Published in final edited form as:

J Am Chem Soc. 2009 February 18; 131(6): 2056–2057. doi:10.1021/ja8085005.

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

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Abstract

An efficient method for the asymmetric gold(I)-catalyzed preparation of medium sized rings has been developed. The method provides 7- to 9-membered rings in excellent yield. High enantioselectivities can be achieved for 7- and 8-membered ring products employing chiral gold(I) complexes. The results provide insight into the mechanism, showing the fluxional nature of gold(I)-stabilized vinyl carbenoid intermediates.

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 gold(I)-carbenoid is absent in the gold(I)-catalyzed asymmetric olefin cyclopropanation reaction (eq 1).^{5a} Moreover, the reactions of propargyl esters represent a rare class of gold-catalyzed carbon-carbon bond forming transformations that work efficiently in an intermolecular sense.^{5–7} Given this unique reactivity, we hypothesized that the gold-catalyzed olefin cyclopropanation reaction might provide an opportunity for the enantioselective preparation of medium-sized ring compounds,^{5,6a} despite the fact that enantioselective gold(I)-catalyzed enyne cycloisomerization reactions remain rare.⁸

(1)

We were pleased to find that triphenylphosphinegold(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 gold-catalyzed intramolecular cyclopropanation reaction also allowed for the synthesis of a 9-membered ring, albeit in diminished yields.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)

On the basis of these results we turned our attention towards the development of a catalytic enantioselective intramolecular cyclopropanation. To this end, 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; thus lowering the temperature of the xylyl-BINAP gold-catalyzed reaction to -25°C allowed for the isolation of **10** in 92% ee (entry 9).

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 to 6). Substitution at the propargyl position is well tolerated (Table 2, entries 3 to 6). For example, the gold-catalyzed reaction of propargyl ester **13** containing two alkenes selectively affords the larger 8-membered ring (**14**) over the five-membered ring. This result, taken with the poor yield of the 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-Segphos(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 gold-mediated 1,2-shift of the propargyl ester to generate a gold-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.

In order to examine this hypothesis, we looked at the gold-catalyzed reaction of propargyl ester **25** in the presence and absence of 1,1-diphenylethylene. In its absence, the intramolecular

reaction occurred, forming 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 gold(I)-stabilized vinyl carbenoids are fluxional¹⁷ and that 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 gold(I)-stabilized vinyl carbenoid intermediates generated from the rearrangement of propargyl esters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We gratefully acknowledge NIHGM (RO1 GM073932), Merck Research Laboratories, Bristol-Myers Squibb, and Novartis for funding. Takasago International is thanked for the generous donation of phosphine ligands. I.D.G.W. thanks NSERC for a postdoctoral fellowship. S.R. thanks DAAD for a fellowship. Dr. David J. Gorin is thanked for initial experiments and helpful discussions.

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Scheme 1.
Isomeric Carbenoid Intermediates.

Table 1

Au(I)-Catalyzed Asymmetric Cyclopropanation

<p> 5 R = Piv 9 R = Ac </p> <p> 2.5 mol% L(AuCl)₂, 5 mol% AgSbF₆ </p> <p>solvent [0.1 M], temp.</p> <p> 6 R = Piv 10 R = Ac </p>					
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 ₂ Cl 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

product	cond ^a	yield (%)	ee (%)
A	94	92
A	91	92
A	98	90
A	80	90

product	cond ^e	yield (%)	ee (%)
18	A	96	90
20	B	88	75

cond ^a	yield (%)	ee (%)
c	91	49

product

22

product	cond ^e	yield (%)	ee (%)
24	D	49	15
26	D	44	85

–25°C; **B** = (R)-Difluorophos(AuCl)₂, –25°C; **C** = (R)-xylyl-BINAP(AuCl)₂, rt; **D** = (R)-