Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2025, **23**, 10596

Received 26th September 2025,
Accepted 30th October 2025

DOI: 10.1039/d5ob01546d

rsc.li/obc

Synthesis of chiral α-alkynyl-α-hydroxyamides by enantioselective alkynylation of α-keto amides

Elena Prieto, Celia Andrés * and Javier Nieto *

The α-hydroxyamide moiety is an important structural component in a wide variety of biologically active compounds and natural products. Herein, we describe a highly efficient and practical approach towards chiral quaternary α-alkynyl-α-hydroxyamides by Me_2Zn-mediated addition of terminal alkynes to α-keto amides. The desired products are obtained in good yields and enantioselectivities with broad substrate and reagent scopes.

Introduction

α-Hydroxyamides are highly relevant core structures in chemical synthesis. Their structures appear in various natural products such as (+)-kopsihainanina A,[1] aspergiline A[2] or chimonamidine,[3] and molecules that exhibit a wide range of biological activities, including anticonvulsant,[4] antimicrobial,[5] antifungal,[6] anti-inflammatory,[7] antipsoriatic[8] or antiandrogen.[9] α-Hydroxyamide derivatives are also known to behave as HIV protease inhibitors,[10] matrix metalloproteinase inhibitors that induce tissue synthesis and degradation,[11] or inhibitors of some kinases involved in the pathogenesis of autoimmune diseases.[12] In addition, α-hydroxyamides are versatile intermediates in the synthesis of compounds with more complex structures[13] and some of them are valuable ligands in asymmetric catalysis.[14]

The synthesis of these core structures in an enantioselective manner is crucial when it comes to achieving the desired pharmacological properties. Among the different methods for synthesizing optically active α-hydroxyamides are the amidation of chiral α-hydroxy acids,[15] the hydration of chiral cyanohydrins,[16] the ring opening of chiral α,β-epoxy amides,[17] the enantioselective Passerini-type reaction,[18] the kinetic and enzymatic resolution of racemic mixtures of α-hydroxyamides[19] and, the most used, the chemo- and enantioselective reduction of α-keto amides.[20] Alternatively, the enantioselective addition of carbon nucleophiles to α-keto amides leads to α-hydroxy amides with a quaternary stereocenter. However, although this option has been frequently reported using cyclic α-keto amides as isatins,[21] in acyclic keto amides, it has hardly been explored except for cyclization and annulation reactions.[22] Examples of enantioselective nucleophilic addition leading to chiral acyclic α-hydroxy amides with a quaternary stereocenter are very rare. To the best of our knowledge, only four cases have been reported[23] and neither involves the enantioselective addition of organometallic reagents to α-keto amides.

Recently, we have gained interest in the synthesis of functionalized chiral tertiary propargylic alcohols through the addition of acetylides to activated ketones[24] and in this context, we decided to embark on the synthesis of α-alkynyl-α-hydroxyamides by enantioselective alkynylation of α-keto amides with alkynylzinc derivatives.[25]

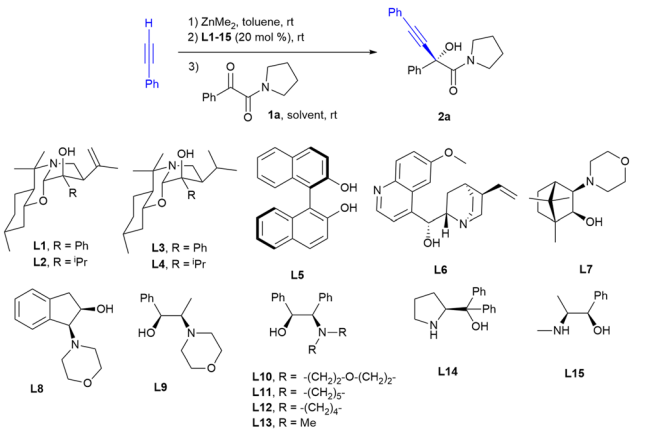
Results and discussion

We first scanned a series of chiral ligands **L1–15** (20 mol%), some of which had provided good enantioselectivities on the addition of organozinc derivatives to carbonyl compounds in previous works,[26] in the model reaction of 1-phenyl-2-(pyrrolidine-1-yl)ethane-1,2-dione **1a**, with the alkynylzinc derivative prepared from phenylacetylene and dimethylzinc in a dichloromethane–toluene 3 : 1 mixture at rt for 24 hours and the results are collected in Table 1.

1,3-Benzoxazine **L2** that had given us good results in previous works as a chiral ligand in the alkynylation of α-keto esters and α-diketones[24] provided poor results in terms of enantioselectivity and chemical yield (entry 2 in Table 1). The highest enantioselectivities were achieved with ligand **L10** (er = 95 : 5, entry 10 in Table 1), also achieving a good chemical yield. The use of only toluene as a solvent or a mixture of toluene and THF, diethyl ether or ethyl acetate did not improve either the chemical yield or the enantioselectivity of the reaction (entries 17–19 in Table 1). On the other hand, when lowering the reaction temperature from rt to 0 °C, a slight loss of enantioselectivity was observed in addition to a marked decrease in chemical yield due to a marked decrease in the rate of reaction (entry 20 in Table 1).

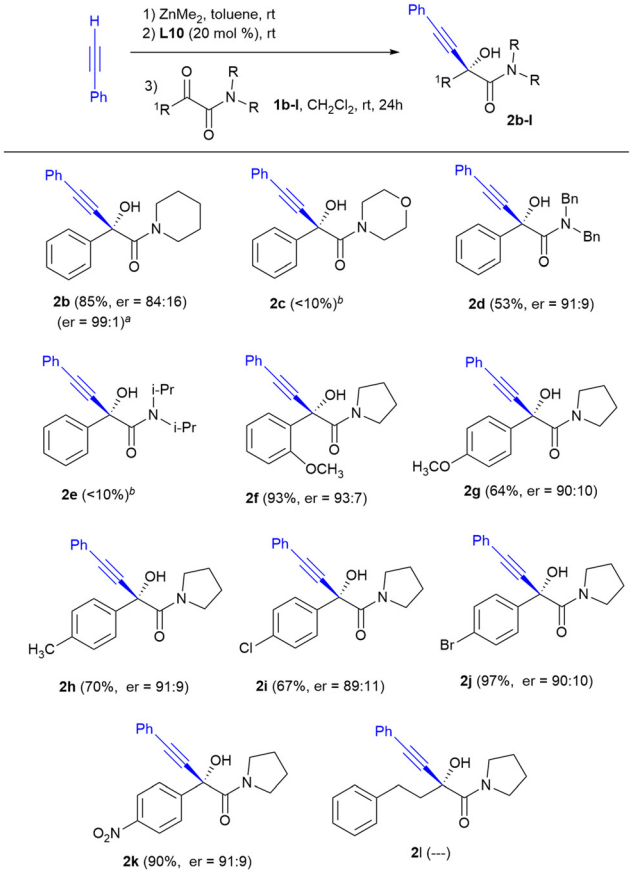
Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Paseo de Belén, 7, 47011 Valladolid, Spain.
E-mail: franciscojavier.nieto@uva.es

Table 1 Screening studies of enantioselective addition of phenylacetylene to 1-phenyl-2-(pyrrolidine-1-yl)ethane-1,2-dione **1a**[a]



Entry	Ligand	Solvent	t (h)	Yield[b] (%)	er[c]
1	**L1**	CH_2Cl_2–toluene 3 : 1	24	45	38 : 62
2	**L2**	CH_2Cl_2–toluene 3 : 1	24	34	19 : 81
3	**L3**	CH_2Cl_2–toluene 3 : 1	24	51	23 : 77
4	**L4**	CH_2Cl_2–toluene 3 : 1	24	35	45 : 55
5	**L5**	CH_2Cl_2–toluene 3 : 1	24	17	—
6	**L6**	CH_2Cl_2–toluene 3 : 1	24	5	—
7	**L7**	CH_2Cl_2–toluene 3 : 1	24	60	86 : 14
8	**L8**	CH_2Cl_2–toluene 3 : 1	24	67	57 : 43
9	**L9**	CH_2Cl_2–toluene 3 : 1	24	72	85 : 15
10	**L10**	CH_2Cl_2–toluene 3 : 1	24	81	95 : 5
11	**L11**	CH_2Cl_2–toluene 3 : 1	24	66	87 : 13
12	**L12**	CH_2Cl_2–toluene 3 : 1	24	35	89 : 11
13	**L13**	CH_2Cl_2–toluene 3 : 1	24	76	81 : 19
14	**L14**	CH_2Cl_2–toluene 3 : 1	24	65	64 : 36
15	**L15**	CH_2Cl_2–toluene 3 : 1	24	71	34 : 66
16	**L10**	Toluene	24	62	84 : 16
17	**L10**	AcOEt–toluene 3 : 1	24	26	70 : 30
18	**L10**	THF–toluene 3 : 1	24	28	68 : 32
19	**L10**	Et_2O–toluene 3 : 1	24	48	80 : 20
20[d]	**L10**	CH_2Cl_2–toluene 3 : 1	33	34	93 : 7
21	**L10**	CH_2Cl_2–toluene 3 : 1	1	53	95 : 5
22	**L10**	CH_2Cl_2–toluene 3 : 1	15	72	95 : 5
23	**L10**	CH_2Cl_2–toluene 3 : 1	30	77	94 : 6

[a] Reaction conditions: 0.1 mmol of **1a**, 0.4 mmol of dimethylzinc, 0.4 mmol of phenylacetylene and 0.02 mmol of ligands **L1–15**, solvent (3.3 mL). [b] Yield of the isolated product after purification by flash column chromatography. [c] Enantiomeric ratio was determined by HPLC on a chiral stationary phase. [d] The reaction was carried out at 0 °C.



Scheme 1 Substrate scope of the alkynylation of α-keto amides. Reaction conditions: 0.25 mmol of **1b–l**, 1.0 mmol of dimethylzinc, 1.0 mmol of phenylacetylene and 0.05 mmol of ligand **L10**, in a CH_2Cl_2–toluene 3 : 1 mixture (3.3 mL) at rt for 24 h. Yield of the isolated product after purification by flash column chromatography. The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [a] Enantiomeric ratio after recrystallization in hexane. [b] Detected by ^{1}H NMR of the reaction mixtures but not isolated.

In previous works on the alkynylation of α-keto esters[27] and α-diketones,[24b] a kinetic resolution of the resulting tertiary propargylic alcohols has been observed due to the over-addition of the organometallic reagent; however, in our case, no appreciable variation of the enantioselectivity with the reaction time was observed (entries 10 and 21–23 in Table 1).

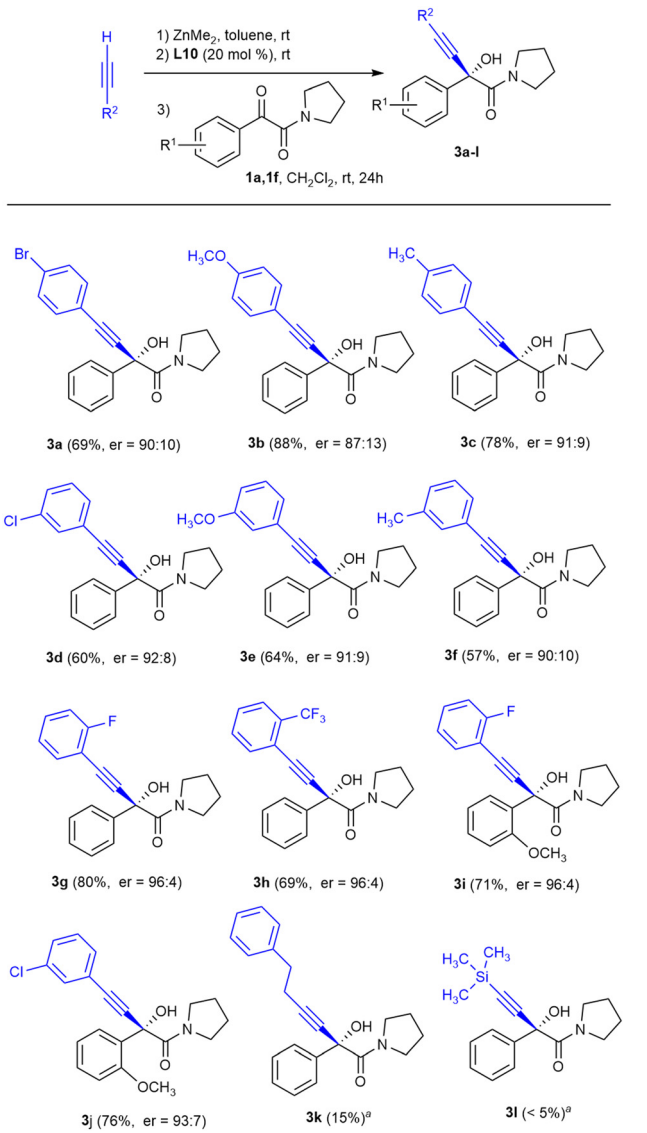
After the optimal reaction conditions were determined (4 equiv. of phenylacetylene and dimethylzinc, 20 mol% of **L10** as the ligand, at rt in a mixture of CH_2Cl_2 : toluene 3 : 1 for 24 h), the substrate scope for the alkynylation of a series of aromatic and aliphatic α-keto amides was explored and the results are shown in Scheme 1.

The nitrogen substitution of the amide function appears to be a critical factor that drastically affects the chemical yield of the reaction. The morpholine-derived ketoamide **1c**, as well as ketoamide **1e** with two bulky isopropyl substituents, underwent little conversion to the alkynylation products **2c** and **2e**, recovering in both cases the starting ketoamide as the only by-product. In contrast, when using the ketoamides derived from piperidine **1b** and dibenzylamine **1d**, the corresponding hydroxyketones **2b** and **2d** were obtained with enantioselectivities comparable to those achieved with the aromatic amides derived from pyrrolidine **1a** and **1f–k**. In addition, the recrystallization of product **2b** allowed the enantioselectivity to increase up to an excellent ratio of enantiomers of 99 : 1.

The enantiocontrol in the alkynylation of diverse aromatic α-keto amides derived from pyrrolidine seemed not to be influenced by electronic effects. The presence of both electron-donating substituents such as the methyl or methoxy groups (products **2f–h**) or electron-withdrawing substituents such as Cl, Br or $-NO_2$ (products **2i–k**) in the *ortho* or *para* positions of

the aromatic ring was tolerated without significant changes of enantioselectivity. All the reactions proceeded with good chemical yields. The decrease in chemical yield observed in some products was due to losses during the chromatographic purification. In contrast, when the reaction was performed with an alkyl-substituted α-keto amide namely 4-phenyl-1-(pyrrolidin-1-yl)butane-1,2-dione **1l**, formation of α-hydroxyamide **2l** was not observed.

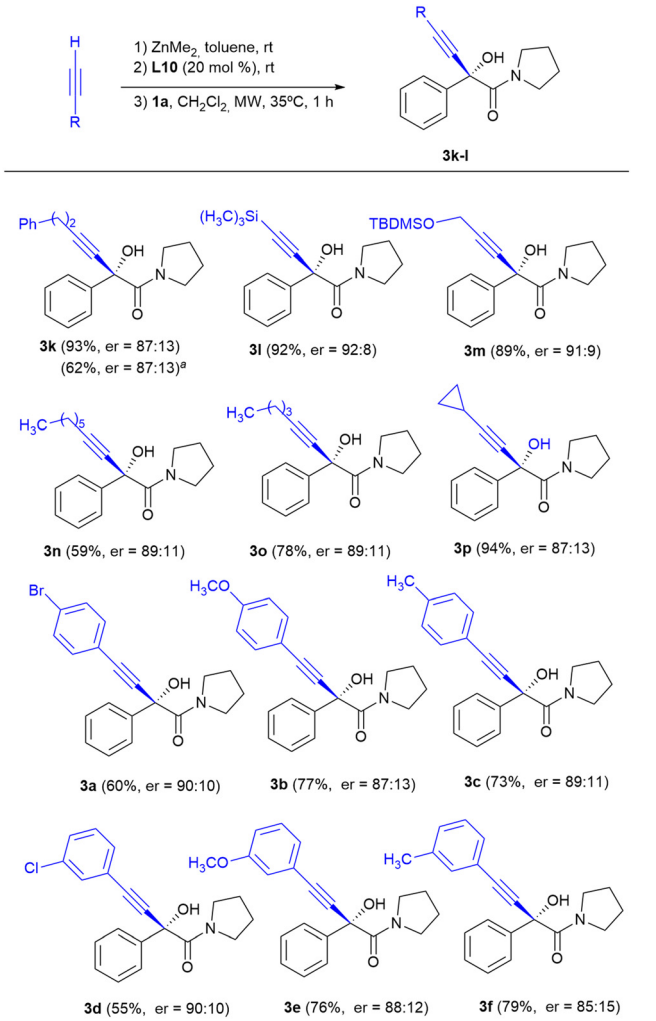
To test the generality of this reaction with respect to the alkyne, we studied the influence of the electronic effects of some arylacetylenes, as well as the addition of aliphatic alkynes to α-keto amides **1a** and **1f** (Scheme 2).



Scheme 2 Scope of the reaction of α-keto amides **1a** and **1f** with terminal alkynes. Reaction conditions: 0.25 mmol of **1a** or **1f**, 1.0 mmol of dimethylzinc, 1.0 mmol of alkyne and 0.05 mmol of ligand **L10**, in a CH_2Cl_2–toluene 3 : 1 mixture (3.3 mL) at rt for 24 h. Yield of the isolated product after purification by flash column chromatography. The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [a] Undetermined enantiomeric ratio.

For arylacetylenes the corresponding α-alkynyl-α-hydroxyamides were obtained with good enantioselectivities (Scheme 2, compounds **3a–j**), although the best results in terms of enantioselectivity were obtained when the aromatic ring in the alkyne was substituted in the *ortho* position by an electro-attracting fluorine or by a trifluoromethyl group (products **3g–i**, er = 96 : 4). Unfortunately, the reactions of **1a** with the aliphatic alkyne 4-phenyl-1-butyne and trimethylsilylacetylene did not provide appreciable amounts of alkynylation products **3k** and **3l**, recovering most of the untransformed ketoamide **1a**.

In order to solve this lack of reactivity, the addition of 4-phenyl-1-butyne to ketoamide **1a** in the presence of **L10** was



Scheme 3 Scope of the reaction of α-keto amide **1a** with terminal alkynes under microwave irradiation. Reaction conditions: 0.25 mmol of **1a**, 1.0 mmol of dimethylzinc, 1.0 mmol of alkyne and 0.05 mmol of ligand **L10**, in a CH_2Cl_2–toluene 3 : 1 mixture (3.3 mL) at 35 °C for 1 h. The reaction was carried out in a CEM Discover 300 W microwave reactor, applying an initial power of 80 W. Yield of the isolated product after purification by flash column chromatography. The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [a] The reaction was carried out at 35 °C in a conventional oil bath for one hour.

studied. Heating to 35 °C in a conventional oil bath for one hour allowed the isolation of hydroxyamide **3k** with an enantioselectivity of er = 87 : 13 and a chemical yield of 62%. To our delight, the chemical yield improved up to 93% and enantioselectivity remained similar when heating was carried out under microwave irradiation. Under these conditions, in the absence of **L10**, formation of less than 5% of the racemate of **3k** is observed.

Therefore, heating at 35 °C under microwave irradiation for 1 hour were chosen as the ideal conditions for the enantioselective addition of aliphatic terminal alkynes to α-ketoamides and the scope of the reaction for different aliphatic alkynes was studied (Scheme 3).

The addition of aliphatic terminal alkynes under these conditions occurred with moderate to good chemical yields and enantioselectivities slightly lower than those provided with the terminal aromatic alkynes at room temperature. The best results in terms of enantiocontrol were obtained upon the addition of alkynes with trimethylsilyl or *tert*-butyl(dimethyl) silyloxy substituents, with enantioselectivities comparable to those obtained upon the addition of arylacetylenes (compounds **3l**, er = 92 : 8 and **3m**, er = 91 : 9). Alkynylation of **1a** with arylacetylene derivatives in the presence of **10L** under microwave irradiation at 35 °C for 1 hour was also explored, and α-alkynyl-α-hydroxyamides **3a–f** were obtained with yields similar to those achieved when the alkynylations were carried out at room temperature for 24 h; however, the enantioselectivities were slightly lower (compare the results of Scheme 2 with those of Scheme 3 for **3a–f**).

The configuration of the newly formed stereogenic center of **2a** was established by X-ray diffraction analysis and has been extended to all of the other α-alkynyl-α-hydroxyamides **2b–k** and **3a–p** based on mechanistic analogy.

Conclusions

In summary, we have developed an efficient method for the preparation of enantioenriched α-alkynyl-α-hydroxyamides with a quaternary stereocenter *via* Me_2Zn-mediated addition of terminal alkynes to α-keto amides using the 1,2-amino alcohol **L10** as a chiral ligand. A variety of aromantic α-keto amides bearing electron-withdrawing or electron-donating substituents on the aromatic ring and aromatic and aliphatic terminal alkynes were investigated, which gave rise to 1,2-addition products in moderate to good chemical yields and enantioselectivities.

Experimental section

General information

All reactions were carried out in anhydrous solvents under a nitrogen atmosphere in dried glassware by means of Schlenk techniques. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 126 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane with the residual $CHCl_3$ resonance as an internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in hertz, and integration. Specific rotations were measured using a 2 mL cell with a 1 dm path length and a sodium lamp, and concentration is given in g per 100 mL. High resolution mass spectrometry analysis (HRMS) was performed using a quadrupole spectrometer with a TOF analyzer. Infrared spectra are reported in frequency of absorption and only the structurally most important peaks are given. Flash chromatography was carried out using silica gel (230–240 mesh). TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F254 indicator and visualized by either UV irradiation or staining with I_2 or phosphomolybdic acid solution. Chiral HPLC analysis was performed using Chiralpak AD-H, Phenomenex Lux Amylose-1, Phenomenex Lux i-Amylose-3, Phenomenex Lux i-Amylose-1 and Phenomenex Lux Cellulose-2 columns. UV detection was monitored at 254 nm.

Microwave-assisted synthesis was carried out in a CEM Discover microwave reactor containing a single-mode microwave cavity in sealed reaction vessels and operating at a maximal microwave power of up to 80 W. The temperature at the bottom of the reaction vessel was automatically controlled with an IR sensor located below the microwave cavity floor. Reaction times refer to the hold times at the temperatures indicated and not to the total irradiation times.

Commercially available reagents were used as purchased without further treatment.

General procedure for the catalytic enantioselective addition of phenyl acetylene derivatives to α-keto amides

To a solution of 1.2 M of $ZnMe_2$ in toluene (1.0 mmol, 0.83 mL) was added the corresponding alkyne (1.0 mmol) and the mixture was stirred under a nitrogen atmosphere at rt for 1 h. Then, a solution of 0.05 M of ligand **L10** in CH_2Cl_2 (0.05 mmol, 1.0 mL) was added and the reaction was stirred for another 30 min, whereupon a solution of the keto amide (0.25 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise and the reaction was stirred at rt for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel using a hexane/ethyl acetate mixture as the eluent.

General procedure for the microwave assisted catalytic enantioselective addition of aliphatic terminal alkynes to α-keto amides

In an oven-dried microwave tube equipped with a magnetic stir bar, containing the aliphatic alkyne (1.0 mmol), a solution of 1.2 M of $ZnMe_2$ in toluene (1.0 mmol, 0.83 mL) was added. The mixture was stirred under a nitrogen atmosphere at rt for 1 h and then a solution of 0.05 M of ligand **L10** in CH_2Cl_2

(0.05 mmol, 1.0 mL) was added and the reaction was stirred for another 30 min, whereupon a solution of the keto amide (0.25 mmol) in CH_2Cl_2 (1.5 mL) was added, and the reaction mixture was irradiated in a CEM Discover microwave reactor operating at a microwave power of 80 W at 35 °C for 1 h. After cooling, the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel using a hexane/ethyl acetate mixture as the eluent.

(*R*)-2-Hydroxy-2,4-diphenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (2a). This compound was obtained from keto amide **1a** (0.25 mmol, 51 mg). Yield: 62 mg, 81%. White solid. Mp (from hexane) 114–116 °C. $[\alpha]_D^{25}$ = +46.2 (*c* 1.0, CH_2Cl_2, 90% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (m, 1H), 1.79 (m, 3H), 2.68 (m, 1H), 3.59 (m, 1H), 3.66 (m, 1H), 3.72 (m, 1H), 6.06 (s br, 1H), 7.31–7.42 (7H), 7.54 (m, 2H), 7.63 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 72.4, 86.7, 87.5, 122.0, 126.6, 128.4, 128.6, 128.6, 128.9, 131.8, 139.8, 168.3. IR (neat) ν 3312, 1641, 1487, 1378, 1067, 760, 687 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{19}NNaO_2^+$ $[M + Na]^+$ 328.1308, found 328.1315. HPLC: Phenomenex Lux i-Amylose-3, hexane : ^{i}PrOH = 60 : 40, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 19.4 min *R* enantiomer, t_R = 22.7 min *S* enantiomer.

(*R*)-2-Hydroxy-2,4-diphenyl-1-(piperidin-1-yl)but-3-yn-1-one (2b).[28] This compound was obtained from keto amide **1b** (0.25 mmol, 54 mg). Yield: 67 mg, 85%. White solid. Mp (from hexane): 139–141 °C. $[\alpha]_D^{25}$ = +23.9 (*c* 0.7, CH_2Cl_2, 98% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (m, 2H), 3.57 (m, 2H), 3.71 (m, 4H), 7.45 (m, 2H), 7.58 (m, 1H), 7.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.5, 46.1, 66.5, 66.6, 129.0, 129.5, 132.9, 134.9, 165.4, 191.1. IR (neat) ν 3284, 1632, 1448, 1250, 1070, 1000, 769, 692 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calculated for $C_{21}H_{21}NNaO_2^+$ $[M + Na]^+$ 342.1464, found 342.1472. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 13.7 min *R* enantiomer, t_R = 20.0 min *S* enantiomer.

(*R*)-*N*,*N*-Dibenzyl-2-hydroxy-2,4-diphenylbut-3-ynamide (2d).[29] This compound was obtained from keto amide **1d** (0.25 mmol, 82 mg). Yield: 57 mg, 53%. Yellow oil. $[\alpha]_D^{25}$ = −10.7 (*c* 0.5, CH_2Cl_2, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (d, *J* = 15.8 Hz, 1H), 4.49 (d, *J* = 14.8 Hz, 1H), 4.63 (d, *J* = 15.9 Hz, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.84 (dt, *J* = 7.7, 1.4 Hz, 2H), 7.14–7.20 (5H), 7.26–7.40 (11H), 7.68 (dd, *J* = 7.5, 2.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.7, 50.6, 72.4, 86.1, 88.7, 121.7, 126.4, 127.6, 127.6, 127.7, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.9, 128.9, 131.8, 134.6, 135.9, 140.4, 171.1. IR (neat) ν 3346, 1643, 1444, 1353, 1074, 754, 703 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{30}H_{25}NNaO_2^+$ $[M + Na]^+$: 454.1777, found: 454.1787; HPLC: Phenomenex Lux i-Amylose-1, hexane : ^{i}PrOH 85 : 15, flow rate = 1 mL min^{-1}, λ = 254, t_R = 10.7 min *R* enantiomer, t_R = 13.5 min *S* enantiomer.

(*S*)-2-Hydroxy-2-(2-methoxyphenyl)-4-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (2f). This compound was obtained from keto amide **1f** (0.24 mmol, 57 mg). Yield: 76 mg, 93%. Yellow oil. $[\alpha]_D^{25}$ = +28.6 (*c* 0.6, CH_2Cl_2, 86% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 3H), 1.82 (tt, *J* = 10.6, 3.6 Hz, 1H), 2.45 (m, 1H), 3.52–3.67 (3H), 3.74 (s, 3H), 5.38 (s broad, 1H), 6.86 (dt, *J* = 8.4, 1.4 Hz, 1H), 6.99 (td, *J* = 7.5, 1.2 Hz, 1H), 7.28–7.33 (4H), 7.49 (m, 2H), 8.00 (dt, *J* = 7.6, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.3, 47.3, 47.7, 55.8, 71.2, 86.8, 86.9, 111.9, 120.7, 122.2, 127.9, 128.3, 128.7, 129.8, 130.3, 131.8, 157.0, 168.4; IR (neat) ν 3342, 1650, 1485, 1265, 1077, 1022, 758, 692 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{21}NNaO_3^+$ $[M + Na]^+$ 358.1414, found 358.1416. HPLC: Phenomenex Lux Amylose-1, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 18.8 min *S* enantiomer, t_R = 28.0 min *R* enantiomer.

(*R*)-2-Hydroxy-2-(4-methoxyphenyl)-4-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (2g). This compound was obtained from keto amide **1g** (0.25 mmol, 58 mg). Yield: 53 mg, 64%. Yellow oil. $[\alpha]_D^{25}$ = +39.5 (*c* 0.4, CH_2Cl_2, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 1H), 1.79 (m, 3H), 2.73 (dt, *J* = 11.5, 6.3 Hz, 1H), 3.59 (m, 1H), 3.66 (m, 1H), 3.70 (m, 1H), 3.81 (s, 3H), 6.00 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.32–7.38 (3H), 7.51–7.55 (4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 55.3, 71.9, 86.5, 87.3, 113.9, 122.1, 128.0, 128.4, 128.8, 131.8, 132.1, 159.7, 168.5. IR (neat) ν 3331, 1635, 1503, 1367, 1250, 1176, 1066, 831, 762, 695 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{21}NNaO_3^+$ $[M + Na]^+$ 358.1414, found 358.1426. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 44.8 min *R* enantiomer, t_R = 29.5 min *S* enantiomer.

(*R*)-2-Hydroxy-4-phenyl-1-(pyrrolidin-1-yl)-2-(*p*-tolyl)but-3-yn-1-one (2h). This compound was obtained from keto amide **1h** (0.25 mmol, 58 mg). Yield: 60 mg, 70%. Yellow oil. $[\alpha]_D^{25}$ = +32.5 (*c* 0.4, CH_2Cl_2, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.67 (m, 1H), 1.78 (m, 3H), 2.37 (s, 3H), 2.73 (m, 1H), 3.59 (m, 1H), 3.65 (m, 1H), 3.71 (m, 1H), 6.01 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.32–7.39 (3H), 7.48–7.55 (4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.5, 26.2, 47.3, 48.0, 72.2, 86.4, 87.3, 122.1, 126.5, 128.4, 128.8, 129.3, 131.8, 136.9, 138.4, 168.4. IR (neat) ν 3320, 1635, 1375, 1184, 1070, 824, 758, 692 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{22}NO_2^+$ $[M + H]^+$ 320.1645, found 320.1648. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 32.6 min *R* enantiomer, t_R = 24.7 min *S* enantiomer.

(*R*)-2-(4-Chlorophenyl)-2-hydroxy-4-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (2i). This compound was obtained from keto amide **1i** (0.26 mmol, 61 mg). Yield: 58 mg, 67%. Yellow oil. $[\alpha]_D^{25}$ = +37 (*c* 0.2, CH_2Cl_2, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 1H), 1.81 (m, 3H), 2.70 (dt, *J* = 10.4, 6.2 Hz, 1H), 3.58 (m, 1H), 3.65 (m, 1H), 3.73 (m, 1H), 6.05 (s, 1H), 7.33–7.41 (5H), 7.51–7.58 (4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.1, 71.8, 85.7, 87.8, 121.7, 128.2, 128.4, 128.8, 129.0, 131.8, 134.6, 138.4, 167.9. IR (neat) ν 3317, 1639, 1481, 1375, 1180, 835, 754, 695 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{18}ClNNaO_2^+$ $[M + Na]^+$ 362.0918, found 362.0917. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 16.5 min *R* enantiomer, t_R = 13.8 min *S* enantiomer.

(*R*)-2-(4-Bromophenyl)-2-hydroxy-4-phenyl-1-(pyrrolidin-1-yl) but-3-yn-1-one (2j). This compound was obtained from keto amide **1j** (0.24 mmol, 68 mg). Yield: 90 mg, 97%. Yellow oil. $[\alpha]_D^{25}$ = +29 (*c* 0.6, CH_2Cl_2, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 1H), 1.81 (m, 3H), 2.70 (dt, *J* = 10.2, 6.3 Hz, 1H), 3.58 (dt, *J* = 12.7, 6.5 Hz, 1H), 3.65 (m, 1H), 3.72 (dd, *J* = 10.9, 6.4 Hz, 1H), 6.05 (s, 1H), 7.33–7.41 (3H), 7.48–7.54 (6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.1, 71.9, 85.6, 87.9, 121.7, 122.8, 128.4, 128.5, 129.1, 131.8, 131.8, 139.0, 167.8. IR (neat) ν 3302, 1635, 1367, 1066, 824, 758, 688 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{18}BrNNaO_2^+$ $[M + Na]^+$ 406.0413, found: 406.0429. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 17.3 min *R* enantiomer, t_R = 13.8 min *S* enantiomer.

(*R*)-2-Hydroxy-2-(4-nitrophenyl)-4-phenyl-1-(pyrrolidin-1-yl) but-3-yn-1-one (2k). This compound was obtained from keto amide **1k** (0.26 mmol, 65 mg). Yield: 83 mg, 90%. Yellow oil. $[\alpha]_D^{25}$ = +19.3 (*c* 0.6, CH_2Cl_2, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (m, 1H), 1.82 (m, 3H), 2.64 (dt, *J* = 10.1, 6.3 Hz, 1H), 3.59 (m, 1H), 3.68 (m, 1H), 3.78 (dt, *J* = 10.9, 6.3 Hz, 1H), 6.14 (s, 1H), 7.26–7.43 (3H), 7.54 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 26.2, 47.4, 48.3, 71.8, 84.8, 88.6, 121.4, 123.9, 127.9, 128.5, 129.3, 131.8, 146.6, 147.9, 167.1. IR (neat) ν 3280, 1646, 1511, 1353, 1074, 853, 751, 684 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{18}N_2NaO_4^+$ $[M + Na]^+$ 373.1159, found 373.1165. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, 1 mL min^{-1}, λ = 254 nm, t_R = 25.8 min *R* enantiomer, t_R = 29.1 min *S* enantiomer.

(*R*)-4-(4-Bromophenyl)-2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl) but-3-yn-1-one (3a). This compound was obtained from keto amide **1a** (0.27 mmol, 55 mg). Yield: 72 mg, 69%. Yellow oil. $[\alpha]_D^{25}$ = +22.0 (*c* 0.6, CH_2Cl_2, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.79 (m, 3H), 2.68 (dt, *J* = 10.8, 6.4 Hz, 1H), 3.59 (dt, *J* = 11.8, 7.0 Hz, 1H), 3.66 (ddd, *J* = 10.7, 8.9, 4.9 Hz, 2H), 6.05 (s, 1H), 7.33–7.41 (5H), 7.49 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.60 (dd, *J* = 7.0, 1.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 72.4, 86.4, 87.4, 120.9, 123.3, 126.6, 128.7, 131.7, 133.2, 139.5, 168.0. IR (neat) ν 3324, 1635, 1367, 1059, 831, 765, 688 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{19}BrNO_2$ $[M + H]^+$ 384.0594, found 384.0599. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254, t_R = 22.2 min *R* enantiomer, t_R = 30.4 min *S* enantiomer.

(*R*)-2-Hydroxy-4-(4-methoxyphenyl)-2-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (3b). This compound was obtained from keto amide **1a** (0.26 mmol, 53 mg). Yield: 77 mg, 88%. Yellow oil. $[\alpha]_D^{25}$ = +29.8 (*c* 1.0, CH_2Cl_2, 74% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (dt, *J* = 6.6, 5.4 Hz, 1H), 1.79 (m, 3H), 2.67 (m, 1H), 3.58 (ddd, *J* = 12.0, 7.5, 5.8 Hz, 1H), 3.65 (m, 1H), 3.72 (dt, *J* = 10.7, 6.5 Hz, 1H), 3.82 (s, 3H), 6.04 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.31–7.40 (3H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 55.3, 72.4, 84.8, 87.5, 114.0, 114.1, 126.7, 128.5, 128.6, 133.3, 139.9, 160.0, 168.5; IR (neat) ν 3291, 2219, 1635, 1514, 1246, 1176, 1066, 842, 703 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{22}NO_3^+$ $[M + H]^+$ 336.1594, found 336.1605. HPLC: Phenomenex Lux i-Amylose-3, hexane : ^{i}PrOH 60 : 40, flow rate = 1 mL min^{-1}, λ = 254, t_R = 34.6 min *R* enantiomer, t_R = 41.8 min *S* enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)-4-(*p*-tolyl)but-3-yn-1-one (3c). This compound was obtained from keto amide **1a** (0.27 mmol, 55 mg). Yield: 67 mg, 78%. Yellow oil. $[\alpha]_D^{25}$ = +34.5 (*c* 0.6, CH_2Cl_2, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.79 (m, 3H), 2.37 (s, 3H), 2.68 (m, 1H), 3.58 (ddd, *J* = 12.1, 7.6, 5.8 Hz, 1H), 3.66 (m, 1H), 3.73 (dt, *J* = 12.1, 6.7 Hz, 1H), 6.05 (s, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.32–7.40 (3H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 23.5, 26.2, 47.3, 48.0, 72.4, 85.5, 87.7, 118.9, 126.7, 128.1, 128.5, 128.6, 129.1, 131.7, 139.1, 139.9, 168.4. IR (neat) ν 3317, 1632, 1375, 1063, 817, 703 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{21}NNaO_2^+$ $[M + Na]^+$ 342.1464, found 342.1473. HPLC: Phenomenex Lux i-Amylose-3, hexane : ^{i}PrOH 60 : 40, flow rate = 1 mL min^{-1}, λ = 254, t_R = 26.3 min *R* enantiomer, t_R = 32.9 min *S* enantiomer.

(*R*)-4-(3-Chlorophenyl)-2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl) but-3-yn-1-one (3d). This compound was obtained from keto amide **1a** (0.27 mmol, 54 mg). Yield: 54 mg, 60%. Yellow oil. $[\alpha]_D^{25}$ = +32.3 (*c* 0.4, CH_2Cl_2, 84% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (m, 1H), 1.80 (m, 3H), 2.68 (dt, *J* = 11.3, 6.3 Hz, 1H), 3.56–3.69 (3H), 6.05 (s, 1H), 7.26–7.43 (6H), 7.51 (m, 1H), 7.59 (dd, *J* = 8.1, 1.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 72.4, 86.0, 87.4, 123.7, 126.6, 128.7, 128.7, 129.2, 129.7, 130.0, 131.6, 134.2, 139.5, 168.0. IR (neat) ν 3320, 1635, 1375, 1066, 762, 692, 673 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{20}H_{19}ClNO_2^+$ $[M + H]^+$: 340.1099, found 340.1108. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254, t_R = 17.4 min *R* enantiomer, t_R = 25.5 min *S* enantiomer.

(*R*)-2-Hydroxy-4-(3-methoxyphenyl)-2-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (3e). This compound was obtained from keto amide **1a** (0.26 mmol, 52 mg). Yield: 55 mg, 64%. Yellow oil. 64%. $[\alpha]_D^{25}$ = +25.5 (*c* 0.4, CH_2Cl_2, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.79 (m, 3H), 2.69 (dt, *J* = 11.2, 6.2 Hz, 1H), 3.58 (m, 1H), 3.66 (m, 1H), 3.72 (m, 1H), 3.82 (s, 3H), 6.05 (s, 1H), 6.93 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.06 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.32–7.41 (3H), 7.62 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.2, 47.3, 48.0, 55.3, 72.4, 86.0, 87.4, 115.3, 116.8, 123.0, 124.3, 126.6, 128.6, 128.6, 129.4, 139.7, 159.3, 168.2. IR (neat) ν 3298, 1635, 1437, 1367, 1287, 1213, 1162, 776, 688 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calculated for $C_{21}H_{21}NNaO_3^+$ $[M + Na]^+$ 358.1414, found: 358.1412. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254, t_R = 28.8 min *R* enantiomer, t_R = 37.2 min *S* enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)-4-(*m*-tolyl)but-3-yn-1-one (3f). This compound was obtained from keto amide **1a** (0.25 mmol, 51 mg). Yield: 46 mg, 57%. Yellow oil. $[\alpha]_D^{25}$ = +38.2 (*c* 0.2, CH_2Cl_2, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.79 (m, 3H), 2.36 (s, 3H), 2.69 (dt, *J* = 11.6, 6.3 Hz, 1H), 3.58 (m, 1H), 3.65 (m, 1H), 3.72 (dt, *J* = 11.0, 6.3 Hz, 1H), 6.05 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz,

1H), 7.32–7.41 (5H), 7.63 (d, J = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2, 23.5, 26.2, 47.3, 48.0, 72.4, 85.8, 87.7, 121.8, 126.6, 128.3, 128.5, 128.6, 128.9, 129.8, 132.3, 138.1, 139.8, 168.3. IR (neat) ν 3306, 1635, 1444, 1367, 1066, 784, 692 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{21}H_{22}NO_2^+$ $[M + H]^+$ 320.1645, found 320.1644. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254, t_R = 20.7 min R enantiomer, t_R = 29.5 min S enantiomer.

(*R*)-4-(2-Fluorophenyl)-2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (3g). This compound was obtained from keto amide **1a** (0.26 mmol, 52 mg). Yield: 66 mg, 80%. Yellow oil. $[\alpha]_D^{25}$ = +40.7 (c 0.5, CH_2Cl_2, 92% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.78 (m, 3H), 2.65 (dt, J = 11.6, 6.4 Hz, 1H), 3.62 (m, 2H), 3.80 (dt, J = 10.8, 6.1 Hz, 1H), 6.09 (s, 1H), 7.12 (m, 2H), 7.31–7.41 (4H), 7.54 (td, J = 7.4, 1.8 Hz, 1H), 7.64 (d, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5, 26.1, 47.3, 48.0, 72.5, 81.0, 91.4 (d, J = 3.5 Hz), 110.7 (d, J = 15.5 Hz), 115.5 (d, J = 20.7 Hz), 124.1 (d, J = 3.7 Hz), 126.7, 128.6, 128.6 (d, J = 5.1 Hz), 128.7, 130.6 (d, J = 8.0 Hz), 133.6, 139.5, 163.1 (d, J = 251.7 Hz), 168.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.8. IR (neat) ν 3291, 1643, 1496, 1378, 1257, 1188, 1055, 762, 699 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{20}H_{19}FNO_2^+$ $[M + H]^+$ 324.1394, found 324.1401. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254, t_R = 20.2 min R enantiomer, t_R = 29.1 min S enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)-4-(2-(trifluoromethyl)phenyl)but-3-yn-1-one (3h). This compound was obtained from keto amide **1a** (0.25 mmol, 50 mg). Yield: 63 mg, 69%. Yellow oil. $[\alpha]_D^{25}$ = +45.5 (c 0.6, CH_2Cl_2, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.86 (4H), 2.52 (dt, J = 10.7, 6.8 Hz, 1H), 3.61 (m, 2H), 3.71 (dt, J = 11.6, 6.1 Hz, 1H), 6.11 (s, 1H), 7.32–7.41 (3H), 7.46 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.61 (m, 2H), 7.69 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.0, 47.1, 48.0, 72.7, 83.0, 92.0, 120.3 (q, J = 2.2 Hz), 123.5 (q, J = 273.3 Hz), 125.8 (q, J = 5.2 Hz), 126.8, 128.6, 128.7, 131.2 (q, J = 30.7 Hz), 131.6, 134.8, 139.4, 167.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.6. IR (neat) ν 3313, 1643, 1444, 1323, 1110, 769, 699 cm^{-1}. HRMS (ESI-TTOF) m/z calculated for $C_{21}H_{19}F_3NO_2^+$ $[M + H]^+$ 374.1362, found 374.1372. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 14.1 min R enantiomer, t_R = 22.7 min S enantiomer.

(*S*)-4-(2-Fluorophenyl)-2-hydroxy-2-(2-methoxyphenyl)-1-(pyrrolidin-1-yl)but-3-yn-1-one (3i). This compound was obtained from keto amide **1f** (0.26 mmol, 60 mg). Yield: 65 mg, 71%. Yellow oil. $[\alpha]_D^{25}$ = +57.5 (c 0.2, CH_2Cl_2, 92% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–1.88 (4H), 2.44 (m, 1H), 3.54–3.69 (3H), 3.77 (s, 3H), 5.93 (s, 1H), 6.88 (dt, J = 8.3, 1.0 Hz, 1H), 7.01 (tt, J = 7.5, 1.0 Hz, 1H), 7.10 (m, 2H), 7.33 (m, 2H), 7.52 (td, J = 7.3, 1.7 Hz, 1H), 8.04 (ddd, J = 7.7, 1.7, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.2, 47.3, 47.8, 55.8, 71.3, 80.2, 92.2 (d, J = 3.5 Hz), 110.8 (d, J = 15.5 Hz), 111.8, 115.4 (d, J = 20.7 Hz), 120.8, 124.0 (d, J = 3.7 Hz), 127.7, 130.0, 130.3, 130.5 (d, J = 8.0 Hz), 133.6 (d, J = 1.1 Hz), 157.0, 163.1 (d, J = 251.7 Hz), 168.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.8 (m, 1F). IR (neat) ν 3324, 1650, 1492, 1250, 1063, 919, 758, 725 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{20}FNNaO_3^+$ $[M + Na]^+$ 376.1319, found 376.1325. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 21.8 min S enantiomer, t_R = 29.0 min R enantiomer.

(*S*)-4-(3-Chlorophenyl)-2-hydroxy-2-(2-methoxyphenyl)-1-(pyrrolidin-1-yl)but-3-yn-1-one (3j). This compound was obtained from keto amide **1f** (0.28 mmol, 65 mg). Yield: 78 mg, 76%. Colorless oil. $[\alpha]_D^{25}$ = +36.6 (c 0.3, CH_2Cl_2, 86% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (m, 3H), 1.86 (tdd, J = 10.4, 5.6, 3.3 Hz, 1H), 2.47 (m, 1H), 3.53 (ddd, J = 7.2, 6.3, 3.3 Hz, 1H), 3.58 (m, 1H), 3.66 (dt, J = 11.7, 7.1 Hz, 1H), 3.77 (s, 3H), 5.91 (s, 1H), 6.89 (dd, J = 8.3, 1.1 Hz, 1H), 7.02 (td, J = 7.5, 1.1 Hz, 1H), 7.28 (m, 1H), 7.34 (m, 2H), 7.410 (dt, J = 7.6, 1.4 Hz, 1H), 7.49 (td, J = 1.8, 0.5 Hz, 1H), 7.97 (dd, J = 7.7, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.4, 47.3, 47.7, 55.8, 71.2, 85.3, 88.2, 111.9, 120.7, 123.8, 127.6, 129.0, 129.6, 129.7, 130.0, 130.4, 131.6, 134.1, 157.0, 168.1. IR (neat) ν 3320, 1654, 1371, 1254, 1055, 923, 725, 677 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{21}H_{20}ClNNaO_3^+$ $[M + Na]^+$ 392.1024, found 392.1033. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 18.3 min S enantiomer, t_R = 21.1 min R enantiomer.

(*R*)-2-Hydroxy-2,6-diphenyl-1-(pyrrolidin-1-yl)hex-3-yn-1-one (3k). This compound was obtained from keto amide **1a** (0.25 mmol, 50 mg). Yield: 76 mg, 93%. Colorless oil. $[\alpha]_D^{25}$ = +59.9 (c 0.7, CH_2Cl_2, 74% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (dt, J = 12.4, 6.6 Hz, 1H), 1.57–1.78 (3H), 2.40 (dt, J = 10.9, 6.8 Hz, 1H), 2.71 (td, J = 7.2, 3.6 Hz, 2H), 2.92 (td, J = 7.2, 2.3 Hz, 2H), 3.28 (dt, J = 10.8, 6.6 Hz, 1H), 3.52 (m, 2H), 5.96 (s, 1H), 7.20–7.32 (8H), 7.40–7.44 (2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 23.4, 26.0, 34.4, 47.0, 47.8, 71.9, 78.1, 87.6, 126.3, 126.6, 139.9, 140.2, 168.5. IR (neat) ν 3331, 2961, 1646, 1437, 1375, 1146, 688 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{22}H_{23}NNaO_2^+$ $[M + Na]^+$ 356.1621, found 356.1616. HPLC: Phenomenex Lux Cellulose-1, hexane : ^{i}PrOH 85 : 15, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 17.3 min R enantiomer, t_R = 15.0 min S enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)-4-(trimethylsilyl)but-3-yn-1-one (3l). This compound was obtained from keto amide **1a** (0.27 mmol, 54 mg). Yield: 74 mg, 92%. Colorless oil. $[\alpha]_D^{25}$ = +75.2 (c 0.5, CH_2Cl_2, 84% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 9H), 1.64 (m, 1H), 1.77 (m, 3H), 2.56 (dt, J = 10.7, 6.6 Hz, 1H), 3.55 (ddd, J = 12.2, 7.7, 5.9 Hz, 1H), 3.62 (m, 1H), 3.67 (m, 1H), 5.93 (s, 1H), 7.30–7.37 (3H), 7.53 (dd, J = 8.2, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.22, 23.5, 26.0, 47.3, 47.9, 72.2, 92.9, 101.9, 126.6, 128.5, 128.5, 139.4, 168.0. IR (neat) ν 3328, 2961, 1632, 1356, 1243, 1077, 835, 765, 699 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{23}NNaO_2Si^+$ $[M + Na]^+$ 324.1390, found 324.1403. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 12.5 min R enantiomer, t_R = 17.2 min S enantiomer.

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)pent-3-yn-1-one (3m). This compound was obtained from keto amide **1a** (0.26 mmol, 52 mg). Yield: 85 mg, 89%. Colorless oil. $[\alpha]_D^{25}$ = +47.3 (c 0.6, CH_2Cl_2, 82% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.63 (m, 1H), 1.76 (m, 3H), 2.56 (m, 1H), 3.57 (m, 2H), 3.67 (dt, J = 10.7, 6.5 Hz, 1H), 4.45 (d, J = 16.1 Hz, 1H), 4.50 (d, J = 16.1 Hz, 1H), 5.95 (s, 1H), 7.29–7.37 (3H), 7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.2, 18.1, 25.7, 26.1, 47.2, 47.9, 51.8, 72.0, 81.6, 86.4, 126.6, 128.5, 128.5, 139.5, 168.1. IR (neat) ν 3331, 2935, 1639, 1375, 1088, 824, 773, 684 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{21}H_{31}NNaO_3Si^+$ $[M + Na]^+$ 396.1965, found 396.1976. HPLC: Phenomenex Lux Cellulose-2, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 27.2 min R enantiomer, t_R = 15.7 min S enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)dec-3-yn-1-one (3n). This compound was obtained from keto amide **1a** (0.26 mmol, 52 mg). Yield: 47 mg, 59%. Colorless oil. $[\alpha]_D^{25}$ = +50.3 (c 0.3, CH_2Cl_2, 78% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.31 (m, 4H), 1.43 (m, 2H), 1.57–1.68 (3H), 1.69–1.85 (3H), 2.36 (td, J = 7.1, 2.5 Hz, 2H), 2.55 (dt, J = 11.4, 6.9 Hz, 1H), 3.61 (m, 3H), 5.94 (s br, 1H), 7.29–7.37 (3H), 7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.9, 22.5, 23.5, 26.1, 28.4, 28.6, 31.2, 47.2, 47.8, 72.0, 77.2, 88.7, 126.6, 128.3, 128.4, 140.1, 168.8. IR (neat) ν 3324, 2935, 1635, 1433, 1371, 1140, 765, 695 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{20}H_{27}NNaO_2^+$ $[M + Na]^+$ 336.1934, found 336.1935. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 11.5 min R enantiomer, t_R = 8.5 min S enantiomer.

(*R*)-2-Hydroxy-2-phenyl-1-(pyrrolidin-1-yl)oct-3-yn-1-one (3o). This compound was obtained from keto amide **1a** (0.27 mmol, 55 mg). Yield: 60 mg, 78%. Colorless oil. $[\alpha]_D^{25}$ = +53.8 (c 0.4, CH_2Cl_2, 78% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.46 (m, 2H), 1.56–1.66 (3H), 1.69–1.84 (3H), 2.36 (td, J = 7.1, 2.2 Hz, 2H), 2.54 (dt, J = 11.2, 6.8 Hz, 1H), 3.55 (ddd, J = 12.0, 7.7, 5.8 Hz, 1H), 3.60 (m, 1H), 3.65 (m, 1H), 5.92 (s br, 1H), 7.28–7.36 (3H), 7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.6, 22.0, 23.5, 26.1, 30.5, 47.2, 47.8, 72.0, 77.2, 88.6, 126.6, 128.3, 128.5, 140.1, 168.8; IR (neat) ν 3324, 2957, 1632, 1437, 1375, 1132, 1044, 762, 692 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{23}NNaO_2^+$ $[M + Na]^+$ 308.1621, found 308.1641. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 13.6 min R enantiomer, t_R = 8.8 min S enantiomer.

(*R*)-4-Cyclopropyl-2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)but-3-yn-1-one (3p). This compound was obtained from keto amide **1a** (0.24 mmol, 50 mg). Yield: 62 mg, 94%. Colorless oil. $[\alpha]_D^{25}$ = +54.4 (c 0.5, CH_2Cl_2, 74% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (m, 2H), 0.84 (m, 2H), 1.39 (tt, J = 8.2, 5.1 Hz, 1H), 1.62 (m, 1H), 1.76 (m, 3H), 2.55 (m, 1H), 3.53 (m, 1H), 3.60 (m, 2H), 5.90 (s, 1H), 7.26–7.35 (3H), 7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.36, 8.36, 8.39, 23.5, 26.1, 47.2, 47.8, 71.9, 72.3, 91.5, 126.6, 128.3, 128.4, 140.1, 168.7; IR (neat) ν 3361, 2953, 1617, 1433, 1367, 1059, 916, 706 cm^{-1}; HRMS (ESI-TOF) m/z calculated for $C_{17}H_{19}NNaO_2^+$ $[M + Na]^+$ 292.1308, found 292.1311. HPLC: Chiralpak AD-H, hexane : ^{i}PrOH 80 : 20, flow rate = 1 mL min^{-1}, λ = 254 nm, t_R = 17.6 min R enantiomer, t_R = 12.0 min S enantiomer.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article are available within the article and its supplementary information (SI). Supplementary information: preparation and characterization data of starting α-keto amides, copies of NMR spectra and chromatograms of new compounds and crystallographic data for **2a**. See DOI: https://doi.org/10.1039/d5ob01546d.

CCDC 2391708 (**2a**) contains the supplementary crystallographic data for this paper.[30]

Acknowledgements

The authors thank Junta de Castilla y León (projects FEDER-VA115P17 and VA149G18) for financial support. The authors also thank Dr José M. Martín-Álvarez for his assistance in the determination of the X-ray structure.

References

1 M. Mizutani, S. Yasuda and C. Mukai, *Chem. Commun.*, 2014, **50**, 5782–5785.
2 M. C. Nakhla and J. L. Wood, *J. Am. Chem. Soc.*, 2017, **139**, 18504–18507.
3 H. Takayama, Y. Matsuda, K. Masubuchi, A. Ishida, M. Kitajima and N. Aimi, *Tetrahedron*, 2004, **60**, 893–900.
4 (*a*) S. L. Shapiro, I. M. Rose and L. Freedman, *J. Am. Chem. Soc.*, 1959, **81**, 6322–6329; (*b*) P. J. Jones, Y. Wang, M. D. Smith, N. J. Hargus, H. S. Eidam, H. S. White, J. Kapur, M. L. Brown and M. K. Patel, *J. Pharmacol. Exp. Ther.*, 2007, **320**, 828–836.
5 (*a*) D. Chen, H. Y. Chow, K. H. L. Po, W. Ma, E. L. Y. Leung, Z. Sun, M. Liu, S. Chen and X. Li, *Org. Lett.*, 2019, **21**, 5639–5644; (*b*) M. Terreni, J. G. Tchamkam, U. Sarnataro, S. Rocchietti, R. Fernández-Lafuente and J. M. Guisán, *Adv. Synth. Catal.*, 2005, **347**, 121–128; (*c*) T. Komori and H. Sakaguchi, WO2004016594, 2004, Sumitomo Chemical Company; (*d*) N. Matsumoto, I. Momose, M. Umekita, N. Kinoshita, M. Chino, H. Iinuma, T. Sawa, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1998, **51**, 1087–1092.
6 S.-J. Yu, C. Zhu, Q. Bian, C. Cui, X.-J. Du, Z.-M. Li and W.-G. Zhao, *ACS Comb. Sci.*, 2014, **16**, 17–23.
7 H. Schäcke, A. Schottelius, W.-D. Döcke, P. Strehlke, S. Jaroch, N. Schmees, H. Rehwinkel, H. Hennekes and K. Asadullah, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 227–232.
8 (*a*) B. P. Klaholz, J.-P. Renaud, A. Mitschler, C. Zusi, P. Chambon, H. Gronemeyer and D. Moras, *Nat. Struct. Biol.*, 1998, **5**, 199–202; (*b*) M. Belema, F. C. Zusi and

K. M. Tramposch, WO0016769, 2000, Bristol Myers Squibb Co.

9 (*a*) D. Masiello, S. Cheng, G. J. Bubley, M. L. Lu and S. P. Balk, *J. Biol. Chem.*, 2002, **277**, 26321–26326; (*b*) M. C. Hodgson, I. Astapova, A. N. Hollenberg and S. P. Balk, *Cancer Res.*, 2007, **67**, 8388–8395.

10 T. Punniyamurthy and J. Iqbal, *Tetrahedron Lett.*, 1997, **38**, 4463–4466.

11 T. Hiruma, K. Kobayashi and S. Inomata, WO03020711, 2003.

12 (*a*) N. Blaquiere, G. M. Castanedo, J. D. Burch, L. M. Berezhkovskiy, H. Brightbill, S. Brown, C. Chan, P. C. Chiang, J. J. Crawford, T. Dong, P. Fan, J. Feng, N. Ghilardi, R. Godemann, E. Gogol, A. Grabbe, A. J. Hole, B. Hu, S. G. Hymowitz, M. H. A. Ismaili, H. Le, P. Lee, W. Lee, X. Lin, N. Liu, P. A. McEwan, B. McKenzie, H. L. Silvestre, E. Suto, S. Sujatha-Bhaskar, G. Wu, L. C. Wu, Y. Zhang, Z. Zhong and S. T. Staben, *J. Med. Chem.*, 2018, **61**, 6801–6813; (*b*) N. Blaquiere, J. Burch, G. Castanedo, J. A. Feng, B. Hu, S. Staben, G. Wu and P. Yen, WO2015025025, 2015, Hoffmann-La Roche; Genentech, Inc.

13 (*a*) V. Pastore, L. Sabatier, A. Enrique, M. Marder and L. E. Bruno-Blanch, *Bioorg. Med. Chem.*, 2013, **21**, 841–846; (*b*) C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf and R. Zeun, *Bioorg. Med. Chem.*, 2008, **16**, 1531–1545; (*c*) J. H. George and R. M. A. Adlington, *Synlett*, 2008, 2093–2096; (*d*) R. Peters, M. Althaus and A.-L. Nagy, *Org. Biomol. Chem.*, 2006, **4**, 498–509.

14 (*a*) G. Blay, I. Fernandez, V. Hernández-Olmos, A. Marco-Aleixandre and J. R. Pedro, *Tetrahedron: Asymmetry*, 2005, **16**, 1953–1958; (*b*) G. Blay, L. Cardona, I. Fernández, A. Marco-Aleixandre, M. C. Muñoz and J. R. Pedro, *Org. Biomol. Chem.*, 2009, **7**, 4301–4308; (*c*) P. Geoghegan and P. O'Leary, *ACS Catal.*, 2012, **2**, 573–591.

15 (*a*) M. Huang, S. Zhong, M. Xu and Y. Liu, *J. Chem. Res.*, 2015, **39**, 274–276.

16 (*a*) T. Kanda, A. Naraoka and H. Naka, *J. Am. Chem. Soc.*, 2019, **141**, 825–830; (*b*) P. Crochet and V. Cadierno, *Eur. J. Inorg. Chem.*, 2021, 3225–3238.

17 (*a*) C. Sappino, A. Mari, A. Mantineo, M. Moliterno, M. Palagri, C. Tatangelo, L. Suber, P. Bovicelli, A. Ricelli and G. Righi, *Org. Biomol. Chem.*, 2018, **16**, 1860–1870; (*b*) H. Kakei, T. Nemoto, T. Ohshima and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2004, **43**, 317–320; (*c*) V. K. Aggarwal, G. Hynd, W. Picoul and J.-L. Vasse, *J. Am. Chem. Soc.*, 2002, **124**, 9964–9965; (*d*) T. Nemoto, H. Kakei, V. Gnanadesikan, S.-Y. Tosaki, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2002, **124**, 14544–14545.

18 (*a*) S. E. Denmark and Y. Fan, *J. Org. Chem.*, 2005, **70**, 9667–9676; (*b*) L. Moni, L. Banfi, D. Cartagenova, A. Cavalli, C. Lambruschini, E. Martino, R. V. A. Orru, E. Ruijter, J. M. Saya, J. Sgrignani and R. Riva, *Org. Chem. Front.*, 2020, **7**, 380–398; (*c*) S. E. Denmark and Y. Fan, *J. Am. Chem. Soc.*, 2003, **125**, 7825–7827.

19 (*a*) A. Westerbeek, W. Szymański, B. L. Feringa and D. B. Janssen, *ACS Catal.*, 2011, **1**, 1654–1660; (*b*) T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata and I. Shiina, *Molecules*, 2018, **23**, 2003; (*c*) W. Szymanski and R. Ostaszewski, *J. Mol. Catal. B: Enzym.*, 2007, **47**, 125–128; (*d*) S.-S. Weng, M.-W. Shen, J.-Q. Kao, Y. S. Munot and C. T. Chen, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 3522–3527.

20 (*a*) F.-H. Zhang, C. Wang, J.-H. Xie and Q.-L. Zhou, *Adv. Synth. Catal.*, 2019, **361**, 2832–2835; (*b*) R. Agarwal, Y. Liao, D.-J. Lin, Z.-X. Yang, C.-F. Lai and C.-T. Chen, *Org. Chem. Front.*, 2020, **7**, 2505–2510; (*c*) S. K. Gediya, V. K. Vyas, G. J. Clarkson and M. Wills, *Org. Lett.*, 2021, **23**, 7803–7807; (*d*) N. C. Mamillapalli and G. Sekar, *Chem. – Eur. J.*, 2015, **21**, 18584–11858; (*e*) B. Ma, T. Miao, Y. Sun, Y. He, J. Liu, Y. Feng, H. Chen and Q.-H. Fan, *Chem. – Eur. J.*, 2014, **20**, 9969–9978; (*f*) S. Stella and A. Chadha, *Catal. Today*, 2012, **198**, 345–352.

21 (*a*) P. Brandão and A. J. Burke, *Tetrahedron*, 2018, **74**, 4927–4957; (*b*) Z.-Y. Cao, F. Zhou and J. Zhou, *Acc. Chem. Res.*, 2018, **51**, 1443–1454; (*c*) A. Kumar and S. S. Chimni, *RSC Adv.*, 2012, **2**, 9748–9762.

22 (*a*) R. Di Sanza, T. L. N. Nguyen, N. Iqbal, S. P. Argent, W. Lewis and H. W. Lam, *Chem. Sci.*, 2020, **11**, 2401–2406; (*b*) L. Wang, Q. Ni, M. Blümel, T. Shu, G. Raabe and D. Enders, *Chem. – Eur. J.*, 2015, **21**, 8033–8037; (*c*) A.-B. Xia, G.-J. Pan, C. Wu, X.-L. Liu, X.-L. Zhang, Z.-B. Li, X. H. Du and D.-Q. Xu, *Adv. Synth. Catal.*, 2016, **358**, 3155–3160; (*d*) M. Hatano and T. Nishimura, *Angew. Chem., Int. Ed.*, 2015, **54**, 10949–10952; (*e*) C. Joie, K. Deckers, G. Raabe and D. Ender, *Synthesis*, 2014, 1539–1546; (*f*) C. Joie, K. Deckers and D. Enders, *Synthesis*, 2014, 799–808; (*g*) S. Goudedranche, D. Pierrot, T. Constantieux, D. Bonne and J. Rodriguez, *Chem. Commun.*, 2014, **50**, 15605–15608; (*h*) T. Shirai, H. Ito and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2014, **53**, 2658–2661; (*i*) L. Yin, M. Kanai and M. A. Shibasaki, *Angew. Chem., Int. Ed.*, 2011, **50**, 7620–7623; (*j*) L. Zhen, S. Tong, J. Zhu and M.-X. Wang, *J. Org. Chem.*, 2020, **85**, 13211–13219; (*k*) H. Yang, W. Li, X.-M. Xu and Z.-L. Wang, *Org. Lett.*, 2020, **22**, 8814–8818; (*l*) X.-M. Xu, L. Zhao, J. Zhu and M.-X. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 3799–3803; (*m*) L. Zhen, S. Tong, J. Zhu and M.-X. Wang, *Chem. – Eur. J.*, 2020, **26**, 401–405; (*n*) X.-M. Xu, M. Xie, J. Li and M.-X. Wang, *Org. Chem. Front.*, 2021, **8**, 721–726; (*o*) L. Yang, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *J. Am. Chem. Soc.*, 2009, **131**, 10390–10391.

23 (*a*) H. Echave, R. López and C. Palomo, *Angew. Chem., Int. Ed.*, 2016, **55**, 3364–3368; (*b*) K. Kon, H. Takai, T. Kobayashi, Y. Kohari and M. Murata, *Synlett*, 2021, 829–832; (*c*) W. Luo, J. Zhao, J. Ji, L. Lin, X. Liu, H. Mei and X. Feng, *Chem. Commun.*, 2015, **51**, 10042–10045; (*d*) H. Xu and C. Wolf, *Angew. Chem., Int. Ed.*, 2011, **50**, 12249–12252.

24 (*a*) R. Infante, A. Gago, J. Nieto and C. Andrés, *Adv. Synth. Catal.*, 2012, **354**, 2797–2804; (*b*) R. Infante, J. M. Martín-Alvarez, C. Andrés and J. Nieto, *Org. Lett.*, 2017, **19**, 1516–

1519; (*c*) E. Prieto, J. D. Martín, J. Nieto and C. Andrés, *Org. Biomol. Chem.*, 2023, **21**, 6940–6948.

25 The diastereoselective version of this reaction has been previously described: S. W. Youn, Y. H. Kim, J.-W. Hwang and Y. Do, *Chem. Commun.*, 2001, 996–997.

26 For reviews of enantioselective alkynylation of carbonyl compounds, see: (*a*) B. M. Trost and A. H. Weiss, *Adv. Synth. Catal.*, 2009, **351**, 963–983; (*b*) V. Bisai and V. K. Singh, *Tetrahedron Lett.*, 2016, **57**, 4771–4784.

27 H.-B. Chen, W.-H. Lai, Y. Zhao, D.-D. Qin, Y.-P. Ruan and Z.-H. Zhou, *Synlett*, 2014, 809–812.

28 Racemic **2b** has been previously described: K. Dhara, A. Kapat, T. Ghosh and J. Dash, *Synthesis*, 2016, 4260–4268.

29 Racemic **2d** has been previously described: D. Tejedor, L. Cotos and F. García-Tellado, *Org. Lett.*, 2011, **13**, 4422–4425.

30 CCDC 2391708: Experimental Crystal Structure Determination, 2025, DOI: 10.5517/ccdc.csd.cc2l8rwj.