: C2–N1 1.397(7), C4–O1 1.412(6), C1–Cl1 1.742(6), C3–C4 1.512(8), C3–C5 1.547(6), O1–C4–C3 112.9(5), N1–C3–C5 115.4(4), N1–C3–C4 108.4(4), C1–C2–N1 121.8(5).

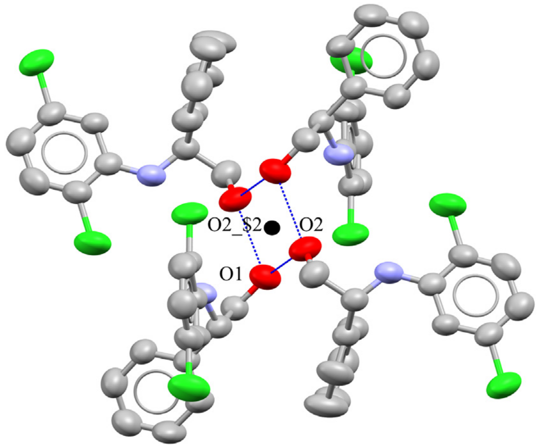


Fig. 2. Depiction of intercellular R4,4(8) hydrogen-bonding with [O1···O2_\$2···2.724(5)Å and O1···O2 2.754(5)Å]. Thermal ellipsoids are set at the 40% probability level. The dark spot in the middle of the rectangle indicates the location of the center of symmetry. Hydrogen atoms are omitted for clarity. \$2 is generated by x, y+1, z.

and <DHA = 154°(5)] locking four molecules of the compound around a single lattice center of symmetry (Fig. 2). The crystal structure of **13** reveals another hydrogen bonding between the oxygen atom and the amino hydrogen atom [N1–H10···O1 *d*(H···A = 2.795(7) Å and <DHA = 137.9°(6)] in an intramolecular fashion.

4. Conclusions

$BiCl_3/SiO_2$ as a heterogeneous Lewis acid catalyst exhibited excellent catalytic activity and high regioselectivity for the ring-opening of epoxides with aromatic and aliphatic amines to produce β-amino alcohols under microwave and thermal conditions. All the reactions have been conducted in a low loading bismuth ion (1.25 mol%). $BiCl_3/SiO_2$ is superior in terms of catalytic activity compared to homogeneous $BiCl_3$. It could be recycled and reused for five consecutive reaction cycles with no decrease in catalytic activity maintaining high selectivity. The innocuous and non-leaching nature of the catalyst makes it a greener alternative to conventional homogeneous catalysts (e.g., Lewis acid salts) used for the aminolysis of epoxides.

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[30] CCDC-1426089 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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