Res Chem Intermed
DOI 10.1007/s11164-016-2551-6

An efficient and green $La(OTf)_3$ catalyzed Petasis borono–Mannich reaction for the synthesis of tertiary amines

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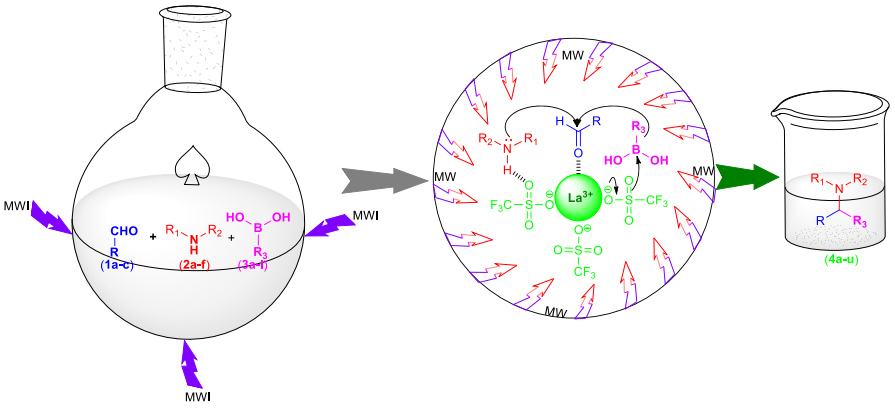
Received: 7 February 2016 / Accepted: 18 April 2016

Abstract A variety of tertiary amine derivatives have been prepared by a one-pot three-component Petasis borono–Mannich reaction of two different salicylaldehydes and 2-formylpyridine, substituted morpholine/piperidines and aryl boronic acids. These reactions were carried out under microwave irradiation using a catalytic amount of $La(OTf)_3$ in a short reaction time. This procedure has the advantages of high conversions with excellent chemoselectivity.

Graphical Abstract The attractive features of this methodology are simple procedure, green reaction, reusability and high efficiency of the catalyst and easy workability.



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Published online: 13 May 2016

Keywords 4-(5-methyl-2-phenyl-2*H*-1,2,4-triazol-3-yl) piperidine · $La(OTf)_3$ · 2-hydroxybenzaldehyde · PBM reaction

Introduction

Natural products, pharmaceutical agents and synthetic materials contain amine functionality. They have a major role in the medicinal chemistry/pharmaceutical industries. For this reason, the synthesis of amines is of prime importance for many synthetic applications. Over the past decades, various methodologies have been developed for the synthesis of a broad range of amines. Even so, in synthetic organic chemistry, a rapid search for new compounds with preferred properties is still in progress.

Nowadays, the generation of molecular diversity and complexity from simple and readily available substrates is a major challenge. Therefore, the formation of several bonds in a single operation is highly desirable to develop industrial processes. In this way, a multi-component reaction (MCR) is one of the most efficient ways to rapidly increase the molecular complexity of products with high levels of atom efficiency [1, 2]. These reactions are convergent chemical processes and involve well-defined condensation of more than two reactants to form a product [3], while avoiding expensive starting materials, numbers of reaction steps, time-consuming isolation and purification of synthetic intermediates [4–6]. Other advantages of MCRs are numerous possible reagent combinations which usually result in a high exploratory power, environmentally friendly procedures and high product selectivity [7]. Therefore, MCRs exhibit the possibility of automatization and allow systematic variations by their experimental simplicity [8–10]. With these reasons, MCRs are especially suitable for diversity-oriented synthesis (DOS) [11–14] and combinatorial synthesis [15].

Among the various MCRs, the Petasis reaction or borono–Mannich reaction (BMR) [16–20] has been reported for the preparation of several small organic molecules with distinct functional groups and has received much attention due to its power to produce various amino compounds (e.g., substituted α-amino acids, α/β-hydroxyl amines, alkylaminophenols, 2-hydroxyl morpholines, heterocyclic compounds, carboxylic acids and 2*H*-chromenes) by a three-component coupling of an aldehyde, an amine and aryl/vinyl boronic acid. However, it requires a period of 24 h or more (also, in some cases, refluxing) in various solvents. In recent years, Petasis BMR has been reported in solvent-free conditions [21] and also with various type of catalysts, such as $BF_3.OEt_2$ [22], $(TFA)_2$ [23], and solid phase catalysts [24]. Candeias et al. [25] reported that water was a suitable medium for this reaction. Chiral α-amino acids with various functionalities can also be conveniently prepared using a chiral biphenol as a catalyst in toluene [26].

In this way, binaphthol catalyzed asymmetric Petasis reactions in the presence of 4 Å molecular sieves (MS) has been reported for products with up to 99 % *ee* [27]. Recently, we reported trititanate nanotubes as a robust solid–acid catalystst for this reaction [28]. However, these procedures require a longer reaction time.

On the other hand, in recent years, the use of microwave irradiation (MWI) as a thermal source to accelerate organic reactions has gained popularity [29]. The advantages of this technique over conventional methods are shorter reaction times, cleaner reactions, easy work-up and minimization of thermal decomposition of products. To date, several three-component reactions have been reported using this environmentally benign green protocol [30]. Tye and co-workers reported the reaction between *ortho* hydroxy benzaldehyde with aryl boronic acids to generate the products in moderate yields of amino acids under a microwave source [31]. Therefore, the development of a rapid and efficient method for the synthesis of 2-((4-(5-methyl-2-phenyl-2*H*-1,2,4-triazol-3-yl)piperidin-1-yl)(phenyl)methyl) phenol derivatives is desirable, and we have sought to speed up the Petasis reaction using focused $La(OTf)_3$ as a catalyst and microwave sources.

Materials and methods

All the chemicals, solvents and reagents procured from Sigma-Aldrich (Hyderabad, India), Merck (Mumbai, India), Lancaster Chemical (Mumbai, India) and SD Fine Chemicals were used as received without further purification. All the solvents for the spectroscopic and other physical studies were reagent grade and were further purified, employing the reported methods. All the reported melting points in the experiment were determined in open capillary tubes on a Mel-Temp apparatus. All the NMR spectra were recorded on a Bruker 400 MHz spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The compounds were dissolved in $CDCl_3$ and DMSO and the chemical shifts were referenced to TMS. Coupling constants were calculated in hertz (Hz). The elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer, and the mass spectra were recorded on Agilent LC/MSD SL 1100 instrument. All the microwave reactions were carried out in a CEM Focused microwave reactor.

General procedure

Synthetic procedures for the model reaction: Synthesis of methyl 3-((2-chlorophenyl)(morpholino)methyl)-4-hydroxybenzoate ***(4a)***

MWI method A dry Pyrex tube fitted with an air-tight rubber cap was charged with methyl 3-formyl-4-hydroxybenzoate (**1a**, 100 mg, 0.55 mmol), morpholine (**2a**, 48 mg, 0.55 mmol), and 2-chloro phenylboronic acid (**3a**, 86.0 mg, 0.55 mmol). Under argon, $La(OTf)_3$ (3.0 mg, 0.005 mmol) and argon-purged 1,4-dioxane (2 mL) were added. The resulting mixture was placed in the CEM microwave reactor and allowed to react at 39–110 °C for 2–22 min (Table 2). Then the reaction mixture was cooled and filtered and the filtrate was transferred to a separating funnel and diluted with ethyl acetate and water. The organic phase was separated and dried over anhydrous sodium sulfate. The organic solution was filtered and the filtrate concentrated prior to silica gel chromatography using hexane–ethyl acetate (50:1).The fractions were concentrated and dried in vacuum to get 196 mg (yield,

98 %) of methyl 3-((2-chlorophenyl)(morpholino)methyl)-4-hydroxybenzoate (**4a**) as a white solid, m.p. 140–142 °C. The used catalyst from different experiments was combined by filtration, washed with ether and dried overnight in a vacuum oven and reused for further reactions.

Conventional/oil bath heating method In the second regular conventional method, all the mentioned reactants in the MWI method were stirred at RT and 60 °C for 10–26 h in an oil bath, and the workup procedure and the purification of the products were carried out in a similar way by following the MWI procedure.

The above MWI procedure was applied successfully for the preparation of all the other titled compounds (**4b–q**) which were obtained (TLC) in 2 min at high yields (Table 2). These compounds were characterized by ^{1}H and ^{13}C NMR and LC/MSD spectral data.

*Synthesis of tert-butyl 4-(3-methyl-1-phenyl-1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate **(6)***

To a stirred solution of 1-(tert-butoxycarbonyl) piperidine-4-carboxylic acid **5** (5.0 g, 21.83 mmol) in DMF (5.0 mL) was added *N, N*-isopropylehylamine (5.5 mL, 32.74) followed by acetamidinehydrochloride (2.45 g, 26.2 mmol) and HATU (9.9 g, 26.2 mmol) at RT, then stirred for 2 h. Next, phenylhydrazine hydrochloride (3.4 g, 24 mmol) and acetic acid (4 mL, 65.5 mmol) were added (Scheme 2). The resulting reaction mixture was stirred at 80 °C for 4 h. The reaction mass was diluted with water and extracted by ethyl acetate, dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude compound. The crude compound was triturated with diethyl etherto give compound **6** (7 g, quantitative yield) as an off-white solid. It was used for the next step without further purification.

*Synthesis of 4-(3-methyl-1-phenyl-1H-1,2,4-triazol-5-yl)piperidine (**2b**)*

To a stirred solution of *tert*-butyl 4-(5-methyl-2-phenyl-2*H*-1, 2, 4-triazol-3-yl) piperidine-1-carboxylate (2 g, 5.8 mmol) in dioxane HCl (10 mL) and stirred for 16 h (Scheme 2). Then, the solvent was concentrated under reduced pressure to obtain a residue, which was triturated with diethyl ether to give **2b** (1.3 g, 78 %) as a salt.

IR (KBr, ν_{max} (cm^{-1})): 3412, 3215, 2772, 2714, 1626, 1557, 1296; ^{1}H NMR (400 MHz, dmso-d_6) δ: 8.86 (s, 1H), 8.69 (br s, 1H), 7.60–7.50 (m, 5H), 3.28 (d, J = 12.8 Hz, 2H), 3.17–3.09 (m, 1H), 2.92 (d, J = 10.0 Hz, 2H), 2.30 (s, 3H), 1.97–1.92 (m, 4H);^{13}C NMR (100.57 MHz, dmso-d_6) δ: 156.5, 156.5, 136.0, 129.9, 129.9, 125.6, 42.0, 30.4, 26.6, 12.6.

Physical, analytical, and spectral data for the titled compounds, (4a–q)

Methyl 3-((2-chlorophenyl)(morpholino)methyl)-4-hydroxybenzoate (**4a**) Yield 97 %; white solid, m.p. 158–160 °C; IR (KBr, ν_{max} (cm^{-1})): 3624 (Ar-OH), 3042

(C–H_{Ar}), 2964 (C–H_{ali}), 1740 (C=O), 1575 (Ar–C=C), 1230 (C–N), 1102 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.6 (s, 1H), 7.84 (d d, $J_1 = 1.2$ Hz, $J_2 = 8.4$ Hz, 1H), 7.73 (d, $J = 2.0$ Hz, 1H), 7.56 (m, 1 H), 7.40 (t, $J = 3.6$ Hz, 1H), 7.20 (m, 2H), 6.88 (d,$J = 8.4$ Hz, 1 H), 5.3 (s, 1 H), 3.82 (s, 3 H), 3.6 (m, 4 H), 2.7 (m, 2 H), 2.58 (m, 2 H); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 166.6, 160.2, 136.0, 134.1, 131.4, 130.9, 130.0, 129.4, 127.8, 124.0, 121.6, 117.2, 69.6, 66.8. 51.8. Anal. Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87 %; Found: C, 63.04; H, 5.54; N, 3.83.

Methyl 4-hydroxy-3-(morpholino (p-tolyl) methyl) benzoate (**4b**) Yield 98 %; thick liquid, IR (KBr, ν_{max} (cm^{-1})): 3624 (Ar-OH), 3046 (C–H_{Ar}), 2960 (C–H_{ali}), 1742 (C=O), 1570 (Ar–C=C), 1236 (C–N), 1101 (C–O);^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.58 (s, 1H), 7.81 (dd,$J_1 = 2$ Hz, $J_2 = 8.4$ Hz, 1H), 7.67 (d, $J = 2.0$ Hz, 1H), 7.27 (t, $J = 4.4$ 2H), 7.11 (d, $J = 8.0$ Hz, 2 H), 7.86 (d, $J = 8.4$ Hz, 1H), 4.44 (s, 1 H), 3.8 (s, 3 H), 3.79 (m, 4 H), 2.45 (m, 4 H), 2.29 (s, 3 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 166.7, 160.8, 138.2, 135.6, 131.5, 130.6, 129.7, 128.3, 124.5, 121.5, 117.0, 76.2, 66.8, 53.4, 21.0. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10 % Found C, 70.34; H, 6.75; N, 4.7.

Methyl 4-hydroxy-3-(morpholino(4-morpholinophenyl)methyl)benzoate (**4c**) Yield 97 %; white solid, m.p. 160–162 °C; IR (KBr, ν_{max} (cm^{-1})): 3620 (Ar-OH), 3048 (C–H_{Ar}), 2962 (C–H_{ali}), 1744 (C=O), 1576 (Ar–C=C), 1230 (C–N), 1103 (C–O);^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.65 (s, 1 H), 7.81 (m, 1H), 7.67 (d, $J = 2.0$ Hz, 1H), 7.27 (t, $J = 4.4$ 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 7.86 (d, $J = 8.4$ Hz, 1H), 4.44 (s, 1H), 3.8 (s, 3H), 3.79 (m, 4 H), 2.45 (m, 4H), 2.29 (s, 3 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 166.7, 160.8, 138.2, 135.6, 131.5, 130.6, 129.7, 128.3, 124.5, 121.5, 117.01 76.2, 66.8, 53.4, 21.0. Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79 % Found, 66.95; H, 6.80; N, 6.76.

Methyl 4-hydroxy-3-((3-(methylsulfonamido)phenyl)(morpholino)methyl)benzoate (**4d**) Yield 96 %; thick liquid, IR (KBr, ν_{max} (cm^{-1})): 3627 (Ar–OH), 3054 (C–H_{Ar}), 2969 (C–H_{ali}), 1749 (C=O), 1579 (Ar–C=C), 1233 (C–N), 1106 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.40 (s, 1 H), 7.37 (d, $J = 8.4$ Hz, 2 H), 7.27 (t, $J = 8.8$ Hz, 2 H), 7.13(m, 1 H), 7.40 (t, $J = 3.6$ Hz, 1 H), 7.20(m, 2 H), 6.88 (d, $J = 8.4$ Hz, 1 H), 5.3 (s, 1 H), 3.82 (s, 3 H), 3.6(m, 4 H), 2.0.7 (m, 2 H), 2.58 (m, 2 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 166.6, 160.2, 136.0, 134.1, 131.4, 130.9, 130.0, 129.4, 127.8, 124.0, 121.6, 117.23 69.6, 66.8. 51.8. Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66 % Found: C, 57.10; H, 5.71; N, 6.62.

Methyl 3-((3,5-dimethylisoxazol-4-yl)(morpholino)methyl)-4-hydroxybenzoate (**4e**) Yield 95 %; white solid, m.p. 158–160 °C; IR (KBr, ν_{max} (cm^{-1})): 3622 (Ar–OH), 3051 (C–H_{Ar}), 2963 (C–H_{ali}), 1744 (C=O), 1567 (Ar–C=C), 1230 (C–N), 1101 (C–O) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.39 (s, 1 H), 7.83–7.80 (m, 1 H), 7.52 (d, $J = 1.6$ Hz, 1 H), 6.81 (d, $J = 8.8$ Hz, 1 H), 4.65 (s, 1 H), 3.84 (s, 3 H), 3.7 (m, 4 H), 2.5 (m, 4 H), 2.3 (s, 3 H), 2.2 (s, 3 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 167.5, 166.5, 161.5, 131.1, 121.8, 120.6, 115.0, 66.5, 51.8. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48 % Found: C, 65.40; H, 6.67; N, 8.45.

2-((2-Chlorophenyl)(morpholino)methyl)phenol (**4f**) Yield 98 %; white solid, m.p. 84–86 °C; IR (KBr, ν_{max} (cm^{-1})): 3639 (Ar–OH), 3023 (C–H_{Ar}), 2969 (C–H_{ali}), 1568 (Ar–C=C), 1215 (C–N), 1101 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.5 (s, 1 H), 7.82 (m, 1 H), 7.70 (d, $J = 2.0$ Hz, 1H), 7.32–7.31 (m, 4 H), 6.87 (d, $J = 3.6$ Hz, 1H), 6.86 (d, $J = 4.8$ Hz, 2 H), 4.47 (s, 1 H), 3.82 (s, 3 H), 3.77 (m, 4 H), 3.0 (s, 3 H), 2.49 (m, 4 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 166.8, 160.7, 140.4, 137.8, 137.7, 136.0, 131.4, 131.0.130.7, 130.5, 124.2, 121.6, 112.5, 107.5, 69.7, 66.8. 51.9, 39.6. Anal. Calcd for $C_{17}H_{18}ClNO_2$ C, 67.21; H, 5.97; N, 4.61 % Found: C, 67.17; H, 11.64; N, 4.58.

2-((3, 4-Dimethoxyphenyl)(morpholino)methyl)phenol (**4g**) Yield 97 %; white solid, m.p. 47–50 °C; IR (KBr, ν_{max} (cm^{-1})): 3615 (Ar–OH), 3029(C–H_{Ar}), 2960 (C–H_{ali}), 1567 (Ar–C=C), 1220 (C–N), 1105 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.65 (s, 1 H), 7.12 (t d, $J_1 = 1.6$ Hz, $J_2 = 7.2$ Hz, 1 H), 6.99 (s, 1H), 6.94 (d d, $J_1 = 1.6$ Hz, $J_2 = 6.4$ Hz, 2 H), 6.85 (d, $J = 8.4$ Hz, 1 H), 6.79–6.71 (m, 2 H), 4.3 (s, 1 H), 3.86 (s, 6 H), 3.79–3.65 (m, 4 H), 2.5 (m, 2 H), 2.45(m, 2 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 156.0, 149.2,131.9, 129.3, 128.6, 125.0, 121.0, 119.6, 117.0, 111.0, 156.0, 148.8, 131.9, 129.3, 128.6, 125.0, 121.0, 119.6, 117.0, 111.0, 66.9, 55.8, 52.2. Anal. Calcd for $C_{19}H_{23}NO_4$ C, 69.28; H, 7.04; N, 4.25 % Found: C, 69.25; H, 7.01; N, 4.21.

2-((4-Methoxyphenyl)(morpholino)methyl) phenol (**4h**) Yield 94 %; white solid; m.p. 46–48 °C; IR (KBr, ν_{max} (cm^{-1})): 3630 (Ar–OH), 3035 (C–H_{Ar}), 2969 (C–H_{ali}), 1580 (Ar–C=C), 1225 (C–N), 1103 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.65 (s, 1 H), 7.32 (d, $J = 8.4$ Hz, 2 H), 7.11 (t d, $J_1 = 1.6$ Hz, J_2, 8.8 Hz, 1 H), 6.92 (d d, $J_1 = 1.2$ Hz, $J_2 = 7.6$ Hz, 2 H), 6.84 (t, $J = 8.8$ Hz, 2 H), 6.72 (t, $J = 7.2$ Hz, 2 H), 4.37 (s, 1 H), 3.7 (s, 1 H), 3.76 (m, 4 H), 2.46–2.42 (m, 4 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 159.3, 156.1,131.3, 129.7,129.3, 128.5, 125.1, 119.5, 117.0, 114.2, 76.0, 67.0, 55.2, 52.1. Anal. Calcd for $C_{18}H_{21}NO_3$ C, 72.22; H, 7.07; N, 4.68 % Found C, 72.17; H, 7.0; N, 4.60.

2-((2-(Cyclopropylmethoxy) phenyl) (morpholino) methyl) phenol (**4i**) Yield 94 %; white solid; m.p. 94–96 °C; IR (KBr, ν_{max} (cm^{-1})): 3635 (Ar–OH), 3030 (C–H_{Ar}), 2957 (C–H_{ali}), 1582 (Ar–C=C), 1229 (C–N), 1102 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.9 (s, 1 H), 7.4 (d, 7.2 Hz, 1 H), 7.26–7.09 (m, 2 H), 7.49–7.43 (m, 2 H), 7.01 (d, J = 7.6 Hz, 1 H), 6.89–6.82 (m, 3 H), 6.71 (t, $J = 6.8$ Hz, 1 H), 5.32 (s, 1 H), 3.91–3.82 (m, 2 H), 3.76–3.74 (m, 4 H), 2.69–2.54 (m, 4 H), 1.35- 1.32 (m, 1H), 0.68 (d, $J = 7.6$ Hz, 1H), 0.39 (s, 1 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 157.0, 156.3, 129.5, 129.3, 128.8, 128.4, 127.0, 125.0, 119.2, 116.8, 111.8, 72.9, 67.1, 65.7, 10.3, 3.3 Anal. Calcd for $C_{21}H_{25}NO_3$ C, 74.31; H, 7.42; N, 4.13 % Found C, 72.27; H, 7.40; N, 4.11.

2-(Morpholino (naphthalen-2-yl) methyl) phenol (**4j**) Yield 96 %; white solid; m.p. 74–76 °C; IR (KBr, ν_{max} (cm^{-1})): 3630 (Ar–OH), 3035 (C–H_{Ar}), 2965 (C–H_{ali}), 1587 (Ar–C=C), 1237 (C–N), 1103 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.8 (s, 1 H), 7.82–7.76 (m, 4 H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.49–7.43 (m, 2 H), 7.12 (t d, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz,1H), 7.99 (d, $J = 7.2$ Hz, 1 H), 6.88 (d,

J = 7.6 Hz, 1 H), 6.72 (t, J = 7.2 Hz, 1H), 4.58 (s, 1 H), 3.76 (m, 4 H), 2.66–2.47 (m, 4 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 156.0, 136.8, 133.3, 133.0, 129.5, 129.0, 128.7, 128.0, 127.6, 126.3, 125.7, 124.5, 119.6, 117.1, 66.9, 52.3, 29.7 Anal. Calcd for $C_{21}H_{21}NO_2$ C, 78.97; H, 6.63; N, 4.39 % Found C, 78.94; H, 6.60; N, 4.34.

2-(Morpholino(thiophen-2-yl)methyl)phenol (**4k**) Yield 92 %; white solid; m.p. 110–112 °C; IR (KBr, ν_{max} (cm^{-1})): 3637 (Ar–OH), 3040 (C–H_{Ar}), 2967 (C–H_{ali}), 1564 (Ar–C=C), 1230 (C–N), 1114 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.85 (s, 1 H), 7.28 (m, 2 H), 7.19–7.12 (m, 2 H), 7.49–7.43 (m, 2 H), 7.01 (d, J = 7.6 Hz, 1 H), 6.89-6.82 (m, 3 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.85 (d, J = 7.6 Hz, 1 H), 6.74 (t, J = 7.2 Hz, 1 H), 4.7 (s, 1H), 3.79–3.74 (m, 4 H), 2.58–2.43 (m, 4 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 156.1, 139.5, 129.1, 128.8, 127.1, 126.7, 127.0,124.4, 123.7, 116.7, 119.5, 116.9, 71.1, 66.9, 51.8. Anal. Calcd for $C_{15}H_{17}NO_2S$ C, 65.43; H, 6.22; N, 5.09 % Found C, 65.40; H, 6.20; N, 5.04.

2-((2-Chlorophenyl)(4-(5-methyl-2-phenyl-2H-1,2,4-triazol-3-yl)piperidin-1-yl)methyl) phenol (**4l**) Yield 82 %; white solid;m.p. 180–182 °C; IR (KBr, ν_{max} (cm^{-1})): 3630 (Ar–OH), 3071 (C–H_{Ar}), 2939(C–H_{ali}), 1594 (Ar–C=C), 1296 (C–N), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.36 (brs, 1 H), 7.66 (d, J = 6.8 Hz, 1 H), 7.56–7.42 (m, 5 H), 7.39–7.28 (m, 2 H), 7.26–7.21 (m, 1 H), 6.76–6.69 (m, 2 H), 5.21 (s, 1 H), 2.89–2.69 (m, 4 H), 2.29 (s, 3 H), 2.10–2.01(m, 2 H), 1.83–1.76 (m, 4 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 159.6, 159.1, 156.4, 137.5, 133.7, 129.7, 129.3, 129.2, 129.1, 129.0, 129.0, 128.5, 128.0, 126.4, 125.6, 119.5, 116.2, 65.0, 51.3, 50.8, 33.2, 31.2, 14.0. Anal. Calcd for $C_{27}H_{27}ClN_4O$; C, 70.65; H, 5.93; N, 12.21 % Found C, 70.60; H, 5.90; N, 12.19.

2-((4-(5-Methyl-2-phenyl-2H-1, 2, 4-triazol-3-yl) piperidin-1-yl) (phenyl) methyl) phenol (**4m**) Yield 80 %; white solid; m.p. 183–185 °C; IR (KBr, ν_{max} (cm^{-1})): 3637 (Ar–OH), 3067 (C–H_{Ar}), 2940 (C–H_{ali}), 1590 (Ar–C=C), 1286 (C–N), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.71 (brs, 1 H), 748–7.26 (m, 10 H), 7.08 (d, J = 7.16 Hz, 1 H), 6.86 (t, J = 7.96 Hz, 2 H), 6.68 (s 1 H), 4.47 (s, 1 H), 3.25 (d, J = 8.6 Hz, 1 H), 2.89 (d, J = 8.2 Hz, 1 H), 2.78 (s, 1H), 2.42 (s, 3H), 2.19–2.02 (m, 4 H), ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 156.46, 156.43, 136.07, 129.95, 129.88, 125.59, 41.95, 30.37, 26.56, 12.56. Anal. Calcd for $C_{27}H_{28}N_4O$, C, 76.39; H, 6.65; N, 13.20 % Found, 76.35; H, 6.61; N, 13.18.

2-((4-(5-Methyl-2-phenyl-2H-1,2,4-triazol-3-yl)piperidin-1-yl)(4-morpholinophenyl) methyl)phenol (**4n**) Yield 89 %;white solid; m.p. 184–186 °C; IR (KBr, ν_{max} (cm^{-1})): 3640 (Ar–OH), 3070 (C–H_{Ar}), 2950 (C–H_{ali}), 1585 (Ar–C=C), 1270 (C–N), 1115 (C–O)^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.9 (br s, 1 H), 7.47 (t, J = 7.36 Hz, 3 H), 7.33(d, J = 7.12 Hz, 2 H), 7.26 (s, 2 H), 7.07 (d, J = 7.6 Hz, 2 H), 6.85 (d, J = 5.5 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 4 H), 6.66 (d, J = 7.3 Hz, 1 H), 4.40 (s, 1H), 3.82 (t, J = 8.3 Hz, 4 H), 3.21 (d, J = 10.3 Hz, 1 H), 3.12 (d, J = 3.8 Hz, 4 H), 2.42 (s, 3 H), 2.14–2.07 (m, 4 H), 1.86–1.25 (m, 4 H) ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 160.1, 158.5, 156.7, 150.6, 137.2, 130.2, 129.4, 129.0,

128.2, 125.3, 125.3, 119.0, 117.0, 115.3, 75.3, 66.8, 52.5, 50.0, 48.8, 33.2, 31.0, 30.7, 29.6,13.7, 125.6, 42.0, 30.4, 26.6, 12.6 Anal. Calcd for $C_{31}H_{35}N_5O_2$.

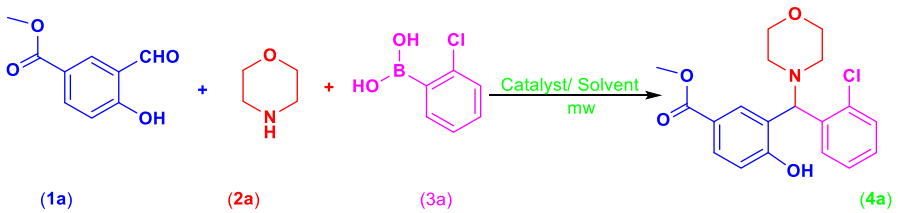
2-((4-(5-Methyl-2-phenyl-2H-1, 2, 4-triazol-3-yl) piperidin-1-yl) (4-phenoxyphenyl) methyl) phenol (**4o**) Yield 89 %; white solid; m.p. 118–120 °C; IR (KBr, ν_{max} (cm^{-1})): 3645 (Ar–OH), 3067 (C–H_{Ar}), 2958 (C–H_{ali}), 1590 (Ar–C=C), 1274 (C–N), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.73 (br s, 1 H), 7.48 (d, $J = 7.12$ Hz, 3 H), 7.36–7.26 (m, 6 H), 7.12 (d, $J = 5.76$ Hz, 2 H), 7.99 (d, $J = 7.68$ Hz, 2 H), 6.91–6.84 (m, 4 H), 6.71 (d, $J = 7.12$ Hz, 1 H), 4.43 (s, 1H), 3.23 (d, $J = 8.56$ Hz, 1 H), 2.99 (d, $J = 9.04$ Hz, 2 H), 2.79 (s, 1 H), 2.43 (s, 3 H),2.19–1.84 (m, 4 H), 1.84–1.26 (m, 4 H) ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 160.1, 158.4, 157.0, 156.6, 156.5, 137.2, 133.9, 130.9, 129.7, 129.4, 129.0, 128.4, 125.3, 123.5, 119.2, 119.0, 118.5, 117.0, 75.41, 52.5, 50.0, 33.2, 30.7, 13.7; Anal. Calcd for $C_{33}H_{32}N_4$ C, 76.72; H, 6.24; N, 10.84 % Found C, 76.70; H, 6.20; N, 10.80.

2-((4-(3-Methyl-1-phenyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)(phenyl)methyl)pyridine (**4p**) Yield 75 %; white solid; m.p. 118–120 °C; IR (KBr, ν_{max} (cm^{-1})): 3067 (C–H_{Ar}), 2970 (C–H_{ali}), 1580 (Ar–C=C), 1269 (C–N), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (s, 1 H), 8.05 (s, 1 H), 7.58 (d, $J = 7.78$ Hz, 2H), 7.52–7.46 (m, 3 H), 7.43(d, $J = 7.28$ Hz, 2 H), 7.37 (d, $J = 7.39$ Hz, 2 H), 7.25 (t, $J = 7.43$ Hz, 2 H), 7.15 (d, $J = 5.16$ Hz, 2 H), 4.42 (s, 1 H), 2.78–2.7 (m, 3 H), 1.86–1.69 (m, 6 H) ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 159.4, 159.2, 149.1, 141.7, 137.4, 137.1, 134.8, 134.4, 130.9, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.3, 125.5, 122.4, 122.0, 77.1, 66.0, 63.1, 51.7, 51.3, 33.3, 30.0, 13.9. Anal. Calcd for $C_{26}H_{27}N_5$ C, 76.25; H, 6.65; N, 17.10 % Found C, 76.20; H, 6.60; N, 17.08.

4-(4-((4-(3-Methyl-1-phenyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)(pyridin-2-yl)methyl)phenyl)morpholine (**4q**) Yield 79 %; white solid; m.p. 118–120 °C; IR (KBr, ν_{max} (cm^{-1})): 3080 (C–H_{Ar}), 2967 (C–H_{ali}), 1573 (Ar–C=C), 1275 (C–N), 1107 (C–O), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (d, $J = 3.6$ Hz, 1 H), 7.71 (t, $J = 7.44$ Hz, 1 H), 7.57–7.42 (m, 5 H), 7.21–7.14 (m, 3H), 6.82 (d, $J = 8.08$ Hz, 2 H), 4.30 (s, 1 H), 3.67 (s, 4 H), 3.0–2.92 (m, 4 H), 2.79-2.70 (m, 3H), 2.27 (s,3 H), 1.89-1.2(m, 6 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 162.9, 159.4, 159.2, 150.3, 149.0, 137.4, 137.02, 132.1, 129.9, 129.2, 129.0, 125.5, 122.2, 122.0, 121.7, 115.3, 76.6, 66.4, 51.9, 51.2, 48.7, 33.4, 31.0, 31.0, 14.10, 129.7, 129.3, 129.2, 129.1, 129.0, 128.7, 128.5, 127.9, 126.4, 125.6, 119.5, 116.2, 65.0, 51.3, 50.8, 33.2, 31.2, 14.0. Anal. Calcd for $C_{26}H_{27}N_5$ C, 76.25; H, 6.65; N, 17.10 % Found C, 76.20; H, 6.60; N, 17.08.

Results and discussion

Our initial efforts focused on developing optimal reaction conditions for the condensation of methyl 3-formyl-4-hydroxybenzoate (**1a**), morpholine (**2a**) and 2-chlorophenylboronic acid (**3a**) to generate methyl 3-((2-chlorophenyl)(morpholino)methyl)-4-hydroxybenzoate (**4a**) as a model reaction (Scheme 1). This



Scheme 1 Synthesis of methyl 3-((2-chlorophenyl) (morpholino) methyl)-4-hydroxybenzoate (**4a**)

Table 1 Optimization of reaction conditions for the synthesis of methyl 3-((2-chlorophenyl)(morpholino)methyl)-4-hydroxybenzoate (**4a**)

Entry	Catalyst (mol%)	Solvent	Conventional method			MWI method[a]		
			Temp (°C)	Time (h)	Yield (%)[b]	Temp (°C)	Time (min)	Yield (%)[b]
1	Free	1,4-dioxane	RT	26	40	100	22	68
2	CuI (5)	1,4-dioxane	60	12	54	80	7	75
3	AgF (5)	1,4-dioxane	60	15	58	80	8	72
4	InF_3 (5)	1,4-dioxane	60	11	60	80	6	75
5	$FeCl_3.SiO_2$ (5)	1,4-dioxane	60	16	61	80	7	80
6	$Pd(PPh_3)_4$ (5)	1,4-dioxane	60	12	63	80	6	84
7	$PdCl_2$ (5)	1,4-dioxane	60	12	62	80	6	82
8	$Pd(OAc)_2$ (5)	1,4-dioxane	60	12	65	80	6	85
9	$Y(OAc)_3.H_2O$ (5)	1,4-dioxane	60	10	64	80	4	87
10	$Yb(OAc)_2$ (5)	1,4-dioxane	60	10	65	80	4	86
11	$Yb(OTf)_3$ (5)	1,4-dioxane	60	10	66	80	4	85
12	AgOTf (5)	1,4-dioxane	60	10	68	80	4	85
13	$Sc(OTf)_3$ (5)	1,4-dioxane	60	10	73	80	4	86
14[c]	$La(OTf)_3$ (5)	1,4-dioxane	60	10	80	80	2	97,94,91,87
15	$La(OTf)_3$ (1)	1,4-dioxane	60	12	50	60	2	62
16	$La(OTf)_3$ (2)	1,4-dioxane	60	10	65	80	2	75
17	$La(OTf)_3$ (3)	1,4-dioxane	60	10	88	80	2	90
18	$La(OTf)_3$ (7)	1,4-dioxane	60	10	90	80	2	98
19	$La(OTf)_3$ (10)	1,4-dioxane	60	10	90	80	2	98
20	$La(OTf)_3$ (5)	Ethanol	60	10	84	78	2	95
21	$La(OTf)_3$ (5)	THF	60	10	82	66	2	92
22	$La(OTf)_3$ (5)	Toluene	60	10	78	110	2	94
23	$La(OTf)_3$ (5)	MeOH	60	10	81	101	2	94
24	$La(OTf)_3$ (5)	DCM	60	10	83	39	2	94
25	$La(OTf)_3$ (5)	CCl_4	60	10	82	76	2	93

Reaction of 3-formyl-4-hydroxy benzoate (**1a**, 0.55 mmol), morpholine (**2a**, 0.55 mmol), and 2-chloro phenyl boronic acid (**3a**, 0.55 mmol)

[a] All the reactants irradiated with 100 W microwaves

[b] Isolated yields with >95 % purity as determined by ^{1}H NMR and LC–MS analysis

[c] Catalyst was reused five times

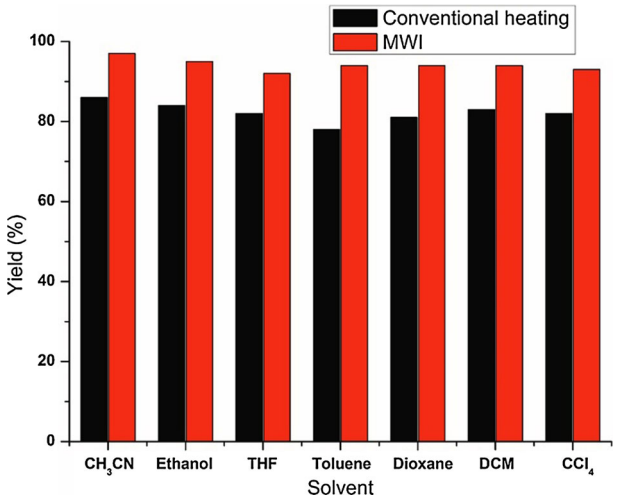


Fig. 1 Effect of solvent on catalytic activity of $La(OTf)_3$ in Petasis reaction

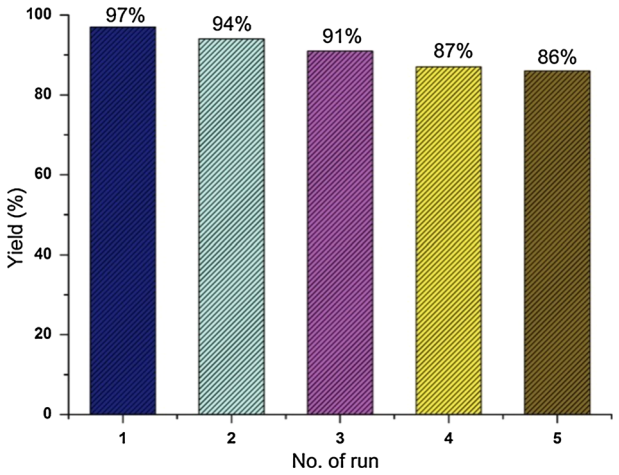
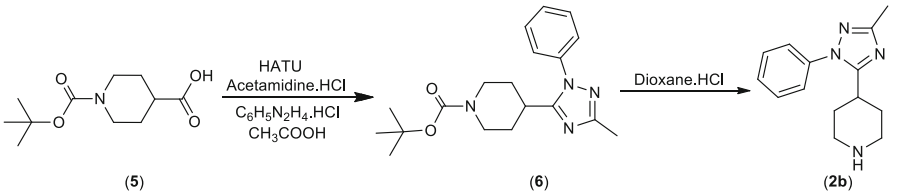
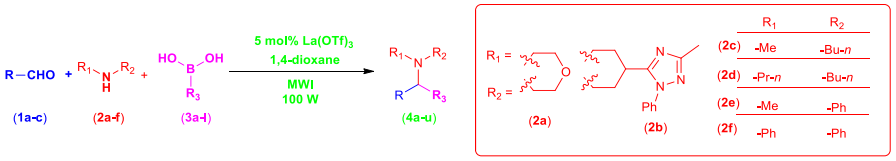


Fig. 2 Reusability of the $La(OTf)_3$ catalyst in Petasis reaction



Scheme 2 Synthesis of 4-(3-methyl-1-phenyl-1*H*-1,2,4-triazol-5-yl)piperidine (**2b**)



Scheme 3 Synthesis of substituted phenyl/dimethylisoxazol/naphthalene/thiophen (morpholino/substituted piperidin) phenyl/phenol/substituted benzoate/pyridine methyl derivatives (**4a–q**)

was investigated by utilizing different solvents and various catalysts under both conventional and microwave conditions (Table 1).

We first investigated the model reaction without a catalyst in 1, 4-dioxane. The desired product (**4a**) was obtained in lower yield even after a prolonged reaction time under both conditions (Table 1, entry 1). When the reaction was performed using various catalysts, it proceeded effectively to produce the desired product in high yields (Table 1, entries 2–4). This indicates that the reaction is faster in the presence of catalyst than that of the un-catalyzed pathway. Consequently, the reaction was performed in the presence of La(OTf)$_3$ to obtain **4a** in high yields under both conditions even at a lower catalytic amount (Table 1, entry 14).

In addition to this, we observed that the concentration of the catalyst played a major role in this Petasis reaction as, when varying the concentration of La(OTf)$_3$ from just 2 to 10 mol%, the product yield varied from 75 to 98 % (Table 1, entries 14–19). This shows that 5 mol% of La(OTf)$_3$ is the suitable and sufficient choice for the optimum reaction rate and yield (Table 1, entry 14). Considerable increases in yields were not observed when an excess amount of the catalyst was used. These results clearly indicate that 5 mol% La(OTf)$_3$ is optimal for the synthesis of titled compounds.

Next, we studied the influence of solvents in the model reaction using various organic solvents at different reaction temperatures with 5 mol% of La(OTf)$_3$ (Fig. 1). A slow rate of reaction was observed in CCl_4, MeOH, DCM, THF, toluene, and EtOH with low product yields (Table 1, entries 20–25). There was a better rate of reaction with improved product yield in 1, 4-dioxane (Table 1, entry 14). High yields were observed in 1,4-dioxane at 60 and 80 °C in conventional and MWI conditions, respectively (Table 1, entry 14).

In order to investigate the recyclability and reusability of the catalyst, it was recovered by simple filtration, washing twice with dry ether (10 mL) and dried in vacuum at 60 °C. Under similar reaction conditions, the dried catalyst was reused for subsequent experiments in at least five consecutive cycles without much appreciable loss in its catalytic activity (Table 1, entry 14). These data demonstrate the high stability of the catalyst under the reaction conditions (Fig. 2) under microwave irradiation conditions.

A novel amine, 4-(5-methyl-2-phenyl-2*H*-1, 2,4-triazol-3-yl) piperidine (**2b**), was prepared in two steps (Scheme 2). First, a commercially available 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (**5**) was treated with phenylhydrazine hydrochloride in the presence of HATU, DIPEA and acetamidine.HCl to obtain the

Table 2 Synthesis of substituted phenyl/dimethylisoxazol/naphthalene/thiophen (morpholino/substituted piperidin) phenyl/phenol/substituted benzoate/pyridine methyl derivatives (**4a–q**)

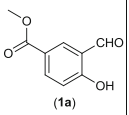
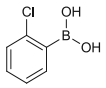
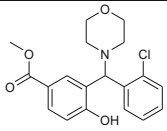
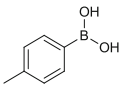
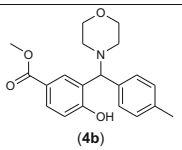
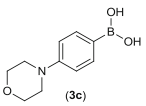
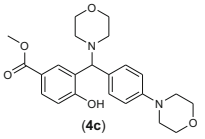
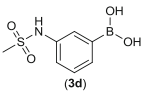
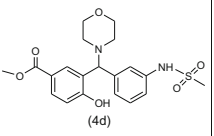
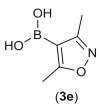
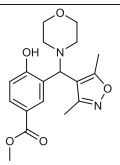
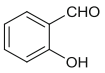
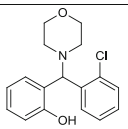
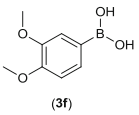
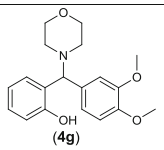
Entry	Aldehyde (R)	Amine (2a-f)	R_3	Time (min)	Product	Yield (%)[a]
1	 (1a)	 (2a)	 (3a)	2	 (4a)	97
2	1a	2a	 (3b)	2	 (4b)	98
3	1a	2a	 (3c)	2	 (4c)	97
4	1a	2a	 (3d)	2	 (4d)	96
5	1a	2a	 (3e)	2	 (4e)	95
6	 (1b)	2a	3a	2	 (4f)	98
7	1b	2a	 (3f)	2	 (4g)	97

Table 2 continued

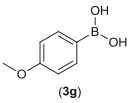
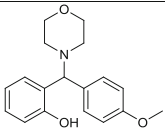
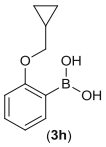
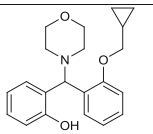
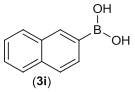
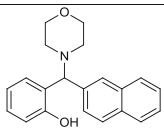
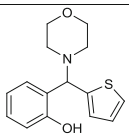
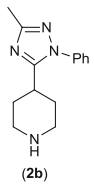
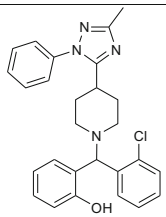
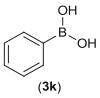
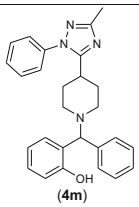
Entry	Aldehyde (R)	Amine (2a-f)	R_3	Time (min)	Product	Yield (%)[a]
8	**1b**	**2a**	 (**3g**)	2	 (**4h**)	94
9	**1b**	**2a**	 (**3h**)	2	 (**4i**)	94
10	**1b**	**2a**	 (**3i**)	2	 (**4j**)	96
11	**1b**	**2a**	 (**3j**)	2	 (**4k**)	92
12	**1b**	 (**2b**)	**3a**	2	 (**4l**)	82
13	**1b**	**2b**	 (**3k**)	2	 (**4m**)	80

Table 2 continued

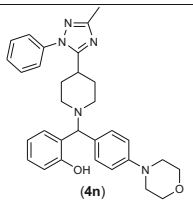
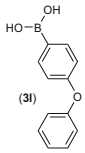
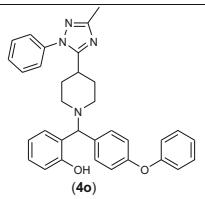
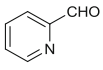
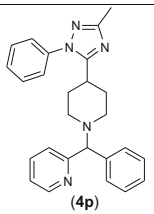
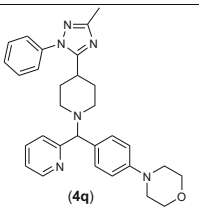
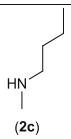
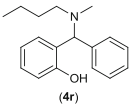
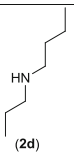
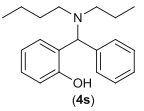
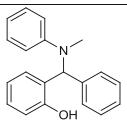
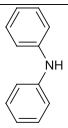
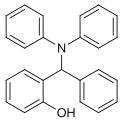
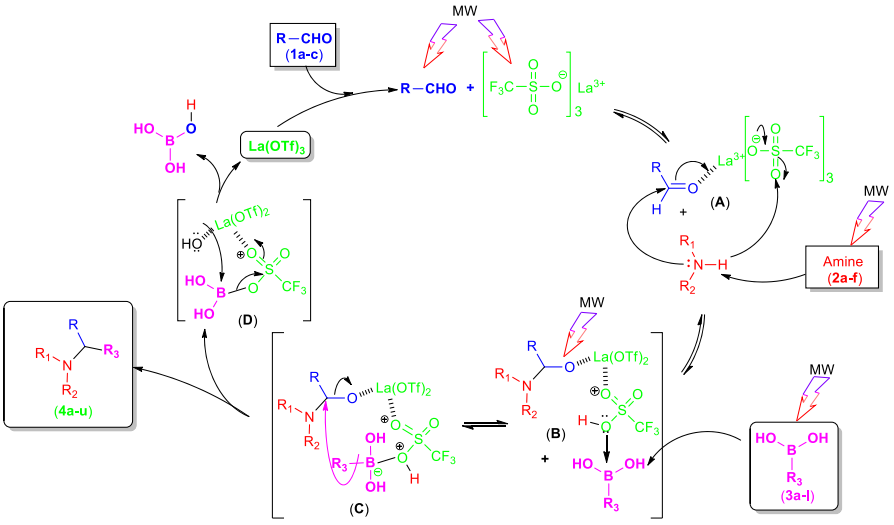
Entry	Aldehyde (R)	Amine (2a-f)	R_3	Time (min)	Product	Yield (%)[a]
14	**1b**	**2b**	**3c**	2	 (**4n**)	89
15	**1b**	**2b**	 (**3l**)	2	 (**4o**)	86
16	 (**1c**)	**2b**	**3k**	2	 (**4p**)	75
17	**1c**	**2b**	**3c**	2	 (**4q**)	78
18	**1b**	 (**2c**)	**3k**	15	 (**4r**)	---
19	**1b**	 (**2d**)	**3k**	15	 (**4s**)	---

Table 2 continued

Entry	Aldehyde (R)	Amine (2a-f)	R_3	Time (min)	Product	Yield (%)[a]
20	**1b**	 (**2e**)	**3k**	12	 (**4t**)	13
21	**1b**	 (**2f**)	**3k**	12	 (**4u**)	19

Reaction conditions: various aldehydes (**1a–c**), various amines (**2a–f**) and aryl boronic acids (**3a–l**) on 5 mol% $La(OTf)_3$ catalyst at 100 W power MWI in 1,4-dioxane

[a] Isolated yields



Scheme 4 Schematic illustration of formation of the titled compounds (**4a–u**)

tert-butyl 4-(5-methyl-2-phenyl-2*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate (**6**). In the next step, Boc group was de-protected using dioxane.HCl to obtain the desired amine **2b**.

The condensation of various aldehydes (**1a–c**) and amines (**2a–b**) with a range of aryl boronic acids (**3a–l**) using 5 mol% $La(OTf)_3$ gave the desired compounds (**4a–q**) in good to excellent yields without the formation of side products under MWI with 100 W power at 80 °C in 1,4-dioxane (Scheme 3), and the results are presented in Table 2. Notably, all *ortho*-hydroxy aldehydes participated effectively in this reaction and the corresponding products were obtained in excellent product yields (Table 2, entries 1–15). But aldehydes without a hydroxyl group at the *ortho*-position did not result in good yields (Table 2, entries 16 and 17). Other than this effect, none of the factors (e,g., electron donor) influenced the rate of reaction to obtain the product yields. In addition to these cyclic secondary amines, to further establish the scope and ultimate utility of the chemistry we were tested the reaction with few general secondary amines (**2c–f**). In this study, most of the simple amines are not proceed the reaction at all, even at higher temperatures and longer reaction times (Table 2, entries 18 and 19). Even the phenyl substituted amines did not shown significant product yields (Table 2, entries 20 and 21).

Reaction mechanism of formation of titled compounds

At the beginning of this one-pot three-component Petasis BMR, the $La(OTf)_3$ catalyst should connect with the two components of aldehyde followed by the amine to form the exiplex complex (**B**) under MWI. Then, this complex can also interact with boronic acid derivatives by one of the OTf ligands and form the complex **C**. All these are together at one place on the catalyst surface and interact with each other in the Mannich condensation followed by elimination of the OH group and the formation of the desired titled products (**4a–u**) selectively in higher yields (Scheme 4). Finally, the catalyst complex with boronic acid derivative residues undergoes cleavage as the pure catalyst with boronic acid as a byproduct.

Conclusion

In summary, a series of tertiary amine derivatives were synthesized by one-step Petasis reaction under microwave irradiation using $La(OTf)_3$ as an efficient catalyst. The procedure exhibits several advantages such as mild reaction conditions, shorter reaction times, high efficiency, a wide range of functional group tolerance and excellent product yields. Their structures were characterized ^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis.

Acknowledgments The authors express their grateful thanks to the Department of Chemistry, Vellore Institute of Technology, Vellore-632014, Tamil Nadu, India for providing financial assistance and infrastructure facilities for this work.

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