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# Montmorillonite K10 catalyzed highly regioselective azidolysis of epoxides: A short and efficient synthesis of phenylglycine

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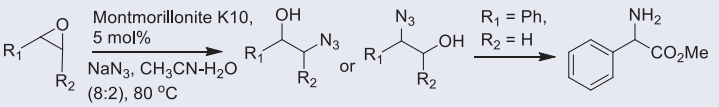
**ABSTRACT**

A series of β-hydroxyazides were effectively synthesized from the regioselective ring opening of epoxides by sodium azide using montmorillonite K10 as a novel heterogeneous catalyst in aqueous acetonitrile in good to excellent yields. The utility of this method has been demonstrated by achieving a short synthesis of phenylglycine in 33.5% overall yield.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
Azidolysis; β-azido alcohols; epoxide; montmorillonite K10; phenylglycine

## Introduction

Epoxides are the most useful synthetic intermediates in organic synthesis.[1] Because of their ring strain and high reactivity, their reactions with various nucleophiles lead to high regio and stereoselective ring-opening products.[2] Among them, the azidolysis of epoxides are the most important for preparation of azido alcohols.[3] 1,2-Azido alcohols are very important precursors of β-amino alcohols and vicinal diamines, which are present in various natural products and different bioactive compounds.[4] Furthermore, β-amino alcohols have played significant roles in the chemistry of carbohydrates and nucleosides.[5] α-Amino acids can be prepared from corresponding β-amino alcohols by oxidation of alcohol group. Conventionally, epoxide ring opening with azides is out using $NaN_3$ as reagent and $NH_4Cl$[4a,4c–f,6] as coordinating salt in alcohol-water at 65–80 °C. Under these conditions, azidolysis is generally carried out over a long reaction time (12–48 h), and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement products.[3,4a] Beside this, the azidolysis of epoxide is promoted by homogeneous systems as metal chlorides,[7] salts,[8] and alkyl metal azides[9] some heterogeneous catalysts, such as ammonium-12-molybdophosphate,[10] amberlite

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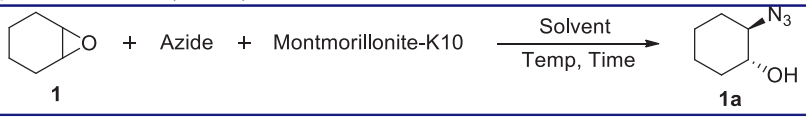
Supplemental data (full experimental details, spectral, and analytical data of synthesized compounds, and copies of $^1H$ and $^{13}C$ NMR) can be accessed on the publisher's website.

**Table 1.** Optimization of azidolysis of cyclohexene oxide.




1 1a

| Entry | Azide | Catalyst (mol%) | Solvent | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $NaN_3$ | 40 | DMF | RT | 24 | 00 |
| 2 | $NaN_3$ | 40 | DMF | 90 | 24 | 10 |
| 3 | $NaN_3$ | 40 | $H_2O$ | RT | 24 | 10 |
| 4 | $NaN_3$ | 40 | $CH_3CN$ | RT | 24 | 00 |
| 5 | $NaN_3$ | 40 | $CH_3CN$ | 80 | 18 | 31 |
| 6 | $NaN_3$ | 20 | $CH_3CN/H_2O$ (8:2) | 80 | 10 | 80 |
| 7 | $NaN_3$ | 10 | $CH_3CN/H_2O$ (8:2) | 80 | 10 | 81 |
| 8 | $NaN_3$ | 10 | $CH_3CN/H_2O$ (8:2) | 80 | 8 | 82 |
| 9 | $NaN_3$ | 5 | $CH_3CN/H_2O$ (8:2) | 80 | 8 | 85 |
| 10 | $NaN_3$ | 0 | $CH_3CN/H_2O$ (8:2) | 80 | 48 | 60 |
| 11 | $NaN_3$ | 5 | $CH_3CN/H_2O$ (8:2) | RT | 36 | 61 |
| 12[a] | $TMSN_3$ | 5 | $CH_3CN/H_2O$ (8:2) | 80 | 36 | 39 |

The reaction was conducted with 1 eqv. of substrate and 1.5 eqv. of Azide.
[a]3 eqv. $TMSN_3$ was used.

IRA-400 supported azide,[11] oxone,[12] sodium azide supported on Zeolite CaY,[13] quaternized ammonium salt,[14] and quaternized amino functionalized cross-linked polyacrylamide[15] have been reported. Ring opening of epoxides with $NaN_3$ by controlling the pH in water has also been reported.[16] The combination of trimethylsilyl azide with $BF_3.OEt_2$ has been used for ring opening of vinyl epoxides.[17] All the above methods and procedures have their own advantages, but many of these methodologies suffer from one or more different disadvantages such as unsatisfactory yields, strong acidic conditions, hygroscopic in nature, lack of regioselectivity, cost, and stability of the reagent.

Montmorillonite K10 is a commercially available cheap solid acid, considered as an enviornmentally benign catalysts for electrophilic activation in organic reaction[18] including epoxide ring opening with amines.[18b,c] Herein, we report the use of montmorillonite K10 as an efficient catalyst for regioselective azidolysis of epoxides with $NaN_3$ in aqueous acetonitrile and synthesis of phenylglycine using this methodology as a key step.

## Results and discussion

To standardize the reaction conditions for screening the catalyst, a series of experiments were carried out for a representative reaction of cyclohexene oxide (Table 1).

Different solvents like DMF, $H_2O$, $CH_3CN$, and mixed solvent $CH_3CN$–$H_2O$ were screened for the azidolysis of cyclohexene oxide by treating with 1.5 mmol of sodium azide in presence of 5–40 mol% of catalyst in different reaction conditions. Among these, only mixed solvent, $CH_3CN$–$H_2O$ was found to be suitable for this reaction and 5 mol% catalyst was effective to give maximum yield when the reaction was carried out at 80 °C (Table 1, Entry 9). When $NaN_3$ was replaced by $TMSN_3$, the yield was poor (Table 1, Entry 12).

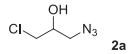
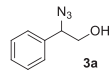
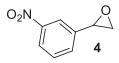
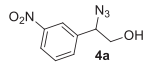
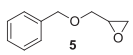
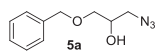
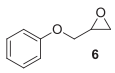
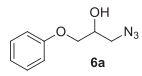
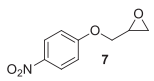
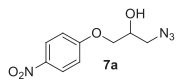
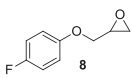
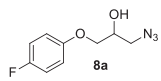
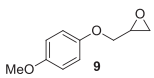
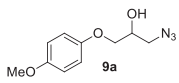
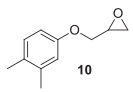
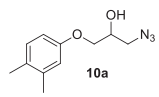
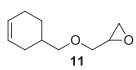
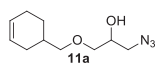
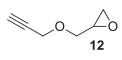
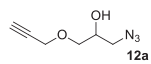
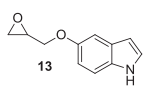
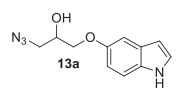
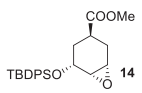
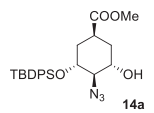
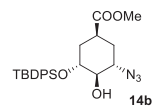
To generalize the validity of the protocol, a wide range of substituted epoxides were treated with $NaN_3$ under the standardized conditions. The result is summarized in

Table 2 showing that β-azidoalcohols were obtained in excellent yields with high or exclusive regioselectivity. In contrast to the earlier report[18b] on ring opening of epoxide of epichlorohydrin by aniline in 69% yield, we got very clean azido alcohol **2a** in 94% yield (Table 2, Entry 2). Compound **2a** could be useful for making aziridine ring. 2-Aryl epoxides afforded 2-azidoalcohols as major product by the attack of azide nucleophile at the benzylic position due to the formation of the stabilized benzylic cation (Table 2, Entry 3–4) which is consistent with the previously reported results[7a–c,10,12] and the expected outcome of the regioselectivity of ring opening of styrene oxide by azide was discussed earlier by Sarangi et al.[7c] This is a suitable substrate for the preparation of phenylglycine (*vide infra*). In the case of monoalkyl-substituted epoxides, desired β-azido alcohols were obtained with a reversal of regioselectivity because of the predominant attack of azide ion on the less hindered carbon of the epoxide (Table 2, Entry 5–13). All the terminal epoxides gave highly regioselective azidohydrins in almost quantitative yields. We applied this methodology on enantiomerically pure functionalized cyclohexene oxide **14**. As a part of our research,[19] **14** was synthesized according to Scheme 1 via the formation of lactone **15**.[20] **15** on treatment with NaOMe in MeOH gave methyl ester **16**. After mesylation followed by ketal deprotection yielded free diol **18** in excellent yield. **18** was treated with DBU to obtain the epoxide **19** in 74% yield. After TBDPS protection, the desired epoxide **14** was obtained which was subjected to montmorillonite-K10 mediated ring opening to get a mixture of products in which **14a** was the major product due to the attack of azide ion on the less hindered carbon center. Reaction occurred smoothly in $S_N2$ fashion and only trans product was obtained (Table 2, Entry 1, 14), confirmed from corresponding $^1$H NMR spectrum. These highly functionalized stereoselective cyclohexane derivatives could be useful as a building block for organic synthesis.[21]

Plaussible mechanism in the ring opening reaction by montmorillonite K10 is shown in Scheme 2. For 2-aryl epoxides, oxygen of epoxide interacts with the Mont K10 catalyst and generates a stable benzylic cation. Finally, azide ion attack to the positive carbon center via $S_N1$ pathway to form terminal alcohol. For alkyl substituted epoxides, oxygen atom interacts with the Mont K10 and azide ion attack from the less hindered carbon center to form terminal azide.

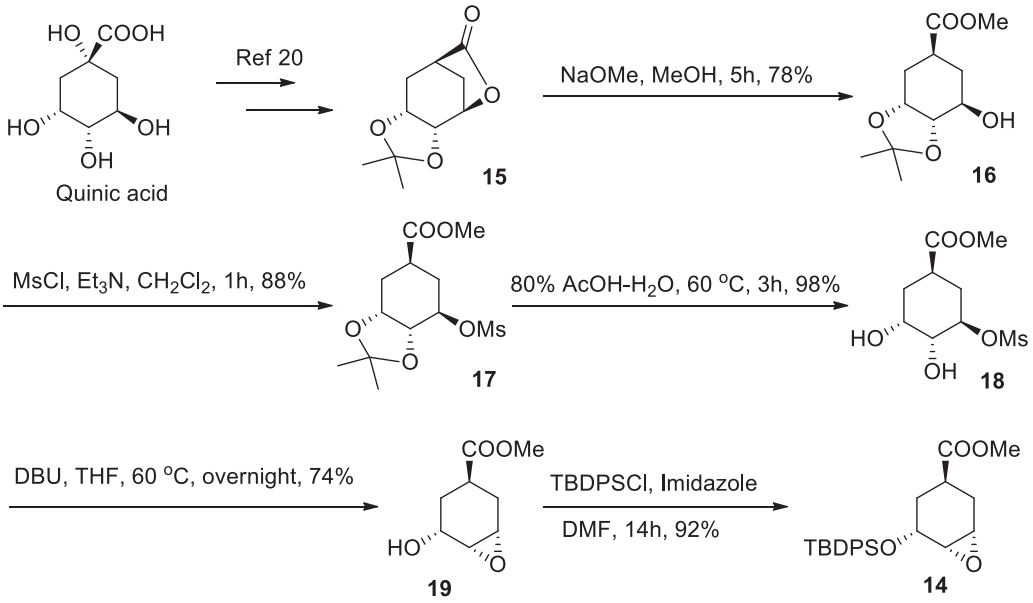
Encouraged by these results, we then decided to employ this method for the synthesis of phenyl glycine. Arylglycines are the important nonproteinogenic class of amino acids.[22] The isolation of arylglycines from natural sources is rare but has increased in frequency over the past 40 years. For example, 3-hydroxy and 3,5-dihydroxyphenylglycine were isolated from latex.[23] Aryl glycines are found in numerous glycopeptide antibiotics,[24] such as in vancomycin, teicoplanin. Vancomycin consists of a heptapeptide in which three of the amino acid residues are functionalized arylglycines. Several substituted phenylglycine derivatives, including 3-hydroxyphenylglycine, have been described as potent and selective agonists or antagonists of glutamate receptors of the central nervous system (CNS).[25] Another natural source of arylglycines is the family of monocyclic β-lactam antibiotics known as the nocardicins. Nocardicins contain two p-hydroxyphenylglycine derivatives which are thought to serve as the starting material for nocardicin biosynthetically.[26] Beside from the naturally occurring arylglycines, there are also a number of unique synthetic arylglycines. D-arylglycines are used as a

**Table 2.** Ring-opening of epoxides with $NaN_3$ in $CH_3CN–H_2O$ (8:2) using Montmorillonite-K10 (5 mol%) at 80 °C.

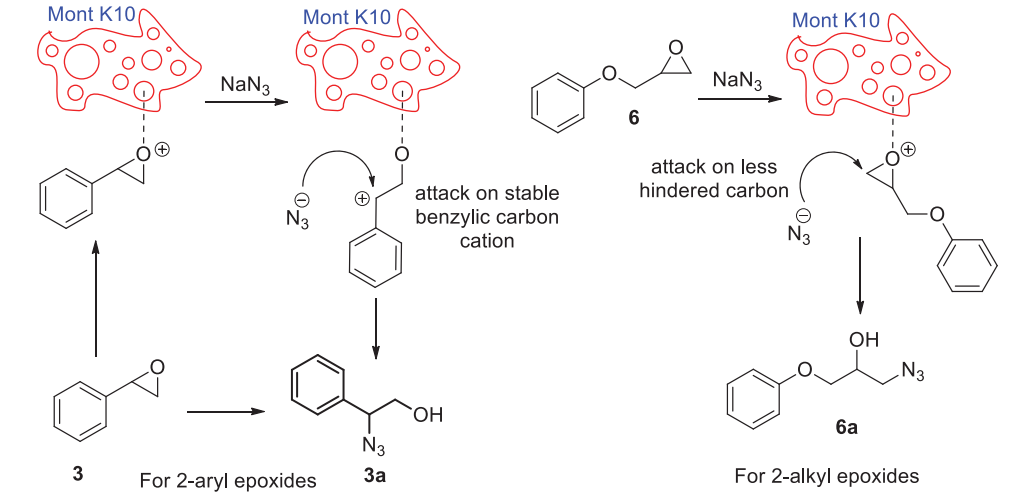
| Entry | Epoxide | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  1 |  1a | 8 | 85 |
| 2 |  2 |  2a | 7 | 94 |
| 3 |  3 |  3a | 8 | 75(15) |
| 4 |  4 |  4a | 8 | 67(17) |
| 5 |  5 |  5a | 8 | 91 |
| 6 |  6 |  6a | 8 | 95 |
| 7 |  7 |  7a | 8 | 86(5) |
| 8 |  8 |  8a | 8 | 96 |
| 9 |  9 |  9a | 7 | 98 |
| 10 |  10 |  10a | 7 | 98 |
| 11 |  11 |  11a | 8 | 95 |
| 12 |  12 |  12a | 8 | 92 |
| 13 |  13 |  13a | 7 | 97 |
| 14 |  14 |  14a  14b | 8 | 39(22) |

[a] The products obtained were characterized by 1H ,13C NMR, IR and mass spectra.

[b] isolated pure product, yields in parantheses corresponds to the other isomer.

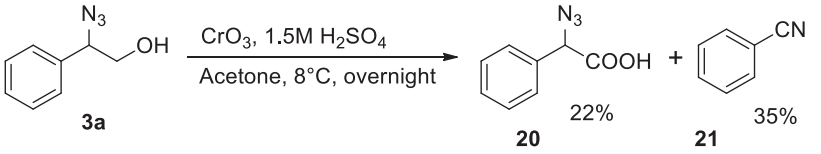



**Scheme 1**. Synthesis of compound 14.

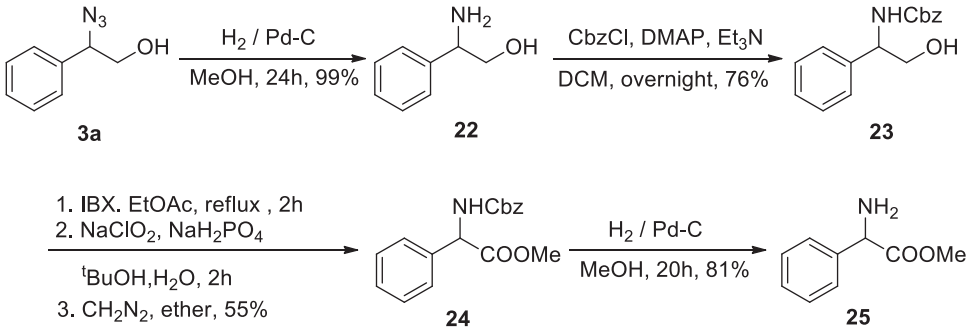



**Scheme 2**. Tentative mechanistic pathway of the epoxide ring opening reaction.

side chain moiety of semisynthetic penicillins and cephalosporins. For example, phenylglycine present as a side-chain constituent in synthetic antibiotic cephalexin[27] and p-hydroxyphenylglycine is used as a side-chain moiety in the antibiotics cefadroxil and amoxicillin.[28] Because of their significant biological importance, lot of attention has been given to their synthesis. We started our synthesis from 2-azido-2-phenylethanol **3a**. Initially, we tried to oxidize the azido alcohol to azido acid using Jones reagent,[29] but we got the desired azido acid **20** as a minor product (22%) along with benzonitrile **21** as a major product (Scheme 3). Similar result was observed during $RuCl_3$ catalyzed oxidation[30] of azido alcohol **3a**.




**Scheme 3**. Oxidation of azido alcohol.




**Scheme 4**. Synthesis of phenylglycine.

So, we modified our synthetic route. The 2-azido alcohol **3a** was reduced to 2-amino alcohol **22** via hydrogenation.[31] Amine of **22** was protected with Cbz-chloride to afford protected[32] amino alcohol **23**. Here, we decided to follow stepwise conversion of alcohol to acid via formation of aldehyde. Accordingly, alcohol **23** was treated with IBX to form aldehyde which was oxidized to acid under Pinnick condition.[33] Interestingly, two steps oxidation gave better yield in compare to Jones oxidation. The acid on treatment with diazomethane furnished methyl ester **24**.[34] Finally, hydrogenation of **24** afforded the free amino ester **25** in 33.5% yield from **3a** (Scheme 4). It is worth to mention here that synthesis of phenylglycine was not possible using previously reported amine-mediated ring opening of epoxides by K-10[18b,c] as the generation of free amine was impossible.

## Conclusion

We have developed a mild and simple method for the preparation of 1,2-azidoalcohols by ring-opening of epoxides with $NaN_3$ using only 5 mol% of montmorillonite K10 as a heterogeneous catalyst. The advantages of the present method such as simplicity in operation, the low cost of reagents, high yields of products, excellent regioselectivity make it a valuable alternative to the existing methods reported in the literature. Furthermore, we have described an efficient synthesis of phenyl glycine using this methodology as a key step.

## Experimental section

All reagents were purchased from commercial sources and used without further purification unless otherwise stated. Petroleum ether (PE) refers to the fraction of petroleum boiling between 60 °C and 80 °C. The following abbreviations are

used for CbzCl = Benzyl chloroformate, MsCl = Methanesulfonyl chloride, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, MeOH = methanol, TBDPSCl = *tert*-Butyldiphenylchlorosilane, DMAP = 4-Dimethylaminopyridine, IBX =2-iodoxybenzoic acid, THF = Tetrahydrofuran, DMF = Dimethylformamide, DCM = dichloromethane, EtOAc = ethyl acetate. All the reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents, standard syringe, and septum techniques unless otherwise indicated. Organic extracts were dried over anhydrous $Na_2SO_4$ and then filtered prior to removal of all volatiles under reduced pressure on rotary evaporation. Chromatographic purification of products was accomplished using column chromatography on silica gels (mesh 100–200). Thin-layer chromatography (TLC) was carried out on aluminum sheets, Silica Gel 60 F254 (Merck; layer thickness 0.25 mm). Visualization of the developed chromatogram was performed using UV light and/or ninhydrin, CAM stains. IR spectra were recorded as thin films (for liquids). $^1H$ and $^{13}C$ NMR spectra were recorded at 300, 400, or 500 MHz and 75, 100, or 125 MHz, respectively using $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm relative to the solvent residual peak or TMS as internal standard. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High Resolution Mass Spectra (HRMS) were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface on Micro (YA-263) mass spectrometer (Manchester, UK).

### General method for epoxide ring opening of styrene oxide

To a mixture of epoxide (1 equiv.) and $NaN_3$ (1.5 equiv.) in $CH_3CN$–$H_2O$ (8:2, 10 mL) Montmorillonite K 10 (5% w/w) was added. The reaction mixture was stirred at 80 °C for a specified time as required to complete the reaction. After completion as indicated using TLC, the reaction mixture was then filtered, the filter pad was washed with $CH_3CN$, and the combined filtrates were evaporated. The reaction mixture was extracted with EtOAc, the combined organic layers were washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. The crude product was then purified using column chromatography over silica gel using EtOAc/petroleum ether as eluent to provide the pure azido alcohol.

### 2 -Azido-2-phenylethanol (3a)

Isolated yield: 520 mg (75%); colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.44–7.31 (m, 5H), 4.68 (t, $J = 6.3$ Hz, 1H), 3.75 (t, $J = 6.3$ Hz, 2H), 2.20 (d, $J = 6.3$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 136.4, 129.1, 128.8, 127.3, 68.0, 66.6; IR (Neat) $\nu_{max}$ 3411, 3014, 2918, 2106, 1454 $cm^{-1}$.[7a]

### 2 -Amino-2-phenylethanol (22)

A solution of 2-Azido-2-phenylethanol **3a** (540 mg, 3.31 mmol) in MeOH (10 mL) was degassed with Argon. 10% Pd/C (35 mg) was added and the mixture was stirred under $H_2$ for 24 h at room temperature. After filtration over celite, the solvent was removed

under reduced pressure to give the title compound **22** as slightly yellow oil (450 mg, 99%). The crude product was used in the next step without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 4.03 (m, 1H), 3.71 (m, 1H), 3.55 (t, $J = 9.5$ Hz, 1H), 2.49–2.34 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 142.7, 128.7, 127.6, 126.6, 68.1, 57.5; IR (Neat) $\nu_{max}$ 3367, 3064, 1602, 1492, 1215 cm$^{-1}$; HRMS (ESI): $m/z$ $[M + H]^+$ calcd for $C_8H_{12}NO$: 138.0913; found: 138.0911.[32]

### Benzyl (2-hydroxy-1-phenylethyl)carbamate (23)

To a solution of **22** (778 mg, 5.67 mmol) and DMAP (7 mg, 0.056 mmol) in DCM (20 mL) was added dropwise benzyl chloroformate (971 µL, 60 mmol) at 0 °C, followed by $Et_3N$ (1.98 mL, 14.2 mmol). The resulting mixture was stirred at room temperature for overnight. The solvent was evaporated. The reaction mixture was extracted with EtOAc and the combined organic layers were washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. Crude product was purified by column chromatography using EtOAc-pet ether (3:7) on silica gel to afford **23** as a colorless oil (1.16 g, 76% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32–7.24 (m, 10H), 5.75 (s, 1H), 5.07 (s, 2H), 4.81 (s, 1H), 3.77 (s, 2H), 2.77 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.6, 139.3, 136.4, 128.9, 128.6, 128.3, 127.9, 126.7, 67.1, 66.4, 57.2; IR (Neat) $\nu_{max}$ 3365, 2931, 2106, 1734, 1109 cm$^{-1}$; HRMS (ESI): $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{17}NO_3Na$: 294.1106; found: 294.1107.[32]

### Methyl 2-(((benzyloxy)carbonyl)amino)-2-phenylacetate (24)

To a solution of the alcohol **23** (310 mg, 1.14 mmol) in EtOAc (15 mL) was added 2-iodoxybenzoic acid (IBX) (640 mg, 2.29 mmol) portion wise, and it was refluxed for 2 h in open atmosphere. After completion of the reaction (TLC), the mixture was cooled to room temperature and filtered through a celite pad. Solvent removal under reduced pressure afforded the crude aldehyde (307 mg) which was used in the next step without further purification.

To a solution of the above crude aldehyde in *t*-BuOH (6 mL) and 2-methyl-2-butene (3 mL) was added a solution of $NaClO_2$ (465 mg, 5.14 mmol) and $NaH_2PO_4$ (475 mg, 3.43 mmol) in $H_2O$ (3 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and diluted with saturated aqueous $NH_4Cl$ solution (1 mL). The organic layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography, eluting with DCM-MeOH (97:3), to afford the corresponding acid as white foam (291 mg). Product was confirmed by mass spectrometry. HRMS (ESI): $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{15}NO_4Na$: 308.0899; found: 308.0898.

The free acid (291 mg, 1.02 mmol) was then dissolved in diethyl ether (5 mL, minimum volume). Diazomethane in diethyl ether was added slowly at 0 °C until a yellow color persisted (monitored by TLC). Removal of ether followed by silica gel column chromatography purification using EtOAc—petroleum ether (1:4) gave the product **24** as colorless to faint yellow oil (185 mg, 55%, after 3 steps from amino alcohol **23**). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.39–7.31 (m, 10H), 5.99 (d, $J = 7.5$ Hz, 1H), 5.42

(d, $J = 7.5$ Hz, 1H), 5.11 (d, $J = 3.9$ Hz, 2H), 3.71 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.4, 155.4, 136.6, 136.2, 129.0, 128.6, 128.5, 128.2, 127.2, 67.1, 58.0, 52.8; IR (Neat) $\nu_{max}$ 3338, 2945, 1739, 1707, 1512, 1234 cm$^{-1}$; HRMS (ESI): $m/z$ $[M + Na]^+$ calcd for $C_{17}H_{17}NO_4Na$: 322.1055; found: 322.1056.

### *Methyl 2-amino-2-phenylacetate (25)*

A solution of compound **24** (135 mg, 0.45 mmol) in MeOH (5 mL) was degassed with Argon. 10% Pd/C (15 mg) was added, and the mixture was stirred under $H_2$ for 20 h at room temperature. After filtration over celite, the solvent was removed under reduced pressure to give the title compound which was purified by column chromatography using EtOAc/pet ether (2:3) on silica gel to afford **25** as a slightly yellow oil (60 mg, 81% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.61 (s, 1H), 3.69 (s, 3H), 1.93 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.6, 140.4, 128.9, 128.1, 126.9, 58.8, 52.4; IR (Neat) $\nu_{max}$ 3377, 3029, 2952, 1735, 1454, 1186 cm$^{-1}$; HRMS (ESI): $m/z$ $[M + H]^+$ calcd for $C_9H_{12}NO_2$: 166.0863; found: 166.0865.

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