


Cite this: *Catal. Sci. Technol.*, 2025,  
15, 5055

# Access to valuable 1,4- and 1,5-diketones through gold(I) catalysis in water: application to chemoenzymatic cascades†

Lorena Escot, Sergio González-Granda,‡  
Vicente Gotor-Fernández \* and Iván Lavandera §\*

1,4- and 1,5-diketones are remarkable structures in different fields as they serve as precursors of many valuable derivatives such as heterocycles and they are also present in the skeleton of a wide variety of natural products and biologically active compounds. Herein, we propose a novel and general methodology that combines the use of both Weinreb and gold chemistries under mild conditions. Thus, starting from pent-4-ynoic or hex-5-ynoic acid, the corresponding Weinreb amides were efficiently obtained, and then after the reaction with a suitable Grignard reagent, a series of alk-4-yn-1-ones and alk-5-yn-1-ones were synthesized in high to excellent yields (74–94%). Later, these compounds were hydrated using the gold(I) catalyst JohnPhosAuCl and the additive NaBAR<sub>4</sub><sup>F</sup> at very low loadings in an aqueous medium and at mild temperature, affording the desired dicarbonylic derivatives at high extent (92–98%). This method was also applied to various aliphatic 1,ω-diyne, which were transformed into the corresponding diketones (88–93%). Due to the mildness of this reaction, it could be combined with different biocatalysts in a one-pot sequential or concurrent approach to access a valuable tetrahydropyridine (1 g scale, 94% isolated yield, >99% ee) or a relevant diol (200 mg scale, 88% isolated yield, >99% ee, >99% de).

Received 27th January 2025,  
Accepted 15th July 2025

DOI: 10.1039/d5cy00107b

rsc.li/catalysis

## Introduction

1,4-Diketones<sup>1</sup> – also known as  $\gamma$ -diketones – and 1,5-diketones<sup>2</sup> – also known as  $\delta$ -diketones – are considered as privileged scaffolds since they are present in numerous natural products and bioactive molecules. Moreover, they are precursors of several valuable and diverse compounds such as heterocycles as a result of their high synthetic versatility.<sup>3,4</sup> Due to this prominence, many different chemical approaches have been described to obtain these derivatives.<sup>1</sup> Among them, few have been recurrently pursued (Fig. 1a) such as the (i) organocatalytic Stetter reaction,<sup>5,6</sup> (ii) the metal-catalyzed addition of an enolate or a silyl enol ether to the enol form of a carbonyl moiety through oxidative coupling or

to an  $\alpha,\beta$ -unsaturated ketone *via* the Michael addition,<sup>7,8</sup> and (iii) (photochemical) radical C–C formation.<sup>9–12</sup> However, some of these methods have several drawbacks including the use of high catalyst loadings or toxic metal species, hazardous reaction conditions and sophisticated setups, low atom economy and efficiency, and the generation of highly reactive intermediates that reduce the selectivity and productivity of the process. In this context, it is surprising that the hydration of (di)alkynes to produce diketones has been largely overlooked.<sup>13,14</sup>

Based on the synthetic possibilities of gold catalysis and its suitability to combine with biocatalysis in cascade transformations,<sup>15–18</sup> we have envisioned the design of metal-enzymatic routes to valorize carbonyl derivatives obtained after gold-catalyzed hydration reactions. Biocatalysis has demonstrated to be a powerful tool to access valuable natural products like alkaloids<sup>19,20</sup> or nitrogen-containing heterocycles,<sup>21,22</sup> and also different chemoenzymatic approaches have been considered to obtain these derivatives.<sup>23</sup> A nice example is the combination of well-implemented chemical methods with enzymes to obtain chiral and highly appealing disubstituted 2,5-pyrrolidines and 2,6-piperidines,<sup>24</sup> starting from 1,4- and 1,5-diketones,<sup>25–33</sup> respectively. These processes usually occur through the monoamination of one of the ketone groups, forming a  $\Delta 1$ -pyrroline or a  $\Delta 1$ -piperidine intermediate after

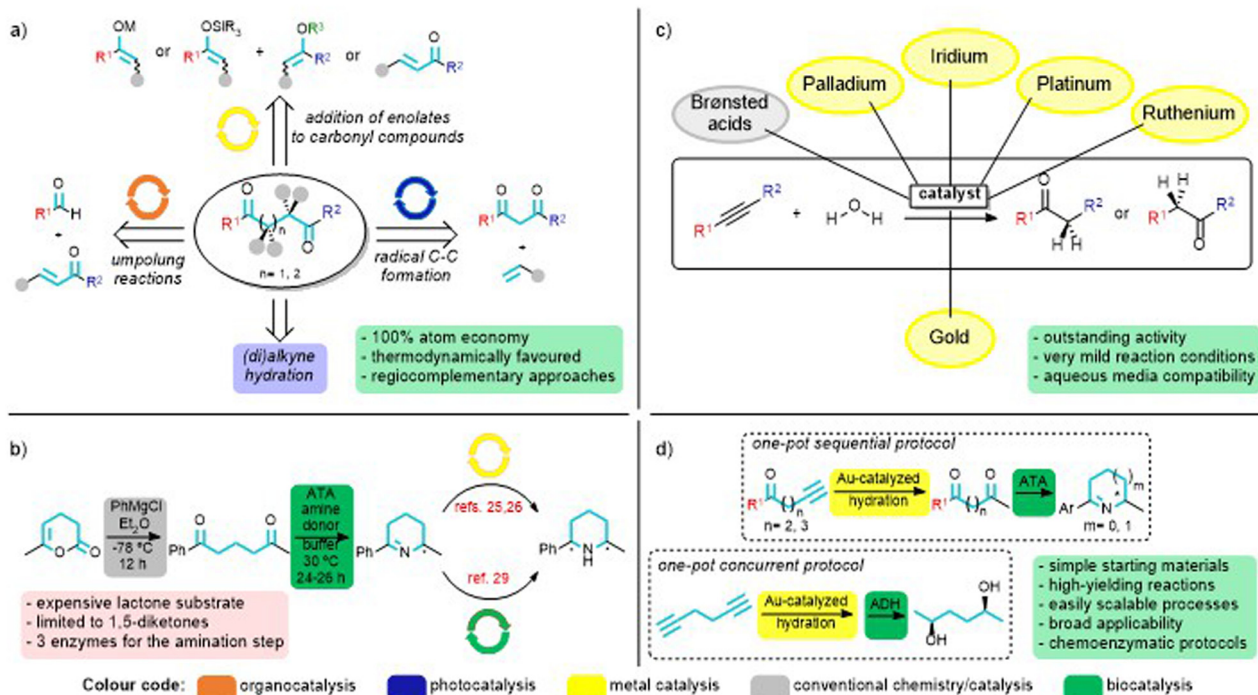
*Organic and Inorganic Chemistry Department, Instituto Universitario de Química Organometálica “Enrique Moles”, University of Oviedo, Avenida Julián Clavería 8, 33006 Oviedo, Asturias, Spain. E-mail: vicgotfer@uniovi.es, lavanderaivan@uniovi.es*

† Electronic supplementary information (ESI) available: Characterization of compounds, enzymatic screenings, analytical data, *E*-factor calculations and NMR spectra. See DOI: <https://doi.org/10.1039/d5cy00107b>

‡ Current affiliation: Department of Chemistry, UBC Faculty of Science, Vancouver Campus, The University of British Columbia, Vancouver, BC V6T 1Z1, Canada.

§ The authors are deeply grateful for the contributions of Prof. Ivan Lavandera, not only with this manuscript, but also during his outstanding scientific career, who sadly passed away during the preparation of this work.





**Fig. 1** a) Selected examples of synthetic approaches towards 1,4- and 1,5-diketones. b) Previously described syntheses of a chiral disubstituted 2,6-piperidine through the  $\Delta^1$ -piperidine intermediate target of this study. c) Types of catalysis to achieve the hydration of alkynes. d) Proposed methodologies to obtain  $\gamma$ - and  $\delta$ -diketones and further applications to one-pot sequential or concurrent chemoenzymatic protocols to synthesize valuable enantiopure derivatives.

spontaneous cyclization, which afterwards is reduced into the final enantioenriched heterocyclic product (Fig. 1b).

The addition of a water molecule to a C–C triple bond to provide a carbonyl derivative is a very useful and studied synthetic transformation.<sup>34</sup> In fact, alkynes are known as “carbonyl surrogates”,<sup>35</sup> being platform molecules for masking a ketone or an aldehyde when planning a chemical route. This thermodynamically favoured transformation occurs with a complete atom economy and can be mediated by many different catalytic species (Fig. 1c), which can provide the corresponding regiocomplementary products (Markovnikov or anti-Markovnikov addition).<sup>36,37</sup> Since it was discovered in the 19th century that mercury salts could catalyze this reaction, several alternatives have been investigated due to the toxicity of this metal. Among them, Brønsted acids and metal species from Ru, Rh, Pd, Pt, Ir, and Cu have demonstrated great versatility.<sup>38</sup> In this field, gold(i) complexes have emerged as a powerful tool since they can mediate this transformation under very mild conditions with high efficiency, demonstrating an excellent Markovnikov preference and chemoselectivity in the presence of other functionalities.<sup>35,37,39</sup> Specifically, N-heterocyclic carbene (NHC) ligands under acid-free conditions have been shown to accelerate this reaction at very low loadings and even at room temperature in aqueous media.<sup>40–42</sup>

Herein, we propose a novel methodology to synthesize a series of interesting linear diketones based on the Weinreb amide<sup>43</sup> and gold(i)-catalyzed alkyne hydration chemistries. This synthetic pathway provides the desired  $\gamma$ - and

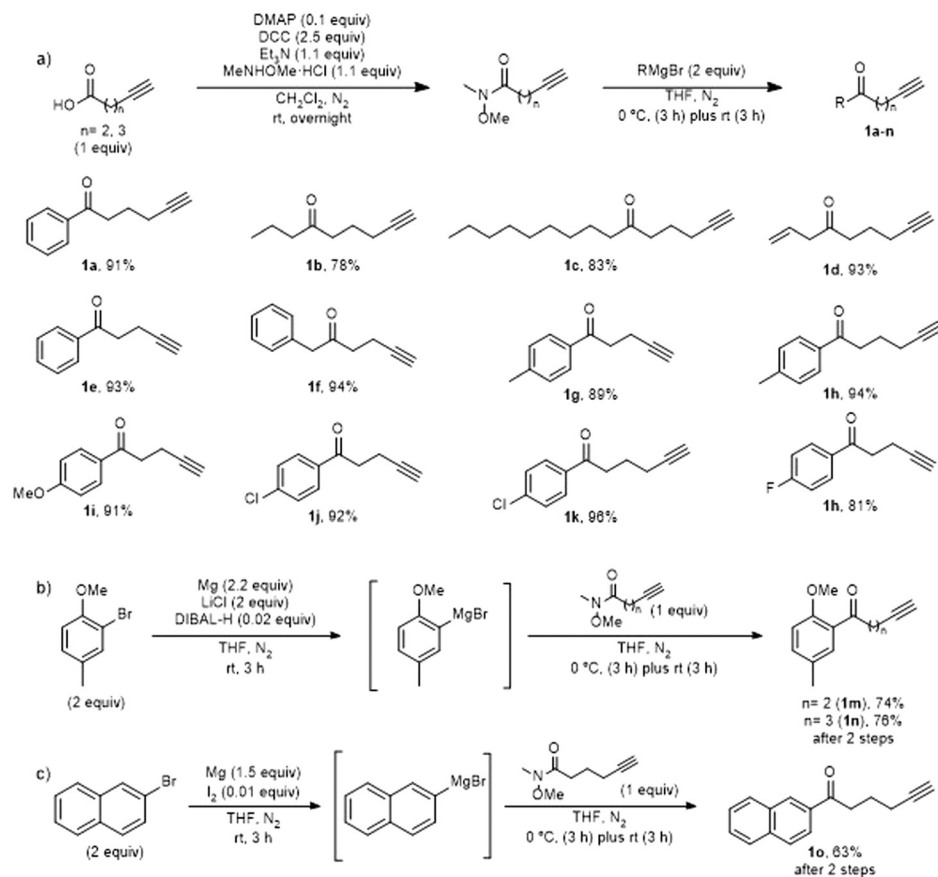
$\delta$ -diketones in very high yields under mild conditions from simple and accessible starting materials through selective, straightforward, and scalable transformations. Moreover, due to the mildness of the metal-catalyzed reaction, its application in a one-pot chemoenzymatic sequential process will be exemplified to access relevant enantiopure  $\Delta^1$ -piperidine<sup>25,26,29</sup> and pyrrole derivatives (Fig. 1d, top). Also, starting from commercial 1, $\omega$ -diynes, a series of diketones will be accessed through gold(i) catalysis, and in one case, it will be combined in a concurrent manner with a biocatalyst (ADH) to synthesize a valuable enantiopure diol<sup>44</sup> (Fig. 1d, bottom).

## Results and discussion

### Synthesis of alk-4-yn-1-ones and alk-5-yn-1-ones

After an extensive survey of the different methods available for the preparation of alkynones (see Table S1†), we selected the combination of Weinreb and Grignard chemistries to synthesize the desired compounds. In this method depicted in Scheme 1a, the first step consists of the Weinreb amide formation of commercially available pent-4-ynoic acid using a coupling reagent, followed by the addition of a Grignard reagent to afford the corresponding alk-4-yn-1-one. Due to the special reactivity of these amides,<sup>43</sup> by simply selecting the adequate nucleophilic reagent (aryl or alkyl), a broad spectrum of derivatives could be made. Although this methodology was only described starting from pent-4-ynoic acid,<sup>45–47</sup> it was envisaged that by changing it to hex-5-ynoic





**Scheme 1** a) Synthesis of alk-4-yn-1-ones and alk-5-yn-1-ones **1a–o**. b) Synthesis of alkyne **1m** and **1n**. c) Synthesis of alkyne **1o**.

acid, the access towards alk-5-yn-1-ones would also be straightforward.

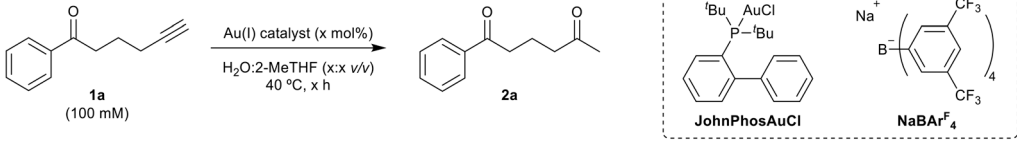
The synthesis of the target alkyne derivatives could be easily scaled up (9.3 mmol) and the products were obtained in good to excellent overall yields (63–96%, Scheme 1a), independently on the carboxylic acid used as the starting material, and also worked fine for aliphatic substrates (**1b** and **1c**) and aryl compounds containing methyl, methoxy, and halogen atom groups. In the reaction scope, disubstituted derivatives were included (**1m** and **1n**, 74–76%, Scheme 1b) as well as a bulkier naphthalene derivative **1o** (63%, Scheme 1c). In the specific case of alk-5-yn-1-ones **1a–c**, they were isolated after simple liquid–liquid extraction avoiding the utilization of a chromatography column, which was compulsory for the rest of the derivatives to obtain them in excellent purity for the hydration step.

### Gold-catalyzed synthesis of 1,4- and 1,5-diketones

The next stage was to focus on the synthesis of the desired  $\gamma$ - and  $\delta$ -diketones from the corresponding alk-4-yn-1-ones and alk-5-yn-1-ones in the previous section. Herein, it is important to highlight that Au-catalyzed hydration of alkynes functionalized by carbonyl groups is facilitated by the assistance of the carbonyl group as reported by different research groups.<sup>46,48,49</sup> To study the gold-catalyzed hydration

step, alkyne **1a** was selected as the benchmark substrate, and a series of gold(i) catalysts were applied in this transformation (Table 1). Among them, we can highlight the employment of commercially available IPrAuNTf<sub>2</sub> ([1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene][bis(trifluoromethanesulfonyl)imide] gold(i)) that has shown to be very active in the regioselective hydration of terminal alkynes under very mild reaction conditions.<sup>50</sup> We performed these reactions at 40 °C and in a mixture of water and 2-methyltetrahydrofuran (2-MeTHF), a solvent that can be derived from natural resources,<sup>51</sup> to improve the substrate solubility. Hence, different gold catalysts (2.5–5 mol%) were tried in this transformation (Table 1, entries 1–11). Among them, PPh<sub>3</sub>AuCl, BrettPhosAuNTf<sub>2</sub> and JohnPhosAuNTf<sub>2</sub> led to complete conversions towards diketone **2a**. In some cases with other catalysts, a small quantity (<7%) of unknown secondary products were attained in this reaction. Due to the excellent result observed with JohnPhosAuNTf<sub>2</sub> (Table 1, entry 11), its use in lower loading was attempted (0.5–1 mol%) also finding excellent results (Table 1, entries 12 and 13). At this point, we decided to study the use of chloro[(1,1'-biphenyl-2-yl)di-*tert*-butylphosphine] gold(i) (JohnPhosAuCl, 311 € per g, Sigma-Aldrich) driven by its lower price in comparison to AuIPrNTf<sub>2</sub> (450 € per g, Sigma-Aldrich). As expected, JohnPhosAuCl did not show significant activity due to the highly coordinating character of the chloride anion



**Table 1** Influence of the gold(I) catalysts (species and loading), reaction media and time for the hydration of 1-phenylhex-5-yn-1-one (**1a**, 100 mM)


Entry	Catalyst (mol%)/additive <sup>a</sup> (mol%)	H <sub>2</sub> O : 2-MeTHF (v/v)	t (h)	<b>1a</b> <sup>b</sup> (%)	<b>2a</b> <sup>b</sup> (%)	By-products <sup>b</sup> (%)
1	[IPrAu] <sub>3</sub> [PO <sub>4</sub> ] (5)	4 : 1	24	95	5	<1
2	IPrAuOCS (5)	4 : 1	24	53	46	1
3	IPrAuOTf (5)	4 : 1	24	39	61	<1
4	IPrAu(MeCN)BF <sub>4</sub> (2.5)	4 : 1	24	58	42	<1
5	IPrAuNTf <sub>2</sub> (2.5)	4 : 1	24	<1	97	3
6	IPrAuOTf (2.5)	4 : 1	24	<1	93	7
7	IPr*AuOTf (2.5)	4 : 1	24	<1	97	3
8	PPh <sub>3</sub> AuCl (2.5)/NaBAR <sup>F</sup> <sub>4</sub> (2.5)	4 : 1	24	<1	>99	<1
9	BrettPhosAuNTf <sub>2</sub> (2.5)	4 : 1	24	<1	>99	<1
10	JohnPhos(MeCN)BF <sub>6</sub> (2.5)	4 : 1	24	53	47	<1
11	JohnPhosAuNTf <sub>2</sub> (2.5)	4 : 1	24	<1	>99	<1
12	JohnPhosAuNTf <sub>2</sub> (1)	4 : 1	24	<1	>99	<1
13	JohnPhosAuNTf <sub>2</sub> (0.5)	4 : 1	24	<1	>99	<1
14	JohnPhosAuCl (2.5)	4 : 1	24	92	8	<1
15 <sup>c</sup>	JohnPhosAuCl (2.5)/NaBAR <sup>F</sup> <sub>4</sub> (5)	4 : 1	24	<1	92	8
16 <sup>c</sup>	JohnPhosAuCl (2.5)/NaBAR <sup>F</sup> <sub>4</sub> (2.5)	4 : 1	24	<1	96	4
17 <sup>c</sup>	JohnPhosAuCl (1)/NaBAR <sup>F</sup> <sub>4</sub> (1)	4 : 1	24	<1	>99	<1
18 <sup>c</sup>	JohnPhosAuCl (1)/NaBAR <sup>F</sup> <sub>4</sub> (1)	9 : 1	24	<1	>99	<1
19 <sup>c</sup>	JohnPhosAuCl (0.75)/NaBAR <sup>F</sup> <sub>4</sub> (0.75)	9 : 1	24	<1	>99	<1
20 <sup>c</sup>	JohnPhosAuCl (0.5)/NaBAR <sup>F</sup> <sub>4</sub> (0.5)	9 : 1	24	<1	>99	<1
21 <sup>c</sup>	JohnPhosAuCl (0.25)/NaBAR <sup>F</sup> <sub>4</sub> (0.25)	9 : 1	24	95	3	2
22 <sup>c</sup>	JohnPhosAuCl (0.5)/NaBAR <sup>F</sup> <sub>4</sub> (0.5)	9 : 1	16	<1	>99	<1
23 <sup>c</sup>	JohnPhosAuCl (0.5)/NaBAR <sup>F</sup> <sub>4</sub> (0.5)	9 : 1	8	13	87	<1
24 <sup>c</sup>	JohnPhosAuCl (0.5)/NaBAR <sup>F</sup> <sub>4</sub> (0.5)	9 : 1	6	30	70	<1
25 <sup>c</sup>	JohnPhosAuCl (0.5)/NaBAR <sup>F</sup> <sub>4</sub> (0.5)	9 : 1	4	65	35	<1

<sup>a</sup> The amounts of the corresponding catalysts and additives (in mol%) appear in parentheses. <sup>b</sup> Conversion values were measured by GC analyses (see Section X in the ESI†). <sup>c</sup> Both JohnPhosAuCl and NaBAR<sup>F</sup><sub>4</sub> were previously dissolved in 2-MeTHF.

(Table 1, entry 14), hindering an adequate action of the metal catalyst. To improve it, this ion must be previously removed and substituted by another non-coordinating anion, which will lead to the formation of a more active species.<sup>52</sup>

Among the various options that exist in the literature, the use of sodium tetrakis((3,5-bistrifluoromethyl)phenyl)borate (NaBAR<sup>F</sup><sub>4</sub>) as an additive can be very advantageous due to the excellent results observed for other transformations,<sup>53</sup> and also because of its low price (~4 € per g, BLDpharm). Gladly, using this pair of components, it was possible to diminish the Au(I) catalyst loading to 1 mol%, affording exclusively 1,5-diketone **2a** (Table 1, entries 15–17).

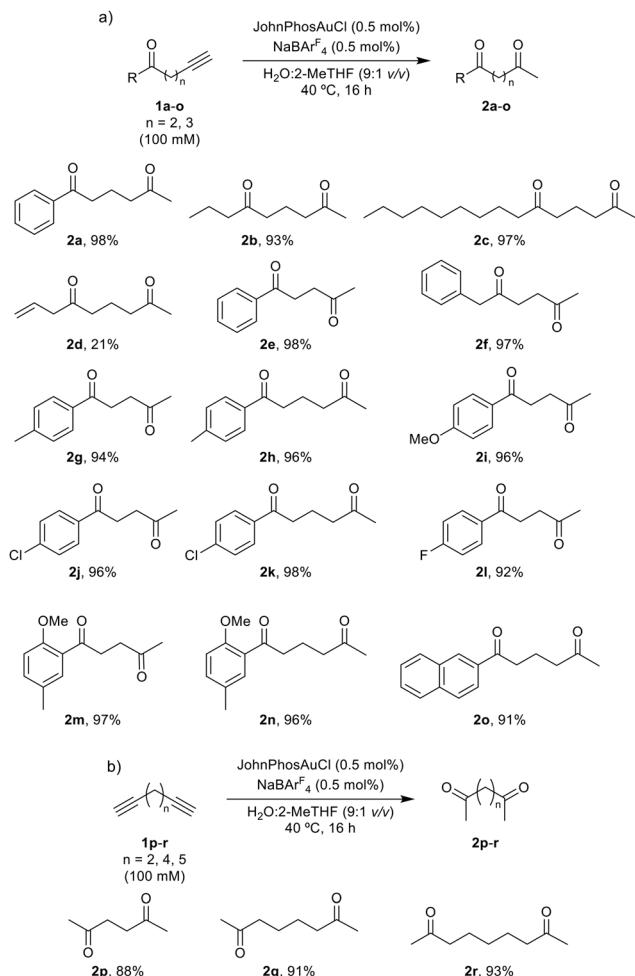
Since the combination of this protocol with different enzymatic reactions was envisaged, the quantity of the organic solvent was reduced from 4:1 to 9:1 v/v (Table 1, entries 18–21). Under these conditions, we could even reduce both JohnPhosAuCl and NaBAR<sup>F</sup><sub>4</sub> to 0.5 mol%, not compromising the excellent performance of the process after 24 h. Finally, a time study of the reaction was performed (Table 1, entries 22–25), observing that at least 16 h were necessary to reach total conversion towards **2a** with excellent selectivity (Table 1, entry 22).

Once the reaction conditions were optimized, the substrate scope of this transformation was studied

(Scheme 2). Satisfyingly, independent of the substitution pattern, both alk-4-yn-1-ones and alk-5-yn-1-ones **1a–o** (2 mmol-scale, 100 mM) were quantitatively hydrated providing the corresponding diketones **2a–o** in excellent isolated yields and purity (91–98%) without the need of chromatography column purification (Scheme 2a), the only exception was ketone **2d** (21% yield) that was recovered after simple liquid–liquid extraction in low yield due to its volatility. As an additional development of this process, we also tried the gold(I)-catalyzed hydration on 1,ω-diyne **1p–r** under the same conditions (Scheme 2b). The results were again excellent, and diketones **2p–r** could be isolated under a chromatography-free set-up in excellent yields (88–93%). Using this methodology, among the aliphatic products obtained, it was remarkable that 1,6-diketone (**2q**) and 1,7-diketone (**2r**) could be easily accessed, opening the door for future applications with other types of substrates.

The synthetic application of some of these diketones is highlighted in Fig. 2. For instance, starting from 1,5-diketone **2b**,<sup>31</sup> dihydropinidine, a natural alkaloid found in coniferous trees, which exhibits antifeedant activity against large pine weevils, and isosolenopsin (from **2c**),<sup>27</sup> an alkaloid secreted by fire ants, which has demonstrated different relevant biological activities, were synthesized. 1,4-Diketones have shown to be excellent molecule platforms for accessing



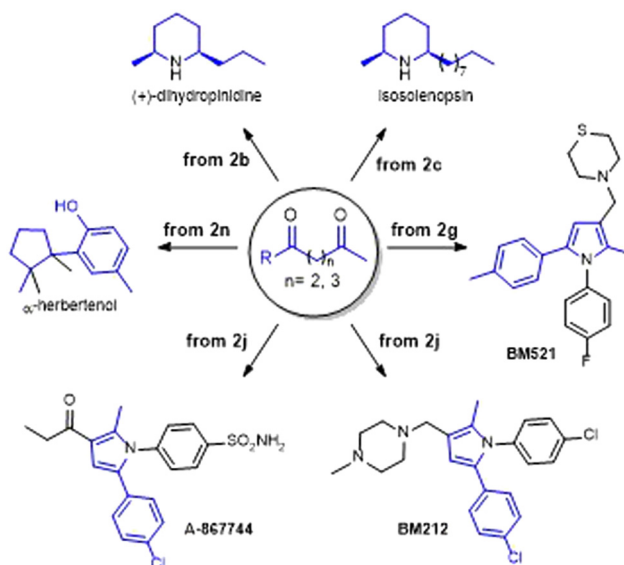


**Scheme 2** a) Synthesis of  $\gamma$ - and  $\delta$ -diketones **2a–o** through the Au(I)-catalyzed alkyne hydration reaction. b) Synthesis of aliphatic diketones **2p–r** starting from **1, $\omega$ -diynes**.

antimycobacterial compounds, such as BM521 (ref. 54) (obtained from **2g**) and BM212 (ref. 55) (synthesized from **2n**). The importance of diketones as synthons has also been demonstrated, for instance for the synthesis of an allosteric modulator of the  $\alpha 7$  nicotinic acetylcholine receptor (A-867744) that can be beneficial for, e.g. Alzheimer's disease.<sup>56</sup> As a final example,  $\delta$ -diketone **2k** has been described as a precursor of  $\alpha$ -herbertenol,<sup>57</sup> a sesquiterpene with antifungal activity found in a wide variety of liverworts.

### Application of the hydration reaction to chemoenzymatic protocols

The design of one-pot sequential or concurrent chemoenzymatic protocols has become a valuable synthetic tool to enhance the productivity of a synthetic route, while diminishing the time, energy, resources and waste due to the avoidance of intermediate isolation and purification steps.<sup>18,58–63</sup> In recent years, gold chemistry and biocatalysis have been successfully merged to synthesize relevant enantioenriched compounds.<sup>17,18</sup> Obviously, the main



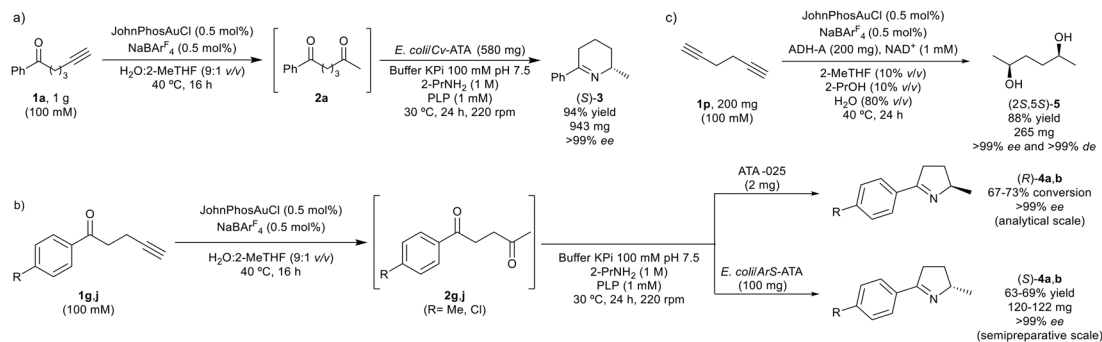
**Fig. 2** Examples of biologically active compounds obtained from the 1,4- and 1,5-diketones synthesized in this study. In blue is the part of the molecule that is directly derived from the target diketone.

problem when carrying out these transformations has been finding adequate conditions to couple both catalyst actions. For instance, when applying gold(I) or gold(III) salts in the reaction medium, with few exceptions,<sup>64,65</sup> the protocol was performed in a sequential manner as the pH, the temperature or the reaction media were not compatible.<sup>66–69</sup> Different breakthroughs have been followed to overcome this issue such as the employment of compartmentalization techniques like gold encapsulation,<sup>70–72</sup> micelle formation,<sup>73</sup> (modular) catalyst(s) immobilization,<sup>74,75</sup> or the use of gold-enzyme biohybrids.<sup>76</sup>

Also, the utilization of stable NHC-Au(I) complexes has allowed the development of concurrent processes in aqueous media using oxidoreductases such as alcohol dehydrogenases (ADHs)<sup>50,77–79</sup> and ene-reductases,<sup>80</sup> however, in the case of amination enzymes such as amine transaminases (ATAs),<sup>50,81,82</sup> a sequential mode was compulsory due to the cross-reactivity between the gold catalyst and the amine donor necessary for the ATA.<sup>83</sup> Thus, having on our hands an appropriate method to obtain diketones, we envisaged the combination of our gold(I)-catalyzed method with two different types of enzymes to synthesize (2*S*)-2-methyl-6-phenyl-2,3,4,5-tetrahydropyridine [(*S*)-**3**], 2-methyl-5-(*p*-tolyl)-3,4-dihydro-2*H*-pyrrole (**4a**) enantiomers, 5-(4-chlorophenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole (**4b**) enantiomers and (2*S*,5*S*)-hexane-2,5-diol [(2*S*,5*S*)-**5**] (Scheme 3).

In the first case, starting from alkynone **1a** and after the hydration process, an ATA would be necessary to achieve the regioselective monoamination of the diketone intermediate **2a**, which after spontaneous cyclization, would provide the desired product. Previous attempts to synthesize this compound and others similar ones presented some drawbacks (Fig. 1c),<sup>25,26,29</sup> such as the high price of the

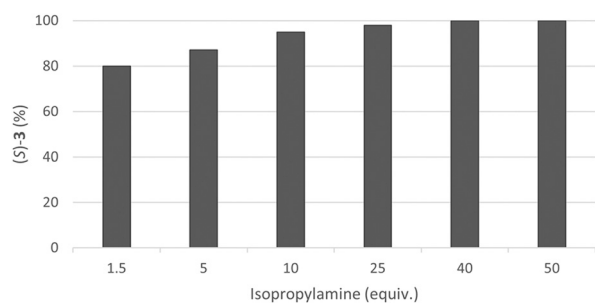




**Scheme 3** Au(I)-ATA one-pot combinations: a) synthesis of tetrahydropyridine (S)-3 on a preparative scale through a sequential approach. b) Access to dihydropyrroles (S)-4a and (S)-4b on analytical and semipreparative scale through a sequential approach. c) Synthesis of diol (2S,5S)-5 on a semipreparative scale through a concurrent process.

lactone used as the starting material (~850 € per g, Sigma-Aldrich), limiting the method to the synthesis of 1,5-diketones, and also the use of three enzymes for the biocatalytic step. Our methodology can overcome the first two problems, and for the last stage we tried to find suitable stereoselective ATAs that could accept isopropylamine (2-PrNH<sub>2</sub>) as the amine donor, largely simplifying the reaction development. By carrying out an enzymatic screening (Table S1 in the ESI<sup>†</sup>), we discovered different possible candidates to promote this biotransformation. Hence, among them, we selected ATA from *Chromobacterium violaceum* (Cv-ATA)<sup>84</sup> that afforded (S)-3 quantitatively and in excellent enantiomeric excess (>99% ee, Scheme 3a). The amount of 2-PrNH<sub>2</sub> was analyzed to minimize its use, which can be explained due to the favourable shift in equilibrium towards imine formation due to the cyclization step (Fig. 3). Different amine donor loadings were tested (1.5–50 equiv.) in order to find the optimal conditions for its implementation in the gold-ATA sequence, finding that 40 equiv. were necessary to reach full conversion after 24 h at 30 °C (see further details in Table S5<sup>†</sup>).

Due to the incompatibility between the gold catalyst and the amine donor,<sup>50</sup> employed in large molar excess regarding the ketone substrate, a sequential mode was compulsory. Once the hydration step finished, the buffer containing 2-PrNH<sub>2</sub> and the cofactor pyridoxal 5'-phosphate (PLP) and lyophilized cells of *Escherichia coli* heterologously expressing Cv-ATA were added to the same recipient, leaving the reaction



**Fig. 3** Influence of the isopropylamine loading in the Cv-ATA-catalyzed biotransformation of 2a.

at 30 °C for 24 h. To demonstrate the applicability of this protocol, the chemoenzymatic approach was scaled up to 1 g of 1a, affording enantiopure (S)-3 in 94% isolated yield (Scheme 3a). The environmental impact of this sequential system was evaluated using the *E*-factor concept,<sup>85</sup> focusing on the waste generated, and finding that the downstream process affected by 52.5% the overall procedure. The organic solvent contribution for product isolation was around 50% and the total contribution of water, used as a reaction medium, was 45% (Fig. S5 in the ESI<sup>†</sup>). Excluding solvents, for this sequential transformation, a remarkable *E*-factor value of 23.2 was obtained, being silica gel as the highest contributor (16.2) due to the use of a chromatography column (Fig. S4 in the ESI<sup>†</sup>).

The methodology was further extended for the synthesis of dihydropyrrole derivatives 4a and 4b starting from alk-4-yn-1-ones 1g and 1j in good yields (63–73%), accessing both possible enantiomers (R)- and (S)-4a,b by selecting stereocomplementary transaminases such as ATA-025 and *E. coli*/ArS-ATA, respectively (Scheme 3b). In the third example, it was decided to combine the Au(I)-catalyzed reaction with ketone bioreduction using an ADH (Scheme 3c) to synthesize (2S,5S)-hexane-2,5-diol, a key starting material, for instance to produce various chiral phosphine ligands.<sup>86–88</sup> Hence, starting from dialkyne 1p, the JohnPhosAuCl and NaBAR<sub>4</sub> system would hydrate it to form diketone 2p, and then a suitable stereoselective ADH would give the desired final diol (2S,5S)-5. Among the different biocatalysts described to catalyze this bioreduction, the ADH from *Rhodococcus ruber* (ADH-A)<sup>89</sup> was selected, as this Prelog ADH can be efficiently expressed in *E. coli*, is very stable in the presence of high proportions of organic solvent and at elevated temperatures, and can simply use propan-2-ol (2-PrOH) for recycling the nicotinamide cofactor (NAD<sup>+</sup>). In our case, we employed a partially purified enzyme obtained after shock heating treatment. Due to our previous experience in the combination of these oxidoreductases with other gold catalysts,<sup>50</sup> a concurrent approach where all catalysts and reagents were added from the beginning was tried. Gladly, the transformation was complete after 24 h at 40 °C, and it could be easily scaled up to 200 mg of



**1p**, isolating enantiopure and diastereopure (2*S*,5*S*)-**5** in 88% yield (Scheme 3c).

## Conclusions

Well-established chemical protocols such as the Weinreb and Grignard transformations, together with the use of catalytic gold(i) chemistry, have been merged to create a novel pathway towards  $\gamma$ - and  $\delta$ -diketones. A chemical route was designed that involved the formation of a Weinreb amide from easily accessible starting materials, followed by the addition of a Grignard reagent that afforded selectively a series of alk-4-yn-1-ones and alk-5-yn-1-ones in good to high yields (63–96%). Then, it was envisaged to employ gold chemistry to hydrate these final derivatives in a regioselective way to provide the desired 1,4- and 1,5-diketones. By carrying out a catalyst screening, the JohnPhosAuCl and NaBAR<sup>F</sup><sub>4</sub> system was selected as it could deliver the final products at minimum catalyst loading under very mild conditions in an aqueous medium and a selective manner. Thus, eleven dicarbonylic derivatives were synthesized in very high to excellent yields (92–98%). This method was very general and could be applied to relevant precursors containing aromatic compounds with different substitution patterns and aliphatic derivatives. Also, it could be used with three different 1, $\omega$ -diynes that were selectively hydrated at both sides giving the corresponding diketones, mostly with very high yields (21–93%).

As an application of the metal-catalyzed transformation, it was combined with two different biocatalytic systems, one employing an amine transaminase and the second using an alcohol dehydrogenase, to provide two chemoenzymatic cascade processes. In the first case, a valuable tetrahydropyridine was synthesized through a one-pot sequential approach due to the incompatibility of the Au(i) catalyst and the amine donor necessary in the enzymatic process. The reaction could be easily scaled up to 1 g, isolating the desired enantiopure product in 94% yield. The sequential strategy was also demonstrated for the synthesis of dihydropyrrole derivatives, the access to both possible enantiomers being possible by selecting stereocomplementary transaminases. In the third example, a relevant diol was obtained enantiopure and diastereopure due to the combination of the metal-mediated alkyne hydration with ADH-catalyzed ketone bioreduction in a concurrent manner, and was scaled up to 200 mg affording the target diol in 88% isolated yield. Overall, we believe that this short and simple methodology can be broadly applied to the synthesis and derivatization of  $\gamma$ - and  $\delta$ -diketones in excellent yields and will be of interest for researchers of different fields.

## Experimental

### General

Non-commercially available terminal alkynes were chemically synthesized, exhibiting physical and spectral data in agreement

with those reported in the literature (see Sections III–V in the ESI<sup>†</sup> for full characterization). Alkynes **1p–r** were purchased from commercial sources. Chemical reagents and cofactors (NAD<sup>+</sup> and PLP) were purchased from Sigma-Aldrich, except the additive NaBAR<sup>F</sup><sub>4</sub>, which was obtained from BLDpharm. Some gold(i) catalysts such as IPrAuNTf<sub>2</sub>, PPh<sub>3</sub>AuCl, BrettPhosAuNTf<sub>2</sub> and JohnPhosAuCl were obtained from Sigma-Aldrich, while JohnPhosAuNTf<sub>2</sub> was synthesized from the corresponding chloride derivative. Other gold species were obtained as previously described in the literature:<sup>90–92</sup> [IPrAu]<sub>3</sub>-PO<sub>4</sub>,<sup>90</sup> IPrAuOCs,<sup>91</sup> IPrAuOTs,<sup>91</sup> IPrAu(MeCN)BF<sub>4</sub>,<sup>91</sup> IPr<sup>\*</sup>AuOTf,<sup>92</sup> and [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene][trifluoromethanesulfonate] gold(i) (IPrAuOTf).<sup>92</sup>

### General procedure for the synthesis of alkynes **1a–c**

This procedure was adapted from the one described by Yuan *et al.*<sup>46</sup> *N,N*-Dimethylaminopyridine (DMAP, 244 mg, 2 mmol, 0.10 equiv.), *N,N*-cyclohexylcarbodiimide (DCC, 10.3 g, 50 mmol, 2.50 equiv.), triethylamine (Et<sub>3</sub>N, 3.1 mL, 22 mmol, 1.10 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (2.15 g, 22 mmol, 1.10 equiv.) were successively added to a solution of hex-5-ynoic acid (2.2 mL, 20 mmol, 1 equiv.) in dry dichloromethane (50 mL) inside a Schlenk flask. The solution was stirred at room temperature overnight under a nitrogen atmosphere. After this time, the solvent was evaporated under reduced pressure and the mixture was purified by column chromatography (SiO<sub>2</sub>, 70% Et<sub>2</sub>O/hexane), furnishing the corresponding Weinreb amide as a smelly yellowish oil (2.88 g, 93% isolated yield). A portion of the resulting product was used for the synthesis of propargylic ketones **1a–c**.

Subsequently, a 2 M solution of the corresponding Grignard reagent in THF (18.6 mmol, 2.0 equiv.) was added dropwise to a stirred solution of *N*-methoxy-*N*-methylhex-5-ynamide (1.4 g, 9.3 mmol) in dry THF (35 mL) at 0 °C inside a Schlenk flask under a nitrogen atmosphere. After 3 h of stirring at this temperature, the reaction was warmed to rt and stirred for additional 3 h. At this point, the reaction was quenched with an aqueous saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, 10% EtOAc/hexane for **1a** and 70% Et<sub>2</sub>O/hexane for **1b,c**) afforded the corresponding alkynes **1a–c** as colorless oils (1.56 g of **1a**, 98% yield; 1.08 g of **1b**, 84% yield; and 1.72 g of **1c**, 89% yield).

### General procedure for the synthesis of alkynes **1d–l**

This procedure was adapted from the one described by Yuan *et al.*<sup>46</sup> *N,N*-Dimethylaminopyridine (DMAP, 311 mg, 2.55 mmol, 0.10 equiv.), *N,N*-cyclohexylcarbodiimide (DCC, 13.1 g, 53.75 mmol, 2.50 equiv.), triethylamine (Et<sub>3</sub>N, 4.0 mL, 28.05 mmol, 1.10 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (2.74 g, 28.05 mmol, 1.10 equiv.) were successively added to a



solution of pent-4-ynoic acid (2.5 g, 25.5 mmol, 1 equiv.) in dry dichloromethane (50 mL) inside a Schlenk flask. The solution was stirred at room temperature overnight under a nitrogen atmosphere. After this time, the solvent was evaporated under reduced pressure and the mixture was purified by column chromatography (SiO<sub>2</sub>, 80% Et<sub>2</sub>O/hexane), furnishing the corresponding Weinreb amide as a smelly yellowish oil (3.46 g, 96% isolated yield). A portion of the resulting product was used for the synthesis of propargylic ketones **1d-l**.

Subsequently, a 2 M solution of the corresponding Grignard reagent in THF (18.6 mmol, 2.0 equiv.) was added dropwise to a stirred solution of *N*-methoxy-*N*-methylpent-4-ynamide (1.3 g, 9.3 mmol) in dry THF (35 mL) at 0 °C inside a Schlenk flask under a nitrogen atmosphere. After 3 h of stirring at this temperature, the reaction was warmed to rt and stirred for additional 3 h. At this point, the reaction was quenched with an aqueous saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, 40% Et<sub>2</sub>O/hexane for **1d**; 10% EtOAc/hexane for **1e**; 20% EtOAc/hexane for **1f**, 30% EtOAc/hexane for **1i** and **1j**; 40% EtOAc/hexane for **1g**, **1h**, and **1l**; and 70% EtOAc/hexane for **1k**) afforded the corresponding alkynes **1d-l** (266 mg of **1d**, 93% yield; 271 mg of **1e**, 97% yield; 298 mg of **1f**, 98% yield; 283 mg of **1g**, 93% yield; 226 mg of **1h**, 94% yield; 316 mg of **1i**, 95% yield; 326 mg of **1j**, 96% yield; 256 mg of **1k**, 96% yield; and 261 mg of **1l**, 84% yield).

#### General procedure for the synthesis of alkynes **1m** and **1n**

This procedure was adapted from the one described by Grigolo and Smith.<sup>93</sup> Magnesium (Mg, 182 mg, 7.44 mmol, 2.2 equiv.), lithium chloride (LiCl, 288.4 mg, 6.8 mmol, 2 equiv.) and diisobutylaluminium hydride (DIBAL-H, 68 μL, 0.068 mmol, 0.02 equiv.) were successively added to a Schlenk flask with dry THF (7 mL) under a nitrogen atmosphere. Then, 2-bromo-1-methoxy-4-methylbenzene (1 mL, 6.8 mmol, 2 equiv.) was added to this solution and stirred for 3 h at rt. After this time, a solution of the Weinreb amide (*N*-methoxy-*N*-methylpent-4-ynamide, 494.1 mg, 3.5 mmol, 1 equiv., or *N*-methoxy-*N*-methylhex-5-ynamide, 543.2 mg, 3.5 mmol, 1 equiv.) in THF was added dropwise at 0 °C and stirred for 3 h. After this time, the reaction was warmed to rt and stirred for additional 3 h. The reaction was quenched with an aqueous saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, 30% EtOAc/hexane) afforded the corresponding alkynes **1m** and **1n** (1.01 g of **1m**, 74% yield and 1.10 g of **1n**, 76% yield).

#### General procedure for the synthesis of alkyne **1o**

This procedure was adapted from the one described by Yu and co-workers.<sup>94</sup> Magnesium (Mg, 124.1 mg, 5.07 mmol, 1.5

equiv.) and iodine (I<sub>2</sub>, 8.58 mg, 0.034 mmol, 0.01 equiv.) were successively added to a Schlenk flask with dry THF (5 mL) under a nitrogen atmosphere. Then, 2-bromonaphthalene (1.41 g, 6.8 mmol, 2 equiv.) was added to this solution and stirred for 1 h at rt. After this time, a solution of the Weinreb amide (*N*-methoxy-*N*-methylpent-4-ynamide, 494.1 mg, 3.5 mmol, 1 equiv., or *N*-methoxy-*N*-methylhex-5-ynamide, 543.2 mg, 3.5 mmol, 1 equiv.) in THF was added dropwise at 0 °C and stirred for 3 h. After this time, the reaction was warmed to rt and stirred for additional 3 h. The reaction was quenched with an aqueous saturated NH<sub>4</sub>Cl solution (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, 40% EtOAc/hexane) afforded the corresponding **1o** (952 mg, 63% yield).

#### General procedure for the gold-catalyzed hydration of alkynes **1a-o**

Alkynes **1a-o** (2 mmol), JohnPhosAuCl (0.5 mol%, 0.01 mmol) and NaBAR<sub>4</sub><sup>F</sup> (0.5 mol%, 0.01 mmol) were pre-dissolved in 2-MeTHF (2.0 mL) inside a round-bottom flask. Then, distilled water (18.0 mL) was added, and the mixture was stirred for 16 h at 40 °C. After this time, the reaction mixture was cooled to rt and extracted with EtOAc (2 × 15 mL for **2a**) or Et<sub>2</sub>O (2 × 15 mL for **2b-n**), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Diketones **2a-o** were obtained attaining the following results: 373 mg of **2a**, 98% yield; 290 mg of **2b**, 93% yield; 467 mg of **2c**, 97% yield; 80 mg of **2d**, 21% yield; 345 mg of **2e**, 98% yield; 370 mg of **2f**, 97% yield; 358 mg of **2g**, 94% yield; 392 mg of **2h**, 96% yield; 395 mg of **2i**, 96% yield; 405 mg of **2j**, 96% yield; 440 mg of **2k**, 98% yield; 358 mg of **2l**, 92% yield; 426 mg of **2m**, 97% yield; 450 mg of **2n**, 96% yield; 437 mg of **2o**, 91% yield; 202 mg of **2p**, 88% yield; 260 mg of **2q**, 91% yield; 290 mg of **2r**, and 93% yield.

#### Synthesis of tetrahydropyridine (*S*)-**3** on a preparative scale

Alkyne **1a** (1 g, 5.8 mmol), JohnPhosAuCl (16.0 mg, 0.5 mol%, 0.029 mmol) and NaBAR<sub>4</sub><sup>F</sup> (25.5 mg, 0.5 mol, 0.029 mmol) were dissolved in 2-MeTHF (5.8 mL) inside an Erlenmeyer flask, and then distilled water (52.2 mL) was added. The mixture was stirred at 40 °C for 16 h. After this time, 100 mM KPi buffer pH 7.5 (174 mL) containing PLP (1 mM) and 2-PrNH<sub>2</sub> (1 M) and lyophilized cells of *E. coli* heterologously expressing Cv-TA (580 mg) were added. The mixture was kept under orbital shaking at 220 rpm at 30 °C for 24 h. After this time, the solution was extracted with EtOAc (2 × 80 mL), the organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (15.3 g SiO<sub>2</sub>, 10% EtOAc/hexane, 15 mL/135 mL) afforded the corresponding tetrahydropyridine (*S*)-**3** (>99% ee) as a smelly yellowish oil (943 mg, 94% isolated yield, see Sections X and XI in the ESI† for analysis details).



### Synthesis of dihydropyrrole derivatives (*S*)-4a and (*S*)-4b on a semipreparative scale

Alkyne **1g** or **1j** (1 mmol), JohnPhosAuCl (2.8 mg, 0.5 mol%, 0.005 mmol) and NaBar<sup>F</sup><sub>4</sub> (4.4 mg, 0.5 mol%, 0.005 mmol) were dissolved in 2-MeTHF (1 mL) inside an Erlenmeyer flask, and then distilled water (9 mL) was added. The mixture was stirred at 40 °C for 16 h. After this time, 100 mM KPi buffer pH 7.5 (30 mL) containing PLP (1 mM) and 2-PrNH<sub>2</sub> (1 M) and the transaminase *ArS*-ATA (100 mg) were added. The mixture was kept under orbital shaking at 220 rpm at 30 °C for 24 h. After this time, the solution of each reaction was extracted with EtOAc (2 × 15 mL), and the organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solution was concentrated, measuring the conversion and the enantiomeric excess of (*S*)-4a and (*S*)-4b by HPLC analyses (see Section X in the ESI†). These enantiopure dihydropyrrole derivatives were obtained as a smelly yellowish oil (120 mg, 69% isolated yield for **4a** and 122 mg, 63% isolated yield for **4b**) after column chromatography purification on silica gel using a mixture of 20% EtOAc/hexane as the eluent.

### Synthesis of diol (2*S*,5*S*)-5 on a semipreparative scale

Hexa-1,5-diyne (200 mg, 2.56 mmol), JohnPhosAuCl (7.7 mg, 0.5 mol%, 0.0128 mmol) and NaBar<sup>F</sup><sub>4</sub> (11.3 mg, 0.5 mol%, 0.0128 mmol) were dissolved in 2-MeTHF (2.56 mL) inside a round-bottom flask. Then, 2-PrOH (2.56 mL), distilled water (20.5 mL) containing NAD<sup>+</sup> (1 mM) and semi-purified expressed ADH-A (200 mg) from heat treatment were added. The mixture was kept under magnetic stirring at 40 °C for 24 h. After this time, the solution was extracted with Et<sub>2</sub>O (2 × 10 mL), and the organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, 50% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>) afforded (2*S*,5*S*)-hexane-2,5-diol (**5**, >99% ee and >99% de, see Sections X and XI in the ESI†) as a colorless oil (265 mg, 88% yield).

### Data availability

The data supporting this article have been included as part of the ESI.†

### Author contributions

L. E. performed the experiments. L. E. and S. G.-G. analyzed the results. The study was conceptualized by I. L. and V. G.-F. I. L. wrote the first version of the manuscript, which was later corrected and revised by all the authors.

### Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support from the Spanish Ministry of Science and Innovation (MCI, PID2019-109253RB-I00 and PID2022-137893OB-I00 projects) is gratefully acknowledged. L. E. thanks the Asturian regional government for a predoctoral fellowship inside the Severo Ochoa programme (PA-22-BP21-058). Technical support from the Scientific-Technical Services (University of Oviedo) is acknowledged. Prof. Wolfgang Kroutil (University of Graz, Austria) and Prof. Nicholas J. Turner (University of Manchester, UK) are also acknowledged for providing us with ADHs and TAS heterologously expressed in *E. coli* cells.

## Notes and references

- 1 M. Lemmerer, M. Schupp, D. Kaiser and N. Maulide, *Nat. Synth.*, 2022, **1**, 923–935.
- 2 V. G. Kharchenko, L. I. Markova, O. V. Fedotova and N. V. Pchelintseva, *Chem. Heterocycl. Compd.*, 2003, **39**, 1121–1142.
- 3 S. Khaghaninejad and M. M. Heravi, *Adv. Heterocycl. Chem.*, 2014, **111**, 95–146.
- 4 N. Kaur, P. Bhardwaj and M. Gupta, *Curr. Org. Chem.*, 2021, **25**, 2765–2790.
- 5 S. R. Yetra, A. Patra and A. T. Biju, *Synthesis*, 2015, **47**, 1357–1378.
- 6 M. M. Heravi, V. Zadsirjan, K. Kafshdarzadeh and Z. Amiri, *Asian J. Org. Chem.*, 2020, **9**, 1999–2034.
- 7 J.-i. Matsuo and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 9109–9118.
- 8 S. Murarka and A. P. Antonchick, *Synthesis*, 2018, **50**, 2150–2162.
- 9 C. Che, Z. Qian, M. Wu, Y. Zhao and G. Zhu, *J. Org. Chem.*, 2018, **83**, 5665–5673.
- 10 Y. Zhou, L. Zhao, M. Hu, X.-H. Duan and L. Liu, *Org. Lett.*, 2023, **25**, 5268–5272.
- 11 S. Sau, K. M. Das, B. Mondal and A. Thakur, *J. Org. Chem.*, 2024, **89**, 7095–7108.
- 12 N. Salaverri, J. Alemán and L. Marzo, *Adv. Synth. Catal.*, 2024, **366**, 156–167.
- 13 For a report on the synthesis of *cis*-4-oxo-2-en-1-ones combining alkyne hydration with alkene oxidation, see: A. M. Jadhav, S. A. Gawade, D. Vasu, R. B. Dateer and R.-S. Liu, *Chem. – Eur. J.*, 2014, **20**, 1813–1817.
- 14 For a report on the synthesis of β-diketones, see: J. Kuang, T. Zhou, T. You, J. Chen, C. Su and Y. Xia, *Org. Biomol. Chem.*, 2019, **17**, 3940–3944.
- 15 N. Ríos-Lombardía, J. García-Álvarez and J. González-Sabín, *Catalysts*, 2018, **8**, 75.
- 16 S. Gonzalez-Granda, J. Albarrán-Velo, I. Lavandera and V. Gotor-Fernández, *Chem. Rev.*, 2023, **123**, 5297–5346.
- 17 S. González-Granda, L. Escot, I. Lavandera and V. Gotor-Fernández, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217713.
- 18 A. Patwa, C. Pegu, B. Paroi and N. T. Patil, *Tetrahedron Lett.*, 2025, **154**, 155382.



- 19 J. H. Schrittwieser and V. Resch, *RSC Adv.*, 2013, **3**, 17602–17632.
- 20 E. Cigan, B. Eggbauer, J. H. Schrittwieser and W. Kroutil, *RSC Adv.*, 2021, **11**, 28223–28270.
- 21 J. I. Ramsden, S. C. Cosgrove and N. J. Turner, *Chem. Sci.*, 2020, **11**, 11104–11112.
- 22 J. Feng, W.-C. Geng, H. Jiang and B. Wu, *Biotechnol. Adv.*, 2022, **54**, 107813.
- 23 E. P. Vanable, L. G. Habgood and J. D. Patrone, *Molecules*, 2022, **27**, 6373.
- 24 Y. Lazib, J. G. Naves, A. Labande, P. Dauban and T. Saget, *ACS Org. Inorg. Au*, 2023, **3**, 120–129.
- 25 R. C. Simon, B. Grischek, F. Zepeck, A. Steinreiber, F. Belaj and W. Kroutil, *Angew. Chem., Int. Ed.*, 2012, **51**, 6713–6716.
- 26 R. C. Simon, F. Zepeck and W. Kroutil, *Chem. – Eur. J.*, 2013, **19**, 2859–2865.
- 27 R. C. Simon, C. S. Fuchs, H. Lechner, F. Zepeck and W. Kroutil, *Eur. J. Org. Chem.*, 2013, **2013**, 3397–3402.
- 28 E. O'Reilly, C. Iglesias, D. Ghislieri, J. Hopwood, J. L. Galman, R. C. Lloyd and N. J. Turner, *Angew. Chem., Int. Ed.*, 2014, **53**, 2447–2450.
- 29 S. P. France, S. Hussain, A. M. Hill, L. J. Hepworth, R. M. Howard, K. R. Mulholland, S. L. Flitsch and N. J. Turner, *ACS Catal.*, 2016, **6**, 3753–3759.
- 30 B. Z. Costa, J. L. Galman, I. Slabu, S. P. France, A. J. Marsaioli and N. J. Turner, *ChemCatChem*, 2018, **10**, 4733–4738.
- 31 N. Alvarenga, S. E. Payer, P. Petermeier, C. Kohlfuerst, A. L. Meleiro Porto, J. H. Schrittwieser and W. Kroutil, *ACS Catal.*, 2020, **10**, 1607–1620.
- 32 J. I. Ramsden, B. Z. da Costa, R. S. Heath, J. R. Marshall, S. R. Derrington, J. Mangas-Sanchez, S. L. Montgomery, K. R. Mulholland, S. C. Cosgrove and N. J. Turner, *ACS Catal.*, 2024, **14**, 14703–14710.
- 33 For a recent example to obtain trisubstituted piperidines, see: P. Petermeier, C. Kohlfuerst, A. Torvisco, R. C. Fischer, A. Mata, D. Dallinger, C. O. Kappe, J. H. Schrittwieser and W. Kroutil, *Adv. Synth. Catal.*, 2023, **365**, 2188–2202.
- 34 L. Hintermann and A. Labonne, *Synthesis*, 2007, **2007**, 1121–1150.
- 35 W. E. Brenzovich Jr., *Angew. Chem., Int. Ed.*, 2012, **51**, 8933–8935.
- 36 X. Liu, J.-L. Pozzo, A. Hamze, M. Alami and O. Provot, *ACS Catal.*, 2023, **13**, 10115–10136.
- 37 J. A. Goodwin and A. Aponick, *Chem. Commun.*, 2015, **51**, 8730–8741.
- 38 F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079–3159.
- 39 C. H. Leung, M. Baron and A. Biffis, *Catalysts*, 2020, **10**, 1210.
- 40 N. Marion, R. S. Ramón and S. P. Nolan, *J. Am. Chem. Soc.*, 2009, **131**, 448–449.
- 41 A. Mariconda, M. Sirignano, R. Troiano, S. Russo and P. Longo, *Catalysts*, 2022, **12**, 836.
- 42 P. Gao and M. Szostak, *Coord. Chem. Rev.*, 2023, **485**, 215110.
- 43 S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, **2008**, 3707–3738.
- 44 M. Müller, M. Katzberg, M. Bertau and W. Hummel, *Org. Biomol. Chem.*, 2010, **8**, 1540–1550.
- 45 H. Zheng, R. J. Felix and M. R. Gagné, *Org. Lett.*, 2014, **16**, 2272–2275.
- 46 T. Yuan, X. Ye, P. Zhao, S. Teng, Y. Yi, J. Wang, C. Shan, L. Wojtas, J. Jean, H. Chen and X. Shi, *Chem*, 2020, **6**, 1420–1431.
- 47 T. Rigotti and T. Bach, *Org. Lett.*, 2022, **24**, 8821–8825.
- 48 W. Wang, B. Xu and G. B. Hammond, *J. Org. Chem.*, 2009, **74**, 1640–1643.
- 49 T. Yuan, Q. Tang, C. Shan, X. Ye, J. Wang, P. Zhao, L. Wojtas, N. Hadler, H. Chen and X. Shi, *J. Am. Chem. Soc.*, 2021, **143**, 4074–4082.
- 50 S. González-Granda, G. Steinkellner, K. Gruber, I. Lavandera and V. Gotor-Fernández, *Adv. Synth. Catal.*, 2023, **365**, 1036–1047.
- 51 A. R. Alcántara and P. Domínguez de María, *Curr. Green Chem.*, 2018, **5**, 86–103.
- 52 A. Collado, D. J. Nelson and S. P. Nolan, *Chem. Rev.*, 2021, **121**, 8559–8612.
- 53 M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Angew. Chem., Int. Ed.*, 2005, **44**, 5284–5288.
- 54 M. Biava, G. C. Porretta, G. Poce, S. Supino, D. Deidda, R. Pompei, P. Molicotti, F. Manetti and M. Botta, *J. Med. Chem.*, 2006, **49**, 4946–4952.
- 55 D. Deidda, G. Lampis, R. Fioravanti, M. Biava, G. C. Porretta, S. Zanetti and R. Pompei, *Antimicrob. Agents Chemother.*, 1998, **42**, 3035–3037.
- 56 R. Faghih, S. M. Gopalakrishnan, J. H. Gronlien, J. Malysz, C. A. Briggs, C. Wetterstrand, H. Ween, M. P. Curtis, K. A. Sarris, G. A. Gfesser, R. El-Kouhen, H. M. Robb, R. J. Radek, K. C. Marsh, W. H. Bunnelle and M. Gopalakrishnan, *J. Med. Chem.*, 2009, **52**, 3377–3384.
- 57 D. C. Harrowven and J. C. Hannam, *Tetrahedron Lett.*, 1998, **39**, 9573–9574.
- 58 X. Huang, M. Cao and H. Zhao, *Curr. Opin. Chem. Biol.*, 2020, **55**, 161–170.
- 59 Y. Liu, P. Liu, S. Gao, Z. Wang, P. Luan, J. González-Sabín and Y. Jiang, *Chem. Eng. J.*, 2021, **420**, 127659.
- 60 L. Bering, J. Thompson and J. Micklefield, *Trends Chem.*, 2022, **4**, 392–408.
- 61 C. Ascaso-Alegre and J. Mangas-Sanchez, *Eur. J. Org. Chem.*, 2022, **2022**, e202200093.
- 62 H. Gröger, F. Gallou and B. H. Lipshutz, *Chem. Rev.*, 2023, **123**, 5262–5296.
- 63 C. Gastaldi, A. Gautier, C. Forano, V. Hélaine and C. Guérard-Hélaine, *ChemCatChem*, 2024, **16**, e202301703.
- 64 M. Asikainen and N. Krause, *Adv. Synth. Catal.*, 2009, **351**, 2305–2309.
- 65 M. Odachowski, M. F. Greaney and N. J. Turner, *ACS Catal.*, 2018, **8**, 10032–10035.
- 66 M. J. Rodríguez-Álvarez, N. Ríos-Lombardía, S. Schumacher, D. Pérez-Iglesias, F. Morís, V. Cadierno, J. García-Álvarez and J. González-Sabín, *ACS Catal.*, 2017, **7**, 7753–7759.



- 67 P. Schaaf, V. Gojic, T. Bayer, F. Rudroff, M. Schnürch and M. D. Mihovilovic, *ChemCatChem*, 2018, **10**, 920–924.
- 68 S. Mathew, A. Sagadevan, D. Renn and M. Rueping, *ACS Catal.*, 2021, **11**, 12565–12569.
- 69 Z. Li, Z. Wan, W. Wang, L. Chen and P. Ji, *ACS Catal.*, 2024, **14**, 8786–8793.
- 70 Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond and F. D. Toste, *Nat. Chem.*, 2013, **5**, 100–103.
- 71 F. Chang, C. Wang, Q. Chen, Y. Zhang and G. Liu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202114809.
- 72 This protocol was performed in a sequential manner: J. Liu, J. Bai, Y. Liu, L. Zhou, Y. He, L. Ma, G. Liu, J. Gao and Y. Jiang, *JACS Au*, 2024, **4**, 2281–2290.
- 73 This protocol was done in a sequential manner: M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J.-Y. Berthon and B. H. Lipshutz, *Nat. Commun.*, 2019, **10**, 2169.
- 74 C. Gastaldi, V. Hélaine, M. Joly, A. Gautier, C. Forano and C. Guérard-Hélaine, *Catal. Sci. Technol.*, 2023, **13**, 1623–1627.
- 75 J. Santiago-Arcos, D. Andrés-Sanz, N. Ríos-Lombardía, S. Carregal-Romero, D. di Silvio, I. Llarena, J. García-Álvarez, J. González-Sabín and F. López-Gallego, *Cell Rep. Phys. Sci.*, 2024, **5**, 102015.
- 76 J. M. Naapuri, N. Losada-Garcia, R. A. Rothemann, M. C. Pichardo, M. H. G. Precht, J. M. Palomo and J. Deska, *ChemCatChem*, 2022, **14**, e202200362.
- 77 S. González-Granda, I. Lavandera and V. Gotor-Fernández, *Angew. Chem., Int. Ed.*, 2021, **60**, 13945–13951.
- 78 S. González-Granda, L. Escot, I. Lavandera and V. Gotor-Fernández, *ACS Catal.*, 2022, **12**, 2552–2560.
- 79 L. Escot, S. González-Granda, V. Gotor-Fernández and I. Lavandera, *Org. Biomol. Chem.*, 2022, **20**, 9650–9658.
- 80 L. Escot, S. González-Granda, D. Méndez-Sánchez, Y. Wang, H. C. Hailes, I. Lavandera and V. Gotor-Fernández, *Adv. Synth. Catal.*, 2024, **366**, 4737–4746.
- 81 S. González-Granda, N. V. Tzouras, S. P. Nolan, I. Lavandera and V. Gotor-Fernández, *Adv. Synth. Catal.*, 2022, **364**, 3856–3866.
- 82 M. Daghmoum, N. Sabat, M. Lecoq, T. Viraize and X. Guinchard, *ACS Catal.*, 2025, **15**, 2484–2491.
- 83 With aldolases, it was also necessary to follow a sequential protocol although in this case due to incompatibilities of the reaction conditions, see: C. Gastaldi, G. Mekhloufi, C. Forano, A. Gautier and C. Guérard-Hélaine, *Green Chem.*, 2022, **24**, 3634–3639.
- 84 U. Kaulmann, K. Smithies, M. E. B. Smith, H. C. Hailes and J. M. Ward, *Enzyme Microb. Technol.*, 2007, **41**, 628–637.
- 85 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283.
- 86 M. J. Burk, J. E. Feaster and R. L. Harlow, *Organometallics*, 1990, **9**, 2653–2655.
- 87 M. J. Burk, *J. Am. Chem. Soc.*, 1991, **113**, 8518–8519.
- 88 M. J. Burk, J. E. Feaster and R. L. Harlow, *Tetrahedron: Asymmetry*, 1991, **2**, 569–592.
- 89 G. de Gonzalo, I. Lavandera, K. Faber and W. Kroutil, *Org. Lett.*, 2007, **9**, 2163–2166.
- 90 M. Brill, F. Nahra, A. Gómez-Herrera, C. Zinser, D. B. Cordes, A. M. Z. Slawin and S. P. Nolan, *ChemCatChem*, 2016, **9**, 117–120.
- 91 N. V. Tzouras, M. Saab, W. Janssens, T. Cauwenbergh, K. Van Hecke, F. Nahra and S. P. Nolan, *Chem. – Eur. J.*, 2020, **26**, 5541–5551.
- 92 T. A. C. A. Baryrakdar, F. Nahra, O. Zugazua, L. Eykens, D. Ormerod and S. P. Nolan, *Green Chem.*, 2020, **22**, 2598–2604.
- 93 T. A. Grigolo and J. M. Smith, *Chem. – Eur. J.*, 2022, **28**, e202202813.
- 94 C. Wu, J. Lv, H. Fan, W. Su, X. Cai and J. Yu, *Chem. – Eur. J.*, 2024, **30**, e202304231.

