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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 alkynes 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]

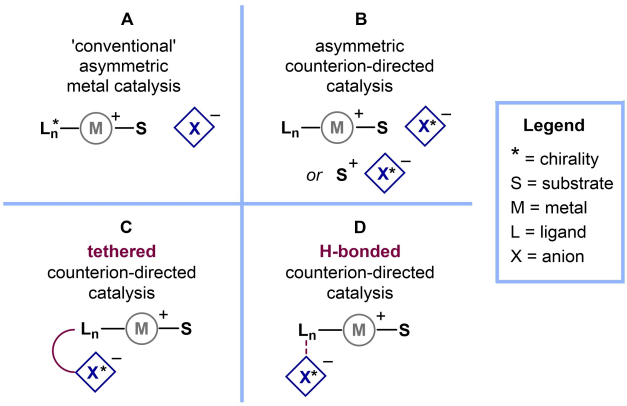

Figure 1. Simplified representations of metal catalysis employing chiral ligands (**A**), asymmetric counterion-directed catalysis (ACDC, **B**), tethered counterion-directed catalysis (TCDC, **C**) and H-bonded counterion-directed catalysis (HCDC, **D**).

An appealing alternative consists in placing the stereochemical information not on the ligand of the cationic metal complex, but on its counteranion 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

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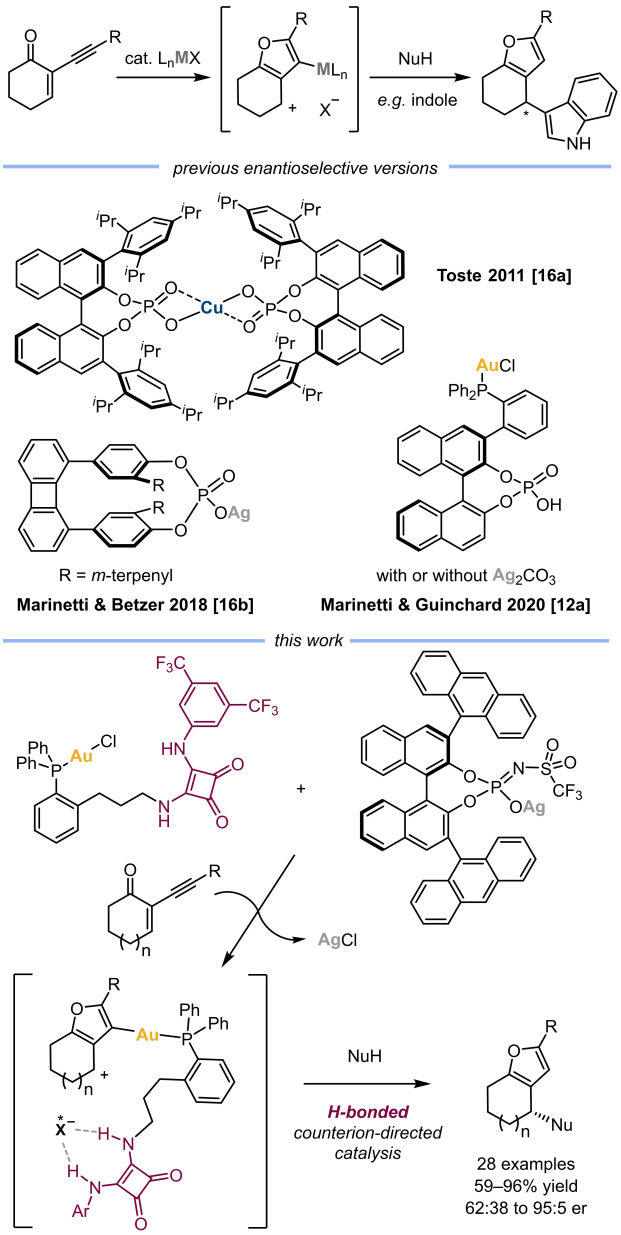
coworkers presented an interesting variant of this concept, named "tethered-counterion directed catalysis" (TCDC, Figure 1C), wherein a chiral phosphoric acid is covalently bound to the scaffold of a phosphine Au(I) chloride complex.[12] This catalyst was able, with or without Ag(I) additives, to promote enantioselective reactions such as the tandem cycloisomerization-nucleophile addition to 2-alkynyl enones,[12a] the dearomatization of 1-naphthols with allenamides[12b] and the multicomponent annulation of 2-alkynyl enones with nitrones formed *in situ* from aldehydes and hydroxylamines.[12c] Inspired by these works, in 2022 our group disclosed a "H-bonded asymmetric counterion-directed catalysis" strategy (HCDC, Figure 1D).[13] 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.[13] 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[14] affording substituted furans (Scheme 1, top).[15] The stereocenter is set during the intermolecular nucleophilic addition onto a benzylic carbocation formed by the initial cycloisomerization.[16] This study thus complements our previous investigations on 1,6-enyne cyclizations, where the enantiodetermining step was intramolecular.[13] 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,[16a] and Marinetti and Betzer[16b] 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.[12a] 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.



Scheme 1. Enantioselective metal-catalyzed tandem cycloisomerization-nucleophile addition to 2-alkynyl enones. Top: Targeted reaction. Center: Previously reported chiral catalytic systems. Bottom: This work.

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.[13] 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).[13,17] 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 (Figure 2B), with a countercation capable of abstracting the chloride from the Au(I) precatalyst, such as Ag(I), Cu(II) and Na(I).[18] 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.[13] Salts **Ag1-10**, **Cu6** and **Na6** were accessed in 2–3 steps from 3,3'-substituted (*R*)-BINOL,[13] (*R*)-VAPOL and

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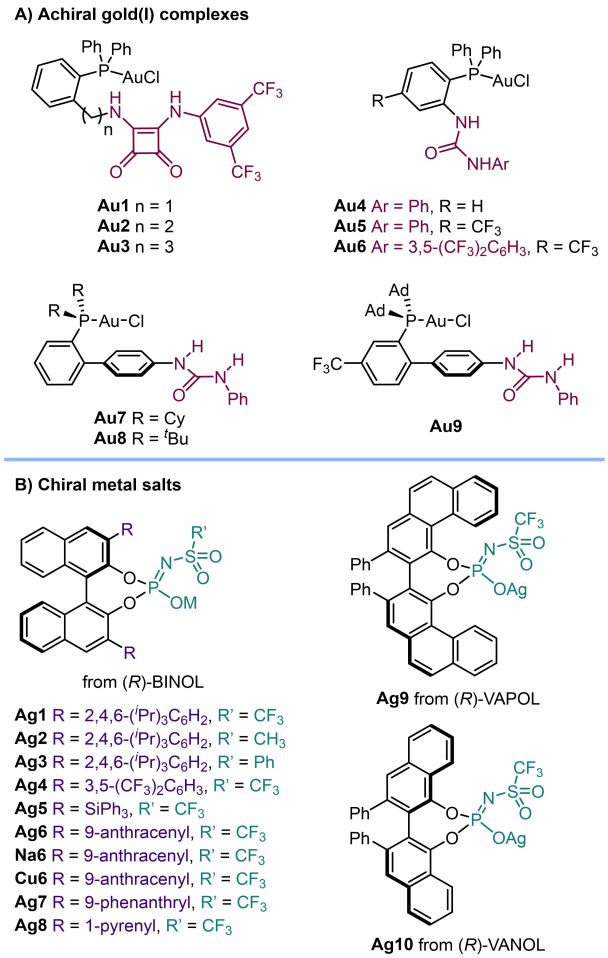


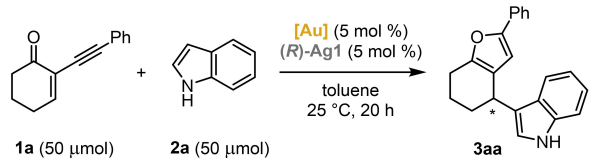
Figure 2. Library of achiral Au(I) chloride complexes and chiral metal salts.

(*R*)-VANOL scaffolds.[19] 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.[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,[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).[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.

Table 1. Initial studies on the model cycloisomerization-indole addition to 2-alkynyl enone **1a**.



1a (50 μmol) **2a** (50 μmol) **3aa**

Entry	[Au]	Conditions	Yield [%][a]	Er[b]
1[c]	**Au3**	Without **Ag1**	21	n.d.[d]
2	**Au3**	0.1 M	>95	62:38
3	**Au3**	0.2 M	>95	61:39
4	**Au3**	0.05 M	>95	62:38
5	**Au3**	0.1 M, 1:2 Au:Ag	>95	66:34
6	**Au3**	0.1 M, 1:0.5 Au:Ag	>95	64:36
7	–	0.1 M	55	27.5:72.5
8	[(JohnPhos)AuCl]	0.1 M	>95	42:58
9	[(Ph_3P)AuCl]	0.1 M	>95	40:60
10	**Au3**	AgTRIP instead of **Ag1**	>95	64:36

[a] Yield determined by ^{1}H-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] Result taken from ref. 10. [d] Not determined.

[(JohnPhos)AuCl] and [(Ph_3P)AuCl] in combination with **Ag1** delivered the product in quantitative yield but lower er, with a preference for the same enantiomer as the Ag(I) salt alone (Table 1, entries 8 and 9). (*R*)-Ag(I)TRIP, namely the phosphate analogue of phosphoramidate **Ag1**, when used with **Au3** had a catalytic performance similar to the **Au3**/**Ag1** couple (Table 1, entry 10).

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.[19]

HTE data are provided in a heat map (Table 2), where the color scale from blue to red indicates enantioenrichment of product **3aa**. In general, results were quite diverse when comparing either the same Au(I) complex with different chiral salts or different Au(I) complexes with the same chloride 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.[19] Complexes **Au1-3** 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.[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

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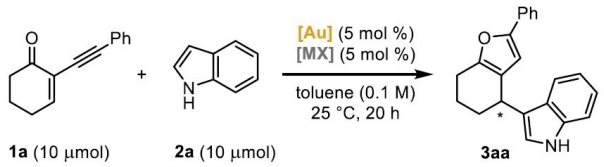
Table 2. High-throughput screening on the combination of achiral gold(I) complexes **Au1-7** and chiral metal salts; er shown.[a]



1a (10 μmol) **2a** (10 μmol) **3aa**

	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	23.5:76.5	81.5:18.5	29.5:70.5
(*R*)-Cu6	56:44	70.5:29.5	83.5:16.5	36:64	38:62	25.5:74.5	76:24	35:65

90:10–80:20
80:20–70:30
70:30–60:40
60:40–50:50
50:50–40:60
40:60–30:70
30:70–20:80
20:80–90:10

[a] (*S*)-**3aa**:(*R*)-**3aa** ratio determined by UPC^2 on chiral stationary phase. See the Supporting Information for details.

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 in favour of product (*R*)-**3aa**. This trend suggests that a stronger H-bonding interaction with the anion is beneficial for enantiocontrol. Phosphinosquaramide complexes **Au1-3** and JohnPhos-type phosphinourea complex **Au7** favored the formation of (*S*)-**3aa**, in up to 81:5:18.5 er when mixed with **Ag6**. All in all, these data highlight the effect on enantiocontrol played by the relative position of the H-bond donor with respect to the Au(I) center.

Regarding the chiral Ag(I) phosphoramidate salts, the HTE screening confirmed that the reaction can be catalyzed by those alone, in the absence of the gold(I) catalyst, albeit with reduced yields and favoring the (*S*)-enantiomer (Table 2, column 8).[19] This finding is in line with the previously reported enantioselective versions employing Cu(II)[16a] and Ag(I)[16b] phosphates. It is interesting to compare the performance of **Ag1**-**3** bearing 3,3′-triisopropylphenyl 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.[16a,b] Variations in enantiocontrol 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)[18] 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

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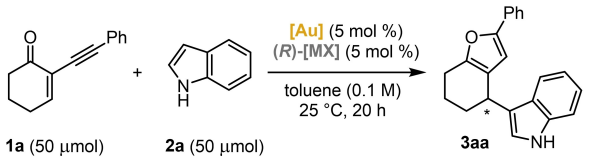
Table 3. Screening of Au(I) catalyst and chiral metal salts for the model cycloisomerization-indole addition to 2-alkynyl enone **1a**.



1a (50 μmol) **2a** (50 μmol) **3aa**

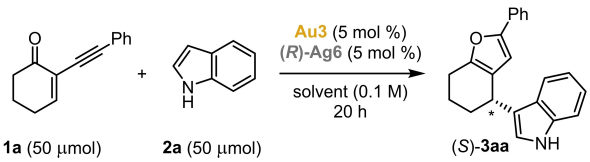
Entry	[Au]	(*R*)-[MX]	Yield [%][a]	Er[b]
1	**Au3**	**Ag6**	87	89:11
2	**Au3**	**Cu6**	79	83:17
3	**Au3**	**Na6**	86	81:19
4	–	**Ag6**	87	30.5:69.5
5	–	**Cu6**	68	28:72
6	–	**Na6**	0	n.d.[c]
7	**Au7**	**Ag6**	>95	80:20
8	**Au8**	**Ag6**	>95	78:22
9	**Au9**	**Ag6**	>95	80:20
10	**Au3**	**Ag7**	>95	87:13
11	**Au3**	**Ag8**	>95	80:20
12	**Au3**	**Ag9**	>95	62:38
13	**Au3**	**Ag10**	>95	55:45

[a] Yield determined by ^{1}H-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.

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).

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



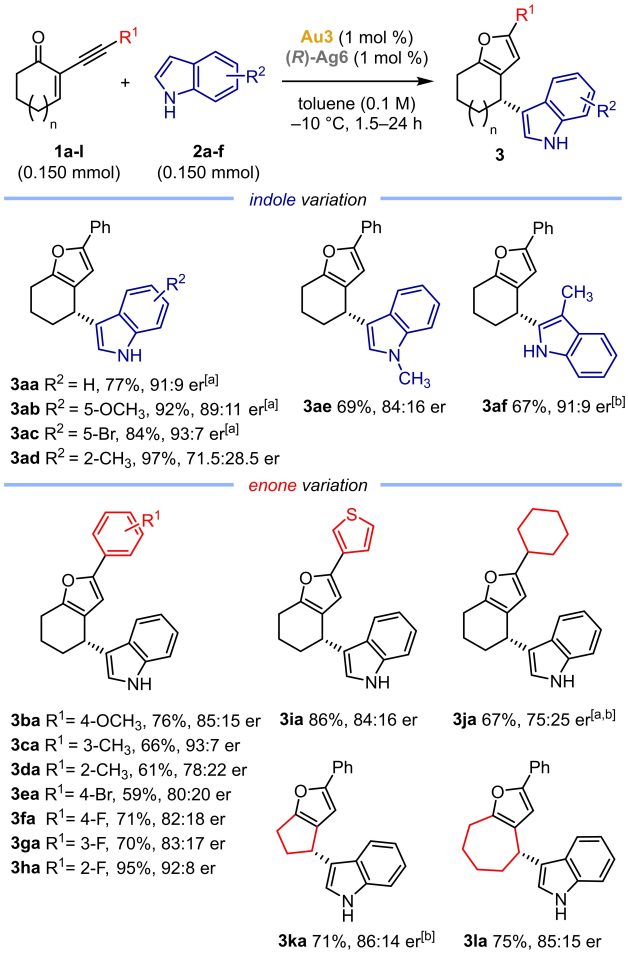
1a (50 μmol) **2a** (50 μmol) (*S*)-**3aa**

Entry	Solvent	T (°C)	Yield (%)[a]	Er[b]
1	1,2-DCE	25	78	69:31
2	$CHCl_3$	25	81	75:25
3	THF	25	79	66:34
4	$C_6H_5CF_3$	25	58	78:22
5	benzene	25	>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[c]	toluene	−10	72	92:8
12[d]	toluene	−10	83	92:8

[a] Yield determined by ^{1}H-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**.

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



Scheme 2. Enantioselective addition of indoles **2a**–**f** to 2-alkynyl enones **1**. Reactions performed under Ar or N_2 atmosphere in anhydrous toluene. Yields given for isolated material after purification. Er determined by HPLC or SFC on chiral stationary phase. [a] Result taken from ref. [13]. [b] With 3 mol% loading of catalysts.

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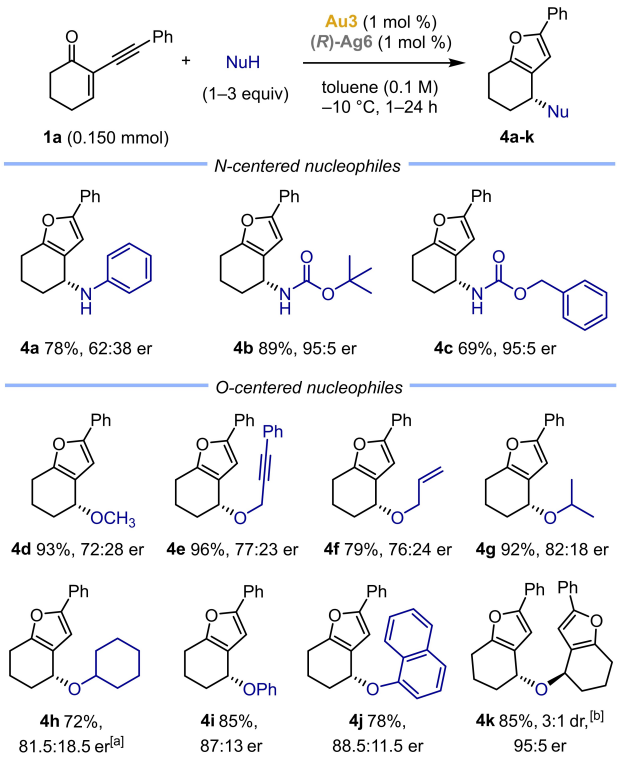
of the *ortho* position of the aryl ring, leading to cyclized product **3da** with a 78:22 er. Enones with 3-thienyl and cyclohexyl alkyne groups afforded furans bearing heteroaromatic and alkyl substituents with moderate yield and enantioselectivity (**3ia**, **3ja**). Cyclopentenone and cycloheptenone 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 alkyne 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.



Scheme 3. Enantioselective addition of N- and O-centered nucleophiles to enone **1a**. Reactions performed under Ar or N_2 atmosphere in anhydrous toluene. Yields given for isolated material after purification. Er determined by HPLC or SFC on chiral stationary phase. [a] With 3 mol% loading of catalysts. [b] Ratio between chiral and meso diastereomers.

Conclusion

The combinatorial nature of H-bonded counterion-directed catalysis has been exploited in the context of the enantioselective tandem cycloisomerization-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 (3 aa)

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

and the order of elution under identical HPLC conditions.[12a,16a,b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br s, 1H), 7.64–7.55 (m, 3H), 7.38 (dt, J = 8.1, 0.9 Hz, 1H), 7.36–7.30 (m, 2H), 7.24–7.16 (m, 2H), 7.15–7.09 (m, 1H), 6.88 (s, 1H), 6.45 (s, 1H), 4.26 (t, J = 5.7 Hz, 1H), 2.88–2.64 (m, 2H), 2.25–2.09 (m, 1H), 2.05–1.93 (m, 2H), 1.93–1.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 151.4, 136.7, 131.5, 128.7, 126.8, 126.7, 123.4, 122.2, 122.1, 120.4, 119.41, 119.37, 111.3, 106.2, 31.3, 31.1, 23.6, 21.3. HPLC (Chiralpak IA (250×4.6 mm, 5 μm), 95:5 *n*-hexane:*i*-PrOH, 1.0 mL/min, 25 °C, 280 nm): en1 (major, 91%) min 12.66, en2 (minor, 9%) min 15.68. $[\alpha]^{26.0}_D$ −27 (c 0.89, $CHCl_3$, sample with 91:9 er); lit: $[\alpha]^{20}_D$ −30 (c 0.5, $CHCl_3$, sample with 93:7 er).[16b]

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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.

Keywords: Asymmetric catalysis · Gold · Chiral counterion · Hydrogen bonding · Ynenones

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