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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. Transition metal catalyzed cycloisomerization and cycloaddition reactions are powerful methods to access these ring systems. However, only a few of these methods are applicable to the enantioselective synthesis of medium-sized rings. Although cyclization with rhodium carbenes generated from diazo-precursors has provided some limited success, dimerization can be a significant problem. 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). 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. 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, despite the fact that enantioselective Au(I)-catalyzed enyne cycloisomerization reactions remain rare.

We were pleased to find that triphenylphosphine gold(I) catalyzed the cycloisomerization of propargyl ester 3 to cycloheptene 4 in quantitative yield (eq 2). 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. Surprisingly, reaction of propargyl ester 1 provided 6-membered ring product 2 in only 10% yield. 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.

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 cyclopane 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).

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). 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 (Table 2, entry 6). 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).

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. 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. Moreover, we have recently found that the stereoechemical outcome of the reaction of related electrophilic gold-carbenoid intermediates depends on the nature of the nucleophile, 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...


**Table 2. Reaction Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>cond$^a$</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<td>R = Me, R$^1$ = R$^2$ = H</td>
<td>9</td>
<td>A</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>R = ac, R$^1$ = R$^2$ = H</td>
<td>11</td>
<td>A</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>R = Ac, R$^1$ = R$^2$ = H</td>
<td>13</td>
<td>A</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>R = Ac, R$^1$ = (CH$_2$)$_2$R, R$^2$ = H</td>
<td>15</td>
<td>A</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>R = Ac, R$^1$ = Me, R$^2$ = H</td>
<td>17</td>
<td>A</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>R = Ac, R$^1$ = Me, R$^2$ = Me</td>
<td>19</td>
<td>B</td>
<td>88</td>
<td>75</td>
</tr>
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<td>7</td>
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<td>C</td>
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<tr>
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<td>R = Ac</td>
<td>23</td>
<td>D</td>
<td>49</td>
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</tr>
<tr>
<td>9</td>
<td>R = Piv</td>
<td>25</td>
<td>D</td>
<td>44</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions; 2.5 mol% catalyst, 5 mol% AgSbF$_6$, MeNO$_2$ [0.1 M]; A = (R)-xyllyl-BINAP(AuCl)$_2$, -25 °C; B = (R)-Difluorophos(AuCl)$_2$, -35 °C; C = (R)-xyllyl-BINAP(AuCl)$_2$; rt; D = (R)-DTBM-Segphos(AuCl)$_2$, rt. $^b$ The absolute stereochemistry was determined by the mandelate method (see Supporting Information).

Table 2 shows the reaction scope of the propargyl ester 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.

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**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**

(2) Yet, L. Chem. Revs. 2000, 100, 2963.

(8) For additional information see the Supporting Information.

(10) For all additional information see the Supporting Information.

The AB- and DE-species of the Au(I)-catalyzed cycloisomerization of propargyl esters were observed in a 1,1-diphenylethene geometry required for an intramolecular reaction. In contrast, when the reaction was conducted in the presence of 1,1-diphenylethene, an intermolecular cyclopropanation reaction occurs selectively to form 27 as the (Z)-olefin isomer.8 In this case, the reaction is operating through gold(I)-carbenoid intermediate B. Taken together, these results suggest that Au(I)-stabilized vinyl carbenoids are fluxional 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. 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.