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Metal-Free β-Amino Alcohol Synthesis: A Two-step Smiles Rearrangement

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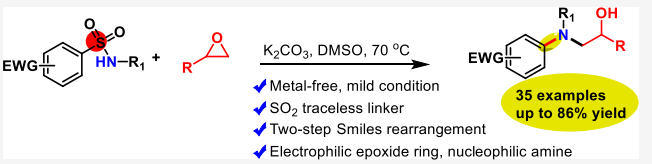
ABSTRACT: A novel method for the synthesis of β-amino alcohols has been demonstrated under mild reaction conditions with a broad scope via a two-step Smiles rearrangement. What is more, theoretical calculations have been performed to confirm the rationality of the mechanism. The method has been proved to be notably effective for N-arylated amino alcohols, which are difficult to synthesize by traditional methods.



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1. INTRODUCTION

β-Amino alcohols have attracted tremendous interest among natural product synthesis because of the wide existence of their skeleton in drugs,[1] including antihypertensives,[2] antianginal agents,[3] antiasthmatic agents,[4] antimalarial agents,[5] anti-HBV drugs,[6] and so on (Scheme 1).[7] β-amino alcohols are considered as promising molecular structures which are widely present in biologically active, natural, and unnatural amino acids.[8] As an intermediate, they can be candidates for heterocyclic organic synthesis, such as indoles[9] and benzoxazines.[10] In addition, they are widely used as chiral auxiliaries in organic synthesis (Scheme 1).[11]

Because of their great value, the preparation of amino alcohols has gained much attention.[12] The classical method was the opening of epoxides with an amine under heating.[13] Among the investigated efforts, a lot of metal catalysts such as Bi, In, and Fe were used to afford amino alcohols (Scheme 2a) via opening the rings.[14] The use of a Lewis acid catalyst generally promoted the reaction of nitrogen-based nucleophiles with epoxides whose reactivity could be enhanced by complexation with the Lewis acid. In addition, construction of chiral amino alcohols also required the participation of chiral metal catalysts. Recently, a cascade reaction to construct amino alcohols was reported including a three-component reaction (Scheme 2b).[15] However, severe reaction conditions, such as excess requirement of amines, high temperatures, long reaction times, and the unavoidable use of metal catalysts would not meet the concept of green chemistry. The discovery of a mild and simple method to synthesize β-amino alcohols would, therefore, be a worthy study in the field.

To solve the problem, we seek the readily available aryl sulfonamides, which are widely present in pharmaceuticals and agrochemicals. They not only exhibit desirable physicochemical properties along with excellent stability but also can result in reactivity that treats SO_2 as the traceless linker in sulfonamides to achieve the Smiles rearrangement, which is an intramolecular nucleophilic aromatic substitution reaction and can be easily incorporated in tandem reactions.[16]

In this work, we envisaged a cascade reaction that offered β-amino alcohols starting from an alkyl sulfonamide and an epoxide ring via benzene sulfonamide−styrene oxide addition, ipso-substitution, SO_2 extrusion, and the subsequent two-step Smiles rearrangement (Scheme 2). What is more, the reaction achieved an effective method to synthesize aromatic-substituted amino alcohols which are tough to obtain by traditional ways. All in all, it might broaden the sight of designing multicomponent reactions for the Smiles rearrangement.

2. RESULTS AND DISCUSSION

2.1. Optimization for the Synthesis of β-Amino Alcohols. As the Smiles rearrangement frequently required strong electron-withdrawing groups to stabilize the Meisenheimer intermediate and enable the successful Smiles rearrangement, we sought to use the readily available 4-nitrobenzenesulfonamide. At the outset, our investigation commenced with the reaction of 4-nitrobenzenesulfonamide (**1a**, 0.5 mmol) and 2-phenyloxirane (**2a**, 1.5 mmol) in the presence of Li_2CO_3 (1 mmol) at 70 °C in commercially available dimethyl sulfoxide (DMSO) (2 mL) under an air atmosphere, and the target product (**3a**) was obtained in 13% yield after 4 h (Table 1, entry 1).

As shown in Table 1, other bases such as Na_2CO_3 could catalyze the reaction, but no satisfactory results were acquired (Table 1, entries 2−8). Delightfully, an excellent yield of 86%

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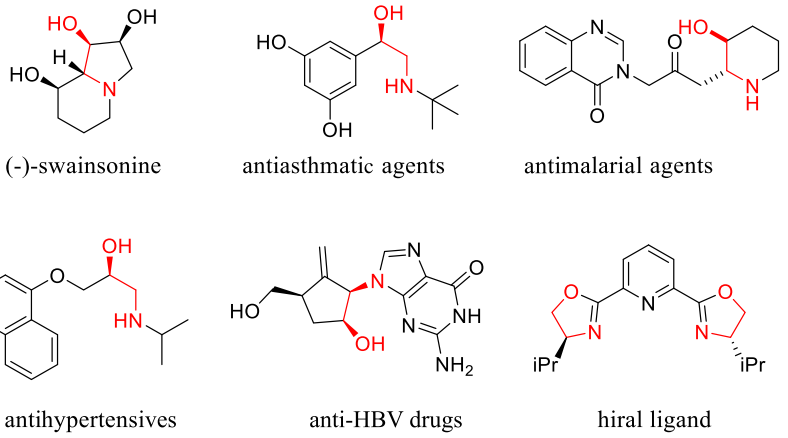
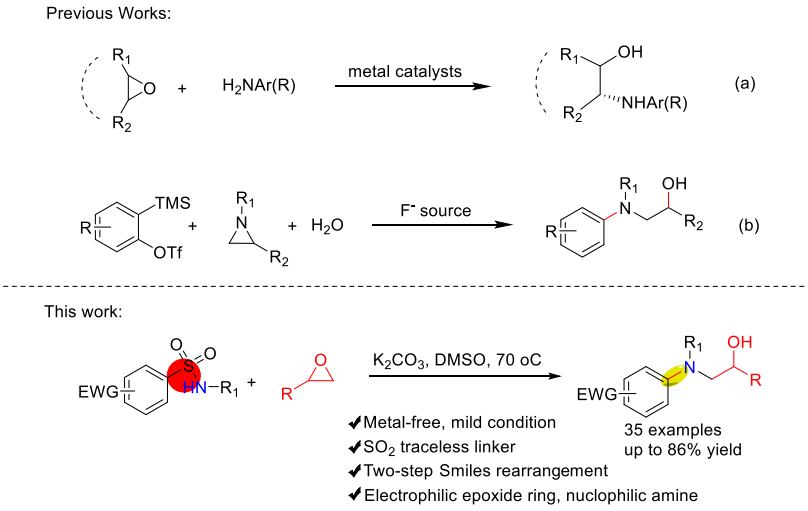
Scheme 1. Selected Example Compounds with the β-Amino Alcohol Skeleton



Scheme 2. Synthesis of N-Substituted β-Amino Alcohols via Ring Opening



was achieved when K_2CO_3 was employed as a base. Compared with CH_3COONa, the yield was sharply reduced when *t*-BuONa was used (Table S1, entries 4−6). When we used an organic base such as Et_3N in the reaction, **3a** was not obtained (Table S1, entries 1−3). The next step optimized the concentration of K_2CO_3 in the reaction without obvious improvement in the product yield (Table 1, entries 9−10). Neither the decrease nor the increase of temperature was conducive to the reaction, and no product was obtained at room temperature (Table 1, entries 11−12). After screening of solvents, DMSO was identified as the solvent of choice (Table 1, entries 14−20). The other relevant reaction conditions are summarized in the ESI (Tables S2−S4).

2.2. Synthesis. With these simple reaction conditions in hand, we examined the scope of the reaction for a range of aryl sulfonamides with different substituents (Table 2). We first investigated compounds with electron-withdrawing groups such as chlorine and heteroaryl sulfonamides, but there were no target products (**3ba−3ca**). We realized that the existence of a strong electron-deficient group was necessary, which could be achieved by using other functional groups (**3da−3ea**). Switching the nitro group to the ortho or even meta position was effective with satisfactory yields (**3ea−3ga**).

Turing to the N-substituted sulfonamide compounds, *N*-alkyl sulfonamides were first investigated, all of them with good yields (Table 3). Even the N-substituted sulfonamides with a large steric hindrance or long chain were well tolerated with satisfying yields (**3ia−3ma**). The extension of applicability was subsequently performed on N-aryl. The aryl ring of the sulfonamide includes electron-withdrawing or electron-donating substituents that were well tolerated, with the corresponding products formed with moderate to excellent yields (**3na−3va**). We delightedly found that alternative N-substituted groups such as heterocycles were effective in the reaction (**3wa**), but some attrition in yield was observed. We noticed that the N-substituted sulfonamide with a heteroatom directly presented a satisfactory reactivity, thus producing the target product (**3xa**) in good yield.

Having established the scope of the reaction for substituted sulfonamides, we were keen to develop a more general procedure with a broad substrate scope for 2-phenyloxirane under the optimized reaction conditions (Table 4). Despite the weak nucleophilicity of sulfonamide, the scope of epoxy compounds with a variety of primary and secondary alkyl- and aryl-substituted alkynes was proved to be very broad, producing β-amino alcohols in good to excellent yields (**3ab−3ak**). Interestingly, considerable yields (**3al−3am**) were obtained when polycyclic aromatic substrates were used.

To explore the practicality, a reaction of **1na** on a 10 mmol scale was performed. The target product **3na** was isolated in 79% yield (Scheme 3a).

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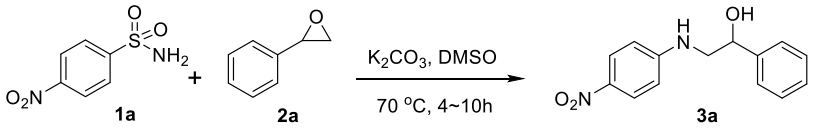
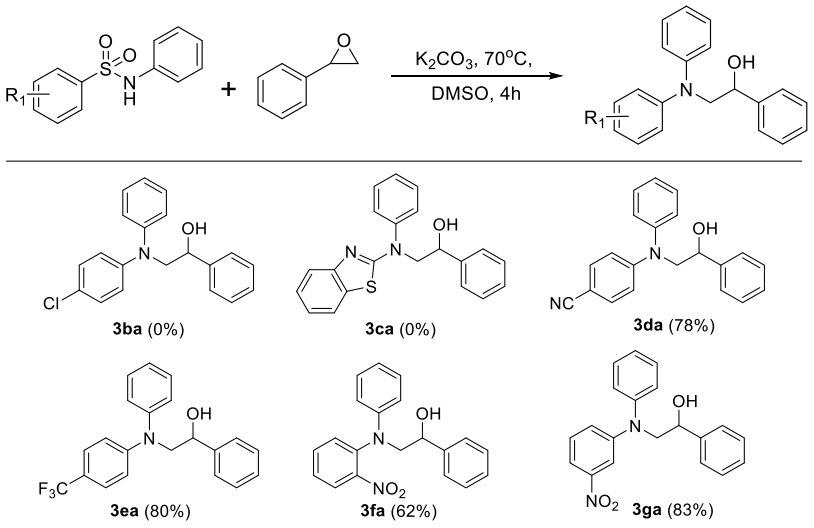
Table 1. Optimization of the Reaction Conditions[a]



entry	base	equiv	solvent	T (°C)	yield (%)[b]
1	Li_2CO_3	2	DMSO	70	13[b]
2	Na_2CO_3	2	DMSO	70	20
3	**K_2CO_3**	**2**	**DMSO**	**70**	**86**
4	Cs_2CO_3	2	DMSO	70	84
5	K_3PO_4	2	DMSO	70	85
6	LiOH	2	DMSO	70	76
7	NaOH	2	DMSO	70	74
8	CsOH	2	DMSO	70	58
9	K_2CO_3	1	DMSO	70	73
10	K_2CO_3	3	DMSO	70	80
11	K_2CO_3	2	DMSO	r.t	n.p.[c]
12	K_2CO_3	2	DMSO	60	62
13	K_2CO_3	2	DMSO	80	80
14	K_2CO_3	2	None	70	NR[d]
15	K_2CO_3	2	DMF	70	78
16	K_2CO_3	2	CH_3CN	70	51
17	K_2CO_3	2	NMP	70	64
18	K_2CO_3	2	1,4-dioxane	70	13
19	K_2CO_3	2	TBA	70	trace
20	K_2CO_3	2	EtOH	70	70

[a]Reaction conditions: 4-nitrobenzenesulfonamide **1a** (0.5 mmol), 2-phenyloxirane **2a** (1.5 mmol), K_2CO_3 (1 mmol), DMSO (2 mL), 70 °C, 4 h. [b]Isolated yields. [c]n.p. = no product. [d]NR = no reaction.

Table 2. Synthesis of Products 3ba−3ga[ab]



[a]Unless specifically noted otherwise, reaction conditions: **1a** (0.5 mmol), 2-phenyloxirane **2a** (1.5 mmol), K_2CO_3 (1 mmol), DMSO (2 mL), 70 °C, 4 h. [b]Isolated yields.

Furthermore, we assumed that the presence of an ortho-amino group in 4-nitro-*N*-phenylbenzenesulfonamide was nicely realized by the tandem of the Smiles rearrangement and the Ullmann reaction to produce 3,4-dihydro-2*H*-1, 4-benzoxazines (Scheme 3b). To our delight, we successfully obtained the target product (**4a**) in 35% yield when using *N*-(2-chlorophenyl)-4-nitrobenzenesulfonamide. Notably, both −Br and −I as the *N*-(2)-substituent in 4-nitro-*N*-phenylbenzenesulfonamide gave good yields, while no desired product was obtained when using −F as the *N*-(2)-substituent. This phenomenon further illustrated the application prospect of the method.

2.3. Mechanism Investigation. To elucidate the mechanism of the reaction, several control experiments were conducted. The first control used benzene sulfonamide without an electron-withdrawing group as the raw material that reacted with styrene oxide, and no product was collected as expected (Scheme 4a). Next, amide with a nitro substitution

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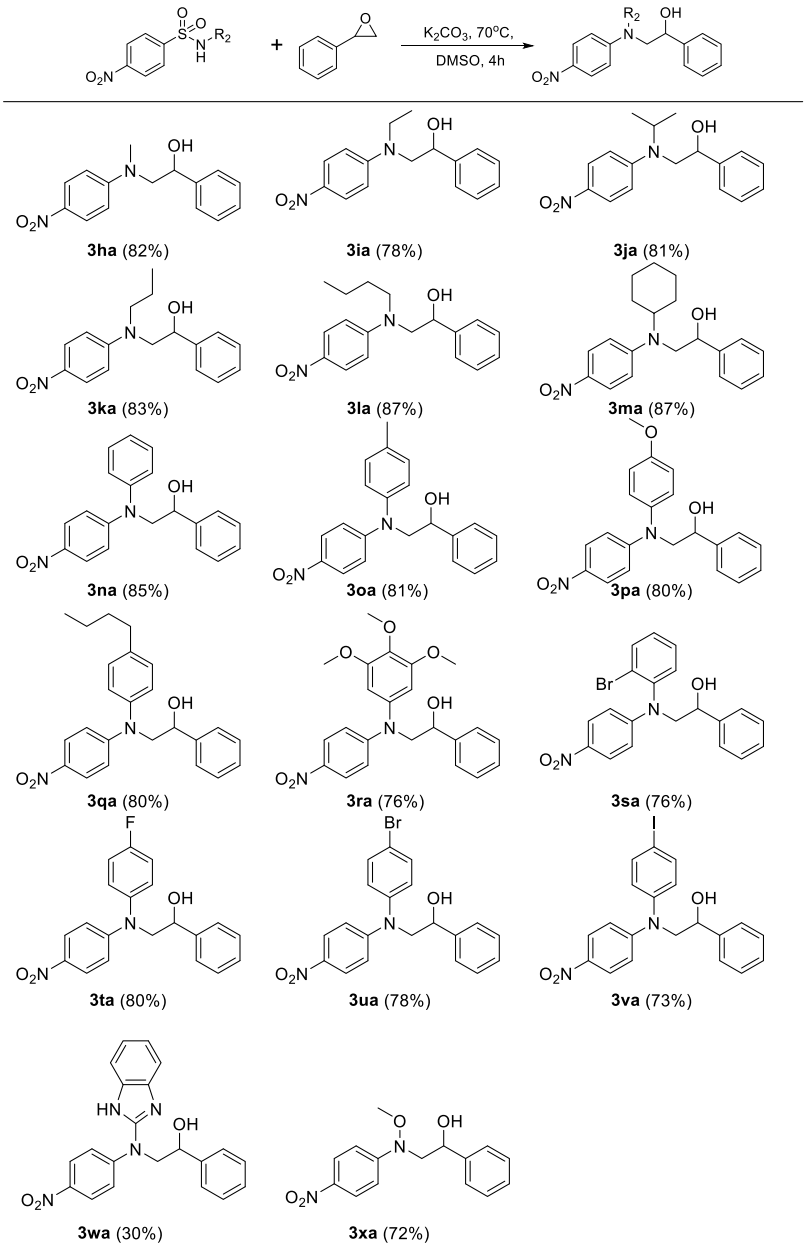
Table 3. Synthesis of Products 3ha−3ya[ab]



[a]Unless specifically noted otherwise, reaction conditions: **1a** (0.5 mmol.), 2-phenyloxirane **2a** (1.5 mmol), K_2CO_3 (1 mmol), DMSO (2 mL), 70 °C, 4 h. [b]Isolated yields.

in the ortho position was used as the raw material, and there was no product either, which accounts for the necessity of removing SO_2 during the reaction (Scheme 4b). Finally, tertiary sulfonamides turned out to be unreactive (Scheme 4c).

Based on the above control experiments and our previous work[17] on the Smiles rearrangement, a possible mechanism for this reaction was proposed, as shown in Scheme 5. Starting with the readily available aryl sulfonamides **1**, addition of styrene oxide should give the adduct **b**. This intermediate **b** could then undergo an O/S Smiles-type ipso substitution with SO_2 extrusion from intramolecular cyclization, thus offering a sulfonamide anion intermediate **d**. Subsequently, **d** formed the intermediate **e** via the N/O Smiles rearrangement, by undergoing another intramolecular cyclization and capturing a proton from $KHCO_3$, which led to the corresponding product **3**.

2.4. Theoretical Results. Because of the reliable accuracy to evaluate structures and energetics, theoretical calculations have been strongly confirmed as a convincing method for many chemical processes. The methods were used to rationalize the experimental process from the intermediate 2-phenoxy-*N*-phenylaniline to product **3**. First, the geometries of minimal and transition states were optimized and calculated using Gaussian 09, which are shown in Figure 1a. The free energy barrier from 2-phenoxy-*N*-phenylaniline to compound **3** is 7.76 kcal/mol, indicating that the secondary rearrangement product was more stable than the intermediate. Also, it was in good agreement with the experiments that through the

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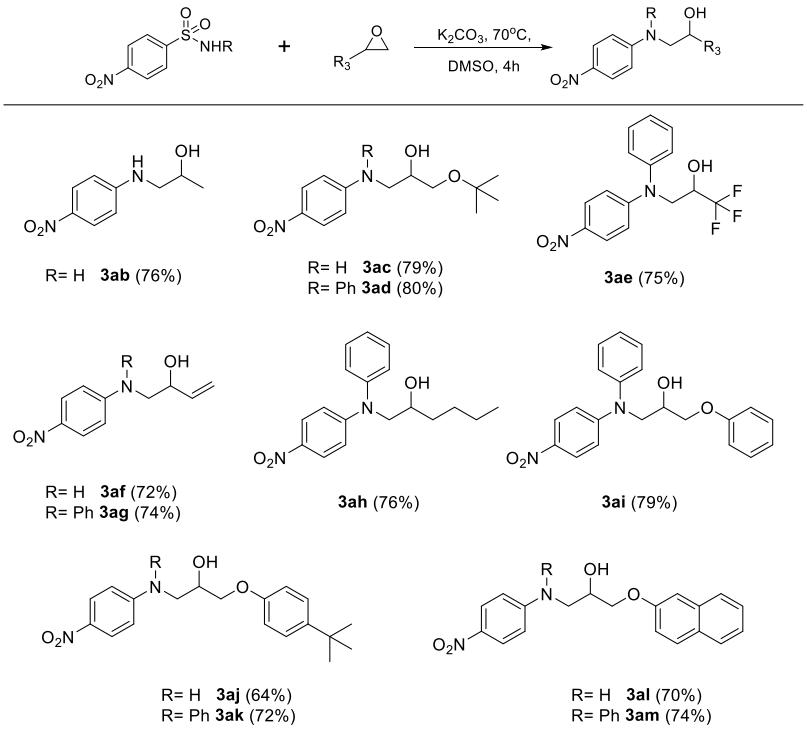
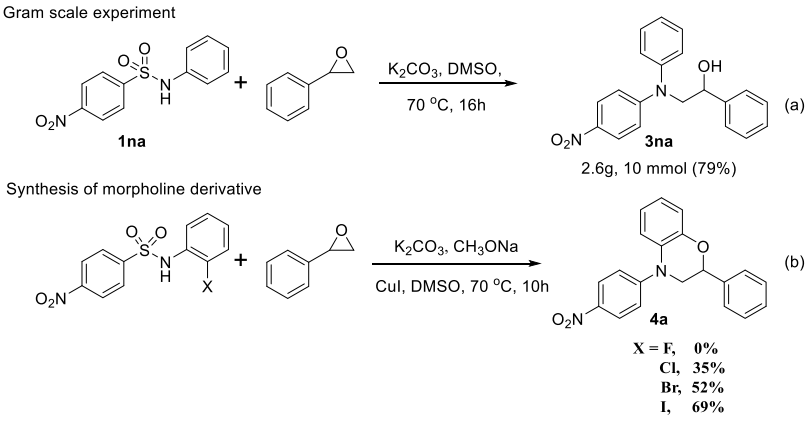
Table 4. Synthesis of Products 3ab–3an[ab]

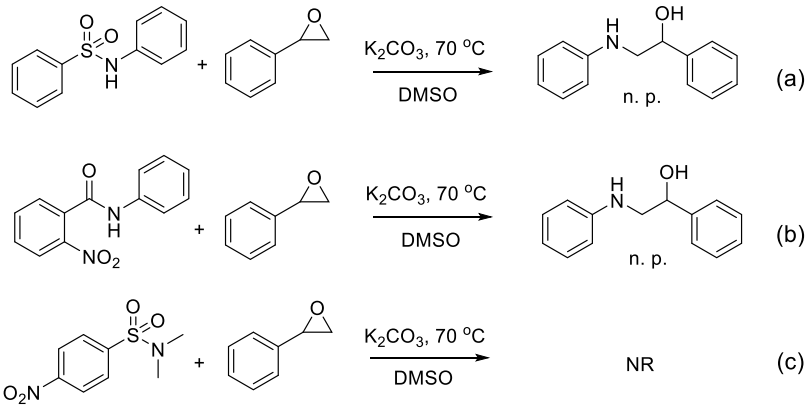


[a]Unless specifically noted otherwise, reaction conditions: **1a** (0.5 mmol), 2-phenyloxirane **2a** (1.5 mmol), K_2CO_3 (1 mmol), DMSO (2 mL), 70 °C, 4 h. [b]Isolated yields.

Scheme 3. Gram-Scale Experiment and Synthesis of 3,4-Dihydro-2*H*-1,4-Benzoxazines



Scheme 4. Control Experiments



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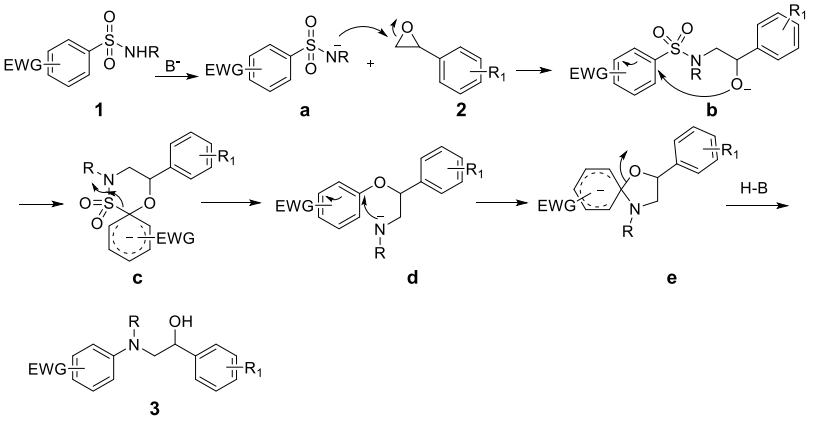
Scheme 5. Proposed Mechanism



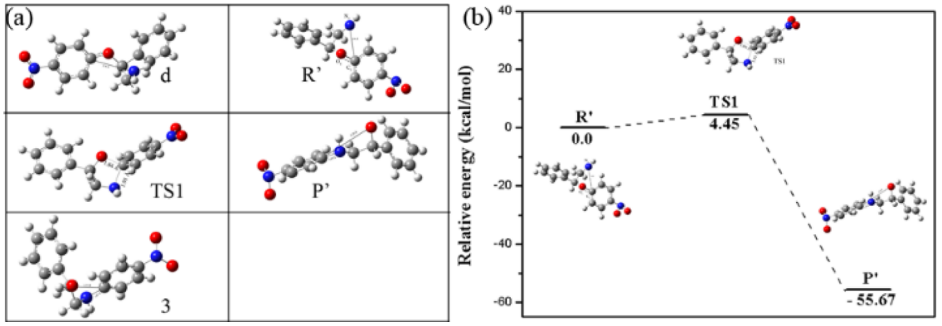


Figure 1. (a) Optimized structures for transition states, intermediate, and products and (b) calculated relative free-energy profiles.

two-step Smiles rearrangement produced the target product β-amino alcohols.

Figure 1b presents the calculated free-energy profiles. R′ denotes the most stable geometry of the anionic reactant, and it was the common starting point of the results of intrinsic reaction coordinate (IRC) calculations. TS1 corresponds to the transition state and the negatively charged N_1 atom was ready to attack C_1. The forward product from TS1 was the precursor of the Smiles rearrangement product P′, a metastable intermediate located on the potential energy surface, where the C_1−N bond had formed and the C_1−O bond had broken. Then, the Smiles rearrangement pathway was completed. From Figure 1b, the free-energy barrier from R′ to P′ is calculated to be 55.67 kcal/mol. The result also confirmed the rationality of the speculation on the mechanism.

3. CONCLUSIONS

To conclude, we have demonstrated that metal-free β-amino alcohol synthesis is possible under mild reaction conditions with a broad scope through a novel benzene sulfonamide−styrene oxide addition, ipso-substitution, SO_2 extrusion sequence, and the subsequent two-step Smiles rearrangement, which might give a new sight for designing multicomponent reactions for the Smiles rearrangement. Moreover, we realized the tandem of the Smiles rearrangement and the Ullmann reaction to produce morpholine derivatives by a one-pot method, further making it a promising candidate for improving the value of the method. What is more, theoretical calculations were performed to confirm the rationality of the speculation on the mechanism. The reaction is notably effective for aromatic-substituted amino alcohols, which are difficult to synthesize by traditional methods. Applications of these β-amino alcohols will be the subject of future investigations in our laboratory.

4. EXPERIMENTS

4.1. General Information. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 MHz spectrometer, with DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Melting points (mp) were measured on a Tektronix XT-4 instrument. All reactions were carried out under an air atmosphere. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} plates (Yinlong) and column chromatography was performed over silica gel (mesh 300−400). Melting points were determined on an XD-4 digital micro melting point apparatus. High-resolution mass spectra were obtained on a Q-TOF6510 spectrograph (Agilent). Single-distilled water was used throughout all experiments; other reagents were commercially available and were used without further purification. DMSO was refluxed and distilled in the presence of Na_2SO_4 in the system.

4.2. Compounds 1a−m Were Prepared According to the Literature (Scheme S1).[18] Amines (4.7 mmol) and sodium acetate (7 mmol) were dissolved in water (6 mL). 4-Nitrobenzensulfonyl chloride (4.5 mmol) was added rapidly to the above mixture. The reaction was stirred and heated at 85 °C until the reaction was finished (modified by TLC). A dark, viscous solid formed initially, but continued heating and stirring converted the product to pale yellow. The solid was collected by reduced pressure filtration and washed with water. The crude product was purified by recrystallization in ether with 20% ethyl acetate, forming 1 g of white crystalline flakes (Scheme S1).

4.3. General Procedures. 4-Nitrobenzenesulfonamide (101 mg, 0.5 mmol) and 2-phenyloxirane (180 mg, 1.5 mmol) in DMSO (2 mL) with K_2CO_3 (1 mmol) were stirred at 70 °C. With the progress of the reaction, the color of the solution gradually deepened and the solution turned from pale yellow to dark brown yellow until the reaction was completed (monitored by TLC). After cooling down to

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room temperature, brine (30 mL) was added to the mixture to quench the reaction. The solution was extracted three times with EtOAc (20 mL × 3). The organic phase was dried with anhydrous magnesium sulfate overnight. After filtration, the solvent was removed under reduced pressure to get a yellow product. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1, v/v) to obtain the desired product.

4.4. Gram-Scale Synthesis of 2-((4-Nitrophenyl)(phenyl)-amino)-1-phenylethan-1-ol (3oa). 4-Nitro-*N*-phenylbenzenesulfonamide (2.78 g), K_2CO_3 (2.76 g), and 2-phenyloxirane (3.6 g) were dissolved in DMSO (15 mL). The mixture was stirred and heated at 70 °C under the air conditions. Until the reaction completed in about 15 h (monitored by TLC), brine (200 mL) was poured to dilute the mixture. After extraction with ethyl acetate (150 mL × 3), the organic solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (10:1, v/v) to obtain the desired product.

4.5. Synthesis of 4-(4-Nitrophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (4a). 4-Nitro-*N*-phenylbenzenesulfonamide (139 mg, 0.5 mmol), 2-phenyloxirane (180 mg, 1.5 mmol), K_2CO_3 (1 mmol), CH_3COOK (0.25 mmol), and CuI (0.025 mmol) with DMSO (2 mL) were stirred at 70 °C until the reaction was completed (monitored by TLC). After cooling down to room temperature, brine (50 mL) was added into the mixture to quench the reaction. The solution was extracted three times with EtOAc (20 mL × 3). The organic phase was dried with anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure to get a deep yellow product. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15:1, v/v) to obtain the desired product.

4.6. Theoretical Calculations. Theoretical calculations were carried on a representative system in the framework of density functional theory, introducing the popular B3LYP functional with the standard 6-311+g (d, p) basis set, as implemented in the Gaussian 09 GaussView software package.

*4.6.1. 2-((4-Nitrophenyl)amino)-1-phenylethan-1-ol (**3a**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3a** as a yellow oil (111 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$-d_6): δ 8.07−8.04 (m, 2H), 7.41−7.26 (m, 5H), 6.55 (d, J = 1 Hz, 2H), 4.97−4.95 (m, 1H), 3.51−3.39 (m, 2H); ^{13}C NMR (101 MHz, CDCl-d_6): 153.2, 141.3, 138.3, 128.9, 128.6, 126.5, 125.9, 111.5, 50.5, HR-MS m/z: $[M + H]^+$ calcd for $[C_{14}H_{15}N_2O_3^+]$, 259.1083; found, 259.1086.

*4.6.2. 4-((2-Hydroxy-2-phenylethyl)(phenyl)amino)benzonitrile (**3da**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3da** as a white oil (122 mg, 78% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.40−7.36 (m, 2H), 7.32−7.28 (m, 1H), 7.10−7.03 (m, 4H), 6.66 (d, J = 8 Hz, 2H), 6.53 (t, J = 8 Hz, 1H), 5.89 (t, J = 8 Hz, 1H), 5.57 (dd, J = 8 Hz, 1H), 3.58−3.49 (m, 1H), 3.45−3.39 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 161.7, 148.7, 139.2, 134.6, 129.4, 129.2, 128.6, 126.9, 119.4, 117.2, 116.5, 112.7, 103.4, 78.9, 50.4; HR-MS m/z: $[M + H]^+$ calcd for $[C_{21}H_{19}N_2O^+]$, 315.1497; found, 315.1492.

*4.6.3. 1-Phenyl-2-(phenyl(4-(trifluoromethyl)phenyl)amino)-ethan-1-ol (**3ea**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ea** as a colorless oil (142 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52−7.45 (m, 3H), 7.41−7.37 (m, 2H), 7.33−7.28 (m, 2H), 7.26−7.15 (m, 4H), 6.97−6.91 (m, 3H), 6.66 (t, J = 8 Hz, 1H), 5.72−5.69 (m, 1H), 5.03−4.91 (m, 1H), 4.04−3.97 (m, 1H), 3.61−3.56 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 160.8, 149.5, 140.2, 139.5, 129.3, 128.7, 128.0, 127.2, 126.7, 117.6, 116.5, 115.0, 79.2, 65.3, 62.8, 54.5; HR-MS m/z: $[M + H]^+$ calcd for $[C_{21}H_{19}F_3N_2O^+]$, 358.1419; found, 358.1414.

*4.6.4. 2-((2-Nitrophenyl)(phenyl)amino)-1-phenylethan-1-ol (**3fa**).* Purification on silica gel (petroleum ether/ethyl acetate = 8:1) afforded compound **3fa** as a yellow solid (104 mg, 62% yield), mp 122−124 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (dd, J = 8 Hz, 1H), 7.72−7.67 (m, 1H), 7.49 (dd, J = 8 Hz, 1H), 7.42−7.33 (m, 5H), 7.30−7.26 (m, 1H), 7.77 (t, J = 8 Hz, 1H), 5.63 (s, 1H), 4.92−4.88 (m, 1H), 3.85−3.73 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 147.4, 146.6, 144.0, 140.9, 134.9, 131.3, 129.6, 128.7, 127.8, 126.6, 126.3, 126.0, 119.7, 115.8, 70.3, 61.0; HR-MS m/z: $[M + H]^+$ calcd for $[C_{20}H_{19}N_2O_3^+]$, 335.1396; found, 335.1397.

*4.6.5. 2-((3-Nitrophenyl)(phenyl)amino)-1-phenylethan-1-ol (**3ga**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ga** as a yellow solid (138 mg, 83% yield), mp 133−135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (dd, J = 8 Hz, 2H), 7.68−7.67 (m, 1H), 7.53−7.47 (m, 3H), 7.41−7.35 (m, 3H), 7.33−7.30 (m, 1H), 7.10−7.07 (t, J = 8 Hz, 2H), 6.57−6.53 (m, 1H), 5.62−5.60 (m, 1H), 3.53−3.44 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 158.7, 149.0, 148.8, 139.1, 131.1, 129.4, 129.2, 126.9, 123.3, 116.6, 116.0, 112.7, 110.9, 79.0, 50.1; HR-MS m/z: $[M + H]^+$ calcd for $[C_{20}H_{18}N_2O_3^+]$, 335.1396; found, 335.1389.

*4.6.6. 2-(Methyl(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ha**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ha** as a yellow oil (111 mg, 82% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06−8.02 (m, 2H), 7.42 (d, J = 8 Hz, 2H), 7.37−7.34 (m, 2H), 7.30−7.25 (m, 1H), 6.83−6.79 (m, 2H), 5.61 (d, J = 4 Hz, 1H), 4.89−4.85 (m, 1H), 3.67−3.57 (m, 2H), 3.01 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.3, 143.7, 136.0, 128.6, 127.8, 126.5, 126.2, 111.3, 70.7, 60.2; HR-MS m/z: $[M + H]^+$ calcd for $[C_{15}H_{17}N_2O_3^+]$, 273.1239; found, 273.1231.

*4.6.7. 2-(Ethyl(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ia**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ia** as a yellow oil (112 mg, 78% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05−8.03 (m, 2H), 7.46−7.44 (m, 2H), 7.38−7.34 (m, 2H), 7.30−7.27 (m, 1H), 6.84−6.81 (m, 2H), 5.64 (s, 1H), 4.87 (m, 1H), 3.62−3.57 (m, 1H), 3.52−3.47 (m, 2H), 3.40−3.35 (m, 1H), 1.06 (t, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 153.4, 143.5, 135.7, 128.6, 127.8, 126.6, 126.4, 111.3, 70.8, 58.3, 46.2, 12.0; HR-MS m/z: $[M + H]^+$ calcd for $[C_{19}H_{16}N_2O_3^+]$, 287.1396; found, 287.1391.

*4.6.8. 2-(Isopropyl(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ja**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ja** as a yellow oil (121 mg, 81% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J = 8 Hz, 2H), 7.44−7.27 (m, 5H), 6.97 (d, J = 8 Hz, 2H), 5.59 (d, J = 4 Hz, 1H), 4.84−4.80 (m, 1H), 4.23−4.16 (m, 1H), 3.54−3.48 (m, 1H), 3.42−3.37 (m, 1H), 1.20 (d, J = 8 Hz, 3H), 1.04 (d, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.4, 144.2, 136.1, 128.7, 127.8, 126.6, 126.1, 112.7, 71.0, 52.9, 50.0, 20.5, 20.1; HR-MS m/z: $[M + H]^+$ calcd for $[C_{17}H_{20}N_2O_3^+]$, 301.1552; found, 301.1555.

*4.6.9. 2-((4-Nitrophenyl)(propyl)amino)-1-phenylethan-1-ol (**3ka**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ka** as a yellow oil (124 mg, 83% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, J = 8 Hz, 2H), 7.42 (d, J = 4 Hz 4H), 7.29 (s, 1H), 6.70 (dd, J = 8 Hz, 2H), 5.03 (q, J = 4 Hz,1H), 3.75−3.69 (q, J = 8 Hz, 2H), 3.62−3.57 (dd, J = 4 Hz, 2H), 3.42−3.38 (m, 1H), 3.33−3.29 (m, 1H), 1.67−1.60 (m, 2H), 0.91−0.93 (t, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 153.6, 143.8, 135.7, 128.6, 126.6, 126.4, 122.0, 111.3, 70.6, 58.8, 53.4, 19.6, 11.5; HR-MS m/z: $[M + H]^+$ calcd for $[C_{17}H_{20}N_2O_3^+]$, 301.1552; found, 301.1550.

*4.6.10. 2-(Butyl(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3la**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3la** as a yellow oil (136 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05−8.01 (m, 2H), 7.44−7.41 (m, 2H), 7.37−7.34 (m, 2H), 7.30−7.26 (m, 1H), 6.80 (d, J = 8 Hz, 2H), 5.61 (d, J = 4 Hz, 1H), 4.87−4.83 (m, 1H), 3.62−3.50 (m, 2H), 1.55−1.43 (m, 2H), 1.40−1.35 (m, 2H), 1.32−1.23 (m, 2H), 0.93−0.80 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 153.5, 143.8, 135.7, 128.6, 127.8, 126.6, 126.5, 111.3, 70.6, 58.8, 51.5, 28.5, 20.0, 14.2; HR-MS m/z: $[M + H]^+$ calcd for $[C_{18}H_{23}N_2O_3^+]$, 315.1709; found, 315.1704.

*4.6.11. 2-(Cyclohexyl(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ma**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ma** as a yellow oil (148 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, J = 8 Hz, 2H), 7.44−7.42 (m, 2H), 7.39−7.34 (m, 2H), 7.30−7.26 (m, 1H), 6.97 (d, J = 8 Hz, 2H), 5.58 (d, J = 4 Hz, 1H), 4.83−4.79 (m, 1H), 3.37−3.72 (m, 1H),

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3.36−3.39 (m, 3H), 1.82−1.71 (m, 3H), 1.64−1.54 (m, 3H), 1.42−1.33 (n, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.4, 144.1, 136.1, 128.7, 127.8, 126.6, 126.2, 112.6, 71.4, 58.3, 53.3, 30.8, 30.0; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{25}N_2O_3^+$], 341.1856; found, 341.1853.

*4.6.12. 2-((4-Nitrophenyl)(phenyl)amino)-1-phenylethan-1-ol (**3na**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3na** as a yellow oil (142 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04−8.00 (m, 2H), 7.45 (t, J = 8 Hz, 2H), 7.39−7.27 (m, 8H), 6.80−6.76 (m, 2H), 5.73 (d, J = 4 Hz, 1H), 4.89−4.84 (m, 1H), 4.01−3.95 (m, 1H), 3.92−3.87 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.3, 145.5, 143.5, 137.3, 130.6, 128.7, 128.0, 127.9, 127.2, 126.6, 126.0, 113.8, 70.3, 60.5; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{18}N_2O_3^+$], 335.1396; found, 335.1513.

*4.6.13. 2-((4-Nitrophenyl)(p-tolyl)amino)-1-phenylethan-1-ol (**3oa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3oa** as a yellow oil (141 mg, 81% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 8 Hz, 2H), 7.39−7.32 (m, 4H), 7.28 (d, J = 8 Hz, 3H), 7.17 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H), 4.88−4.86 (m, 1H), 3.96−3.85 (m, 2H), 2.35 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.7, 143.6, 143.0, 137.2, 136.7, 131.1, 128.7, 128.0, 127.8, 126.6, 126.0, 113.4, 70.4, 60.6, 21.1; HR-MS m/z: [M + H]$^+$ calcd for [$C_{21}H_{20}N_2O_3^+$], 349.1522; found, 349.1548.

*4.6.14. 2-((4-Methoxyphenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3pa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3pa** as a yellow oil (146 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, J = 8 Hz, 2H), 7.34−7.32 (m, 4H), 7.27 (d, J = 4 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 6.71 (d, J = 8 Hz, 2H), 5.74 (d, J = 4 Hz, 1H), 4.88−4.87 (m, 1H), 3.95−3.93 (m, 2H), 3.80 (s, 3H), 3.39 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 158.2, 154.9, 143.6, 129.6, 128.7, 128.6, 127.9, 126.0, 115.9, 113.3, 70.5, 60.8, 55.8; HR-MS m/z: [M + H]$^+$ calcd for [$C_{21}H_{20}N_2O_4^+$], 365.1501; found, 365.1496.

*4.6.15. 2-((4-Butylphenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3qa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3qa** as a yellow oil (156 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02−8.00 (m, 2H), 7.37−7.32 (m, 4H), 7.31−7.26 (m, 3H), 7.19−7.17 (m, 2H), 6.75−6.73 (m, 2H), 5.70 (d, J = 4 Hz, 1H), 4.86−4.82 (m, 1H), 3.98−3.92 (m, 1H), 3.87−3.83 (m, 1H), 2.59 (t, J = 8 Hz, 2H), 1.61−1.55 (m, 2H), 1.37−1.32 (m, 2H), 0.91 (t, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.6, 143.6, 143.2, 141.5, 137.3, 130.4, 129.8, 128.7, 127.9, 126.6, 126.1, 121.8, 113.5, 70.4, 60.6, 34.8, 22.3, 14.3; HR-MS m/z: [M + H]$^+$ calcd for [$C_{24}H_{27}N_2O_3^+$], 391.2022; found, 391.2021.

*4.6.16. 2-((4-Nitrophenyl)(3,4,5-trimethoxyphenyl)amino)-1-phenylethan-1-ol (**3ra**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ra** as a yellow oil (161 mg, 76% yield), mp 113−115 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, J = 8 Hz, 2H), 7.40−7.32 (m, 4H), 7.29−7.25 (m, 1H), 6.79 (d, J = 8 Hz, 2H), 6.25 (s, 2H), 5.74 (s, 1H), 4.89 (s, 1H), 4.05−3.99 (m, 1H), 3.86−3.83 (m, 1H), 3.70−3.69 (m, 9H), 3.36 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.6, 154.2, 143.6, 141.2, 137.3, 136.6, 128.7, 127.9, 126.8, 126.1, 113.5, 105.6, 70.3, 60.5, 56.4; HR-MS m/z: [M + H]$^+$ calcd for [$C_{23}H_{25}N_2O_6^+$], 425.1713; found, 425.1712.

*4.6.17. 2-((2-Bromophenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3sa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3sa** as a yellow oil (157 mg, 76% yield), mp 121−123 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09−8.04 (d, 2H), 7.82 (d, J = 8 Hz, 1H), 7.51 (s, 1H), 7.40−7.32 (m, 5H), 7.30−7.26 (m, 1H), 6.61 (d, J = 8 Hz, 2H), 5.74 (d, J = 4.4 Hz, 1H), 4.95 (s, 1H), 3.35 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 143.5, 137.8, 134.7, 132.7, 130.4, 130.0, 129.8, 128.7, 128.0, 127.0, 126.7, 126.2, 123.6, 112.6, 70.7, 59.8; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{18}BrN_2O_3^+$], 413.0501; found, 413.0506.

*4.6.18. 2-((4-Fluorophenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ta**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ta** as a yellow oil (141 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05−8.02 (m, 2H), 7.40−7.26 (m, 9H), 6.78−6.75 (m, 2H), 5.74 (d, J = 4 Hz, 1H), 4.89−4,85 (m, 1H), 3.07−3.85 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 162.1, 159.6, 154.4, 143.5, 137.5, 130.4, 128.7, 127.9, 126.6, 126.1, 117.2, 113.5, 70.3, 60.7; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{18}FN_2O_3^+$], 353.1301; found, 353.1299.

*4.6.19. 2-((4-Bromophenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3ua**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ua** as a pale yellow oil (161 mg, 78% yield), mp 125−128 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, J = 9.2 Hz, 2H), 7.65−7.63 (dd, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 736−7.32 (t, J = 8 Hz, 2H), 7.29−7.27 (m, 3H), 5.75 (d, J = 4 Hz, 1H), 4.89−4.84 (m, 1H), 3.92 (d, J = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.0, 145.1, 143.4, 138.0, 133.4, 129.9, 128.7, 127.9, 126.6, 126.0, 119.4, 114.4, 70.3, 60.4; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{18}BrN_2O_3^+$], 413.0501; found, 413.0499.

*4.6.20. 2-((4-Iodophenyl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3va**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3va** as a yellow oil (168 mg, 73% yield), mp 145−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (dd, J = 8 Hz, 2H), 7.80 (dd, J = 8 Hz, 2H), 7.40−7.32 (m, 4H), 7.29−7.29 (m, 1H), 7.13 (dd, J = 8 Hz, 2H) 5.26 (d, J = 4 Hz, 1H), 3.92 (d, J = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 153.9, 145.5, 143.3, 139.4, 137.9, 130.0, 128.6, 126.4, 125.9, 114.5, 91.8, 70.3, 60.4; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{18}N_2O_3I^+$], 461.0362; found, 461.0364.

*4.6.21. 2-((1H-Benzo[d]imidazole-2-yl)(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3wa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3wa** as an orange solid (56 mg, 30% yield), mp 133−134 °C;^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 8.23 (d, J = 8 Hz, 2H), 8.00−7.96 (m, 2H), 7.49−7.47 (m, 1H), 7.41 (d, J = 8 Hz, 2H), 7.39−7.37 (m, 1H), 7.33−7.28 (m, 2H), 7.21−7.18 (m, 1H), 7.14−7.08 (m, 2H), 6.00 (s, 1H), 4.99−4.96 (m, 1H), 4.56−4.50 (m, 1H), 4.46−4.42 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 149.2, 147.8, 142.7, 141.6, 140.5, 134.2, 128.5, 127.9, 126.6, 125.6, 121.8, 121.1, 117.3, 117.2, 109.9, 71.5, 50.0; HR-MS m/z: [M + H]$^+$ calcd for [$C_{21}H_{19}N_4O_3^+$], 375.1457; found, 375.1450.

*4.6.22. 2-(Methoxy(4-nitrophenyl)amino)-1-phenylethan-1-ol (**3xa**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3xa** as a yellow oil (104 mg, 72% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99−7.97 (m, 2H), 7.44−7.42 (m, 2H), 7.38−7.33 (m, 3H), 6.73−6.71 (m, 2H), 5.62 (d, J = 4 Hz, 1H), 4.79−4.76 (m, 1H), 3.39−3.38 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6): 155.1, 143.9, 136.1, 129.2, 128.6, 127.7, 126.6, 126.6, 71.3, 51.0; HR-MS m/z: [M + H]$^+$ calcd for [$C_{15}H_{17}N_2O_4^+$], 289.1188; found, 289.1185.

*4.6.23. 1-((4-Nitrophenyl)amino)propan-2-ol (**3ab**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ab** as a yellow oil (75 mg, 76% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, J = 8 Hz, 2H), 7.27 (t, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 2H), 4.81 (d, J = 4 Hz, 1H), 3.84−3.78 (m, 1H), 3.16−3.04 (m, 2H), 1.11 (d, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 155.3, 135.8, 126.7, 111.4, 65.2, 50.6, 21.7; HR-MS m/z: [M + H]$^+$ calcd for [$C_9H_{13}N_2O_3^+$], 197.0926; found, 197.0920.

*4.6.24. 1-(tert-Butoxy)-3-((4-nitrophenyl)amino)propan-2-ol (**3ac**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ac** as a yellow oil (106 mg, 79% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00−7.97 (m, 2H), 7.24 (t, J = 4 Hz, 1H), 6.71−6.68 (m, 2H), 4.93 (d, J = 4 Hz, 1H), 3.34−3.27 (m, 3H), 3.14−3.07 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): 155.4, 135.9, 126.6, 111.5, 72.9, 69.2, 64.3, 27.8; HR-MS m/z: [M + H]$^+$ calcd for [$C_{12}H_{19}N_2O_3^+$], 269.1501; found, 269.1499.

*4.6.25. 1-(tert-Butoxy)-3-((4-nitrophenyl)(phenyl)amino)propan-2-ol (**3ad**).* Purification on silica gel (petroleum ether/ethyl acetate = 15:1) afforded compound **3ad** as a yellow oil (138 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02−8.00 (m, 2H), 7.52−7.49 (m, 2H), 7.40−7.34 (m, 3H), 6.79−6.77 (m, 2H), 5.06 (d, J = 4 Hz, 1H), 3.72−3.66 (m, 1H), 3.35−3.31 (m, 1H), 3.26−3.22 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.6, 145.7, 137.3, 130.6, 128.1, 127.2, 126.0, 72.9, 68.2, 64.4, 56.5, 27.7; HR-MS m/z: [M + H]$^+$ calcd for [$C_{18}H_{23}N_2O_3^+$], 345.1814; found, 345.1818.

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*4.6.26. 1,1,1-Trifluoro-3-((4-nitrophenyl)(phenyl)amino)propan-2-ol (**3ae**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ae** as a yellow oil (122 mg, 75% yield), mp 105−107 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08−8.04 (m, 2H), 7.52 (t, J = 8 Hz, 2H), 7.42−7.36 (m, 3H), 6.85−6.76 (m, 3H), 4.28−4.22 (m, 1H), 4.12−4.07 (m, 1H), 4.03−3.97 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.2, 145.0, 138.1, 130.8, 128.1, 127.6, 126.0, 113.8, 67.5, 67.2, 66.9, 66.7, 52.6; HR-MS m/z: [M + H]$^+$ calcd for [$C_{15}H_{14}F_3N_2O_3^+$], 327.0957; found, 327.0954.

*4.6.27. 1-((4-Nitrophenyl)amino)but-3-en-2-ol (**3af**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3af** as a yellow oil (75 mg, 72% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, J = 8 Hz, 2H), 7.26 (t, J = 4 Hz, 1H), 6.69 (d, J = 8 Hz, 2H), 5.97−5.89 (m, 1H), 5.32−5.27 (m, 1H), 5.19 (d, J = 4 Hz, 1H), 5.13−5.11 (m, 1H), 4.20−4.17 (m, 1H), 3.28−3.22 (m, 1H), 3.16−3.10 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 155.2, 140.2, 136.0, 126.6, 115.4, 111.2, 70.1, 49.0; HR-MS m/z: [M + H]$^+$ calcd for [$C_{10}H_{13}N_2O_3^+$], 209.0926; found, 209.0925.

*4.6.28. 1-((4-Nitrophenyl)(phenyl)amino)but-3-en-2-ol (**3ag**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ag** as a yellow oil (105 mg, 74% yield), mp 94−96 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04−8.00 (m, 2H), 7.53−7.49 (m, 2H), 7.40−7.33 (m, 3H), 6.75 (dd, J = 8 Hz, 2H), 5.96−5.87 (m, 1H), 5.34 (d, J = 4 Hz, 1H), 5.31−5.26 (m, 1H), 5.12−5.09 (m, 1H), 4.29−4.25 (m, 1H), 3.87−3.73 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.5, 145.5, 139.9, 137.4, 130.7, 128.2, 127.3, 126.1, 115.7, 113.6, 69.3, 58.5; HR-MS m/z: [M + H]$^+$ calcd for [$C_{17}H_{17}N_2O_3^+$], 285.1239; found, 285.1259.

*4.6.29. 1-((4-Nitrophenyl)(phenyl)amino)hexan-2-ol (**3ah**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ah** as a pale yellow oil (120 mg, 76% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03−7.99 (m, 2H), 7.49 (t, J = 8 Hz, 2H), 7.40−7.33 (m, 3H), 6.77−6.73 (m, 2H), 4.97 (d, J = 4 Hz, 1H), 3.78−3.70 (m, 3H), 1.42−1.28 (m, 4H), 1.26−1.20 (m, 2H), 0.81 (t, J = 8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.7, 145.7, 137.2, 130.7, 128.2, 127.3, 126.1, 113.4, 67.9, 59.1, 34.7, 27.7, 22.7, 14.4; HR-MS m/z: [M + H]$^+$ calcd for [$C_{18}H_{23}N_2O_3^+$], 315.1709; found, 315.1701.

*4.6.30. 1-((4-Nitrophenyl)(phenyl)amino)-3-phenoxypropan-2-ol (**3ai**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ai** as a yellow solid (144 mg, 79% yield), mp 100−102 °C ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03−7.99 (m, 2H), 7.50−7.48 (m, 2H), 7.43−7.40 (m, 2H), 7.36−7.32 (m, 1H), 7.30−7.25 (m, 2H), 6.93−6.90 (m, 3H), 6.82−6.78 (m, 2H), 5.48 (d, J = 4 Hz, 1H), 4.13−4.05 (m, 2H), 3.99−3.96 (m, 2H), 3.92−3.87 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 158.8, 154.6, 145.6, 137.5, 130.8, 129.9, 128.1, 127.3, 126.0, 121.2, 115.0, 113.6, 70.3, 67.0, 55.9; HR-MS m/z: [M + H]$^+$ calcd for [$C_{21}H_{21}N_2O_4^+$], 365.1501; found, 365.1459.

*4.6.31. 1-(4-(tert-Butyl)phenoxy)-3-((4-nitrophenyl)amino)-propan-2-ol (**3aj**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3aj** as a yellow oil (110 mg, 64% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99−7.95 (m, 2H), 7.36−7.27 (m, 3H), 6.89−6.85 (m, 3H), 6.71−6.69 (m, 1H), 5.41−5.30 (m, 1H), 4.13−4.07 (m, 1H), 3.94−3.92 (m, 2H), 3.84−3.80 (m, 1H), 3.61−3.55 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): 156.7, 155.3, 153.8, 143.4, 136.0, 126.5, 114.5, 111.5, 70.3, 68.0, 67.0, 34.2, 31.8; HR-MS m/z: [M + H]$^+$ calcd for [$C_{19}H_{25}N_2O_4^+$], 345.1814; found, 345.1818.

*4.6.32. 1-(4-(tert-Butyl)phenoxy)-3-((4-nitrophenyl) (phenyl)-amino)propan-2-ol (**3ak**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3ak** as a yellow oil (151 mg, 72% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01−7.97 (m, 2H), 7.51−7.47 (m, 2H), 7.41−7.30 (m, 2H), 7.34−7.31 (m, 1H), 7.27−7.25 (m, 2H), 6.84−6.77 (m, 4H), 5.45 (d, J = 4 Hz, 1H), 4.10−4.08 (m, 1H), 3.96−3.94 (m, 1H), 3.90−3.84 (m, 1H), 1,24 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): 161.4, 159.2, 150.4, 148.1, 142.2, 135.4, 132.8, 132.0, 131.2, 130.7, 119.3, 118.3, 75.2, 71.8, 60.7, 39.0, 36.5; HR-MS m/z: [M + H]$^+$ calcd for [$C_{25}H_{29}N_2O_4^+$], 421.2127; found, 421.2129.

*4.6.33. 1-(Naphthalen-2-yloxy)-3-((4-nitrophenyl)amino)-propan-2-ol (**3al**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3al** as a yellow oil (118 mg, 70% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28−8.25 (m, 4H), 7.97−7.94 (m, 2H), 7.87−7.84 (m, 1H), 7.52−7.45 (m, 3H), 7.41−7.34 (m, 2H), 6.93 (d, J = 8 Hz, 1H), 6.72 (dd, J = 8 Hz, 2H), 5.55 (d, J = 4 Hz, 1H), 4.20−4.14 (m, 3H), 3.55−3.50 (m, 1H), 3.41-3-38 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 155.2, 154.4, 127.9, 127.0, 126.7, 126.6, 125.7, 122.2, 120.5, 105.7, 70.6, 68.0, 46.2; HR-MS m/z: [M + H]$^+$ calcd for [$C_{19}H_{19}N_2O_4^+$], 339.1345; found, 339.1346.

*4.6.34. 1-(Naphthalen-2-yloxy)-3-((4-nitrophenyl) (phenyl)-amino)propan-2-ol (**3am**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **3am** as a yellow solid (153 mg, 74% yield), mp 118−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (d, J = 8 Hz, 1H), 7.99−7.97 (m, 2H), 7.85 (d, J = 8 Hz, 1H), 7.55−7.39 (m, 8H), 7.34−7.30 (m, 1H), 6.90 (d, J = 8 Hz, 1H), 6.86−6.82 (m, 2H), 5.60 (d, J = 4 Hz, 1H), 4.30−4.27 (m, 1H), 4.22−4.16 (m, 3H), 4.04−3.99 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 154.5, 154.3, 145.6, 137.5, 134.5, 130.7, 128.0, 127.9, 126.9, 126.6, 126.0, 125.7, 122.1, 120.6, 113.7, 105.7, 70.6, 67.2, 56.0; HR-MS m/z: [M + H]$^+$ calcd for [$C_{25}H_{23}N_2O_4^+$], 415.1658; found, 415.1651.

*4.6.35. 4-(4-Nitrophenyl)-2-phenyl-3,4-dihydro-2H-benzo[b]-[1,4]oxazine (**4a**).* Purification on silica gel (petroleum ether/ethyl acetate = 10:1) afforded compound **4a** as a yellow solid, mp 135−137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16−8.12 (m, 2H), 7.46−7.44 (m, 2H), 7.41−7.35 (m, 5H), 7.32−7.29 (m, 2H), 7.10−7.01 (m, 2H), 6.94−6.90 (m, 1H), 5.30 (dd, J = 8 Hz, 1H), 4.21−4.17 (m, 1H), 3.79−3.74 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): 152.1, 147.1, 140.4, 138.3, 128.9, 128.3, 127.0, 125.9, 124.3, 121.1, 120.3, 119.0, 118.2, 75.8, 52.4; HR-MS m/z: [M + H]$^+$ calcd for [$C_{20}H_{17}N_2O_3^+$], 333.1239; found, 333.1231.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01543.

Reaction conditions, calculation of quantity, characterization, ^{1}H NMR and ^{13}C NMR spectra of all compounds, and Cartesian coordinates and absolute energies for all structures involved in theoretical calculations (PDF)

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Notes

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