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Autocatalysis

Tandem Gold Self-Relay Catalysis for the Synthesis of 2,3-Dihydropyridin-4(1*H*)-ones: Combination of σ and π Lewis Acid Properties of Gold Salts

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Abstract: The dual ability of gold salts to act as π- and σ Lewis acids has been exploited in a tandem self-relay catalysis. Thus, triphenylphosphanegold(I) triflate mediated the intramolecular carbonyl addition of the amide functionality of homoprogargyl amides to a triple bond. The formation of a σ complex of the gold salt with the intermediate oxazine promoted a nucleophilic addition followed by a Petasis–Ferrier rearrangement. This tandem protocol, catalyzed by the same gold salt under the same reaction conditions, gave rise to the efficient synthesis of 2,3-dihydropyridin-4-(1*H*)-ones, which contain a cyclic quaternary α-amino acid unit. The asymmetric version was performed by generating the starting materials from the corresponding sulfinylimines.

Introduction

Tandem catalysis can be defined as a set of reactions catalyzed independently by one or more catalysts in a consecutive manner. Because one of the main interests of academia and industry is the enhancement of synthetic efficiency, this methodology is becoming increasingly important in several areas of organic chemistry, including natural-products synthesis, drug discovery, and process chemistry.[1] Additionally, this process is one of the strategies used by nature in the preparation of biomolecules.[2] In this manner, by using single starting materials, molecular complexity can be increased in a single operation, thus allowing the synthesis of complex molecules and avoiding the loss of time and product associated with the isolation and purification of intermediates in multistep sequences. This approach provides environmental and economic benefits and also fulfills the principles of green chemistry.

Among the different types of tandem catalysis, auto-catalysis (also named self-relay catalysis) is probably the most efficient.[3] This technique involves the combination of two or more distinct reactions promoted by the same catalyst, all of which occur under the same reaction conditions in a concurrent manner. In comparison with other types of tandem catalysis (assisted and orthogonal), no interference between the catalytic species is possible in this case; therefore, the use of catalysts is very efficient and favorable in terms of time and energy. However, the difficulty in the optimization of the separated processes independently has made these processes very challenging.

On the other hand, the π Lewis acidity of gold(I) salts has been extensively explored. The ability of these salts to activate alkynes under mild conditions toward the addition of a wide variety of nucleophiles has converted gold complexes into appreciated catalysts to promote tandem reactions.[4] Although explored to a lesser extent, gold salts also exhibit interesting behavior as σ Lewis acids. This type of Lewis acidity of gold salts has been shown in the activation of several oxygen-[5] and nitrogen-containing compounds.[6] However, examples in which gold salts play a dual role, that is, by taking advantage of both hard (σ Lewis acid) and soft (π Lewis acid) Lewis acidity, are scarce even though they constitute a new paradigm in the reactivity of gold complexes.[7]

Homopropargyl amines are usual partners in gold-catalyzed reactions. Depending on the substituent attached to the nitrogen atom, these compounds undergo cyclization to render a great variety of pyrrolidine and piperidine scaffolds.[8] In this context, Rhee and co-workers reported that *tert*-butoxycarbonyl (Boc)- or carbobenzyloxy (Cbz)-protected amines bearing a methoxymethyl moiety in the presence of gold salts evolve in a formal aza-Prins cyclization, thus giving rise to piperidine enol ethers that were subsequently hydrolyzed to the corresponding piperidones (Scheme 1).[8h] On the other hand, Zhang and co-workers reported that the alkyne moiety of homopropargyl amides can be activated by gold, thus promoting addition of a carbonyl group to furnish the corresponding oxazines; furthermore, due to their high lability, these compounds were reduced in situ with a borane to the hemiaminal, which in turn underwent a spontaneous aza-Petasis–Ferrier rearrangement and final reduction of the carbonyl moiety

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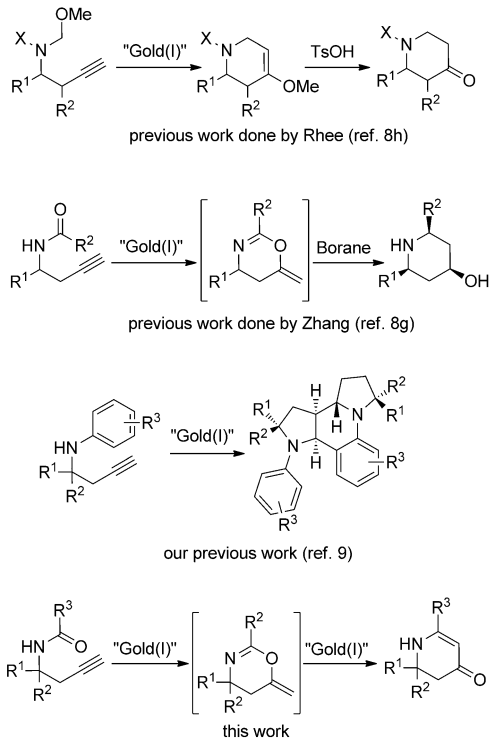


Scheme 1. Reactivity of homopropargyl amines versus gold salts. TsOH = toluenesulfonic acid.

(Scheme 1). The overall process constitutes a modular approach to the preparation of 4-piperidinols.[8g]

In the context of an ongoing project in our laboratory, we evaluated the reactivity of protected homopropargylic amines bearing a quaternary center, which have not been studied to date. We hypothesized that depending on the nature of the protecting group, we could expect a differential reactivity; thus, when these amines contain an aryl substituent, they evolve in the presence of gold salts in a tandem hydroamination/formal aza-Diels–Alder reaction sequence to generate tetracyclic frameworks (Scheme 1).[9]

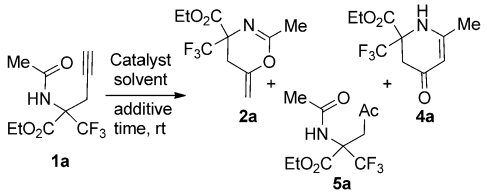
Herein, we describe the reactivity of these amines after their conversion into the corresponding amides toward gold(I) salts. Homopropargyl amides **1** underwent a new tandem reaction in the presence of gold(I) salts to give access to a new family of 2,3-dihydropyridin-4(1*H*)-ones, skeletons that have been used as versatile intermediates in the synthesis of several piperidine, indolizidine, and quinolizidine alkaloids[10] (Scheme 1). The overall process, which could be considered to be a gold self-relay catalysis, takes advantage of the dual behavior of gold salts as hard and soft Lewis acids. It is important to mention that, in comparison with previous reports, the entire process is promoted by gold in this case, thus displaying a new reactivity pattern. The presence of the quaternary center was crucial in this observed divergent reactivity. The scope of this process and a plausible mechanistic proposal are disclosed herein. Additionally, the use of chiral sulfinylimines allowed us to develop an asymmetric version of this protocol.

Abstract in Spanish: La doble capacidad de las sales de oro para actuar como ácidos de Lewis π y σ ha sido utilizada en un proceso tándem catalítico de tipo *self-relay*. De esta forma, el triflato de trifenilfosfina oro(I) promueve la adición intramolecular del grupo carbonilo de la función amida de amidas homopropargílicas sobre el triple enlace. Posteriormente, la formación de un complejo σ de la sal de oro con la oxazina intermedia induce un ataque nucleofílico seguido de un reagrupamiento tipo Petasis-Ferrier. El proceso tándem, que está catalizado por la misma sal de oro en las mismas condiciones de reacción, conduce de forma eficaz a 2,3-dihidropiridin-4-(1*H*)-onas, compuestos que adicionalmente contienen una unidad α-amino ácido en su estructura. La versión asimétrica se llevó a cabo generando los sustratos de partida a partir de las correspondientes sulfinil iminas.

Results and Discussion

Compound **1a** was used as a model substrate to evaluate the reactivity toward gold salts. Initially, we treated substrate **1a** with $AuCl_3$ in dichloromethane at room temperature. Oxazine **2a**, which arises from the addition of the carbonyl group to the triple bond, was obtained after 24 hours in 40% yield with 40% of **5a**, which comes from the hydration of the alkyne toward the methyl ketone (Table 1, entry 1). Similar results were obtained with AuCl (Table 1, entry 2). However, the use of $[AuClPPh_3]$ in combination with AgOTf led to a drastic decrease

Table 1. Reactivity toward gold(I) salts.



Entry	Catalyst	Additive	Solvent	*t* [h]	Yield **2a** [%]	Yield **4a** [%]	Yield **5a** [%]
1	$AuCl_3$	–	CH_2Cl_2	24	40	–	40
2	AuCl	–	CH_2Cl_2	24	37	–	35
3	$[AuClPPh_3]$	AgOTf	CH_2Cl_2	3	57	–	30
4	$[AuClPPh_3]$	$AgNTf_2$	CH_2Cl_2	6	50	–	30
5	$[AuClPPh_3]$	AgOTf/MS (3 Å)	CH_2Cl_2	3	72 (83)[a]	–	–
6	AgOTf	–	CH_2Cl_2	24	–	–	–
7	TfOH	–	CH_2Cl_2	24	–	–	–
8	$[AuClPPh_3]$	AgOTf	toluene	24	25[b]	–	35
9	$[AuClPPh_3]$	AgOTf	CH_3CN	22	35[b]	–	34
10	$[AuClPPh_3]$	AgOTf	MeOH	3	–	93	–
11	$[AuClPPh_3]$	$AgNTf_2$	MeOH	5	–	87	–
12	AuCl	–	MeOH	24	–	47	33

[a] The yield determined by GC-MS is given in brackets. [b] The conversion was not complete and some starting material was recovered. MS = molecular sieves, NTf_2 = bis(trifluoromethylsulfonyl)imide, Tf = trifluoromethanesulfonyl.

in reaction time. Total consumption of the starting material was observed after 3 hours, and oxazine **2a** was isolated in 57% yield, again with the acetyl derivative **5a** (Table 1, entry 3). The use of a different silver salt (i.e., silver triflimide) led to comparable results (Table 1, entry 4). At this point, it is important to mention that TLC analysis revealed that product **5a** was derived from oxazine **2a** and can be assumed to form from traces of water present in the reaction medium. To avoid this hydrolysis, the reaction was performed in the presence of molecular sieves (3 Å), which led to a significant improvement in the yield (Table 1, entry 5). Although the yield determined by GC-MS was 83%, the yield of the isolated oxazine **2a** was 72%, thus indicating that this compound is labile and decomposes during purification. Substrate **1a** was inert either in the presence of the silver salt or triflic acid, thus indicating the role of gold in catalyzing the reaction (Table 1, entries 6 and 7). The next step of our study was the evaluation of the solvent in the process. The use of toluene or acetonitrile as solvents led to a decrease in efficiency (Table 1, entries 8 and 9). However, the use of methanol gave a surprising result, in which the exclusive formation of dihydropyridone **4a** was observed in excellent yield after 3 hours (Table 1, entry 10). The use of silver triflimide gave comparable results, although with longer reaction times (Table 1, entry 11). On the other hand, it took 24 hours to complete the process and a mixture of **4a** and **5a** was obtained when AuCl was used as catalyst (Table 1, entry 12).

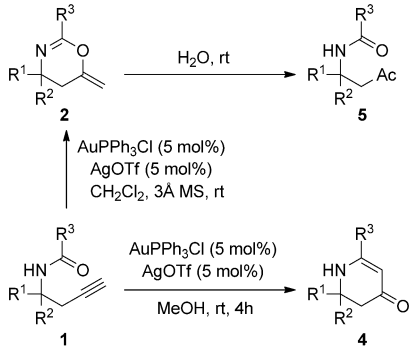
With these results, we proceeded to study the behavior of other homopropargylic amides under the optimized conditions. Thus, when homopropargyl amides **1** were treated with $[AuClPPh_3]$ in combination with AgOTf in dichloromethane in the presence of molecular sieves, a clean formation of oxazines **2** was observed (Table 2, entries 1–7). As mentioned before, these compounds partially decompose during purification, but obtaining good yields of the isolated products was possible. Hydrolysis of oxazines **2** took place in almost quantitative yields in all cases to render the alkyne hydrolysis products **5** (Table 2, entries 1–7). It seems that the hydration of the triple bond under gold catalysis is assisted by the carbonyl group. The solvent played a crucial role in the process, and the exclusive formation of dihydropyridones **4** in methanol was observed in good-to-excellent yields (Table 2, entries 1–7).

In all cases, a quaternary center is present in the starting amides **1**. The reactivity of substrates that arise from non-fluorinated aldimines (Table 1, entry 8) has been described before;[8g] although the formation of the corresponding oxazine has been reported, these compounds were unstable and were subjected to further transformations without isolation. Additionally, this substrate was inert in the presence of the gold salt in methanol, even in the presence of acidic additives, thus preventing the complexation of gold and the basic nitrogen atom (Table 2, entry 8). It is clear that the presence of the quaternary center plays a significant role in the process, but we do not have an explanation so far for this different behavior.

The next step of our study was an asymmetric version of the sequence. To this end, sulfinylimines were used as chiral auxiliaries. Thus, ethyl trifluoropyruvate (**6**) was subjected to an aza-Wittig reaction with chiral phosphazene **7** and the corresponding iminoester **8** was treated in situ with propargyl bromide and activated zinc in DMF under Barbier-type conditions. The addition of propargylzinc was completely selective, thus affording homopropargylic sulfinylamine **9** as a single diastereoisomer. Protecting-group removal and acetylation led to the starting amide **1a** in enantiomerically pure form.[11] Reaction of **1a** with $[AuOTfPPh_3]$ gave oxazine **2a** in dichloromethane, acetyl derivative **5a** upon hydrolysis, and dihydropyridone **4a** in methanol (Scheme 2). Compound **4a** contains a cyclic quaternary α-amino acid unit, which infers more relevance to the asymmetric process.

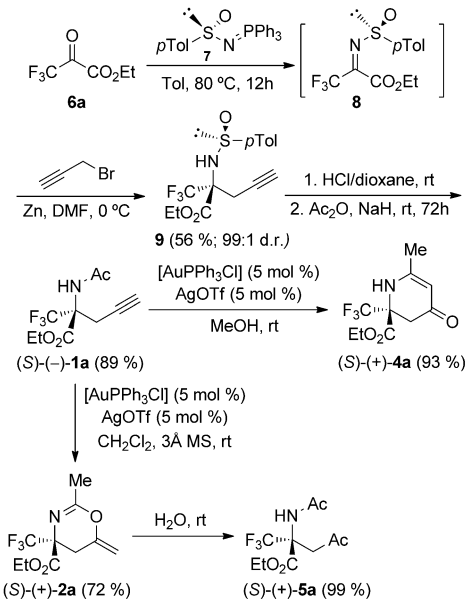
As mentioned before, hydration products **5** come from oxazines **2**. In the same way, we observed by TLC analysis that the first step in the reaction performed in methanol was once again the formation of oxazines **2**, thus indicating that these compounds are also intermediates in the formation of dihydropyridones **4**. To prove this observation and the role of the gold salt in the process, several experiments were performed. First, when oxazine **2a** was dissolved in dry methanol, it remained unaltered after 24 hours at room temperature (Table 3, entry 1). When a catalytic amount of triflic acid was added to the reaction mixture, total consumption of the starting material was observed after 6 hours, thus giving rise to **4a** in 61% yield (Table 3, entry 2). On the other hand, the reaction in the presence of AgOTf did not proceed, thus recovering the starting material untouched after 24 hours at room temperature

Table 2. Preparation of oxazines **2**, dihydropyridones **4**, and acetyl derivatives **5**.



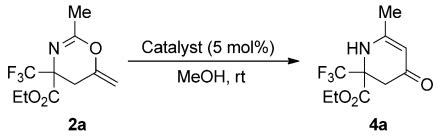
Entry	R^1	R^2	R^3	Yield **2** [%]	Yield **4** [%]	Yield **5** [%]
1	CF_3	CO_2Et	Me	**2a** 72 (83)[a]	**4a** 93	**5a** 99
2	CF_2Ph	CO_2Et	Me	**2b** 70 (86)[a]	**4b** 93	**5b** 99
3	CF_2Bn	CO_2Et	Me	**2c** 80 (94)[a]	**4c** 80	**5c** 99
4	CF_2allyl	CO_2Et	Me	**2d** 88 (98)[a]	**4d** 94	**5d** 99
5	CF_3	CO_2Et	Et	**2e** 61 (95)[a]	**4e** 70[b]	**5e** 99
6	Ph	CO_2Et	Me	**2f** 76	**4f** 75	**5f** 84
7	CF_3	Ph	Me	**2g** 74	**4g** 76	**5g** 99[c]
8	Ph	H	Me	–[d]	–	–

[a] The yield determined by GC-MS is given in brackets. [b] The formation of 28% of **5e** was also observed. [c] To carry out the hydrolysis in this case, it was necessary to add 5 mol% of the gold(I) salt to activate the oxazine for the nucleophilic attack. [d] The substrate remained unaltered in methanol.[8]



Scheme 2. Asymmetric version of the tandem process. DMF = *N*,*N*-dimethylformamide, Tol = toluene.

Table 3. Transformation of oxazine **2a** into dihyropyridone **4a**.

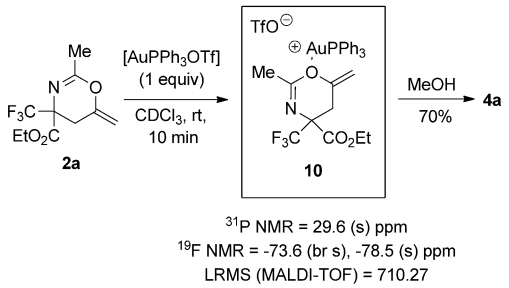


Entry	Catalyst	*t* [h]	Yield **4a** [%][a]
1	–	24	–
2	TfOH	6	61
3	AgOTf	24	–
4	[AuClPPh$_3$]/AgOTf	0.5	71
5	BF$_3$·OEt$_2$	4	84

[a] Yield of the isolated product after flash chromatography.

(Table 3, entry 3). A completely different situation emerged with the addition of [AuClPPh$_3$] in combination with AgOTf. The reaction was complete after 30 minutes, thus affording **4a** in 71% yield (Table 3, entry 4). Finally, the use of a Lewis acid (e.g., BF$_3$·OEt$_2$) gave rise to the final product **4a** in 4 hours (Table 3, entry 5). Additional evidence of this dual role played by gold salts can be inferred from the reaction performed with AuCl (Table 1, entry 11). This neutral gold species (softer than the cationic [AuOTfPPh$_3$]) is less effective in the σ activation of the imidate, which led to longer reaction times and the appearance of an increased amount of hydration product **5a**. These observations clearly indicate that the gold salt acts as a σ Lewis acid and promotes the transformation of oxazine **2a** into dihydropyridone **4a** more efficiently than a strong Brønsted or Lewis acid (i.e., triflic acid or BF$_3$·OEt$_2$, respectively).

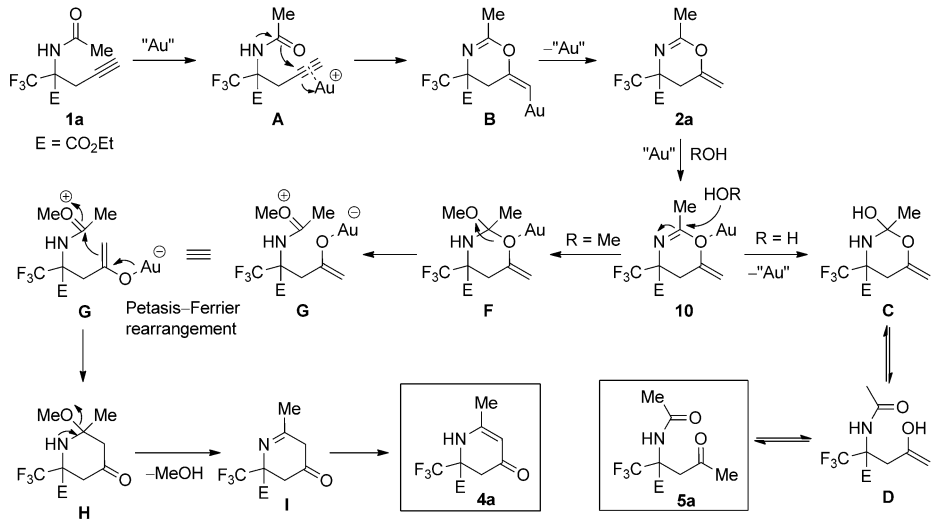
With these results achieved, we decided to firmly establish the ability of this gold salt to perform the σ activation. For this purpose, we planned an isolation of the intermediate complex of [AuOTfPPh$_3$] with oxazine **2a** to prove the identity of the involved species. To this end, **2a** was treated with one equivalent of the gold salt (previous filtration of the AgCl formed during the preparation of the catalytic species) in CDCl$_3$, and the clean formation of a new species was observed after 10 minutes. ^{31}P NMR spectroscopic analysis showed a singlet at $\delta =$ 29.6 ppm (shifted downfield in comparison with the signal for free [AuOTfPPh$_3$], which appears at $\delta = 27.5$ ppm, according to its less cationic character after forming the σ complex with the oxazine), whereas ^{19}F NMR spectroscopic analysis revealed two signals that correspond to the CF$_3$ groups of the oxazine moiety and the counterion. Low-resolution mass-spectrometric analysis spectra indicated the existence of complex **10** (*m*/*z* 710.27); in addition, ^{1}H and ^{13}C NMR spectroscopic data were also in agreement with the presence of this complex (see the Supporting Information).[12] As expected, complex **10** turned into dihydropyridone **4a** after removal of the solvent and the addition of methanol (Scheme 3).



Scheme 3. Preparation of σ gold complex **10**. LRMS = low-resolution mass spectrometry, MALDI-TOF = matrix-assisted laser desorption ionization/time of flight,

A plausible explanation of the reaction outcome is depicted in Scheme 4. Initially, when amide **1a** was treated with [AuOTfPPh$_3$] in dichloromethane, coordination with the triple bond occurred (**A**), thus activating the bond to the addition of the carbonyl group. Proto-deauration of intermediate **B** rendered oxazine **2a**. The next step was the coordination of the gold salt with the oxygen atom of the imidate functionality, which activates it to the addition of an external nucleophile. When the nucleophile was water (R = H), the addition to complex **10** gave rise to hemiacetal **C**, which is in equilibrium with the opened intermediate **D**, thus rendering hydration product **5a** after tautomerization. A completely different situation appeared when the nucleophile was methanol (R = Me); namely, the mixed acetal **F** formed, which is susceptible to undergoing a gold-catalyzed Petasis–Ferrier rearrangement.[13] Thus, the acetal moiety undergoes ring opening to form the oxonium ion **G**, which cyclized again into pyridine **H**. Methanol elimination and further isomerization of the double bond of **I** gave rise to dihydropyridone **4a** (Scheme 4).

Therefore, the formation of **4a** involved a tandem reaction catalyzed by the same gold salt (self-relay catalysis). The overall process took advantage of the dual role of the gold catalyst,



Scheme 4. Mechanistic proposal.

which initially activated the triple bond in a π Lewis acid-type activation and subsequently the imidate functionality for both the addition of the methanol and the Petasis–Ferrier rearrangement in a σ Lewis acid-type activation. This case is a new example of gold-mediated self-relay catalysis.

Conclusion

A new self-relay gold-catalyzed cascade carbonyl addition/nucleophilic addition/Petasis–Ferrier rearrangement has been described. The tandem process, which takes advantage of and unifies the σ- and π Lewis acid properties of gold salts, gives rise to a new family of dihydropyridones, an important structural pattern for the synthesis of several natural products. Finally, the asymmetric version of the process was also developed by means of chiral sulfinylimines, thus allowing the preparation of new amino acid derivatives bearing a quaternary stereocenter in an enantiomerically pure form.

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Keywords: alkaloids · autocatalysis · gold · Lewis acids · transition-metal catalysis

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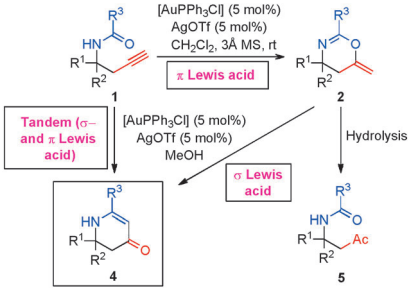
FULL PAPER

Working together: The bifunctional Lewis acid properties of gold(I) salts were exploited to implement a tandem process. Homopropargylic amides **1** reacted with triphenylphosphanegold(I) triflate in a triple self-relay catalytic process to render 2,3-dihydropyridin-4-(1*H*)-ones **4** (see picture; MS = molecular sieves, Tf = trifluoromethanesulfonyl). This protocol takes advantage of the dual behavior of gold salts as σ- and π Lewis acids; this ability of gold salts to act as σ Lewis acids was demonstrated by the isolation and characterization of the σ complex.



Autocatalysis

S. Fustero, J. Miró, M. Sánchez-Roselló, C. del Pozo**

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Tandem Gold Self-Relay Catalysis for the Synthesis of 2,3-Dihydropyridin-4(1*H*)-ones: Combination of σ and π Lewis Acid Properties of Gold Salts