## Asymmetric Au(I)-catalyzed synthesis of bicyclo[4.1.0]heptene derivatives *via* a cycloisomerization process of 1,6-enynes<sup>†</sup>

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The enantioselective asymmetric gold-catalyzed cycloisomerization reactions of heteroatom tethered 1,6-enynes are conducted in the presence of a chiral cationic Au(1) catalyst ((R)-4-MeO-3,5-(t-Bu)<sub>2</sub>-MeOBIPHEP-(AuCl)<sub>2</sub>/AgOTf system) in toluene under mild conditions and lead to functionalized bicyclo[4.1.0]heptene derivatives in excellent enantiomeric excesses ranging from 90–98%.

The construction of bicyclo[4.1.0]heptene derivatives is of particular interest, given their synthetic challenge and potential applications as intermediates for natural or biologically active compounds.<sup>1</sup> The groups of Blum and Fürstner independently reported the synthesis of this structural moiety during their study of the cycloisomerization of heteroatom-linked 1,6-enynes in the presence of Pt catalysts.<sup>2</sup> This type of reactivity (Scheme 1) relying on the carbophilic Lewis acid behaviour of late transition metals has also been observed with gold complexes.<sup>3,4</sup> Indeed, during the last decade, gold catalysis has emerged as an ever increasing area of research in line with the flurry of highly selective chemical transformations mediated.<sup>5</sup>

Our ongoing research program on metal-catalyzed cycloisomerization reactions<sup>6</sup> with a special emphasis on asymmetric catalytic processes<sup>7</sup> prompted us to examine possibility that chiral gold(1) complexes might act as promoters for this reaction.<sup>8</sup> Asymmetric gold-catalyzed examples are still scarce,<sup>9</sup> and to the best of our knowledge, enantioselective gold-catalyzed cyclopropanation reactions are so far limited to the reports by Toste's group on the cycloisomerization of propargylic esters.<sup>10</sup> We wish, therefore, to report the asymmetric gold-catalyzed cycloisomerization of 1,6-enynes leading to bicyclo[4.1.0]heptene derivatives.



Scheme 1 Proposed intermediates for metal-catalyzed cycloisomerization reaction.

 Table 1
 Cycloisomerization of enyne 1a

		Ph 3 m 6 mo -Ar solv	01% [Au] I% AgOTf → ent, T, t	o Mar	
	<b>1a</b> Ar = 4-MeO [Au] = ( <i>R</i> )-4	C <sub>6</sub> H <sub>4</sub> -MeO-3,5-( <i>t</i> -	Bu) <sub>2</sub> MeOBIP	<b>2a</b> 'HEP(AuCl) <sub>2</sub>	
ntry	Solvent	$T/^{\circ}C$	t/min	Yield $(\%)^a$	ee (%) <sup>t</sup>

Entry	Solvent	$T/^{\circ}\mathrm{C}$	<i>t</i> /min	Yield $(\%)^d$	ee $(\%)^{b}$
1	Toluene	RT	30	57	92 (-)
2	$CH_2Cl_2$	RT	25	26	70 (-)
3	Et <sub>2</sub> O	RT	25	35	91 (-)
4	THF	RT	25	43	85 (-)
5	CH <sub>3</sub> CN	RT	600	$10^{c}$	d
6	MeNO <sub>2</sub>	RT	600	_	
7	Toluene	0	120	56	96 (-)

<sup>*a*</sup> Isolated yield. <sup>*b*</sup> Determined by HPLC. <sup>*c*</sup> Conversion. <sup>*d*</sup> Not determined.



Initial experiments were performed using substituted propargylic 1,6-enyne **1a** as a model substrate. The cycloisomerization was first attempted in the presence of 3 mol% of (*R*)-4-MeO-3,5-(*t*-Bu)<sub>2</sub>-MeOBIPHEP-(AuCl)<sub>2</sub><sup>7d,e,9,11</sup> associated with silver salt AgOTf (6 mol%) under various solvent and temperature conditions (Table 1). The chiral gold complex was prepared according to a literature procedure.<sup>11</sup> As anticipated, the reaction proceeded smoothly, and afforded the desired alkene **2a** in 57% yield and 92% ee (Table 1, entry 1).<sup>12</sup> The reaction was found to be highly solvent-dependent as enantiomeric excesses vary from 70–92% (Table 1, entries 1–7) in various solvents. The use of acetonitrile or nitromethane led to low conversion and sluggish reaction, respectively (Table 1, entries 5–6).

Toluene was chosen as the reaction solvent for further optimizations. Decreasing the temperature to 0 °C allowed the formation of **2a** in an excellent enantiomeric excess (96%), despite a prolonged reaction time (Table 1, entry 7). The stereoselectivity was based on the proposed mechanism for the Pt-catalyzed reaction.<sup>2,13</sup> The 6-*endo*-type nucleophilic attack of the alkene group stereospecifically leads to the formation a cyclopropylcarbene and is followed by a 1,2-hydride shift (Scheme 1).<sup>14</sup> The absolute configuration, which had never been determined in the presence of iridium or platinum for nitrogen-linked enynes,<sup>8</sup> was assigned *via* a concerted

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 Table 2
 Asymmetric gold-catalyzed cycloisomerization of 1,6-enynes 1b-j

Entry	Enyne		Time (h)	Product	Yield $(\%)^a$	ee (%) <sup>b</sup>
		0R2				
$     \begin{array}{c}       1 \\       2 \\       3 \\       4 \\       5 \\       6 \\       7^c     \end{array} $	1b 1c 1d 1e 1f 1g 1a	$\begin{array}{l} R_2 = 3,4\text{-OCH}_2\text{OC}_6\text{H}_3 \\ R_2 = 3,5\text{-Me}_2\text{C}_6\text{H}_3 \\ R_2 = \text{Ph} \\ R_2 = 4\text{-CO}_2\text{Me}\text{C}_6\text{H}_4 \\ R_2 = 4\text{-NO}_2\text{C}_6\text{H}_4 \\ R_2 = 3\text{-Br}\text{C}_6\text{H}_4 \\ R_2 = 4\text{-Me}\text{OC}_6\text{H}_4 \end{array}$	1 3.5 16 15 15 15 13 6	2b 2c 2d 2e 2f 2g 2a	55 54 34 25 39 59 47 6	96 (-) 93 (+) 98 (+) 94 (-) 96 (-) 95 (-) 96 (-)
8 9	1h 1i	$\begin{array}{l} \mathbf{R}_2 \ = \ \mathbf{Ph} \\ \mathbf{R}_2 \ = \ 3\text{-}\mathbf{Br}\mathbf{C}_6\mathbf{H}_4 \end{array}$	0.7 0.7	2h 2i 2i	51 61	90 (+) 96 (-)
10	1j	°	22	-, <u>H</u> (1)Ph	24	91 (+)

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by HPLC analysis. <sup>c</sup> 1 mol% catalyst, 2 mol% AgOTf, toluene, RT.

use of *ab initio* time-dependant density functional theory calculations and by circular dichroism on compound 2d (see the ESI†).<sup>15</sup>

We then decided to evaluate the reactivity of other enynes under the optimized conditions. According to classical methodologies,<sup>14</sup> we prepared several 1,6-envnes bearing an oxygen atom as a link between the alkene and the alkyne moieties. We were pleased to find that the use of 3 mol% of (R)-4-MeO-3,5-(t-Bu)<sub>2</sub>-MeOBIPHEP-(AuCl)<sub>2</sub> associated with 6 mol% of AgOTf afforded the corresponding bicyclo[4.1.0]heptenes **2b-i** (Table 2). We were delighted to find that the stereoselectivity of the cycloisomerization process was high in the presence of a variety of disubstituted alkynes. Substitution of the alkyne partner either by a phenyl or an aryl, bearing an electron-donating or -withdrawing group (Table 2, entries 1-6) led to the corresponding bicyclic derivatives 2b-g with high ee values (94-98%).<sup>12</sup> Functional groups such as CO<sub>2</sub>Me and NO<sub>2</sub> (Table 2, entries 4-5) or bromine (Table 2, entry 6) are well tolerated. The functionalized cyclopropane 2g was, for example, isolated in 59% yield and 95% ee (Table 2, entry 6). The catalyst loading was successfully reduced to 1 mol% in the case of enyne 1a and afforded product 2a in good yield and high enantiomeric excess after 6 h at room temperature (Table 2, entry 7).

The catalytic system was also evaluated for oxygen-linked enynes **1h–i** possessing an electron-rich aromatic alkene substituent. The enantiomerically enriched bicyclic derivatives **2h–i** were isolated in good yields, and in 90 and 96% ee, respectively. The enantioselective process was not limited to aryl-substituted alkynes as the ethyl derivative **2j** was obtained in 91% ee, despite a low yield (Table 2, entry 10).

The asymmetric cycloisomerization was also tested in the case of nitrogen-linked 1,6-enyne 1k (Scheme 2). The use



Scheme 2 Asymmetric gold-catalyzed cycloisomerization of nitrogentethered enynes.

of the (*R*)-4-MeO-3,5-(*t*-Bu)<sub>2</sub>-MeOBIPHEP-(AuCl)<sub>2</sub>/AgOTf system successfully allowed the formation of **2k** with 74% conversion and 98% ee at 60 °C in toluene. The reaction was slower than in the case of oxygen-tethered enynes, and higher ee values were obtained at 40 and 60 °C compared to room temperature. Further studies will be dedicated to explain this intriguing observation.

In conclusion, we have developed an asymmetric goldcatalyzed cycloisomerization reaction that provides bicyclo-[4.1.0]heptene derivatives. The combination of atropisomeric chiral ligand 4-MeO-3,5-(t-Bu)<sub>2</sub>-MeOBIPHEP associated to Au(1) and silver salts promotes the enantioselective rearrangement of oxygen and nitrogen-tethered 1,6-enynes under mild conditions. The enantiomerically enriched functionalized cyclopropyl heterocycles were isolated in low to moderate yields, and with excellent ee values ranging from 90–98%. Further studies will be focused on applications of this methodology.

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