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Enantioselective Au(I)-catalyzed dearomatization of 1-naphthols with allenamides through Tethered Counterion-Directed Catalysis†‡

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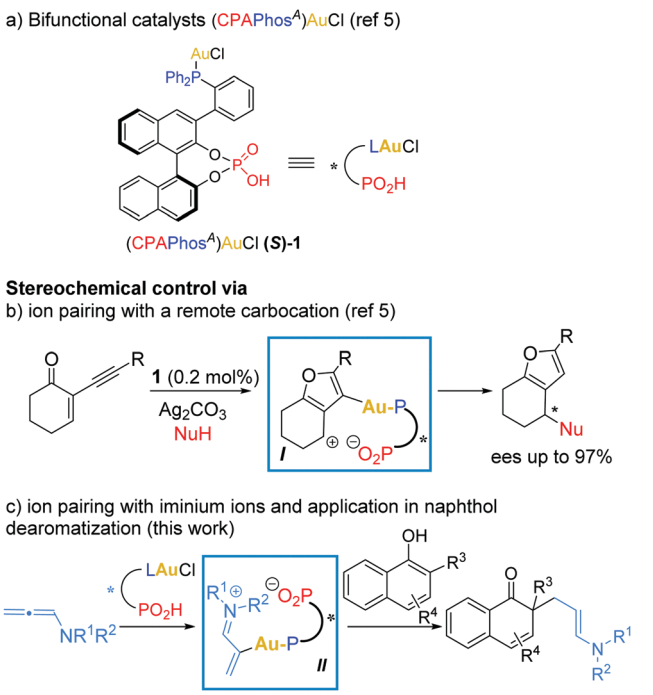
The Tethered Counterion-Directed Catalysis (TCDC) approach has been applied to the enantioselective Au(I) catalyzed dearomatizations of 1-naphthols with allenamides. Stereocontrol is ensured by the intramolecular ion-pairing between the chiral gold-tethered phosphate and an iminium unit, that provides a rigid, well-defined chiral environment to the key electrophilic intermediate.

The impressive potential of gold(I) catalysis for the synthesis of complex molecular scaffolds[1] has largely motivated the design of chiral gold(I) complexes that enable enantioselective variants.[2] Beyond classical approaches based on chiral ligands, the asymmetric counteranion-directed catalysis (ACDC) approach[3] that takes advantage of chiral phosphate counterions as the only source of stereocontrol, proved highly successful in this field, despite being mainly applied to hydrofunctionalizations of unsaturated bonds.[4] As a complement to the ACDC approach, we have disclosed recently[5] that tethering of a phosphate counterion to gold itself *via* a phosphorus ligand, as in the (CPAPhos^{A})AuCl complex **1** (Scheme 1a), may create additional conformational and steric constraints, that contribute to overcome some of the limitations of ACDC, notably in terms of enantioselectivity. This new approach has been named 'Tethered Counterion Directed Catalysis' (TCDC). Thus, in the tandem cycloisomerisation/nucleophilic addition reactions of 2-alkynyl-enones shown in Scheme 1b, (CPAPhos^{A})AuCl **1** provided bicyclic furans with up to 97% ee, at an unusually low catalyst loading (0.2 mol%). This reaction is postulated to proceed *via* the key carbocationic intermediate ***I*** that forms a tight intramolecular ion pair with the tethered phosphate counteranion, triggering high enantioselectivity in the addition of the nucleophile.

In this context, with the aim to further expand the scope of the TCDC approach, we have investigated other classes of reactions. Especially, we have postulated that the gold tethered phosphate might form tight ion pairs also with iminium ions that are generated from allenamides under gold activation[6] (***II*** in Scheme 1c). Therefore, enantioselective nucleophilic addition reactions involving allenamides might benefit, in terms of stereochemical control, from such intramolecular ion-pairing effects.



Scheme 1 Models for the stereochemical control in reactions involving pre-catalyst **1**.

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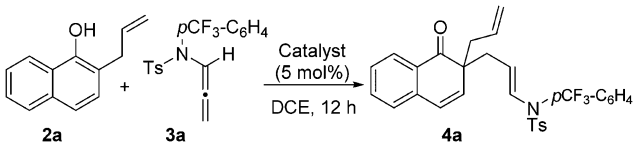
In this paper we report preliminary results that validate this working hypothesis, by showing that catalyst **1** gives high enantioselectivity in the catalytic dearomatization of 1-naphthols with allenamides. Generally speaking, catalytic dearomatization has grown as a convenient and reliable strategy for the synthesis of chiral compounds, as it converts flat, achiral derivatives into three dimensional scaffolds decorated by a variety of functional groups[7,8] Naphthols are privileged substrates, since they produce partially dearomatized naphthalenone units often encountered in natural and biologically active products.[9] Despite the extensive development of transition metal catalysts[10] and organocatalysts[11] for these reactions, some substrate combinations remain barely investigated. This is the case notably for the intermolecular dearomatization of naphthols with allenamides that has been reported recently by Shao[11f] and Bandini[10i,j] using phosphoric acids and gold phosphates as catalysts, respectively. Bandini's method required highly hindered 3, 3′-polyacene-BINOL-based catalysts to achieve high levels of enantioselectivity and was applied only to 2-naphthols. Overall, this state of art, that shows only a few sparse reactions involving allenamides, has motivated our attempts to fill this gap by taking advantage of catalyst **1**.

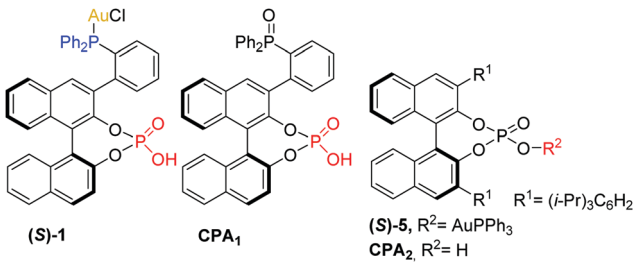
The dearomatization of 2-allylnaphthol **2a** with *N*-tosylallenamide **3a** has been selected as a model catalytic reaction. After a few optimization studies (see the ESI,‡ for full details), the reaction could be carried out in the presence of 5 mol% of (CPAPhos^{A})AuCl **1** as the pre-catalyst (Table 1). Complex **1** was treated *in situ* with Ag_2CO_3, in order to remove the chloride atom from gold and concomitantly generate a phosphate counteranion. The catalytic reaction was carried out at 0 °C in 1,2-dichloroethane for 12 h and, gratifyingly, the expected benzocyclohexenone **4a** was produced in good yield (68%) and high enantioselectivity (88% ee, entry 1). The absolute (*R*)-configuration of **4a** has been assigned from literature data.[11f]

Table 1 Dearomatization of 1-naphthol **2a** with allenamide **3a** promoted by activated **1** (entry 1) and control experiments (entries 2–6)



2a 3a 4a

	Catalyst	Additive	Yield (%)	ee (%)
1	(*S*)-**1**	Ag_2CO_3	68	88
2	(*S*)-**1**	None	19	0
3	**CPA$_1$**	Ag_2CO_3	0	—
4	**CPA$_1$**	None	<5	—
5	(*S*)-**5**	None	5	55
6	**CPA$_2$**	None	38	57

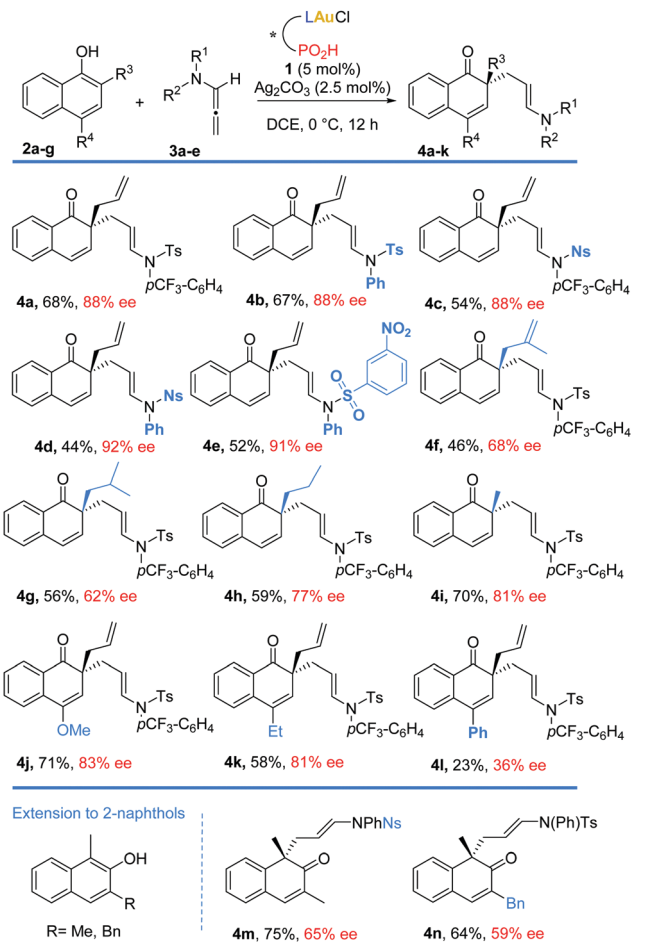


Beyond this extremely positive preliminary result, our aim was to substantiate the working hypothesis of the key role of the phosphate-tethered ligand in this catalytic process. Therefore, a few control experiments have been carried out to get more insights on the nature of the catalytically active species (Table 1). The results are the following:

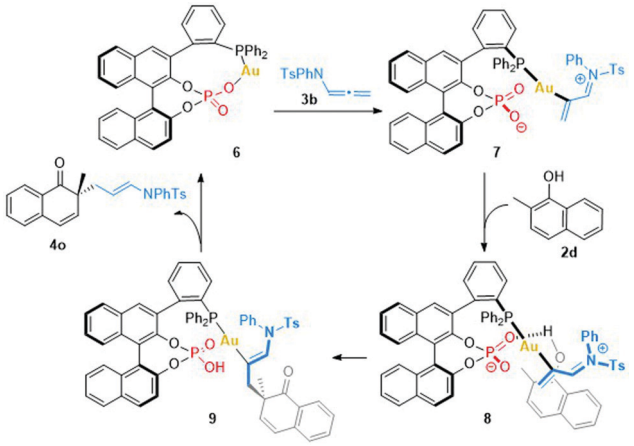
(a) The non-activated gold complex **1** promoted the reaction with low conversion rate (19% yield) and provided **4a** as a racemic product (entry 2). This demonstrated that the catalytic activity of **1** cannot be due to the phosphoric acid function alone.

(b) The phosphine oxide CPA1, a gold-free analog of (*S*)-**1** was catalytically inactive both in the presence (entry 3) and in the absence (entry 4) of silver carbonate. The results obtained with (*S*)-**1** (entry 1) hence cannot be attributed to silver phosphate nor to an organocatalytic process.

(c) The non-tethered (triphenylphosphine)Au(phosphate) complex **5**, gave **4a** in a very low yield (5%), with a moderate 55% ee, under the same reaction conditions (entry 5). This shows that a non-tethered chiral gold phosphate operating *via* the ACDC approach does not compete with **1** in terms of both catalytic activity and enantioselectivity, even when the well-known TRIP phosphate is used as the chiral counterion.



Scheme 2 Scope of the enantioselective dearomatization of 1-and 2-naphthols with allenamides, using pre-catalyst (CPAPhos^{A})AuCl, **1**.



Scheme 3 Putative mechanistic pathways for the enantioselective dearomatization of 1-naphthols with allenamides.

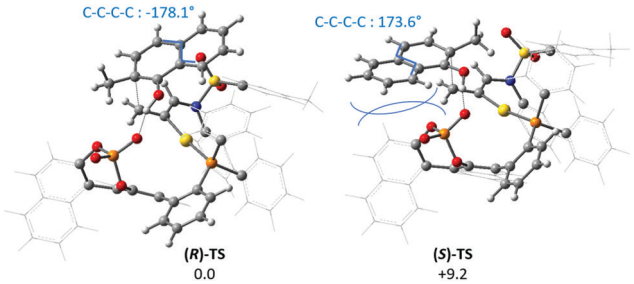


Fig. 2 Optimized geometry of transition states connecting intermediate **8** and **9**. Relative Gibbs free energy (in kJ mol^{-1}). For clarity, a wire frame representation of some aryl groups is used.

(d) The phosphoric acid TRIP (CPA_2 in Table 1) promoted the reaction with only moderate yields and ee (38% yield, 57% ee, entry 6).

Overall, these experiments support the synergistic effects between the gold center and the tethered phosphate counteranion of **1** that finally produce an effective catalyst.

Based on these encouraging outcomes, we have investigated the scope of this dearomatization reaction promoted by (CPAPhos[4])AuCl **1**. Results are shown in Scheme 2. The *N*-*p*-(trifluoromethyl)phenyl substituent of allenamide **3a** could be replaced by a phenyl group, leading to **4b** in 88% ee. The Ts protecting groups of allenamides could then be replaced by either *p*-Ns or *m*-Ns groups, giving **4c**, **4d** and **4e** in 88%, 92% and 91% ee respectively. This first set of results expands, to some extent, the scope of the dearomatization reaction, since the established method using chiral phosphoric acids ensures high enantioselectivities only with Ts/*p*-$CF_3C_6H_4$ substituted allenamides.

A drop of the enantiomeric excess to 68% was observed for R^3 = methallyl (**4f**), indicating that the reaction is sensitive to the bulkiness of the substituent R^3. This was further confirmed by the reaction with 2-*i*-Bu-1-naphthol, that resulted in a further decrease of the ee to 62% (**4g**). On the contrary, naphthols with propyl or methyl groups at the R^3 position maintained a good level of enantioselection, leading to **4h** and **4i** in 77 and 81% ee, respectively. The reaction with the sterically hindered 2-*t*-Bu-naphthol (R^3 = *t*-Bu) did not proceed, while the reaction with 2-phenyl-1-naphthol led to the *O*-addition product in 84% yield (see the ESI‡). Naphthols with substituents on their R^4 position were tolerated also: methoxy and ethyl substituted naphthols led to **4j** and **4k** in 83% and 81% ee respectively. A phenyl substituent in this position however led to a drop of ee to 36% (**4l**).

α-Amino allenylphosphonates are known to be useful synthons for the synthesis of diverse functionalized molecules.[12] Thus, a range of α-amino allenylphosphonates have been engaged in the reaction but unfortunately did not lead to any conversion. Remarkably, none of the reactions in Scheme 2 afforded products resulting from para addition of allenamides on the naphthols.

For comparison, a few experiments have been carried out on 2-naphthols. Under the same conditions, 1,3-dimethyl-2-naphthol delivered naphthalenone **4m** in 75% yield and 65% ee, while 1-methyl-3-benzyl-2-naphthol afforded **4n** in 64% yield and 59% ee. These results indicated that 2-naphthols are suitable substrates in these reactions, but lead to globally lower enantioselectivities.

Overall, the experimental results in Table 1 and Scheme 2 demonstrate the beneficial effect of tethering the counterion to the gold center in a catalytic reaction radically different from those disclosed in our previous study (Scheme 1).[5] Thus, to give further rationale to the TCDC concept, we have investigated the mechanism and stereochemical outcome of this

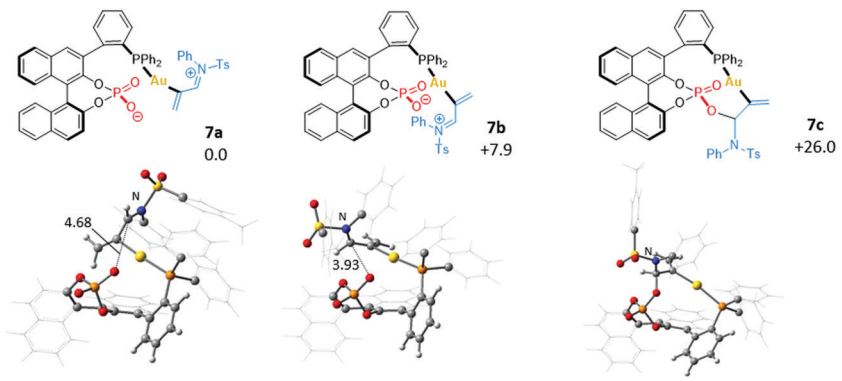


Fig. 1 Selected optimized geometries of intermediates **7**. Relative Gibbs free energy (in kJ mol^{-1}).

reaction by theoretical methods (see the ESI,‡ for computational details).

The postulated mechanism (Scheme 3) involves activation of the allenamide by the catalyst **6** to form **7**, association of 1-naphthol to **7** through H-bonding (**8**) and addition of naphthol to the complexed allenamide to produce the σ-complex **9**. Protodeauration will be the final step releasing catalyst **6** and product **4**. Computational studies have been carried out at the DFT level for the key reaction intermediates in Scheme 3.

The most stable conformations of the postulated catalytically active species **6** had been determined in our previous studies.[5] We hence started here by considering the interaction of **6** with allenamide **3b**. The σ-bonded intermediates **7** proved slightly more stable than the corresponding η^2-complexes (see ESI,‡ conformers **7a–7y**). A thorough exploration of the possible conformations allowed to identify **7a** as the lowest energy structure (Fig. 1). Unexpectedly, **7a** exhibits a long-range iminium-phosphate intramolecular electrostatic interaction ($P–O^-\cdots C{=}N^+$ distance = 4.68 Å). In **7b**, the $P–O^-\cdots C{=}N^+$ ion-pair distance is reduced to 3.93 Å but this conformation is higher in energy relative to **7a** (+7.9 kJ mol^{-1}) due to the geometrical constraints created by the phosphate group. The formation of a covalent C–O bond (see the ESI‡), as previously proposed in organocatalytic approaches,[11f] is also energetically demanding.

The most stable conformation **7a** allows the 2-methyl-1-naphtol **2d** to approach the terminal CH_2 group of the allenamide while enabling its activation through hydrogen bonding with the phosphate group.

The potential energy surface for the addition of 1-naphtol **2d** to **7a** has been computed at the DFT level. The lowest relative energy transition state leads to an (*R*) configured product **4o**, in agreement with experiments, whereas the (*S*)-product is obtained through a TS located 9.2 kJ mol^{-1} higher in Gibbs free energy (Fig. 2). The higher energy of (*S*)-TS is likely to result from steric hindrance between the naphtol backbone and the phosphoric acid moiety, as revealed by its distortion from planarity (dihedral angle -178.1° *vs.* 173.6°).

Overall, calculations provide an accurate stereochemical model for these reactions. They confirm that the rigidity, bulkiness and three-dimensional arrangement of the intramolecular ion pair **7**, together with hydrogen bonding of 1-naphthol with the phosphate P(O) function, direct the addition of 1-naphthol to the activated allenamide in an enantioselective manner.

In conclusion, we have demonstrated here a second application of the asymmetric Tethered Counterion-Directed Catalysis strategy: the Au(I)-catalyzed dearomatization of 1-naphthols with allenamides. In this reaction, the bifunctional nature of the ($CPAPhos^A$)AuCl complex **1** fully reveals its potential, since the phosphate not only contributes to create a rigid ion paring within the allenamide-gold adduct, but also directs the addition of the naphthol *via* H-bonding. Further relevant applications of the TCDC approach will be reported shortly.

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Conflicts of interest

There are no conflicts to declare.

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