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Enantioselective Gold(I)-Catalyzed Vinylogous [3 + 2] Cycloaddition between Vinyldiazoacetates and Enol Ethers

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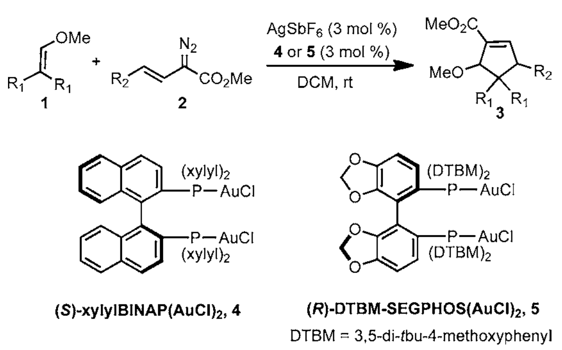
Supporting Information

ABSTRACT: The reaction of vinyldiazoacetates with enol ethers catalyzed by the binuclear gold complex (*R*)-DTBMSegphos(AuCl)$_2$ activated by silver hexafluoroantimonate results in a highly enantioselective [3 + 2] cycloaddition. The [3 + 2] cycloaddition proceeds with dynamic kinetic resolution when the enol ether is a 4-substituted 1-(methoxymethylene)cyclohexane. The reaction is initiated by nucleophilic attack of the vinyl ethers at the vinylogous position of the gold vinylcarbene intermediate.

Dirhodium catalysts have played a pivotal role in the development of the chemistry of metal carbenes derived from diazo compounds.[1] In contrast, the application of gold(I) catalysts to the decomposition of diazo compounds is a relatively unexplored area of research.[2] Activity in this area has increased in recent years, but the vast majority of the work still involves achiral gold catalysts.[3] Recently, we reported the enantioselective cyclopropenation of internal alkynes with aryldiazoacetates[4] using digold(I)−BINAP complexes, such as **4** and **5**.[5] Inspired by the high level of enantioselectivity exhibited in these cyclopropenation reactions, we have begun to explore digold-catalyzed carbene reactions, with a particular emphasis on developing new reactions that do not occur under rhodium catalysis. The focus of our studies has been on the reactions of metal-bound donor/acceptor carbenes because the attenuated reactivity caused by the donor group makes these carbenes highly versatile synthetic intermediates. In this paper we describe the highly enantioselective Au(I)-catalyzed [3 + 2] cycloaddition reaction between enol ethers **1** and vinyldiazoacetates **2** to generate cyclopentenecarboxylates **3** (Scheme 1).

Scheme 1. Digold-Catalyzed [3 + 2] Cycloaddition between Vinyl Ethers and Vinyldiazoacetates



From our studies on metal-bound donor/acceptor carbenes, we have found that the silver and gold carbenes are more reactive than the corresponding rhodium carbenes.[6] They are capable of cyclopropanating and cyclopropenating sterically crowded alkenes and alkynes, which do not react under rhodium catalysis. Furthermore, silver-catalyzed reactions of vinylcarbenes display enhanced electrophilic character at the vinylogous position of the vinylcarbenes.[7] Therefore, we decided to explore gold-catalyzed reactions of vinylcarbenes with the expectation that the enhanced vinylogous reactivity that is likely to occur[3h] would lead to new transformations that had not been observed under rhodium-catalyzed conditions.

A breakthrough in this project was made when we studied the reaction of gold vinylcarbenes with enol ethers. Recently, we reported that the Rh$_2$(*S*-DOSP)$_4$-catalyzed reaction of cyclic enol ether **6** with styryldiazoacetate **7** resulted in a combined C−H insertion/Cope rearrangement (CHCR) affording the vinylogous Mukaiyama aldol-type product **8** in a highly diastereo- and enantioselective fashion (Scheme 2).[8] In contrast, when we conducted the (*R*)-DTBMSegphos(AuCl)$_2$ ((***R***)-**5**)-catalyzed reaction of **6** with **7** an entirely different product was formed. The formal [3 + 2] cycloadduct **9** was obtained in 81% yield with neither C−H insertion nor cyclopropanation products observed (Scheme 2). Furthermore, **9** was formed as a single diastereomer and with a high level of enantioselectivity (88% ee).[9]

Scheme 2. Effect of Catalyst on the Reaction between 6 and 7

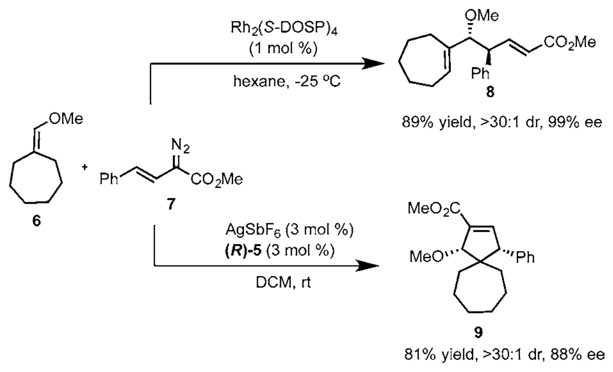


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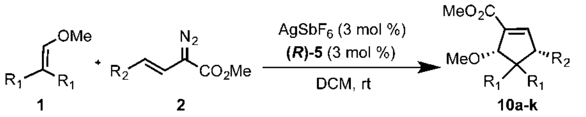
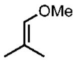
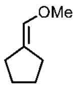
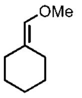
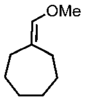
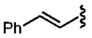
Table 1. Au(I)-Catalyzed Vinylogous [3 + 2] Reaction of Enol Ethers and Various Vinyl Diazoacetates



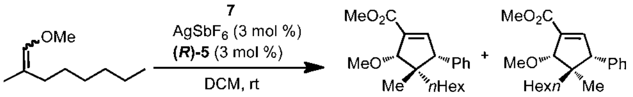
entry[a]	ethers	R_2	product[b]	yield (%)[c]	ee (%)[d]
1		Ph	**10a**	73	92
2		Ph	**10b**	68	90
3		Ph	**10c**	71	90
4		Ph	**10d**	81	88
5		2-Naph	**10e**	77	94
6[e]		p-OMePh	**10f**	79	91
7		m,p-diClPh	**10g**	76	95
8		p-BrPh	**10h**	84	93
9		Me	**10i**	90	91
10		Et	**10j**	84	95
11[e]			**10k**	70	91

[a] Standard reaction conditions: **2** (0.6 mmol, 1.2 equiv) in degassed dichloromethane (8 mL) was added to a 2 mL dichloromethane solution of **1** (0.5 mmol, 1.0 equiv), $AgSbF_6$ (0.015 mmol), and (**R**)-**5** (0.015 mmol) at 23 °C. [b] The dr is >30:1 in all cases. [c] Isolated yield of **10**. [d] Determined by chiral HPLC. [e] (**S**)-**4** was used as catalyst.

The scope and generality of this unusual [3 + 2] cycloaddition was then examined with various trisubstituted enol ethers. Various cyclic and acyclic enol ethers were synthesized *via* a known procedure[8] and subjected to the standard reaction conditions (Table 1). The reaction worked well with both cyclic and acyclic substrates, providing the desired cyclopentene derivatives **10a**−**d** in good yields (68−81%) and excellent enantioselectivity (88−92%). Again, it is noteworthy that the reaction is chemoselective toward the formation of the cyclopentene products. The reaction can also be expanded to different aryl and alkyl vinyldiazoacetates using enol ether **6** as the representative substrate (entries 5−11). The cyclopentene derivatives **10e**−**k** were obtained in good yields (70−90%) and excellent enantioselectivity (91−95% ee).

The study was then extended to the trisubstituted enol ether **11**, in which the two alkyl substituents were different (Scheme 3). The reaction was conducted on a stereoisomeric mixture of *E* and *Z* enol ethers (*ca.* 1:1 ratio). The reaction provided a 1:1 mixture of diastereomers **12** and **13**, in good overall yield and both diastereomers were generated with high levels of asymmetric induction. The relative configuration of each diastereomer was determined by NOE analyses. This result suggests that the gold catalyst does not distinguish between the *E*/*Z* isomers of **11**, but the facial selectivity during the [3 + 2] cycloaddition event of both isomers of **11** is still high.

Scheme 3. Au(I)-Catalyzed Reaction of *E*/*Z* Mixture of 11 and 7



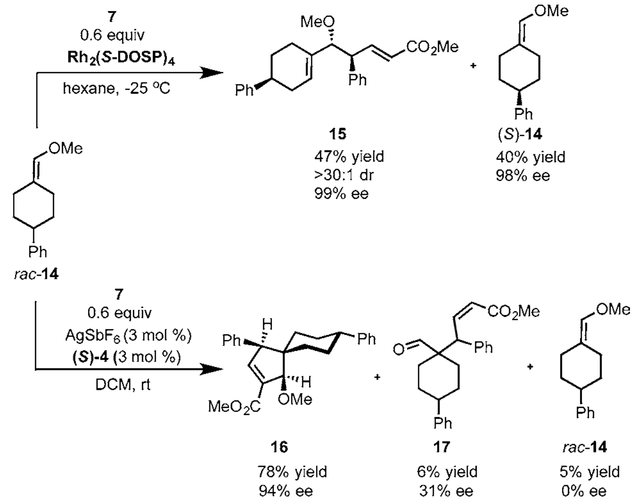
11 *ca.* 1:1 mixture

12 36% yield 90% ee

13 39% yield 96% ee

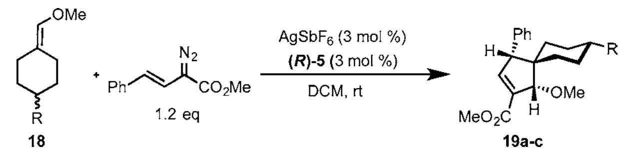
One of the most intriguing substrates for the Au-catalyzed reaction of vinylcarbenes is the 4-substituted 1-(methoxymethylene)cyclohexane (**14**). In the case of the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of the vinyldiazoacetate **7** (0.6 equiv) with **14**, we reported that the CHCR reaction demonstrated exceptional kinetic resolution, generating **15** as a single diastereomer with 99% ee (Scheme 4).[8] The enantioenriched enol ether (**S**)-**14** was recovered in 40% yield and 98% ee. When the reaction was conducted using the gold catalyst (**S**)-**4** a very interesting result was obtained. The [3 + 2] cycloadduct **16** was obtained in 78% yield and 94% ee, but the recovered **14** was racemic. The absolute configuration of **16** was determined by X-ray crystallographic analysis.[10] A minor product, aldehyde **17**, was also formed in the reaction and was isolated in 6% yield and 31% ee. The relative configuration of **17** was not determined. The formation of **16** in good yield and enantioselectivity with the starting material **14** recovered as a racemate suggests that **14** is isomerizing under the reaction conditions. Evidence to support this hypothesis was obtained by exposing (**S**)-**14** (98% ee) to the catalyst mixture for 12 h at room temperature. Under these conditions, (**S**)-**14** partially racemized to material of 43% ee.

Scheme 4. Reaction of Enol Ether 14 and 7 under Rh(II) and Au(I) Catalysis



The observation that the enol ether **14** isomerizes under the reaction conditions indicates that a dynamic kinetic resolution may be feasible. In order to explore this possibility, we conducted a series of reactions in which the enol ether substrate was the limiting reagent (Table 2). Under these conditions, the spirocyclic products **19a**−**c** were produced as single diastereomers in greater than 50% isolated yield (62−70%) and with

Table 2. Dynamic Kinetic Resolution in the Au(I)-Catalyzed Vinylogous [3 + 2] Reaction



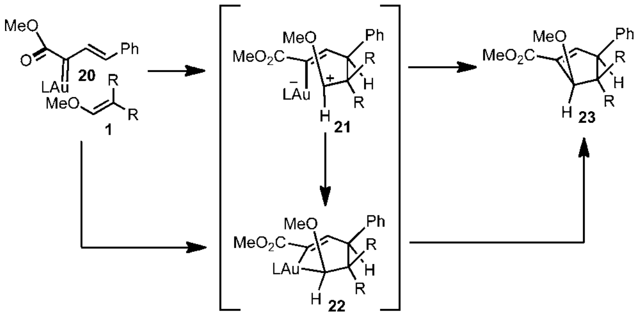
entry[a]	R	product	dr[b]	yield (%)[c]	ee (%)[d]
1	Me	**19a**	>30:1	65	93
2	Ph	**19b**	>30:1	62	93
3	*t*Bu	**19c**	>30:1	70	97

[a] Standard reaction conditions: **7** (0.6 mmol, 1.2 equiv) in degassed dichloromethane (8 mL) was added to a 2 mL dichloromethane solution of enol ether **18** (0.5 mmol, 1.0 equiv), AgSbF$_6$ (0.015 mmol), and (*R*)-**5** (0.015 mmol) at 23 °C. [b] Isolated yield of **19**. [c] The dr was determined from the crude reaction mixture. [d] Determined by chiral HPLC.

excellent enantioselectivity (93−97% ee). The absolute configuration of spirocyclic product **19c** was also confirmed by X-ray crystallographic analysis.[10] Formation of the aldehyde product (analogous to **17**) was minimal in all cases.

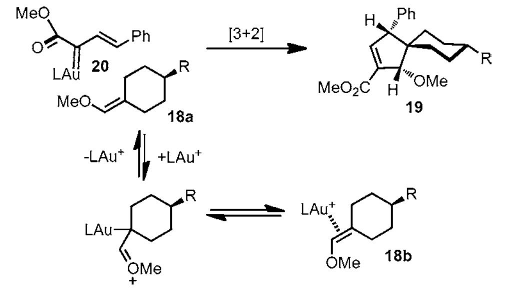
These studies demonstrate that the gold-catalyzed reactions of vinyldiazoacetates with trisubstituted vinyl ethers are very different from the corresponding rhodium-catalyzed reactions. Considering the similarity between silver- and gold-catalyzed reactions, it would be reasonable to assume that the initial attack of the gold carbene **20** is occurring at the vinylogous position of the carbene (Scheme 5). In the case of the silver-catalyzed O−H insertion of vinylcarbenes, the experimental and computational studies suggest that the vinylogous reaction proceeds through the *s*-cis isomer of the silver vinylcarbenes.[7] Vinylogous attack of the vinyl ether **1** on the *s*-cis configuration of the vinylcarbene **20** would generate a zwitterionic intermediate **21**. Alternatively, the reaction could behave like a highly asynchronous [4 + 2] cycloaddition generating a metallocyclohexene **22**. The zwitterionic intermediate has the correct geometry to cyclize to the metallocyclohexane or close directly to the cyclopentene **23**. Reductive elimination of the metallocyclohexene **22** would be an alternative way of generating **23**. If the reaction does involve zwitterionic intermediates, the high diastereo- and enantioselectivity suggest that the cyclization event is very fast, as otherwise scrambling of the stereocontrol would occur.

Scheme 5. Proposed Mechanism of Au(I)-Catalyzed [3 + 2] Cycloaddition



The mechanism for the dynamic resolution can be rationalized as illustrated in Scheme 6. The gold catalyst is a sufficiently strong Lewis acid to cause equilibration of the enol ether **18**.[11] Only the isomer **18a** is matched for reaction at the *re* face of the carbene **20** leading to the enantioselective formation of **19**. Even though a number of examples of kinetic resolutions using carbene intermediates are known,[12−14] as far as we are aware, this is the first carbene example of dynamic kinetic resolution.

Scheme 6. Dynamic Kinetic Resolution Model



We have developed the highly enantioselective Au(I)-catalyzed vinylogous [3 + 2] cycloaddition of enol ethers and vinyldiazoacetates. This reaction accesses highly functionalized cyclopentene derivatives possessing three stereocenters constructed in a single step. Moreover, dynamic kinetic resolution was achieved when cyclic enol ethers bearing axial substituents were used as substrates for the reaction. This report constitutes the first example of dynamic kinetic resolution in metal carbenoid chemistry. This work illustrates the synthetic potential of the growing field of asymmetric gold-catalyzed carbene transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic details and spectral data. 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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