Gold Catalysis

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Gold(I)-Catalyzed Asymmetric Cycloisomerization of Eneallenes into Vinylcyclohexenes**

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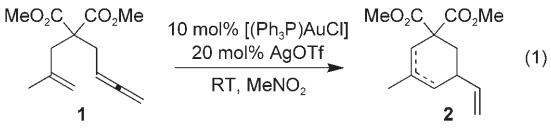
The use of gold(I) catalysts for organic synthesis continues to be the subject of considerable attention, as unique reactivity patterns are often observed.[1] Of the remarkably diverse array of transformations catalyzed by Au^I, the number that have asymmetric variants remains low,[2–4] most likely as a result of the enforced linear coordination geometry of gold(I), which spatially separates ligand chirality from the reacting substrate.[2]

The divergent reactivity of Au^I catalysts came into view during efforts to logically extend a project on diene cycloisomerization[5] to 1,6-eneallenes. Although the initially tested Pt^{II} catalysts were not effective, compound **1** was found to react with 10 mol% of the catalyst generated from [(Ph_3P)AuCl] and AgOTf to give vinylcyclohexene **2**,[6,7] a rare six-membered-ring product of eneallene cycloisomerization [Eq. (1)]. Although numerous studies of eneallene

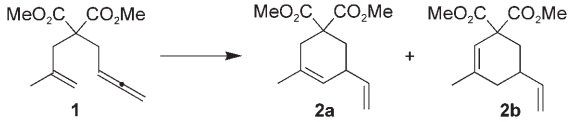


cycloisomerization reactions have been reported (e.g. with Rh,[8] Pd,[9] Ru,[10] Ni/Cr[11]), five-membered (typically) and seven-membered (less common) rings are usually obtained, and apparently, none of these reactions tolerates internal substitution at the alkene.[12] This unknown selectivity for cyclohexene derivatives was therefore pursued.[13]

Although the reaction rate was good and the PPh_3-based catalyst well-behaved, we decided to use this success as a starting point for the discovery of heretofore unknown enantioselective variants. Since the phosphine ligand provided the obvious point for creating a chiral catalyst environment, a preliminary screen of chiral phosphines was initiated. From this examination, [3,5-xylyl-binap($AuCl)_2$] (3,5-xylyl-binap = 2,2′-bis(di(3,5-xylyl)phosphino)-1,1′-binaphthyl) was identified as a promising catalyst precursor, and additional optimization studies were carried out with this complex.[14]

The regioselectivity was moderately dependent on solvent polarity, though the enantioselectivities were strongly dependent on this parameter (Table 1). Attempts to further optimize these two parameters by modifying the counterion were partially successful, but the counterion that delivered the best regioselectivity for the formation of **2** (OTs^-) was not the same as that which provided the best enantioselectivity (OTf^-; Table 1).

Table 1: Optimization of reaction conditions for the conversion of **1** to **2a**,**b** using the [(*R*)-3,5-xylyl-binap($AuCl)_2$] precursor.[a]



Solvent	Activator	Regioselectivity **2a**:**2b**	*ee* [%][e]
CH_2Cl_2	$AgNTf_2$[b]	2.5:1	30
toluene	$AgNTf_2$	1:2	29
chlorobenzene	$AgNTf_2$	2:1	51
$EtNO_2$	$AgNTf_2$	3:1	42
$MeNO_2$	$AgNTf_2$	**4:1**	**65**
$MeNO_2$	$AgSbF_6$	4:3	57
$MeNO_2$	$AgBF_4$	incomplete conversion	30
$MeNO_2$	AgOTs[c]	**10:1**	50
$MeNO_2$	$AgPF_6$	9:1	65
$MeNO_2$	AgOTf[d]	4:1	**72**

[a] Reaction conditions: 5 mol% [(*R*)-3,5-xylyl-binap($AuCl)_2$], 15 mol% AgX, 0.1 M **1**,.RT, 16 h. The best regioselectivites and *ee* values are shown in bold. [b] $NTf_2 = N(SO_2CF_3)_2$. [c] OTs = $OSO_2(4\text{-}MeC_6H_4)$. [d] OTf = OSO_2CF_3. [e] The *ee* values are an average of **2a** and **2b** on chiral-phase GC; see the Supporting Information.

Using the conditions providing optimum enantioselectivities with 3,5-xylyl-binap, a variety of chiral diphosphine ligands were re-examined; however, none provided a better enantioselectivity (Table 2). Interestingly, DTBM-SEGPHOS [(4,4′-bi-1,3-benzodioxole)-5,5-diylbis(di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine)], previously shown to be optimum in related gold(I) allene chemistry,[15] was unreactive in this system. Also intriguing was the reversed regioselectivity in the [QUINAP(AuCl)] case, though the enantioselectivity was poor.

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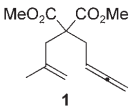
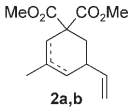
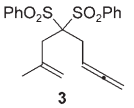
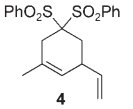
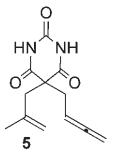
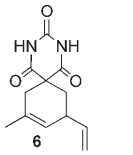
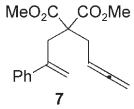
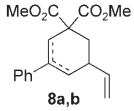
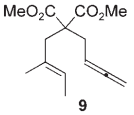
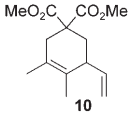
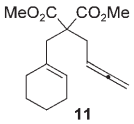
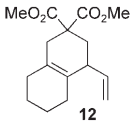
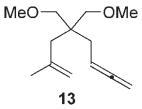
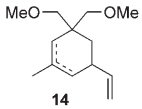
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Chiral ligand screening for the conversion of **1** to **2a**/**2b**.[a]

Catalyst	*ee* [%][b]	Regioselectivity **2a**:**2b**[c]
[(*S*,*S*)-DIOP(AuCl)$_2$][d]	4	1:1
[(*R*)-QUINAP(AuCl)][e]	10	1:3
[(*R*)-xylyl-PHANEPHOS(AuCl)$_2$][f]	16	2.5:1
[(*R*)-xylyl-SOLPHOS(AuCl)$_2$][g]	28	3.5:1
[(*R*)-SYNPHOS(AuCl)$_2$][h]	33	3:1
[(*R*)-4,4′-TMS-binap(AuCl)$_2$]	66	1:1.5
[(*R*)-SEGPHOS(AuCl)$_2$][i]	66	3.3:1
[(*R*)-3,5-xylyl-binap(AuCl)$_2$]	**72**	**3.5:1**

[a] Only two products seen by GC after isolation; conversion monitored by ^{1}H NMR. The best regioselectivity and *ee* are shown in bold. [b] Average of both regioisomers. [c] GC peak integration. [d] DIOP = 1,4-bis(diphenylphosphino)-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol. [e] QUINAP = 1-(2-diphenylphosphino-1-naphthyl)isoquinoline. [f] xylyl-PHANEPHOS = 4,12-bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane. [g] SOLPHOS = 7,7′-bis[di(3,5-xylyl)phosphino]-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bi(2H-1,4-benzoxazine). [h] SYNPHOS = [(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine). [i] SEGPHOS = 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphine).

Table 3: Cycloisomerization catalyzed by [(*R*)-3,5-xylyl-binap(AuCl)$_2$] and AgOTf.[a]

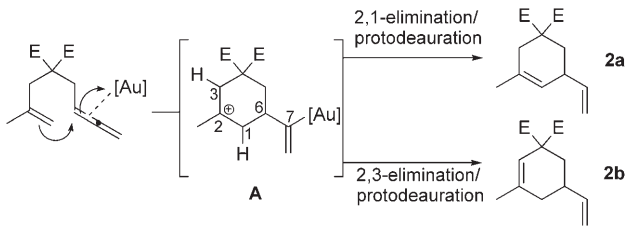
Substrate	Product	Yield [%][a] (isomer ratio)[b]	*ee* [%][c]
 **1**	 **2a,b**	83 (3.5:1)	72 (77)[d]
 **3**	 **4**	82	6
 **5**	 **6**	82	57[e]
 **7**	 **8a,b**	70 (1.5:1)	45
 **9**	 **10**	80 (5:1)	59
 **11**	 **12**	70	65
 **13**	 **14**	77 (1:1)	64

[a] Catalyst generated in situ using standard reaction conditions, see the Experimental Section. [b] 2,1:2,3 olefin isomer. [c] Major regioisomer. [d] When cooled to −12 °C, 0.08 M, 24 h. [e] Poor resolution (chiral-phase supercritical fluid chromatography) limits the accuracy of this measurement (±10%).

Eneallenes for examining the scope of this chemistry were readily available[8,16] and enabled several structural variations to be examined. Alkenes that were only monosubstituted at the internal position were unreactive, though substitution at the alkene terminus was tolerated. In the latter cases, this tolerance provided sufficient bias to favor one product regioisomer (**10**, **12**, Table 3). In the case of methallyl- (**1**) or phenallyl-substituted substrates (**7**) lacking this element, a mixture of regioisomers was obtained. This result, however, was not universal, as the sulfone and urea variants of the methallyl substrate were quite regioselective for the 1,2-product. Substitution at the internal allene hydrogen position, on the other hand, led to lower yields and enantioselectivities, along with competitive isomerization of starting material (not shown).

Enantioselectivities were found to be moderate for most substrates, and a slight increase in *ee* was possible when the reaction was run at −12 °C (77% *ee* for **2**). Sulfone **3** was the unusual case, as **4** was obtained in virtually racemic form. Nevertheless, these results represent a significant subset of the known gold-catalyzed asymmetric transformations of allenes.

The skeletal divergence of Au^I in this cycloisomerization suggested a significantly different mechanism from that typically found for Rh,[8] Pd,[9] and Ru[10] catalysts, which are prone to oxidative C–C coupling processes and give *exo*,*exo*-cyclopentene products.[17] Our current mechanistic hypothesis explaining the observed reactivity patterns involves the electrophilic activation of the internal allene double bond by Au^I.[6,18] In this scenario, the alkene acts as a nucleophile to generate putative carbenium ion **A** (Scheme 1); the catalytic cycle is then completed by 2,3- or 2,1-elimination and protodeauration. In cases where C1 and C2 are each substituted, elimination to the more highly substituted alkene product provides the observed major isomer (**10** and **12**). The role of the alkene as a nucleophile also explains why internal disubstitution of the alkene is essential, since this



Scheme 1. Proposed mechanism for eneallene cycloisomerization. [Au] represents the active catalytic species.

ensures the generation of a tertiary carbenium ion in the putative intermediate. This mechanism is also consistent with the observed regiochemical sensitivity to counterions, since they can presumably act as a weak general bases in the β-elimination step.

Since asymmetric induction in Au^I-catalyzed processes is relatively rare, we obtained a crystal structure of the dinuclear catalyst precursor (Figure 1).[19,20] Interestingly, a key π–π stacking interaction between two P-bound aryl groups (plane-

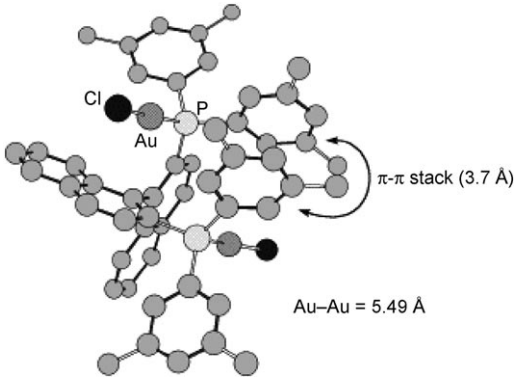


Figure 1. X-ray structure of [3,5-xylyl-binap(AuCl)$_2$]; one of two molecules in the asymmetric unit is shown; hydrogen atoms are omitted for clarity.

to-plane distance of 3.7 Å) lends the structure of this precursor a degree of rigidity and thus establishes a well-defined chiral environment in the solid state. The same conformational preference was observed in a tol-binap di-gold structure (tol = tolyl),[3] which suggests that it may be a common structural feature capable of sculpting the reactive environment of a complex that is otherwise constrained to a linear geometry.[21] Several observations that complicate the identification of the active catalyst occurred while investigating the cyclization of **1** to **2** with an isolated catalyst. When 5 mol% isolated [(*R*)-3,5-xylyl-binap(AuOTf)$_2$] was utilized under the standard conditions, slow reactions and low enantioselectivities were obtained (21% *ee*, more than 24 h for completion), contrasting with studies of in situ generated catalysts. Suspecting a role for Ag^+ in these processes, we repeated the reactions using 5 mol% [(*R*)-3,5-xylyl-binap-(AuOTf)$_2$] and a 15 mol% excess of AgOTf. Although a fast rate returned, the enantioselectivity remained low (21%). Unexpectedly, a control reaction using 5 mol% [(*R*)-3,5-xylyl-binap(AuOTf)$_2$] and added AgCl (15 mol%) increased the *ee* to 34%. While we do not yet have an explanation for these observations, the in situ protocol reproducibly provides products with good selectivities.

In conclusion, an enantioselective gold(I) catalyst has been developed for the cycloisomerization of eneallenes into vinylcyclohexene products. This carbon skeleton is unusual, as five- and seven-membered-ring products are the norm with other metal catalysts. The Au^I catalyst is tolerant of functional groups, it appears to selectively activate the allene over the alkene, and it can be used to generate bicyclic products.

Experimental Section

In a glovebox charged with nitrogen, an oven-dried 1-dram vial was charged with [(*R*)-3,5-xylyl-binap(AuCl)$_2$] (5.0 mg, 4.2 mmol), silver triflate (3.0 mg, 12.6 mmol), and nitromethane (0.8 mL). After stirring the suspension for 5 min, **1** (20 mg, 84 mmol) was added. A yellow color was usually noted within 10 min, and the reaction was usually blue-gray upon completion. After consumption of the starting material (determined by ^{1}H NMR spectroscopy), the reaction mixture was loaded directly onto a silica gel column for purification and eluted with hexanes/ethyl acetate (8:1).

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[13] Six-membered-ring products have been observed from Pauson–Khand-type reactions and thermal [2+2] cyclizations of enealllenes. See, for example: a) F. Inagaki, C. Mukai, *Org. Lett.* **2006**, *8*, 1217 – 1220; b) A. Padwa, M. Meske, S. S. Murphee, S. H. Watterson, Z. Ni, *J. Am. Chem. Soc.* **1995**, *117*, 7071 – 7080; c) H. Ohno, T. Mizutani, Y. Kadoh, K. Miyamura, T. Tanaka, *Angew. Chem.* **2005**, *117*, 5243 – 5245; *Angew. Chem. Int. Ed.* **2005**, *44*, 5113 – 5115.
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[15] The [xylyl-binap(Au(3,5-NO_2-benzoate)$_2$)] catalyst recently reported for the cyclization of allenylsulfonamides was inactive for the reactions described herein (20 h at 50 °C; see footnote [6f]). The *t*Bu_2MeO-BIPHEP digold catalyst reported by Widenhoefer and co-workers for the cyclization of allenyl alcohols gave full conversion but low *ee* in the present system (see footnote [6e]).
[16] P. A. Wender, M. P. Croatt, N. M. Deschamp, *Angew. Chem.* **2006**, *118*, 2519 – 2522; *Angew. Chem. Int. Ed.* **2006**, *45*, 2459 – 2462.
[17] For a discussion of cycloisomerization mechanisms, see: G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215 – 236.
[18] A related ionic pathway is proposed for the Au^I-catalyzed asymmetric alkoxy cyclization of ene-ynes, see reference [3].
[19] For structural information, contact Dr. Peter White in the UNC–Chapel Hill X-ray Facility (pswhite@email.unc.edu).
[20] Crystal data for [3,5-xylyl-binap(AuCl)$_2$] at 100 K: $C_{52}H_{48}Au_2Cl_2P_2$, 1/2 H_2O, $M_r = 1200.76\ g\,mol^{-1}$, orthorhombic, space group $P2_12_12_1$, $a = 12.6526(5)$, $b = 19.0582(7)$, $c = 38.1147(13)$ Å, $V = 9190.8(6)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.746\ mg\,m^{-3}$, $R_1 = 0.0423$ (0.0527), $wR_2 = 0.0933$ (0.0996), for 4688 reflections with $I > 2\sigma(I)$ (for 26863 reflections ($R_{int} = 0.0604$) with a total of 219861 measured reflections), goodness-of-fit on $F^2 = 1.029$, largest diff peak (hole) = 4.909 (−4.305 e Å^{-3}).
[21] The L-Au^I-L bond angle is typically in the 170–180° range. See, for example: a) A. A. Mohamed, J. Chen, A. E. Bruce, M. R. M. Bruce, J. A. K. Bauer, D. T. Hill, *Inorg. Chem.* **2003**, *42*, 2203 – 2205; b) J. R. Stork, D. Rios, D. Pham, V. Bicocca, M. M. Olmstead, A. L. Balch, *Inorg. Chem.* **2005**, *44*, 3466 – 3472.

