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Introducing deep eutectic solvents as biorenewable media for Au(I)-catalysed cycloisomerisation of γ-alkynoic acids: an unprecedented catalytic system†

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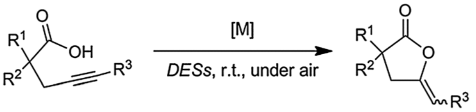
Cycloisomerisation of γ-alkynoic acids into cyclic enol-lactones was conveniently performed, for the first time, in the eutectic mixture *1ChCl/2Urea* under standard bench experimental conditions (at room temperature, under air and in the absence of co-catalysts) by using a new iminophosphorane–Au(I) complex as the catalyst. Furthermore, the catalytic system could be recycled up to four runs.

The 12 *principles* of *green chemistry* have become a widely accepted set of criteria for the rapid assessment of the "*greenness*" of a given chemical reaction.[1] In this sense, one of the crucial points in realizing a *catalytic green chemical process*[2] involves the choice of a safe, non-toxic, biorenewable, and cheap solvent. However, the use of *green solvents* still remains a lasting challenge, even when conventional hazardous volatile organic solvents (*VOCs*, commonly used as reaction media in metal-mediated organic procedures) can cause well-established environmental and safety-related problems.[3] In this sense, recent pioneering work from several synthetic laboratories around the world has recognised the potential of deep eutectic solvents (*DESs*) as superior *green* and biorenewable solvents.[4] These eutectic mixtures [which can be defined as molecular complexes typically formed between a simple halide salt (*i.e.* choline chloride) and a hydrogen bond donor] have found a wide variety of applications in different fields of modern chemistry, including (i) organic synthesis, (ii) biocatalytic reactions, (iii) dissolution of metal oxides, (iv) electrodeposition of metals, and (v) materials chemistry.[5] However, and as far as we are aware, the number of studies reporting the ability of *DESs* to serve as *green* and biorenewable reaction media in metal-catalysed organic reactions is still scarce.[6]

Together with the choice of a safe, non-toxic, biorenewable and cheap solvent (like *DESs*), the design of metal-catalysed organic reactions proceeding (i) with energy efficiency (synthetic methods conducted at room temperature) and atom economy,[7] (ii) under aerobic conditions, and (iii) as selective and specific processes with high yields is one of the major goals in organic synthesis (from a *green chemistry* point of view).[1] In this sense, the metal-catalysed cycloisomerisation of γ-alkynoic acids (Scheme 1),[8] conducted in *DESs*, under air and at room temperature, fulfills the aforementioned *principles* of *green chemistry*.



Scheme 1 Metal-catalysed cycloisomerisation of γ-alkynoic acids in *DESs*.

With these precedents in mind, and following our interest in studying (i) the catalytic activity of organometallic complexes containing iminophosphorane ligands[9] and (ii) new metal-mediated organic reactions in *DESs*,[10] herein we report a new neutral gold(I) complex, namely $[AuCl\{\kappa^1\text{-}S\text{-}(PTA){=}NP({=}S)(OPh)_2\}]$ (**3**) (PTA = 1,3,5-triaza-7-phosphaadamantane), which is an efficient and selective catalyst for the regio and selective cycloisomerisation of γ-alkynoic acids in *DESs*. The following features of this catalytic system are remarkable: (i) this is the first example reported in the literature for the metal-catalysed cycloisomerisation of γ-alkynoic acids in *DESs*, (ii) the reaction takes place under standard bench experimental conditions (at room temperature, under air and in the absence of co-catalysts), and (iii) the use of the eutectic mixture 1*ChCl*/2*Urea* as a reaction medium allows the catalytic recycling (up to 4 consecutive runs).

Iminophosphorane–Au(I) complex **3** was readily prepared by the treatment of the PTA-based iminophosphorane ligand[9c] **1** with an equimolecular amount of $[AuCl(SMe_2)]$ (**2**) in CH_2Cl_2 at room temperature (Scheme 2). This compound, which results from the expected exchange of labile SMe_2, was isolated as an air stable white solid in excellent yield (84%). The characterisation of complex **3** was achieved by means of elemental analysis and IR and multinuclear (^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$) NMR spectroscopy (see ESI†). In particular, the κ^1-*S* coordination of ligand **1** is clearly reflected in the

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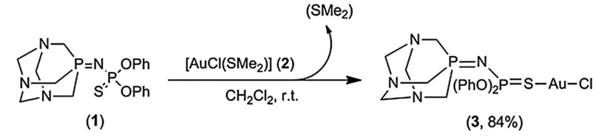
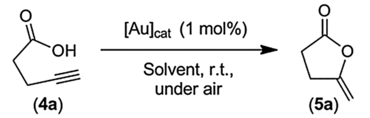


Scheme 2 Synthesis of the iminophosphorane–Au(I) complex **3**.

$^{31}P\{^1H\}$ NMR spectrum of **3** by (i) an appreciable downfield shift of the $(PhO)_2P{=}S$ signal ($\Delta\delta$ = 18.8 ppm) and (ii) conversion of the doublet signals of the P=N and $(PhO)_2P{=}S$ groups in the free ligand into two broad signals of complex **3** (see the ESI† for additional data). Moreover, the formation of neutral complex **3** was unambiguously confirmed by a single-crystal X-ray diffraction study (see ESI†).

The catalytic activity of complex **3** in *DESs* was firstly evaluated by the cycloisomerisation of the commercially available 4-pentynoic acid (**4a**) as a model reaction (Table 1). To our satisfaction, complex **3** is an active and selective catalyst at room temperature, under aerobic conditions and with a catalyst loading of 1 mol% in the three *ChCl*-based eutectic mixtures tested [1*ChCl*/2*Urea* (entry 1, Table 1), 1*ChCl*/2*Gly* (*Gly* = glycerol, entry 2, Table 1) and 1*ChCl*/2*EG* (*EG* = ethyleneglycol, entry 3, Table 1)], affording the desired enol-lactone **5a** as the unique reaction product. It is important to note that in no case, the addition of any co-catalyst was needed, since the participation of a chloride abstractor (commonly used in Au(I) chemistry)[11] or base was not required. No by-products derived from the addition of the components of *DESs* to the C≡C bond of **4a** or hydrolysis of the generated enol-lactone **5a** were detected (CG or NMR). Thus, we found that complex **3** displays much higher activity in the eutectic mixture 1*ChCl*/2*Urea*, leading to quantitative conversion in only 15 min (entry 1, Table 1). This fact can be probably attributed to (i) the previously reported basic character of the eutectic mixture 1*ChCl*/2*Urea*[5,12] and (ii) the more dipolar nature of this eutectic mixture;[5,13] when compare with its polyalcohol-based counterparts (*Gly* or *EG*). These ideas are also in accordance with the lower activity and selectivity observed when the carboxylic acid-based eutectic mixture 1*ChCl*/2*Lac* (*Lac* = lactic acid, entry 4, Table 1) was employed as a reaction medium, as extensive hydrolysis reaction of **5a** took place, yielding a mixture containing **5a** and 3-acetylpropanoic acid (in a ratio of 7 : 3). The observed rate of the reaction was strongly dependent on the nature of the Au(I)-catalyst.[14] Remarkably, the presence of iminophosphorane ligand **1** in the catalyst was crucial, as the efficiency of the reaction was remarkably lowered when other Au(I) or Au(III) sources, such as [AuCl(PPh$_3$)] (entry 5, Table 1) or Au$_2$O$_3$ (entry 6, Table 1) were employed as catalysts. It is also worth noting that the reaction proceeds at a higher rate in the eutectic mixture 1*ChCl*/2*Urea* than in (i) other *green* solvents (water entry 7; glycerol entry 8), or (ii) conventional volatile organic solvents (toluene, entry 9), thus disclosing a new example of an accelerated organic reaction in *DESs*.[4] Finally, no catalytic reaction was observed in the absence of catalytic amounts of complex **3** (entry 10) or when free iminophosphorane ligand **1** was used as a catalyst (entry 11). These experimental results confirm that complex **3** is responsible for the catalytic activity observed in the cycloisomerisation reaction.

Table 1 Cycloisomerisation of 4-pentynoic acid (**4a**) into enol-lactone **5a** catalysed by the iminophosphorane–Au(I) complex **3** in different *DESs*[a]

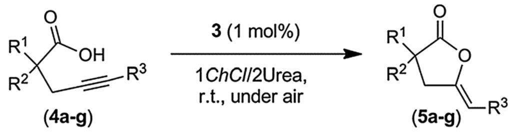


Entry	Catal.	Solvent	Time (min)	Yield[b] (%)
1	**3**	1*ChCl*/2*Urea*	15	99
2	**3**	1*ChCl*/2*Gly*	30	99
3	**3**	1*ChCl*/2*EG*	30	99
4	**3**	1*ChCl*/2*Lac*	30	70[c]
5	[AuCl(PPh$_3$)]	1*ChCl*/2*Urea*	30	25
6	Au$_2$O$_3$	1*ChCl*/2*Urea*	75	84
7	**3**	H$_2$O	30	89
8	**3**	Glycerol	60	94
9	**3**	Toluene	45	32
10	—	1*ChCl*/2*Urea*	60	1
11	**1**	1*ChCl*/2*Urea*	60	1

[a] General conditions: reactions performed under air, at r.t. using 1 mmol of the alkynoic acid **4a** and 1 mol% of catalyst **3** in 1 gr of the desired solvent. [b] Lated yields. [c] Formation of a mixture in a 7 : 3 ratio of **5a** and 3-acetylpropanoic acid.

The high efficiency shown by complex **3** in the cycloisomerisation of the γ-alkynoic acid **4a** into enol-lactone **5a** in *DESs* (1*ChCl*/2*Urea*) prompted us to extend the study to a variety of γ-alkynoic acids, to prove the scope of this catalytic transformation (Table 2). Thus, catalyst **3** shows a wide range of applications and tolerance to functional groups in the cycloisomerisation of a variety of terminal alkynes, being compatible with the presence of ester (entries 2, 3 and 5–7), amino (entry 4), alkenyl (entry 5) and alkynyl (entry 6) groups. For the cycloisomerisation of these γ-alkynoic acids (**4a–f**), it is important to note that (i) no traces of the corresponding 6-membered ring enol-lactones, resulting from an *endo* instead of an *exo* cyclization, were detected, (ii) no hydrolysis of the enol-lactones **5a–f** to form the corresponding keto-acids was observed, and (iii) in the cycloisomerisation of the symmetric 1,6-diyne **5f**, one of the propargylic groups remained unaltered, *i.e.* it did not undergo a hydration

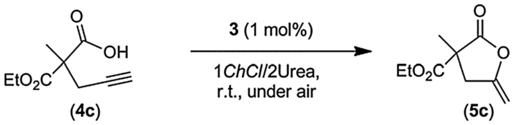
Table 2 Cycloisomerisation of γ-alkynoic acids **4a–g** catalysed by the iminophosphorane–Au(I) complex **3** in the eutectic mixture 1*ChCl*/2*Urea*[a]



Entry	R^1	R^2	R^3	Product	Time [h]	Yield[b] [%]
1	H	H	H	**5a**	0.25	99
2	CO$_2$Me	H	H	**5b**	2	98
3	CO$_2$Et	Me	H	**5c**	1	98
4	NH(Boc)	H	H	**5d**	3.5	99
5	CO$_2$Me	H$_2$C=CH(CH$_2$)–	H	**5e**	1	99
6	CO$_2$Me	HC≡C(CH$_2$)–	H	**5f**	1.5	97
7	CO$_2$Et	Me	Et	**5g**	1.75	90[c]

[a] General conditions: reactions performed under air, at r.t. using 1 mmol of the corresponding alkynoic acid and 1 mol% of catalyst **3** in 1 gr of the eutectic mixture 1*ChCl*/2*Urea*. [b] Isolated yields. [c] Formation of a mixture in a 10 : 1 ratio of the corresponding 5- and 6-membered ring enol-lactone was observed.

Table 3 Cycloisomerisation of the γ-alkynoic acid **4c** catalysed by the iminophosphorane–Au(I) complex **3** in 1*ChCl*/2*Urea*: catalyst recycling[a]



Cycle	Time [h]	Yield[b] [%]	TON[c]
1	1	99	99
2	1	90	189
3	1.75	95	284
4	2	90	374

[a] General conditions: reactions performed under air, at r.t. using 1 mmol of the alkynoic acid **4c** and 1 mol% of catalyst **3** in 1 gr of the eutectic mixture 1*ChCl*/2*Urea*. [b] Determined by GC. [c] Cumulative TON values (turnover number = (mol product/mol Au)).

reaction or the addition of the components of *DESs*. Finally, this catalytic system was also active with internal alkynes (entry 7). However, in this case, a small amount of the corresponding 6-membered ring enol-lactone was detected (in a ratio of 10 : 1).[15]

The lifetime of a catalytic system and its level of reusability are very important factors.[16] Thus, under the previously optimised reaction conditions (1 mol% of **3**, 1*ChCl*/2*Urea*, r.t. and air) and using the cycloisomerisation of alkynoic acid **4c** as a model reaction (see Table 3), we found that the catalytic system remains active (90–99%) after recycling up to four consecutive runs, with a gradual decrease of the activity after each cycle. Thus, for the first two cycles 1 hour was needed to achieve high conversions, while 2 hours were required in the fourth cycle, probably due to both leaching during the work-up and decomposition of the catalyst.

In summary, we have designed a new air-stable catalyst, *i.e.* the Au(I) complex $[\mathrm{AuCl}\{\kappa^1\text{-}S\text{-(PTA)=NP(=S)(OPh)}_2\}]$ (**3**), for the cycloisomerisation of γ-alkynoic acids in the eutectic mixture 1*ChCl*/2*Urea*. The reaction proceeds under remarkably mild and aerobic conditions, displaying a broad substrate scope and functional compatibility. The following catalytic features of the catalytic system merit highlighting: (i) complex **3** is the first active catalyst reported to date for the cycloisomerisation of γ-alkynoic acids in *DESs*, (ii) the catalytic reaction takes place under standard bench experimental conditions (at room temperature, under air and in the absence of co-catalysts), providing a pivotal contribution to *green chemistry*, (iii) its high selectivity precludes either the addition of the components of *DESs* to the $C{\equiv}C$ bond or the concomitant hydrolysis of enol-lactones **5a–g**, and (iv) the catalytic system can be efficiently recycled (up to four consecutive runs). Thus, this methodology represents an important contribution to the almost unexplored field of metal-catalysed organic reactions in *DESs*. Further efforts devoted to the development of new catalytic systems active and recoverable in *DESs* are currently underway.

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