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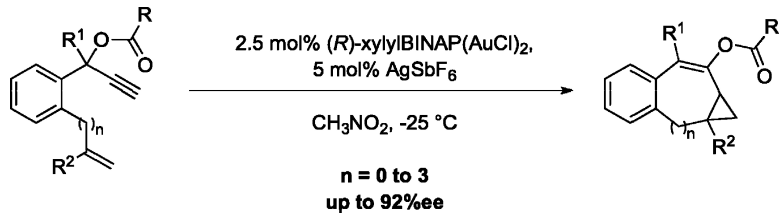

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Asymmetric Synthesis of Medium-Sized Rings by Intramolecular Au(I)-Catalyzed Cyclopropanation

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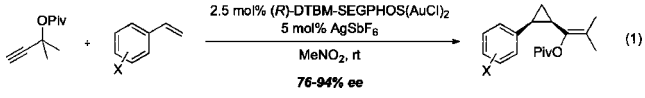
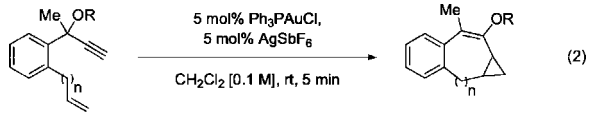
The construction of medium-sized rings is an important and challenging goal in organic synthesis.[1] Transition metal catalyzed cycloisomerization and cycloaddition reactions are powerful methods to access these ring systems.[2] However, only a few of these methods are applicable to the enantioselective synthesis of medium-sized rings.[3] Although cyclization with rhodium carbenes generated from diazo-precursors has provided some limited success, dimerization can be a significant problem.[4] On the other hand, dimerization of the propargyl ester derived Au(I)-carbenoid is absent in the Au(I)-catalyzed asymmetric olefin cyclopropanation reaction (eq 1).[5a] Moreover, the reactions of propargyl esters represent a rare class of Au-catalyzed C−C bond forming transformations that work efficiently in an intermolecular sense.[5−7] Given this unique reactivity, we hypothesized that the Au-catalyzed olefin cyclopropanation reaction might provide an opportunity for the enantioselective preparation of medium-sized ring compounds,[5,6a] despite the fact that enantioselective Au(I)-catalyzed enyne cycloisomerization reactions remain rare.[8]



(1)

We were pleased to find that triphenylphosphine gold(I) catalyzed the cycloisomerization of propargyl ester **3** to cycloheptene **4** in quantitative yield (eq 2).[9,10] A similar result was obtained for the formation of 8-membered ring **6** from propargyl ester **5**. The Au-catalyzed intramolecular cyclopropanation reaction also allowed for the synthesis of a 9-membered ring, albeit in diminished yield.[11] Surprisingly, reaction of propargyl ester **1** provided 6-membered ring product **2** in only 10% yield.[12] Moreover, reaction of **3** or **5** in the presence of styrene only resulted in the intramolecular 7- or 8-membered ring products (**4** and **6** respectively); no intermolecular cyclopropanation was observed.



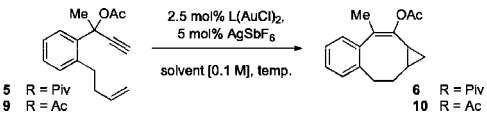
(2)

1 n = 0, R = Ac
3 n = 1, R = Piv
5 n = 2, R = Piv
7 n = 3, R = Ac

2 10%
4 99%
6 99%
8 44%

Based on these results, we focused on the development of a catalytic enantioselective intramolecular cyclopropanation. We first examined the catalyst system developed for the intermolecular enantioselective cyclopropanation reaction (eq 1); however, we were disappointed to find that under these conditions cyclooctene **10** was formed with very low enantiomeric excess (Table 1, entry 1). Further experiments found that the BINAP family of ligands was optimal with xylyl-BINAP giving the highest enantioselectivity (entries 2−4). In contrast to the intermolecular reaction in which pivaloate esters were required to achieve high enantioselectivity, acetate ester **9** afforded the cyclopropane with noticeably better enantioselectivity than the corresponding pivaloate ester **5** (entries 4 and 5). As in the intermolecular version, nitromethane was the best solvent (Table 1, entries 4, 6, and 7). A significant temperature effect was observed, lowering the temperature of the xylyl-BINAP Au-catalyzed reaction to −25 °C allowed for the isolation of **10** in 92% ee (entry 9).

Table 1. Au(I)-Catalyzed Asymmetric Cyclopropanation



5 R = Piv
9 R = Ac

6 R = Piv
10 R = Ac

entry	R	ligand	solvent	*T* (°C)	ee (%)
1	Ac	(*R*)-DTBM-Segphos	$MeNO_2$	rt	3
2	Ac	(*R*)-BINAP	$MeNO_2$	rt	53
3	Ac	(*S*)-Tol-BINAP	$MeNO_2$	rt	−61
4	Ac	(*R*)-xylyl-BINAP	$MeNO_2$	rt	70
5	Piv	(*R*)-xylyl-BINAP	$MeNO_2$	rt	49
6	Ac	(*R*)-xylyl-BINAP	CH_2Cl_2	rt	64
7	Ac	(*R*)-xylyl-BINAP	PhMe	rt	20
8	Ac	(*R*)-xylyl-BINAP	$MeNO_2$	−20	84
9	Ac	(*R*)-xylyl-BINAP	$MeNO_2$	−25	92

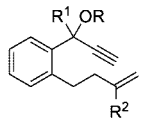
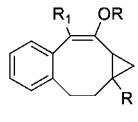
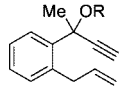
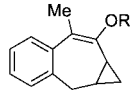
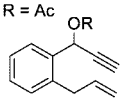
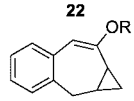
When these conditions were applied to the reaction, a wide range of 8-membered ring products were prepared in excellent yields and enantioselectivities (Table 2, entries 1−6). Substitution at the propargyl position is well tolerated (Table 2, entries 2−5). For example, the Au-catalyzed reaction of propargyl ester **13** containing two alkenes selectively affords the 8-membered ring (**14**) over the five-membered ring. This result, taken with the poor yield of 6-membered ring product **2**, emphasizes the remarkable selectivity of the reaction for medium-sized rings. Substitution at the internal position of the olefin lowers the enantioselectivity; however, this can be increased by simply using difluorophos$(AuCl)_2$ as the catalyst (Table 2, entry 6).[13] Interestingly, the optimal conditions for secondary propargyl pivaloate **25** more closely resembled our originally developed conditions, producing the 7-membered ring product **26** in 85% ee with (*R*)-DTBM-Segpho$s(AuCl)_2$ as the catalyst, while the acetate (**23**) gave the product with much lower selectivity (Table 2, entries 8 and 9).[10]

The proposed mechanism of the intramolecular cyclopropanation reaction (Scheme 1) involves the Au-mediated 1,2-shift of the propargyl ester to generate a Au-stabilized vinyl carbenoid.[14] Recent computational studies indicate that the *syn*-intermediate (**A**) is formed under kinetic control, while the *anti*-intermediate (**B**) is thermodynamically favored by 3.6 kcal mol^{-1}.[15] Moreover, we have recently found that the stereochemical outcome of the reaction of related electrophilic gold-carbenoid intermediates depends on the nature of the nucleophile,[5f] suggesting that intermediates **A** and **B** may equilibrate.

To examine this hypothesis, we looked at the Au-catalyzed reaction of propargyl ester **25** in the presence and absence of 1,1-diphenylethylene. In its absence, the intramolecular reaction occurred, forming

10.1021/ja8085005 CCC: $40.75

Table 2. Reaction Scope

entry	substrate	product	cond[a]	yield (%)	ee (%)
					
1	**9** R = Ac, R^1 = Me, R^2 = H	**10**	A	94	92
2	**11** R = Ac, R^1 = Et, R^2 = H	**12**	A	91	92
3	**13** R = Ac, R^1 = allyl, R^2 = H	**14**	A	98	90
4	**15** R = Ac, R^1 = $(CH_2)_2$Ph, R^2 = H	**16**	A	80	90
5	**17** R = Ac, R^1 =  , R^2 = H	**18**	A	96	90
6	**19** R = Ac, R^1 = Me, R^2 = Me	**20**	B	88	75
					
7	**21** R = Ac	**22**	C	91	49
					
8	**23** R = Ac	**24**	D	49	15
9	**25** R = Piv	**26**	D	44	85[b]

[a] Reaction conditions, 2.5 mol% catalyst, 5 mol% $AgSbF_6$, $MeNO_2$ [0.1 M]: **A** = (*R*)-xylyl-BINAP$(AuCl)_2$, −25 °C; **B** = (*R*)-Difluorophos$(AuCl)_2$, −25 °C; **C** = (*R*)-xylyl-BINAP$(AuCl)_2$, rt; **D** = (*R*)-DTBM-Segphos$(AuCl)_2$, rt. [b] The absolute stereochemistry was determined by the mandelate method (see Supporting Information).

the expected 7-membered ring product **26**. This product suggests that the reaction is proceeding through intermediate **A** which contains the (*E*)-olefin geometry required for an intramolecular reaction. In contrast, when the reaction was conducted in the presence of 1,1-diphenylethylene, an intermolecular cyclopropanation reaction occurs to selectively form **27** as the (*Z*)-olefin isomer.[16] In this case, the reaction is operating through gold(I)-carbenoid intermediate **B**. Taken together, these results suggest that Au(I)-stablized vinyl carbenoids are fluxional[17] and in some cases the reactions may even proceed through the thermodynamically less stable isomer.

In conclusion, the enantioselective synthesis of 7- and 8-membered rings can be accomplished by a Au(I)-catalyzed asymmetric intramolecular alkene cyclopropanation reaction. These results significantly extend the scope of enantioselective transition metal catalyzed enyne cycloisomerization reactions, which have generally been limited to the synthesis of 5- and 6-membered rings.[18] Moreover, these studies provide additional evidence for the fluxional nature of the Au(I)-stabilized vinyl carbenoid intermediates generated from the rearrangement of propargyl esters.

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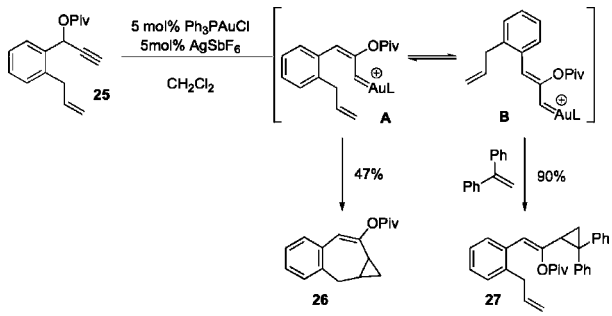
Scheme 1. Isomeric Carbenoid Intermediates



Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.
(2) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.
(3) For asymmetric transition metal catalyzed synthesis of medium-sized rings by: C−C bond formation: (a) Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302. (b) Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H *J. Am. Chem. Soc.* **2002**, *124*, 2868. (c) Weatherhaed, G. A.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5805. (d) Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, *58*, 4513. C−O bond formation: (e) Shen, Z.; Khan, H. A.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916.
(4) (a) Doyle, M. P.; Hu, W.; Chapman, B.; Marnett, A. B.; Peterson, C. S.; Vitale, J. P.; Stanley, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 5718. (b) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B.; Parker, D. L.; Ene, D. G.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 8826. For medium-sized ring formation with rhodium carbenes, see : (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(5) (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480. (c) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021. (d) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (e) Davies, P. W.; Albrecht, S. J.-C. *Chem. Commun.* **2008**, 238. (f) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244.
(6) For representative examples of intermolecular annulations: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (c) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814.
(7) For general reviews on Au chemistry, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.
(8) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293.
(9) (a) Boyer, F.-D.; Le Goff, X.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163. (b) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43. (c) Comer, E.; Rohan, E.; Deng, L., Jr *Org. Lett.* **2007**, *9*, 2123. (d) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (e) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488.
(10) For additional information see the Supporting Information.
(11) This is partially due to the formation of indene byproducts : (a) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (b) Nakanishi, Y.; Miki, K.; Ohe, K. *Tetrahedron* **2007**, *63*, 12138.
(12) This contrasts with secondary alkyl propargyl esters which undergo Au(I)-catalyzed cycloisomerizations to give 5- and 6-membered ring products: (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (b) Fürstner, A.; Hannen, P. *Chem.—Eur. J.* **2006**, *12*, 3006. (c) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901.
(13) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799.
(14) Under identical reaction conditions, the corresponding propargyl alcohol and methyl ether gave no reaction, suggesting an enyne first mechanism is not operative. See ref 12c.
(15) Soriano, E.; Marco-Contelles, J. *Chem.—Eur. J.* **2008**, *14*, 6771.
(16) The absence of intermolecular products in the case of tertiary propargyl esters may reflect a decrease in the relative thermodynamic stability of the *trans*-intermediate of type **A**.
(17) (a) Olefin isomerizations have been observed in rhodium-stabilized vinyl carbenoids. See: Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, 4417. (b) For a discussion of isomerization of allyl cations, see: Mayr, H.; Förner, W.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1979**, *101*, 6032.
(18) (a) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (b) Lie, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (c) Lie, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198. (d) Lie, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472. (e) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (f) Mikami, K.; Kataika, S.; Yusa, Y.; Aikawa, K. *Org. Lett.* **2004**, *6*, 3699. (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *127*, 2764.

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