UNIVERSIDADE DE SANTIAGO DE COMPOSTELA
CAMPUS VIDA CAMPUS DE EXCELENCIA INTERNACIONAL
CiQUS Center for Research on Biological Chemistry and Molecular Materials

Axially Chiral Triazoloisoquinolin-3-ylidene Ligands in Gold(I)-Catalyzed Asymmetric Intermolecular (4 + 2) Cycloadditions of Allenamides and Dienes

Javier Francos, Francisca Grande-Carmona, Hélio Faustino, Javier Iglesias-Sigüenza, Elena Díez, Isaac Alonso, Rosario Fernández, José M. Lassaletta, Fernando López, José L. Mascareñas

Accepted Manuscript

How to cite:

Francos, J., Grande-Carmona, F., Faustino, H., Iglesias-Sigüenza, J., Díez, E., Alonso, I., Fernández, R., Lassaletta, J.M., López, F. and Mascareñas, J.L. (2012). Axially Chiral Triazoloisoquinolin-3-ylidene Ligands in Gold(I)-Catalyzed Asymmetric Intermolecular (4 + 2) Cycloadditions of Allenamides and Dienes. *J. Am. Chem. Soc.*, 134, 35, 14322-14325. doi: 10.1021/ja3065446

Copyright information:

Axially Chiral Triazoloisoquinolin-3-ylidene Ligands in Gold(I)-Catalyzed Asymmetric Intermolecular (4+2) Cycloadditions of Allenamides and Dienes

Javier Francos,† Francisca Grande-Carmona,§ Hélio Faustino,† Javier Iglesias-Sigüenza,∫ Elena Díez,∫ Isaac Alonso,† Rosario Fernández*,∫ José M. Lassaletta,*,§ Fernando López,*,‡ and José L. Mascareñas,*,†

†Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica. Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15782, Santiago de Compostela, Spain

‡ Instituto de Química Orgánica General CSIC, Juan de la Cierva 3, 28006, Madrid, Spain

§Instituto Investigaciones Químicas (CSIC-USe), Avda. Américo Vespucio, 49, 41092 Sevilla, Spain

∫Departamento de Química Orgánica, C/ Prof. García González, 1, 41012 Sevilla, Spain

Supporting Information Placeholder

ABSTRACT: The first highly enantioselective intermolecular (4+2) cycloaddition between allenes and dienes is reported. The reaction provides good yields of optically active cyclohexenes featuring diverse substitution patterns and up to three stereocenters. Key for the success of the process is the use of newly designed axially chiral *N*-heterocyclic carbene-gold catalysts.

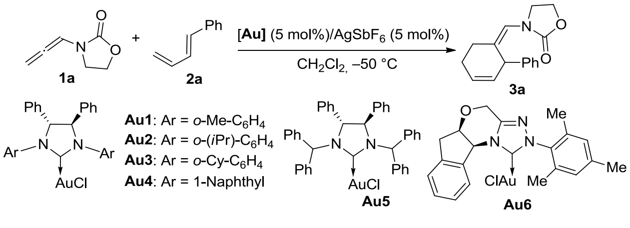
Catalytic asymmetric Diels-Alder (DA) cycloadditions are among the most effective strategies to construct optically active six-membered carbocycles.[1] In the last decades there have been many reports on enantioselective intermolecular versions of these annulations, which are typically promoted by chiral Lewis acids or by organocatalysts. In most of the cases, however, these transformations are circumscribed to alkenyl dienophiles equipped with carbonyl-activating groups (e.g. α,β-unsaturated aldehydes, ketones, esters, amides).[2,3] Enantioselective intermolecular DA reactions involving other types of dienophiles are much less frequent and, particularly, those between allenes and dienes are virtually unexplored.[4]

We have recently reported a gold–catalyzed intermolecular (4+2) cycloaddition between allenamides and dienes.[5-7] The transformation provides a simple, versatile and stereoselective entry to a variety of cyclohexenyl products incorporating an *exo* enamide group and up to two new stereocenters. The reaction is better carried out using AuCl as catalyst, but can also be promoted by other gold (I) catalysts such as IPrAuCl/AgSbF$_6$ (IPr=1,3-bis(diisopropyl-phenyl)imidazole-2-ylidene), although in this case it is somewhat less selective with respect to a competitive (2+2) annulation that provides cyclobutane side adducts.[5a,8]

On the above bases, we were challenged to explore the viability of achieving this type of allene-diene cycloadditions in an enantioselective manner, using chiral NHC-gold catalysts. Curiously, despite the wide use of racemic NHC-gold catalysts,[9] applications of their chiral counterparts are very scarce;[10] and only recently *ee* values above 90% have been reported for a couple of reactions, both of them promoted by chiral acyclic diaminocarbene gold complexes.[10g,h] Herein, we demonstrate that a newly designed chiral NHC-gold(I) complex, **Au8**, in which the carbene gold ligand is embedded in the cyclic backbone of an axially chiral unit, is able to catalyze the (4+2) cycloaddition between allenamides and a large number of dienes with total regio- and stereo-selectivity, and excellent enantioselectivity.

We initially focused on C_2–symmetric dihydroimidazole NHC–gold complexes **Au1**-**Au5**, incorporating the 1,2-diphenylethylene backbone.[11,12] These complexes promoted the (4+2) cycloaddition between **1a** and **2a** to afford the desired cycloadduct **3a** in moderate to good yields and complete stereoselectivity;[13] however, the enantioselectivity was consistently poor (Table 1). We were then curious to know the performance of chiral triazolylidene-gold complexes. Triazole-based NHCs have been successfully used in asymmetric oganocatalysis,[14] however, their organometallic complexes and, in particular, the gold counterparts, are essentially unexplored.[15] Interestingly, Au(I) complex **Au6**, prepared from Bode`s triazolylidene ligand,[16] promoted the cycloaddition in just 15 min at –50 °C, providing **3a** in an excellent 91% yield, albeit with low ee.

Table 1. Preliminary screening of chiral NHC-gold catalyst



entry	[Au]	*t* (min)	**3a**, yield (%)[a]	ee (%)[b]
1	**Au1**	60	79	10
2	**Au2**	60	88	4

3	**Au3**	60	74	4
4	**Au4**	60	76	23
5	**Au5**	60	51	24
6	**Au6**	15	91	16

[a] Isolate yield. [b] Determined by HPLC on chiral stationary phases.

In view of the good catalytic activity of **Au6**, we decided to explore other triazole-based NHC ligands that could generate a more effective chiral environment at the proximity of the gold center. Relying on our recent work on imidazo[1,5-a]pyridin-3-ylidene (**A**)[17] and [1,2,4]triazolo[4,3-a]pyridin-3-ylidene (**B**)[18] NHC architectures, we envisioned that gold complexes of type **C** (Figure 1) could be particularly well poised for this task. The rigid bicyclic structure of these NHC units should fix the relative orientation of the C(carbene)-Au bond while forcing the C(5)-aryl substituent in close proximity to this reacting center, and therefore might favor an efficient transfer of axial chirality. Additionally, the asymmetric induction might be further tuned by modulating the steric demands of substituents R, and particularly R'.[19]

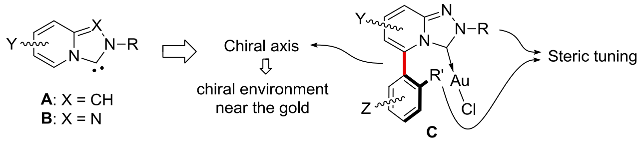
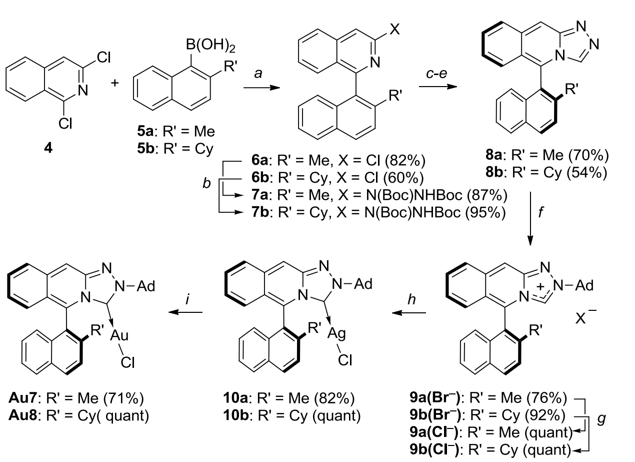


Figure 1. Design of new chiral NHC ligands.

To test the efficacy of these ligands we prepared the complexes of **Au7** (R' = Me) and **Au8** (R' = Cy), according to the reaction sequence indicated in the Scheme 1. The process involves a selective Suzuki coupling between 1,3-dichloroisoquinoline **4** and boronic acids **5a,b,** (→**6a,b**),[20] followed by Buchwald-Hartwig amination with BocNHNHBoc (→**7a,b**).[21] After deprotection, formylation and cyclization (→**8a,b**), the racemic mixtures were resolved by chiral HPLC.[22] Ensuing alkylation with 1-adamantyl bromide [→**9a,b(Br)**] and anion exchange[23] gave the triazolium salts **9a(Cl)** and **9b(Cl)** and, finally, metallation with Ag_2O (→**10a,b**) followed by transmetallation with AuCl·Me_2S gave the desired gold complexes **Au7** and **Au8**.

Scheme 1. Synthesis of Au7 and Au8[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, CsF, DME, Reflux, 15 h; (b) BocNHNHBoc, $Pd_2(dba)_3$, dppf, $CsCO_3$, toluene; (c) HCl 4M dioxane; (d) HCOOH, reflux; (e) *i*) $POCl_3$, toluene, reflux, *ii*) HPLC chiral resolution (*f)* 1-BrAd, AcOH, reflux; (*g*) Dowex 22 (Cl^-); (*h*) Ag_2O, $CHCl_3$, MS 4Å; (*i*) AuCl·Me_2S, toluene.

The X-ray structure of complex (R_a)-**Au8** (Figure 2) was used for the assignment of the absolute configuration of the chiral axis and for the quantification of the steric demand of the ligand, measured as percentage of buried volume (%V_{bur}) around the gold center. Using the Samb*V*ca software developed by Cavallo and co-workers,[24] an extremely high %V_{bur} value of 46.2, among the highest described for monodentate NHCs,[19b] was calculated for the carbene ligand in (R_a)-**Au8**. Additionally, the analysis of this structure confirmed that there might be substantial differences in the accessibility of either prochiral face of the allyl-cation gold intermediate that is presumably formed by activation of the allenamide.[5a,b]

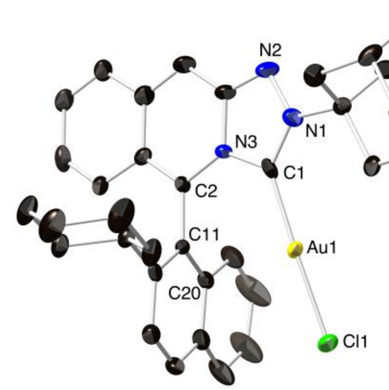
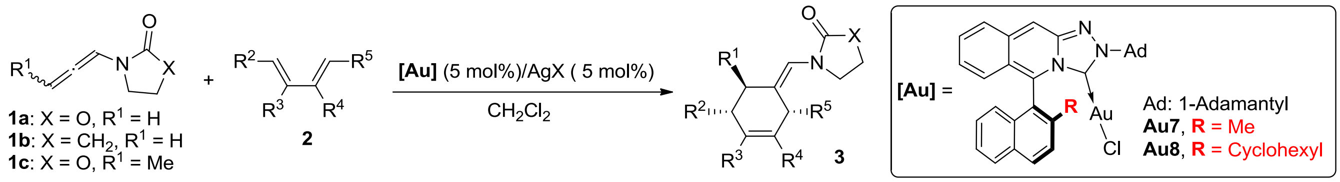
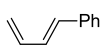
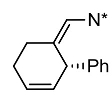
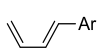
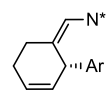
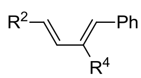
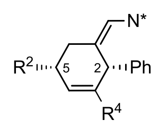
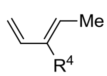
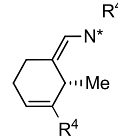
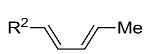
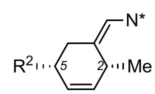
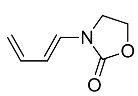
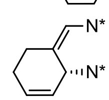
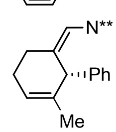
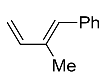
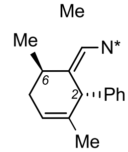
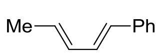
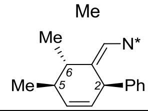


Figure 2. X-ray structure of (R_a)-**Au8**. H atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (deg): Au(1)-C(1) 1.968(6), Au(1)-Cl(1) 2.2685(13), Au(1)-C(11) 3.026, C2-N(3)-C(1)-Au(1) 10.9(8), N(3)-C(2)-C(11)-C(20) 84.9(6).

Gratifyingly, complex **Au7**/$AgSbF_6$ catalyzed the cycloaddition of **1a** and **2a**, providing the expected cycloadduct **3a** in good yield and a promising 63% ee (Table 2, entry 1). Importantly, the cyclohexyl-substituted derivative **Au8**, provided a similar yield but an excellent 90% ee (entry 2). This ee value could be improved by using $AgNTf_2$ as silver salt (entry 3),[25] and further increased up to >99% by lowering the temperature (entry 4). As can be seen in entries 5 and 6, the presence of different types of substituents at the aryl group of the diene did not significantly affect the enantioselectivity of the process, so **3b** and **3c** could be isolated with 94% and 96% ee, respectively.[26] The presence of substituents at the internal position of the diene is well tolerated (entry 7) and, 1,4-disubstituted dienes such as **2e** and **2f** also participate in the cycloaddition providing a direct and diastereoselective access to 1,4-*cis* disubstituted cyclohexenyl products (**3e** and **3f**) with moderate to good yields, and excellent ee's (entries 8 and 9).[27,28] Dienes lacking aryl substituents such as (*E*)-penta-1,3-diene (**2g**) or (*E*)-3-methylpenta-1,3-diene (**2h**) are also suitable substrates, providing the corresponding adducts with *ee*'s varying from 91 to 94% (entries 10 and 11). Even challenging 1,4-dialkyl-substituted dienes (e.g. **2i**, **2j**) provided satisfactory results under the standard conditions (entries 12 and 13), producing the expected adducts with complete chemo-,[29] regio- and diastereo-selectivity, and ee's close to 90%.[30] Excellent enantioselection was obtained in the cycloaddition of oxazolidinone-diene **2k**, which provides a *N*-substituted chiral cyclohexene (entry 14). Other allenamides, like **1b** (entry 15) or, more importantly, terminally substituted derivatives such as **1c**, do also provide excellent results. For instance, cycloaddition of **2d** with allenamide **1c** provided a 6:1 mixture of diastereisomeric cycloadducts **3dc** and **3dc'** with 75% combined yield and 96% ee (entry 16). Gratifyingly, the diastereoselectivity of this reaction could be increased by performing the reaction with catalyst **Au7**/$AgSbF_6$ at –50 ºC, which provided exclusively **3dc**, still with a good yield an excellent 93% ee (entry 17). Finally, the excellent performance and wide scope of this catalyst was again demonstrated in the cycloaddition of **2f** to **1c**, which provided the cyclohexenyl adduct **3fc,** featuring three new stereogenic centers with complete regio- and diastereoselectivity as well as an excellent 91% ee (entry 18).[31]

Table 2. Catalyst identification and scope of the enantioselective (4+2) DA cycloaddition of allenamides and dienes.[a]



entry	Diene, 2		Cat	Product, 3[b]		T (°C)	*t* (h)	3, yield (%)[c]	ee (%)[d]
1		**2a**	(S_a)-**Au7**/$AgSbF_6$	(*R*)-**3a**		–50	0.75	82	63
2		**2a**	(R_a)-**Au8**/$AgSbF_6$	(*S*)-**3a**		–50	1	81	90
3		**2a**	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3a**		–50	1	82	94
4		**2a**	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3a**		–78	3	88	>99
5		**2b**, Ar: 3,4,5-$(OMe)_3C_6H_2$	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3b**		–50	1	58[e]	94
6		**2c**, Ar: 4-Br-C_6H_4	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3c**		–50	1	55[e]	96
7		**2d**, R^4 = Me; R^2 = H,	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3d**		–50	1	88	95
8[f]		**2e**, R^4 = H; R^2 = Ph	(S_a)-**Au8**/$AgNTf_2$	(2*R*,5*S*)-**3e**[g]		0	0.25	48	96
9		**2f**, R^4 = H; R^2 = Me	(R_a)-**Au8**/$AgNTf_2$	(2*S*,5*R*)-**3f**		–50	1	85	94
10		**2g**, R^4 = H	(R_a)-**Au8**/$AgNTf_2$	(*R*)-**3g**		–50	3	71	91
11		**2h**, R^4 = Me	(R_a)-**Au8**/$AgNTf_2$	(*R*)-**3h**		–78	2	56	94
12		**2i**, R^2 = Me	(R_a)-**Au8**/$AgNTf_2$	(2*R*,5*R*)-**3i**		–50	12	56	87
13		**2j**, R^2 = CH_2OTBS	(R_a)-**Au8**/$AgNTf_2$	(2*R*,5*R*)-**3j**		–50	12	50	89
14		**2k**	(R_a)-**Au8**/$AgNTf_2$	(*R*)-**3k**		–50	1	69	>99
15[h]		**2d**	(R_a)-**Au8**/$AgNTf_2$	(*S*)-**3db**		–50 → rt	3	50	90
16[i]		**2d**	(R_a)-**Au8**/$AgNTf_2$	(2*S*,6*R*)-**3dc**: (2*S*,6*S*)-**3dc'**		–50→–15	2	75, (dr = 6:1)[j]	96[k]
17[i]		**2d**	(S_a)-**Au7**/$AgSbF_6$	(2*R*,6*S*)-**3dc**		–50	16	64, (dr > 20:1)[l]	93
18[i]		**2f**	(S_a)-**Au8**/$AgNTf_2$	(2*R*,5*R*,6*S*)-**3fc**[g]		+10	3	51	91

[a] Conditions: Diene (3 equiv) and allenamide (1 equiv) were added to a cooled solution of (R_a)-**Au8** and AgX in CH_2Cl_2 (0.1 M) unless otherwise noted. Conv. > 99%. [b] N* = (2-oxo)oxazolidin-3-yl, N** = (2-oxo)pyrrolidin-1-yl. The absolute configuration of (*S*)-**3c** was determined by X-ray diffraction analysis, see the Supporting Information. The absolute configuration of all other products **3** was assigned by analogy. [c] Isolated yields. [d] Determined by HPLC on chiral stationary phases. [e] Unoptimized yield. [f] Carried out with 4 equiv of diene. [g] Carried out with (S_a)-**Au8**, instead of (R_a)-**Au8**. [h] Carried out with allenamide **1b**. [i] Carried out with allenamide **1c**. [j] Ratio of (2*S*,6*R*)-**3dc**: (2*S*,6*S*)-**3dc'** (crude ^{1}H-NMR). [k] Same ee values (97%) were observed for both diastereoisomers, (2*S*,6*R*)-**3dc** and (2*S*,6*S*)-**3dc'**. [l] Ratio of (2*R*,6*S*)-**3dc**: (2*R*,6*R*)-**3dc'** (crude ^{1}H-NMR).

In summary, we described the first examples of a highly enantioselective intermolecular (4+2) cycloaddition between allenes and dienes, which also represents the first asymmetric intermolecular (4+2) cycloaddition promoted by a chiral carbophilic metal complex. The reaction provides a versatile and practical approach to a variety of optically active cyclohexene products which are not obviously accessible using alternative methodologies. The success in the asymmetric induction relies on the development of a novel class of designed ligands featuring a triazole unit embedded in a rigid axially chiral cyclic frame. These ligands might find utility in other metal-catalyzed asymmetric processes; in particular, the excellent results obtained with catalyst **Au-8** augurs well for further applications in other gold-catalyzed transformations.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures, characterization data, crystallographic data and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* joseluis.mascarenas@usc.es, fernando.lopez@iqog.csic.es, ffernan@us.es, jmlassa@iiq.csic.es

ACKNOWLEDGMENT

This work was supported by the Spanish MINECO, (SAF2010-20822-C02, CTQ2010-15297, CTQ2010-14974, and Consolider Ingenio 2010 CSD2007-00006), the ERDF funds, the Xunta de Galicia (INCITE09209084PR, GRC2010/12) and the Junta de Andalucía (2008/FQM-3833 and 2009/FQM-4537, predoctoral fellowship to F. G.-C). HF acknowledges the Fundação para a Ciência e Tecnologia (FCT, Portugal) and POPH/FSE for a Ph. D. grant (Grant SFRH/BD/60214/2009). Johnson-Matthey PLC is acknowledged for a gift of metal complexes.

REFERENCES

(1) For general reviews on asymmetric Diels-Alder reactions, see e.g.: (a) Corey, E. J. *Angew. Chem. Int. Ed*. **2002**, *41*, 1650. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed*. **2002**, *41*, 1668.

(2) For selected examples of DA reactions catalyzed by chiral Lewis acids, see: (a) Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc.* **2010**, *132*, 3652. (b) Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 5625. (c) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498. (d) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536, and references therein.

(3) For selected examples with chiral organocatalysts, see: (a) Momiyama, N.; Konno, T.; Furiya, Y.; Iwamoto, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 19294. (b) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458, and references therein.

(4) Asymmetric DA reactions with allenyl dienophiles are limited to chiral auxiliary strategies. See: (a) Henderson, J. R.; Chesterman, J. P.; Parvez, M.; Keay, B. A. *J. Org. Chem.* **2010**, *75*, 988 and references therein. (b) Ikeda, I.; Honda, K.; Osawa, E.; Shiro, M.; Aso, M.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 2031. (c) Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S. *Chem. Commun*. **1998**, 2363. For isolated examples of enantioselective hetero-DA reactions involving allenyl dienophiles and Lewis base catalysts, see: (d) Wang, X.; Fang, T.; Tong, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 5361. (e) Ashtekar, K. D.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 5732.

(5) (a) Faustino, H.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Sci.* **2011**, *2*, 633. See also: (b) Wang, Q. R.; Wang, G. A.; Zou, Y.; Li, Z. M.; Goeke, A. *Adv. Synth. Catal.* **2011**, *353*, 550. For thermal intramolecular (4+2) cycloadditions of allenamides and dienes, see: (c) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (d) Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J.* **2003**, *9*, 2419.

(6) For reviews on gold-catalyzed cycloadditions, see: (a) López, F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2011**, *7*, 1075. (c) Fernández, I.; Mascareñas, J. L. *Org. Biol. Chem.* **2012**, *10*, 699.

(7) For intramolecular enantioselective (4 + 2) cycloadditions of allenes and dienes, see: (a) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020. (b) González, A. Z.; Toste, F. D. *Org. Lett.* **2010**, *12*, 200. (c) Teller, H.; Flugge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949. For a related (4+3) intramolecular enantioselective cycloaddition of allenedienes, see: (d) Alonso, I.; Faustino, H.; López, F.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11496.

(8) For examples of (2+2) cycloadditions of allenamides, see: (a) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1658. (b) Li, X.-X.; Zhu, L.-L.; Zhou, W.; Chen, Z. *Org. Lett.* **2012**, *14*, 436. (c) Suárez-Pantiga, S.; Hernández-Díaz, C.; Piedrafita, M.; Rubio, E.; González, J. M. *Adv. Synth. Catal.* **2012**, *354*, 1651.

(9) (a) Nolan, S. P. *Acc. Chem. Res*. **2011**, *44*, 91. (b) Gaillard, S.; Cazin, C. S. J.; Nolan, S. P. *Acc. Chem. Res*. **2012**, *45*, *778*. (c) Diez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

(10) (a) Espinet, P.; Bartolome, C.; Garcia-Cuadrado, D.; Ramiro, Z. *Inorg. Chem.* **2010**, *49*, 9758. (b) Arnanz, A.; González-Arellano, C.; Juan, A.; Villaverde, G.; Corma, A.; Iglesias, M.; Sánchez, F. *Chem. Commun.* **2010**, *46*, 3001. (c) Wang, W.; Yang, J.; Wang, F.; Shi, M. *Organometallics* **2011**, *30*, 3859. (d) Wilckens, K.; Lentz, D.; Czekelius, C. *Organometallics* **2011**, *30*, 1287. (e) Yang, J.; Zhang, R.; Wang, W.; Zhang, Z.; Shi, M. *Tetrahedron: Asymmetry* **2011**, *22*, 2029. (f) Yamada, K.-I.; Matsumoto, Y.; Selim, K. B.; Yamamoto, Y.; Tomioka, K. *Tetrahedron* **2012**, *68*, 4159. (g) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972. (h) Handa, S.; Slaughter, L. M. *Angew. Chem. Int. Ed.* **2012**, 51, 2912. For a review covering asymmetric NHC-gold catalysis, see: (i) Wanga, F.; Liua, L.-J.; Wanga, W.; Li, S.; Shi, M. *Coord. Chem. Rev.* **2012**, *256*, 804. See also, (j) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382. (k) Sengupta, S.; Shi, X. *Chem. Cat. Chem.* **2010**, *2*, 609. (l) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501.

(11) For other types of transition-metal catalysts incorporating these C2-symmetric chiral NHC ligands, and their applications, see: (a) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2006**, *128*, 1840. (b) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568. (d) Selim, K.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8733. (e) Matsumoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578. (f) Lee, K.; Hoveyda, A. H. *J. Org. Chem*. **2009**, *74*, 4455 and references therein. (g) See also ref. 10i.

(12) See the Supporting Information for details concerning the synthesis of these chiral NHC-gold complexes. See also refs 11f and 10f.

(13) (2+2) Cycloadducts were not detected.

(14) (a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, 290, *77*.

(15) For the preparation of a chiral triazolylidene-gold complex, see: (a) Paul, S.; Schweizer, W. B.; Ebert, M.-O.; Gilmour, R. *Organometallics* **2010**, *29*, 4424. For isolated examples of achiral triazolylidene-gold complexes, see: (b) de Fremont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411. (c) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542.

(16) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(17) (a) Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc*. **2005**, *127*, 3290. See also (b) Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, 61, 6207.

(18) (a) Iglesias-Sigüenza, J.; Ros, A.; Díez, E.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Dalton Trans.* **2009**, 7113. See also (b) Ma, Y.; Wei, S.; Lan, J.; Wang, J.; Xie, R.; You, J. *J. Org. Chem.* **2008**, *73*, 8256.

(19) For recent reviews analyzing the steric properties of NHC ligands, see: (a) Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940. (b) Clavier, H.; Nolan, S. P. *Chem. Commun*. **2010**, *46*, 841.

(20) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 927.

(21) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351.

(22) The racemic mixtures **8a,b** were resolved by preparative HPLC (Chiracel IA). See the Supp. Info for further details.

(23) The anion exchange to Cl prevents the presence of Cl/Br mixtures after transmetallation of the NHC-AgBr intermediate with $AuCl{\cdot}SMe_2$.

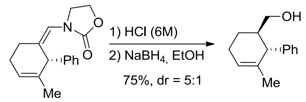
(24) (a) Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo L. *Eur. J. Inorg. Chem.*, **2009**, 1759; (b)

http://www.molnac.unisa.it/OMtools.php. The calculated value (H atoms omitted) was obtained using the standard parameters: radius of sphere = 3.5 Å; distance from sphere = 2.1 Å; mesh step = 0.05.

(25) Equivalent results to those of entries 2 and 3 were obtained when the cationic catalyst was previously filtered through celite. For a pertinent discussion on the "silver effect", see: Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012 and references therein.

(26) A highly electron-withdrawing *p*-NO_2 substituent at the aryl group of the diene still provided the reaction product with 92% ee, although in just 11% yield. On the other hand, furan did not participate in this type of cycloaddition. See the Supp. Info for details.

(27) The synthetic potential of the *exo*-enamide group was explored with cycloadduct (*S*)-**3d** by transforming it into a hydroxylmethyl group, upon treatment under acidic conditions and subsequent reduction with $NaBH_4$.[5a]

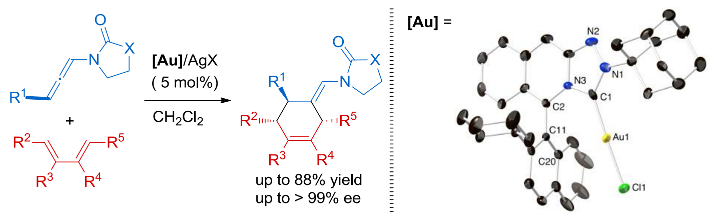


(28) The reaction of (1*Z*,3*E*)-**2f** with **1a** under standard conditions or even at higher temperatures did not provide any (4+2) cycloadduct, suggesting that a concerted cycloaddition between the diene (in a *s*-cis conformation) and the gold-allyl cation derived from **1a** could be taking place. Both, concerted (4+2) or (4+3) cycloadditions, this later followed by a 1,2-ring contraction, could be equally feasible. See the Supp. Info., and references 5a,b and 7a for related mechanistic information.

(29) In contrast to the reaction of **2i** and **1a** promoted by IPrAuCl/ $AgSbF_6$,[5a] we haven't observed (2+2) products when using **Au8**/$AgNTf_2$.

(30) Cycloaddition experiments of allenamide **1a** with dienes **2i**, **2a** and **2h** employing gold catalysts featuring chiral phosphoramidites or bisphosphine ligands led to low ee's and/or yields. See the Supp. Info. for details.

(31) This reaction fails with AuCl or IPrAuCl/$AgSbF_6$,[5a] which further highlights the potential and efficiency of **Au8**.


[Au]/AgX
(5 mol%)
CH2Cl2
up to 88% yield
up to > 99% ee
[Au] =
N2
N1
N3
C1
C2
C11
Au1
C20
Cl1