Journal of Organometallic Chemistry 896 (2019) 90–101

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthesis of β-hydroxyamides through ruthenium-catalyzed hydration/transfer hydrogenation of β-ketonitriles in water: Scope and limitations

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A R T I C L E I N F O

Article history:
Received 12 April 2019
Accepted 17 May 2019
Available online 30 May 2019

Dedicated to the memory of Professor Pascual Royo

Keywords:
Ruthenium
Aqueous catalysis
Cascade processes
Nitrile hydration
Transfer hydrogenation

A B S T R A C T

A cascade process for the straightforward *one-pot* conversion of β-ketonitriles into β-hydroxyamides is presented. The process, that proceeds in water employing the arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ as catalyst in combination with sodium formate, involves the initial hydration of the β-ketonitrile substrates to generate the corresponding β-ketoamide intermediates, which subsequently undergo the transfer hydrogenation (TH) of the carbonyl group. Employing a family of forty different β-ketonitriles, featuring diverse substitution patterns, the scope and limitations of the process have been established.

1. Introduction

Catalytic cascade reactions, a concept that encompasses all those processes in which two or more catalytic transformations occur sequentially in a single reaction vessel [1], are of prime interest in contemporary chemistry since, in comparison with classical multistep syntheses, they allow an easier, cheaper and cleaner access to a wide variety of organic products [2]. In this context, in connection with our studies on the metal-catalyzed hydration of nitriles [3], we recently communicated that this hydration reaction can be combined in a concurrent manner with the transfer hydrogenation (TH) of carbonyl compounds, thus opening a straightforward access to synthetically useful β-hydroxyamides **C** from β-ketonitriles **A**, *via* the corresponding β-ketoamide intermediates **B** (Scheme 1) [4]. Interestingly, this unprecedented cascade process proceeds in water, without the need of any organic co-solvent, and making use of a single metal source, *i.e.* the half-sandwich chlorophosphine ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**), in combination with inexpensive sodium formate (NaO_2CH) [5,6].

At present, three general routes for the synthesis of β-hydroxyamides can be found in the literature: (*i*) the amidation of β-hydroxy-esters and -acids [7], (*ii*) the aldol addition of amide enolates to carbonyl compounds [8], and (*iii*) the reduction of β-ketoamides [9]. However, these protocols have been rarely employed in the preparation of *N*-unsubstituted β-hydroxyamides **C** [7g,8d,9c,e,k]. The generation of such compounds is usually achieved by hydration of the corresponding β-hydroxynitriles **D** employing classical acid/base-promoted reactions [10] or enzymatic catalysis [11], but problems associated with the overhydrolysis of the amides into carboxylic acids have been in most cases observed. Surprisingly, the use of metal catalysts for the hydration of β-hydroxynitriles **D** remains practically unexplored [12]. In this regard, the most outstanding work in the field was published by Saito and co-workers, who developed a straightforward procedure for the synthesis of β-hydroxyamides **C** from aldehydes and nitriles through a sequential *one-pot* two-steps aldolization/hydration process, involving compounds **D** as intermediates (Scheme 2) [13]. Both steps are catalyzed by the rhodium(I) dimer $[\{Rh(\mu\text{-OMe})(cod)\}_2]$ (cod = 1,5-cyclooctadiene), with the hydration of the C≡N bond of

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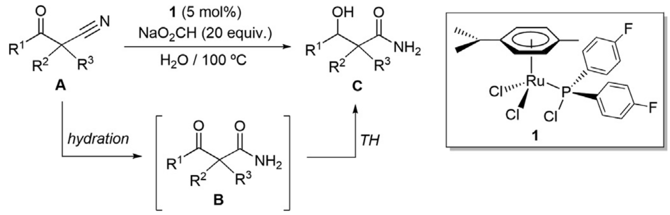
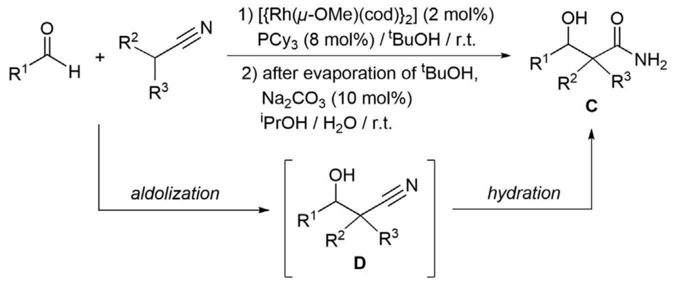
https://doi.org/10.1016/j.jorganchem.2019.05.016



Scheme 1. Access to β-hydroxyamides **C** by Ru-catalyzed hydration/TH of β-ketonitriles **A**.



Scheme 2. Rhodium-catalyzed a nitrile aldolization/hydration process.

D requiring the addition of a base to the reaction medium. However, although novel and appealing, a major drawback of this protocol is the large excess of the nitrile partner employed (38–77 equiv.).

All these precedents, along with the ease of access to the starting β-ketonitriles **A** (many are commercially available) [14], confer to the ruthenium-catalyzed tandem reaction depicted in Scheme 1 a high synthetic value [15,16]. In this regard, given that in our preliminary communication we basically focused on the behavior of α-unsubstituted aromatic β-ketonitriles, *i.e.* substrates of type ArC(=O)CH$_2$C≡N, we considered pertinent to carry out a broader study in order to outline the scope and limitations of the process. Accordingly, a full report on this reaction is herein presented. A family of forty different β-ketonitriles featuring diverse substitution patterns has been employed along this study.

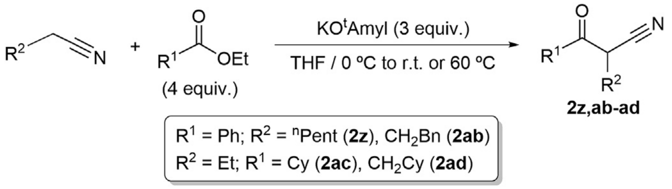
2. Experimental

2.1. General information

All the manipulations were performed under argon atmosphere using vacuum-line and standard sealed-tube techniques. The ruthenium(II) catalyst $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**) was synthesized by following the method reported in the literature [3e]. The β-ketonitriles **2a-n,o-p,af-ah,an** were obtained from commercial suppliers and used as received. The β-ketonitriles **2q-ae,ai-aj** were synthesized by acylation of the corresponding nitrile following the general procedure developed by Trenkle and co-workers [17]. Compounds **2z,ab-ad** have not been previously reported (details on their synthesis and characterization are given below). The α-disubstituted β-ketonitriles **2ak-am** were prepared following the methods reported in the literature [18]. IR spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. NMR spectra were obtained on Bruker DPX-300, AV-400 or AV600 spectrometers. ^{13}C{^{1}H} and ^{1}H chemical shifts were referenced to the residual signal of deuterated solvent. All data are reported in ppm downfield from $(CH_3)_4Si$. For ^{19}F{^{1}H} NMR spectra, the chemical shifts were referenced to the $CFCl_3$ standard. All NMR measurements were carried out at 25 °C. HRMS data were obtained on a ESI-q-TOF Bruker Impact II mass spectrometer. For column chromatography, Merck silica gel 60 (230–400 mesh) was employed.

2.2. *Synthesis and characterization of the novel β-ketonitriles* ***2z,ab-ad***

These compounds were obtained by following the acylation procedure developed by Trenkle and co-workers [17]:



2z,ab-ad

To a solution of the corresponding nitrile R^{2}CH$_2$C≡N (4 mmol) in THF were added dropwise, at 0 °C and in an ice bath, 6.24 mL of a 1.7 M solution of KO^{t}Amyl in toluene (12 mmol). The corresponding ethyl ester R^{1}CO$_2$Et (16 mmol) was subsequently added at 0 °C, and the resulting mixture stirred at room temperature (R^1 = Ph) or 60 °C (R^1 = alkyl) till complete consumption of the starting nitrile (TLC monitoring; *ca.* 4 h). Then, 100 mL of a 0.97 M solution of HCl in water and 100 mL of EtOAc were added. The organic phase was separated, washed with water (2 × 50 mL) and brine (2 × 50 mL), dried with anhydrous $MgSO_4$ and filtered. Evaporation of the organic solvents under vacuum led to a yellow oily residue which was purified by flash column chromatography over silica gel using a mixture hexane/EtOAc (4:1) as eluent. Characterization data for compounds **2z,ab-ad** are as follows:

2-Benzoylheptanenitrile (2z): Colourless oil. Yield: 0.809 g (94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.99–7.97 (m, 2H), 7.70–7.65 (m, 1H), 7.58–7.52 (m, 2H), 4.37 (dd, 1H, J = 7.5 and 6.6 Hz), 2.06–1.97 (m, 2H), 1.65–1.52 (m, 2H), 1.39–1.32 (m, 4H), 0.92 (t, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 190.9, 134.4, 134.0, 129.1 (2C), 128.7 (2C), 117.4, 40.1, 31.1, 29.9, 26.8, 22.3, 13.9 ppm. IR (film): ν = 2250 (C≡N), 1694 (C=O) cm^{-1}. HRMS (ESI): *m/z* 238.120130, [M + Na$^+$] (calcd for $C_{14}H_{17}NONa$: 238.120235).

2-Benzoyl-4-phenylbutanenitrile (2ab): Colourless oil. Yield: 0.907 g (91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.85–7.82 (m, 2H), 7.67–7.47 (m, 3H), 7.39–7.23 (m, 5H), 4.28 (dd, 1H, J = 7.2 and 7.2 Hz), 3.04–2.82 (m, 2H), 2.37–2.30 (m, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 190.6, 139.2, 134.5, 133.8, 129.1 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 126.8, 117.1, 38.9, 32.9, 31.4 ppm. IR (film): ν = 2250 (C≡N), 1691 (C=O) cm^{-1}. HRMS (ESI): *m/z* 272.104550, [M + Na$^+$] (calcd for $C_{17}H_{15}NONa$: 272.104585).

2-(Cyclohexanecarbonyl)butanenitrile (2ac): Colourless oil. Yield: 0.645 g (90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.47 (dd, 1H, J = 7.5 and 6.0 Hz), 2.79–2.72 (m, 1H), 1.98–1.70 (m, 6H), 1.42–1.25 (m, 6H), 1.10 (t, 3H, J = 7.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 203.8, 117.5, 49.2, 43.7, 28.6, 28.3, 25.5, 25.3, 25.2, 22.5, 11.5 ppm. IR (film): ν = 2245 (C≡N), 1711 (C=O) cm^{-1}. HRMS (ESI): *m/z* 202.120632, [M + Na$^+$] (calcd for $C_{11}H_{17}NONa$: 202.120235).

4-Cyclohexyl-2-ethyl-3-oxobutanenitrile (2ad): Colourless oil. Yield: 0.727 g (94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.34 (dd, 1H, J = 7.8 and 6.0 Hz), 2.56 (d, 2H, J = 6.6 Hz), 1.94–1.89 (m, 3H), 1.72–1.69 (m, 5H), 1.32–1.17 (m, 3H), 1.11 (t, 3H, J = 7.2 Hz), 1.02–0.94 (m, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 200.5, 117.5, 48.6, 45.9, 33.4, 33.0, 32.9, 26.0, 25.9 (2C), 22.6, 11.3 ppm. IR (film): ν = 2244 (C≡N), 1725 (C=O) cm^{-1}. HRMS (ESI): *m/z* 216.136105, [M + Na$^+$] (calcd for $C_{12}H_{19}NONa$: 216.135885).

2.3. General procedure for the catalytic conversion of β-ketonitriles into β-hydroxyamides

Under argon atmosphere, the corresponding β-ketonitrile **2** (1 mmol), water (3 mL), the ruthenium(II) complex **1** (0.028 g, 0.05 mmol; 5 mol%) and NaO$_2$CH (1.360 g, 20 mmol) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 100 °C for 24–48 h. The solvent was then removed under vacuum and the resulting solid residue purified by flash column chromatography over silica gel using, unless otherwise stated, a mixture of MeOH/EtOAc (1:10) as eluent. Characterization data for the isolated β-hydroxyamides are as follows:

3-(4-Fluorophenyl)-3-hydroxypropanamide (4a) [7g]: Light brown solid. Mp 108–110 °C. Yield: 0.135 g (74%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.37$ (dd, 2H, $J = 8.7$ and 5.7 Hz), 7.30 (br, 1H), 7.14 (dd, 2H, $J = 8.7$ and 8.7 Hz), 6.84 (br, 1H), 5.43 (d, 1H, $J = 4.5$ Hz), 4.95 (m, 1H), 2.46–2.29 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): $\delta = 172.6$, 161.6 (d, $J = 241.9$ Hz), 142.0, 128.1 (d, 2C, $J = 7.9$ Hz), 115.1 (d, 2C, $J = 21.2$ Hz), 69.5, 45.8 ppm. ^{19}F{^{1}H} NMR (CD$_3$OD, 282 MHz): $\delta = -117.5$ (s) ppm.

3-Hydroxy-3-phenylpropanamide (4b) [10c,e]: Light brown solid. Mp 117–119 °C (Lit. 120 °C). Yield: 0.135 g (82%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.35$–7.20 (m, 6H), 6.83 (br, 1H), 5.37 (d, 1H, $J = 4.5$ Hz), 4.94 (m, 1H), 2.51–2.29 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.8$, 145.9, 128.4 (2C), 127.2, 126.2 (2C), 70.1, 45.9 ppm.

3-(4-Chlorophenyl)-3-hydroxypropanamide (4c) [10a]: Light brown solid. Mp 129–131 °C (Lit. 130–131.5 °C). Yield: 0.176 g (88%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.37$ (m, 4H), 7.31 (br, 1H), 6.85 (br, 1H), 5.48 (d, 1H, $J = 3.3$ Hz), 4.94 (m, 1H), 2.45–2.29 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.5$, 144.9, 131.7, 128.4 (2C), 128.1 (2C), 69.4, 45.7 ppm.

3-(3-Chlorophenyl)-3-hydroxypropanamide (4d) [10a]: Light brown solid. Mp 133–135 °C (Lit. 134–135 °C). Yield: 0.139 g (70%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.38$–7.26 (m, 5H), 6.85 (br, 1H), 5.53 (d, 1H, $J = 4.5$ Hz), 4.94 (m, 1H), 2.46–2.32 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.4$, 148.5, 133.2, 130.4, 127.2, 126.0, 124.9, 69.5, 45.6 ppm.

3-(2-Chlorophenyl)-3-hydroxypropanamide (4e) [10a]: Light brown solid. Mp 190–192 °C (Lit. 192.5–193 °C). Yield: 0.140 g (70%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.60$ (dd, 1H, $J = 7.8$ and 7.8 Hz), 7.39–7.26 (m, 4H), 6.90 (br, 1H), 5.55 (d, 1H, $J = 4.5$ Hz), 5.29 (m, 1H), 2.38–2.23 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.4$, 143.1, 130.9, 129.4, 128.9, 128.0, 127.7, 66.7, 43.8 ppm.

3-(3,4-Dichlorophenyl)-3-hydroxypropanamide (4f): Light brown solid. Mp 140–142 °C. Yield: 0.171 g (73%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.57$ (m, 2H), 7.36–7.30 (m, 2H), 6.87 (br, 1H), 5.61 (d, 1H, $J = 4.8$ Hz), 4.94 (m, 1H), 2.46–2.33 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.2$, 147.1, 131.1, 130.7, 129.6, 128.2, 126.6, 69.0, 45.5 ppm. IR (KBr): $\nu = 3399$ (O-H), 3294 (N-H), 3192 (N-H), 1655 (C=O) cm^{-1}. HRMS (ESI): m/z 255.989536, [M + Na^{+}] (calcd for C$_9$H$_9$Cl$_2$O$_2$NNa: 255.990255).

3-(4-Bromophenyl)-3-hydroxypropanamide (4g) [11b]: Light brown solid. Mp 137–139 °C. Yield: 0.207 g (85%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.50$ (d, 2H, $J = 8.1$ Hz), 7.29 (d, 2H, $J = 8.1$ Hz), 6.82 (br, 1H), 5.47 (d, 1H, $J = 4.5$ Hz), 4.92 (m, 1H), 2.50–2.29 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.5$, 145.3, 131.3 (2C), 128.5 (2C), 120.2, 69.5, 45.7 ppm.

3-Hydroxy-3-(3-trifluoromethylphenyl)propanamide (4h): Light brown solid. Mp 99–101 °C. Yield: 0.179 g (77%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.69$–7.53 (m, 4H), 7.32 (br, 1H), 6.88 (br, 1H), 5.62 (d, 1H, $J = 4.5$ Hz), 5.04 (m, 1H), 2.47–2.36 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.4$, 147.3, 130.4, 129.5, 129.2 (q, $J = 31.4$ Hz), 124.8 (q, $J = 272.4$ Hz), 124.0 (q, $J = 3.6$ Hz), 122.6 (q, $J = 3.5$ Hz), 69.5 (s), 45.6 (s) ppm. ^{19}F{^{1}H} NMR (DMSO-d_6, 282 MHz): $\delta = -61.0$ (s) ppm. IR (KBr): $\nu = 3391$ (O-H), 3310 (N-H), 3195 (N-H), 1657 (C=O) cm^{-1}. HRMS (ESI): m/z 256.055747, [M + Na^{+}] (calcd for C$_{10}$H$_{10}$F$_3$O$_2$NNa: 256.055584).

3-Hydroxy-3-(4-methylphenyl)propanamide (4i) [11b]: Light brown solid. Yield: 0.150 g (84%). Mp 136–138 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.28$ (br, 1H), 7.21 (d, 2H, $J = 8.1$ Hz), 7.11 (d, 2H, $J = 8.1$ Hz), 6.82 (br, 1H), 5.31 (d, 1H, $J = 4.5$ Hz), 4.90 (m, 1H), 2.51–2.27 (m, 2H), 2.27 (s) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.8$, 142.9, 136.2, 129.0 (2C), 126.1 (2C), 69.9, 45.8, 21.1 ppm.

3-Hydroxy-3-(3-methylphenyl)propanamide (4j): Light brown solid. Mp 125–127 °C. Yield: 0.147 g (82%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.29$ (br, 1H), 7.22–7.10 (m, 3H), 7.25 (d, 1H, $J = 7.2$ Hz), 6.83 (br, 1H), 5.33 (d, 1H, $J = 4.5$ Hz), 4.89 (m, 1H), 2.44–2.27 (m, 2H), 2.29 (s, 3H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.8$, 145.8, 137.4, 128.3, 127.8, 126.8, 123.3, 70.1, 45.8, 21.6 ppm. IR (KBr): $\nu = 3381$ (O-H), 3303 (N-H), 3189 (N-H), 1657 (C=O) cm^{-1}. HRMS (ESI): m/z 202.084358, [M + Na^{+}] (calcd for C$_{10}$H$_{13}$O$_2$NNa: 202.083849).

3-Hydroxy-3-(4-methoxyphenyl)propanamide (4k) [10b]: Light brown solid. Mp 179–181 °C (Lit. 184 °C). Yield: 0.166 g (85%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.28$ (br, 1H), 7.25 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, $J = 8.7$ Hz), 6.81 (br, 1H), 5.28 (d, 1H, $J = 4.5$ Hz), 4.88 (m, 1H), 3.73 (s, 3H), 2.45–2.27 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.9$, 158.6, 137.8, 127.3 (2C), 113.8 (2C), 69.7, 55.4, 45.8 ppm.

3-(3,5-Dimethoxyphenyl)-3-hydroxypropanamide (4l): Light brown solid. Mp 105–107 °C. Yield: 0.194 g (86%). ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 7.28$ (br, 1H), 6.82 (br, 1H), 6.50 (d, 2H, $J = 2.0$ Hz), 6.34 (s, 1H), 5.36 (d, 1H, $J = 4.4$ Hz), 4.87 (m, 1H), 3.72 (s, 6H), 2.41–2.29 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.8$, 160.6 (2C), 148.5, 104.0 (2C), 98.9, 70.1, 55.5 (2C), 45.8 ppm. IR (KBr): $\nu = 3389$ (O-H), 3370 (N-H), 3197 (N-H), 1651 (C=O) cm^{-1}. HRMS (ESI): m/z 248.089455, [M + Na^{+}] (calcd for C$_{11}$H$_{15}$O$_4$NNa: 248.089329).

3-Hydroxy-3-(5,6,7,8-tetrahydronaphthalen-2-yl)propanamide (3n): Light brown solid. Mp 150–152 °C. Yield: 0.167 g (76%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.26$ (br, 1H), 6.99 (m, 3H), 6.79 (br, 1H), 5.23 (d, 1H, $J = 4.5$ Hz), 4.84 (m, 1H), 2.68 (br, 4H), 2.38–2.27 (m, 2H), 1.71 (br, 4H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.9$, 142.8, 136.4, 135.4, 128.9, 126.7, 123.4, 70.0, 45.8, 29.4, 28.9, 23.3 (2C) ppm. IR (KBr): $\nu = 3400$ (O-H), 3362 (N-H), 3214 (N-H), 1657 (C=O) cm^{-1}. HRMS (ESI): m/z 242.114808, [M + Na^{+}] (calcd for C$_{13}$H$_{17}$O$_2$NNa: 242.115149).

4-(3-Amino-1-hydroxy-3-oxopropyl)benzamide (4n): White solid. Mp 195–197 °C. Yield: 0.181 g (87%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.94$ (br, 1H), 7.82 (d, 2H, $J = 8.3$ Hz), 7.40 (d, 2H, $J = 8.3$ Hz), 7.33 (br, 1H), 7.31 (br, 1H), 6.84 (br, 1H), 5.51 (d, 1H, $J = 4.5$ Hz), 5.02–4.96 (m, 1H), 2.50–2.32 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.7$, 168.3, 149.1, 133.2, 127.7 (2C), 125.9 (2C), 69.8, 45.6 ppm. IR (KBr): $\nu = 3383$ (O-H and N-H), 3186 (N-H), 1653 (C=O) cm^{-1}. HRMS (ESI): m/z 231.074429, [M + Na^{+}] (calcd for C$_{10}$H$_{12}$O$_3$N$_2$Na: 231.074013).

3-(2-Furyl)-3-hydroxypropanamide (4o) [13]: Light brown solid. Mp 121–123 °C. Yield: 0.124 g (80%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.56$ (d, 1H, $J = 1.8$ Hz), 7.37 (br, 1H), 6.87 (br, 1H), 6.37 (dd, 1H, $J = 3.0$ and 1.8 Hz), 6.85 (d, 1H, $J = 3.0$ Hz), 5.45 (d, 1H, $J = 5.4$ Hz), 4.91 (m, 1H), 2.50 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 172.2, 157.8, 142.2, 110.6, 105.7, 63.7, 42.2 ppm.

3-Hydroxy-3-(2-thienyl)propanamide (4p): Light brown solid. Mp 94–96 °C. Yield: 0.120 g (70%). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.37$ (m, 2H), 6.94 (m, 2H), 6.87 (br, 1H), 5.74 (d, 1H, $J = 4.8$ Hz), 5.18 (m, 1H), 2.56–2.41 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): $\delta = 172.3$, 150.4, 127.0, 124.6, 123.1, 66.3, 45.9 ppm. IR (KBr): $\nu = 3390$ (O-H), 3303 (N-H), 3188 (N-H), 1658 (C=O) cm^{-1}. HRMS (ESI): m/z 194.024385, [M + Na^{+}] (calcd for C$_7$H$_9$O$_2$NSNa:

194.024620).

4,4-Dimethyl-3-hydroxypentanamide (4q) [13]: Light brown solid. Mp 96–98 °C. Yield: 0.118 g (81%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.31 (br, 1H), 6.84 (br, 1H), 4.69 (d, 1H, J = 4.8 Hz), 3.50 (m, 1H), 2.18 (dd, 1H, J = 14.4 and 2.7 Hz), 2.18 (dd, 1H, J = 14.4 and 10.2 Hz), 0.82 (s, 9H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 174.8, 75.2, 38.1, 34.9, 26.2 ppm.

3-Hydroxy-4-methylpentanamide (4r) [19]: Light brown oil. Yield: 0.073 g (56%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.27 (br, 1H), 6.80 (br, 1H), 4.57 (d, 1H, J = 4.8 Hz), 3.63–3.56 (m, 1H), 2.14–2.01 (m, 2H), 1.59–1.48 (m, 1H), 0.82 (d, 3H, J = 6.6 Hz), 0.80 (d, 3H, J = 6.6 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 174.2, 72.3, 33.5, 19.2, 17.7 ppm.

3-Cyclohexyl-3-hydroxypropanamide (4s) [13]: Light brown solid. Mp 92–94 °C. Yield: 0.121 g (71%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.26 (br, 1H), 6.80 (br, 1H), 4.55 (d, 1H, J = 5.1 Hz), 3.62–3.55 (m, 1H), 2.19–2.02 (m, 2H), 1.70–1.59 (m, 5H), 1.21–0.92 (m, 6H) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz): δ = 175.7, 72.7, 43.4, 39.5, 28.8, 28.3, 26.4, 26.1, 26.0 ppm.

3-Cyclopropyl-3-hydroxypropanamide (4t) [11c]: Light brown oil. Yield: 0.067 g (52%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.27 (br, 1H), 6.79 (br, 1H), 4.67 (d, 1H, J = 4.5 Hz), 3.36–3.23 (m, 1H), 2.22 (d, 2H, J = 6.3 Hz), 0.82–0.75 (m, 1H), 0.35–0.16 (m, 4H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 174.5, 71.1, 43.9, 17.8, 2.7, 2.3 ppm.

3-(Adamantan-1-yl)-3-hydroxypropanamide (4u): Light brown solid. Mp 169–171 °C. Yield: 0.172 g (77%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.28 (br, 1H), 6.81 (br, 1H), 4.55 (d, 1H, J = 4.8 Hz), 3.34–3.28 (m, 1H), 2.21–1.99 (m, 5H), 1.69–1.42 (m, 12H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 175.0, 75.5, 38.1 (3C), 37.3 (3C), 36.7, 36.5, 28.2 (3C) ppm. IR (KBr): ν = 3380 (O-H), 3304 (N-H), 3177 (N-H), 1674 (C=O) cm^{-1}. HRMS (ESI): m/z 246.145915, [M + Na^{+}] (calcd for $C_{13}H_{21}O_2NNa$: 246.146450).

4-Cyclohexyl-3-hydroxybutanamide (4v): White solid. Mp 93–95 °C. Yield: 0.154 g (83%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.25 (br, 1H), 6.77 (br, 1H), 4.55 (d, 1H, J = 5.4 Hz), 3.94–3.84 (m, 1H), 2.12–2.09 (m, 2H), 1.77–1.63 (m, 5H), 1.42 (m, 1H), 1.24–1.16 (m, 5H), 0.91–0.78 (m, 2H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 173.7, 65.3, 45.2, 44.4, 34.2, 33.8, 32.7, 26.7, 26.4, 26.2 ppm. IR (KBr): ν = 3318 (O-H and N-H), 3158 (N-H), 1673 (C=O) cm^{-1}. HRMS (ESI): m/z 208.130494, [M + Na^{+}] (calcd for $C_{10}H_{19}O_2NNa$: 208.130800).

3-Hydroxy-2-methyl-3-phenylpropanamide (4w) [20]: This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.53):* White solid. Mp 132–135 °C (Lit. 134–136 °C). Yield: 0.070 g (39%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.36–7.22 (m, 6H), 6.78 (br, 1H), 5.34 (d, 1H, J = 4.5 Hz), 4.52 (dd, 1H, J = 8.7 and 4.5 Hz), 2.48–2.43 (m, 1H), 0.70 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 177.2, 144.5, 128.4 (2C), 127.5, 127.2 (2C), 75.5, 47.6, 15.3 ppm. *Anti diastereoisomer (Rf = 0.35):* White solid. Mp 87–90 °C (Lit. 84–85 °C). Yield: 0.088 g (49%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.32–7.18 (m, 6H), 6.64 (br, 1H), 5.29 (d, 1H, J = 4.8 Hz), 4.64 (dd, 1H, J = 7.2 and 4.8 Hz), 2.48–2.44 (m, 1H), 1.04 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 176.8, 144.7, 128.1 (2C), 127.1, 126.9 (2C), 74.2, 47.7, 13.9 ppm.

2-(Hydroxy(phenyl)methyl)butanamide (4x) [21]: This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.30):* White solid. Mp 130–133 °C. Yield: 0.081 g (42%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.35–7.21 (m, 6H), 6.85 (br, 1H), 5.33 (d, 1H, J = 4.8 Hz), 4.51 (dd, 1H, J = 8.7 and 4.8 Hz), 2.29 (m, 1H), 1.32 (m, 1H), 0.90 (m, 1H), 0.71 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 176.2, 144.9, 128.4 (2C), 127.5, 127.2 (2C), 74.9, 55.3, 22.7, 12.1 ppm. *Anti diastereoisomer (Rf = 0.59):* White solid. Mp 119–122 °C. Yield: 0.064 g (33%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.31–7.15 (m, 6H), 6.63 (br, 1H), 5.27 (br, 1H), 4.55 (d, 1H, J = 8.1 Hz), 2.34 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 0.83 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 175.6, 144.9, 128.1 (2C), 127.2 (3C), 74.2, 55.7, 21.9, 12.3 ppm. A Mp range of 117–118 °C was given in the literature for the mixture of diastereoisomers.

2-(Hydroxy(phenyl)methyl)hexanamide (4y): This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.37):* White solid. Mp 104–106 °C. Yield: 0.095 g (43%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.34–7.22 (m, 6H), 6.81 (br, 1H), 5.31 (d, 1H, J = 4.8 Hz), 4.49 (dd, 1H, J = 8.4 and 4.8 Hz), 2.39–2.33 (m, 1H), 1.38–1.30 (m, 1H), 1.14–1.07 (m, 4H), 0.85 (m, 1H), 0.72 (t, 3H, J = 6.0 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ = 176.4, 145.0, 128.4 (2C), 127.5, 127.2 (2C), 75.1, 53.6, 29.5, 29.2, 22.5, 14.2 ppm. IR (KBr): ν = 3331 (O-H), 3283 (N-H), 3166 (N-H), 1685 (C=O) cm^{-1}. HRMS (ESI): m/z 244.130570, [M + Na^{+}] (calcd for $C_{13}H_{19}O_2NNa$: 244.130800). *Anti diastereoisomer (Rf = 0.67):* White solid. Mp 103–105 °C. Yield: 0.119 g (54%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.31–7.20 (m, 5H), 7.12 (br, 1H), 6.59 (br, 1H), 5.24 (d, 1H, J = 4.4 Hz), 4.53 (dd, 1H, J = 7.6 and 4.4 Hz), 2.38 (m, 1H), 1.67 (m, 1H), 1.58–1.50 (m, 1H), 1.29–1.15 (m, 4H), 0.84 (t, 3H, J = 6.8 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 175.7, 144.8, 128.0 (2C), 127.1 (3C), 74.4, 54.1, 29.8, 28.5, 22.7, 14.4 ppm. IR (KBr): ν = 3359 (O-H), 3303 (N-H), 3178 (N-H), 1683 (C=O) cm^{-1}. HRMS (ESI): m/z 244.130933, [M + Na^{+}] (calcd for $C_{13}H_{19}O_2NNa$: 244.130800).

2-(Hydroxy(phenyl)methyl)heptanamide (4z): This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.33):* Light brown solid. Mp 127–129 °C. Yield: 0.066 g (28%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.31–7.21 (m, 6H), 6.79 (br, 1H), 5.29 (d, 1H, J = 4.8 Hz), 4.48 (dd, 1H, J = 9.3 and 4.8 Hz), 2.39–2.30 (m, 1H), 1.31–1.22 (m, 2H), 1.16–1.04 (m, 6H), 0.76 (t, 3H, J = 5.7 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 176.8, 145.4, 128.8 (2C), 127.9, 127.6 (2C), 75.5, 54.1, 32.0, 29.9, 27.3, 22.8, 14.7 ppm. IR (KBr): ν = 3376 (O-H), 3305 (N-H), 3164 (N-H), 1684 (C=O) cm^{-1}. HRMS (ESI): m/z 258.146230, [M + Na^{+}] (calcd for $C_{14}H_{21}O_2NNa$: 258.146450). *Anti diastereoisomer (Rf = 0.74):* Light brown solid. Mp 102–104 °C. Yield: 0.094 g (40%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.28–7.21 (m, 5H), 7.12 (br, 1H), 6.59 (br, 1H), 5.24 (d, 1H, J = 4.5 Hz), 4.51 (dd, 1H, J = 8.1 and 4.5 Hz), 2.41–2.34 (m, 1H), 1.68–1.47 (m, 2H), 1.23 (br, 6H), 0.83 (t, 3H, J = 5.9 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 175.7, 144.8, 128.0 (2C), 127.1 (3C), 74.4, 54.1, 31.9, 28.8, 27.1, 22.5, 14.4 ppm. IR (KBr): ν = 3359 (O-H), 3313 (N-H), 3172 (N-H), 1682 (C=O) cm^{-1}. HRMS (ESI): m/z 258.146986, [M + Na^{+}] (calcd for $C_{14}H_{21}O_2NNa$: 258.146450).

2-Benzyl-3-hydroxy-3-phenylpropanamide (4aa): This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.77):* Light brown solid. Mp 116–118 °C. Yield: 0.145 g (57%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.37–7.12 (m, 10H), 6.93 (br, 1H), 6.46 (br, 1H), 5.47 (d, 1H, J = 4.8 Hz), 4.62 (dd, 1H, J = 7.5 and 4.8 Hz), 3.03–2.71 (m, 3H) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 174.4, 144.4, 140.9, 129.2 (2C), 128.4 (2C), 128.1 (2C), 127.3, 127.2 (2C), 126.1, 74.6, 56.1, 34.8 ppm. IR (KBr): ν = 3399 (O-H and N-H), 3186 (N-H), 1653 (C=O) cm^{-1}. HRMS (ESI): m/z 278.115523, [M + Na^{+}] (calcd for $C_{16}H_{17}O_2NNa$: 278.115149). *Anti diastereoisomer (Rf = 0.46):* Light brown solid. Mp 60–63 °C. Yield: 0.038 g (15%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.37–7.03 (m, 11H), 6.75 (br, 1H), 5.51 (d, 1H, J = 5.1 Hz), 4.58 (dd, 1H, J = 7.2 and 5.1 Hz), 2.82–2.67 (m, 2H), 2.29 (dd, 1H, J = 12.0 and 2.7 Hz) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 75 MHz): δ = 175.3, 144.6, 140.1, 129.1 (2C), 128.5 (4C), 127.6, 127.2 (2C), 126.2, 74.7, 55.1, 35.5 ppm. IR

(KBr): $\nu = 3362$ (O-H and N-H), 3156 (N-H), 1685 (C=O) cm^{-1}. HRMS (ESI): *m/z* 278.115557, [M + Na^+] (calcd for $C_{16}H_{17}O_2NNa$: 278.115149).

2-(Hydroxy(phenyl)methyl)-4-phenylbutanamide (4ab): This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.41):* Light brown solid. Mp 128–130 °C. Yield: 0.097 g (36%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.41$ (br, 1H), 7.28–7.11 (m, 8H), 7.00–6.95 (m, 3H), 5.39 (d, 1H, $J = 4.8$ Hz), 4.58 (dd, 1H, $J = 8.1$ and 4.8 Hz), 2.49–2.43 (m, 2H), 2.34–2.28 (m, 1H), 1.67–1.61 (m, 1H), 1.19–1.11 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 176.1$, 144.7, 142.3, 128.7 (2C), 128.4 (4C), 127.5, 127.2 (2C), 126.1, 74.8, 53.7, 33.5, 31.7 ppm. IR (KBr): $\nu = 3318$ (O-H and N-H), 3195 (N-H), 1684 (C=O) cm^{-1}. HRMS (ESI): *m/z* 292.130825, [M + Na^+] (calcd for $C_{17}H_{19}O_2NNa$: 292.130800). *Anti diastereoisomer (Rf = 0.74):* Light brown solid. Mp 139–142 °C. Yield: 0.124 g (46%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.29$–7.12 (m, 11H), 6.71 (br, 1H), 5.32 (d, 1H, $J = 4.5$ Hz), 4.59 (dd, 1H, $J = 7.8$ and 4.5 Hz), 2.58–2.37 (m, 3H), 1.98–1.85 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 175.3$, 144.7, 142.7, 128.7 (2C), 128.5 (2C), 128.1 (2C), 127.2, 127.1 (2C), 126.1, 74.3, 54.1, 33.7, 31.0 ppm. IR (KBr): $\nu = 3384$ (O-H and N-H), 3196 (N-H), 1653 (C=O) cm^{-1}. HRMS (ESI): *m/z* 292.130540, [M + Na^+] (calcd for $C_{17}H_{19}O_2NNa$: 292.130800).

2-(Cyclohexyl(hydroxyl)methyl)butanamide (4ac) [22]: This compound was obtained as an inseparable mixture of the *syn* and *anti* diastereoisomers in 1.4:1 ratio. Light brown solid. Mp 160–163 °C (Lit. 164–165 °C). Yield: 0.121 g (61%). *Syn diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.35$ (br, 1H), 6.79 (br, 1H), 4.38 (d, 1H, $J = 5.7$ Hz), 3.26–3.16 (m, 1H), 2.24–2.12 (m, 1H), 1.67–1.09 (m, 13H), 0.81 (t, 3H, $J = 7.2$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 176.7$, 75.5, 51.2, 41.1, 30.7, 26.7, 26.6, 26.4, 25.8, 22.2, 12.4 ppm. *Anti diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.32$ (br, 1H), 6.92 (br, 1H), 4.56 (d, 1H, $J = 7.5$ Hz), 3.26–3.16 (m, 1H), 2.24–2.12 (m, 1H), 1.67–1.09 (m, 13H), 0.85 (t, 3H, $J = 7.5$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 177.7$, 75.7, 49.3, 41.7, 29.9, 27.9, 26.6, 26.4, 26.2, 23.4, 12.4 ppm.

4-Cyclohexyl-2-ethyl-3-hydroxybutanamide (4ad): This compound was obtained as an inseparable mixture of the *syn* and *anti* diastereoisomers in 1.2:1 ratio. Light brown solid. Mp 135–137 °C. Yield: 0.117 g (55%). IR (KBr): $\nu = 3350$ (O-H), 3294 (N-H), 3174 (N-H), 1681 (C=O) cm^{-1}. HRMS (ESI): *m/z* 236.161645, [M + Na^+] (calcd for $C_{12}H_{23}O_2NNa$: 236.162100). *Syn diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.24$ (br, 1H), 6.75 (br, 1H), 4.42 (d, 1H, $J = 6.3$ Hz), 3.51–3.43 (m, 1H), 1.83–1.73 (m, 1H), 1.62–1.13 (m, 15H), 0.83 (t, 3H, $J = 7.2$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 176.4$, 68.9, 55.5, 43.3, 34.7, 33.7, 32.2, 26.7, 26.5, 26.1, 22.1, 12.4 ppm. *Anti diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.24$ (br, 1H), 6.85 (br, 1H), 4.48 (d, 1H, $J = 6.9$ Hz), 3.64–3.56 (m, 1H), 2.15–2.01 (m, 1H), 1.62–1.13 (m, 15H), 0.80 (t, 3H, $J = 7.5$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 176.9$, 68.7, 53.7, 43.0, 34.5, 33.8, 32.5, 26.7, 26.5, 26.1, 22.2, 12.5 ppm.

2-Benzyl-3-hydroxypropanamide (4ae) [11d]: Light brown solid. Mp 122–125 °C (Lit. 127–130 °C). Yield: 0.090 g (50%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.28$–7.14 (m, 6H), 6.74 (br, 1H), 4.70 (t, 1H, $J = 5.1$ Hz), 3.57–3.50 (m, 1H), 3.40–3.33 (m, 1H), 2.54–2.78 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 175.5$, 140.6, 129.2 (2C), 128.5 (2C), 126.2, 62.8, 50.7, 34.9 ppm.

3-Hydroxy-2-(4-methoxyphenyl)-3-phenylpropanamide (4ai): This compound was obtained as an inseparable mixture of the *syn* and *anti* diastereoisomers in 1.4:1 ratio *(Rf = 0.49)*. Light brown solid. Mp 107–109 °C. Yield: 0.089 g (33%). IR (KBr): $\nu = 3520$ (O-H), 3415 (O-H), 3305 (N-H), 3169 (N-H), 1653 (C=O) cm^{-1}. HRMS (ESI): *m/z* 294.109547, [M + Na^+] (calcd for $C_{16}H_{17}O_3NNa$: 294.110064). *Syn diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.39$–7.22 (m, 8H), 6.86 (d, 2H, $J = 8.7$ Hz), 6.54 (br, 1H), 5.11 (d, 1H, $J = 5.1$ Hz), 5.04–4.97 (m, 1H), 3.74 (s, 3H), 3.62 (d, 1H, $J = 10.0$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 174.0$, 158.4, 144.8, 130.2, 128.1 (2C), 127.5 (2C), 127.4 (2C), 127.4, 113.6 (2C), 74.3, 58.9, 55.5 ppm. *Anti diastereoisomer:* ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.45$ (br, 1H), 7.39–7.22 (m, 7H), 6.80 (br, 1H), 6.68 (d, 2H, $J = 8.7$ Hz), 5.47 (d, 1H, $J = 4.8$ Hz), 5.04–4.97 (m, 1H), 3.69 (d, 1H, $J = 8.4$ Hz), 3.64 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 174.7$, 158.2, 144.2, 130.0, 128.0 (2C), 127.5 (2C), 127.3 (2C), 127.1, 113.6 (2C), 75.3, 59.0, 55.3 ppm. The amide **8** *(Rf = 0.69)* was also isolated in 10% yield (0.016 g).

2-(3,4-Dimethoxyphenyl)-3-hydroxy-3-phenylpropanamide (4aj): This compound was obtained as a mixture of diastereoisomers which could be separated by column chromatography using EtOAc as eluent. *Syn diastereoisomer (Rf = 0.32):* White solid. Mp 141–143 °C. Yield: 0.084 g (28%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.40$–7.20 (m, 6H), 7.04–6.86 (m, 3H), 6.57 (br, 1H), 5.11 (d, 1H, $J = 5.1$ Hz), 5.01 (dd, 1H, $J = 9.3$ and 5.1 Hz), 3.74 (s, 6H), 3.66 (d, 1H, $J = 9.3$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 173.9$, 148.5, 148.1, 144.7, 131.8, 128.1 (2C), 127.5 (2C), 127.3, 121.6, 113.1, 111.8, 74.3, 59.3, 56.0, 55.9 ppm. IR (KBr): $\nu = 3371$ (O-H and N-H), 3191 (N-H), 1666 (C=O) cm^{-1}. HRMS (ESI): *m/z* 324.120168, [M + Na^+] (calcd for $C_{17}H_{19}O_4NNa$: 324.120629). *Anti diastereoisomer (Rf = 0.64):* White solid. Mp 150–152 °C. Yield: 0.042 g (14%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.45$ (br, 1H), 7.15–7.11 (m, 5H), 6.81 (br, 1H), 6.75–6.66 (m, 3H), 5.47 (d, 1H, $J = 4.5$ Hz), 5.02 (dd, 1H, $J = 8.4$ and 4.5 Hz), 3.63 (s, 3H), 3.61 (s, 3H), 3.59 (d, 1H, $J = 8.4$ Hz) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 174.6$, 148.3, 147.8, 144.3, 130.7, 128.0 (2C), 127.4 (2C), 127.1, 121.2, 112.9, 111.5, 75.3, 59.4, 55.8, 55.7 ppm. IR (KBr): $\nu = 3398$ (O-H and N-H), 3195 (N-H), 1654 (C=O) cm^{-1}. HRMS (ESI): *m/z* 324.121060, [M + Na^+] (calcd for $C_{17}H_{19}O_4NNa$: 324.120629). The amide **9** *(Rf = 0.77)* was also obtained in 16% yield (0.031 g).

3-Hydroxy-2,2-dimethyl-3-phenylpropanamide (4ak) [10c]: Light brown solid. Mp 132–134 °C (Lit. 134–136 °C). Yield: 0.116 g (60%). ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.31$–7.21 (m, 5H), 7.08 (br, 1H), 6.87 (br, 1H), 5.53 (d, 1H, $J = 4.5$ Hz), 4.77 (d, 1H, $J = 4.5$ Hz), 1.00 (s, 3H), 0.92 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 179.1$, 143.0, 128.1 (2C), 127.7 (2C), 127.2, 77.4, 47.0, 22.9, 21.1 ppm.

3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethylpropanamide (4 al): Light brown solid. Mp 127–129 °C. Yield: 0.168 g (74%). IR (KBr): $\nu = 3345$ (O-H), 3284 (N-H), 3230 (N-H), 1663 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 7.35$–7.29 (m, 4H), 7.06 (br, 1H), 6.88 (br, 1H), 5.60 (d, 1H, $J = 4.4$ Hz), 4.78 (d, 1H, $J = 4.4$ Hz), 1.00 (s, 3H), 0.90 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 178.7$, 142.0, 131.8, 129.8 (2C), 127.6 (2C), 76.5, 47.1, 22.3, 21.4 ppm. HRMS (ESI): *m/z* 250.060362, [M + Na^+] (calcd for $C_{11}H_{14}O_2ClNNa$: 250.060527).

3-(3-Chlorophenyl)-3-hydroxy-2,2-dimethylpropanamide (4am): Light brown solid. Mp 133–135 °C. Yield: 0.171 g (75%). IR (KBr): $\nu = 3344$ (O-H), 3283 (N-H), 3243 (N-H), 1665 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.32$–7.24 (m, 4H), 7.07 (br, 1H), 6.93 (br, 1H), 5.67 (br, 1H), 4.78 (br, 1H), 1.01 (s, 3H), 0.91 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): $\delta = 178.6$, 145.8, 132.6, 129.6, 127.7, 127.2, 126.7, 76.5, 47.1, 22.1, 21.6 ppm. HRMS (ESI): *m/z* 250.060264, [M + Na^+] (calcd for $C_{11}H_{14}O_2ClNNa$: 250.060527).

3. Results and discussion

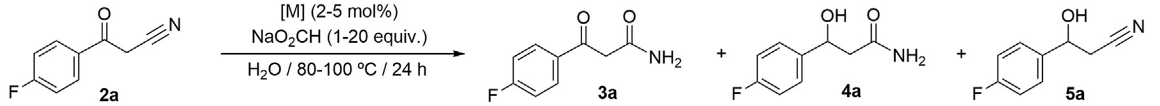
In a previous study we demonstrated the utility of the arene-ruthenium(II) complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**) as catalyst for the hydration of β-ketonitriles **A** into β-ketoamides **B** in pure water [3e]. This fact along with known ability of Ru(II) complexes to promote the TH of carbonyl compounds in aqueous media, employing NaO_2CH as the hydrogen source [6], led us to screening the potential of the **1**/NaO_2CH combination for the *one-pot* conversion of β-ketonitriles into β-hydroxyamides. Commercially available 3-(4-fluorophenyl)-3-oxopropanenitrile (**2a**) was chosen as model substrate to monitor conveniently the course of the reactions by $^{19}F\{^1H\}$ NMR spectroscopy (see Table 1).

Thus, in a first series of experiments solutions of **2a** in water were treated with complex **1** (2 mol%) at 80 °C for 24 h in the presence of variable amounts of sodium formate (from 1 to 20 equivalents; entries 1–4). In all the cases, complete consumption of the starting β-ketonitrile took place as assessed by $^{19}F\{^1H\}$ NMR spectroscopy [23]. The major reaction products in the crude reaction mixtures were the β-ketoamide **3a** and the desired β-hydroxyamide **4a**, increasing the amount of the latter with the quantity of NaO_2CH added (up to 71% yield with 20 equiv. of sodium formate; see entry 4). Minor amounts of some unidentified products were also observed in the crudes, but in no case the β-hydroxynitrile **5a** resulting from the TH of **2a** was present. These results clearly indicate that the transfer hydrogenation step is the rate limiting one of the hydration/TH cascade process, with the β-ketoamide intermediate **3a** forming rapidly in the reaction medium prior to the reduction of the carbonyl functionality [24]. Further experiments at a higher temperature (100 °C) and with a higher ruthenium loading (5 mol%) allowed to increase the yield of **4a** from 71 to a maximum of 92% (entries 5–6). As shown in entry 6, employing 5 mol% of complex **1**, 20 equivalents of sodium formate and a working temperature of 100 °C, the intermediate β-ketoamide **3a** was not longer present in the crude. From this experiment, the β-hydroxyamide **4a** could be isolated in 74% yield after solvent removal and subsequent chromatographic purification.

On the other hand, in complete accord with our previous findings indicating that, when dissolved in water, hydrolysis of the chlorophosphine ligand in complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**) readily takes place leading to the phosphinous acid derivative $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2OH\}]$ [3e], the direct use of this latter compound as catalyst in the cascade process led to almost identical results (entry 7). The key role played by the *in situ* formed phosphinous acid ligand in the reaction was fully confirmed with the experiments collected in entries 8–15, where different commercially available or easily accessible ruthenium compounds lacking of P-OH or hydrolizable P-Cl ligands where employed as potential catalysts [25]. Only trace amounts of the desired β-hydroxyamide **4a** were generated, and in most cases the β-hydroxynitrile **5a** resulting from the exclusive TH of **2a** was the major product present in the reaction crudes. Additional experiments were also performed employing other transition-metal complexes bearing the phosphinous acid ligand PMe_2OH (entries 16–19). All these compounds, that were successfully employed in previous reports as nitrile hydration catalysts [3b,d,g,26], were able to generate **4a** as the major reaction product. Among them, the osmium(II) derivative $[OsCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$ (entry 18) and the Parkins-Ghaffar catalyst $[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$ (entry 19) showed an effectiveness and selectivity comparable to that of $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**). However, from a practical point of view, the use of these compounds instead of **1** is less convenient given the higher price of Os and Pt in comparison to Ru.

Having established the optimal reaction conditions, we next focused on the scope of the process. To this end, the behavior of a broad family of α-unsubstituted β-ketonitriles was firstly investigated (see Table 2). Thus, as observed for **2a** (entry 1), other aromatic systems **2b-m** could be cleanly converted into the corresponding β-hydroxyamides **4b-m**, regardless of the substitution pattern and electronic properties of the aromatic ring (entries 2–13). After appropriate chromatographic work-up, amides **4b-m** were isolated in 70–88% yield and their identity confirmed by multinuclear NMR spectroscopy, as well as IR and high resolution mass spectrometry (HRMS) in the case of previously unreported examples (details are given in the Experimental section). Interestingly, when 4-(2-cyanoacetyl)benzonitrile **2n** was employed as substrate, the corresponding diamide **4n** was exclusively formed as the result of the hydration of the two nitrile functionalities plus the TH of the carbonyl group (87% isolated yield; entry 14). On the other hand, as exemplified with **2o** and **2p**, the present hydration/TH process tolerates the use of heteroaromatic β-ketonitriles (entries

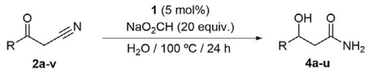
Table 1
Metal-catalyzed hydration/transfer hydrogenation of the β-ketonitrile **2a**: Optimization of the reaction conditions.[a]



Entry	Catalyst	Loading	NaO_2CH	Temp.	Conv.[b]	Yield **3a**[b]	Yield **4a**[b]	Yield **5a**[b]
1	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	2 mol%	1 equiv.	80 °C	>99%	91%	5%	0%
2	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	2 mol%	5 equiv.	80 °C	>99%	67%	27%	0%
3	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	2 mol%	10 equiv.	80 °C	>99%	44%	52%	0%
4	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	2 mol%	20 equiv.	80 °C	>99%	24%	71%	0%
5	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	2 mol%	20 equiv.	100 °C	>99%	15%	76%	0%
6	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2Cl\}]$ (**1**)	5 mol%	20 equiv.	100 °C	>99%	0%	92%	0%
7	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_2OH\}]$	5 mol%	20 equiv.	100 °C	>99%	0%	91%	0%
8	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$	5 mol%	20 equiv.	100 °C	>99%	0%	0%	62%
9	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$	5 mol%	20 equiv.	100 °C	>99%	4%	0%	22%
10	$[RuCl_2(\eta^6\text{-}p\text{-cymene})\{P(4\text{-}C_6H_4F)_3\}]$	5 mol%	20 equiv.	100 °C	98%	18%	1%	18%
11	$[RuCl_2(PPh_3)_3]$	5 mol%	20 equiv.	100 °C	>99%	3%	0%	24%
12	$[RuCl_2(DMSO)_4]$	5 mol%	20 equiv.	100 °C	>99%	2%	1%	34%
13	$[RuCl(\eta^5\text{-}C_5Me_5)(PPh_3)_2]$	5 mol%	20 equiv.	100 °C	>99%	1%	0%	24%
14	$[RuCl(\eta^5\text{-Indenyl})(PPh_3)_2]$	5 mol%	20 equiv.	100 °C	95%	1%	0%	75%
15	$RuCl_3 \cdot nH_2O$	5 mol%	20 equiv.	100 °C	>99%	7%	5%	44%
16	$[RuCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$	5 mol%	20 equiv.	100 °C	>99%	0%	86%	0%
17	$[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PMe_2OH)]$	5 mol%	20 equiv.	100 °C	>99%	30%	34%	8%
18	$[OsCl_2(\eta^6\text{-}p\text{-cymene})(PMe_2OH)]$	5 mol%	20 equiv.	100 °C	>99%	0%	92%	0%
19	$[PtH\{(PMe_2O)_2H\}(PMe_2OH)]$	5 mol%	20 equiv.	100 °C	>99%	0%	91%	0%

[a] Reactions performed under Ar atmosphere with 1 mmol of the β-ketonitrile **2a** (0.33 M in water).
[b] Determined by $^{19}F\{^1H\}$ NMR spectroscopy.

Table 2
Ru-catalyzed synthesis of β-hydroxyamides **4a-v** from β-ketonitriles **2a-v**.[a]



2a-v **4a-u**

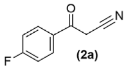
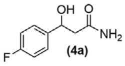
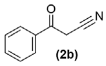
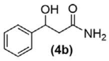
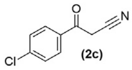
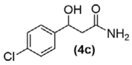
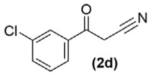
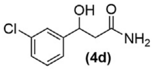
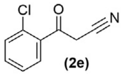
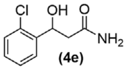
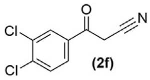
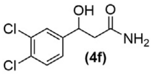
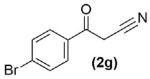
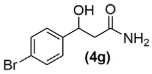
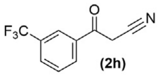
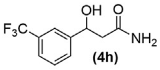
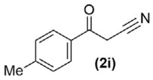
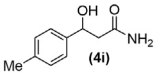
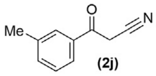
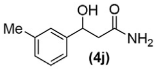
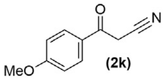
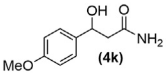
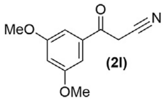
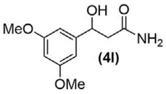
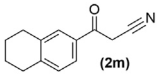
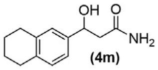
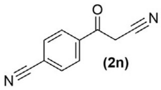
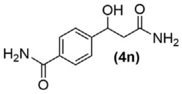
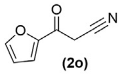
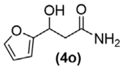
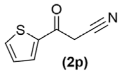
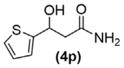
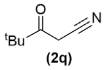
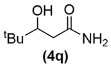
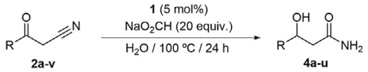
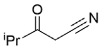
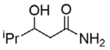
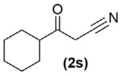
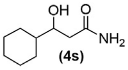
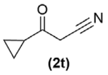
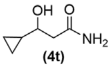
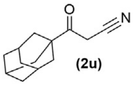
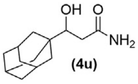
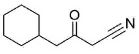
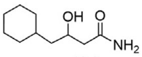
Entry	β-Ketonitrile **2**	β-Hydroxyamide **4**	Yield (%)[b]
1	 **(2a)**	 **(4a)**	74
2	 **(2b)**	 **(4b)**	82
3	 **(2c)**	 **(4c)**	88
4	 **(2d)**	 **(4d)**	70
5	 **(2e)**	 **(4e)**	70
6	 **(2f)**	 **(4f)**	73
7	 **(2g)**	 **(4g)**	85
8	 **(2h)**	 **(4h)**	77
9	 **(2i)**	 **(4i)**	84
10	 **(2j)**	 **(4j)**	82
11	 **(2k)**	 **(4k)**	85
12	 **(2l)**	 **(4l)**	86
13	 **(2m)**	 **(4m)**	76
14	 **(2n)**	 **(4n)**	87
15	 **(2o)**	 **(4o)**	80
16[c]	 **(2p)**	 **(4p)**	70
17	 **(2q)**	 **(4q)**	81

Table 2 (*continued*)



Entry	β-Ketonitrile **2**	β-Hydroxyamide **4**	Yield (%)[b]
18	 **(2r)**	 **(4r)**	56
19	 **(2s)**	 **(4s)**	71
20	 **(2t)**	 **(4t)**	52
21	 **(2u)**	 **(4u)**	77
22	 **(2v)**	 **(4v)**	82

[a] Reactions performed in a Teflon-capped sealed tube under Ar atmosphere with 1 mmol of the corresponding β-ketonitrile (0.33 M in H_2O).
[b] Isolated yields after chromatographic work-up.
[c] Reaction time 48 h.

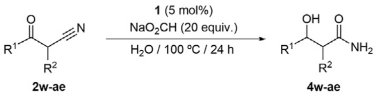
15 and 16). However, we should note that a longer reaction time (48 *vs* 24 h) was needed to convert 3-oxo-(2-thienyl)propanenitrile (**2p**) into 3-hydroxy-3-(2-thienyl)propanamide (**4p**) in high yield (70%), due probably to the competing coordination of sulfur atom to the metal [27]. As shown in entries 17–22, different β-ketonitriles containing aliphatic substituents **2q-v** could also be transformed into the corresponding β-hydroxyamides **4q-v** in moderate to good yields (52–82%) applying the standard reaction conditions, thus confirming the wide scope of the process concerning the nature of the substituent of the carbonylic unit. In all the reactions collected in Table 2 the only by-products detected by ^{1}H NMR spectroscopy in the crudes were the corresponding β-ketoamide intermediates (present in *ca.* 3–10%).

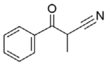
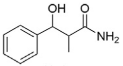
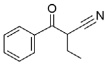
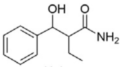
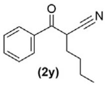
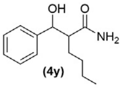
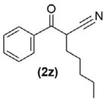
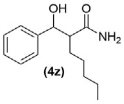
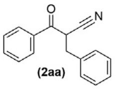
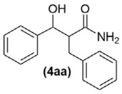
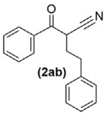
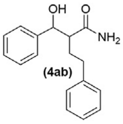
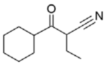
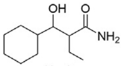
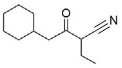
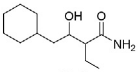
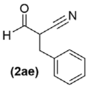
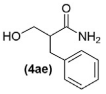
To delineate more precisely the scope of the process, we next explored the reactivity of a series of α-monosubstituted β-ketonitriles. In this regard, we were glad to find that, under identical reaction conditions, the alkyl-, benzyl- and homobenzyl-substituted substrates **2w-ae** also participate in the hydration/TH cascade reaction delivering the respective β-hydroxyamides **4w-ae** in moderate to excellent yields (50–97%; see Table 3). Only in the case of the sterically hindered ketonitrile **2ac** the reaction time had to be extended from 24 to 48 h to generate the amide product **4ac** with a satisfactory yield (entry 7). The result obtained with the β-formylnitrile **2ae** merits to be highlighted since it demonstrates that the process is not restricted to ketone substrates (entry 9). On the other hand, during the hydration/TH reaction of compounds **2w-ad** two stereogenic carbons are generated, and consequently the final β-hydroxyamide products **4w-ad** were isolated as mixtures of the corresponding *syn* and *anti* diastereoisomers in ratios ranging from 3.8:1 to 1:1.4 (entries 1–8). In the case of compounds **4w-ab**, the two diastereoisomers could be separated by column chromatography and their *syn* or *anti* nature determined by comparison of the $^3J_{HH}$ coupling constants between the C*H*OH and C*H*R(=O)NH$_2$ protons of both isomers, assuming that, accordingly to previous studies on related systems [28], the *syn* configuration gives rise to a larger coupling constant in comparison with the *anti* one (the measured $^3J_{HH}$ values are given in Table 4).

In contrast to **4w-ab**, all attempts to separate the *syn* and *anti* diastereoisomers of the aliphatic β-hydroxyamides **4ac-ad** by column chromatography were unsuccessful, and the overlapping of the C*H*OH and C*H*R(=O)NH$_2$ signals of both isomers in the ^{1}H NMR spectra of the mixtures prevented to determine in a straightforward manner the configuration of the major and minor isomers. In these cases, the assignments were made indirectly by reducing first the β-ketonitriles **2ac-ad** to the β-hydroxynitriles **5ac-ad** with NaBH$_4$ in MeOH (Scheme 3). The *syn* and *anti* isomers of **5ac-ad** could neither be separated by column chromatography but, fortunately, no overlapping of the respective C*H*OH and C*H*RC≡N signals was observed in the ^{1}H NMR spectra, thus allowing to assign a *syn* configuration to the major stereoisomer formed in both reactions (as in the case of **4w-4 ab**, a $J_{syn} > J_{anti}$ was assumed) [29,30]. Subsequent hydration of **5ac-ad** by means of complex [RuCl$_2$(η^6-*p*-cymene){P(4-C$_6$H$_4$F)$_2$Cl}] (**1**) generated the β-hydroxyamides **4ac-ad**. As shown in Scheme 3, the hydration reactions were performed under neutral and mild temperature conditions to avoid racemization processes. To our delight, the isomeric ratios found for **4ac-ad** were identical to those of the starting nitriles **5ac-ad**. In this way, comparison of the ^{1}H NMR spectra recorded for these experiments with those obtained in the hydration/TH reactions collected in Table 3 (entries 7 and 8) allowed to determine the *syn/anti* ratio of the products generated in the latter.

The behavior of different α-aryl-β-ketonitriles was also explored and the results obtained brought to light an important limitation of the present Ru-catalyzed hydration/TH cascade reaction. Thus, as shown in Scheme 4, when the phenyl-substituted substrates **2af-ah** were subjected to the combined action of complex **1** and NaO$_2$CH, in all the cases, 2-phenylacetamide **6** was the major reaction product that could be isolated after the chromatographic work-up (77–91% yield). Formation of **6** can be rationalized in terms of the instability of the desired β-hydroxyamide products **4af-ah** under the reaction conditions needed for the hydration/TH process to proceed. A retro-aldol type reaction of compounds **4af-ah**, facilitated by the NaO$_2$CH base, could explain the formation of **6**. Inspection of the crude reaction mixtures before solvent removal by gas chromatography indicated also the presence in solution of the corresponding alcohols **7af-ah**, resulting from TH of the retro-aldol

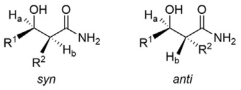
Table 3
Ru-catalyzed synthesis of β-hydroxyamides **4w-ae** from the α-substituted β-ketonitriles **2w-ae**.[a]



Entry	β-Ketonitrile **2**	β-Hydroxyamide **4**	Yield (%)[b]	*syn/anti* ratio
1	 **(2w)**	 **(4w)**	88	1:1.3
2	 **(2x)**	 **(4x)**	75	1.3:1
3	 **(2y)**	 **(4y)**	97	1:1.3
4	 **(2z)**	 **(4z)**	68	1:1.4
5	 **(2aa)**	 **(4aa)**	72	3.8:1
6	 **(2ab)**	 **(4ab)**	82	1:1.3
7[c]	 **(2ac)**	 **(4ac)**	61	1.4:1
8	 **(2ad)**	 **(4ad)**	55	1.2:1
9	 **(2ae)**	 **(4ae)**	50	–

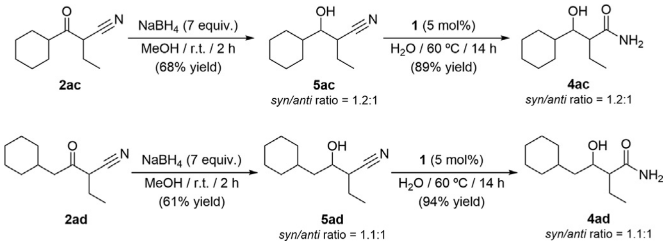
[a] Reactions performed in a Teflon-capped sealed tube under Ar atmosphere with 1 mmol of the corresponding β-ketonitrile (0.33 M in H_2O).
[b] Isolated yields after chromatographic work-up.
[c] Reaction time 48 h.

Table 4
Comparison of the coupling constants of the *syn* and *anti* diastereoisomers of β-hydroxyamides **4w-ab**.[a]

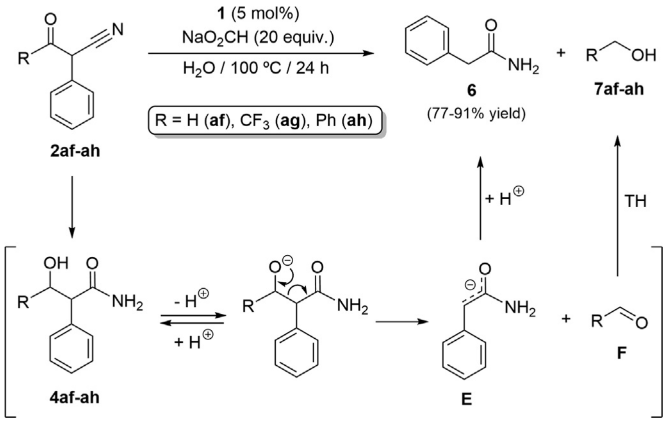


Entry	β-Hydroxyamide **4**	J_{HaHb} *syn*	J_{HaHb} *anti*
1	**4w** ($R^1 = Ph$; $R^2 = Me$)	8.7 Hz	7.2 Hz
2	**4x** ($R^1 = Ph$; $R^2 = Et$)	8.7 Hz	8.1 Hz
3	**4y** ($R^1 = Ph$; $R^2 = {}^nBu$)	8.4 Hz	7.6 Hz
4	**4z** ($R^1 = Ph$; $R^2 = {}^nPent$)	9.3 Hz	8.1 Hz
5	**4aa** ($R^1 = Ph$; $R^2 = Bn$)	7.5 Hz	7.2 Hz
6	**4 ab** ($R^1 = Ph$; $R^2 = CH_2Bn$)	8.1 Hz	7.8 Hz

[a] ^1H NMR spectra recorded in DMSO-d_6.



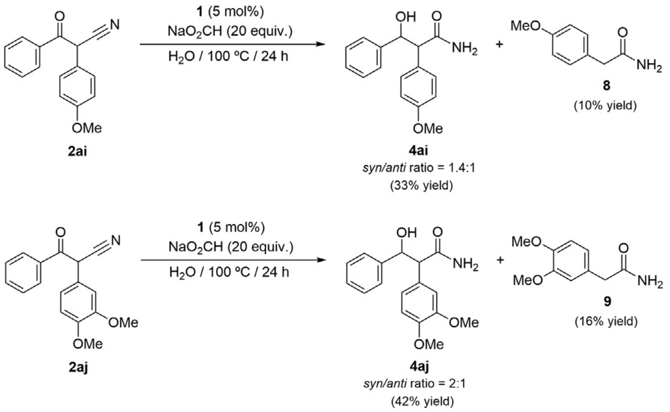
Scheme 3. Two-step synthesis of β-hydroxyamides **4ac-ad** from β-ketonitriles **2ac-ad**.



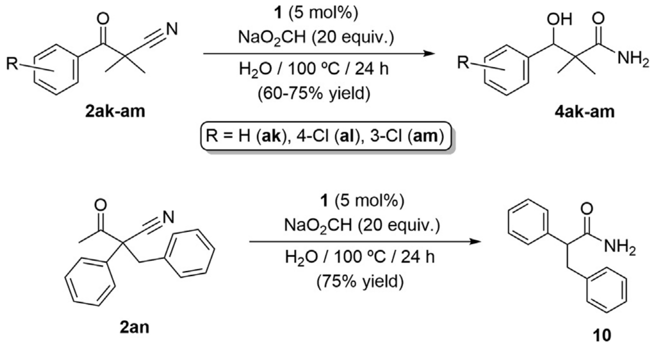
Scheme 4. Generation of 2-phenylacetamide **6** from the α-phenyl substituted β-ketonitriles **2af-ah**.

aldehyde products **F**. The marked differences in stability between the α-phenyl-β-hydroxyamides **4af-ah** and their alkyl-, benzyl- and homobenzyl-substituted counterparts **4w-ae** (Table 3) is probably related with the electronic delocalization of the negative charge in the amide enolate intermediate **E** by conjugation with the aromatic ring, which would facilitate the cleavage of the C-C bond of β-hydroxyamides **4af-ah**.

We reasoned that the introduction of electron donating substituents on the aromatic ring should decrease the stability of amide enolates of type **E**, thus disfavoring the competing retro-aldol reaction. To confirm this hypothesis, the β-ketonitriles **2ai** and **2aj**, containing methoxy-substituted aryl groups in α-position, were synthesized and their behavior explored (Scheme 5). In complete accord with our expectations, the corresponding β-hydroxyamides **4ai** and **4aj** were stable enough to be isolated.



Scheme 5. The Ru-catalyzed hydration/TH of β-ketonitriles **2ai-aj**.



Scheme 6. Catalytic reactions involving the α-disubstituted β-ketonitriles **2ak-an**.

Nonetheless, the yields were only modest since the retro-aldol reaction could not be completely suppressed, as evidenced by the isolation of significant amounts of the cleaved amides **8** and **9** after the chromatographic work-up of the reactions [31]. As in the previous examples (see Table 3), α-substituted-β-hydroxyamides **4ai** and **4aj** were generated as mixtures of the corresponding *syn* and *anti* diastereosiomers, which could be separated by column chromatography only in the case of **4aj**. The coupling constants between the C*H*OH and C*H*Ar(=O)NH_2 protons were again employed for configuration assignments.

Finally, to complete the study, some examples of α-disubstituted-β-ketonitriles were also considered. Thus, as shown in Scheme 6, while the dimethyl-substituted substrates **2ak-am** could be converted into the corresponding β-hydroxyamides **4ak-am** without major problems, starting from **2an**, in which a phenyl substituent is present, the only amide-containing product that could be isolated was 2,3-diphenylpropanamide **10** [32]. The formation of **10** evidences again the low tolerance of the present hydration/TH process to α-aryl substituted substrates.

4. Conclusions

In summary, a catalytic procedure for the *one-pot* conversion of β-ketonitriles into β-hydroxyamides in water, involving a ruthenium(II)-catalyzed hydration/transfer hydrogenation cascade process, has been developed. In particular, in this contribution we have presented a detailed study on the optimization of the reaction conditions and the scope and limitations of this unprecedented transformation. Forty different β-ketonitriles, featuring diverse substitution patterns, have been employed along the study leading in most cases to satisfactory results. The only restriction found concerns the presence of aryl substituents on the central α-position of the substrates. In these cases, the corresponding β-hydroxyamide products were found to be unstable under the experimental conditions needed for the hydration/TH process to proceed, decomposing through a retro-aldol type reaction. Regardless of this, we believe that the feasibility and scope of this catalytic aqueous transformation represents a competitive and very appealing methodology for the preparation of valuable β-hydroxyamide derivatives, which could find applications in different synthetic programs in the near future.

Acknowledgments

Financial support from the Spanish Ministry of Economy, Industry and Competitiveness (MINECO; Project CTQ2016-75986-P) and the Regional Government of Asturias (Project GRUPIN14-006) is gratefully acknowledged. R.G.-F. thanks MECD of Spain for the award of a FPU fellowship.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.05.016.

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