Introduction

Activation of gold(I) chloride complexes \([\text{LAuCl}]\), required to bring the catalytic activity of Au(I) precatalysts to meaningful levels, is generally performed by chloride abstraction using Ag(I) additives, either in situ or as a separate prior step. While typically very effective, this procedure has the drawback of requiring silver as an additional metal, whose salts are often hygroscopic and light-sensitive. Moreover, if chloride scavenging is done in situ, silver can interfere with the catalysis operated by gold, often with detrimental effects (“silver effect”), although some examples of beneficial Au–Ag cooperative systems have recently been reported. To obviate the practical issues associated with the use of silver salts, the development of silver-free methods for the activation of Au(I) chloride precatalysts has lately become the focus of intense research efforts. Thus, several groups have reported the use of other external activators (e.g., NaBArF\(_4\), salts of other metals\(^{[4]}\) and halogen-bond donors\(^{[5]}\)) and self-activating \([\text{LAuCl}]\) complexes possessing tailored ligands, such as phosphaalkenes,\(^{[6]}\) phosphinines,\(^{[7]}\) carbenes or phosphines with redox-switchable phosphoric acid moiety (\([\text{NHC}]\)), capable of catalyzing the silver-free tandem cycloisomerization-indole addition reaction of 2-alkynyl enones.\(^{[8]}\) Regarding NHC-based Au(I) complexes, the group of Helaja very recently presented complexes \(C\) equipped with an monodentate H-bond donor (HBD) groups (Figure 1, top).\(^{[9,10,11]}\)

In this context, the group of Gabbaï disclosed that Au(I) chloride complex \(A\) bearing a trifluoroacetamide group on a modified PPh\(_3\) scaffold could catalyze the silver-free cyclization of \(N\)-propargyl benzamide.\(^{[12]}\) The activity of \(A\) was attributed to the ability of the trifluoroacetamide to establish a hydrogen-bond interaction with the chloride ligand, which would facilitate its abstraction from Au(I), thus rendering the metal center catalytically active. Although providing an excellent proof of concept, the study included only a single complex (\(A\)), whose activity was modest and limited to the cyclization of \(N\)-propargyl benzamide. Marinetti, Guinchard and coworkers described another isolated example of a phosphine Au(I) chloride complex with a pendant phosphoric acid moiety (\(B\)), capable of catalyzing the silver-free tandem cycloisomerization-indole addition reaction of 2-alkynyl enones.\(^{[13]}\)

Silver-Free Au(I) Catalysis Enabled by Bifunctional Urea- and Squaramide-Phosphine Ligands via H-Bonding

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Abstract: A library of gold(I) chloride complexes with phosphine ligands incorporating pendant (thio)urea and squaramide H-bond donors was prepared with the aim of promoting chloride abstraction from Au(I) via H-bonding. In the absence of silver additives, complexes bearing squaramides and trifluoromethylated aromatic ureas displayed good catalytic activity in the cyclization of \(N\)-propargyl benzamides, as well as in a 1,6-enzyme cycloisomerization, a tandem cyclization-indole addition reaction and the hydrohydratination of phenylacetylene. Kinetic studies and DFT calculations indicate that the energetic span of the reaction is accounted for both the chloride abstraction step, facilitated by the bidentate H-bond donor via an associative mechanism, and the subsequent cyclization step.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202101751

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amide side arm, which displayed excellent performances in the absence of additives, but once again only in the cyclization of terminal N-propargyl benzamides. Based on calculations, the authors proposed that the NH groups of both the benzamide substrate and the ligand concurred to stabilize the displaced chloride ion.

Complementing these previous reports, we decided to investigate systematically a library of PPh₃-based complexes D endowed with classical bidentate H-bond donors (Figure 1, bottom). In order to explore structure-activity relationships, the linker length and the nature of the HBD (squaramides, thioureas and ureas) were varied, covering various geometries and H-bonding abilities (pKₐ values are shown as an approximate proxy for H-bonding ability). These H-bond donor groups were chosen for their well-known ability to aid chloride abstraction from organic molecules. Herein, we envisaged abstracting the chloride from an electrophilic metal center, with the intention of translating this common “anion-binding” organocatalytic activation strategy to the realm of metal catalysis.

Results and Discussion

Twelve phosphine Au(I) chloride complexes with tethered squaramides (1–3), thioureas (4 and 6) and ureas (5, 7–9) were readily prepared in 3–7 steps (Scheme 1A, for details see Supporting Information, Section 2). Late-stage introduction of the HBD groups on the ligands, achieved by reaction of the desired aminophosphines with the mixed squarate or iso(thio)cyanate of choice, allowed easy diversification of the key HBD moiety. Ligand exchange with (dimethylsulfide)gold(I) chloride then afforded complexes 1–9 as bench-stable solids. All complexes were characterized also by single-crystal X-ray diffraction, which provided valuable information on their connectivity and H-bonding ability in the solid state (Scheme 1B, for details and ORTEP plots see Supporting Information, Section 9).

Phosphinosquaramide complexes 1–3 display Au–Cl distances of 2.282(1)–2.287(1) Å and a 2-point H-bond between the squaramide and a molecule of DMSO, the
crystallization solvent. In phosphinoureia complexes 5, 8a and 9a, the Au–Cl distance falls in the 2.275(2)–2.283(1) Å range, and the urea moiety engages in intermolecular H-bonds with another urea. Instead, in the crystal structures of phosphinoureia complexes 7a, 7b, 8b and 9b, the urea establishes H-bonds with the chloride ligand of another [LAuCl] unit, causing weakening of the Au–Cl bond, as attested by its elongation to 2.297(2)–2.326(1) Å. Complex 8b adopts a dimeric structure very similar to the one described by Gabbaï for complex A,[11] held together also by aurophilic interactions, as evidenced by the short Au–Au distance (3.077(1) Å) and smaller P–Au–Cl angle (169.67(3)°). Finally, the X-ray structures of phosphinothiourea complexes 4 and 6 show a dimeric core (with a Au–Au distance of 3.416(9) Å for 6), where the thiourea of one molecule coordinates via S to the Au atom of another unit. The displaced chloride ligands are stabilized by H-bonds with the thiourea NH groups and with polar solvent molecules (CHCl3 and adventitious water, for details see Supporting Information, Section 9).

Having prepared a library of complexes, some of which were found to H-bond with the chloride ligand (7a, 7b, 8b, 9b) or the chloride anion (4, 6) in the solid state, we performed catalytical tests without silver additives to see whether such H-bonding interactions would prove strong enough in solution to render the metal center catalytically active. The cyclization of N-propargyl benzamide 12a was chosen as benchmark reaction, as it is a model transformation for silver-free Au(I) catalysis,[4b, 5b, 11] and, to further aid comparison, the same conditions employed by Gabbaï were used (Scheme 1).[11] Importantly, this reaction under Au(I) catalysis affords exclusively methylene oxazoline 13a,[25] whereas isomerized oxazole 14a is obtained in the presence of Au(III) or acidic additives,[26, 27] being thus ideally suited to discriminate a pure Au(I) manifold from catalytic activity due to impurities or degradation/disproportionation products.

Complex 1, bearing a pendant squaramide, as well as complexes 8b and 9b, incorporating electron-poor aromatic ureas, provide excellent yields of oxazoline 13a in 24 h at 23 °C (96–99%, Table 1, entries 1, 10 and 12). Their activity greatly outperforms the one shown by complex A (36% yield under the same conditions, Table 1, entry 13)[11] thus highlighting the importance of ligand design to achieve catalytic efficiency. By comparing the performances of homologous phosphinosquaramide complexes 1–3, a significant drop in activity is observed with increasing linker length (Table 1, entries 1–3). Thus, the tether between the P and N atoms has to possess an optimal length (3 C atoms), which presumably reduces the entropic cost of placing the H-bond donor in close proximity to the Au-bound chloride. Comparison between phosphinosquaramide complex 1 and analogous phosphino(thio)urea complexes 4 and 5, which have the same optimal linker but provide much lower conversions (Table 1, entries 4–5), reveals that also the nature of the H-bond donor group is important. Stronger H-bond donors such as urea rings systematically outperform their non-fluorinated counterparts 7a and/or oxazole 9a (Table 1, entries 7–12), and (ii) within each a/b series, the activity of catalysts 7a and/or oxazole 9a is supported by the known thiophilicity of Au(I)[28] and the P–Au–S coordination motif observed in the solid-state structures of 4 and 6.

The use of [(Me2S)AuCl] (a precursor employed in the preparation of most [LAuCl] complexes, including 1–9) leads to the exclusive formation of isomerized oxazole 14a (Table 1, entry 14), accompanied by decomposition of the complex as judged by visual inspection of the reaction mixture (dark suspension). This result indirectly attests the purity of complexes 1–9, as their use did not result in the formation of

| Entry | [Au] | 13a | 13a [%] | Entry | [Au] | 13a [%] |
|-------|------|-----|--------|-------|------|--------|
| 1     | 1    | 98  | 13     | A     | 36   |        |
| 2     | 2    | 57  | 14     | [Me2S]AuCl | <5 | [J2] |
| 3     | 3    | <5  | 15     | [Ph3P]AuCl | <5 |        |
| 4     | 4    | 5   | 16     | E + 10/E+11 | <5 |        |
| 5     | 5    | 23  | 17     | E + AgBF4 | 95 | [5]    |
| 6     | 6    | <5  | 18     | E + AgNtF | 95 | [5]    |
| 7     | 7    | 23  | 19     | E + AgOTf | 81 |        |
| 8     | 7    | 76  | 20     | E + NaBArF | 99 |        |
| 9     | 8    | 65  | 21     | L1, L8, L9 | <5 |        |
| 10    | 8    | 96  | 22     | Diphenylthiourea | <5 |        |
| 11    | 9    | 64  | 23     |        |        |        |
| 12    | 9    | 99  | 24     | 1 + TBACl | 18 |        |

[a] Yields for 13a and 14a (indicated in brackets only if >5%) were determined by 1H NMR analysis using n-dodecane or tetraethoxysilane as internal standard; average of at least 2 independent repeats. An error margin of ca. 5% is assumed. The remaining mass is unreacted 12a. [b] Data taken from ref. 11. [c] Using 5 mol% additive.
significant amounts of oxazole 14a, and is in line with the common notion that strongly coordinating ligands, such as phosphines[11] or carbenes,[13] are required to impart sufficient stability to the Au(I) center during catalysis. On the other hand, [(Ph3P)AuCl], alone or in combination with urea 10 and squaramide 11, does not promote the reaction, indicating that the H-bond donor has to be tethered on the ligand backbone in order for this strategy to be viable (Table 1, entries 15 and 16). As expected, intermolecular chloride scavenging from [(Ph3P)AuCl] using common additives such as AgSbF6, AgNTf2, AgOTf and NaBArF4 affords high yields of product 13a (Table 1, entries 17–20), and the reaction cannot be catalyzed by squaramides or (thio)ureas on their own (Table 1, entries 21–23). When complex 1 is mixed with tetrabutylammonium chloride in equimolar ratio, the yield for product 13a decreases from 98% to 18% (Table 1, entry 1 vs. 24), as the metal center is saturated by exogenous chloride ions.

Monitoring the reaction profile by 1H NMR confirmed the correlation between catalytic activity and H-bonding ability for complexes 7–9 (Figure 2). The activity of the bifunctional complexes spans the range between [(Ph3P)AuCl]/AgSbF6, which gives rise to a very fast catalytic system (grey line), and [(Ph3P)AuCl], which is barely active (black line).

Employing the most active phosphinosquaramide Au(I) chloride complex 1, the cyclization of N-propargyl benzamides 12b–d, bearing respectively p-methoxy, p-chloro and p-trifluoromethyl substituents on the aromatic ring, was studied (Figure 3). The reaction was found to be faster for more electron-rich substrates, while it required more than 24 h to reach completion with electron-poor amides 12c and 12d. Whereas electronic variations on the standard substrate 12 were tolerated, complexes 1–5, 8b and 9b did not to catalyze the silver-free cyclizations of N-(but-3-yn-1-yl)benzamide, bearing a homopropargylic substituent, and of the less reactive 13,25 N-(3-phenylprop-2-yn-1-yl)benzamide possessing an internal alkyne.[29]

The new complexes were tested also in a range of other intra- and intermolecular reactions of alkynes in the absence of external activators (for a complete overview, see Supporting Information, Section 5). Complexes 1, 8b and 9b display moderate activity at room temperature in the cycloisomerization of benzene-tethered enyne 15 (Scheme 3A).[30] Interestingly, although the conversion was only partial, diene 16 was observed as the sole product, in stark contrast with the formation of dimers 17 and 18 as major products when the

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**Figure 2.** Formation of product 13a in the reaction of 12a (0.1 M in CD2Cl2, 25 °C) catalyzed by [Au] (5 mol %), monitored by 1H NMR against internal standard.

**Figure 3.** Formation of product 13 in the reaction of 12 (0.1 M in CD2Cl2, 25 °C) catalyzed by 1 (5 mol %), monitored by 1H NMR against internal standard.

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**Scheme 3.** Additional intra- and intermolecular silver-free reactions catalyzed by complexes 1–9. Yields determined by 1H NMR analysis against internal standard. A) Cycloisomerization of 1,6-enzyme 15. B) Tandem cycloisomerization-indole addition reaction of 2-alkynylenone 19. C) Hydrohydrodrazination of phenylacetylene.
activation of standard Au(I) chloride complexes is performed using silver salts and NaBARFiais. Complexes 1, 2, 8b and 9b were also catalytically competent in the tandem cyclodimerization-endoaddition reaction of 2-alkynylene 19, affording good yields of furan 21 and outperforming simple [(Ph,P) AuCl] on its own (Scheme 3B). Finally, very good activity was observed in the hydroxydrazination of phenylacetylene (Scheme 3C). These results allow once again to appreciate the dependence of catalytic activity on tether length and H-bond donor strength, thus painting a consistent picture across different transformations.

The chloride abstraction step is generally overlooked when performing mechanistic studies on Au-catalyzed transformations, under the assumption that chloride scavenging from [LAuCl] complexes using Ag salts is fast, quantitative and irreversible, which is not correct. In order to shed light on this often neglected step, DFT calculations for the Au–Cl bond activation were conducted considering both associative and dissociative mechanisms (Scheme 4, for details see Supporting Information, Section 10). It was found that chloride abstraction occurs with a remarkable low barrier of 6.7 kcal/mol, via an associative ligand exchange mechanism, wherein the displaced chloride ion is stabilized by a triple H-bond established with the two NH groups of the squaramide and the NH functionality of amide 12a. Helaja and coworkers computed a very similar barrier found for this step indicates that Au–Cl bond activation on its own cannot be turnover-limiting, since the reaction requires several hours at room temperature to go to completion.

To shed light on the nature of the turnover-limiting step, kinetic studies on the cyclization of 12a catalyzed by phosphinosquaramide Au(I) chloride complex 1 in CDCl3 at 25°C were undertaken (Scheme 5). With the initial-rate method, the reaction was determined to be first order in catalyst (1.05 ± 0.02, Scheme 5A) and approximately zeroth order in substrate (0.20 ± 0.05, Scheme 5B); no appreciable induction period was observed. We note that a first order in catalyst is common to most catalyzed transformations, as long as the catalyst does not form oligomers. Similarly, a zeroth order in substrate can be expected for unimolecular catalyzed transformations that follow Briggs-Haldane kinetics (of which the well-known Michaelis-Menten regime is regarded as a special case), provided that the Michaelis-Menten constant of the reaction (Km) is much smaller than substrate concentration ([S]) (Scheme 5G). If instead Km was much larger than [S], a first order in substrate would be observed. To understand which was the case for the transformation under study, the reaction progress kinetic analysis (RPKA) popularized by Blackmond was applied to the entire reaction profile and the double reciprocal Lineweaver-Burk plot was constructed (Scheme 5C). From it, a Michaelis-Menten constant (Km) of 42 ± 2 mM was obtained. Given this value, and considering the 0–100 mM substrate concentration present during the reaction, it indeed appears that the current transformation lies in an intermediate scenario between the two limit cases described above (zeroth and first order in substrate), thus justifying a fractional order in substrate included between 0 and 1. Furthermore, since the concentration of 12a changes during the reaction, the order in substrate is also expected to vary, a phenomenon that can be quantified by the elasticity coefficient ε introduced by Burés. Thus, applying the formula for deriving ε from Km in Briggs-Haldane kinetic regimes, the order in substrate was calculated to be closer to 0 at the beginning of the reaction (0.3, in good agreement with the 0.2 order determined by initial-rate kinetics) and to approach 1 towards the end of the reaction (Scheme 5D). An intermediate order in substrate of 0.4 was determined for the entire reaction profile using the variable-time normalization analysis (VTNA) described by Burés.

Next, we conducted a Hammett analysis comparing the initial rate of the reactions of substrates 12a–d (Scheme 5E). A very good correlation in the Hammett plot was found using the standard σ values for para substituents. The rather small, negative sensitivity constant ρ (−0.53 ± 0.04) is indicative of a slight build-up of positive charge in the transition state. While the negative sign of ρ would be consistent with nucleophilic addition of the amide to the Au(I)-activated alkene being turnover limiting, as in this elementary step a significant build-up of positive charge occurs on the amide functionality conjugated with the aromatic ring, the low magnitude of ρ makes it very unlikely. We thus propose that the energetic span

Scheme 4. DFT calculations for the Au–Cl bond activation by associative ligand exchange with substrate 12a. Energies in kcal/mol: PCM (dichloromethane)-B3LYP-D3/6-31G(d,p) (H, C, N, O, F, P, Cl) + SDD (Au)/B3LYP-D3/6-311G(d,p) (H, C, N, O, F, P, Cl) + SDD (Au).
of the reaction be accounted by both the chloride abstraction step (with a barrier of 6.7 kcal/mol as calculated by DFT, Scheme 4) and the subsequent amide cyclization step. This would also be in line with DFT calculations for the entire reaction profile carried out by Helaja and coworkers on the

DFT: II coincides with computed int_{1a}
Solubility: I dissolves in CDCl$_3$ only if added to a solution of 12a, dissolving faster at higher [12a]
$^1$H NMR monitoring of the reaction mixture:

\[ \text{Shielding of NH}_2 \text{ by 0.45 ppm in the reaction. Involvement of NH}_2 \text{ in H-bond diminishes with increased conversion, because the concentration of its H-bonding partner 12a decreases.} \]

Scheme 5. Mechanistic studies. A) Determination of the order in catalyst (initial-rate method). B) Determination of the order in substrate (initial-rate method). C) Lineweaver-Burk plot. D) Determination of the elasticity coefficient for the order in substrate. E) Hammett analysis. F) Eyring analysis. G) Generic Briggs-Haldane scenario applied to the present reaction. H) Proposed catalytic cycle. I) Computational and experimental evidences for the catalyst-substrate complex II; overlay of $^1$H NMR spectra acquired over 24 h for the cyclization of 12a (0.1 M in CD$_2$Cl$_2$) catalyzed by 1 (5 mol%) at 25 $^\circ$C, in the 8.7–9.2 ppm window (NH resonance).
cyclocyclization of 12a catalyzed by an NHC–Au(I) chloride complex of type C.

Finally, the thermodynamic activation parameters were obtained via Eyring analysis. The excellent linear correlation in the 18–35°C range suggests that only one mechanism is operative (Scheme 5F). The calculated ΔG° at 25°C (21.5 ± 1.5 kcal/mol) is in agreement with the experimental observation that the reaction proceeds relatively slowly at room temperature. The negative entropy of activation (ΔS° = −25.5 ± 2.5 cal mol⁻¹ K⁻¹) supports a scenario in which the energetic span of the catalytic cycle is composed of the chloride abstraction step, proceeding via associative ligand exchange, and the subsequent amide cyclization, since a negative entropy of activation is expected also for the cyclization. The contribution of the cyclization step to the overall barrier might explain why 1 catalyzes the 5-exo-dig cyclization of terminal benzamides 12, but not the energetically more demanding cyclizations of less reactive substrates N-(but-3-yn-1-yl)benzamide and N-(3-phenylprop-2-yn-1-yl)benzamide (the same lack of reactivity with these substrates was observed employing complexes C).[13]

The on the basis of the kinetic and computational data, we thus propose the catalytic cycle depicted in Scheme 5H. Initially, complex 1 interacts with substrate 12a forming intermediate II, where NH groups of the squaramide establish H-bonds with the carbonyl functionality of the amide. Intermediate II corresponds to the so-called catalyst-substrate complex [CS] (Scheme 5I), the putative resting state of the catalytic cycle. Computationally, intermediate II coincides with the calculated int. la (see Scheme 4), which is indeed the lowest energy species located considering several combinations of 12a and 1, being 2.1 kcal/mol more stable than 1 and 12a separately. Experimentally, at the onset of kinetic experiments it was observed that complex 1 (on its own insoluble in CD₂Cl₂) readily dissolves when added to a solution of 12a, and at higher concentration of 12a dissolves faster (1–5 s). A possible interpretation for this observation is that, upon mixing 12a and 1, the soluble [CS] forms, where the carbonyl group of the substrate H-bonds with the squaramide, breaking intramolecular H-bonds between squaramide units which would otherwise make 1 by itself insoluble. Additional evidence comes from ¹H NMR monitoring of the reaction mixture in CD₂Cl₂. The signal for the most acidic squaramide NH (NH₄) moves upfield by 0.45 ppm during the reaction, indicating increased shielding. This can be rationalized considering that the involvement of NH₄⁺ in H-bonding interactions diminishes with increased conversion, because the concentration of its H-bonding partner 12a decreases. From the catalyst-substrate complex, chloride abstraction occurs with a 6.7 kcal/mol barrier as calculated by DFT (Scheme 4). Next, the 5-exo-dig cyclization takes place, contributing to the total energetic span of the catalytic cycle, as indicated by Hammett and Eyring analysis. Deprotonation of intermediate IV by a basic species present in the reaction mixture (such as 12a, 13a, adventitious water, or the chloride anion) is expected to occur readily, affording vinyl gold(I) species V. Protodeauration of the latter would then liberate product 13a and regenerate catalyst 1. We note that this mechanistic picture, while rationalizing all kinetic, computational and experimental results for the cyclization of 12a catalyzed by 1, is in contrast to previous investigations on the same Au(I)-catalyzed reaction in the presence of silver salts.[29] Those studies rather point towards a turnover-limiting protodeauration step, based on the ¹H NMR observation[27d] and isolation[27a,31] of vinyl gold(III) complexes in the reaction of 12a (and analogous substrates possessing an internal alkyn), as well as on ligand effects.[27a] This interesting dichotomy highlights that the chloride abstraction step is far from obvious: the choice of a different chloride scavenging system (e.g. 1 as opposed to Ag salts) can have implications not only for the Au–Cl bond activation, but also for the following steps of the catalytic cycle. Furthermore, in this case the tethered H-bond donor group on the ligand can not only aid chloride scavenging, but potentially also speed up protodeauration by virtue of its Bronsted acidity.

Conclusion

A library of Au(I) chloride complexes with bifunctional phosphine ligands that incorporate classical bidentate H-bond donors, structurally characterized by X-ray diffraction, have been employed as self-activating Au(I) catalysts in both intramolecular and intermolecular reactions of alkynes, in the absence of silver or acidic additives. A correlation between H-bonding ability and activity was found, suggesting that H-bonding interactions indeed aid chloride abstraction from the Au(I) center, as confirmed computationally. The uncovered design principles regarding linker length and H-bond donor strength, together with other recent advances in this field,[11,12,13] should aid the development of more effective (intemolecular and/or chiral) chloride scavengers based on H-bonds for the activation of M–Cl bonds. In this sense, detailed kinetic studies offer solid ground for further mechanism-based developments, and give new insights into the reactivity of Au(I) complexes in the absence of silver scavengers. The synthetic efforts presented herein could also inspire the implementation of Au(I)-catalyzed transformations that take advantage of the presence of a tethered HBD moiety on the ligand.

Acknowledgements

We acknowledge the European Union (Horizon 2020 Marie Skłodowska-Curie COFUND postdoctoral fellowship to A.F., No. 754510), the European Research Council (Advanced Grant No. 835080), Ministerio de Ciencia e Innovación (PID2019-104815GB-I00), Severo Ochoa Excellence Accreditation2020-2023 (CEX2019-000925-S), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support. We also thank Dr Eduardo Escudero for useful discussion, and ICIQ X-ray diffraction, NMR and mass spectrometry units.
