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

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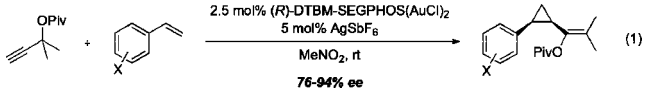
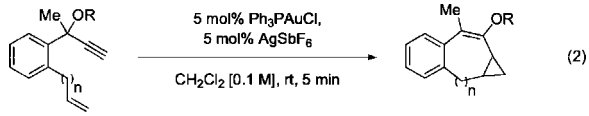
The construction of medium-sized rings is an important and challenging goal in organic synthesis.[1] Transition metal catalyzed cycloisomerization and cycloaddition reactions are powerful methods to access these ring systems.[2] However, only a few of these methods are applicable to the enantioselective 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.



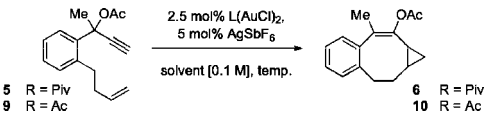
(2)

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

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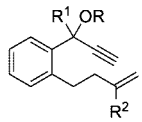
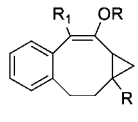
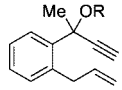
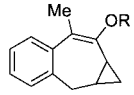
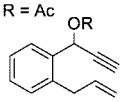
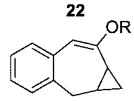
Table 2. Reaction Scope

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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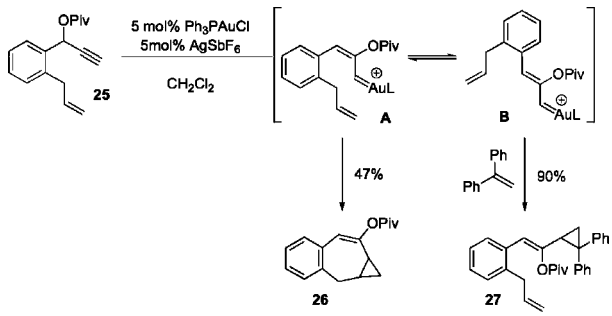
Scheme 1. Isomeric Carbenoid Intermediates



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

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