Organocatalytic hydration of activated alkynes

Authors: Jorge González-Rodríguez[1]†, Sergio González-Granda[1]††, Iván Lavandera[1], Vicente Gotor-Fernández[1], Juan Mangas-Sánchez[1]*

Affiliations:

[1] Organic and Inorganic Chemistry Department, School of Chemistry

Avenida Julián Clavería 8. 33306 Oviedo, Spain

†Current address: Institute of Applied Synthetic Chemistry, Vienna University of Technology

Getreidemarkt 9/163-OC, 1060 Vienna, Austria

††Current address: Chemistry Department, University of Michigan

930 N University Ave, Ann Arbor, MI 48109, USA

*Corresponding author. Email: mangasjuan@uniovi.es.

Abstract: Hydration reactions consist of the introduction of a molecule of water into a chemical compound. This process is a particularly useful method to allow, for instance, the conversion of alkynes into carbonyls, which are strategic intermediates in the synthesis of a plethora of compounds. Herein we demonstrate that L-cysteine can catalyse the hydration of activated alkynes in a very effective and fully regioselective manner to access β-ketosulfones, amides and esters in aqueous conditions. The mild reaction conditions facilitated the integration with enzyme catalysis to access chiral β-hydroxy sulfones from the corresponding alkynes in a one-pot cascade process in good yields and excellent enantiomeric excess. These findings pave the way towards establishing a general method for metal-free, cost-effective, and more sustainable alkyne hydration processes.

Introduction: Carbonyl compounds play a pivotal role in organic chemistry due to their remarkable synthetic versatility, serving as fundamental building blocks for a wide range of industrially relevant chemicals that we encounter in our daily lives. Among the different strategies employed to access this moiety, the addition of water to alkynes, known as alkyne hydration, stands out as a straightforward and atom-economical method.(*1*) Since Kutscheroff's discovery in 1881, which demonstrated that Hg salts can catalyse the hydration of alkynes under mild conditions,(*2*) significant progress has been made employing catalytic strategies (Fig.1A).(*3*) Transition metal species have emerged as key catalysts,(*4*) with special emphasis in recent years on Au salts due to their high capability to activate triple bonds, selectivity and ability to operate under mild conditions.(*5*–*8*) Particularly, significant progress has been achieved in the hydration of activated alkynes using Au species to obtain highly valuable α-functionalised ketones.(*9*–*16*) Despite these remarkable advances, these methods rely on the use precious metals, which are expensive, scarce and unsustainable. Moreover, these processes typically involve the extensive use of large amounts of oil-derived organic solvents and exhibit a lack of regioselectivity, leading to laborious downstream processes and low yields. Therefore, there is a pressing need to explore metal-free alternatives for this transformation from both economic and sustainability perspectives. The discovery and development of such alternatives would offer a potential substitution for existing methods and would allow the mitigation of the environmental impact associated with transition metal-based chemistry. In the pursuit of metal-free strategies, the use of catalytic amounts of different acids has also been extensively implemented.(*3*, *17*) Examples include the use of triflic acid and other Brønsted acids such as trifluorosulfonimide to hydrate non-functionalised alkynes,(*18*) tetrafluoroboric acid to access α-halomethylketones,(*19*) or the use of anion exchange resins.(*20*) Generally, high temperatures and harsh reaction conditions are

required which leads to low functional group compatibility. Furthermore, some enzymes can also catalyse the addition of water to alkynes. For instance, the acetylene hydratase from *Pelobacter acetylenicus* is a tungsten iron-sulfur protein that catalyses the non-redox conversion of acetylene to acetaldehyde.(*21*–*23*) The restricted substrate scope of this enzyme significantly diminishes its general applicability in synthetic chemistry.

In the last two decades, the use of small organic molecules such as amino acids as catalysts – known as organocatalysis – has emerged as a powerful technology in organic chemistry to provide access to a broad variety of functional groups, in many cases under sustainable conditions.(*24*–*29*) Here, we present a highly regioselective and efficient approach to produce β-ketosulfones, amides and esters from the corresponding alkynes via hydration using L-cysteine as the catalyst under aqueous and mild reaction conditions.

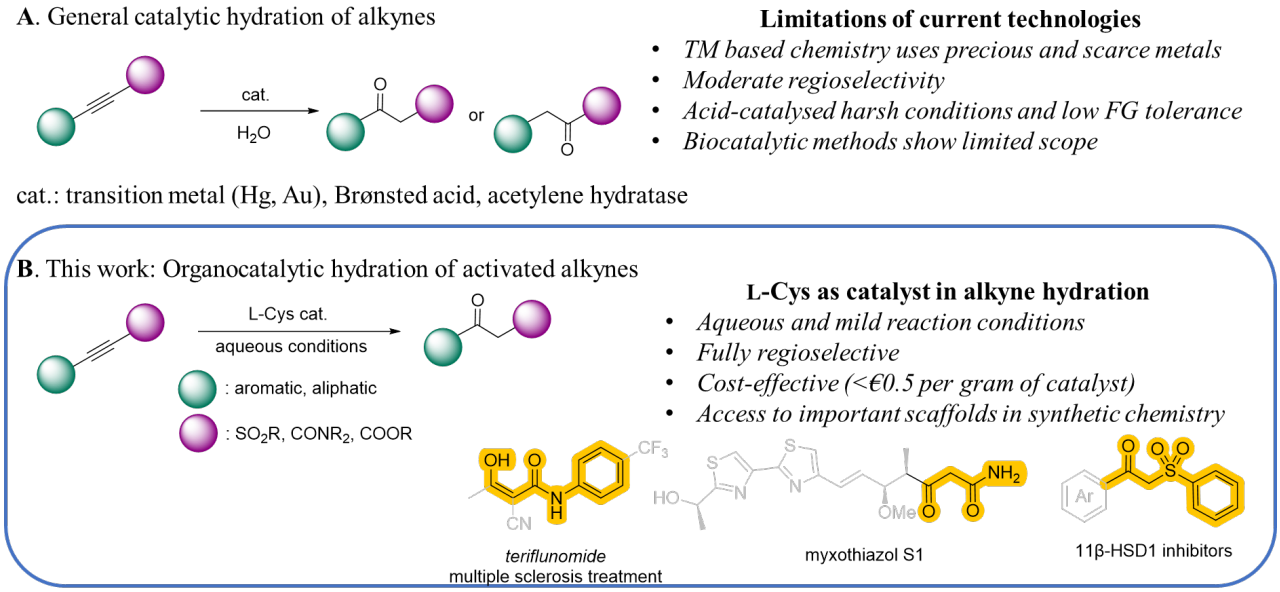


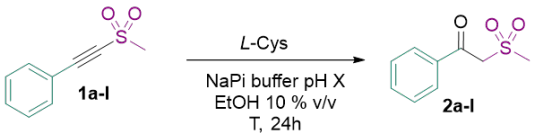
Fig. 1. Strategies for the catalytic hydration of alkynes. (**A**) General scheme of the incorporation of a water molecule (i.e., hydration) into alkynes to form carbonyl compounds through different catalytic strategies. (**B**) In this work, the use of catalytic amounts of L-cysteine to effectively hydrate activated alkynes to access β-ketosulfones, amides and esters is reported.

Results and discussion: Alkynes are important platform chemicals in synthetic chemistry as they serve as starting materials to produce a variety of functional groups.(*11*, *30*, *31*) In our continuous search for novel biocatalytic methods to functionalise activated alkynes under mild conditions, we detected an unexpected side product when alkynylsulfone **1a(l)** was incubated under aqueous conditions in the presence of an oxidoreductase. Upon careful analysis, this product was identified as the hydration product, the corresponding β-ketosulfone **2a(l)**, albeit at a low yield. Control experiments using bovine serum albumin (BSA) confirmed the unspecific character of the reaction, observing a 40% conversion to **2a(l)** (Scheme S8). To gain deeper insight into this unexpected result, an amino acid screening to investigate the potential involvement of specific amino acids was conducted. We were pleased to find that, when employing a large excess (7 equiv.) of histidine and cysteine, 16% and 19% conversions to the hydration product were detected after 5 h., respectively (Table S1). Encouraged by these results, further optimisation involving temperature and pH studies was performed (Fig 2, full study in tables S2-S4), finding that both amino acids enable this reaction below stoichiometric ratios at pH 8 and 50 ºC. However, L-Cys proved to be a more effective catalyst, and the reaction was found to proceed in full conversion at pH 9.5 and 50 ºC at only 10 mol% loading. With the optimised conditions in hand, we started an in-depth exploration of the reaction scope. Initially, our focus

was directed towards the catalytic hydration of a range of structurally diverse alkynylsulfones **1a-g**, categorised as type **I** (methylsulfones) and **II** (phenylsulfones) according to Figure 2.

Concerning β-ketomethylsulfones **2a-c(I)**, important intermediates in the synthesis of active pharmaceutical ingredients such as apremilast, we achieved quantitative conversions across all instances employing 10 mol% of L-Cys at a temperature of 50 ºC with yields ranging from moderate to good (51-68%). Regarding the access to β-ketoarylsulfones **2a-c(II)**, we were motivated by their potential as 11β-HSD1 inhibitors.(*32*, *33*) Following a modified protocol reported by Capaldo *et al.*,(*34*) we successfully prepared a series of alkynylphenylsulfones **1a-g(II)** in good yields and subjected these substrates to organocatalytic hydration. Notably, we achieved remarkable conversions even when dealing with compounds featuring alkyl substituents, such as the instances of **2c(II)** bearing a pentyl group and **2d(II)** incorporating a cyclohexyl moiety. Using 10 mol% L-Cys at 50 °C, **2c(II)** and **2d(II)** were obtained in 78 and 70% isolated yields, respectively. Hydration of arylalkynes presenting both electron-withdrawing and electron-donating groups **1e-g(II)** proved to be more challenging. For instance, a 3% conversion was only obtained after 24h using 10 mol% L-Cys in the hydration of *p*-CF_3-phenylalkyne **1f(II)**. Higher temperatures led to the formation of several side products, therefore higher catalyst loadings were studied instead (Fig S9). Using 40 mol% L-Cys, a 54% conversion to **2f(II)** was observed. Similar behaviour was observed for both *m*-MeO **2e(II)** and *p*-Br **2g(II)** derivatives, finding low conversion values after 24h using 10 mol% catalyst. Good to excellent conversions were found at higher loadings and temperatures, affording **2e(II)** and **2g(II)** in 60 and 57% isolated yields, respectively (40 mol% L-Cys, 50 °C).

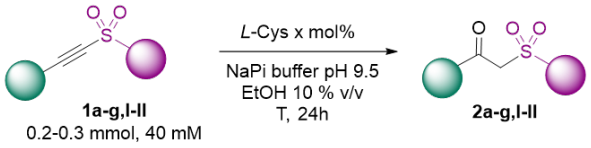
Initial investigations

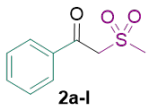


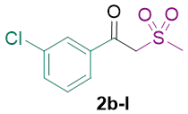
Entry	L-Cys (mol%)	T (°C)	pH	Conv. (%)[a]
1	700	40	7	45
2	700	50	7	62
3	700	40	8	86
4	50	50	8	>99
5	20	50	8	>99
6	10	50	8	38
7	**10**	**50**	**9.5**	**>99**
8[b]	10	50	9.5	>99

[a] Conversions detemined by ^{1}H-NMR. [b] D-Cys used instead

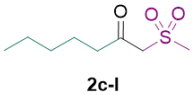
β-ketosulfone synthesis

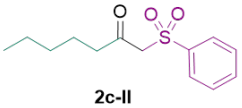


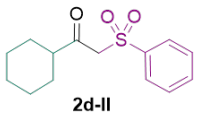

2a-I
10 mol%, 50 ºC
>99% conv., 51% yield

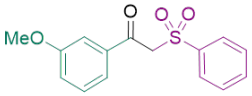


2b-I
10 mol%, 50 ºC
>99% conv., 53% yield

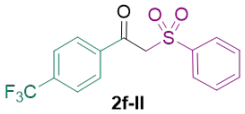

2c-I
10 mol%, 50 ºC
>99% conv., 68% yield


2c-II
10 mol%, 50 ºC,
86% conv., 78% yield

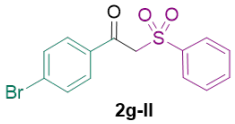

2d-II
10 mol%, 50 ºC
>99% conv., 70% yield



2e-II
10 mol% 50 ºC
26% conv.
40 mol% 60 ºC
>99% conv., 60% yield



2f-II
10 mol% 50 ºC
3% conv.
40 mol% 50 ºC
54% conv., complex mixture



2g-II
10 mol% 50 ºC
9% conv.
40 mol% 60 ºC
66% conv., 53% yield

Fig. 2. L-Cys-catalysed hydration of alkynylsulfones. Initial investigations, optimisation, and scope of the cysteine-mediated organocatalytic hydration of alkynylsulfones. Deviations from standard conditions are in bold.

Extended scope

These results prompted us to further explore this transformation by studying the hydration of other activated alkynes. Firstly, a diverse range of alkynes containing a variety of electron-withdrawing moieties, including carbonyls such as aldehyde, ketone, ester, amide and acid, as well as nitrile and chlorine as weak activators were screened. Employing stoichiometric L-Cys under optimised conditions (i.e., 100 mM KPi pH 9.5 buffer, 50 ºC, 10% vol. EtOH), we successfully identified the formation of the corresponding hydration products for both esters and amides. Unfortunately, no reaction was observed for the remaining tested scaffolds, and in the case of 3-phenylpropionaldehyde, it resulted in the decomposition of the starting material. Subsequently, we proceeded to explore the potential for β-ketoester and β-ketoamide synthesis through the means of organocatalytic alkyne hydration (Fig. 3). We initially studied the hydration of commercially available 3-phenylpropiolamide **3a(III)**, but initial attempts using a 10 mol% catalyst at 50°C yielded no conversion to the desired β-ketoamide **5a(III)**. In response, we increased the catalyst loading to 20 mol%, resulting in a modest 14% conversion to **5a(III)**. To optimise the reaction conditions further, we explored the impact of temperature (Fig. S11). To our delight, we observed excellent conversions at 80°C, ranging from 78% to over 99%, achieving an impressive 98% yield of the desired product at a 0.3 mmol scale. Then, we expanded the study to include a diverse range of *N*-substituted 3-phenylpropiolamides **3a(IV-IX)** synthesised from 3-phenylpropiolic acid incorporating aliphatic, cyclic, and aromatic amines. Remarkably, in the case of the pyrrolidine derivative **3a(V)**, no starting material was detected after 24h, obtaining **5a(V)** in 70% isolated yield. Piperonylamine derivative **3a(VIII)** was also converted into the corresponding β-ketoamide **5a(VIII)** in good conversion under the same reaction conditions (77% conversion, 62% isolated yield). We then attempted the catalytic hydration of Weinreb amide **3a(IV)**. These compounds are important intermediates that offer access to a broad range of functional groups.(*35*, *36*) Initially, a complex mixture of products was observed under standard conditions. However, by optimising the reaction parameters with lower temperatures and higher catalytic loadings (70 °C, 40 mol%) we were able to obtain **5a(IV)** in good yield (73%). Similarly, higher L-Cys loadings were necessary to obtain high conversion rates for aryl and aliphatic amides, affording **5a(VI)** and **5a(VII)** in 73 and 68% yields, respectively. Notably, the aliphatic derivative **5b(VIII)** demonstrated excellent conversion and regioselectivity, resulting in the isolation of the corresponding β-ketoamide **5b(VIII)** with a 72% yield. Unfortunately, no product formation was observed when testing the amino acid derivative **3b(IX)** under these conditions. A preparative scale reaction to test the synthetic applicability was performed starting from 10 mmol (2 g) of **3a(IV)** isolating 1.15 g of **5a(V)** (53% isolated yield).

We next turned our attention towards β-ketoesters which are fundamental synthons in organic chemistry.(*37*–*39*) Preliminary experiments starting from commercially available methyl ester **4a(X)** using stoichiometric catalyst showed that L-Cys can also facilitate this transformation. However, under catalytic conditions (pH 9.5, 50 °C, 10 mol% L-Cys), 3-phenylpropiolic acid was detected as the sole product. As a result, we prepared a series of aliphatic esters in increasing order of resistance to alkaline hydrolysis. The isopropyl derivative **4a(XII)** emerged as the most promising substrate and, after a thorough optimisation (Figs S12 and S13), catalytic alkyne hydration was achieved with an impressive >99% conversion rate, employing 40 mol% L-Cys at 70°C while yielding negligible amounts of 3-phenylpropiolic acid. In this manner, the corresponding β-ketoester **6a(XII)** was afforded in 76% isolated yield. Furthermore, these optimised conditions also enabled the synthesis of the octyl derivative **6b(XII)** in a remarkable 82% isolated yield.

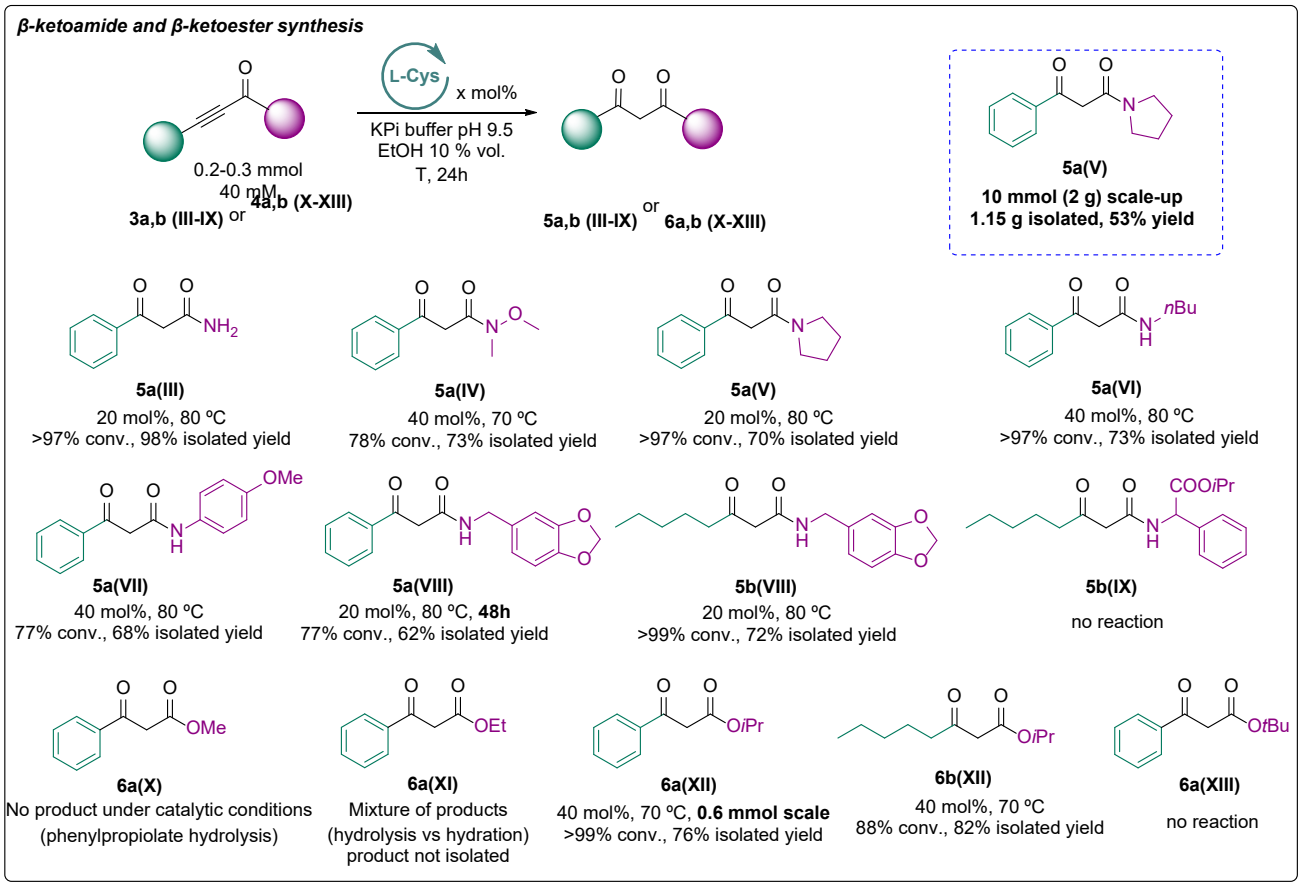


Fig. 3. β-ketoamide and β-ketoester synthesis via organocatalytic hydration of activated alkynes. Conversions determined by ^{1}H-NMR over the reaction crudes after 24h. Isolated yields after flash chromatography purification.

Mechanistic investigations

To shed light on the possible reaction pathway, we carried out mechanistic studies beginning with isotope labeling experiments whereby alkynylsulfone **1a(I)** was subjected to hydration using H_2O^{18} and stoichiometric L-Cys, resulting in **2a(I)** obtained with high ^{18}O incorporation. Complementary, no difference in conversion rate was found when the reaction was performed under N_2 atmosphere, which is consistent with the expected oxygen atom transfer from water to the substrate. We next sought to identify possible reaction intermediates. Considering that the addition of sulfides to alkynes is well-documented,(*15*, *40*, *41*) we hypothesised that the initial step involves the addition of cysteine to the triple bond via the thiolate moiety, which is consistent with the pH dependency observed during the reaction optimisation studies (Table S3). We next probed the role of both acid and amino groups in the mechanism (Fig 4A). Control experiments using 10 mol% *N*-acetyl-Cys and Cys-OMe resulted in a significant drop in conversion (26 and 51% respectively). Interestingly, cystamine was found to catalyse the reaction with a 65% conversion rate, whereas no product was detected when 3-mercaptopropionic acid was employed. These results strongly suggest the vital contribution of the amino group to the mechanism. Notably, when homocysteine was employed as the catalyst, a substantial decrease in conversion was observed. This observation hints at the involvement of a 5-membered thiazolidine ring intermediate. Given that thiazolidine hydrolysis has previously been reported to yield carbonyls,(*42*–*44*) we propose the following reaction mechanism (Fig 4B) in which, upon

thiol 1,4-addition to **1a(l)** to form a vinyl sulfide intermediate **A**, intramolecular Michael addition involving the amino group leads to the formation of thiazolidine intermediate **B**. Subsequent ring opening yields the corresponding imine intermediate **C** which ultimately undergoes hydrolysis to yield the final hydration product **2a(l)**.

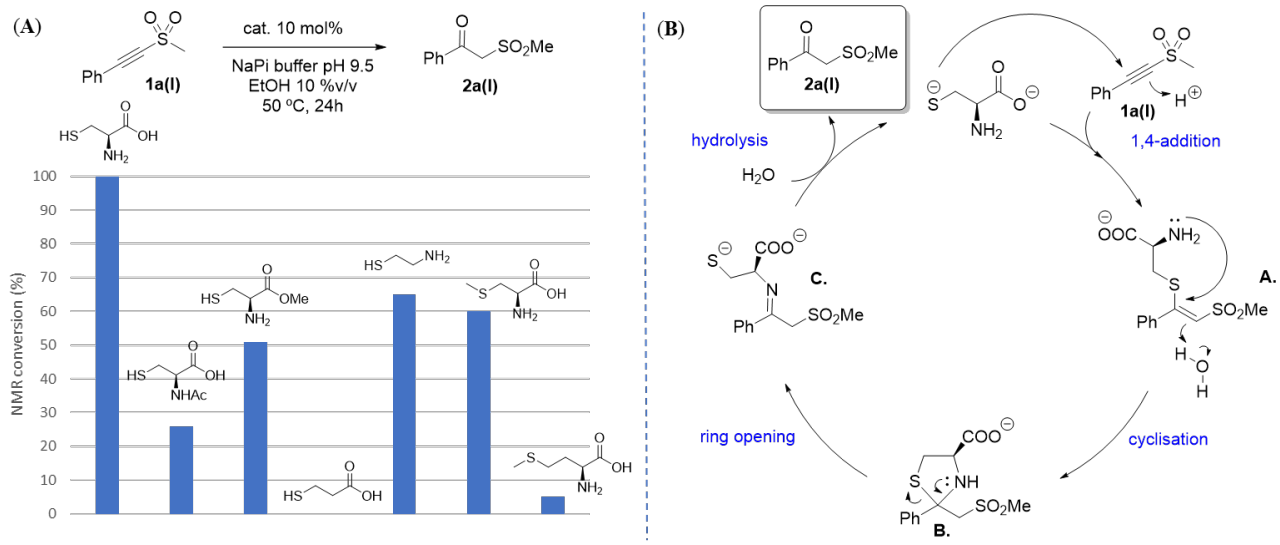


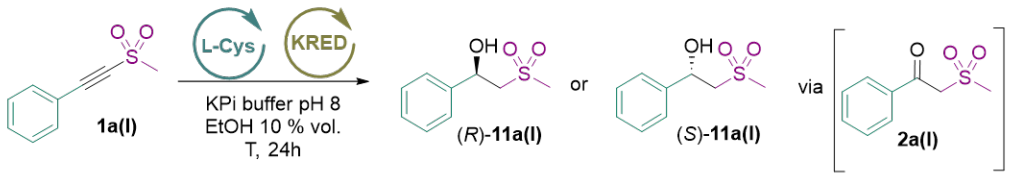
Fig 4. **Proposed mechanism.** (**A**) Catalytic performance of different species. (B) Proposed mechanism for the L-Cys mediated catalytic hydration of activated alkynes.

A chemoenzymatic cascade to access chiral β-hydroxy sulfones.

Cascade processes involve the combination of several synthetic steps within the same reaction vessel, avoiding the need for intermediate isolation and purification. The main advantage of this strategy is that it enables the construction of synthetic complexity with simpler setups.(*45–49*) With our broad experience in the construction of chemoenzymatic cascades by merging chemical and enzyme catalysis,(*46*, *50*, *51*) and considering the mild reaction conditions of the L-Cys-mediated alkyne hydration, we envisaged that the organocatalytic reaction could be combined with an enzyme-mediated asymmetric reduction process to access chiral β-hydroxy sulfones, which are important building blocks in the synthesis of different APIs such as apremilast and bicalutamide. Based on our previous report on the chemoenzymatic oxosulfonylation-bioreduction process combining catalytic amounts of $FeCl_3$ and ketoreductases (KREDs),(*52*) several KREDs from commercial sources and our in-house collection were selected and explored for the one-pot concurrent process, in which all reaction components are added at once. To our delight, commercial KREDs P1-B02 and P1-B05 from Codexis and the ADH from *Ralstonia sp.* (*Ras*ADH) yielded promising results at 40 °C, with (*R*)-**11a(l)** obtained in 32, 52 and 67% conversions, respectively. In all cases, (*R*)-**11a(l)** was obtained in >99% *ee*. We further explored temperature optimisation using *Ras*ADH, which led to enhanced conversion rates, reaching 79% at 45 °C (Table 1 Entry 6). However, attempting the reaction at even higher temperatures (Entry 7) resulted in no product formation, likely due to protein denaturation. Given the non-specific nature of the reaction, we contemplated the potential of *Ras*ADH to mediate both reactions concurrently. Remarkably, employing this single catalyst in a two-step one-pot process yielded (*R*)-**11a(l)** in >99% *ee* (Entry 5). However, the process did not proceed as effectively observing a modest 34% conversion to the final product. Under a sequential set-up, full conversion to (*R*)-**11a(l)** was obtained using P1-B05 (Entry 4). Concerning anti-Prelog KREDs, KRED-119 and KRED-P2-B02 exhibited promising results, observing (*S*)-**11a(l)** in >99 and 70% *ee*, respectively. Unfortunately, a 44% conversion to the product was only observed for KRED-P2-B02 under concurrent conditions (Entry 10), while KRED-119 showed complete inactivity in this setup. A sequential

approach was implemented instead using KRED-119, obtaining (*S*)-**11a(l)** in full conversion and >99% *ee* (Entry 15).

One-pot concurrent cascade to access chiral β-hydroxy sulfones



Entry	KRED	mode	T (°C)	**1a(l)** (%)[a]	**2a(l)** (%)[a]	**11a(l)** (%)[a]	*ee* (%)[b]
1	*Ras*ADH	C	40	30	3	67	>99 (*R*)
2	KRED-P1-B02	C	40	63	5	32	>99 (*R*)
3	KRED-P1-B05	C	40	44	4	52	>99 (*R*)
4	KRED-P1-B05	S	40	<1	<1	>99	>99 (*R*)
5[c]	*Ras*ADH	C	40	57	8	34	>99 (*R*)
6	***Ras*ADH**	**C**	**45**	**20**	**2**	**79**	**>99 (*R*)**
7	*Ras*ADH	C	50	<1	>99	<1	n.a.
8[d]	*Ras*ADH	C	45	18	23	58	>99 (*R*)
9	KRED-119	C	40	3	95	2	n.a.
10	KRED-P2-B02	C	45	41	5	44	70 (*S*)
11	KRED-119	S	45	<1	32	68	>99 (*S*)
12	KRED-P2-B02	S	45	<1	<1	>99	70 (*S*)
13	*Lb*ADH	S	45	<1	82	18	79 (*S*)
14	evo.1.1.200	S	45	<1	>99	<1	n.a.
15	**KRED-119**	**S**	**50**	**<1**	**<1**	**>99**	**>99 (*S*)**
16[d]	KRED-119	S	45	<1	64	36	99 (*S*)

Conditions: 10 mol% L-Cys, 20 mM substrate concentration, C: concurrent. S: sequential. [a] Determined by GC-FID and ^{1}H-NMR analysis. [b] Determined by HPLC using Chiralpak AD-H chiral column. [c] no L-Cys. [d] 15% vol. EtOH.

Table 1. One-pot cascade combining L-Cys-catalysed hydration of alkynylsulfones followed by a bioreduction step.

In summary, we have found that L-Cys enables the incorporation of a molecule of water into activated alkynes in a very effective manner. This groundbreaking discovery brings significant advantages in terms of both economics and sustainability. At a mere cost of less than €0.5 per gram of catalyst, this approach exhibits significant promise as a more economical and environmentally friendly alternative to existing strategies. The synthetic potential is demonstrated through the successful preparation of a wide array of β-ketosulfones, amides and esters in good to excellent yields. Moreover, the bio-compatible conditions also facilitate the effective integration with ketoreductases, allowing streamlined access to synthetically relevant chiral β-hydroxy sulfones from the corresponding alkynes in a two-step one-pot process. We believe our results will inspire the search for novel catalytic species to develop metal-free strategies for general alkyne hydration under mild reaction conditions.

References

1. B. M. Trost, Times to The Atom Economy - A Search for Synthetic Efficiency. *Science*. **254**, 1471–1477 (1991).
2. M. Kutscheroff, Über eine neue methode direkter addition von wasser (hydratation) an die kohlenwasserstoffe der acetylenreihe. *Ber. Dtsch. Chem. Ges.* **14**, 1540–1542 (1981).
3. L. Hintermann, A. Labonne, Catalytic hydration of alkynes and its application in synthesis. *Synthesis*, 1121–1150 (2007).

4. R. Salvio, M. Bassetti, Sustainable hydration of alkynes promoted by first row transition metal complexes. Background, highlights and perspectives. *Inorganica Chim. Acta*. **522**, 120288 (2021).

5. A. S. K. Hashmi, Homogeneous catalysis by gold. *Gold Bull.* **37**, 51–65 (2004).

6. R. P. Herrera, M. C. Gimeno, Main Avenues in Gold Coordination Chemistry. *Chem. Rev.* **121**, 8311–8363 (2021).

7. A. Mariconda, M. Sirignano, R. Troiano, S. Russo, P. Longo, N-Heterocyclic Carbene Gold Complexes Active in Hydroamination and Hydration of Alkynes. *Catalysts*. **12**, 836 (2022).

8. P. Gao, M. Szostak, Hydration reactions catalyzed by transition metal–NHC (NHC = N-heterocyclic carbene) complexes. *Coord. Chem. Rev.* **485**, 215110, (2023).

9. L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, Gold-catalyzed hydration of haloalkynes to α-halomethyl ketones. *J. Org. Chem.* **78**, 9190–9195 (2013).

10. L. Xie, R. Yuan, R. Wang, Z. Peng, J. Xiang, W. He, Gold(I)-catalyzed hydration of alkynylphosphonates: Efficient access to β-ketophosphonates. *Eur. J. Org. Chem.* **2014**, 2668–2671 (2014).

11. S. González-Granda, L. Escot, I. Lavandera, V. Gotor-Fernández, Unmasking the Hidden Carbonyl Group Using Gold(I) Catalysts and Alcohol Dehydrogenases: Design of a Thermodynamically-Driven Cascade toward Optically Active Halohydrins. *ACS Catal.* **12**, 2552–2560 (2022).

12. L. Escot, S. González-Granda, V. Gotor-Fernández, I. Lavandera, Combination of gold and redox enzyme catalysis to access valuable enantioenriched aliphatic β-chlorohydrins. *Org. Biomol. Chem.* **20**, 9650–9658 (2022).

13. S. González-Granda, G. Steinkellner, K. Gruber, I. Lavandera, V. Gotor-Fernández, Gold and Biocatalysis for the Stereodivergent Synthesis of Nor(pseudo)ephedrine Derivatives: Cascade Design Toward Amino Alcohols, Diols, and Diamines. *Adv. Synth. Catal.* **365**, 1036–1047 (2023).

14. J. D. Hamel, T. Hayashi, M. Cloutier, P. R. Savoie, O. Thibeault, M. Beaudoin, J. F. Paquin, Highly regioselective gold-catalyzed formal hydration of propargylic: Gem -difluorides. *Org. Biomol. Chem.* **15**, 9830–9836 (2017).

15. L. Popek, J. J. Cabrera-Trujillo, V. Debrauwer, N. Blanchard, K. Miqueu, V. Bizet, Regio- and Stereoselective Hydroelementation of SF_5-Alkynes and Further Functionalizations. *Angew. Chem. Int. Ed.* **62**, e202300685 (2023).

16. E. I. Chikunova, V. Y. Kukushkin, A. Y. Dubovtsev, Atom-economic synthesis of β-ketosulfones based on gold-catalyzed highly regioselective hydration of alkynylsulfones. *Green Chem.*, **24**, 3314–3320 (2022).

17. N. A. Rebacz, P. E. Savage, Hydration of 1-Phenyl-1-Propyne in high-temperature water with catalysis by water-tolerant lewis acids. *Ind. Eng. Chem. Res.* **49**, 535–540 (2010).

18. T. Tsuchimoto, T. Joya, E. Shirakawa, Y. Kawakami, Bronsted acid-catalyzed hydration of alkynes: A convenient route to diverse carbonyl compounds. *Synlett*, 1777–1778 (2000).

19. M. Ye, Y. Wen, H. Li, Y. Fu, Q. Wang, Metal-free hydration of aromatic haloalkynes to α-halomethyl ketones. *Tetrahedron Lett.* **57**, 4983–4986 (2016).

20. S. Iimura, K. Manabe, S. Kobayashi, Hydrophobic, low-loading and alkylated polystyrene-supported sulfonic acid for several organic reactions in water: Remarkable effects of both the polymer structures and loading levels of sulfonic acids. *Org. Biomol. Chem.* **1**, 2416–

2418 (2003).

21. G. B. Seiffert, G. M. Ullmann, A. Messerschmidt, B. Schink, P. M. H. Kroneck, O. Einsle, Structure of the non-redox-active tungsten/[4Fe:4S] enzyme acetylene hydratase. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 3073–3077 (2007).

22. P. M. H. Kroneck, Acetylene hydratase: A non-redox enzyme with tungsten and iron-sulfur centers at the active site. *J. Biol. Inorg. Chem.* **21**, 29–38 (2016).

23. R. Z. Liao, J. G. Yu, F. Himo, Mechanism of tungsten-dependent acetylene hydratase from quantum chemical calculations. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 22523–22527 (2010).

24. P. I. Dalko, Ed., *Enantioselective organocatalysis* (Wiley-VCH Verlag GmbH, Weinheim, 2007), vol. 2007.

25. D. W. C. MacMillan, The advent and development of organocatalysis. *Nature*. **455**, 304–308 (2008).

26. A. Antenucci, S. Dughera, P. Renzi, Green Chemistry Meets Asymmetric Organocatalysis: A Critical Overview on Catalysts Synthesis. *ChemSusChem*. **14**, 2785–2853 (2021).

27. S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, Asymmetric enamine catalysis. *Chem. Rev.* **107**, 5471–5569 (2007).

28. A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.*, **107**, 5416-5470 (2007).

29. S. Bertelsen, K. A. Jørgensen, Organocatalysis–after the gold rush. *Chem. Soc. Rev.* **38**, 2178–2189 (2009).

30. I. V. Alabugin, E. Gonzalez-Rodriguez, R. K. Kawade, A. A. Stepanov, S. F. Vasilevsky, Alkynes as synthetic equivalents of ketones and aldehydes: A hidden entry into carbonyl chemistry. *Molecules*. **24**, 1036 (2019).

31. J. S. Zhang, L. Liu, T. Chen, L. B. Han, Cross-Dehydrogenative Alkynylation: A Powerful Tool for the Synthesis of Internal Alkynes. *ChemSusChem*. **13**, 4776–4794 (2020).

32. J. Xiang, M. Ipek, V. Suri, M. Tam, Y. Xing, N. Huang, Y. Zhang, J. Tobin, T. S. Mansour, J. McKew, β-Keto sulfones as inhibitors of 11β-hydroxysteroid dehydrogenase type I and the mechanism of action. *Bioorganic Med. Chem.* **15**, 4396–4405 (2007).

33. R. Ge, Y. Huang, G. Liang, X. Li, 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors as Promising Therapeutic Drugs for Diabetes: Status and Development. *Curr. Med. Chem.* **17**, 412–422 (2010).

34. L. Capaldo, D. Ravelli, Decatungstate as Direct Hydrogen Atom Transfer Photocatalyst for SOMOphilic Alkynylation. *Org. Lett.* **23**, 2243–2247 (2021).

35. S. Nahm, S. M. Weinreb, N-methoxy-n-methylamides as effective acylating agents. *Tetrahedron Lett.* **22**, 3815–3818 (1981).

36. M. Nowak, Weinreb amides. *Synlett*. **26**, 561–562 (2015).

37. S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto, V. Zanirato, Mastering β-Keto Esters. *Chem. Rev.* **95**, 1065–1114 (1995).

38. G. B. D. Rao, B. Anjaneyulu, M. P. Kaushik, M. R. Prasad, β-Ketoesters: An Overview and It's Applications via Transesterification. *ChemistrySelect*. **6**, 11060–11075 (2021).

39. K. Uchida, Y. Minami, S. Yoshida, T. Hosoya, Synthesis of Diverse γ-Aryl-β-ketoesters via Aryne Intermediates Generated by C-C Bond Cleavage. *Org. Lett.* **21**, 9019–9023 (2019).

40. A. B. Lowe, Thiol-yne 'click'/coupling chemistry and recent applications in polymer and

materials synthesis and modification. *Polymer (Guildf).* **55**, 5517–5549 (2014).

41. J. C. Worch, C. J. Stubbs, M. J. Price, A. P. Dove, Click Nucleophilic Conjugate Additions to Activated Alkynes: Exploring Thiol-yne, Amino-yne, and Hydroxyl-yne Reactions from (Bio)Organic to Polymer Chemistry. *Chem. Rev.* **121**, 6744–6776 (2021).
42. D. M. Kirschenbaum, F. S. Parker, An infrared study of the hydrolysis of a thiazolidine. *Science*. **128**, 1430–1431 (1958).
43. L. Wlodek, H. Rommelspacher, R. Susilo, J. Radomski, G. Höfle, Thiazolidine derivatives as source of free l-cysteine in rat tissue. *Biochem. Pharmacol.* **46**, 1917–1928 (1993).
44. T. H. Fife, R. Natarajan, C. C. Shen, R. Bembi, Mechanism of Thiazolidine Hydrolysis. Ring Opening and Hydrolysis of 1,3-Thiazolidine Derivatives of p-(Dimethylamino)cinnamaldehyde. *J. Am. Chem. Soc.* **113**, 3071–3079 (1991).
45. S. González-Granda, L. Escot, I. Lavandera, V. Gotor-Fernández, Chemoenzymatic Cascades Combining Biocatalysis and Transition Metal Catalysis for Asymmetric Synthesis. *Angew. Chem. Int. Ed.* **62**, e202217713 (2023).
46. C. Ascaso-Alegre, J. Mangas-Sánchez, Construction of chemoenzymatic linear cascades for the synthesis of chiral compounds. *Eur. J. Org. Chem.*, **2022**, e202200093 (2022).
47. F. Rudroff, M. D. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding, U. T. Bornscheuer, Opportunities and challenges for combining chemo- and biocatalysis. *Nat. Catal.* **1**, 12–22 (2018).
48. S. P. France, L. J. Hepworth, N. J. Turner, S. L. Flitsch, Constructing Biocatalytic Cascades: In Vitro and in Vivo Approaches to de Novo Multi-Enzyme Pathways. *ACS Catal.* **7**, 710–724 (2017).
49. J. H. Schrittwieser, S. Velikogne, M. Hall, W. Kroutil, Artificial Biocatalytic Linear Cascades for Preparation of Organic Molecules. *Chem. Rev.* **118**, 270–348 (2018).
50. C. Ascaso-Alegre, R. P. Herrera, J. Mangas-Sánchez, Stereoselective Three-Step One-Pot Cascade Combining Amino- and Biocatalysis to Access Chiral γ-Nitro Alcohols. *Angew. Chem. Int. Ed.* **61**, e202209159 (2022).
51. S. González-Granda, I. Lavandera, V. Gotor-Fernández, Alcohol Dehydrogenases and N-Heterocyclic Carbene Gold(I) Catalysts: Design of a Chemoenzymatic Cascade towards Optically Active β,β-Disubstituted Allylic Alcohols. *Angew. Chem. Int. Ed.* **60**, 13945–13951 (2021).
52. M. López-Agudo, N. Ríos-Lombardía, J. González-Sabín, I. Lavandera, V. Gotor-Fernández, Chemoenzymatic Oxosulfonylation-Bioreduction Sequence for the Stereoselective Synthesis of β-Hydroxy Sulfones. *ChemSusChem*. **15**, e202101313 (2022).

Acknowledgments: We thank Prof. Carlos Valdés and Dr. Manuel Plaza from the University of Oviedo for fruitful discussions. JM-S, IL, VG-F and MG-B are grateful to the Agencia Estatal de Investigación (AEI/ 10.13039/501100011033) for the financial support through grants PID2020-113351RA-I00 (JMS-S) and PID2022-137893OB-I00 (IL, VG-F). JM-S also thanks AEI and EU for a Ramón y Cajal Fellowship (RYC2021-032021-I).

Author contributions: Methodology: JG-G and SG-G initiated the study. JG-G, SG-G and JM-S designed and carried out the experiments which includes the preparation of starting materials and final product characterisation. Funding acquisition: IL; VG-F, JM-S. Supervision: JM-S directed the project and IL and VG-F provided advice and assistance. Writing – review & editing: JM-S

prepared and edited the manuscript. JG-G and JM-S prepared the supplementary materials. All authors reviewed the results and approved the final version of the manuscript.

Competing interests: The authors declare no competing interests. **Data and materials availability:** All data are available in the main text or the supplementary materials. Correspondence and requests for materials should be addressed to JM-S.