β-Cyclodextrin-NHC-Au(I)-Catalyzed Enantioconvergent 1,5-enyne Cycloisomerizations

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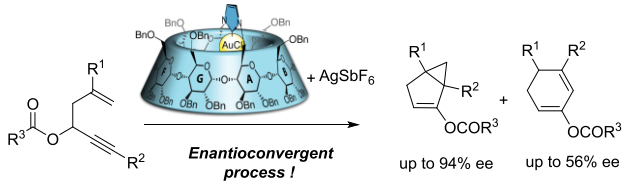
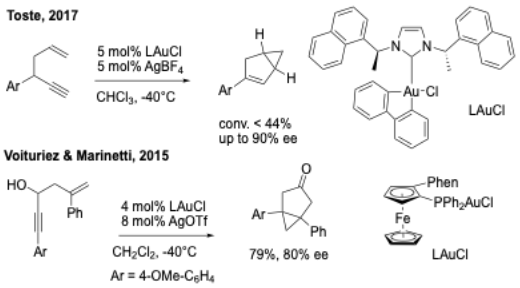


ABSTRACT: Enantioconvergent transformations from racemic mixtures are attractive since they allow to generate optically active products with full conversion despite the possibly adverse kinetic resolution process. When dealing with gold(I)-catalyzed cycloisomerizations, chirality transfer from the precursor is another possible diverting pathway, which renders enantioconvergence challenging. Not surprisingly, enantioconvergent Au(I)-catalyzed processes have remained extremely rare. Herein, we show that cavity-driven catalysis using β-Cyclodextrin-NHC-Au(I) complexes bring opportunities to conduct highly enantioconvergent cycloisomerizations of 1,5-enynes, -enynols and –enynyl esters.

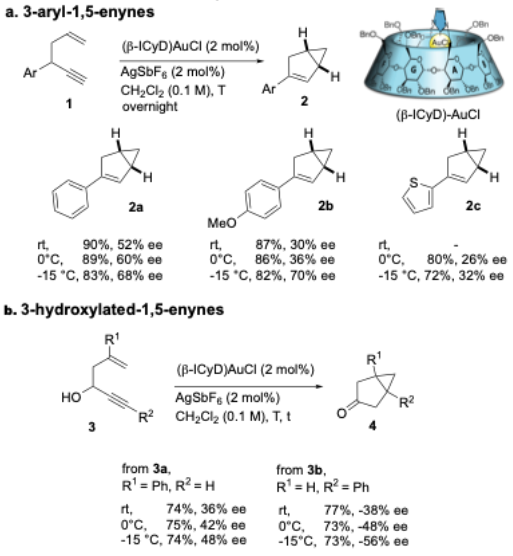
Confined gold(I) catalysis has emerged over the last decade as a valuable strategy to improve diverse transformations through the stabilization of reactive gold intermediates. In numerous instances, it has promoted chemo- or regioselectivities that could not be reached with systems devoid of confinement.[1] Toward that goal, two approaches have been pursued, the first one consisting in preparing supramolecular assemblies that encapsulate a LAuCl complex.[2] Alternatively, covalent hosts have allowed the confinement of linear gold(I) complexes; this being all the easier as they only require a single anchoring point via a Lewis base site like a phosphine or a NHC located on the host. Those have for instance included triethynylphosphine ligands bearing bulky ends[3] as well as the more recent variants consisting in bulky tri-(ortho-biaryl)phosphine ligands,[4] NHC-capped cyclodextrins,[5] and resorcin[4]arene-based cavitands.[6] Naturally, confined catalysis is suited to enantioselective catalysis, which is obviously easier to achieve if the host is intrinsically chiral.[7] In this context, we have been interested over the last decade in the development of NHC-Au(I) complexes attached to α-, β- or γ-cyclodextrins (CD) that could serve as chiral nanoreactors.[8] Previous studies have established that β-CD-NHCAu(I)Cl ((β-ICyD)AuCl) complexes have provided the best environment for a series of asymmetric transformations such as enynes cycloisomerizations and alkoxy cyclizations.[9] Following these initial studies based on achiral substrates, a higher level of performance would consist in engaging chiral ones prone to chirality transfer that can however be countered by the stereoinduction from the catalyst to lead to an enantioconvergent process.[10] We surmised that chiral 1,5-enynes could be probes for such an endeavor as similar strategies have been investigated by Toste's group with chiral NHC-Au(III) complexes on 3-aryl-1,5-enyne systems. Herein, an enantioconvergent kinetic resolution was developed *i.e.* for the reacting enantiomer, the observed ee on the cycloisomerization product was higher than the innate chirality transfer (matched case), while the other enantiomer reacted less efficiently but provided the same enantiomer with lower ee though (mismatched case). While ees ranged from 61% to 90%, reported conversions could not exceed 44%.[11] The group of Marinetti and Voituriez[12] focused on the cycloisomerization of 3-hydroxylated-1,5-enynes with chiral platinum and gold complexes with satisfactory yields and ees up to 80% but the substrates used showed limited structural diversity (Scheme 1).

Scheme 1. Au-catalyzed asymmetric cycloisomerization of chiral 1,5-enynes



To benchmark the asymmetric performance of the (β-ICyD)AuCl complex, the cycloisomerization of 3-aryl-1,5-enynes **1** with a *C*-substituent at the stereogenic propargylic center was studied, using classical reaction conditions. Accordingly, the (β-ICyD)AuCl precatalyst was activated through *in situ* addition of the silver salt $AgSbF_6$ to remove the chloride ligand. In parallel, racemic catalysis was run on substrates **1** with the NHC-based IPrAuCl precatalyst (see SI). For enynes **1a** (Ar = Ph) and **1b** (Ar = p-$MeOC_6H_4$) upon (β-ICyD)AuCl catalysis, a dramatic temperature effect was observed. At room temperature (rt), moderate ees were observed (52% on **2a** and 30% on **2b**), but upon temperature decrease (-15 °C), higher enantioselection was reached (68% and 70% ee respectively) while maintaining yields above 80%. No temperature effect of such magnitude was observed with thiophene-based precursor **1c** (Ar = 2-thienyl), since the best ee on **2c** was 32% at -15 °C. In comparison, Toste's NHC-Au(III) catalyst provided ees of 85% for **2a** and **2b**, but with low conversions (44% and 22% respectively) and gave a lower ee of 61% on **2c** at 36% of conversion (Scheme 2a).

Scheme 2. Benchmarking the (β-ICyD)AuCl performance with 1,5-enynes

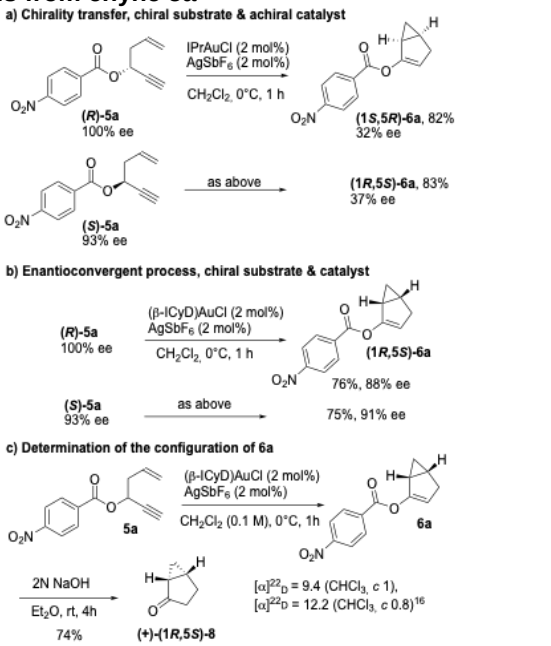


These results proved to be highly encouraging since enantioconvergence could be achieved at full conversion. Enynols **3a** and **3b**, which are regioisomeric at R^1 and R^2 positions, were also assessed (Scheme 2b). The same bicyclic [3.0.1] ketone **4** was formed in good yields (above 73%) and with higher ees than previously observed with chiral NHC-platinum phosphoramidite complexes (35% ee).[12a] Interestingly, precursors **3a** and **3b** provided inversed enantioselectivity (see SI).

Following these benchmarking studies, the cycloisomerization of 1,5-enynyl esters **5**, which offers broad synthetic opportunities and involves a distinct mechanism based on a 1,2-*O*-acyl migration/intramolecular cyclopropanation sequence,[13]was studied. Notably, the cycloisomerization of **5a** was only described with $PtCl_2$.[14]

As a preamble to the study, it was necessary to evaluate the effectiveness of the background chirality transfer as it was evidenced in the cycloisomerization of various enynyl ester systems.[15]Thanks to a lipase resolution, both enantiomers of **5a**, **(*S*)-5a** and **(*R*)-5a** were available (see SI). Upon submitting **(*R*)-5a** to an achiral NHC-Au precatalyst (IPrAuCl, 2 mol%) in the presence of 2 mol% of $AgSbF_6$, a moderate chirality transfer (33% ee) in favor of **(1*S*,5*R*)-6a** was observed, which nevertheless confirmed the challenge of achieving a stereoconvergent process. Gratifyingly, when using 2 mol% of (β-IcyD)AuCl/$AgSbF_6$, a highly enantioselective cycloisomerization took place at 0 °C from both **(*S*)-5a** and **(*R*)-5a** to give **6a** with an ee up to 91% (Scheme 3). The (1*R*,5*S*)-configuration of the major enantiomer of **6a** was deduced from the hydrolysis of **6a** with a 2N NaOH solution giving ketone **8**, the optical rotation of which is known.[16] Comparison of the optical rotations led to the (*1R, 5S*) configuration for both **8** and **6a**, also confirmed by an anomalous X-ray diffraction (XRD) analysis of **6a**.

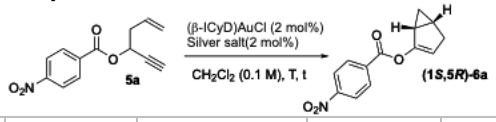
Scheme 3. a) Chirality transfer *vs.* b) asymmetric catalysis from enyne 5a



These preliminary findings confirmed the prevalence of the stereoinduction brought by the CD-based catalyst and that a general enantioconvergent process was within our grasp. We therefore initially focused on the cycloisomerization of racemic **5a** with varying parameters (Table 1). Using $AgSbF_6$, the reactions could be carried out at rt providing total conversion after 1 h (Table 1, entry 1). Delightfully, by decreasing the tempera-

ture to 0 °C and -15 °C, yields of 80% and 78% of the desired product **6a** were obtained with ees of 87% and 90% respectively, in favor of the **(1*S*,5*R*)-6a** enantiomer. Replacement of $AgSbF_6$ with $AgBF_4$ provided 79% of the target product along with 81% ee (entry 4). A similar result was obtained with AgOTf (entry 5). To assess a potential "silver effect" in this gold(I) catalysis,[17] (β-ICyD)$AuNTf_2$ was separately prepared[9a] and engaged (entry 6). These silver-free reaction conditions proceeded without significant differences in the corresponding yield and ee, indicating that only a cationic gold complex was at work in these reactions.

Table 1. Optimization of Conditions

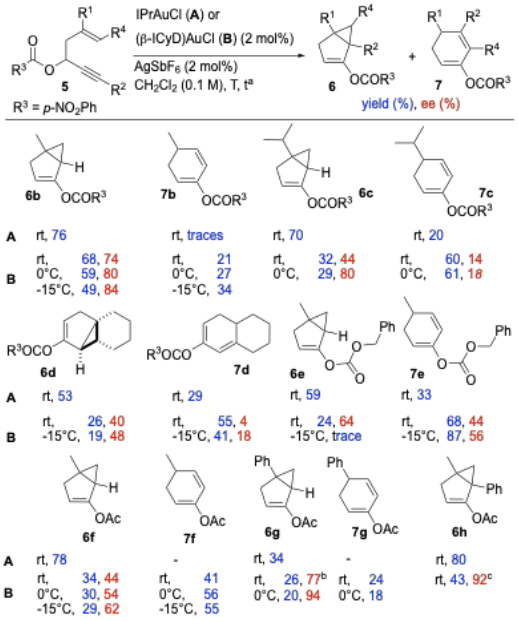


entry	Ag salt	T (°C), t (h)	Yield (%)[a]	ee (%)[b]
1	$AgSbF_6$	rt, 1	81	78
2	$AgSbF_6$	0, 2	80	87
3	$AgSbF_6$	-15, 24	78	90
4	$AgBF_4$	rt, 8	79	81
5	AgOTf	rt, 24	74	82
6[c]	-	0, 5	78	88

[a] Isolated yield; [b] Enantiomeric excesses were determined by chiral HPLC; [c] The reaction was run with 2 mol% β-ICyD-$AuNTf_2$.

This set of encouraging findings drove us to study other enynyl esters **5** (Scheme 4). For this series, we also introduced the results of the IPrAuCl catalysis since it exhibited distinct regioselectivity in some cases. Initiating with a 4-nitrobenzoate group at the propargylic position and introducing a methyl substituent at the R^1 position (**5b**), bicyclo[3.1.0]hexene product **6b** was obtained in 68% yield. An ee of 74% on **6b** was observed, while decreasing temperature showed a significant positive impact on the ee up to 84% at -15 °C. Product **6b** was accompanied by cyclohexadiene derivative **7b** in 21% yield. Its structure was confirmed by XRD analysis (see SI). No ee was determined on this derivative because the corresponding racemic mixture of **7b** was formed in very minor amounts from the reaction with IPrAuCl. For this reason, the compound could not be isolated cleanly. To the best of our knowledge, this type of regioisomers has been observed only once in a $PtCl_2$-catalyzed cycloisomerization of a related 1,5-enyne.[14] Interestingly, a substituent with a larger steric hindrance at the R^2 position (iso-propyl *vs* methyl, **5c**) increased the trend and resulted in a major formation of cyclohexadiene **7c** (60% yield) and a moderate enantioselection: 18% ee at 0°C. A satisfactory ee of 80% was observed on **6c** at 0°C. Bicyclic precursor **5d** with (β-ICyD)AuCl at rt provided 26% and 55% of **6d** and **7d** respectively while during IPrAuCl catalysis, the selectivity was reversed. In this case **6d** was the major product (53%), confirming again the key influence of confinement on the outcome of this cycloisomerization process. Moderate enantioselectivities (up to 48% ee for **6d**) were observed in that case.

Scheme 4. Scope of the reaction



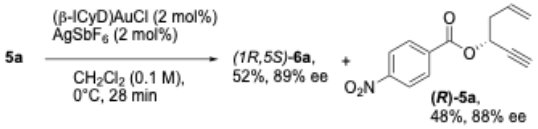
[a] Reaction times ranged from 1 h to 4 h when reactions were performed at room temperature or 0 °C and overnight at -15 °C. [b] Biphenyl (40%) was formed in these reactions. Compound **7g** appears as moderately stable precluding HPLC analysis.[c] No significant conversion was observed at 0 °C.

The nature of the *O*-acyl migrating group was next assessed. With a carbonate migrating group (**5e**), the formation of the corresponding cyclohexadiene **7e** was significantly increased in all entries whether with IPrAuCl or with (β-ICyD)AuCl. The best ees on bicyclo[3.1.0]hexane **6e** and **7e** were respectively reached at 64% (at rt) and 56% (at -15°C). Note that at -15 °C, only trace amount of **6e** was formed. Acetoxy-based precursors (**5f** and **5g**) were also engaged. Substrate **5f** featuring a methyl group at R^1 position provided intermediate results between those observed for **5b** and **5e** regarding the formation of the corresponding cyclohexadiene **7f** derivative. Again, no ee could be determined on **7f** since the corresponding racemic product was not obtained with IPrAuCl. It was generally observed that substrates including an acetoxy group showed lower enantioselectivity: at rt, 44% ee for **6f**, vs. 74% for **6b** and 64% for **6e**. The introduction of a phenyl group at R^2 (**5g**) however resulted in three types of products. The expected products **6g** and **7g** were isolated at rt in 26% and 24% yield, respectively. The major product of this cycloisomerization was biphenyl (40% yield), which presumably originates from cyclohexadiene **7g** through elimination of AcOH. An excellent enantioselectivity of 94% was observed on **6g** at 0°C. Finally, precursor **5h** yielded the desired product **6h** in an excellent ee (92%) at rt and 43% yield.

To gain further insight into this process, we ran a reaction with **5a** at incomplete conversion (Scheme 5). Thus, at 0 °C for 30 min, the reaction was stopped at a stage corresponding to approximatively half-conversion. Product **6a** was formed in 52% yield (89% ee in favor of the expected ***(1R,5S)*-6a** isomer). Starting material **5a** was recovered in 48% yield as major (*R*)-enantiomer (88%

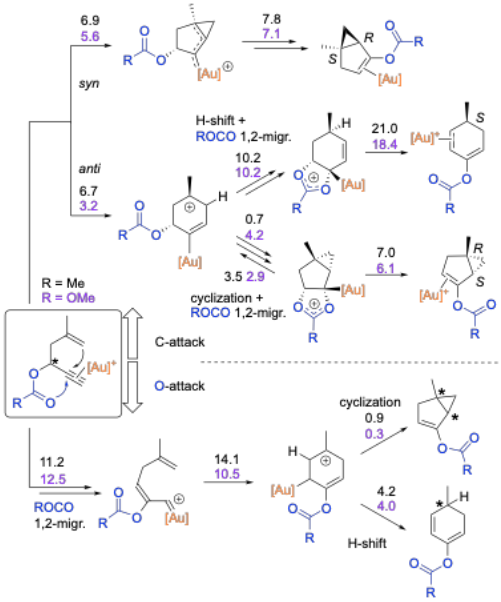
ee) and suggested that some resolution took place. This was confirmed by the fact that the (*S*)-enantiomer of **5a** reacts faster, since only 28 minutes were necessary for full conversion, in contrast to (*R*)-**5a** which needs 1 h of reaction time to provide ***(1R,5S)*-6a** (see scheme 3a). So contrary to Toste's report,[11] the resolution process is not an obstacle to a highly enantioselective process.

Scheme 5. Half-conversion reaction of 5a



In order to get some mechanistic insight into the cycloisomerization reaction, we performed DFT calculations for *O*-acyl- (**5f**, R = Me) and carbonate functionalized (**S1**, R = MeO) substrates with B3LYP-D3/6-31G(d,p) CPCM(DCM) (SI) using $IPrAu^+$ as catalyst (Scheme 6; Table S2, Figure S1 and S2 in SI). Pathways initiated by 1,2-*O*-acyl migration (O-attack) *vs.* cyclization (C-attack) were computed in a similar fashion as performed earlier for Rautenstrauch cycloisomerizations, where the investigated molecules featured 3-acyloxy-5-enyne derivatives with a terminal alkyne and internal alkene.[18] The former pathway would lead to racemization after 1,2-migration while its energy barrier is clearly higher for both substrates (≥ 3.2 kcal/mol) than the C-attack initiated route. In the latter case, energy barriers for the C-C bond formation are 7 kcal/mol for both *anti* and *syn* compounds in the case of **5f** as well as 3 kcal/mol (*anti*) and 5 kcal/mol (*syn*) for **S1**. This pathway would also allow some degree of chirality transfer from the substrate as the barriers for *anti* and *syn* C-attack are slightly different. Furthermore, the *anti* C-attack pathway with the lower energy barrier (**S1**) would explain formation of both 5- and 6-rings, and the enantioselectivities of the products. (Scheme 3a and 4).

Scheme 6. Key intermediates and free energy barriers for migration vs. cyclization first pathways[a]



[a]. Free energy barriers are in kcal/mol. $[Au]^+ = IPrAu^+$

Overall, with the achiral $IPrAu^+$ catalyst the initial nucleophilic C-attack on alkyne is the rate limiting step, exhibiting energy barriers with relatively small differences. This opens an alike access for routes delivering both enantiomers as well as 5/6-membered-ring isomers and is consistent with the fact that the analogous $[Au]^+$-catalysis in the asymmetric CD-cavity leads to enantioconvergence and ring size discrimination.

In conclusion, we have uncovered the first examples of enantioconvergent Au(I)-catalyzed enyne cycloisomerisation at full conversion thanks to the confinement brought by a CD chiral environment. High ee's have been obtained for several enyne systems, the enynyl esters giving in general the best enantioselectivities. Further applications of this process are under scrutiny.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, HPLC spectra, characterization data for all compounds (PDF)

Accession Codes

CCDC 2355716 (**6a**), CCDC 2358388 (**6c**) and 2355717 (**7b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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