Chemical Papers (2021) 75:4045–4053
https://doi.org/10.1007/s11696-021-01636-5

ORIGINAL PAPER

# *CAL-B*-mediated efficient synthesis of a set of valuable amides by direct amidation of phenoxy- and aryl-propionic acids

**Nourelhouda Benamara[1] · Mounia Merabet-Khelassi[1] · Louisa Aribi-Zouioueche[1] · Olivier Riant[2]**

Received: 7 November 2020 / Accepted: 31 March 2021 / Published online: 10 April 2021


## Abstract

An efficient, easy and sustainable amidation of a set of non-activated carboxylic acids with anilines, assisted by *CAL-B*, as biodegradable catalyst, is reported. The enzymatic amidation reactions are performed on set of nonsteroidal anti-inflammatory drugs (NSAIDs), phenoxypropionic acid and protected-prolines by direct condensation of one equivalent of carboxylic acids and two equivalents of anilines derivatives in heptane after 72 h of reaction at 80 °C. The obtained carboxylic amides are recovered with isolated chemical yields varied between moderate and excellent. Fourteen from them are reported for the first time, and an X-ray crystal is obtained for: *N*-(4-iodophenyl)-2-(4-isobutylphenyl)propanamide **1d**.

**Keywords** *CAL-B* · NSAIDs prodrugs · Boc-proline · Direct amidation

## Introduction

Amide bonds are a pivot unit in the elaboration and composition of biological systems, such peptides and proteins. Amides as high valuable molecules constitute versatile synthetic intermediates used in the manufacture of several pharmacological and biological active products, polymers, detergents, lubricants, food additives, flavors, nutrients and drug stabilizers (Greenberg et al. 2000; Lundberg et al. 2014; Lima and Porto 2017; Annunziata et al. 2020). The majority of industrial amidation are based on an activation of a carboxylic acid by a stoichiometric reagent followed by nucleophilic displacement with a free amine. This great importance leads to the American Chemical Society Green Chemistry Institute to identify amide formation avoiding poor atom economy process as a priority area of research for the pharmaceutical industry (Constable et al. 2007). Hence, catalytic pathways were highlighted as a reaction of importance from a "green chemistry" perspective (Montalbetti and Falque 2005). On these lights, several works have been published, using various types of catalysts, for the direct condensation of a carboxylic acid and amine as environmentally benign solution with water as the unique side product (Zheng and Xu 2011; Lanigan and Sheppard 2013; De Figueiredo et al. 2016). Since biocatalysis fits very well with the principles of green chemistry and sustainability, it seems one of the most attractive, clean, sustainable and more eco-friendly pathways to the amide structures, especially for the production of active pharmaceutical ingredients (APIs) (Lundberg et al. 2012, 2017; Cheng et al. 2018; Chandra et al. 2020; Sheldon et al. 2020). Among that, hydrolytic enzymes, and especially lipases (triacylglycerol acyl hydrolases, EC.3.1.1.3) as biocatalysts, dominate the synthesis of amides from carboxylic acids and amines for their ease of use under mild conditions, recyclability, biodegradability and for their remarkable chemo-, regio- and enantioselectivity (Sheldon 2016; Arroyo et al. 2017). More recently, the use of lipases was extended to promiscuous reactions (Hult and Berglund 2007; Guezane-Lakoud et al. 2017; Aissa et al. 2019). The most commonly exploited lipases for the synthesis of primary, secondary and tertiary amides are the *Candida antarctica* lipase immobilized on acrylic resin (*CAL-B*) (Busto et al. 2010; Lima et al. 2019). This lipase is robust, highly active, thermostable, biodegradable, a facile recovery and recyclable, tolerance for polar and non-polar

✉ Mounia Merabet-Khelassi
mounia.merabet@gmail.com;
mounia.merabet@univ-annaba.dz

[1] Ecocompatible Asymmetric Catalysis Laboratory (L.C.A.E), Badji Mokhtar Annaba-University, B.P. 12, 23000 Annaba, Algeria

[2] Institute of Condensed Matter and Nanosciences Molecules, Solids and reactiviTy (IMCN/MOST), Université Catholique de Louvain, Bâtiment Lavoisier. Pl. Louis Pasteur, 1, bte 3. 1348, Louvain La Neuve, Belgium

solvents and broad range of substrates accommodation. It is also environmentally benign making it attractive for wide applications in several domains (Kourist et al. 2011; José et al. 2016; Alalla et al. 2016; Belkacemi et al. 2017; Braia et al. 2018). Under various reaction conditions, respecting some green chemistry criteria's, the *CAL-B*-catalyzed amidation has been reported for the synthesis of achiral or enantiopure amides and amines widely used as biopolymers, building block compounds and drugs (Nechab et al. 2007; Kaushik et al. 2015; Mouad et al. 2016; Lima et al. 2017; Manova et al. 2018).

Previously, we have reported a clean and eco-compatible pathway for both *N*-benzoylation and *N*-acetylation of anilines, amines, diamines and aminoalcohols using activated enol-esters, under free catalyst conditions (Alalla et al. 2014).

In the present paper, we describe our study on the enzymatic amidation of some 2-aryl-propionic acids (profens) with aniline as the nitrogen source. This family of molecules considered as one of the most important non-steroidal anti-inflammatory drugs (NSAIDs). The amidation of a phenoxypropionic acid and some protected-prolines is also reported. At the best of our knowledge, the application of this approach for the amidation of profens has never described yet by others.

## Materials and methods

### General information

All starting materials and reagents used in this study were obtained commercially from Sigma-Aldrich, Acros, TCI or Alfa Aesar and were used as received. The *Candida antarctica* lipase immobilized on acrylic resin *CAL-B* was purchased from Sigma-Aldrich. Specific activity >10,000 U/g was used without any pre-treatment. All reactions were monitored by thin-layer chromatography (TLC)carried out on 0.25 mmE. Merck silica gel plates (60F-254) use UV light (254 nm) as the visualizing agent and ninhydrine solution and heat as developing agents.

NMR spectra were recorded on Brucker spectrometers (300 MHz for $^{1}$H, 75 MHz for $^{13}$C). Chemical shifts are reported in $\delta$ ppm from tetramethylsilane with the solvent resonance as the internal standard for $^{1}$H NMR and chloroform-*d* ($\delta$ 77.0 ppm) for $^{13}$CNMR. Coupling constants (*J)* are given in hertz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. The mass spectra were obtained from the mass-service at Université catholique de Louvain (FINNIGAN-MAT TSQ 7000 and FINNIGAN-MAT LQC spectrometers). Conversions were evaluated by measuring of enantiomeric excesses by a chiral stationary phase HPLC on Chiralcel®OJ-H (4.6 × 250 mm), Chiralpak®OD-H 4.6 × 250 mm, Chiralpak®IC (4.6 × 250 mm), Chiralpak®IA (4.6 × 250 mm) and Chiralpak ®IB 4.6 × 250 mm column. Retention times are reported in minutes. Optical rotations were determined using a MCP100 polarimeter at room temperature using a cell of 1-dm length and $\lambda = 589$ nm.

### Enzymatic amidation of non-activated carboxylic acids

To a solution of 2 mmol amine and the 1 mmol carboxylic acid dissolved in 1 mL of heptane, 50 mg of the molecular sieves 4 Å and 50 mg of the immobilized *CAL-B* are introduced. The reaction mixture is stirred at 80 °C for 72 h. After cooling, the solvent is evaporated and the crude residue was exposed to a standard acido-basic treatment (HCl, 3 M/3 M NaOH). The solvent was removed *in vacuo*, and the residue was crystallized in hexane, or purified by flash chromatography if necessary. As a control reaction, the same procedure is followed without introducing lipase. All the synthesized amides are characterized by $^{1}$H NMR, $^{13}$C NMR spectra and HRMS. Melting points were determined. Separation conditions on chiral HPLC were established. Optical rotations of proline amides **4a–5e** were measured.

#### 2-(4-Isobutylphenyl)-N-phenylpropanamide (1a)

White solid. mp: 151 °C. Yield: 40%. $\mathbf{R_f} = 0.52$ ($CH_2Cl_2$). **$^{1}$H NMR (300 MHz, $CDCl_3$) δ** 7.35–7.33 (d, $J = 7.7$ Hz, 2H), 7.22–7.15 (m, 4H), 7.08–6.95 (m, 4 H), 3.65–3.5 (q, $J = 7.2$ Hz, 1H), 2.41–2.38 (d, $J = 7.2$ Hz, 2H), 1.83–1.72 (m, 1H), 1.52–1.5 (d, $J = 7.2$ Hz, 3H), 0.84–0.82 (d, $J = 6.6$ Hz, 6H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 172.6 (C=O amide), 141.1, 138.0, 137.9, 129.8, 128.9, 127.4, 124.1, 119.6, 47.7, 45.0, 30.2, 22.4, 18.5. **HRMS (ESI+) m/z (found):** 304.1675, **Calculated:** 304.16718.

#### 2-(4-Isobutylphenyl)-N-(p-tolyl)propanamide (1b)

White solid. mp: 115 °C. Yield: 90%. $\mathbf{R_f} = 0.41$($CH_2Cl_2$). **$^{1}$H NMR (300 MHz, $CDCl_3$) δ** 7.23–7.16 (m, 4H), 7.16 (bs, 1H), 7.07–7.04 (d, $J = 8.1$ Hz, 2H), 6.98–6.96 (d, $J = 8.3$ Hz, 2H), 3.63–3.56 (q, $J = 7.1$ Hz, 1H), 2.39–2.37 (d, $J = 7.2$ Hz, 2H), 2.19 (s, 3H); 1.82–1.69 (m, 1H), 1.50–1.48 (d, $J = 7.1$ Hz, 3H), 0.83–0.81 (d, $J = 6.6$ Hz, 6H).**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 172.5 (C=O amide), 140.9, 138.2, 135.4, 133.7, 129.8, 129.3, 127.4, 119.7, 47.6, 45, 33.9, 30.2, 25.6, 25, 22.4, 20.8, 18.5. **HRMS (ESI+)m/z (found):** 296.20071, **Calculated:** 296.20089.

#### 2-(4-Isobutylphenyl)-N-(4-(trifluoromethyl)phenyl) propanamide (1c)

White crystalline solid. mp: 140 °C. Yield: 72%. $\mathbf{R_f}$ = 0.37 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.48–7.41 (q, *J* = 9 Hz, 4H), 7.32 (bs, 1H), 7.19–7.03 (m, 4 H), 3.68–3.61 (q, *J* = 7.1 Hz, 1H), 2.41–2.39 (d, *J* = 7.2 Hz, 2H), 1.84–1.75 (m, 1H), 1.53–1.50 (d, *J* = 7.2 Hz, 3H), 0.85–0.82 (d, *J* = 6.6 Hz, 6H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 171.9 (C=O amide), 140.9, 139.9, 136.5, 128.9, 128.2, 126.3, 126, 125.1, 125, 121.2, 118.1, 124.6, 59.6, 46.7, 43.9, 29.1, 21.3, 17.4, 13. **HRMS (ESI+)m/z (found):** 350.17251, **Calculated:** 350.17263.

#### N-(4-Iodophenyl)-2-(4-isobutylphenyl)propanamide (1d)

White crystalline solid. mp: 131 °C. Yield: 55%. $\mathbf{R_f}$ = 0.82 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.49–7.46 (d, *J* = 8.8 Hz, 2H), 7.24–6.93 (m, 7H), 3.63–3.56 (q, *J* = 7.1 Hz, 1H), 2.41–2.38 (d, *J* = 7.2 Hz, 2H), 1.83–1.48 (m, 1H), 1.53–1.50 (d, *J* = 7.2 Hz, 3H), 0.84–0.82 (d, *J* = 6.6 Hz, 6H).**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 171.9 (C=O amide), 140.5, 137, 136.9, 129.2, 126.6, 120.7, 86.1, 47, 44.2, 29.4, 21.6, 17.7. **HRMS (ESI+) m/z (found):** 408.08187, **Calculated:** 408.08188.

#### N-(4-Bromophenyl)-2-(4-isobutylphenyl)propanamide (1e)

White crystalline solid. mp: 124 °C. Yield: 50%. $\mathbf{R_f}$ = 0.85 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.51–7.10 (m, 8H), 7.06 (bs,1H), 3.74–3.67 (q, *J* = 7.2 Hz, 1H), 2.51–2.49 (d, *J* = 7.2 Hz, 2H), 1.93–1.84 (m, 1H), 1.62–1.59 (d, *J* = 7.1 Hz, 3H), 0.94–0.92 (d, *J* = 6.6 Hz, 6H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ**172.5 (C=O amide), 141.2, 137.7, 136.9, 131.8, 129.9, 127.4, 121.1, 47.7, 45, 30.1, 22.3, 18.4. **HRMS (ESI+) m/z (found):** 360.09582, **Calculated:** 360.09575.

#### N-(4-Chlorophenyl)-2-(4-isobutylphenyl)propanamide (1f)

White crystalline solid. mp: 113 °C. Yield: 45%. $\mathbf{R_f}$ = 0.84 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.31–7.28 (d, *J* = 8.8 Hz, 2H), 7.24–6.93 (ddd,, *J* = 19.2, 13.8, 8.2 Hz,7H), 3.65–3.58 (q, *J* = 7.1 Hz, 1H), 2.42–2.39 (d, *J* = 7.2 Hz, 2H), 1.84–1.75 (m, 1H), 1.52–1.50 (d, *J* = 7.1 Hz, 3H), 0.85–0.83 (d, *J* = 6.6 Hz, 6H).**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 172.7 (C=O amide), 141.2, 137.8, 129.9, 129.1, 128.8, 127.4, 120.9, 136.4, 47.7, 45, 30.2, 22.4, 18.4. **HRMS (ESI+) m/z (found):** 316.14623, **Calculated:** 316.14627.

#### 2-(4-Isobutylphenyl)-N-(4-methoxyphenyl)propanamide (1g)

White crystalline solid. mp: 100 °C. Yield: 60%. $\mathbf{R_f}$ = 0.64 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.28–7.20 (m, 4H), 7.11–7.09 (d, *J* = 8.1 Hz, 2H), 6.94 (bs, 1H), 6.77–6.74 (m, 2H), 3.71 (s, 3H), 3.66–3.59 (q, *J* = 7.2 Hz, 1H), 2.43–2.41 (d, *J* = 7.2 Hz, 2H), 1.86–1.77 (m, 1H), 1.55–1.52 (d, *J* = 7.2 Hz, 3H), 0.87–0.85 (d, *J* = 6.6 Hz, 6H).**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 172.4 (C=O amide), 156.2, 141, 138.1, 131, 129.8, 127.4, 121.4, 114, 55.4, 47.5, 45, 30.2, 22.4, 18.5. **HRMS (ESI+) m/z (found):** 312.19586, **Calculated:** 312.19581.

#### N-Benzyl-2-(4-isobutylphenyl)propanamide (1 h)

White powder. mp: 49 °C. Yield: 34%. $\mathbf{R_f}$ = 0.21 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.29–7.12 (m, 9H), 5.66 (bs, 1H), 4.43–4.41(d, *J* = 5.8 Hz, 2H), 3.64–3.57(q, *J* = 7.2 Hz, 1H), 2.49–2.46 (d, *J* = 7.2 Hz, 2H), 1.91–1.82 (m, 1H), 1.59–1.56 (d, *J* = 7.2 Hz, 3H), 0.93–0.91 (d, *J* = 6.6 Hz, 6H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 174.3 (C=O amide), 140.8, 138.4, 129.6, 128.5, 127.3, 127.3, 46.8, 45, 43.5, 30.2, 22.3, 18.4. **HRMS (ESI+) m/z (found):** 318.1828, **Calculated:** 318.18283 $[M + Na]^+$ ($C_{20}$ $H_{25}$ NONa).

#### 2-(3-Benzoylphenyl)-N-phenylpropanamide (2a)

White solid. mp: 90 °C. Yield: 30%. $\mathbf{R_f}$ = 0.11 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.82–7.06 ($m_a$, 15H), 3.78(q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 196.6 (C=O Benzoyl-), 171.7(C=O amide), 153.8, 141.8, 141.6, 138.1, 137.8, 137.3, 132.6, 132.5, 131.4, 131.3, 130.08, 130.03, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.3, 128.3, 124.3, 119.8, 50.1, 47.9, 45.2, 32.7, 32.5, 31.1, 30.6, 26.1, 26.1, 25.4, 25.2, 24.7, 20.5, 18.8. **HRMS (ESI+) m/z (found):** 330.148, **Calculated:** 330.14886.

#### 2-(3-Benzoylphenyl)-N-(p-tolyl)propanamide (2b)

White solid. mp: 118 °C. Yield: 25%. $\mathbf{R_f}$ = 0.11 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.75–7.71 (m, 3H), 7.64–7.50 (m, 3H), 7.43–7.38 (m, 3H), 7.27–7.24 (d, *J* = 8.4 Hz, 2H), 7.03–7.00 (d, *J* = 8.2 Hz, 3H), 3.72–3.65 (q, *J* = 7.1 Hz, 1H), 2.22 (s, 3H), 1.55–1.53 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 196.6 (C=O Benzoyl-), 171.6 (C=O amide), 156.8, 141.6, 138, 137.3, 135.2, 133.9, 132.6, 131.5, 130, 129.4, 129.3, 129.2, 128.9, 128.3, 119.9, 47.8, 25.5,

24.9, 18.8. **HRMS (ESI+) m/z (found):**247.1783, **Calculated:** 247.17808.

#### 2-(2-Fluoro-[1,1′-biphenyl]-4-yl)-N-phenylpropanamide (3a)

White solid. mp: 177 °C. Yield: 60%. $\mathbf{R_f}$ = 0.48 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.50–7.03 ($m_a$, 14H), 3.70–3.63 (q, *J* = 7.1 Hz, 1H), 1.57–1.55 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.6 (C=O amide), 141.4, 136.8, 134.4, 130.4, 128.1, 128.09, 128.05, 127.6, 126.9, 123.6, 122.7, 118.9, 114.6, 114.3, 46.7, 17.8. **HRMS (ESI+) m/z (found):** 320.14450, **Calculated:** 320.14452.

#### 2-(2-Fluoro-[1, 1′-biphenyl]-4-yl)-N-(p-tolyl)propanamide (3b)

White crystalline solid. mp: 128 °C. Yield: 66%. $\mathbf{R_f}$ = 0.47 ($CH_2Cl_2$).**$^1$H NMR (300 MHz, $CDCl_3$) δ** 749–7.01 ($m_a$, 13H), 3.69–3.61 (q, *J* = 7.1 Hz, 1H), 2.22 (s, 3H), 1.56–1.54 (d, *J* = 7.1 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 171.5 (C=O amide), 142.4, 142.3, 135.3, 135.14, 134.13, 131.2, 129.4, 128.96, 128.92, 128.5, 127.7, 123.6, 119.9, 115.5, 115.2, 47.5, 20.8, 18.6. **HRMS (ESI+) m/z (found):** 334.16004, **Calculated:** 334.16017.

#### 2-Phenoxy-N-phenylpropanamide (4a)

White solid. mp: 120 °C. Yield: 89%. $\mathbf{R_f}$ = 0.48 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.13 (bs, 1H), 7.48–7.45 (m, 2H), 7.28–7.23 (t, *J* = 7.8 Hz, 4H), 7.08–6.90 (m, 4H), 4.75–4.68 (q, *J* = 6.8 Hz, 1H), 1.60–1.58 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.2 (C=O amide), 156.7, 137, 129.9, 129, 124.7, 122.4, 119.96, 115.7, 76.6, 18.7. **HRMS (ESI+) m/z (found):**264.0996, **Calculated:** 264.0995.

#### 2-Phenoxy-N-(p-tolyl) propanamide (4b)

White solid. mp: 117 °C. Yield: 85%. $\mathbf{R_f}$ = 0.41 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.09 (bs, 1H), 7.36–7.18 (m, 4H), 7.06–6.89 (m, 5H), 4.74–4.67 (q, *J* = 6.8 Hz, 1H), 2.24 (s, 3H), 1.59–1.57 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.1 (C=O amide), 156.7, 134.5, 134.3, 129.9, 129.5, 122.4, 120, 115.7, 75.4, 20.9, 18.7. **HRMS (ESI+) m/z (found):**278.1154, **Calculated:** 279.11515 $[M+Na]^+$ ($C_{16}H_{17}NO_2Na$).

#### 2-Phenoxy-N-(4-(trifluoromethyl)phenyl)propanamide (4c)

White solid. mp: 123 °C. Yield: 92%. $\mathbf{R_f}$ = 0.11 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.31 (bs, 1H), 7.63–7-50 (dd, *J* = 32.2 & 8.6 Hz, 4H), 7.30–7.19 (dt, *J* = 18.8 & 12.1 Hz, 2H), 7.02–6.90 (m, 3H), 4.78–4.71(q, *J* = 6.8 Hz, 1H), 2.24 (s, 3H), 1.61–1.59 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.6 (C=O amide), 156.5, 140.1, 130, 126.3, 126.2, 122.7, 119.5, 115.8, 75.4, 18.6. **HRMS (ESI+) m/z (found):** 332.0869, **Calculated:** 332.08688 $[M+Na]+(C_{16}H_{14}NO_2F_3Na)$.

#### N-(4-Methoxyphenyl)-2-phenoxypropanamide (4d)

White crystalline solid. mp: 127 °C. Yield: 90%. $\mathbf{R_f}$ = 0.50 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.04 (bs, 1H), 7.37–7.34 (m, 2H), 7.27–7.18 (m, 2H), 6.98–6.88 (m, 3H), 6.79–6.76 (m, 2H), 4.73–4.67 (q, *J* = 6.7 Hz), 3.70 (s, 3H), 1.59–1.57 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.6 (C=O amide), 156.7, 156.6, 130.1, 129.9, 122.4, 121.7, 115.7, 114.1, 75.4, 55.4, 18.7.

#### N-(4-Iodophenyl)-2-phenoxypropanamide (4e)

White crystalline solid. mp: 147 °C. Yield: 98%. $\mathbf{R_f}$ = 0.92 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.16 (bs, 1H), 7.56–7.53 (m, 2H), 7.28–7.23 (m, 4H), 7.08–6.88 (m, 3H), 4.74–4.67(q, *J* = 6.8 Hz, 1H), 1.59–1.56 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.3 (C=O amide), 156.5, 137.9, 136.8, 129.9, 122.6, 121.8, 115.7, 88, 75.4, 18.6. **HRMS (ESI+) m/z (found):** 368.01409, **Calculated:** 368.01420.

#### N-(4-Bromophenyl)-2-phenoxypropanamide (4f)

White crystalline solid. mp: 132 °C. Yield: 80%. $\mathbf{R_f}$ = 0.88 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.16 (bs, 1H), 7.39–7.17 (m, 6H), 6.99–6.87 (m, 3H), 4.73–4.66(q, *J* = 6.8 Hz, 1H), 1.58–1.55 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 169.1 (C=O amide), 155.3, 134.9, 130.7, 121.3, 120.3, 116.1, 114.5, 128.7, 74.2, 17.4. **HRMS (ESI+) m/z (found):** 320.02809, **Calculated:** 320.02807.

#### N-(4-Chlorophenyl)-2-phenoxypropanamide (4g)

White crystalline solid. mp: 137 °C. Yield: 87%. $\mathbf{R_f}$ = 0.83 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.17 (bs, 1H), 7.43–7.40 (m, 1H), 7.27–7.18(m, 4H), 6.99–6.87 (m, 3H), 4.73–4.66(q, *J* = 6.8 Hz, 1H), 1.57–1.55 (d, *J* = 6.8 Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.3 (C=O amide), 156.6, 135.6, 129.9, 129.6, 129, 122.5, 121.2, 115.7, 135.6, 75.4, 18.6. **HRMS (ESI+) m/z (found):** 276.07867, **Calculated:** 276.07858.

#### N-Benzyl-2-phenoxypropanamide (4h)

White solid. mp: 220 °C. Yield: 64%. $\mathbf{R_f}$ = 0.16 ($CH_2Cl_2$). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 8.17 (bs, 1H), 7.43–7.40 (m,

1H), 7.27–7.18 (m, 4H), 6.99–6.87 (m, 3H), 4.73–4.66 (q, $J = 6.8$ Hz, 1H), 1.57–1.55 (d, $J = 6.8$ Hz, 3H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.3 (C=O amide), 156.6, 135.6, 129.9, 129.6, 129, 122.5, 121.2, 115.7, 135.6, 75.4, 18.65. **HRMS (ESI+) m/z (found):** 279.20659, **Calculated:** 279.20635.

#### Tert-butyl (S)-2-(phenylcarbamoyl) pyrrolidine-1-carboxylate (5a)

White crystalline solid. mp: 187 °C. Yield: 52%. **$R_f$** = 0.28 (AcOEt/Petroleum Ether: 2/8). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 9.49 (bs, 1H), 7.54–7.51 (dd, $J = 8.6$, 1.0 Hz, 2H), 7.30–7.28 (m, 2H), 7.08 (bs, 1H), 4.48 (bs, 1H), 3.46 (bs, 2H), 2.52–1.80 (m, 4H), 1.50 (s, 9H).**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 169.9 (C=O amide), 156.56, 138.3, 128.9, 123.8, 119.65, 80.9, 60.5, 47.2, 28.3, 27.1, 24.5. **HRMS (ESI+) m/z (found):** 291.17023 **Calculated:** 291.17032. $[\alpha]^{20}_D$ (*c* 1,$CH_2Cl_2$) − 147.3 (− 147.3; Litt: − 140.9 (Doherty et al. 2008; Kanemitsu et al. 2012)).

#### Tert-butyl (S)-2-(p-tolylcarbamoyl) pyrrolidine-1-carboxylate (5b)

White crystalline solid. mp: 181 °C. Yield: 72%. **$R_f$** = 0.28 (AcOEt/Petroleum Ether: 2/8). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 9.37 (bs, 1H), 7.42–7.10 (m, 4H arm), 4.46 (bs, 1H), 3.46 (bs, 2H), 2.52–1.94 (m, 4H), 2.32 (s, 3H), 1.50 (s, 9H).**$^{13}$C NMR (75 MHz, $CDCl_3$)** *δ* 169.7 (C=O amide), 135.7, 134.9, 129.4, 119.6, 80.8, 60.4, 47.1, 28.3, 24.3, 20.8. **HRMS (ESI+) m/z (found):**305.18571, **Calculated:** 305.18597. $[\alpha]^{20}_D$ (*c* 1, $CH_2Cl_2$) −111.7

#### Tert-butyl(S)-2-((4-(trifluoromethyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate (5c)

White crystalline solid. mp: 185 °C. Yield: 72%. **$R_f$** = 0.35 (AcOEt/Petroleum Ether: 2/8). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 9.92 (bs, 1H), 7.59–7.46 (m, 4H), 4.53 (bs, 1H), 3.53–3.42 (m, 2H), 2.42–1.96 (m, 4H), 1.52 (s, 9H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.7 (C=O amide), 156.3, 166.7, 141.5, 129.5, 122.3, 118.9, 100.2, 125.9, 81, 60.5, 47.3, 28.4, 27.6, 24.5. **HRMS (ESI+) m/z (found):**359.15763, **Calculated:** 359.15770. $[\alpha]^{20}_D$ (*c* 1,$CH_2Cl_2$) − 127.5

#### Tert-butyl (S)-2-((4-chlorophenyl)carbamoyl) pyrrolidine-1-carboxylate (5d)

White crystalline solid. mp: 185 °C. Yield: 58%. **$R_f$** = 0.28 (AcOEt/Petroleum Ether: 2/8). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 9.66 (bs, 1H), 7.45–7.21(m, 4H), 4.48 (bs, 1H), 3.50–3.40 (m, 2H), 2.43–1.80 (m, 4H), 1.50 (s, 9H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.2 (C=O amide), 156.3, 128.7, 120.6, 137, 80.9, 60.4, 47.2, 28.4, 27.6, 24.5. **HRMS (ESI+) m/z (found):**325.13137, **Calculated:** 325.13135. $[\alpha]^{20}_D$ (*c* 1,$CH_2Cl_2$) -101.9

#### Tert-butyl (S)-2-((4-bromophenyl)carbamoyl) pyrrolidine-1-carboxylate (5e)

Brown crystalline solid. mp: 193 °C. Yield: 60%. **$R_f$** = 0.28 (AcOEt/Petroleum Ether: 2/8). **$^1$H NMR (300 MHz, $CDCl_3$) δ** 9.68 (bs, 1H), 7.39–7.28 (m, 4H), 4.48 (bs, 1H), 3.49–3.40 (m, 2H), 2.37–1.89 (m, 4H), 1.50 (s, 9H). **$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 170.2 (C=O amide), 156.3, 137.5, 131.7, 121, 116.1, 121.4, 80.9, 60.5, 47.2, 28.4, 27.6, 24.5. **HRMS (ESI+) m/z (found):** 391.06272, **Calculated:** 391.06278 $[M+Na]^+$ ($C_{16}$ $H_{21}$ $N_2$ $^{79}$Br $^{23}$Na). $[\alpha]^{20}_D$ (*c* 1, $CH_2Cl_2$) -92.1

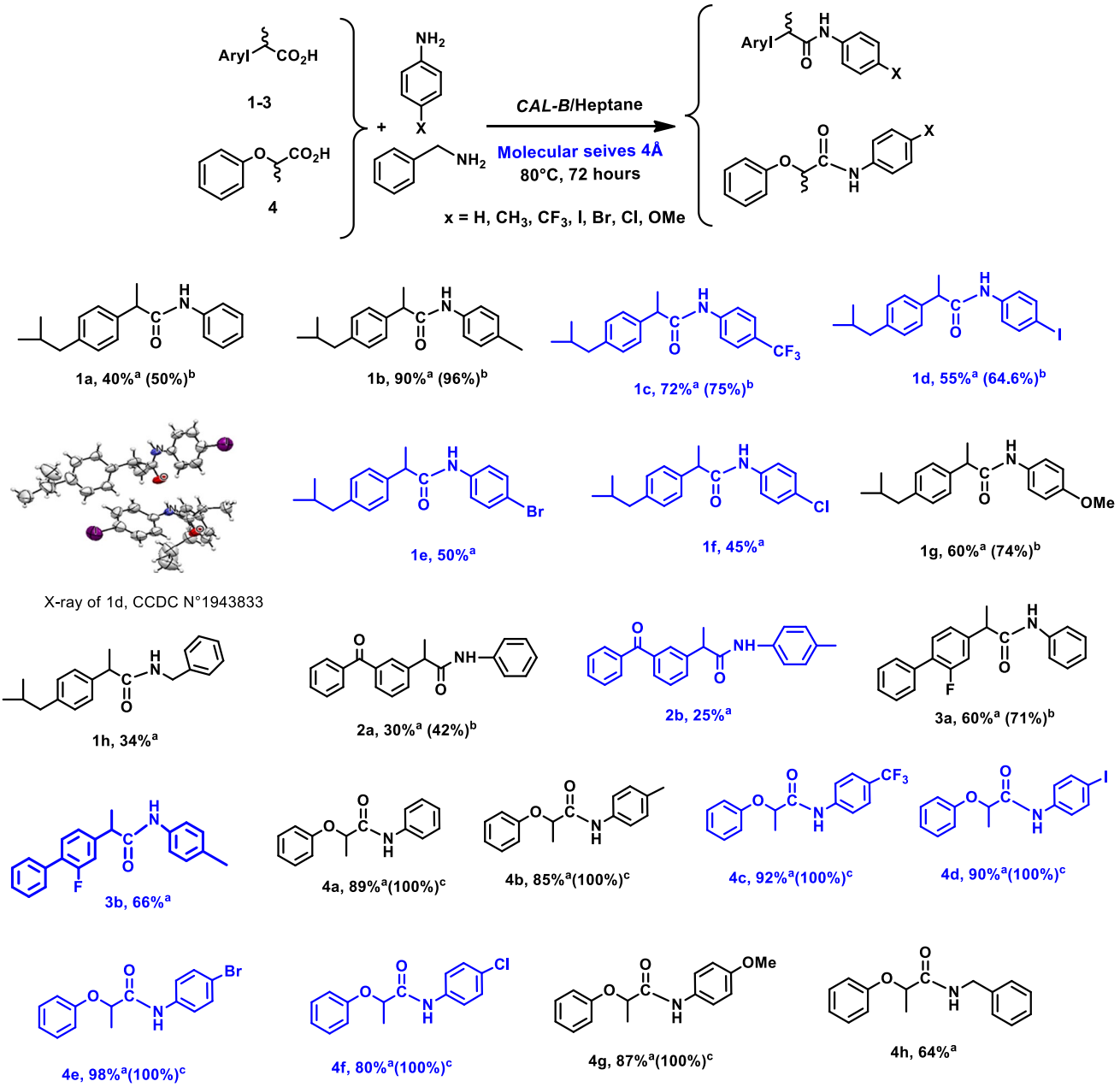
## Results and discussion

Firstly, we have examined the efficiency of the amidation reaction conditions. For thus, we have selected four carboxylic acids: ibuprofen **1**, ketoprofen **2**, flurbiprofen **3**, and the phenoxypropionic acid **4** and diverse anilines derivatives, having different electronic effects, as well as benzylamine.

All condensation experiments were performed on one equivalent of carboxylic acids or ester, two equivalents of aniline and 50 mg of *CAL-B* (> 10,000 U/g) diluted in 1 mL of heptane. 50 mg of molecular sieves 4 Å are added. The suspensions were stirred at 80 °C for 72 h. The reactions mixtures were diluted in ethyl acetate and filtered. The amides formed were recovered by acido-basic liquid–liquid extraction. The structures of the formed amides were characterized by usual spectroscopic analyses (NMR $^1$H, NMR $^{13}$C and HRMS). The conversions were determined by chiral HPLC (Scheme 1).

The enzymatic amidation displays a broad variety of results and offers the synthesized amides with variable yields between 25% ≤ Yield ≤ 98%. These differences depend on the structure of the carboxylic acid and the electronic and steric effects of the primary amines.

The enzymatic amidation of the ibuprofen **1** with anilines possessing different substituents on *para*- position, from strong electro-donating to strong electron-withdrawing effects (–$CH_3$, –$CF_3$, –OMe, I, Br, –Cl), gave the corresponding amides in good-to-excellent yields. The use of *p*-toluidine increases significantly the conversion rates and the isolated yields compared to the aniline. The recorded yields are 90% and 40%, respectively; the same effect was notified with the *p*-$CF_3$-aniline. The amidoprofen **1c** was isolated with 72% of yield. The use of the *p*-Cl-aniline, *p*-Br-aniline, *p*-I-aniline and the *p*-OMe-aniline gave the amidoprofens (**1d**–**1g**) with acceptable yields varying from 45 to




**Scheme 1** Enzymatic amidation of carboxylic acids (1–4) by means of anilines. Reaction Conditions: 1 mmol of carboxylic acid, 2 mmol of aniline derivatives, 50 mg of molecular sieves 4 Å and 50 mg of *CAL-B* in 1 mL of heptane at 80 °C for 72hours. [(a)] Isolated yield. [(b)] Conversion: $C = ee_S/ee_P + ee_s$. [(c)] Monitored by TLC. ND: Not determined

60%. The use of benzylamine instead of anilines decreases significantly the yield of the formed amidoprofen to 34%. On the same lines, the enzymatic amidation of the ketoprofen **2** and the flurbiprofen **3** using aniline and *p*-toluidine as the amidation partners is very different. While the amidation of the ketoprofen **2** was hardly performed (25–30% of isolated yields), those of the flurbiprofen **3** were reached 60–66% of isolated yields.

Moreover, the enzymatic amidation of the phenoxypropionic acid **4** was performed very smoothly compared to the arylpropionic acids (profens) **1–3.** The carboxylic amides (**4a**–**4g**) are recovered with good-to-excellent isolated yields (89% to 98%), with total conversions. The same observation is recorded when benzylamine is used instead anilines; the corresponding amide is obtained with 64% yield. The amide structures (**4c**–**4g**) are reported for the first one. Using the *p*-$CF_3$-aniline, as the amidation partner, the reaction is widely improved by the presence of the *CAL-B* as catalyst; the corresponding amide is isolated with 92% yield. From all the synthesized amidoprofens, the structures **1c**, **1d**, **1e, 2b**

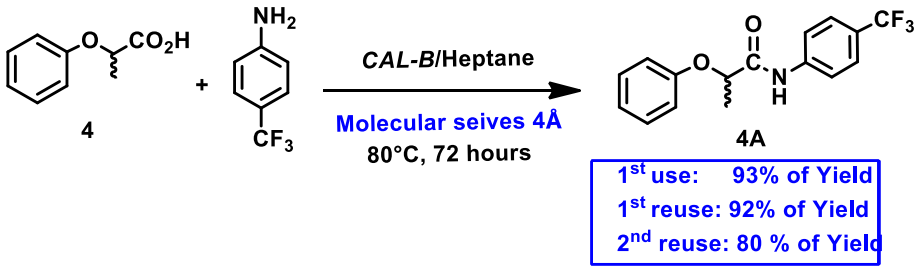
and **3b** are reported for the first time. The **1d** is demonstrated by X-ray data (CCDC deposition number: 1943833).

The reported conditions of the *CAL-B* catalyzed direct amidation allow easily to potent carboxylic amides with a high atom economy and chemical yields depend to the acid structure. Since the *CAL-B* is recyclable and biodegradable, the unique considered waste is water. At the best of our knowledge, the enzymatic amidation of those acid structures, especially, the NSAIDs ones, is described for the first time. It is a cleaner and safer approach with low environmental impact process.

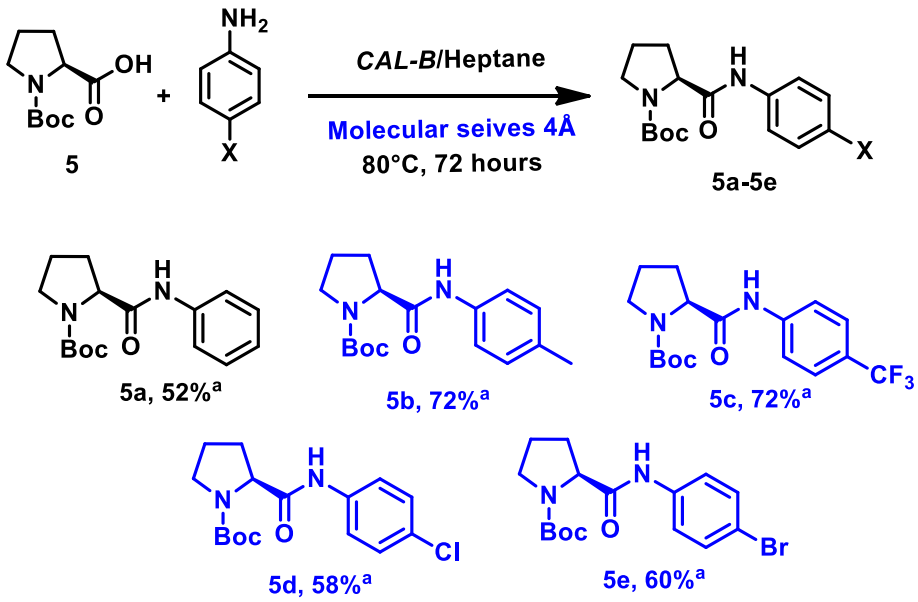
In order to valorize this simple and easy approach, we have done a gram scale reaction. We have applied the optimal conditions on 6 mmol (1 g) of phenoxypropionic acid **4** with 6 mmol (0.193 g) of *p*-$CF_3$-aniline and 300 mg of *CAL-B*. The enzymatic amidation is reproducible, and the amide is isolated with 93% yields. We have recovered and reused the *CAL-B* lipase in second and third times. The amides are obtained with 92% and 88% yields (Scheme 2), showing that until the third use the lipase keeps its performance.

To further extend this enzymatic approach, we have envisaged to applying it for the amidation of a protected amino acid, the Boc-proline. At the best of our knowledge, only the aminolysis using aniline and benzylamine by means of coupling agents was described for the synthesis of the corresponding amides which were used as a potential organocatalysts in the aldolization and imine hydrogenation reactions and exploited without Boc-moiety cleavage (Galanakis et al. 2004). It is well known that several described ways for amidation of aminoacids suffer of serious problem of the loss of the enantiopurity or racemization. In our case, we have applied the optimal enzymatic amidation on the L-Boc-proline, commercially available, with aniline derivatives (Scheme 3). All the obtained amide structures are confirmed by the usual spectroscopic data. Their enantiomeric purity was examined by the measurement of the optical rotations and compared to the literature data for the known structures.

The amidation of the L-Boc-proline without lipase is performed smoothly by the five anilines. The amides are furnished with various yields from 52 to 72% and that depending on the electronic effects due to the substituent on *para-* position of aniline. It is to be underlined that the thermal amidation, without the use of lipase, is possible but with less yields and longer reaction time. The presence of a hydrolytic enzyme improves significantly the amidation, especially in the case of *p-CF3*-aniline, and no cleavage of




**Scheme 2** Gram-scale *CAL-B* catalyzed amidation of **4** with p-$CF_3$-aniline




**Scheme 3** Enzymatic amidation of Boc-proline by means of anilines. 1 mmol of Boc-proline, 2 mmol of aniline derivatives, 50 mg of molecular sieves 4 Å and 50 mg of *CAL-B* in 1 mL of heptane at 80 °C for 72 h. [(a)] Isolated yield

the protected group (-Boc) was observed. So, this enzymatic approach for the amidation of *N*-protected aminoacids constitutes a new path promising, more safe, clean and sustainable.

## Conclusions

In summary, we have developed an efficient direct amidation of a set of non-activated carboxylic acids with anilines and benzylamine, catalyzed by *CAL-B* as biodegradable biotool. A set of nonsteroidal anti-inflammatory drugs (NSAIDs), phenoxypropionic acid and protected-proline are selected to examine the efficiency of the enzymatic pathway. This direct enzymatic amidation system is examined for the first time. The obtained carboxylic amides are recovered with isolated chemical yields varied between moderate and excellent.

Of the twenty five carboxylic amides synthesized, at least fourteen from them are reported for the first time and one from them: *N*-(4-iodophenyl)-2-(4-isobutylphenyl)propanamide **1d** is characterized by X-ray diffraction.

The reported conditions of the *CAL-B*-catalyzed direct amidation allow easily to potent carboxylic amides with a high atom economy, minimal waste production and chemical yields depending on the acid structure. This new sustainable and eco-friendly route opens up very interesting perspectives for easily recoverable applications.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11696-021-01636-5.

**Acknowledgements** Algerian Ministry of Higher Education and Scientific Research (MESRS, FNR 2000) and ANDRU (PNR) are gratefully acknowledged for the financial support of this work. Prof. Olivier RIANT (IMCN/UCL-Louvain-La-Neuve, Belgium) is acknowledged for his assistance and the welcome of NourElhouda BENAMARA and Mounia MERABET-KHELASSI to perform specific analyses.

## References

Aissa R, Guezane-Lakoud S, Kolodziej E, Toffano M, Aribi-Zouioueche L (2019) Diastereoselective synthesis of bis(α-aminophosphonates) by lipase catalytic promiscuity. New J Chem 43:8153. https://doi.org/10.1039/C8NJ06235H

Alalla A, Merabet-Khelassi M, Riant O, Aribi-Zouioueche L (2014) Green synthesis of benzamides in solvent-and activation-free conditions. Synth Commun 44:2364–2376. https://doi.org/10.1080/00397911.2014.898072

Alalla A, Merabet-Khelassi M, Aribi-Zouioueche L, Riant O (2016) Easy kinetic resolution of some β-amino alcohols by *Candida antarctica*lipase B catalyzed hydrolysis in organic media. Tetrahedron Asymmetry 27:1253. https://doi.org/10.1016/j.tetasy.2016.10.003

Annunziata F, Letizia-Contente M, Betti D, Pinna C, Molinari F, Tamborini L, Pinto A (2020) Efficient chemo-enzymatic flow synthesis of high value amides and esters. Catalysts 10:939. https://doi.org/10.3390/catal10080939

Arroyo M, De Le Mata I, García JL, Barredo JL (2017) Biocatalysis for industrial production of active pharmaceutical ingredients (APIs). In: Biotechnology of microbial enzymes, Chap 17. Academic Press, pp 451–473

Belkacemi FZ, Merabet-Khelassi M, Aribi-Zouioueche L, Riant O (2017) Diastereoselective and enantioselective alkaline-hydrolysis of 2-aryl-1-cyclohexyl acetate: a CAL-B catalyzed deacylation/acylation tandem process. Tetrahedron Asymmetry 28:1644. https://doi.org/10.1016/j.tetasy.2017.09.010

Braia N, Merabet-Khelassi M, Aribi-Zouioueche L (2018) Efficient access to both enantiomers of 3-(1-hydroxyethyl) phenol by regioselective and enantioselective CAL-B-catalyzed hydrolysis of diacetate in organic media by sodium carbonate. Chirality 30:1312. https://doi.org/10.1002/chir.23025

Busto E, Gotor-Fernandez V, Gotor V (2010) Hydrolases: catalytically promiscuous enzymes for non-conventional reactions in organic synthesis. Chem Soc Rev 39:4504. https://doi.org/10.1039/C003811C

Chandra P, Singh R, Arora PK (2020) Microbial lipases and their industrial applications: a comprehensive review. Microb Cell Fact 19:169. https://doi.org/10.1186/s12934-020-01428-8

Cheng L, Ge X, Huang L (2018) Direct amidation of non-activated phenylacetic acid and benzylamine derivatives catalysed by $NiCl_2$. Royal Soc Open Sci 5:171870. https://doi.org/10.1098/rsos.171870

Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL, Linderman RJ, Lorenz K, Manley J, Pearlman BA, Wells A, Zaks A, Zhang TY (2007) Key green chemistry research areas—a perspective from pharmaceutical manufacturers. Green Chem 9:411–420. https://doi.org/10.1039/B703488C

De Figueiredo RM, Suppo JS, Campagne JM (2016) Nonclassical routes for amide bond formation. Chem Rev 116:12029–12122. https://doi.org/10.1021/acs.chemrev.6b00237

Doherty S, Knight JG, McRae A, Harrington RW, Clegg W (2008) Oxazoline-substituted prolinamide-based organocatalysts for the direct intermolecular aldol reaction between cyclohexanone and aromatic aldehydes. Eur J Org Chem 10:1759. https://doi.org/10.1002/ejoc.200700922

Galanakis D, Kourounakis AP, Tsiakitzis KC, Doulgkeris C, Rekka EA, Gavalas A, Kravaritou C, Christos C, Kourounakis PN (2004) Synthesis and pharmacological evaluation of amide conjugates of NSAIDs with L-cysteine ethyl ester, combining potent antiinflammatory and antioxidant properties with significantly reduced gastrointestinal toxicity. Bioorg Med Chem Lett 14:3639. https://doi.org/10.1016/j.bmcl.2004.05.025

Greenberg A, Breneman CM, Liebman JF (2000) The amide linkage: structural significance in chemistry, biochemistry and materials science. Wiley, New York

Guezane-Lakoud S, Toffano M, Aribi-Zouioueche L (2017) Promiscuous lipase catalyzed a new P-C bond formation: green and efficient protocol for one-pot synthesis of α-aminophosphonates. Heteroatom Chem 28:e21408. https://doi.org/10.1002/hc.21408

Hult K, Berglund P (2007) Enzyme promiscuity: mechanism and applications. Trends Biotechnol 25(5):231. https://doi.org/10.1016/j.tibtech.2007.03.002

José C, Toledo MV, Briand LE (2016) Enzymatic kinetic resolution of racemic ibuprofen: past, present and future. Crit Rev Biotechnol 36:891. https://doi.org/10.3109/07388551.2015.1057551

Kanemitsu T, Umehara A, Haneji R, Nagata K, Itoh T (2012) A simple proline-based organocatalyst for the enantioselective reduction of imines using trichlorosilane as a reductant. Tetrahedron 68:3893–3898. https://doi.org/10.1016/j.tet.2012.03.035

Kaushik P, Shakil NA, Kumar J, Singh BB (2015) Lipase-catalyzed solvent-free amidation of phenolic acids. Synth Commun 45:569. https://doi.org/10.1080/00397911.2014.974611

Kourist R, De María PD, Miyamoto K (2011) Biocatalytic strategies for the asymmetric synthesis of profens – recent trends and developments. Green Chem 13:2607–2618. https://doi.org/10.1039/C1GC15162B

Lanigan RM, Sheppard TD (2013) Recent developments in amide synthesis: direct amidation of carboxylic acids and transamidation reactions. Eur J Org Chem 2013:7453–7465. https://doi.org/10.1002/ejoc.201300573

Lima RN, Porto AL (2017) Biocatalytic aminolysis of ethyl (*S*)-mandelate by lipase from *Candida antarctica*. Catal Commun 100:157. https://doi.org/10.1016/j.catcom.2017.06.020

Lima RN, Silva VR, Santos LDS, Bezerra DP, Soares MB, Porto AL (2017) Fast synthesis of amides from ethyl salicylate under microwave radiation in a solvent-free system. RSC Adv 7(89):56566. https://doi.org/10.1039/C7RA11434F

Lima RN, dos Anjos CS, Orozco EV, Porto AL (2019) Versatility of *Candida antarctica* lipase in the amide bond formation applied in organic synthesis and biotechnological processes. Mol Catal 466:75. https://doi.org/10.1016/j.mcat.2019.01.007

Lundberg H, Tinnis F, Adolfsson H (2012) Direct amide coupling of non-activated carboxylic acids and amines catalysed by zirconium (IV) chloride. Chem Eur J 18:3822–3826. https://doi.org/10.1002/chem.201104055

Lundberg HF, Tinnis N, Selander N, Adolfsson H (2014) Catalytic amide formation from non-activated carboxylic acids and amines. Chem Soc Rev 43:2714–2742. https://doi.org/10.1039/C3CS60345H

Lundberg H, Tinnis F, Zhang J, Algarra A, Himo F, Adolfsson H (2017) Mechanistic elucidation of zirconium-catalyzed direct amidation. J Am Chem Soc 139:2286–2295. https://doi.org/10.1021/jacs.6b10973

Manova D, Gallier F, Tak-Tak L, Yotava L, Lubin-Germain N (2018) Lipase-catalyzed amidation of carboxylic acid and amines. Tetrahedron Lett 59:2086. https://doi.org/10.1016/j.tetlet.2018.04.049

Montalbetti CAGN, Falque V (2005) Amide bond formation and peptide coupling. Tetrahedron 61:10827–10852. https://doi.org/10.1016/j.tet.2005.08.031

Mouad AM, Taupin D, Lehr L, Yvergnaux F, Porto ALM (2016) Aminolysis of linoleic and salicylic acid derivatives with *Candida antarctica* lipase B: a solvent-free process to obtain amphiphilic amides for cosmetic application. J Mol Cata B Enzym 126:64. https://doi.org/10.1016/j.molcatb.2016.01.002

Nechab M, Azzi N, Vanthuyne N, Bertrand M, Gastaldi S, Gil G (2007) Highly selective enzymatic kinetic resolution of primary amines at 80 °C: a comparative study of carboxylic acids and their ethyl esters as acyl donors. J Org Chem 72:6918. https://doi.org/10.1021/jo071069t

Sheldon RA (2016) Green biocatalysis. In: Patel RN (eds) Biocatalysis and green chemistry. Wiley Online Library, Chap 1. pp 1–15

Sheldon RA, Brady D, Bode ML (2020) The Hitchhiker's guide to biocatalysis: recent advances in the use of enzymes in organic synthesis. Chem Sci 11(10):2587

Zheng GW, Xu JH (2011) New opportunities for biocatalysis: driving the synthesis of chiral chemicals. Curr Opin Biotech 22(6):784. https://doi.org/10.1016/j.copbio.2011.07.002