Heterogeneous & Homogeneous & Bio- & Nano-
CHEMCATCHEM
CATALYSIS

Accepted Article

Title: Gold(I) mediated thiourea organocatalyst activation: A synergic effect for asymmetric catalysis

Authors: M. Concepción Gimeno, Raquel P. Herrera, and Anabel Izaga

To be cited as: *ChemCatChem* 10.1002/cctc.201601527

Link to VoR: http://dx.doi.org/10.1002/cctc.201601527

A Journal of
ChemPubSoc Europe

WILEY-VCH

www.chemcatchem.org

10.1002/cctc.201601527

WILEY-VCH

Gold(I) mediated thiourea organocatalyst activation: A synergic effect for asymmetric catalysis

Anabel Izaga,[a] Raquel P. Herrera,*[b] and M. Concepción Gimeno*[a]

Abstract: Several group 11 metal complexes with chiral thiourea organocatalysts have been prepared and tested as organocatalysts. The promising results on the influence of metal assisted thiourea organocatalysts in the asymmetric Friedel–Crafts alkylation of indole with nitrostyrene are described. Better results with the metal complexes have been achieved because of the cooperative effects between the chiral thiourea and the metal. The synergic effect between both species is higher than the effect promoted by each one separately, especially for gold(I). These outcomes are attributed to a pioneering gold(I) activation of the thiourea catalysts, affording a more acidic and rigid catalytic complex than that provided by the thiourea alone. Furthermore, the use of the gold-thiourea organocatalyst allows reducing the catalyst loading to 1-3 mol%. This contribution could become an important starting point for further investigations opening a new line of research overlooked so far in the literature.

Introduction

In the last decade, between the two main families of catalysts: metal and enzymatic catalysis, a third complementary approach has emerged, *the Organocatalysis*,[1] which has become an important tool able to provide efficient and environmentally friendly access to enantiomerically pure compounds, including many drugs and bioactive natural products.[2]

Although the organocatalysis has experimented great progress in the field of homogeneous catalysis, the organocatalysts still require more improvements in order to emulate and to reach the achievements reported with metal or enzyme catalysts. With this aim, many efforts have been directed towards the synthesis of more efficient organocatalysts through the use of several strategies. One of them has been the development of bifunctional organocatalysts,[3] following the multifunctional catalytic mode exhibited by enzymes. These complex systems have inspired many catalytic systems such as chiral bifunctional thioureas/ureas,[4] among others, which keep simultaneous activation of the nucleophile and the electrophile involved in the process (Figure 1).

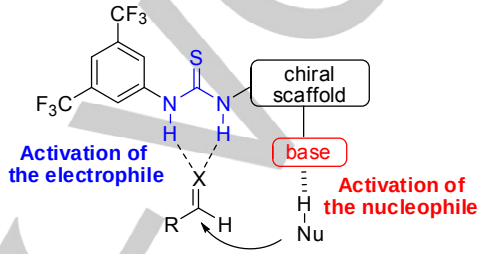


Figure 1. Bifunctional activation mode.

Other strategy to improve the reactivity of the organocatalysts, which has received considerable attention in the last years, has been the use of two different catalysts in a cooperative way, a metal catalyst and an organocatalyst, called *dual catalysis* (Figure 2).[5] This idea has emerged as a promising strategy for developing new and more valuable processes, and also takes advantage of simultaneous activation of the electrophile as well as the nucleophile by two different, but compatible and synergically acting catalysts.

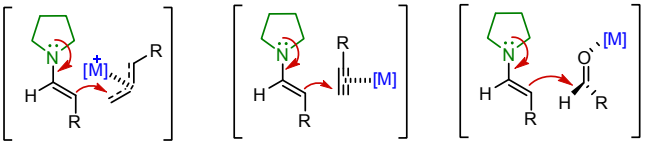


Figure 2. Activation by dual catalysis: combination of enamine nucleophiles and transition metal electrophiles.

The enormous success of chiral ureas and thioureas as hydrogen bond donor organocatalysts in asymmetric synthesis has led to a continuous improvement of these organocatalysts through the use of several modes of activation, trying to improve parameters such as catalysts loading, reaction time and substrate scope for a given reaction. All these efforts made in the last years have materialized in several upgraded catalysts. Among them, Seidel and coworkers have reported the use of an internal Brønsted acid forming a protonated thiourea catalyst (Figure 3a),[6] although it was not the most active catalyst in this work. Later, Smith's group developed new conformationally well-defined but flexible thiourea catalysts, stabilized by intramolecular hydrogen bonds (Figure 3b).[7,8] More recently,

[a] A. Izaga, Prof. M. C. Gimeno
Departamento de Química Inorgánica.
Instituto de Síntesis Química y Catálisis Homogénea (ISQCH),
CSIC-Universidad de Zaragoza.
C/ Pedro Cerbuna, Nº12, E-50009 Zaragoza, Spain
E-mail: gimeno@unizar.es
[b] Dr. R. P. Herrera
Departamento de Química Orgánica. Laboratorio de Organocatálisis Asimétrica
Instituto de Síntesis Química y Catálisis Homogénea (ISQCH),
CSIC-Universidad de Zaragoza.
C/ Pedro Cerbuna, Nº12, E-50009 Zaragoza, Spain.
E-mail: raquelph@unizar.es

Supporting information for this article is given via a link at the end of the document.

Herrera and coworkers have described the use of an external Brønsted acid (Figure 3c),[9] in order to improve the efficiency of the corresponding chiral thiourea catalysts.

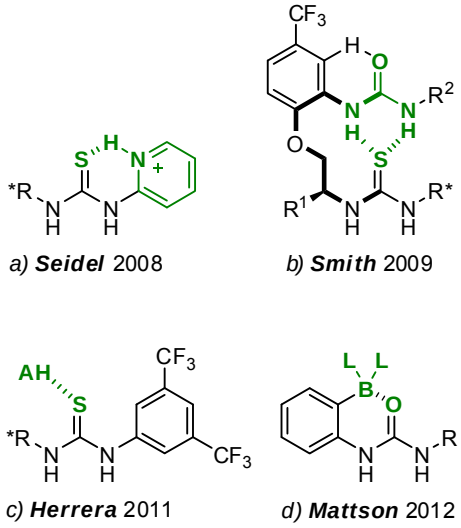


Figure 3. Activation of thiourea organocatalysts through an internal or an external Brønsted acid.

The use of an internal Brønsted acid produced significant rate acceleration and only a slight improvement in enantioselectivity for the Friedel–Crafts reaction.[6] In contrast, the external Brønsted acid was able to assist thiourea catalysts as very effective catalytic species for promoting the enantioselective addition of indoles to nitroalkenes.[9] The synergic effect between both species was demonstrated to be higher than the effect promoted by each one separately and better results in terms of enantioselectivity and reactivity were reached compared with the corresponding thiourea alone.[9] Mattson and co-workers have also developed hybrid transition metals which act as hydrogen bond donor catalysts such as urea palladacycles[10] inspired at the same time in boronates ureas developed by the same research group (Figure 3).[11] However, in these examples the authors only use non-chiral ureas.[12]

In the search of new types of activation of thioureas as organocatalysts, and taking into account this novel concept together with our experience in the chemistry of group 11 metals,[13] encouraged us to face the results described here; where instead of an external Brønsted acid we will use a Lewis acid metal atom (Figure 4, **III**). This will open a novel and interesting line of research where the metal center will activate the thiourea catalyst, and this activation could be fine-tuned by carefully choosing the Lewis acid character of the metal, its oxidation state and also its auxiliary ligands. Interestingly, the metal will not participate in the activation of none of the reagents. The coordination chemistry of gold to thiourea-based ligands has been previously explored with other purposes, mainly because of the interesting biological properties displayed by the complexes. However, this work represents the first example where coordination to chiral thioureas strongly activates them as organocatalysts.[14]

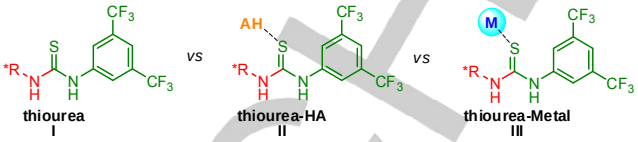


Figure 4. Challenging idea.

In the context of our research program focused on the design and synthesis of more active organocatalysts, we report here an unprecedented mode of activation of thiourea organocatalysts through the use of metallic Lewis acids. A wide range of group 11 metal-thiourea complexes have been synthesized and used as single catalysts in asymmetric catalysis taking advantages of the best part of both species in a synergic way.

Results and Discussion

In order to test our hypothesis, we started our study with the synthesis of a variety of group 11 metal complexes with thioureas as potential catalysts for the Friedel-Crafts alkylation reaction as a model process.

Thioureas **T1-3** were chosen as model catalytic structures since they exhibit different electronic and steric properties (Figure 5). Moreover, **T3** was the best catalyst in our previously developed works.[9,15]

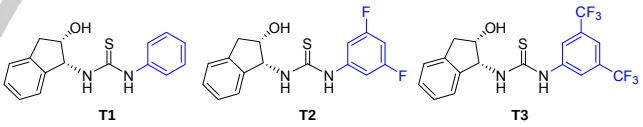
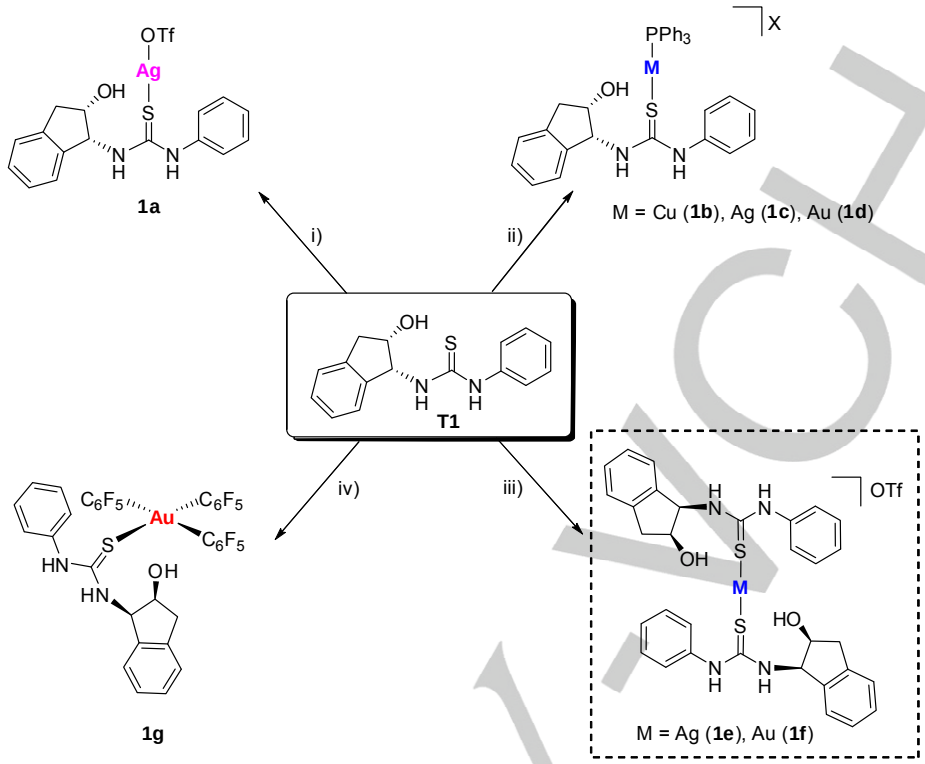


Figure 5. Model thioureas used in this work.

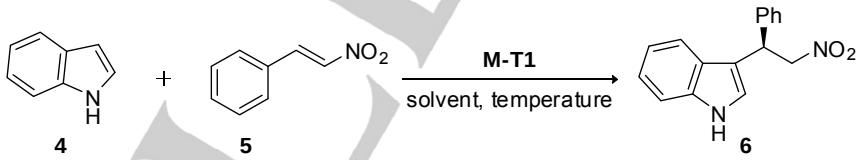
The exploration was started with **T1** presenting less steric hindrance and without electronegative groups in the aromatic ring. The straightforward preparation of the metal complexes **1a-g** is shown in Scheme 1. There are neutral or cationic Cu(I), Ag(I), Au(I) or Au(III) species that have been perfectly identified and characterized by NMR spectroscopy (see Supporting Information).



Scheme 1. Catalytic complex structures **1a-g** with Cu-**T1**, Ag-**T1** and Au-**T1**. *i)* Ag(OTf); *ii)* $[Cu(NO_3)(PPh_3)_2]$ or $[Ag(OTf)(PPh_3)]$ or $[Au(OTf)(PPh_3)]$; *iii)* ½ Ag(OTf) or ½ $[Au(tht)_2]OTf$; *iv)* $[Au(C_6F_5)_3(tht)]$.

Subsequently, the efficiency of these species in the benchmark reaction between indole **4** and nitrostyrene **5** was analyzed and the results of these tests are reported in Table 1.[16]

Table 1. Screening of the reaction promoted by **M-T1** (**1a-g**) complexes.[a]



4 **5** **6**

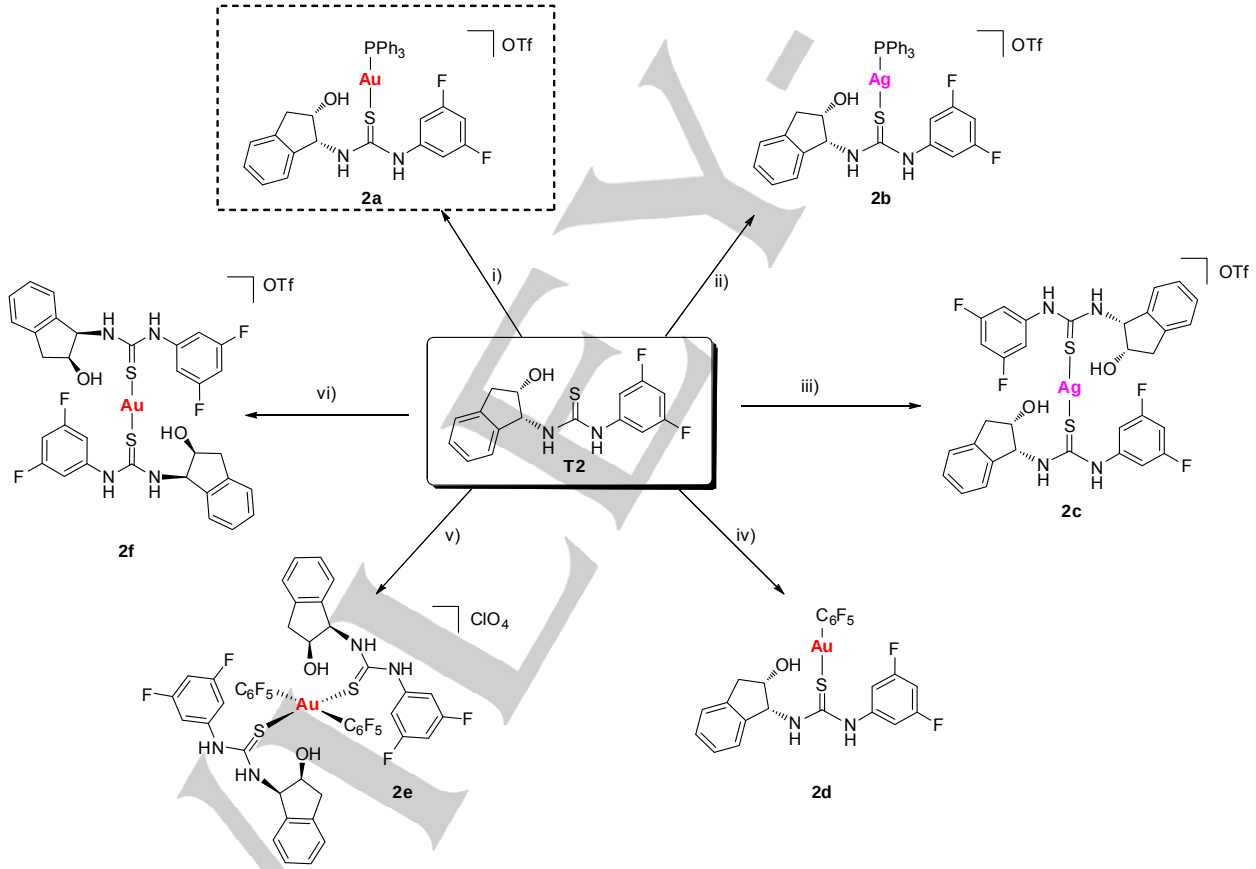
Entry	**M-T1** (mol %)	Solvent (mL)	T (ºC)	t (days)	yield (%)[b]	ee (%)[c]
1	**1a** (10%)	CH_2Cl_2 (0.5)	r.t.	3	22	20
2	**1a** (10%)	CH_2Cl_2 (0.25)	r.t.	3	83	14
3	**1b** (10%)	CH_2Cl_2 (0.5)	r.t.	5	60	6
4	**1c** (10%)	CH_2Cl_2 (0.5)	r.t.	4	38	18
5	**1d** (10%)	CH_2Cl_2 (0.5)	r.t.	3	22	42
6	**1e** (10%)	CH_2Cl_2 (0.5)	r.t.	3	60	20
7	**1e** (10%)	CH_2Cl_2 (0.25)	-17	6	60	32
8	**1e** (10%)	Toluene (0.25)	r.t.	3	75	8
9	**1e** (10%)	$CHCl_3$ (0.25)	r.t.	3	53	20
10	**1f** (10%)	CH_2Cl_2 (0.5)	r.t.	3	19	30
11	**1g** (10%)	CH_2Cl_2 (0.5)	r.t.	4	23	5

12	**T1** (10%)	CH_2Cl_2 (0.5)	r.t.	4	10	Rac.[d]
13	$[Au(tht)_2]OTf$ (5%)	CH_2Cl_2 (0.5)	r.t.	3	10	_

[a] Amount of reagents: indole **4** (0.15 mmol) and nitrostyrene **5** (0.1 mmol). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak Daicel IA, 90:10 Hex:iPrOH, 1 mL/min). [d] Racemic mixture.

Interestingly, with these results we confirmed our hypothesis about the possibility of activation of a potential organocatalyst, since according to these results better yields and enantioselectivities are obtained in all the cases compared with the almost lack of reactivity found with **T1** (entry 12) or the metal precursors alone (entry 13), as a proof of fact of the synergic effect between both species. Moreover, probably the new more hindered complexes make the TS of this reaction more rigid and stable and consequently, able to induce enantioselectivity contrasting the results obtained with thiourea **T1** (entry 12). Excellent reactivity values were found for the silver complexes [Ag(OTf)**T1**] **1a** (entry 2) and [Ag(**T1**)$_2$]OTf **1e** (entry 8) and promising selectivities were achieved for the gold species [Au(PPh$_3$)**T1**]OTf **1d** (entry 5) and [Au(**T1**)$_2$]OTf **1f** (entry 10), with ee values of 42 and 30%, respectively. We can conclude that coordination of a Lewis acid to the thiourea organocatalyst **T1** produces a great increment of reactivity and selectivity, taking into account the values obtained with this thiourea alone.

These initial promising results encouraged us to examine other M-thiourea complexes varying the electronic properties of the thiourea catalyst. Thiourea **T2** was the center of the subsequent study. Since better values were obtained in terms of enantioselectivity with Au-**T1** **1d** and **1f** complexes and in terms of reactivity the best value was obtained with Ag-**T1** **1a**, in the ensuing screening, different Ag-**T2** and Au-**T2** catalysts were designed and tested (Scheme 2 and Table 2).

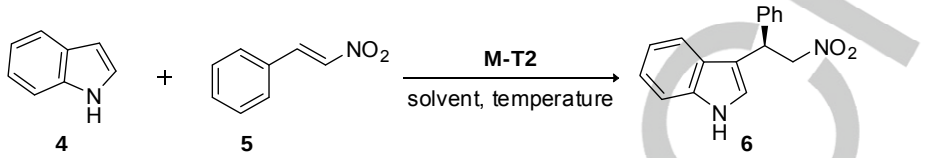


Scheme 2. Catalytic complex structures **2a-f** with Ag-**T2** and Au-**T2**. *i)* [Au(OTf)(PPh$_3$)]; *ii)* [Ag(OTf)(PPh$_3$)]; *iii)* ½ Ag(OTf); *iv)* [Au(C$_6$F$_5$)(tht)]; *v)* [Au(C$_6$F$_5$)$_2$(OEt$_2$)$_2$]ClO$_4$; *vi)* ½ [Au(tht)$_2$]OTf.

In this case, the better ee values were found with complexes **2a** and **2e** (entries 1 and 5, respectively), although in terms of reactivity complex **2e** was the most active one (88%, entry 5), followed by **2f** (60%, entry 6). In summary, the silver(I) **2c**, the gold(I) **2a** and **2f** and the gold(III) **2e** species bearing two thiourea ligands showed better results, as previously observed for **T1** with complexes **1e** and **1f** (Table 1, entries 6-10). As previously found for **T1**, **T2** activated with a metal Lewis acid

affords better results compared with **T2** alone (entry 7, Table 2), which again supports the development of our main idea. It is also remarkable the increase reaction rate observed using 10 mol% of complex **2e** (entry 5) in comparison with 20 mol% of **T2** alone (entry 7), probably due to a considerable decrease in the p*K*a of thiourea **T2**. With the aim of improving the values of reactivity and enantioselectivity of this process, we tested the efficiency of **T3** synthesizing the same promising metal complexes **3a-d** containing Ag or Au (Scheme 3).

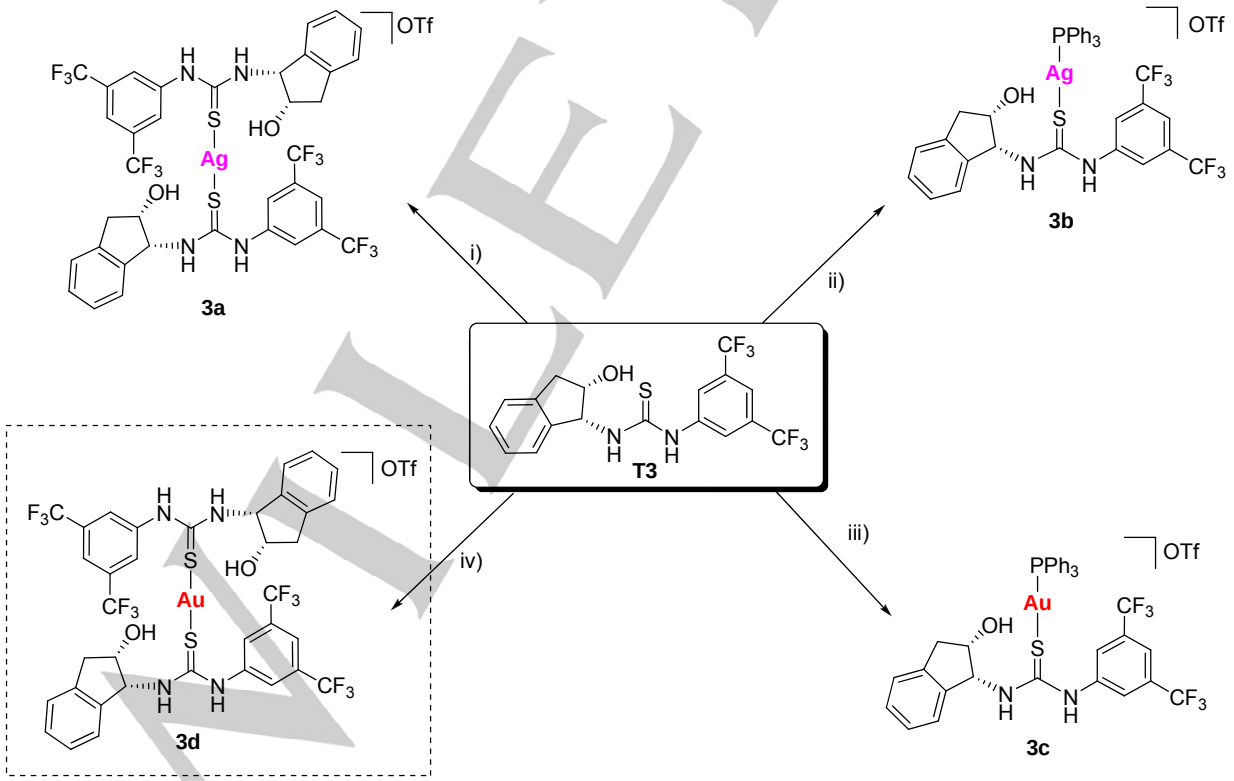
Table 2. Screening of the reaction promoted by **M-T2** (**2a-f**) complexes.[a]



4 + **5** → **6**

Entry	**M-T2** (%)	Solvent (mL)	T (ºC)	t (days)	yield (%)[b]	ee (%)[c]
1	**2a** (10%)	CH_2Cl_2 (0.5)	r.t.	3	45	54
2	**2b** (10%)	CH_2Cl_2 (0.5)	r.t.	3	37	16
3	**2c** (10%)	CH_2Cl_2 (0.5)	r.t.	3	41	28
4	**2d** (10%)	CH_2Cl_2 (0.5)	r.t.	3	19	8
5	**2e** (10%)	CH_2Cl_2 (0.5)	r.t.	3	88	50
6	**2f** (10%)	CH_2Cl_2 (0.5)	r.t.	4	60	40
7	**T2** (20%)	CH_2Cl_2 (0.5)	r.t.	4	22	20

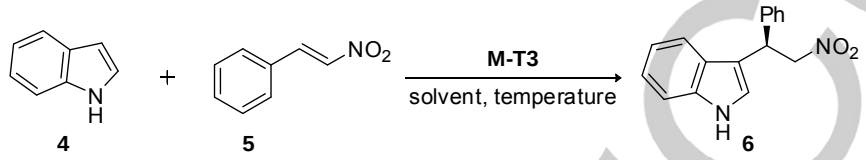
[a] Amount of reagents: indole **4** (0.15 mmol) and nitrostyrene **5** (0.1 mmol). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak Daicel IA, 90:10 Hex:*i*PrOH, 1 mL/min).



Scheme 3. Synthesis of the **M-T3** complexes **3a-d**. *i)* ½Ag(OTf); *ii)* [Ag(OTf)(PPh_3)]; *iii)* [Au(OTf)(PPh_3)]; *iv)* ½ [Au(tht)$_2$]OTf.

All these complexes were completely characterized and the data are collected in the Supporting Information. Subsequently, the efficiency of these species in the benchmark reaction between indole and nitrostyrene was analyzed and the results are reported in Table 3. As thiourea **T3** reaches the best results in this reaction, and because one of our concerns is the high catalyst loading of thioureas as organocatalysts, we decided to test the reaction with only 5 mol% compared with the reported 20 mol% for **T3**.[9,15]

Table 3. Screening of the reaction promoted by **M-T3** (**3a-d**) complexes.[a]



4 **5** **6**

Entry	**M-T3** (%)	Solvent (mL)	T (ºC)	t (days)	yield (%)[b]	ee (%)[c]
1	**3a** (5%)	$CHCl_3$ (0.25)	r.t.	2	>95	32
2	**3b** (5%)	$CHCl_3$ (0.25)	r.t.	5	90	34
3	**3c** (5%)	$CHCl_3$ (0.25)	r.t.	2	79	48
4	**3d** (5%)	$CHCl_3$ (0.25)	r.t.	3	>95	56
5	**T3** (20%)	CH_2Cl_2 (0.5)	r.t.	4	51	38

[a] Amount of reagents: indole **4** (0.15 mmol) and nitrostyrene **5** (0.1 mmol). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak Daicel IA, 90:10 Hex:*i*PrOH, 1 mL/min).

The results show that the gold(I) bis(thiourea) complex **3d** was found to be the most active, leading to the best results in terms of reactivity and enantioselectivity (entry 4). It is remarkable the use of only 5 mol% of catalyst loading of our complexes in comparison with 20 mol% used in the former works with **T3**.[9,15] These data exceed those obtained with the catalyst thiourea **T3** alone, even using a lower catalyst loading (entry 5).

In order to finely tune the optimal reaction conditions with **T3**, we carefully checked the variation of other parameters such as solvent, temperature, and variation in the concentration of all species (Table 4), since on the basis of our experience we realized that small variations in all these parameters could play an important role in governing the enantioselectivity and reactivity of the process. Variations in the amount of indole afforded to changes in the values of enantioselectivity and reactivity. However, at low temperature we discarded the use of only 1 equivalent of indole because the rate of the reaction would decrease more. An increase in the enantioselectivity was observed by lowering the reaction temperature to –15 from 25 °C (Table 5, entries 5-9) although the reaction rate was lower Increasing the concentration of the reaction accelerates the rate of the process and better yields are obtained. Unfortunately, the large differences achieved at room temperature between the reaction performed with the thiourea **T3** alone or with **3d** are not maintained at low temperature, and this may be due to a different mode of coordination between the thiourea catalyst and the metal at different temperature. The solvent of choice was found to be CH_2Cl_2.

Table 4. Screening of the reaction promoted by **3d**.[a]

Entry	Cat. (%)	Solvent (mL)	T (ºC)	t (days)	yield (%)[b]	ee (%)[c]
1[d]	**3d** (5%)	CH_2Cl_2 (0.25)	r.t.	5	72	60
2[d]	**3d** (5%)	CH_2Cl_2 (0.10)	r.t.	5	84	56
3[d]	**3d** (5%)	$CHCl_3$ (0.25)	r.t.	3	83	53
4[e]	**3d** (5%)	$CHCl_3$ (0.25)	r.t.	3	82	48
5	**3d** (5%)	CH_2Cl_2 (0.50)	-15	3	15	63
6	**3d** (5%)	CH_2Cl_2 (0.25)	-15	5	40	76
7	**3d** (5%)	CH_2Cl_2 (0.10)	-15	5	66	72
8	**3d** (5%)	$CHCl_3$ (0.25)	-15	4	38	53
9	**3d** (5%)	$CHCl_3$ (0.10)	-15	4	60	58
10	**3d** (5%)	Toluene (0.25)	-15	3	21	29

11	**3d** (5%)	CH_3CN (0.25)	-15	3	38	33
12	**3d** (5%)	$ClCH_2CH_2Cl$ (0.10)	-15	5	29	74

[a] Amount of reagents: indole **4** (0.15 mmol) and nitrostyrene **5** (0.1 mmol). [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak Daicel IA, 90:10 Hex:*i*PrOH, 1 mL/min). [d] Reaction performed with 1 equiv. of indole. [e] Reaction performed with 2 equiv. of indole.

With the optimal reaction conditions in hand, and giving that one of our concerns in organocatalysis is the high catalyst loading we decided to investigate the changes of reactivity and selectivity between the thioureas **T1**-**3** and the corresponding gold complexes [Au(thiourea)$_2$]OTf, depending on the catalysts loading in the benchmark reaction (Table 5).

Table 5. Comparison of activity of thioureas **T1-3** *versus* [Au(thiourea)$_2$]OTf (**1f,2f,3d**)[a]

Entry	Cat. (%)	yield (%)[a]	ee (%)[b]
1	**T1** (10%)	19	Rac.[d]
2	**1f** (10%)	65	40
3	**1f** (5%)	54	32
4	**1f** (3%)	51	32
5	**1f** (1%)	29	12
6	**T2** (10%)	37	26
7	**2f** (10%)	64	48
8	**2f** (5%)	60	44
9	**2f** (3%)	63	40
10	**2f** (10%)	56	25
11	**T3** (10%)	57	34
12	**T3** (5%)	25	30
13	**T3** (3%)	24	22
14	**T3** (1%)	21	8
15	**3d** (10%)	94	60
16	**3d** (5%)	93	56
17	**3d** (3%)	95	54
18	**3d** (1%)	83	50

[a] Experimental conditions: To a mixture of catalyst (mol%) and nitroalkene **5** (0.1 mmol) in CH_2Cl_2 (0.25 mL), indole **4** (0.15 mmol) was further added, in a test tube at room temperature. After the reaction time, product **6** was isolated by flash chromatography. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak Daicel IA, 90:10 Hex:*i*PrOH, 1 mL/min). [d] Racemic.

As it can be observed **T1** in a 10 mol% of catalyst loading gives very poor values (entry 1), with a yield of only 19% and a racemic mixture. However, the gold complex [Au(**T1**)$_2$]OTf **1f** in a 10% produces a 65% yield and an ee of 40% (entry 2), which means a considerable increase in both reactivity and overall selectivity. The decrease in the catalyst loading to 3 mol % affords only slightly lower values of 51% and 32% ee (entry 3). The same tendency is observed with thiourea **T2**, which values are increased from 35% yield and 26% ee (entry 6) to 64% and 48% for the gold complex **2f** (entry 7). Again, these values are maintained to a lowering of the catalyst amount up to 3%. With thiourea **T3** which provided the best results in previous studies, we have managed to lower the catalyst loading to 1 mol% without a significant decreasing neither the reactivity nor the enantioselectivity (entry 18). Figure 6 shows, for a better vision, the comparative study between the thiourea **T3** alone and the gold complex [Au(**T3**)$_2$]OTf **3d** for a variation in the catalyst loading.

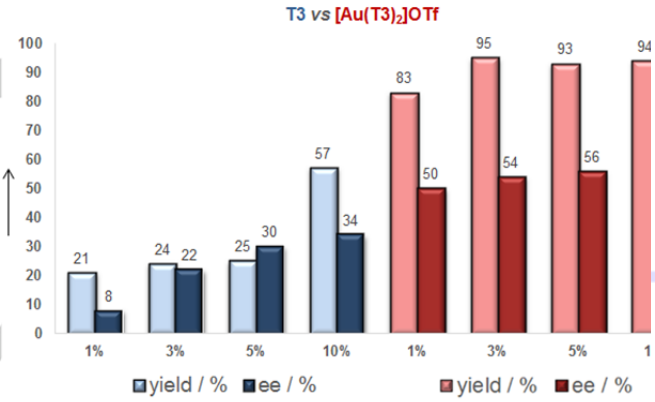


Figure 6. Comparative study of reactivity and selectivity between **T3** and complex [Au(**T3**)$_2$]OTf **3d**.

The effect of the metal over the electronic properties of the thiourea **T3** is disclosed in the NMR-spectra of Figure 7. Under the same concentration (0.005 mmol catalyst/500 µL CD_2Cl_2) in two NMR tubes both compounds, **T3** and **3d**, were analyzed at room temperature.

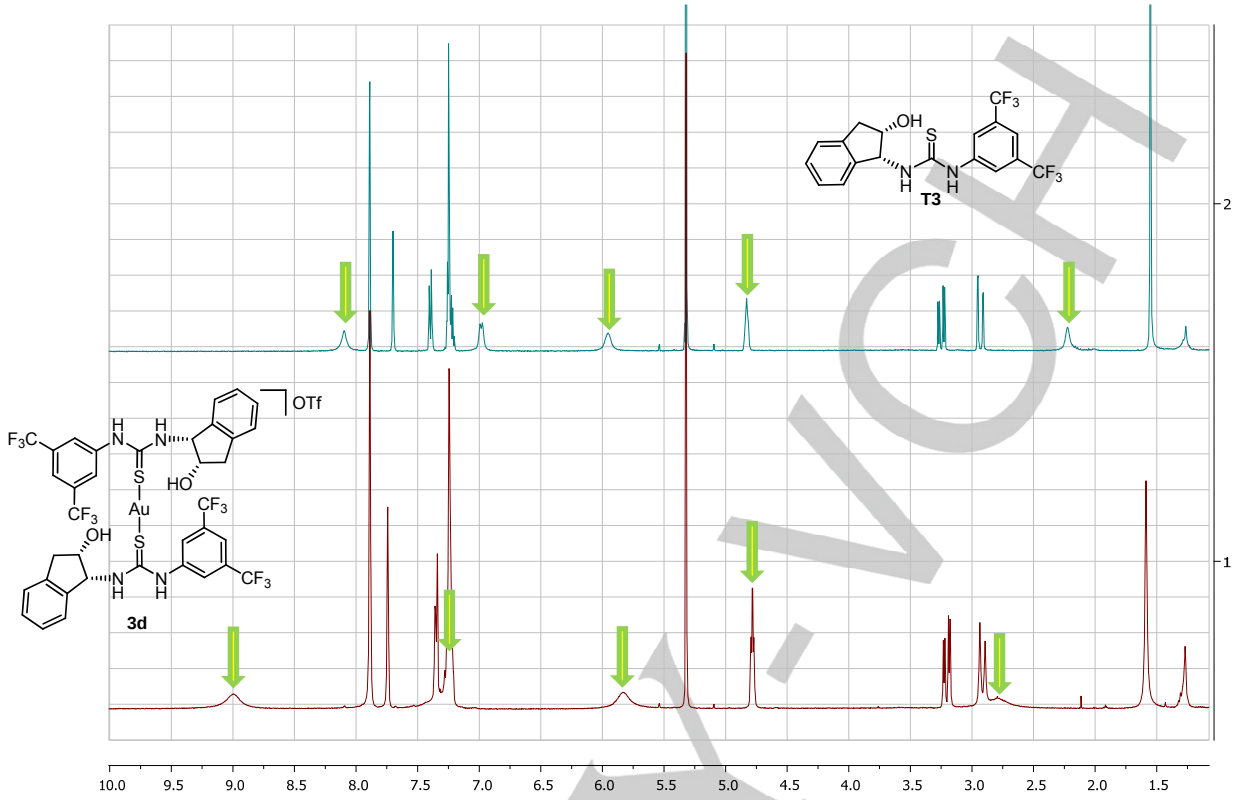


Figure 7. ^{1}H NMR experiments performed in CD_2Cl_2 at room temperature (400 MHz).

Some of the most relevant resonances in the thiourea catalysts **T3** are downfield shifted because of coordination to the Au center in the new catalytic complex **3d**. A displacement of 0.9 ppm (signal from 8.01 ppm to 9.00 ppm) was observed for the thiourea N-H hydrogen atom, and 0.27 ppm (signal from 6.98 ppm to 7.25 ppm) was observed for the aminoindanol N-H hydrogen atom of **T3**. Additionally, a downfield shifting of the OH group in the aminoindanol scaffold was observed of 0.56 ppm (signal from 2.23 ppm to 2.79 ppm). These displacements would be in agreement with our initial hypothesis and the better values of yield found with complex **3d** with a more acidic thiourea skeleton. Both aliphatic C*H*-Het protons experience an upfield shifting (Figure 8).

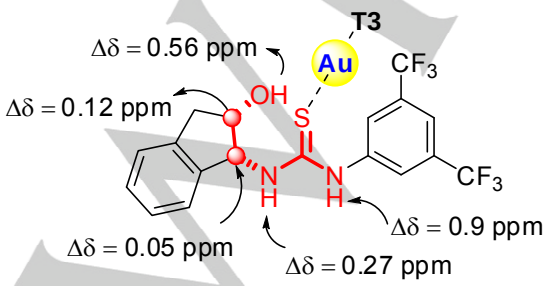


Figure 8. Chemical shifts experienced after coordination of **T3** to gold(I).

Mechanistic study

Interestingly, the sense of the stereoselection in product **6** was in all cases the same as that expected when (*R,R*)-aminoindanol thioureas **T2** and **T3** were the sole catalysts. This fact shows that chirality is preferentially governed by the thiourea catalyst and this outcome prompted us to think that the metal is only activating the thiourea moiety better than simply driving by itself some of the reagents into the transition state. Moreover, it is remarkable that the metal does not activate this process as above mentioned. Based on our previous works (**TSI** and **TSII**),[9,15] we proposed **TSIII** as the plausible mode of activation in our reaction (Figure 9).

It can be assumed that the M-thiourea catalyst complex is the most reactive species, due to the increased acidity of the NH in the thiourea after a synergic coordination with the metal atom, thereby increasing the reaction rate and favoring the activation of the substrates. Furthermore, improvement in the enantioselectivity could be attributed to the formation of a more rigid assembly in the transition state **TSIII** as combination of both structures. This mode of activation **TSIII** (Figure 9) would agree with the fact that the observed enantiomer is given by the enantioselectivity of the thiourea organocatalyst employed as obtained in the previous works.[9,15]

Since the gold atom is joined to two thiourea ligands in the best catalyst **3d**, we cannot discard that the same process is

occurring by both thiourea organocatalysts, supporting the better yields and enantioselectivities observed in this really congested catalyst, in comparison with the thiourea **T3** alone.

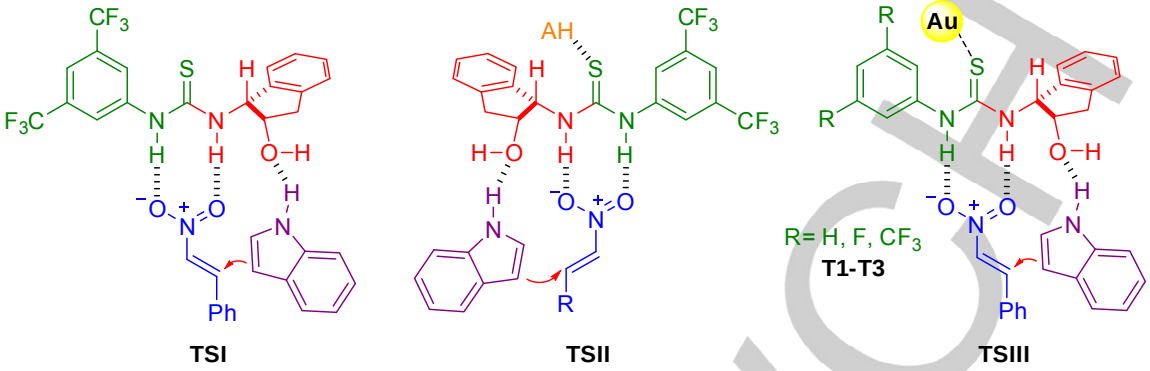


Figure 9. Proposed transition states for the Friedel-Crafts reaction.

Conclusions

The unprecedented activation of thiourea organocatalysts through the coordination of a metallic Lewis acid has been described. Coordination of the metal produces the consequent acidification of the thiourea protons achieving a better activity in terms of conversion and selectivity in the benchmark reaction of addition of indole to nitrostyrene. Three thiourea organocatalysts **T1-3** with different electronic and steric requirements have been used to prepare several group 11 metal complexes **1-3**. All the tested M-thiourea complexes provided better results than the thioureas themselves, being the gold complexes [Au(thiourea)$_2$]OTf the best in terms of reactivity and selectivity. After achieving the best experimental conditions a comparison of the activity of the thioureas versus the [Au(thiourea)$_2$]OTf complexes in different catalysts loading have been carried out. As expected the higher values were achieved with thiourea **T3** and [Au(**T3**)$_2$]OTf **3d** showing a great improvement in the reactivity and selectivity values of the metal thiourea complex compared with the thiourea alone. It has been possible to reduce the catalyst loading to 1 mol% without a significant decrease of the activity, although optimum values are afforded with a 3 mol% of catalyst loading. Thus, a new concept has been proved, the cooperative effect between a metallic Lewis acid and thioureas providing metal complexes acting as organocatalysts.

Experimental Section

Instrumentation. Mass spectra were recorded on a BRUKER ESQUIRE 3000 PLUS, with the electrospray (ESI) technique. The ATR-FTIR spectra of solid samples were recorded on a PerkinElmer FT-IR spectrometer equipped with a universal ATR sampling accessory. ^{1}H and ^{13}C{^{1}H}-APT NMR, including 2D experiments, were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz; ^{19}F, 376.5 MHz) or on a BRUKER AVANCE II 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz; ^{19}F, 282.3 MHz), with chemical shifts (ppm) reported relative to the solvent peaks of the deuterated solvent.[17]

Starting Materials. All reactions were performed under air atmosphere and solvents were used as received without further purification or drying. The complexes [Ag(OTf)(PPh$_3$)],[18] [Au(tht)$_2$]OTf,[19] [Au(C$_6$F$_5$)$_3$(tht)],[20] [Au(C$_6$F$_5$)tht)],[21] [Au(C$_6$F$_5$)$_2$(OEt)$_2$]ClO$_4$[22] were prepared following published procedures. [Au(OTf)(PPh$_3$)] was obtained from [AuCl(PPh)$_3$][20] with Ag(OTf) in dichloromethane. All other reagents were commercially available.

NMR spectra of all synthesized catalysts and the characterization of all new compounds are reported in the Supporting Information.

General Procedure for the Catalyzed Friedel–Crafts Alkylation Reaction: To a mixture of catalyst **M-(T1-T3)** (1-10 mol%), and nitroalkene **5** (0.1 mmol) at the indicated temperature (r.t. or –15 °C) in a test tube with CH_2Cl_2 (0.25 mL), indole **4** (0.15 mmol) was further added. After the appropriate reaction time (see Tables 1-5), the residue was purified by column chromatography (SiO_2; hexane/EtOAc, 8:2) to afford final adduct **6**. Yields and enantioselectivities are reported in Tables 1-5. Spectral and analytical data for compound **6** is in agreement with those previously reported in the literature.[15a]

Acknowledgements

Authors thank the Ministerio de Economía y Competitividad (MINECO/FEDER CTQ2016-75816-C2-1-P), the High Council of Scientific Investigation (CSIC) (PIE-201580I010) and Gobierno de Aragón-Fondo Social Europeo (E77 and E104) for financial support of our research.

Keywords: thiourea • gold • asymmetric • organocatalysis • synergy

[1] a) A. Berkessel, H. Gröger H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**; b) P. I. Dalko (Ed.) *Enantioselective Organocatalysis*; Wiley-VCH: New York, **2007**; c) B. List, K. Maruoka, (Eds.) Science of Synthesis, *Asymmetric Organocatalysis*, Thieme Chemistry, **2012**; d) P. I. Dalko (Ed.) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications;* Wiley-VCH: Weinheim, **2013**.

[2] a) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575-2600; b) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep*. **2010**, *27*, 1138-1167; c) E. Marqués-López, R. P. Herrera, in *Comprehensive Enantioselective Organocatalysis*; (P. I. Dalko, Ed.); Wiley-VCH: Weinheim, **2013**; pp 1359–1383; d) J. Alemán, S. Cabrera,

Chem. Soc. Rev. **2013**, *42*, 774-793; e) B.-F. Sun, *Tetrahedron Lett.* **2015**, *56*, 2133-2140.

[3] For selected reviews, see: a) H. Miyabe, Y. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785-795; b) S. J. Connon, *Chem. Commun.* **2008**, 2499-2510; c) P. Chauhan, S. S Chimni, *RSC Adv.* **2012**, *2*, 737-758; d) S. Narayanaperumal, D. G. Rivera, R. C. Silva, M. W. Paixão, *ChemCatChem* **2013**, *5*, 2756-2773; e) Y. Xi, X. Shi, *Chem. Commun* **2013**, *49*, 8583-8585; f) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051-7071; g) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185-1197; h) I. G. Sonsona, E. Marqués-López, R. P. Herrera, *Beilstein J. Org. Chem.* **2016**, *12*, 505-523.

[4] See for instance: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. **2007**, *107*, 5713-5743; c) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187-1198; d) M. Kotke, P. R. Schreiner, in *Hydrogen Bonding in Organic Synthesis*, (P. M. Pihko, Ed.), Wiley-VCH: Weinheim, **2009**, pp. 141-351; e) E. Marqués-López, R. P. Herrera, *An. Quim.* **2009**, *105*, 5-XXX; f) E. Marqués-López, R. P. Herrera, in *New Strategies in Chemical Synthesis and Catalysis*. (B. Pignataro, Ed.) Wiley-VCH: Weinheim, **2012**, pp. 175-199; g) G. Jakab, P. R. Schreiner, in *Comprehensive Enantioselective Organocatalysis*, (P. I. Dalko, Ed.), Wiley-VCH: Weinheim, **2013**, pp. 315-341, and references therein cited; h) Z. Zhang, Z. Bao, H. Xing, *Org. Biomol. Chem.* **2014**, *12*, 3151-3162; i) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633-2646.

[5] For selected reviews about dual catalysis combining an organocatalyst and a metal catalyst, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev*. **2009**, *38*, 2745-2755; b) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350-9365; c) C. C. J. Loh, D. Enders, *Chem. Eur. J.* **2012**, *18*, 10212-10225; d) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633-658; e) Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337-1378; f) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874-3886; g) X.-Q. Dong, Q. Zhao, P. Li, C. Chen, X. Zhang, *Org. Chem. Front.* **2015**, *2*, 1425-1431.

[6] M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 16464-16465.

[7] C. R. Jones, G. D. Pantoş, A, J. Morrison, M. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 7391-7394.

[8] For a related and more recent example, see also: N. Probst, A. Madarász, A. Valkonen, I. Pápai, K. Rissanen, A. Neuvonen, P. M. Pihko, *Angew. Chem. Int. Ed.* **2012**, *51*, 8495-8499.

[9] E. Marqués-López, A. Alcaine, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2011**, 3700-3705.

[10] a) D. M. Nickerson, V. V. Angeles, T. J. Auvil, S. S. So, A. E. Mattson, *Chem. Commun.* **2013**, *49*, 4289-4291; b) D. M. Nickerson, A. E. Mattson, *Chem. Eur. J.* **2012**, *18*, 8310-8314.

[11] a) S. S. So, J. A. Burkett, A. E. Mattson, *Org. Lett.* **2011**, *13*, 716-719; b) S. S. So, T. J. Auvil, V. J. Garza, A. E. Mattson, *Org. Lett.* **2012**, *14*, 444-447.

[12] For a more recent example of non-chiral ureas, see also: E. A. Hall, L. R. Redfern, M. H. Wang, K. A. Scheidt, *ACS Catal.* **2016**, *6*, 3248-3252.

[13] See for example: a) O. Crespo, M. C. Gimeno, P. G. Jones, A. Laguna, J. M. López-de-Luzuriaga, M. Monge, J. L. Pérez, M. A. Ramón, *Inorg. Chem.* **2003**, *42*, 2061-2068; b) M. C. Gimeno, A. Laguna, in *Comprehensive Coordination Chemistry II; Silver and Gold*, (J. A. McCleverty, T. J. Meyer, Eds.), Elsevior, Oxford, **2004**, vol. 6, 911-1145; c) M. C. Gimeno, in *The Chemistry of Gold in Modern Supramolecular Gold Chemistry. Gold-Metal Interactions and Applications*, (A. Laguna, Ed.), Wiley-VCH, **2008**, 1-63; d) M. C. Gimeno, A. Laguna, R. Visbal, *Organometallics* **2012**, *31*, 7146-7157; e) H. Goitia, Y. Nieto, M. D. Villacampa, C. Kasper, A. Laguna, M. C. Gimeno, *Organometallics* **2013**, *32*, 6069-6078.

[14] The coordination chemistry of thioureas in metal complexes has been also explored for other purposes, such as for their biological properties: a) K. Yan, C.-N. Lok, K. Bierla, C.-M. Che, *Chem. Commun.* **2010**, *46*, 7691-7693; b) M. Yang, A. J. Pickard, X. Qiao, M. J. Gueble, C. S. Day, G. L. Kucera, U. Bierbach, *Inorg. Chem.* **2015**, *54*, 3316-3324; c) S. Ali, G. Yasin, Z. Zuhra, Z. Wu, I. S. Butler, A. Badshah, I. ud Din, *Bioinorg. Chem. Appl.* **2015**, *2015* Article ID 386587. In material science: d) Y. C. Choi, E. J. Yeom, T. K. Ahn, S. I. Seok, *Angew.Chem. Int. Ed.* **2015**, *54*, 4005-4009. Or as ligands in metal complexes: e) K. R. Koch, *Coord. Chem. Rev.* **2001**, *216-217* (473-488; f) J. A. J. Breuzard, M. L. Christ-Tommasino, M. Lemaire, *Top Organomet. Chem.* **2005**, *15*, 231-270; g) J.-H. Pan, M. Yang, Q. Gao, N.-Y. Zhu, D. Yang, *Synthesis* **2007**, 2539-2544.

[15] For a selection of our works using these thioureas, see also: a) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed*. **2005**, *44*, 6576-6579; b) R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 3303-3306; c) D. Roca-López, E. Marqués-López, A. Alcaine, P. Merino, R. P. Herrera, *Org. Biomol. Chem*. **2014**, *12*, 4503-4510; d) E.-M. Schön, E. Marqués-López, R. P. Herrera, C. Alemán, D. D. Díaz, *Chem. Eur. J.* **2014**, *20*, 10720-10731; e) V. Juste-Navarro, E. Marqués-López, R. P. Herrera, *Asian J. Org. Chem.* **2015**, *4*, 884-889; f) M. C. Gimeno, R. P. Herrera, *Cryst. Growth Des.* **2016**, *16*, 5091-5099.

[16] For the pioneering racemic version of this Friedel-Crafts alkylation reaction, see: G. Dessole, R. P. Herrera, A. Ricci, *Synlett* **2004**, 2374-2378.

[17] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176-2179.

[18] M. Bardají, O. Crespo, A. Laguna, A. K. Fischer, *Inorg. Chim. Acta* **2000**, *304*, 7-16.

[19] R. Usón, A. Laguna, A. Navarro, R. V. Parisch, L. S. Moore, *Inorg. Chim. Acta* **1986**, *112*, 205-208.

[20] R. Uson, A. Laguna, *Organomet. Synth*. **1986**, *3*, 322-342.

[21] R. Usón, A. Laguna, M. Laguna, *Inorg. Synth*. **1989**, *26*, 85-91.

[22] R. Usón, A. Laguna, M. L. Arrese, *Synth. React. Inorg. Met-Org. Chem*. **1984**, *14*, 557-567.

10.1002/cctc.201601527

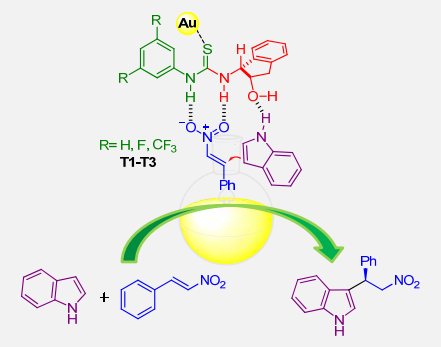
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

A pioneering gold(I) activation of thiourea organocatalysts is described. The synergic effect between both species affords a more acidic and rigid catalytic complex than that provided by the thiourea alone. Considerably better results in terms of reactivity and selectivity are obtained with the use of the gold-thiourea organocatalyst, which has also allowed reducing the catalyst loading to 1-3 mol%.



Anabel Izaga,[a] *Raquel P. Herrera,**[b] *and M. Concepción Gimeno**[a]

Page No. – Page No.

Title