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Asymmetric Au-catalyzed domino cyclization/nucleophile addition reactions of enynes in the presence of water, methanol and electron-rich aromatic derivatives

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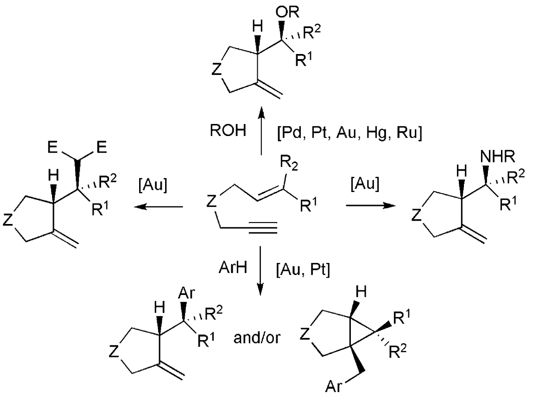
ABSTRACT

An efficient Au(I) catalytic system is described for the asymmetric domino cyclization/functionalization reactions of functionalized 1,6-enynes in the presence of an external nucleophile. The use of (*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIHEP ligand associated with gold led to clean rearrangements implying the formal addition of an oxygen or carbon nucleophile to an alkene followed by a cyclization process. The enantiomeric excesses were highly dependant on the substrate/nucleophile combination. Very good enantiomeric excesses up to 98% were obtained in the case of substrates bearing larger groups (hindered diesters and disulfones) and in the case of hindered carbon nucleophiles.

1. Introduction

Metal-catalyzed cycloisomerization reactions of 1,*n*-enynes have appeared as conceptually and chemically highly attractive processes as they contribute to the concept of atom economy and offer the opportunity to develop new reactions.[1] The recent emergence of interest associated with the studies involving carbophilic Lewis acids, such as gold or platinum opened the way to the development of families of highly active and selective catalysts presenting a unique reactivity.[2,3] A wide variety of carbo- and heterocycles presenting a high degree of structural complexity can be formed using those new catalytic systems. The development of enantioselective variants of these transformations are still rare,[4] probably because of a highly substrate-dependency encountered with these systems. Among the numerous 1,*n*-enynes cycloisomerization transformations, we[5] and others[6] have been interested in domino processes implying an external nucleophile (oxygen, amino or aromatic derivative) and leading to functionalized cyclic cyclopentenes (Scheme 1). The first enantioselective versions have been described, respectively, in the presence of platinum and gold for the alkoxycyclization reactions in 2004[7] and 2005.[8] We expanded these methodologies for the hydroarylation/cyclization domino process and obtained high enantiomeric excesses in the presence of two systems: one based on Pt(II) catalyst associated with a monophosphane (Ph–Binepine ligand)[9] and one based on a dinuclear gold complex associated with the atropisomeric 4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP ligand.[10] Other groups have recently described chiral gold-based systems for domino processes, such as phenoxycyclization, intramolecular hydroarylation/cyclization reactions or 1,3-dipolar cycloaddition, for example.[11] In this paper, we wish to disclose a comprehensive study on gold-catalyzed enantioselective domino nucleophile addition/cyclization reactions putting the stress on the scope and limitations of such systems.



Scheme 1. Domino cyclization/functionalization reactions implying oxygen, amino and carbon nucleophiles.

2. Results and discussion

In order to find the optimized catalytic system, enyne **1a** as the substrate and *N*-methylindole as the nucleophile were reacted in the presence of various cationic bimetallic gold complexes formed from L*(AuCl)$_2$ and 2 equiv of halide scavenging agents (Table 1).

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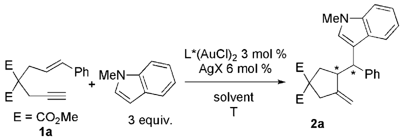
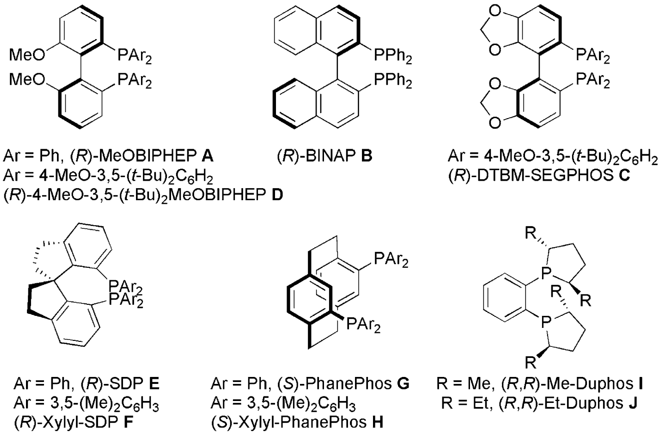
We selected various ligands L* including atropisomeric ligands, such as MeOBIPHEP (**A**, **D**), BINAP (**B**) and SEGPHOS (**C**) ligands and other chiral ones presenting different chirality properties, such as chiral spiro ligands SDP (**E**, **F**), PhanePhos (**G**, **H**) and DuPhos (**I**, **J**) ligands (Scheme 2). We prepared the bimetallic gold complexes starting from (tht)AuCl according to reported procedures.[8,12]

Table 1
Optimization of the catalytic system for the hydroarylation/cyclization reaction



Entry	L*[a]	AgX	Solvent	T [°C]	t [h]	Yield [%]	ee [%][b]
1	**A**	$AgSbF_6$	Ether	rt	0.3	96	26 (+)
2	**A**	AgOBz	Ether	rt	240	0	/
3	**A**	AgOTf	Ether	rt	20	96	46 (+)
4	**A**	$AgNTf_2$	Ether	rt	0.3	91	45 (+)
5	**A**	AgOTf	CH_2Cl_2	rt	48	91	48 (+)
6	**A**	$AgNTf_2$	CH_2Cl_2	rt	0.2	89	43 (+)
7	**A**	AgOTf	Ether	0	24	71	54 (+)
8	**A**	$AgNTf_2$	Ether	0	21	84	58 (+)
9	**A**	$AgNTf_2$	Ether	−10	15	76	56 (+)
10	**A**	$AgNTf_2$	Ether	−20	15	39	55 (+)
11	**B**	AgOTf	Ether	0	36	46	12 (+)
12	**B**	$AgNTf_2$	Ether	0	24	99	20 (+)
13	**C**	AgOTf	Ether	rt	20	58	47 (+)
14	**D**	AgOTf	Ether	0	2	91	80 (+)
15	**D**	$AgNTf_2$	Ether	0	24	90	71 (+)
16	**D**	AgOTf	Ether	rt	48	99	83 (+)
17	**D**	AgOTf	CH_2Cl_2	rt	48	96	63 (+)
18	**E**	AgOTf	Ether	rt	48	65	20 (+)
19	**F**	AgOTf	Ether	rt	48	61	18 (−)
20	**G**	AgOTf	Ether	rt	48	43	7 (−)
21	**H**	AgOTf	Ether	rt	48	41	20 (+)
22	**I**	AgOTf	Ether	rt	48	43	7 (/)
23	**J**	AgOTf	Ether	rt	48	64	2 (/)

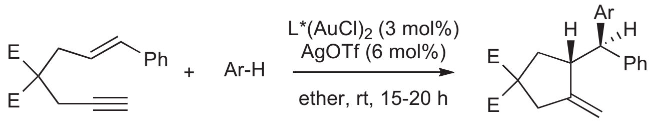
[a] A=(*R*)-MeOBIPHEP, B=(*R*)-BINAP, C=(*R*)-DTBM-SEGPHOS, D=(*R*)-4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP, E=(*R*)-SDP, F=(*R*)-Xylyl-SDP, G=(*S*)-PhanePhos, H=(*S*)-Xylyl-PhanePhos, I=(*R*,*R*)-Me-DuPhos, J=(*R*,*R*)-EtDuPhos.
[b] Determined by HPLC analysis OD-H, hexane/*i*-PrOH 98/2, 1 mL/min.



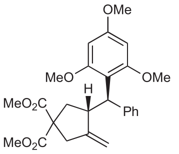
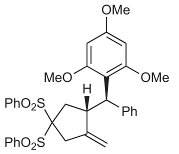
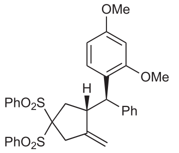
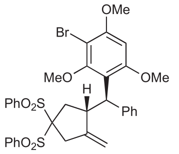
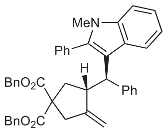
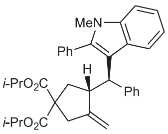
Scheme 2. Chiral ligands.

The use of (*R*)-MeOBIPHEP-$(AuCl)_2$[12] associated with silver salt $AgSbF_6$ in ether has allowed the formation of the desired product **2a** in excellent yield and 26% ee (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.

Table 2
Asymmetric hydroarylation/cyclization in the presence of electron-rich aromatic rings



L* = (*R*)-4-MeO-3,5-(*t*-Bu)$_2$MeOBIPHEP
1a E = CO_2Me; **1b** E = CO_2*i*-Pr; **1c** E = CO_2Bn
2 E = SO_2Ph

Entry	Product		Yield[a] [%]	ee [b] [%]
1		**3a**	92	72 (−)
2		**4**	85	94 (−)
3		**5**	86	98 (−)
4		**6**	85	94 (−)
5		**7**	99	82 (−)
6		**8**	99	95 (−)

[a] Isolated yield.
[b] Determined by HPLC analysis.

The use of dichloromethane instead of ether did not improve the enantioselectivity (Table 1, entries 5 and 6). As the reaction time was generally short, we decided to compare the efficiency of the domino process at lower temperature. Indeed the reactivity was still observed at 0 °C, −10 °C and even −20 °C, unfortunately the influence on the ee was moderate (Table 1, entries 7–10). The use of BINAP (**B**)[13] induced a marked decrease of the observed ee (Table 1, entries 11–12). The outcome of the reaction was positively influenced by hindered MeOBIPHEP or SEGPHOS analogous ligands (**D**, **C**), which previously showed very interesting activities in gold-catalyzed asymmetric reactions.[4,12,14] The analogue of SEGPHOS ligand **C** did not lead to better results compared to MeOBIPHEP ligand **A** (Table 1, entry 13 compared to 3). The use of 4-MeO-3,5-(*t*-Bu)$_2$-MeOBIPHEP ligand **D** afforded a consistent gap of the ee as the desired arylated product **2a** was isolated in 80% ee (Table 1, entry 14). We tried to optimize the conditions by changing the temperature, the silver salts or the solvent. The best result was obtained in