H-Bonded Counterion-Directed Catalysis: Enantioselective Gold(I)-Catalyzed Addition to 2-Alkynyl Enones as a Case Study

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H-bonded counterion-directed catalysis (HCDC) is a strategy wherein a chiral anion that is hydrogen-bonded to the achiral ligand of a metal complex is responsible for enantioinduction. In this article we present the application of H-bonded counterion-directed catalysis to the Au(I)-catalyzed enantioselective tandem cycloisomerization-addition reaction of 2-alkynyl enones. Following the addition of C-, N- or O-centered nucleophiles, bicyclic furans were obtained in moderate to excellent yield and enantioselectivity (28 examples, 59–96% yield, 62:38 to 95:5 er). The optimal catalytic system, comprising a phosphinosquaramide Au(I) chloride complex and a BINOL-derived phosphoramidate Ag(I) salt, was selected in a combinatorial fashion from a larger library with the help of high-throughput screening. An enantioselectivity switch of ca. 120 Δee% was observed upon addition of the achiral Au(I) component to the Ag(I) salt.

Introduction

Over the last two decades, gold(I) catalysis has gained increased attention for its ability to selectively activate C–C multiple bonds under very mild conditions.[1] For instance, the Au(I)-catalyzed activation of alkenes towards intra- or intermolecular nucleophilic attack has provided access to molecularly complex structures from relatively simple substrates.[1] However, performing gold(I) catalysis in an enantioselective fashion has proven not trivial due to the special characteristics of this metal.[2] Gold(I) complexes usually present a linear dicoordinated geometry,[3] which places the ligand on the opposite site of the substrate, thus hampering transmission of the stereochemical information embedded in a chiral ligand to the reaction center (Figure 1A). To further complicate this matter, both the ligand–Au and substrate–Au bonds present relatively free rotation, and the nucleophilic addition generally occurs with an outer-sphere mechanism. Nevertheless, clever design for chiral ligands has allowed to successfully circumvent these problems[2] and high enantioselectivity has been achieved in various gold-catalyzed reactions, for example by using bulky ligands,[4] bifunctional phosphines,[5] or dinuclear complexes.[6]

An appealing alternative consists in placing the stereochemical information not on the ligand of the cationic metal complex, but on its counterion instead, in an approach termed “asymmetric counterion-directed catalysis” (ACDC, Figure 1B).[7,8] In 2007, Toste and coworkers reported the use of an achiral dinuclear Au(I) complex in combination with a BINOL-derived Ag(I) phosphate in the enantioselective cyclization of allenes, demonstrating the possibility of performing enantioselective gold catalysis by using chiral counterions in combination with achiral ligands.[9] Chiral anions have since then enjoyed great popularity in asymmetric gold catalysis, especially with allene substrates.[10,11] More recently, Marinetti, Guinchard and...
coworkers presented an interesting variant of this concept, named “tethered-counterion directed catalysis” (TCDC, Figure 1C), wherein a chiral phosphoric acid is covalently bound to the scaffold of a phosphine Au(I) chloride complex. This catalyst was able, with or without Ag(I) additives, to promote enantioselective reactions such as the tandem cycloisomerization-nucleophile addition to 2-alkynyl enones, the dearomatization of 1-naphthols with allenamides and the multi-component annulation of 2-alkynyl enones with nitrones formed in situ from aldehydes and hydroxylamines. Inspired by these works, in 2022 our group disclosed a “H-bonded asymmetric counterion-directed catalysis” strategy (HCDC, Figure 1D). In this approach, a H-bond donor group tethered on the phosphine ligand of a Au(I) complex enables abstraction of the chiral anionic ligand from the metal via H-bonding, in this way (i) placing the anion close to the active site for efficient transmission of the stereochemical information and (ii) enabling substrate coordination and catalysis at the Au(I) center. More specifically, a JohnPhos Au(I) chloride complex equipped with a distal urea was combined with a BINOL-derived Ag(I) phosphoramidate to perform enantioselective 5-exo-dig and 6-endo-dig cyclizations of 1,6-enynes with and without addition of external nucleophiles. In these reactions, the stereocenter was formed by intramolecular attack of the alkene onto the Au(I)-activated triple bond.

Herein we present the application of HCDC to the tandem cycloisomerization-nucleophile addition to 2-alkynyl enones affording substituted furans (Scheme 1, top). The stereocenter is set during the intermolecular nucleophilic addition onto a benzylic carbocation formed by the initial cycloisomerization. This study thus complements our previous investigations on 1,6-ene cyclizations, where the enantiodetermining step was intramolecular. Additionally, this transformation allows a direct comparison between HCDC and other catalytic systems previously used in enantioselective variants of the same reaction (Scheme 1, center). In this regard, the groups of Toste and Marinetti and Betzer employed chiral Cu(II) or Ag(I) phosphates, while Marinetti, Guinchard and coworkers leveraged the TCDC approach by using a chiral Au(I) catalyst with a pendant phosphoric acid group. Here, we describe instead the combination of an achiral phosphinosquaramide Au(I) chloride complex with a chiral Ag(I) phosphoramidate salt (Scheme 1, bottom). In the proposed mode of action, the chiral anion, H-bonded to the pendant squaramide, determines the enantiofacial selectivity in the addition of the nucleophile onto the secondary carbocation.

Results and Discussion

When using hydrogen-bonded counterion-directed catalysis, the factors that most influence the stereochemical outcome are: 1) the strength and geometry of the H-bond donor, 2) its relative position in the metal complex, and 3) the nature (basicity and steric bulk) of the chiral anion. In order to screen these parameters systematically, we evaluated a library of phosphine Au(I) chloride complexes equipped with urea or squaramide groups on triphenylphosphine- (Au1-6) or JohnPhos-type scaffolds (Au7-9), previously synthesized by our group (Figure 2A). The complexes thus vary in terms of phosphine, H-bond donor and linker between the two. The chiral anion was introduced as a phosphoramidate metal salt and the introduction of an H-bond donor group enabled abstraction of the chloride from the Au(I) precatalyst, such as Ag(I), Cu(II) and Na(I). We chose phosphoramidates, rather than more basic and hence more coordinating phosphates, because our previous studies showed that they are more easily removed from Au via H-bonding. Salts Ag1-10, Cu6 and Na6 were accessed in 2–3 steps from 3,3'-substituted (R)-BINOL and (R)-VAPOL and
We considered various groups in the 3,3'-position, which was hypothesized to be the stereodirecting part of the scaffold, as well as N-sulfonyl residues imparting different basicity to the phosphoramidate anion.\cite{13}

Initial screenings for the tandem cycloisomerization-indole addition to model enone 1a were conducted in toluene at room temperature (Table 1). Phosphinosquaramide Au(I) chloride complex Au3, previously proven to be catalytically active in the targeted reaction without any external chloride scavenger,\cite{17} gave relatively low conversion to furan product 3aa after 24 h (Table 1, entry 1). Upon addition of chiral salt Ag1 the catalytic efficiency improved notably, delivering the desired product in high yield and with promising 62:38 er in favor of the (S) enantiomer (Table 1, entry 2). Concentration and Au3/Ag1 ratio had little impact on the enantioselectivity (Table 1, entries 3–6).\cite{19}

Interestingly, when catalyzed by Ag(I) salt Ag1 alone, the reaction afforded preferentially the (R) enantiomer of the product, opposite to the one obtained when combining Ag1 with the achiral Au(I) complex (Table 1, entry 2 vs entry 7). This switch in enantioinduction points to the fact that a very different chiral pocket forms upon interaction between the H-bond donor of the achiral Au(I) complex and the chiral anion.\cite{19}

With these promising results in hand, we decided to screen various combination of Au(I) chloride complexes and chiral metal salts by means of High Throughput Experimentation (HTE) (Table 2). This approach, which allows to set-up multiple reactions with minimum consumption of substrates and catalysts, suits very well the 2-component nature of the H-bonded counterion-directed catalysis. Thus, 7 chiral salts were tested either alone or in combination with 7 Au(I) complexes, resulting in a total of 56 unique reactions on 10-μmol scale.\cite{19}

HTE data are provided in a heat map (Table 2), where the color scale from blue to red indicates enantoenrichment of product 3aa. In general, results were quite diverse when comparing either the same Au(I) complex with different chiral scavenger. Reactions without the Au(I) catalyst usually had moderate to good conversion, whereas full conversion was observed in most of the cases when Au(I) was added.\cite{19} Complexes Au3 that differ in the linker length between the phosphine aromatic ring and the squaramide displayed notable differences on the enantiocontrol (Table 2, columns 1–3). Au3 possessing the longest and more flexible linker, performed best (up to 86:14 er when combined with Ag6). Indeed, catalyst flexibility is in some cases beneficial for enantiocontrol, as it probably allows maximization of attractive non-covalent interactions along the catalytic cycle.\cite{20} These results also indicate that the distance between the hydrogen-bond donor and the Au(I) center is key for placing the chiral anion in an appropriate...
position in the enantiodetermining step. When comparing the acidity of the H-bond donor in complexes Au4-6 (Table 2, columns 4–6), in 5 out of 6 instances the use of Au6, which possesses the most acidic urea, resulted in higher enantioselectivity (83.5 : 16.5 er) than the one provided by Au4 and Au5 (Table 2, columns 4–6). This finding is in line with the previously reported enantioselective versions employing Cu(II)2,16a and Ag(I)2,16b phosphates. It is interesting to compare the performance of Ag1-3 bearing 3,3'-trisopropylphenyl groups, that differ only in the N-sulfonyl substituents on the phosphoramidate, hence in their basicity. When used on their own, enantioselectivity roughly correlated with basicity: Ag1, bearing a N-triflyl group, gave the product with lower er (23:77) than the more basic N-mesyl Ag2 and N-phenylsulphonyl Ag3 (ca 14:86 er). These results also correlate well with the high enantioselectivity observed when more basic phosphate anions are used.2,16a,b Variations in enantiocatalysis were observed also when comparing N-triflyl phosphoramidate salts with different substituents on 3,3'-positions of the BINOL backbone (Ag4-6). The best salts were found to be Ag6 and Cu6, which present the same chiral scaffold, namely a BINOL-derived phosphoramidate with 9-anthracenyl groups on 3,3'-positions. Ag6 and Cu6 in combination with Au3 yielded the desired product respectively in 93% yield and 86:14 er, and 49% yield and 83.5:16.5 er. It is notable that the addition of the achiral catalytic component determined a switch in the sense of enantioinduction exceeding in some cases 110 Δee%21 (eg Au3/Ag6, Au7/Ag2 and Au7/Ag3 combinations). Overall, the HTE results showed that the basicity of the anion (Ag1-3), the substituents in the 3,3'-position of the anion, the strength (Au4-6) and relative position of the hydrogen-bond donor (Au1–3) are all important parameters influencing enantiocontrol. Since several factors are at play simultaneously, a combinatorial approach offers the best chances of identifying the optimal catalytic system.

In order to validate the HTE screening, the results obtained with Au3, Ag6 and Cu6 were reproduced on 0.05-mmol scale; chiral salt Na6 was also tested (Table 3, entries 1–6). Data were in agreement with HTE results. As expected, Na6 was not catalytically active on its own, while in combination with Au3 gave lower enantiocontrol (81:19 er) than the one provided by Cu6 and Ag6 (83:17 and 89:11 er respectively). This trend in enantiocontrol parallels the chloride scavenging ability of the three cations. Cu(II)2,16b and Na(I) cannot scavenge the chloride ligand as fast and effectively as Ag(I),13,22 likely leading to background non-enantioselective reactivity by the gold(I) chloride complex. Together with Ag6, JohnPhos-type complexes Au7, Au8 and Au9 (the best one in our previously reported cyclizations of 1,6-enynes)13 showed good performance (Table 3, entries 7–9), but remained inferior to Au3 in terms of enantiocontrol. Finally, intrigued by the role of the 3,3'-anthracenyl substituents on the optimal salt Ag6,13 we tested new chiral salts Ag7-10 with polycyclic aromatic moieties in combination with phosphinosquaramide complex Au3 (Table 3, entries 10–13). VAPOL- and VANOL-derived Ag9 and Ag10 provided poor enantiocontrol. Ag7 and Ag8, bearing respectively 9-phenanthryl and 2-pyrenyl groups, gave comparable results to those obtained with 9-anthracenyl, confirming

Table 2. High-throughput screening on the combination of achiral gold(I) complexes Au1-7 and chiral metal salts; er shown.2

|       | Au1 | Au2 | Au3 | Au4 | Au5 | Au6 | Au7 | -         |
|-------|-----|-----|-----|-----|-----|-----|-----|-----------|
| (R)-Ag1 | 56.5:43.5 | 61.5:38.5 | 63.5:36.5 | 39.5:60.5 | 38.62 | 35.5:64.5 | 76.5:23.5 | 23.77 |
| (R)-Ag2 | 63.37 | 48.5:51.5 | 59.41 | 42.58 | 45.5:54.5 | 37.5:62.5 | 79.5:20.5 | 14.5:85.5 |
| (R)-Ag3 | 66.5:33.5 | 54.46 | 58.42 | 42.58 | 46.5:53.5 | 30.5:69.5 | 72.28 | 13.5:86.5 |
| (R)-Ag4 | 61.5:38.5 | 66.5:33.5 | 76.5:23.5 | 35.5:64.5 | 39.5:60.5 | 47.53 | 66.5:33.5 | 34.5:65.5 |
| (R)-Ag5 | 63.37 | 46.54 | 60.5:39.5 | 46.54 | 42.58 | 35.5:64.5 | 73.5:26.5 | 28.5:71.5 |
| (R)-Ag6 | 55.45 | 73.5:26.5 | 86.14 | 36.5:63.5 | 42.58 | 25.5:76.5 | 81.5:18.5 | 20.5:70.5 |
| (R)-Cu6 | 56.44 | 70.5:29.5 | 83.5:16.5 | 36.64 | 38.62 | 25.5:74.5 | 76.24 | 35.65 |

[a] (S)-3aa/(R)-3aa ratio determined by UPC2 on chiral stationary phase. See the Supporting Information for details.
that highly conjugated substituents in 3,3′-position improve the enantioselectivity of the reaction under study. The best combination remained Au3 with Ag6, affording product (S)-3aa with 87% yield and 89:11 er (Table 3, entry 1).

Final refining of the reaction conditions using the Au3/Ag6 catalytic system was undertaken (Table 4). Toluene was the best solvent, while more polar ones led to lower enantiocontrol, presumably because they interfered with ion-pairing and H-bonding (Table 4, entries 1–7). Lowering the temperature to 10 °C in toluene led to an improved 92:8 er for product (S)-3aa (Table 4, entry 9). The reaction was completed after only 1 h using 5 mol% catalyst loading (Table 4, entry 11), which prompted us to test a 50-μmol scale reaction lowering the catalyst loading down to 1 mol%, obtaining furan 3aa in 83% yield and 92:8 er after 4 h (Table 4, entry 12).

The substrate scope of the tandem cycloisomerization-nucleophile addition to enones 1 was then assessed on 0.15-mmol scale with 1 mol % loading of Au3 and Ag6 using indoles as nucleophiles (Scheme 2).

5-Substituted indoles with electron-donating and electron-withdrawing groups on the aromatic ring were suitable nucleophiles (products 3ab and 3ac). Indoles with substituents in position 2 and 1 led to a lower er for products 3ad and 3ae. When using 3-methyl indole, the obtained product resulted from C-2 attack instead (3af, 67% yield, 91:9 er). 2-Alkynyl enones 1 with electron-rich and electron-poor aromatic groups on the alkyne terminus provided the relative products 3ba–3ha with moderate to good yield and enantioselectivity. The reaction, however, was found to be sensitive to the steric bulk

Table 3. Screening of Au(I) catalyst and chiral metal salts for the model cycloisomerization-indole addition to 2-alkynyl enone 1a.

| Entry | [Au] (R)-[MX] | Yield [%] | Er [%] |
|-------|---------------|-----------|--------|
| 1     | Au3 Ag6       | 87        | 89:11  |
| 2     | Au3 Cu6       | 79        | 82:17  |
| 3     | Au3 Na6       | 86        | 81:19  |
| 4     | - Ag6         | 87        | 30.5:69.5 |
| 5     | - Cu6         | 68        | 28:72  |
| 6     | - Na6         | 0         | n.d.   |
| 7     | Au7 Ag6       | > 95      | 80:20  |
| 8     | Au8 Ag6       | > 95      | 78:22  |
| 9     | Au9 Ag6       | > 95      | 80:20  |
| 10    | Au3 Ag7       | > 95      | 87:13  |
| 11    | Au3 Ag8       | > 95      | 80:20  |
| 12    | Au3 Ag9       | > 95      | 62:38  |
| 13    | Au3 Ag10      | > 95      | 55:45  |

[a] Yield determined by 1H-NMR analysis against 1,1,2,2-tetrachloroethane as internal standard. [b] (S)-3aa:(R)-3aa ratio determined by HPLC on chiral stationary phase. [c] Not determined.

Table 4. Final optimization of the reaction catalyzed by the Au3/Ag6 system.

| Entry | Solvent | T (°C) | Yield [%] | Er [%] |
|-------|---------|--------|-----------|--------|
| 1     | 1,2-DCE | 25     | 78        | 69:31  |
| 2     | CHCl3   | 25     | 81        | 75:25  |
| 3     | THF     | 25     | 79        | 66:34  |
| 4     | C6H5CF3 | 25     | 58        | 78:22  |
| 5     | benzene | > 95   | 87:13    |
| 6     | p-xylene| 25     | 77        | 86:14  |
| 7     | toluene | 25     | 87        | 89:11  |
| 8     | toluene | 0      | 84        | 91:9   |
| 9     | toluene | −10    | > 95      | 92:8   |
| 10    | toluene | −20    | 66        | 92:8   |
| 11    | toluene | −10    | 72        | 92:8   |
| 12    | toluene | −10    | 83        | 92:8   |

[a] Yield determined by 1H-NMR analysis against 1,1,2,2-tetrachloroethane as internal standard. [b] (S)-3aa:(R)-3aa ratio determined by HPLC on chiral stationary phase. [c] Reaction completed in 1 h, yield given for isolated 3aa. [d] With 1 mol % catalyst loading, reaction completed in 4 h, yield given for isolated 3aa.
of the ortho position of the aryl ring, leading to cyclized product 3da with a 78:22 er. Enones with 3-thienyl and cyclohexyl alkene groups afforded furans bearing heteroaromatic and alkyl substituents with moderate yield and enantioselectivity (3ia, 3ja). Cyclopentenone and cycloheptenone substrates 1k and 1l led to the corresponding bicyclic furans 3ka and 3la in good yield and 86:14 and 85:15 er, respectively.

Previous reports on the addition of N- and O-centered nucleophiles\(^{[15,16]}\) encouraged us to test them with our Au3/Ag6 system too (Scheme 3). Reaction of enone 1a with aniline required 24 h to go to completion, and a modest 62:38 er was observed for product 4a. Carbamates were instead excellent nucleophiles, providing after 1 h furans 4b and 4c in 95:5 er. Moderate enantioselectivity was observed in the addition of primary alcohols such as methanol, a propargylic alcohol and allylic alcohol to enone 1a (72:28 to 76:24 er for compounds 4d–4f). Interestingly, the presence of an internal alkane or a terminal alkene on the nucleophile did not interfere with the expected reaction course. Higher enantioselectivity was obtained employing secondary alcohols, phenol and 1-naphthol as nucleophiles (81.5:18.5 to 89:11 er for products 4g–4k), suggesting that a certain degree of steric bulk on the nucleophile aids enantioface discrimination of the carbocation intermediate. The water addition product was not directly detected, but instead symmetric ether 4k, arising from nucleophilic attack by the initially formed secondary alcohol, was obtained in 85% yield (3:1 dr) and 95:5 er. Absolute configuration for 11 products was assigned by comparison with the sign of optical rotation reported in the literature.\(^{[19]}\)

Absolute configuration for the other products was assigned by analogy, assuming a uniform stereochemical mechanism, with the H-bonded anion shielding the Si face of the carbocation intermediate depicted in Scheme 1.

**Conclusion**

The combinatorial nature of H-bonded counterion-directed catalysis has been exploited in the context of the enantioselective tandem cyclosimerization-nucleophile addition to 2-alkynyl enones. High-throughput screening allowed to identify a flexible phosphinosquaramide gold(I) chloride complex (Au3) in combination with a Ag(I) phosphoramidate salt derived from (R)-BINOL (Ag6) as the optimal catalyst. Remarkably, the achiral gold(I) complex switches the enantiofacial selectivity for the nucleophilic addition onto the intermediate carbocation with respect to the chiral Ag(I) salt alone, underscoring the distinct mode of action of H-bonded counterion-directed catalysis. Thus, employing a 1 mol% loading for the Au3/Ag6 catalytic system, the addition of C-, O- and N-centered nucleophiles gave bicyclic furan products in moderate to excellent yield and enantioselectivity (28 examples, 59–96% yield, 62:38 to 95:5 er). Further studies on the application of hydrogen-bonded counterion-directed catalysis are ongoing in our group.

**Experimental Section**

**General procedure for the enantioselective tandem cyclization-nucleophile addition to 2-alkynyl enones**

Under N\(_2\), a solution of enone 1 (0.150 mmol, 1 equiv) and nucleophile (1.0–3.0 equiv) in toluene (1.5 mL) cooled to −10°C was added to a microwave vial containing complex Au3 (1.3 mg, 1.5 μmol, 0.01 equiv) and (R)-Ag6 (1.3 mg, 1.5 μmol, 0.01 equiv) kept at −10°C. The resulting mixture was stirred at −10°C under inert atmosphere (N\(_2\) balloon) in the dark, until the enone starting material was consumed, as judged by TLC or GCMS analysis. The reaction was then quenched by addition of triethylamine (0.2 mL) and filtered through a silica-filled glass pipette. Volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (FCC) or preparative thin-layer chromatography (PTLC).

(S)-3-(2-Phenyl-4,5,6,7-tetrahydrobenzofuran-4-yl)-1H-indole (3aa)

Prepared following the general procedure using 2-(phenylethynyl)cyclohex-2-en-1-one (1a, 29.4 mg, 0.150 mmol, 1.0 equiv) and indole (17.6 mg, 0.150 mmol, 1.0 equiv) in toluene (1.5 mL) at −10°C for 4 h. The crude product was purified by PTLC (silica, CyH:AcOEt 95:5). Compound 3aa was obtained as a white solid (35.8 mg, 0.115 mmol, 77% yield) with 91:9 er.

Spectroscopic data for product 3aa matched those reported in the literature.\(^{[12a]}\) The absolute configuration was assigned by comparison with the literature based on both the sign of optical rotation.
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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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