

Formal Intermolecular [2 + 2] Cycloaddition Reaction of Alleneamides with Alkenes via Gold Catalysis

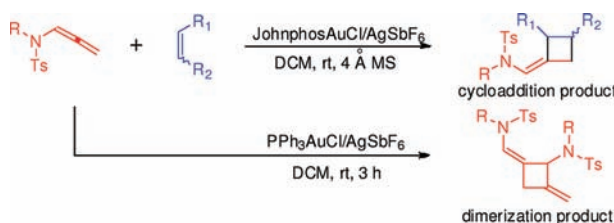
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ABSTRACT



An efficient method was developed to construct the densely functionalized cyclobutane adducts through formal intermolecular cycloaddition of alleneamides with electron-rich olefins via gold catalysis, in which vinyl ethers/amides and electron-rich styrenes worked very well. In addition, a series of alleneamide dimerization products were prepared from the same alleneamide substrates.

[2 + 2] Cycloaddition presents a straightforward method for the synthesis of cyclobutanes and their derivatives. However, thermal [2 + 2] cycloaddition of two double bonds is limited to some special substrates.¹ On the other hand, photochemical [2 + 2] transformation is usually only

efficient in an intramolecular domain.^{2,3} Considering the importance of this cyclobutane skeleton in natural products⁴ and in organic synthesis,⁵ exploring metal, especially transition metal, catalyzed intra- or intermolecular [2 + 2] cycloaddition reactions would be of significant synthetic utility.⁶

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Scheme 1. Gold Complexed Allene



Gold salts have recently been demonstrated to be exceptional reagents for the activation of C–C multiple bonds.⁷ As shown in Scheme 1, the reactivity of gold–allene complexes **I** closely resembled that of the Au–C bond functionalized allylic cation **II** (Scheme 1), which thereby led to the realization of the gold catalyzed intramolecular cycloaddition of the allenes with alkenes or dialkenes, to give various [2 + 2],⁸ [2 + 3],⁹ [4 + 2],¹⁰ and [4 + 3]^{10b,11} cycloadducts.¹² However, extending this strategy to an intermolecular process remains less explored.¹³ We herein will report the gold catalyzed intermolecular [2 + 2] cycloaddition of allene sulfonamides with electron-rich olefins, to provide an efficient new approach to the multifunctional cyclobutane derivatives. In addition, we also prepared a series of allene sulfonamide dimerization products.

Inspired by the gold catalyzed intermolecular reactions of allenes with amines,¹⁴ alcohols,¹⁵ and electron-rich aryl groups,¹⁶ we reasoned that the enhanced olefin nucleophilicity might facilitate the suggested intermolecular [2 + 2] process. Electron-rich vinyl ether **a** was thus employed for the initial investigation. At first, several allenes with different functionalities were investigated (Scheme 2, eq 1). No reaction was found for alkyl allene **1**, probably due to its low reactivity. Alleneamides **2**, **3**, and **4** were tested.

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Scheme 2. Allene Screening for Gold Catalyzed [2 + 2] Cycloaddition Reaction

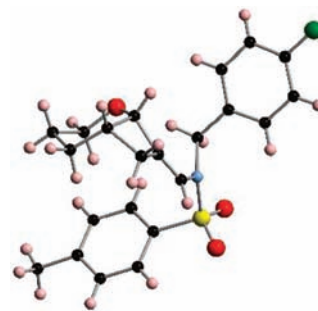
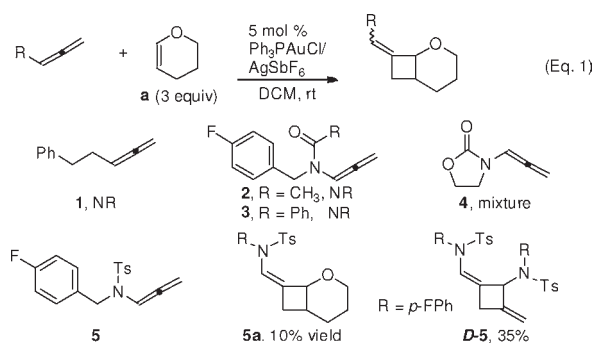


Figure 1. X-ray chromatograph of compound **5a**.

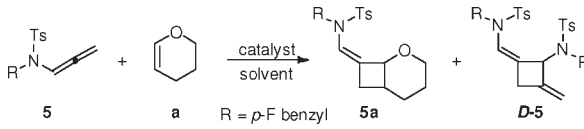
2 and **3** gave no reactions, while 2-oxazolidinone alleneamide **4** afforded an inseparable mixture.¹⁶ Recognizing that amide groups might coordinate and deactivate the gold catalyst, alleneamide **5**, which contains a low Lewis basic sulfonamide group, was then explored.¹⁷ To our delight, the reaction of **5** with vinyl ether **a** gave vinyl cyclobutane **5a** in 10% yield, and dimerization product **D-5** in 35% yield. The structure of **5a**, as shown in Figure 1, was identified to be a vinylamide containing 2-oxabicyclo[4.2.0]octane by its X-ray chromatograph, in which vinylamine oriented toward the oxygen atom selectively.¹⁸

Next, reaction optimizations were performed to improve **5a**'s yield. Addition of 4 Å molecular sieve to remove the residual moisture and lowering the reaction temperature enhanced **5a**'s yield (Table 1, entry 2, 80%).

In silver salt screening experiments, Ph₃PAuCl/AgSbF₆ performed better than other silver combinations (Table 1,

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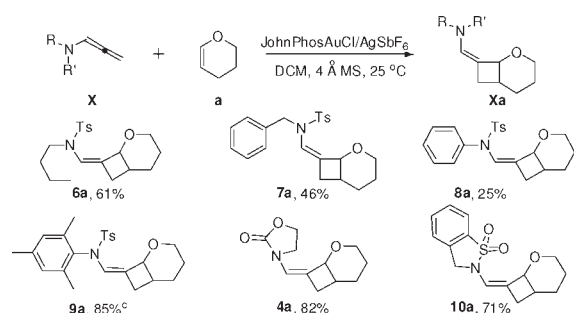
(18) CCDC 838102 contains the supplementary crystallographic data for compound **5a**; CCDC 838101 contains the supplementary crystallographic data for compound **D-5**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Condition Optimization for the Reaction of **5** with **a**^a


	catalyst (%)	soln/temp (°C) /time (h)	yield ^b 5a/D-5 (%)
1 ^c	Ph ₃ PAuCl/AgSbF ₆ (5)	DCM/rt/2	10/35
2	Ph ₃ PAuCl/AgSbF ₆ (5)	DCM/-10/2	80/6
3	Ph ₃ PAuCl/AgBF ₄ (5)	DCM/-10/2	45/10
4	Ph ₃ PAuCl/AgOTf (5)	DCM/-10/2	27/5
5	Ph ₃ PAuCl/AgPF ₆ (5)	DCM/-10/2	55/trace
6	Ph ₃ PAuCl/AgNTf ₂ (5)	DCM/-10/2	70/15
7	IprAuCl/AgSbF ₆ (5)	DCM/-10/2	71/0
8	SIPrAuCl/AgSbF ₆ (5)	DCM/-10/2	70/0
9	(PhO) ₃ PAuCl/AgSbF ₆ (5)	DCM/-10/2	NR
10	JohnphosAuCl/AgSbF ₆ (5)	DCM/-10/2	85/0
11	JohnphosAuCl/AgSbF ₆ (5)	DCM/25/2	87/0
12	JohnphosAuCl/AgSbF ₆ (2)	DCM/25/12	86/0
13 ^d	JohnphosAuCl/AgSbF ₆ (2)	DCM/25/12	81/0
14	JohnphosAuCl/AgSbF ₆ (2)	DCE/25/2	75/0
15	JohnphosAuCl/AgSbF ₆ (2)	Toluene/25/24	66/0
16	JohnphosAuCl/AgSbF ₆ (2)	THF/60/12	NR
17	JohnphosAuCl (2)	DCM/25/2	NR
18	AgSbF ₆ (2)	DCM/25/2	NR
19 ^e	Ph ₃ PAuCl/AgSbF ₆ (2)	DCM/25/3	0/90

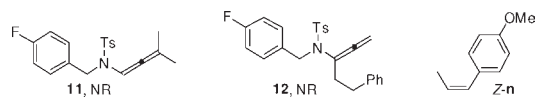
^aUnless noted, all reactions were carried out at 0.1 mmol scale in 2 mL of solvent with the addition of 5 mol % catalyst and 100 mg of 4 Å MS (5/a = 1/3). ^bIsolated yields. ^cNo 4 Å MS was added. ^d2 equiv of compound **a** were added. ^eNo compound **a** was added.

entries 3–6). The catalyst's ligands were then evaluated. IprAuCl and SIPrAuCl showed moderate activities, while (PhO)₃PAuCl was totally inactive (Table 1, entries 7–9). When JohnphosAuCl was utilized, **5a**'s yield was improved to 87%, even at an elevated temperature (Table 1, entries 10–11). 2 mol % of JohnphosAuCl also gave **5a** in 86% yield in 12 h (Table 1, entry 12). Addition of 2 equiv of vinyl ether **a** led to a slight yield loss (Table 1, entry 13). Solvent optimization proved DCM to be the best reaction

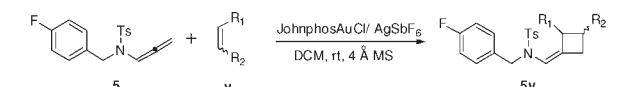
Scheme 3. [2 + 2] Cycloaddition Reaction of Alleneamides with Vinyl Ether **a**^{a,b}

^aUnless noted, all reactions were carried out at 0.1 mmol scale in 2 mL of solvent with the addition of 2 mol % catalyst and 100 mg of 4 Å MS (x/a = 1/3). ^bIsolated yields.

medium (Table 1, entries 14–16). In the control experiments, employing JohnphosAuCl and AgSbF₆ separately gave no desired products (Table 1, entries 17–18). When **5** was treated with 2 mol % of Ph₃PAuCl/AgSbF₆ as a sole reactant, dimerization product **D-5** was obtained in 90% yield.

Scheme 4. Unsuccessful Substrates for [2 + 2] Cycloaddition

We then turned to investigating the substrate scope. A series of alleneamides with different substitution patterns were tested. Butyl substituted alleneamide **6** gave **6a** in moderate yield, while its benzyl and phenyl analogs **7** and **8** afforded the desired products in relatively low yields (Scheme 3).¹⁹ When trimethyl phenyl alleneamide **9** was used as the reactant, cyclobutane adduct **9a** was obtained in 85% yield. Under the optimized conditions, 2-oxazolidinone alleneamide **4** was also tested, which provided **4a** in 82% yield. Similarly, 2,3-dihydrobenzo[*d*]isothiazole **1**, 1-dioxide substituted cyclobutane product **10a** was obtained in 71% yield (Scheme 3). However, the reactions of vinyl ether **a** with alleneamides **11** and **12** gave no desired products even at a high temperature, possibly owing to the improved steric hindrance (Scheme 4).

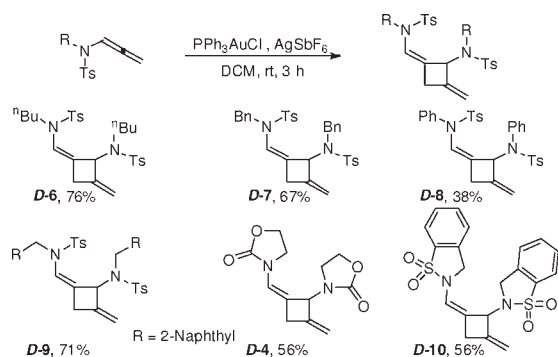
Table 2. [2 + 2] Cycloaddition of Alleneamide **5** with Different Alkenes^{a,b}


entry	substrate	product/yield(%)	entry	substrate	product/yield(%)
1	a , X = O	5a , X = O, 87%	9 ^c	i (Z/E = 1/2)	5i , 84% (syn/anti = 1/2)
2	b , X = NBoc	5b , X = NBoc, 78%			
3	c , X = O	5c , X = O, 89%	10	j , R = EtO	5j , R = EtO, 83%
4	d , X = NBoc	5d , X = NBoc, 87%	11	k , R = CH ₃	5k , R = CH ₃ , 63%
			12	m , R = ^t Bu	5m , R = ^t Bu, 68%
5 ^c	e	5e , 79% (anti/syn = 1.8/1)			
6	f , R = OEt	5f , R = OEt, 73%	13	E-n	trans-5n , 85%
7	g , R = O ^t Bu	5g , R = O ^t Bu, 80%			
8	h	5h , 69%	14	o	5o , 80%

^aUnless noted, all reactions were carried out at 0.1 mmol scale in 2 mL of solvent with the addition of 5 mol % catalyst and 100 mg of 4 Å MS (5/N = 1/3). ^bIsolated yields. ^cThe ratio was determined by ¹H NMR data.

Many other mono- and disubstituted olefins were also examined. As shown in Table 2, cyclic vinyl ethers worked very well. 2,3-Dihydrofuran **c** gave **5c** in 89% yield, while 2-methoxy-3,4-dihydro-2*H*-pyran **e** afforded **5e** in 79% yield (Table 2, entries 3, 5). Two cyclic vinyl amines were explored, which afforded **5b** and **5d** in good yields (Table 2, entries 2, 4). We then investigated the linear vinyl ether's reactions. The reactions of **5** with ethoxy ethene **f** and butoxy ethene **g** occurred, giving **5f** and **5g** in 73% and 80% yields (Table 2, entries 6–7). The reaction of 1,1-disubstituted vinyl ether **h** gave **5h** in 69% yield, while 1,2-disubstituted ether **i** afforded **5i** in 84% yield (Table 2, entries 8–9). Although alkyl olefins and electron-poor styrenes did not work in this transformation, styrenes bearing electron-donating groups, such as ethoxy, methyl, *tert*-butyl, etc., can be employed in this reaction and gave the desired products in moderate to good yields (Table 2, entries 10–12). Disubstituted (*E*)-1-(*p*-methoxyphenyl)-1-propene *E*-**n** was then tested, which provided polyfunctional cyclobutane derivative *trans*-**5n** in good yield (Table 2, entry 13). However, the reaction of *Z*-**n** gave no desired product (Scheme 4). To determine the *Z*-olefin's stereochemistry, deuterated substrate **o** was investigated. It was found that deuterium ratio H_a/H_b in **5o** was lower than that in substrate **o** (Table 2, entry 14).

Scheme 5. Gold Catalyzed Dimerization of Alleneamides^{a,b}

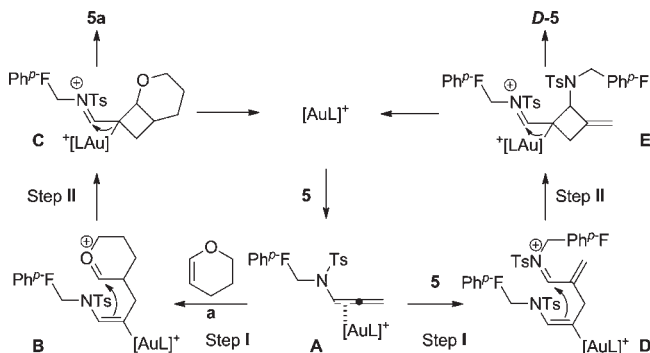


^a Unless noted, all reactions were carried out at 0.1 mmol scale in 2 mL solvent with the addition of 5 mol % catalyst and 100 mg 4 Å MS.
^b Isolated yields.

Using these alleneamide substrates, a series of dimerization products were also prepared. As shown in Scheme 5, butyl and benzyl substituted alleneamide **6** and **7** gave **D-6** and **D-7** in moderate yields, while phenyl analog **8** afforded **D-8** in low yield. Steric 2-naphthalene methyl alleneamide **9** provided cyclobutane adduct **D-9** in 71% yield. 2-Oxazolidinone alleneamide **4** was also tested, which gave **D-4** in 56% yield. Similarly, 2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide substituted alleneamide **10** provided **D-10** in 73% yield (Scheme 5).

A plausible mechanism was then proposed. As shown in Scheme 6, Complexation of the cationic gold catalyst with

Scheme 6. A Plausible Mechanism for Gold Catalyzed [2 + 2] Cycloaddition Reaction and the Dimerization Reaction of Alleneamides



alleneamide **5** generated intermediate **A**.²⁰ Trapping **A** with vinyl ether **a** afforded intermediate **B** (step I), which underwent intramolecular cyclization through nucleophilic addition of vinylamine onto the ketonium carbon (step II), giving cyclobutane iminium intermediate **C**. Deauration via elimination then provided formal [2 + 2] cycloaddition product **5a** and regenerated the cationic gold catalyst. Isomerization occurred in the reaction of a *Z*-styrene substrate (Table 2, entry 14). In intermediate **B** and **C**, the steric hindrance between the sulfonamide group and the gold catalyst determined the configuration of the formed vinylamine in **5**. Similarly, in the absence of olefin reactants, trapping **A** with the second alleneamide molecule **5**, followed by intramolecular cyclization and deauration, would provide dimerization product **D-5** and regenerate the gold catalyst.

In summary, we have developed an efficient method to construct the densely functionalized cyclobutane adducts through the formal intermolecular cycloaddition reactions of alleneamides with electron-rich olefins via gold catalysis. Vinyl ether, amine, and electron-rich styrenes reacted smoothly with alleneamides at rt. Importantly, a series of alleneamide dimerization products were also prepared from these alleneamide substrates in the absence of alkenes. Efforts to extend this reaction and broaden its application are still underway in this laboratory.

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Supporting Information Available. Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(19) The low **7** and **8** yields were due to their Friedel–Crafts type intramolecular cyclization reaction.

(20) Two types of complexation have been suggested, in which coordination of the gold catalyst to the double bond of the vinylamide was presumed to be favorable. See ref 16.