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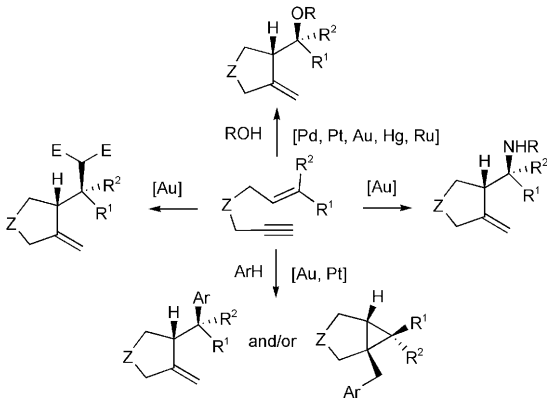
Asymmetric Gold-Catalyzed Hydroarylation/Cyclization Reactions

Chung-Meng Chao, Maxime R. Vitale, Patrick Y. Toullec, Jean-Pierre Genêt, and Véronique Michelet*[a]

Recent years have witnessed a substantial growth in the number of gold-catalyzed reactions implying C–C, C–O or C–N bond-formation processes.[1] Despite the rapid development of several synthetic applications, the enantioselective aspects still require investigations.[2] Some reports described the transfer of chirality from allenes and propargylic esters, and the asymmetric hydroalkoxylation and hydroamination of allenes.[2] Nevertheless examples are still scarce, most probably due to the linear geometry of chiral gold(I) complexes that explains a lack of steric interactions between the chiral inducer and the activated function of the substrate. Ito and Hayashi's groups pioneered the field of asymmetric gold catalysis by conceiving the addition of isocyanoacetates to aldehydes in the presence of a cationic gold catalyst and a chiral diphosphanyl ferrocene ligand.[3] Other groups have recently challenged to discover new applications of linear chiral gold complexes, but to the best of our knowledge, only two of them implied alkyne activation.[4] In the course of our research on metal-catalyzed cycloisomerization reactions of enynes,[5] we and others have described novel rearrangements in the presence of external nucleophiles such as alcohols, electron-rich aromatic rings, amines, carboxylic acids and 1,3-dicarbonyl compounds (Scheme 1).[6]

Despite the fact that these reactions seem mechanistically related, they proved to be highly substrate and nucleophile dependent. This explains the fact that no general asymmetric version was described so far for these tandem atom-economical processes. We described the first asymmetric Pt-catalyzed alkoxycyclization reactions[6d] and Echavarren's group published the first analogous gold-catalyzed process.[4a] In both cases, moderate to good enantioselectivities were observed and only one example has been reported with an *ee* higher than 90%. We envisaged to study these challenging reactions and wish to present our preliminary results leading to enantiomerically enriched functionalized cyclic alkenes starting from 1,6-enynes.



Scheme 1. Metal-catalyzed cycloisomerization of 1,6-enynes in the presence of an external nucleophile.

Initial efforts have focused on the optimization of an efficient system starting from enyne **1a** as a model substrate (Table 1). Based on our experience, we reasoned that the addition of electron-rich aromatic rings would be successful as the kinetics were fast and the steric hindrance of the nucleophile would favor an enantioselective process. According to previously described procedures,[4a] we prepared chiral Au^I catalysts with MeOBIPHEP,[7] BINAP[8] and 4-MeO-3,5-(tBu)$_2$-MeOBIPHEP[7] ligands. The use of (*R*)-MeOBIPHEP–$(AuCl)_2$ associated with silver salt $AgSbF_6$ in diethyl ether[6n] led to the formation of the desired product **2a** in excellent yield and 26% enantiomeric excess (Table 1, entry 1). The influence of silver salts was investigated (Table 1, entries 2–4), silver triflate and silver bis(trifluoromethanesulfonyl)imidate giving the best results. The use of silver benzoate[9] was particularly striking as no conversion was observed at room temperature for 240 h (Table 1, entry 2). Lowering the temperature to 0°C increased the re-

[a] C.-M. Chao, Dr. M. R. Vitale, Dr. P. Y. Toullec, Prof. J.-P. Genêt, Dr. V. Michelet
Laboratoire de Synthèse Sélective Organique et Produits Naturels
UMR 7573, Ecole Nationale Supérieure de Chimie de Paris
rue P. et M. Curie, 75231 Paris cedex 05 (France)
Fax: (+33) 144-071-062
E-mail: veronique-michelet@enscp.fr

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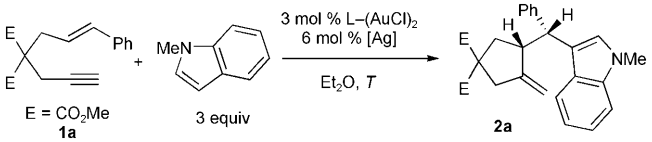
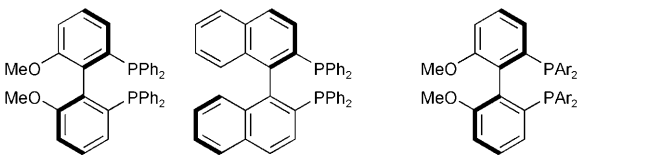
action time but moderately influenced the enantiomeric excesses (Table 1, entries 5–8). The use of BINAP induced an important decrease of the observed *ee* (Table 1, entries 6–7), whereas a hindered and electron-rich ligand 4-MeO-3,5-(tBu)$_2$-MeOBIPHEP recently used in asymmetric styrene cyclopropanation and allene hydroamination reactions allowed a consistent leap as the desired arylated product **2a** was isolated in 80% enantiomeric excess (Table 1, entries 8–9). The best result was obtained in the presence of 3 mol% of 4-MeO-3,5-(tBu)$_2$-MeOBIPHEP(AuCl)$_2$, 6 mol% of AgOTf in diethyl ether at room temperature (Table 1, entry 9). We also investigated the influence of the Ag/Au ratio and observed a decrease of the *ee* when employing one equivalent of silver salts compared to digold complex (Table 1, entry 10). It should be noted that, although competition between Au and Brønsted acids has been reported in the literature,[10] no conversion has been observed from the reaction of enyne **1a** and 1-methylindole in the presence of 10 mol% triflic acid.[11]

Table 1. L–(AuCl)$_2$-catalyzed Friedel–Crafts/cyclization reaction of enyne **1a**.



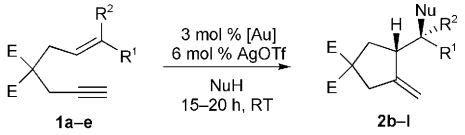
Entry	Cond[a]	[Ag]	T/ [°C], t [h]	Yield[b] [%]	ee[c] [%] (configuration)
1	A	$AgSbF_6$	RT, 0.3	96	26 (+)
2	A	AgOBz	RT, 240	0	–
3	A	AgOTf	RT, 20	96	36 (+)
4	A	$AgNTf_2$	RT, 0.3	91	45 (+)
5	A	AgOTf	0, 24	71	54 (+)
6	B	AgOTf	0, 36	46	12 (+)
7	B	$AgNTf_2$	0, 24	99	20 (+)
8	C	AgOTf	0, 2	91	80 (+)
9	C	AgOTf	RT, 48	99	83 (+)
10	C	AgOTf	0, 1	95	74 (+)

[a] A = (*R*)-MeOBIPHEP(AuCl)$_2$, B = (*R*)-BINAP(AuCl)$_2$, C = (*R*)-4-MeO-3,5-(tBu)$_2$MeOBIPHEP(AuCl)$_2$. [b] Isolated yield. [c] Determined by HPLC analysis OD-H, hexane/*i*PrOH 98:2, 1 mL min^{-1}.



We then decided to screen nucleophiles and react them with various 1,6-enynes in the presence of the optimized catalytic system (Table 2). A single diastereomer of **2** was formed in all 1,6-enyne/nucleophile combinations tested.[6] Addition of 1,3,5-trimethoxybenzene and pyrrole on enyne **1a** was achieved in 72 and 80% *ee*, respectively (Table 2, entries 1–2).

Table 2. Asymmetric Au^I-catalyzed cycloisomerization of 1,6-enynes.



[Au] = (*R*)-4-MeO-3,5-(tBu)$_2$MeOBIPHEP(AuCl)$_2$

1a: E = CO_2Me, R^1 = Ph, R^2 = H
1b: E = CO_2*i*Pr, R^1 = Ph, R^2 = H
1c: E = CO_2Bn, R^1 = Ph, R^2 = H
1d: E = SO_2Ph, R^1 = Ph, R^2 = H
1e: E = SO_2Ph, R^1 = Me, R^2 = Me

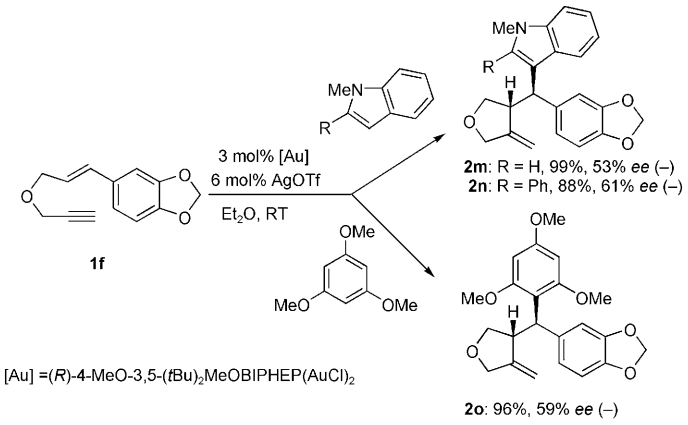
Entry	1	Nucleophile Ar-H	2	Yield[a] [%]	ee[b] [%] (configuration)
1	**1a**	1,3,5-trimethoxybenzene	**2b**	92	72 (−)
2	**1a**	pyrrole	**2c**	86	80 (−)
3	**1b**	1-Me-indole	**2d**	94	95 (+)
4	**1b**	1-Me-2-Ph-indole	**2e**	99	95 (−)
5	**1c**	1-Me-indole	**2f**	99	81 (+)
6	**1c**	1-Me-2-Ph-indole	**2g**	99	82 (−)
7	**1c**	1,3,5-trimethoxybenzene	**2h**	99	82 (−)
8	**1d**	1,3-dimethoxybenzene	**2i**	86	98 (−)
9	**1d**	1,3,5-trimethoxybenzene	**2j**	99	98 (−)
10	**1d**	1,3,5-trimethoxy-2-bromo-benzene	**2k**	85	94 (−)
11	**1e**	1-Me-indole	**2l**	37	88 (−)

[a] Isolated yield. [b] See Supporting Information.

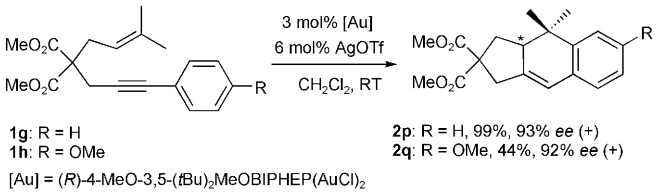
To evaluate the influence of steric crowding of the tethering moiety on enantioselectivity,[12] enynes **1b** and **1c** were engaged in control cycloisomerization reactions in the presence of 1-methylindole and 1-methyl-2-phenylindole. Indeed, a beneficial substrate effect was apparent in the case of **1b** (Table 2, entry 3) as the observed enantiomeric excess (95%) was more than ten points higher than in the case of **1a** (Table 1, entry 9). Increasing the nucleophile hindrance had no detrimental effect on enantioselectivity (Table 2, entry 4). Replacement of *i*Pr with a benzyl ester group did not lead to better results (Table 2, entries 5–7), as the enantioselectivity observed for enyne **1c** turned out to be equivalent to the one of **1a**. In the case of the sulfone-substituted enyne **1d**, the enantioselectivities were excellent as the arylated cyclic derivatives were obtained in 98 and 94% *ee* (Table 2, entries 8–10). It's noteworthy that the presence of a bromine atom on the aromatic nucleophile partner was tolerated (Table 2, entry 10). The addition of 1-Me-indole on a trisubstituted double bond afforded the corresponding cyclic alkene **2l** in a good *ee* (Table 2, entry 11).

The unprecedented reactivity of the challenging substrate **1f** was then investigated in the presence of 4-MeO-3,5-(tBu)$_2$-MeOBIPHEP–(AuCl)$_2$ catalyst (Scheme 2). We were pleased to observe an enantiodiscrimination in the presence of the chiral gold catalyst: the functionalized heterocycles were indeed isolated in good yields and 53–59% *ee*. Notably, these results may open new opportunities for the synthesis of antitumor lignans derivatives.[13]

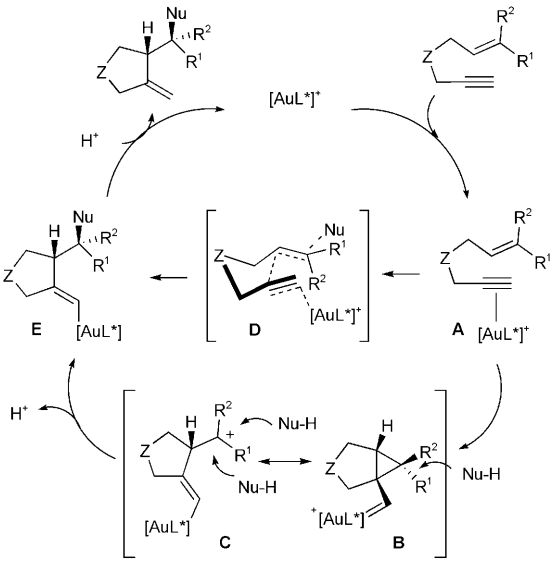
The intramolecular version of this reaction was particularly interesting and challenging considering the occurrence of tricyclic skeletons in natural products.[14] The enantioselective hydroarylation/cyclization reaction was found to be successful (Scheme 3). Cycloisomerization of enynes **1g–h**[6n,q]



Scheme 2. Asymmetric Au^I-catalyzed cycloisomerization of oxygen-tethered 1,6-enynes.



Scheme 3. Asymmetric intramolecular Au^I-catalyzed cycloisomerization of 1,6-enynes.



Scheme 4. Mechanism rationale.

afforded the tricyclic structures **2p** and **2q** in 93 and 92% *ee*. It is remarkable to note that no reaction occurred in the presence of chiral platinum complexes.[6t]

In all 1,6-enyne/nucleophile combinations tested, and in accordance with previous contributions under racemic conditions, a single diastereoisomer of **2** was formed. The *anti* diastereoselectivity of the reaction had been unambiguously established by X-ray analysis of hetero- and carbocyclic derivatives. The mechanism of such transformation has been widely argued and is still under debate (Scheme 4). Based on a combined theoretical and experimental study, the nucleophilic attack/cycloisomerization reaction has been proposed to operate via a transient unstable cyclopropylcarbene **B** by the group of Echavarren.[5,6,15] More recently, Fürstner and Morency proposed an alternative rationale relying on the mesomeric "nonclassical" carbocation **C**.[6r,16] The present results of the asymmetric reactions show a variation of enantioselectivity observed for a given enyne substrate in the presence of different carbon nucleophiles. In this regard, intermediates **B** and **C** do not adequately account for the formation of cyclic alkene **E**. Indeed, considering the *anti* nucleophilic attack on the cyclopropylcarbene intermediate **B** as a stereospecific event, the external carbon nucleophile does not take part in the cyclopropylcarbene formation which represents the enantiodetermining step of the transformation. Considering the variation of enantioselectivity observed for a given enyne substrate and different carbon nucleophiles (Table 2), the major contribution of intermediate **B**, and of its diastereomeric counterpart **B′**, is bound to the existence of an equilibrium between forms **A** and **B/B′**. The intervention of **C** would theoretically lead to a diastereomeric mixture of *syn*/*anti* derivatives if bond rotation of the carbocationic intermediates is faster compared to the addition of the carbon nucleophile, which has never been observed in our hand.

Our experience in this field and recent results concerning asymmetric gold-catalyzed addition of oxygen nucleophiles prompted us to assume that the addition of the nucleophile is concerted with the cyclization.[6u] In the case of more nucleophilic electron-rich aromatic rings, the "carbocation-like" contribution of the intermediate is less pronounced than in the case of oxygen nucleophile, which explains the higher *ee* values. In this scenario, the intervention of a conformationally favored intermediate **D**, as proposed by Fürstner,[6r] would better account for the experimental results. It is indeed observed that the *ee* values increase with the size of the enyne tether Z (see Table 2 and Scheme 2, compare Z = O, $C(CO_2Me)_2$, $C(CO_2iPr)_2$ and $C(SO_2Ph)_2$). Considering a "chair-like" η^2-complex **D**, the addition of the nucleophile would occur in complete analogy with the Stork–Eschenmoser hypothesis,[17] introduced to account for the selectivity of polyene cyclization reactions.

We therefore extended the methodology developed for chiral gold complexes and discovered that the combination of atropisomeric electron-rich and hindered chiral ligand 4-MeO-3,5-$(t\text{Bu})_2$-MeOBIPHEP associated to Au^I and silver salts promotes the enantioselective hydroarylation/cyclization reaction of 1,6-enynes under mild conditions. Some enantiomerically enriched functionalized carbo- and heterocycles were isolated in good to excellent yields and with *ee* values up to 98%. Further studies will be focused on application of this methodology to the synthesis of natural and biologically active compounds.

Experimental Section

Typical experimental procedure: A mixture of L–$(AuCl)_2$ (L = (*R*)-MeO-BIPHEP or (*R*)-4-MeO-3,5-(tBu)$_2$MeOBIPHEP) (3 mol%) and AgOTf (6 mol%) in distilled Et_2O (10^{-2} M) was stirred under argon atmosphere at room temperature for 30 min. The aromatic nucleophile (3 equiv) was then added and the mixture was stirred for 5 min. Enyne (1 equiv) was finally added and the mixture was stirred until completion of the reaction. The mixture was then filtered through a short pad of silica to eliminate the catalyst (EtOAc) and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography (petroleum ether/ethyl acetate 90:10 → 70:30) if necessary.

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Keywords: asymmetric catalysis · cyclization · electron-rich arenes · gold · tandem reaction

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