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Communication

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

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S *Supporting Information*

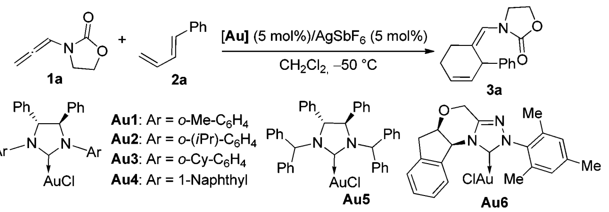
ABSTRACT: The first highly enantioselective intermolecular (4 + 2) cycloaddition between allenes and dienes is reported. The reaction provides good yields of optically active cyclohexenes featuring diverse substitution patterns and up to three stereocenters. Key to the success of the process is the use 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 recent 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 the catalyst but can also be promoted by other gold(I) catalysts such as IPrAuCl/$AgSbF_6$, 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 basis, 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] only recently have *ee* values above 90% been reported for a couple of reactions, both 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 stereoselectivity and excellent enantioselectivity.

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

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 organocatalysis;[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

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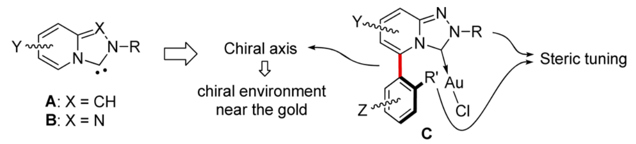


Figure 1. Design of new chiral NHC ligands.

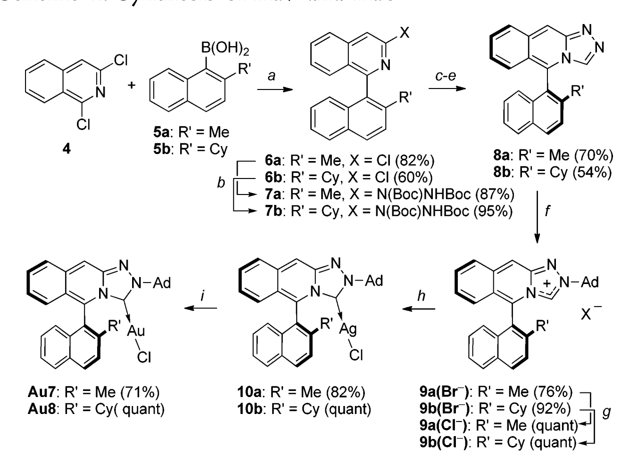
cycloaddition in just 15 min at −50 °C, providing **3a** in an excellent 91% yield, albeit with low ee.

In view of the good catalytic activity of **Au6**, we explored other triazole-based NHC ligands that could generate a more effective chiral environment within 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. Moreover, the asymmetric induction might be further tuned by modulating the steric demands of R, and particularly R′.[19]

To test the efficacy of these ligands we prepared the complexes **Au7** (R′ = Me) and **Au8** (R′ = Cy), according to the reaction sequence indicated in 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, metalation with Ag_2O (→**10a,b**) followed by transmetalation with AuCl·Me_2S gave the desired gold complexes **Au7** and **Au8**.

The X-ray structure of complex (R_a)-**Au8** (Figure 2) allowed the assignment of the absolute configuration and the quantification of the steric demand of the ligand, measured as the percentage of buried volume (%V_{bur}) around the gold center. Using the SambVca software,[24] we calculated a %V_{bur} value of 46.2, among the highest described for monodentate NHCs.[19b]

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 4 M 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 4 Å; (*i*) AuCl·Me_2S, toluene.

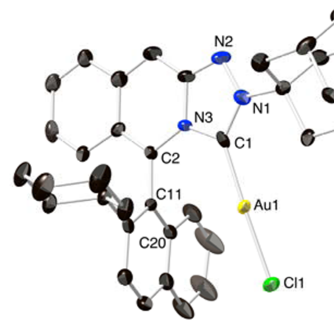


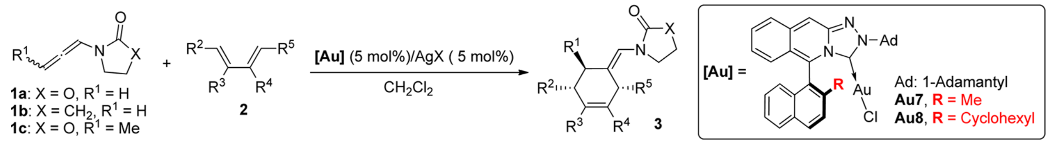
Figure 2. X-ray structure of (R_a)-**Au8**. H-atoms are omitted for clarity.

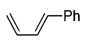
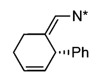
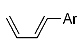
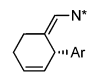
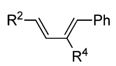
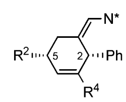
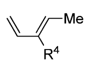
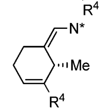
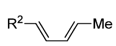
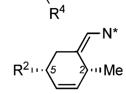
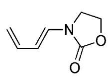
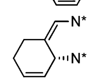
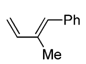
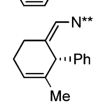
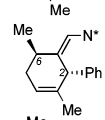
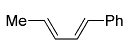
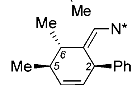
Additionally, the structure suggests that there might be substantial differences in the accessibility of either prochiral face of the allyl−cation gold intermediate that is presumably formed by activation of the allenamide.[5a,b]

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 a 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 reaction tolerates different types of substituents at the aryl group of the diene, thereby **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 process providing a direct and diastereoselective access to 1,4-*cis* disubstituted cyclohexenes (**3e** and **3f**) with excellent ee's (entries 8 and 9).[27] 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). Whereas furan was too reactive and gave a mixture of products, challenging 1,4-dialkyl-substituted dienes such as **2i** and **2j** provided satisfactory results under the standard conditions (entries 12 and 13), producing the expected adducts with complete chemo-,[28] regio-, and diastereoselectivity, and ee's close to 90%.[29] Excellent enantioselection was obtained in the cycloaddition of oxazolidinone-diene **2k**, which provides a *N*-substituted chiral cyclohexene (entry 14). Other allenamides, such as **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 diastereoisomeric cycloadducts **3dc** and **3dc**′ with a 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 °C, which provided exclusively **3dc**, still with a good yield and 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**, including three new stereogenic centers with complete regio- and diastereoselectivity as well as an excellent 91% ee (entry 18).[30]

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

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).

complex. The reaction provides a versatile and practical approach to a variety of optically active cyclohexene products which are not easily accessible using other methodologies.[31] 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 **Au8** augurs well for further applications in other gold-catalyzed transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization and X-Ray data, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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

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(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. See the Supporting Information for details.

(27) The reaction of (1*Z*,3*E*)-**2f** with **1a** did not provide any (4 + 2) adduct, suggesting that it might proceed via concerted rather stepwise pathways. Further mechanistic studies are ongoing.

(28) In contrast to the reaction of **2i** and **1a** catalyzed by IPrAuSbF_6,[5a] we did not observe (2 + 2) adducts when using **Au8**/AgNTf_2.

(29) Cycloaddition experiments of **1a** with dienes **2i**, **2a**, and **2h** using gold catalysts featuring chiral phosphoramidites or bisphosphines led to low ee's and/or yields. See the Supporting Information for details.

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

(31) The exoenamide group can be readily elaborated. For instance, treatment of (*S*)-**3d** with HCl and subsequent reduction ($NaBH_4$) yields the expected alcohol in good yield.[5a]