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ARTICLE TYPE

Introducing Deep Eutectic Solvents as biorenewable media for Au(I)-catalysed cycloisomerisation of γ -alkynoic acids: an unprecedented catalytic system.

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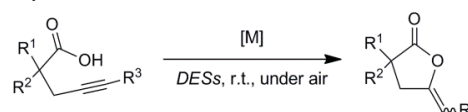
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Cycloisomerisation reactions of γ -alkynoic acids into cyclic enol-lactones can be conveniently performed, for the first time, in the eutectic mixture 1ChCl/2Urea under standard bench experimental conditions (room temperature, in air and in the absence of co-catalysts) by using a new iminophosphorane-Au(I) complex as 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 Process² involve 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 donors] 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*) material 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 reaction is still scarce.⁶

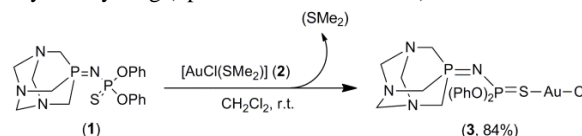
Together with the choice of a safe, non-toxic, biorenewable and cheap solvent (like DESs), the design of metal-catalysed organic reactions proceeding: *i*) with energy efficiency (synthetic methods conducted at room temperature) and atom economy,⁷ *ii*) under aerobic conditions, and *iii*) as selective and specific processes in high yields; are 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, fulfils 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 reaction in DESs;¹⁰ herein we report a new neutral gold(I) complex, namely [AuCl(κ^1 -S-(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 reactions (room temperature, under air and in the absence of any co-catalyst), and *iii*) the use of the eutectic mixture 1ChCl/2Urea as reaction media allows the catalytic recycling (up to 4 consecutive times).

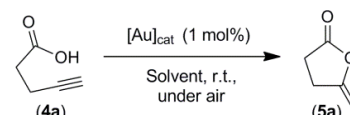


Scheme 2 Synthesis of the iminophosphorane-Au(I) complex 3.

The iminophosphorane-Au(I) complex 3 has been readily prepared by the treatment of the PTA-based iminophosphorane ligand^{9c} 1 with an equimolecular amount of [AuCl(SMe₂)] (2) in CH₂Cl₂ at room temperature (Scheme 2). This compound, which results from the expected exchange of the labile SMe₂, was isolated as an air stable white solid in excellent yield (84%). The characterization of complex 3 was achieved by means of elemental analysis, IR and multinuclear (¹H, ¹³C{¹H} and ³¹P{¹H}) NMR spectroscopy (see ESI). In particular, the κ^1 -S coordination of ligand 1 is clearly reflected in the ³¹P{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 in complex **3** (see ESI for further data). Moreover, the formation of the neutral complex **3** was unambiguously confirmed by a single-crystal X-ray diffraction study (see ESI).

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	Yield (%) ^b
1	3	1 <i>ChCl</i> /2 <i>Urea</i>	15 min	99
2	3	1 <i>ChCl</i> /2 <i>Gly</i>	30 min	99
3	3	1 <i>ChCl</i> /2 <i>EG</i>	30 min	99
4	3	1 <i>ChCl</i> /2 <i>Lac</i>	30 min	70 ^c
5	[AuCl(PPh ₃)]	1 <i>ChCl</i> /2 <i>Urea</i>	30 min	25
6	Au ₂ O ₃	1 <i>ChCl</i> /2 <i>Urea</i>	75 min	84
7	3	H ₂ O	30 min	89
8	3	glycerol	60 min	94
9	3	toluene	45 min	32
10	-	1 <i>ChCl</i> /2 <i>Urea</i>	60 min	1
11	1	1 <i>ChCl</i> /2 <i>Urea</i>	60 min	1

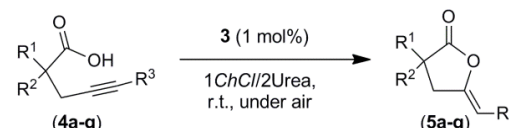
^a General Conditions: Reactions performed under air, at r.t. using 1 mmol of the alkynoic acid **4a** and 1 mol% of catalyst **3** in 1 gr of the desired solvent. ^b Isolated yields. ^c Formation of a mixture in a 7:3 ratio of **5a** and 3-acetylpropanoic acid.

The catalytic activity of complex **3** in *DESs* was firstly evaluated using 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* = ethylenglycol, 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 reaction media, as extensive hydrolysis reaction of **5a** took place, yielding

a mixture containing **5a** and 3-acetylpropanoic acid (in 7:3 ratio). The observed rate of the reaction was strongly dependent on the nature of the Au(I)-catalyst.¹⁴ Remarkably, the presence of the 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(PPh₃)] (entry 5, Table 1) or Au₂O₃ (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 the free iminophosphorane ligand **1** was used as catalyst (entry 11). These experimental facts corroborate that complex **3** is the responsible of the catalytic activity observed in the cycloisomerisation reaction.

The high efficiency showed 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 application and tolerance to functional groups in the cycloisomerisation of a variety of terminal alkynes, being compatible with the presence of ester (entries 2-3, 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-lactone, 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-acid was observed, and *iii*) in the cycloisomerisation of the symmetric 1,6-diyne **5f**, one of the propargylic groups stays unaltered, *i.e.* it does not suffer a hydration reaction or the addition of the components of *DESs*. Finally, this catalytic system is also active with internal alkynes (entry 7). However, in this case, small amount of the corresponding 6-membered ring enol-lactone was detected (in a 10:1 ratio).¹⁵

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*.

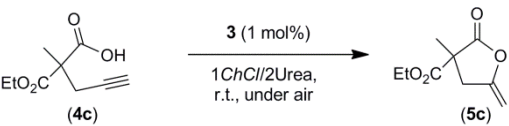


entry	R ¹	R ²	R ³	product	Time[h]	Yield[%] ^b
1	H	H	H	5a	0.25	99
2	CO ₂ Me	H	H	5b	2	98
3	CO ₂ Et	Me	H	5c	1	98
4	NH(Boc)	H	H	5d	3.5	99
5	CO ₂ Me	H ₂ C=CH(CH ₂)-	H	5e	1	99
6	CO ₂ Me	HC≡C(CH ₂)-	H	5f	1.5	97
7	CO ₂ Et	Me	Et	5g	1.75	90 ^c

^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.

The life-time 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 under air) and using as a model reaction the cycloisomerisation of the γ -alkynoic acid **4c** (see Table 3), we have 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 recycling. 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 work-up and decomposition of the catalyst.

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)).

Conclusions

In summary, we have designed a new air-stable catalyst, *i.e.* the Au(I) complex [AuCl{ κ^1 -S-(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 (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 times). 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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[†] Electronic Supplementary Information (ESI) available: For the synthesis of compound **3**, catalytic procedure and crystallographic data for **3**. CCDC 1016771.

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