VIP Asymmetric Catalysis

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Intermolecular [2+2] Reaction of *N*-Allenylsulfonamides with Vinylarenes: Enantioselective Gold(I)-Catalyzed Synthesis of Cyclobutane Derivatives**

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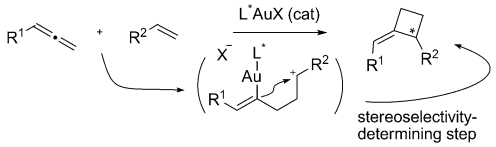
Dedicated to Professor Julio Delgado Martín on the occasion of his 70th birthday

Allenes[1] are useful reagents for the [2+2] cycloaddition reaction,[2] which is a powerful process for the synthesis of cyclobutanes. This carbocyclic motif is present in bioactive compounds[3] and has unique reactivity.[4] Gold catalysis triggers the functionalization of allenes[5] and assists several intramolecular allenene reactions[6] which allow the preparation of bicyclic frames that contain cyclobutane motifs.[7] The gold-catalyzed enantioselective intramolecular [2+2] reaction of allenenes has been recently accomplished.[7b,8] Moreover, racemic versions of related intermolecular processes have been disclosed.[9] An enantioselective version is highly desirable as it would provide a yet unknown and straightforward entry into optically active cyclobutanes from readily available allenamides and alkenes, in a sole synthetic operation. We are pleased to report herein the first asymmetric gold-catalyzed intermolecular allenene[2+2] cycloaddition.

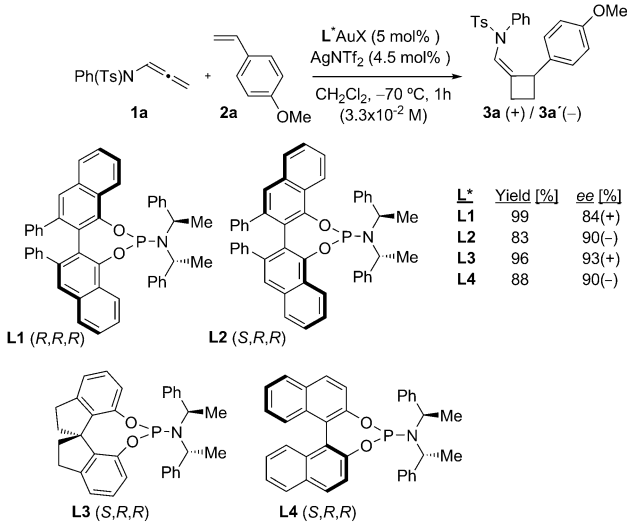
At the start of this study, previous work on the gold-catalyzed cyclization of allenamides and alkenes supported a stepwise reaction (Scheme 1).[9] The activation of the allene by the gold(I) catalyst[10] facilitates a subsequent attack of the olefin. Further evolution of the cationic vinyl gold intermediate[11] gives rise to the cyclobutane. Thus, it should be feasible to control the stereochemistry of the newly formed stereocenter from the remaining ligand on the gold catalyst.[12]



Scheme 1. Gold-catalyzed [2+2] intermolecular allene–alkene cycloaddition.

An exploratory survey to identify appropriate experimental conditions was conducted with sulfonylallenamide (**1a**) and 4-methoxystyrene (**2a**), which were chosen as model compounds on the basis of the high reactivity previously observed (Scheme 2).[13] Gold(I)-complexes derived from enantiopure phosphoramidite ligands were tested and gave satisfactory control of the enantioselectivity.[14–15] Selected representative reaction conditions are summarized in Scheme 2.[16]

Interestingly, the depicted ligands, which are either commercially available or easy to prepare, produce excellent results at −70 °C after just one hour. Gold(I) catalysts obtained from (*R*,*R*)-bis(1-phenylethylamine) and either (*R*)-VANOL or the corresponding (*S*)-1,1′-spirobiindane-7,7′-diol leading to (*S*)-SIPHOS-PE (**L1** and **L3**, respectively) gave chiral cyclobutane **3a** in good yield and enantioselectivity at an unusually low reaction temperature for a gold-catalyzed process, the low temperature can be used because of the high reactivity of the allene. In contrast, related gold(I)



L*	Yield [%]	ee [%]
L1	99	84(+)
L2	83	90(−)
L3	96	93(+)
L4	88	90(−)

Scheme 2. Ligands for the intermolecular [2+2] gold(I)-catalyzed enantioselective cycloaddition of the allenamide **1a** and styrene **2a**. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

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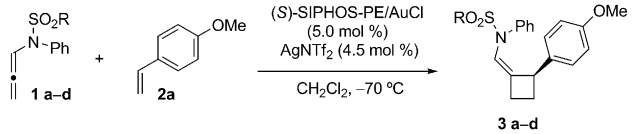
catalysts based on phosphoramidite ligands derived from (*S*)-VANOL or (*S*)-BINOL (**L2** and **L4**) result in the enantiomer **3a′** in a comparable manner.

Also, the effect of the nature of the sulfonyl group was explored (Scheme 3). The gold catalyst used for this study was that based on the (*S*)-SIPHOS-PE ligand (**L3**). For the



R	*t* [h]	Yield [%]	*ee* [%]
4-MeC_6H_5	1	96(**3a**)	93
Me	1	84(**3b**)	89
4-$NO_2C_6H_5$	21	77(**3c**)	95
2,4,6-(*i*Pr)$_3C_6H_2$	2	60(**3d**)	79

Scheme 3. Effect of the sulfonyl moiety on the reaction.

substitution on the sulfonyl group, a bulky aromatic group (**1d**) significantly lowered the yield and the *ee* value of **3d**. In contrast, a methyl group gave the cycloaddition in a comparable reaction time but slightly decreased the efficiency of the process (see **3b**). Finally, the less-electron-rich nosyl group imparts better enantioselectivity (**3c**) than the standard tosyl group (**3a**). However, it requires longer reaction time and thus leads to lower a yield.

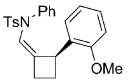
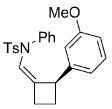
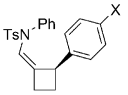
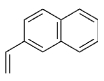
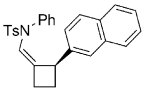
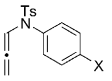
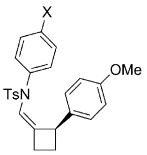
On this basis, the substrate with the tosyl group was used to explore the scope of this catalytic asymmetric cycloaddition between the allenamides **1** and styrene derivatives **2**. The investigated compounds and the results with several catalysts are depicted in Table 1.[17] The effect of the substitution at the different positions of the aromatic ring was tested, and all the 4-methoxystyrene derivatives (*ortho*, *meta*, and *para*) were tolerated without eroding the enantiomeric excess (Scheme 2 and Table 1, entries 1–5). This cycloaddition is compatible with different vinylarenes (electron-rich and moderately deactivated ones), thus giving satisfactory results (Table 1, entries 6–12). Another alkene, such as 2-vinylnaphthalene (**2g**) and additional allenes (**1e** and **1f**) prepared from representative substituted anilines were also tested. For both **1e** and **1f** the enantioselectivity was also high, and for **1e** the cyclization took place almost quantitatively.

The excellent performance of the above-studied catalytic systems prompted us to investigate the possibility of using this intermolecular reaction to prepare cyclobutanes, containing challenging quaternary carbon centers, in enantioenriched form.[18] To this end, prop-1-en-2-yl-benzene (α-methylstyrene; **2h**) was chosen as model alkene and its reaction with allenes **1a** and **1g** was investigated. The results of these demanding asymmetric transformations are summarized in Scheme 4.

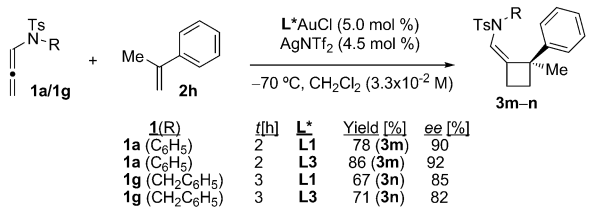
This gold-catalyzed [2+2] cycloaddition offers a useful synthetic resource for a facile assembly of alkylidenecyclobutanes which feature an allylic quaternary stereocenter within the ring. The benzylic sulphonamide **1g** did not perform as well as the aryl-substituted **1a**, but nevertheless the product **3n** is attractive for its potential as a building block through benzylic cleavage. Interestingly, by using the gold precatalyst (*S*)-SIPHOS-PE/AuCl (**L3**), the **1a** reacts with **2h** to give **3m** in both excellent yield and enantioselectivity (Scheme 4).

The asymmetric catalytic cycloaddition introduced herein works efficiently at −70 °C and has proven to be a useful reaction for the synthesis of some classes of chiral cyclobutanes. A desirable feature that would increase the potential utility associated with this transformation would be lowering of the required catalyst loading. Thus, additional experimen-

Table 1: Enantioselective phosphoramidite/gold(I)-catalyzed [2+2] allenamide–vinylarene cyclization.[a]

Entry	Allene **1**	Alkene **2**[b]	Product **3**	*t* [h]	L*	Yield [%][c]	*ee* [%][d]
							
1	**1a**	**2b**	**3e**	1	**L3**	81	84 (*S*)
2	**1a**	**2b**	**3e**	1	**L1**	90	92 (*S*)
							
3	**1a**	**2c**	**3f**	1	**L3**	44	90 (*R*)
4	**1a**	**2c**	**3f**	1	**L1**	49	90 *R*
5[e]	**1a**	**2c**	**3f′**	2	**L4**	21	71 (*S*)
							
6	**1a**	**2d** (X = H)	**3g** (X = H)	24	**L3**	56	82 (*R*)
7	**1a**	**2d** (X = H)	**3g** (X = H)	18	**L1**	69	86 (*R*)
8	**1a**	**2e** (X = F)	**3h** (X = F)	22	**L3**	62	85 (*R*)
9	**1a**	**2e** (X = F)	**3h** (X = F)	21	**L1**	79	87 (*R*)
10[f]	**1a**	**2f** (X = Me)	**3i** (X = Me)	1	**L3**	84	72 (*R*)
11[f]	**1a**	**2f** (X = Me)	**3i** (X = Me)	1	**L1**	95	72 (*R*)
12[e,f]	**1a**	**2f** (X = Me)	**3i′** (X = Me)	3	**L4**	88	94 (*S*)
							
13	**1a**	**2g**	**3j**	2	**L3**	46	95 (*R*)
14	**1a**	**2g**	**3j**	2	**L1**	52	90 (*R*)
							
15	**1e** (X = Me)	**2a**	**3k** (X = Me)	1	**L3**	87	84 (*R*)
16	**1e** (X = Me)	**2a**	**3k** (X = Me)	1	**L1**	95	92 (*R*)
17[e]	**1e** (X = Me)	**2a**	**3k′** (X = Me)	1	**L2**	84	90 (*S*)
18	**1f** (X = Br)	**2a**	**3l** (X = Br)	2.5	**L3**	44	89 (*R*)
19	**1f** (X = Br)	**2a**	**3l** (X = Br)	2.5	**L1**	48	89 (*R*)

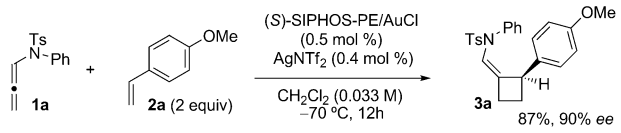
[a] Reaction conditions: **1** (0.1 mmol; 0.033 M, unless otherwise noted), **L***AuCl (5 mol%), and $AgNTf_2$ (4.5 mol%) in CH_2Cl_2 at −70 °C. [b] 5 equiv of **2** added. [c] Yield of isolated product after purification by column chromatography on neutral alumina. [d] Determined by HPLC. Absolute configuration given within parentheses. [e] **3′** corresponds to the enantiomer of the compound depicted. [f] **1a** was 0.0167 M in CH_2Cl_2.



1(R)	t[h]	L*	Yield [%]	ee [%]
1a (C_6H_5)	2	**L1**	78 (**3m**)	90
1a (C_6H_5)	2	**L3**	86 (**3m**)	92
1g ($CH_2C_6H_5$)	3	**L1**	67 (**3n**)	85
1g ($CH_2C_6H_5$)	3	**L3**	71 (**3n**)	82

Scheme 4. Enantioselective access to quaternary carbon centers using a gold-catalyzed [2+2] cycloaddition.

tal work showed that addition of only 0.5 mol% of the gold(I) precatalyst (0.4 mol% for the silver salt) allows the cycloaddition of **1a** and **2a** to furnish **3a** in a satisfactory 87% yield and 90% *ee* (Scheme 5). The amount of **2a** could be efficiently decreased to only two equivalents. Moreover, the reaction time was extended to 12 hours.



Scheme 5. Optimized reaction conditions for the enantioselective [2+2] cycloaddition of allenamides and vinylarenes.

In short, we report the first examples of the intermolecular gold-catalyzed asymmetric [2+2] cycloaddition of sulfonylallenamides and vinylarenes. These results also represent one of the first uses of an allene in an intermolecular gold-catalyzed process involving enantioselective carbon–carbon bond formation.[19] The high reactivity of the starting materials allows the reaction to be run at very low temperature, thus offering a convenient way to modulate the enantioselectivity of the process. Ligands based on known phosphoramidite scaffolds provided satisfactory sterecontrol to access the target transformation, and some ligands displayed useful complementarity. The prepared optically active cyclobutane frames comprise valuable features that make it attractive for their use as chiral building blocks. Work in this direction and attempts to enlarge the scope of the reaction, as well as to further develop other reactions involving related unsaturated systems are currently in progress in our group.

Experimental Section

A suspension of the chiral gold phosphoroamidite (5 mol%, 0.005 mmol) and the silver triflimidate (1.7 mg, 4.5 mol%) in dry CH_2Cl_2 (1 mL), under an argon atmosphere, was cooled down to −90 °C. Separately, under argon atmosphere, the alkene (0.5 mmol, 5 equiv) was added to another solution of the allene (0.1 mmol, 1.0 equiv) in 2 mL of anhydrous CH_2Cl_2. The second solution was then cooled at −90 °C and then added to the previously prepared mixture containing the gold precatalyst and the silver salt, and the temperature was maintained below −80 °C. Once the addition was finished the temperature was raised to −70 °C. The reaction was stirred at this temperature until the total depletion of the starting material (TLC) was observed, and the reaction was stopped by addition of 3.4 mg of PPh_3 (0.015 mmol, 15 mol%). The mixture was concentrated in vacuo and the residue was purified by flash chromatography on neutral alumina [hexanes/AcOEt (20:1) to hexanes/AcOEt (10:1)]. The enantiomeric excess was determined by HPLC using the chiral CHIRACEL IC or CHIRALPAK ADH chromatographic columns.

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[13] In our previous study we noticed that for **1a** and **2a** the TON and TOF values were 188 and 2256 h^{-1}, respectively.[9c] For the racemic intermolecular [2+2] cycloaddition those were the highest values obtained.

[14] For a review on phosphoramidite ligands in asymmetric catalysis: a) J. F. Teichert, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 2538 – 2582; *Angew. Chem. Int. Ed.* **2010**, *49*, 2486 – 2528. For pioneering work on the use of this kind of ligands in gold-catalyzed cycloaddition reactions: b) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A, Lledós, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009**, *131*, 13020 – 13030; c) A. Z. González, F. D. Toste, *Org. Lett.* **2010**, *12*, 202 – 203. Also see Ref. [8].

[15] For selected enantioselective synthesis of cyclobutane derivatives based on other classes of [2+2] intermolecular cycloadditions, see: a) K. Narasaka, H. Kusama, Y. Hayashi, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471 – 1478; b) K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8869 – 8885; c) E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686 – 12687; d) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem.* **2012**, *124*, 4180 – 4183; *Angew. Chem. Int. Ed.* **2012**, *51*, 4104 – 4107.

[16] The Supporting Information contains additional data on the reaction temperature optimization as well as on the performance of alternative phosphoramidite ligands. Characterization and analytical data are described in the accompanying Supporting Information.

[17] The absolute configuration (*R*) for the major enantiomer obtained in these asymmetric cycloaddition reactions giving cyclobytanes **3** was assigned by analogy with that of **3k**, which was determined by X-ray crystallography. CCDC 894272 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The X-ray crystal data have been summarized in the Supporting Information.

[18] Some examples of the racemic version of this process involving 1,1-disubstituted alkenes, and featuring both carbo-[9d] and heterosubstituted[9b,c] olefins, were early presented.

[19] At the time our manuscript was through the refereeing process a nice contribution on gold-catalyzed [4+2] cycloadditions of allenamides and dienes appeared: J. Francos, F. Grande-Carmona, H. Faustino, J. Iglesias-Sigüenza, E. Díez, I. Alonso, R. Fernández, J. M. Lassaletta, F. López, J. L. Mascareñas, *J. Am. Chem. Soc.* **2012**, *134*, 14322 – 14325.

