Sulfonium Ylide Chemistry

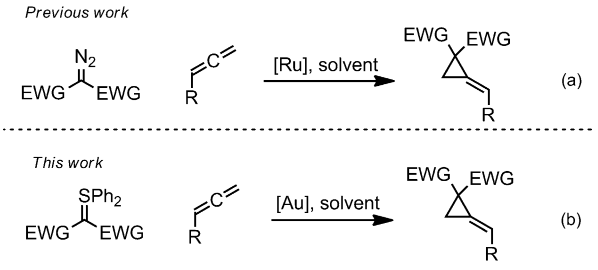
Gold-Catalyzed Intermolecular Synthesis of Alkylidenecyclopropanes through Catalytic Allene Activation

Juliette Sabbatani,[a] Xueliang Huang,[b] Luís F. Veiros,[c] and Nuno Maulide*[a]

Abstract: A stereoselective gold(I)-catalyzed intermolecular cyclopropanation of allenamides with stabilized sulfonium ylides is reported. This transformation enables the direct synthesis of diacceptor alkylidenecyclopropanes and proceeds under very mild conditions through allene activation.

Methylenecyclopropanes or alkylidenecyclopropanes (MCPs or ACPs) are stable compounds that display a high level of ring-strain, endowing them with remarkable chemical reactivity.[1] In particular, ACPs bearing electron-withdrawing groups are prime candidates for engaging in various ionic ring-opening processes, as their electron density distribution favors the formation of negatively charged open intermediates. The versatility of this type of substrate has been exploited in several reactions such as cycloisomerizations,[2] ring-opening rearrangements,[3] cycloadditions,[4] and iodolactonizations.[2] Hence, the development of alternative approaches to their synthesis has been investigated over the last decade. The predominant strategy in this field relies on the cyclopropanation of allenes by in situ generated carbenes; these are most typically formed by decomposition of diazo compounds, either by the action of rhodium catalysts or through photochemical irradiation (Scheme 1a).[3,4] Although this is an efficient synthetic strategy, the known hazards associated with the use of diazo compounds somewhat mitigate its synthetic usefulness, particularly when large-scale applications are considered.

We recently developed a new methodology to directly access stabilized sulfonium ylides in a single step, by a process termed ylide transfer.[5] Those compounds display unique reactivity and electronic features, lending themselves to interesting applications featuring gold catalysis,[6,7] including an unusual *intramolecular* olefin cyclopropanation through catalytic olefin activation.[8] Herein, we describe an *intermolecular* gold-catalyzed synthesis of alkylidenecyclopropanes employing sulfonium ylides and activated allenes,[9] as well as mechanistic studies on this transformation (Scheme 1b).



Scheme 1. Alternative methods for the preparation of alkylidenecyclopropanes.

Since stabilized sulfonium ylides are competent nucleophiles towards gold-activated alkenes[7] and alkynes,[6] we became interested in exploring their behavior regarding allenes. Initial experiments involved reacting ylide **1** with allenamide **2**[10,11] in the presence of 5 mol% of chloro(triphenylphosphine)gold(I) and silver(I) hexafluoroantimonate in chloroform (0.4 M) at 23 °C. The desired product was obtained in an encouraging 51% yield (Table 1, entry 1). Several different co-catalysts were screened, ranging from diverse silver salts to copper(II) triflate (entries 2 to 5).[13] Silver(I) tosylate proved to be the most effective salt from those tested (entry 5), affording the cyclopropanation product in 75% yield. Different phosphine and phosphite ligands were then examined, with triphenylphosphine proving to be superior (entries 6 to 8). A solvent screening confirmed that dichloromethane is the most effective medium for this transformation. Indeed, the reaction becomes significantly slower in solvents such as THF or toluene (entries 10 and 11). Control experiments also revealed that the conjunction of silver(I) and gold(I) species is indispensable for success (entries 12 and 13). This reaction could also be performed in a 1 mmol scale (entry 14), and interestingly did not require strictly anhydrous conditions, affording similar yields even when the reaction vessel was open to air (entry 15).

Using the conditions newly found, a variety of sulfonium ylides were evaluated as possible substrates in the intermolecular cyclopropanation of activated allenes. As shown in Scheme 2, various functional groups are tolerated, and the reactions typically reach full conversion in less than 2 h at room

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[a] J. Sabbatani, Prof. Dr. N. Maulide
Faculty of Chemistry, Institute of Organic Chemistry
University of Vienna
Währinger Strasse 38, 1090 Vienna (Austria)
E-mail: nuno.maulide@univie.ac.at

[b] Prof. Dr. X. Huang
State Key Laboratory of Structural Chemistry
Fujian Institute of Research on the Structure of Matter
Chinese Academy of Sciences
Yangqiao West Road 155#, Fuzhou, Fujian 350002 (P. R. China)

[c] Prof. Dr. L. F. Veiros
Centro de Química Estrutural
Instituto Superior Técnico, Universidade de Lisboa
Av. Rovisco Pais 1, 1049-001 Lisbon (Portugal)

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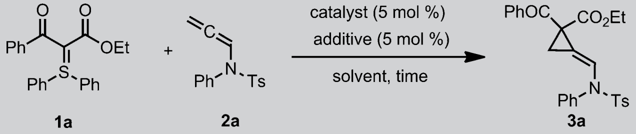
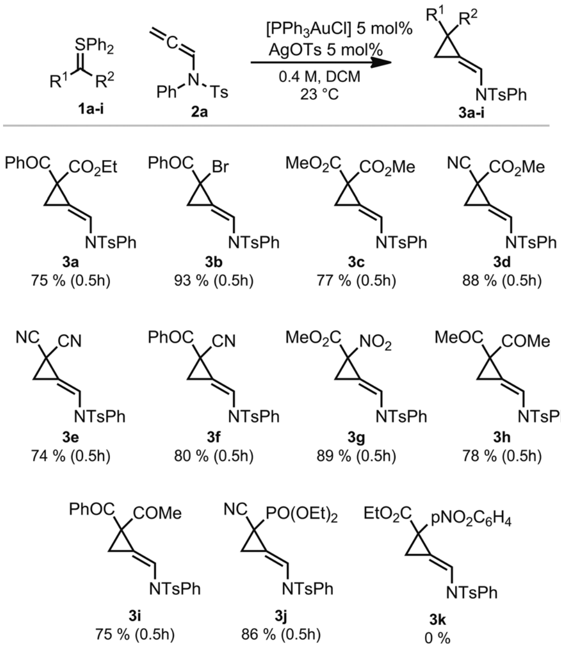
Table 1. Optimization of experimental conditions using the reaction between **1** and **2** as a model system.[a]



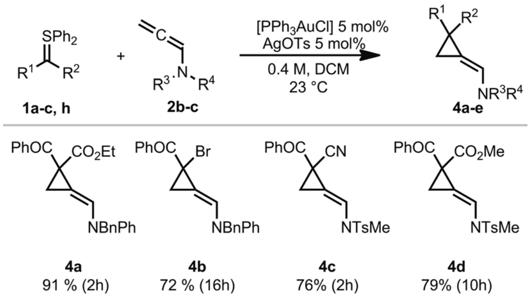
Entry	Solvent	Catalyst/Additive	Time [h]	Yield [%]
1	CH_2Cl_2	$[PPh_3AuCl]/AgSbF_6$	0.5	51
2	CH_2Cl_2	$[PPh_3AuCl]/AgNTf_2$	0.5	45
3	CH_2Cl_2	$[PPh_3AuCl]/AgOTf$	0.5	62
4	CH_2Cl_2	$[PPh_3AuCl]/Cu(OTf)_2$	24	-
5	CH_2Cl_2	$[PPh_3AuCl]/AgOTs$	0.5	75
6	CH_2Cl_2	$[(4\text{-}CF_3C_6H_4)PAuCl]/AgOTs$	1	64
7	CH_2Cl_2	$[(2,6\text{-}t\text{BuC}_6H_3O)PAuCl]/AgOTs$	2	43
8	CH_2Cl_2	$[Cy_3PAuCl]/AgOTs$	16	46
9	$CHCl_3$	$[PPh_3AuCl]/AgOTs$	16	55
10	THF	$[PPh_3AuCl]/AgOTs$	16	12
11	toluene	$[PPh_3AuCl]/AgOTs$	16	22
12	CH_2Cl_2	$[PPh_3AuCl]$	24	–
13	CH_2Cl_2	AgOTs	24	–
14[b]	CH_2Cl_2	$[PPh_3AuCl]/AgOTs$	0.5	75
15[c]	CH_2Cl_2	$[PPh_3AuCl]/AgOTs$	0.5	75

[a] Reactions were carried out under argon in a Schlenk tube, in a 0.10 mmol scale of **1** and **2** using 5 mol% of catalyst in 0.25 mL of solvent at 23 °C, the yield was determined by ^1H NMR spectroscopy of the crude reaction mixture. [b] The reaction was carried out in a 1 mmol scale. [c] The reaction was carried out open to air.



Scheme 2. Scope of the intermolecular gold-catalyzed cyclopropanation.

temperature. The ylide derived from α-bromoacetophenone afforded the halogenated product **3 b** in 93% yield. Symmetrical ylides were viable substrates, including those derived from malononitrile (**1 e**), dimethylmalonate (**1 c**), or acetylacetone (**1 h**). Additionally, ylides bearing diverse electron-withdrawing moieties were also tolerated such as cyanoesters (**1 d**), ketonitriles (**1 f**), or nitroesters (**1 g**).



Scheme 3. Allenamide scope of the intermolecular gold-catalyzed cyclopropanation.

Furthermore, the allenamide substituents could also be varied to some extent as shown in Scheme 3. Therefore, alkyl and aryl moieties could be tolerated on nitrogen.

The exclusive *E*-geometry of the exocyclic double bond of the products was assigned by ^1H NMR analysis. Indeed, a NOE effect was observed between the methylene hydrogens of the three-membered ring and the aromatic protons of the tosyl group. Unambiguous structural determination was obtained upon single-crystal X-ray analysis of the product **3 d**, as depicted in Figure 1.

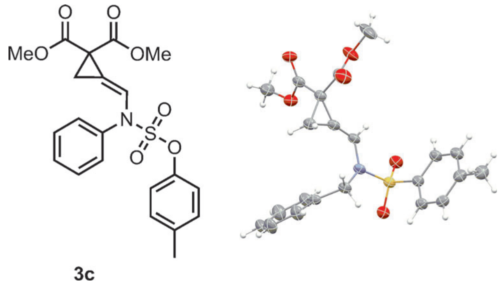
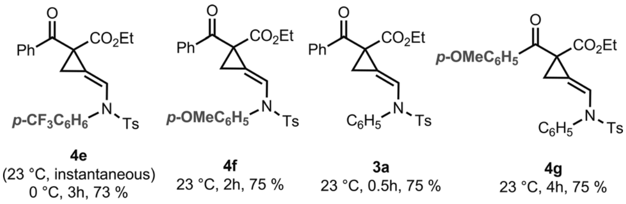


Figure 1. X-ray structure of alkylidenecyclopropane **3 c**.

An additional experiment was carried out to qualitatively study the influence of electronic factors on the reaction rate (Scheme 4). When an allenamide carrying an electron-withdrawing group on nitrogen was employed, the reaction rate was markedly accelerated: complete conversion was virtually instantaneous upon mixing the reagents at 23 °C and required only 3 h at 0 °C (**4 e**). In sharp contrast, an allene bearing an electron-rich arene on nitrogen slowed down the reaction (**4 f**).



Scheme 4. Qualitative influence of electronic properties of the reactants on the reaction rate.

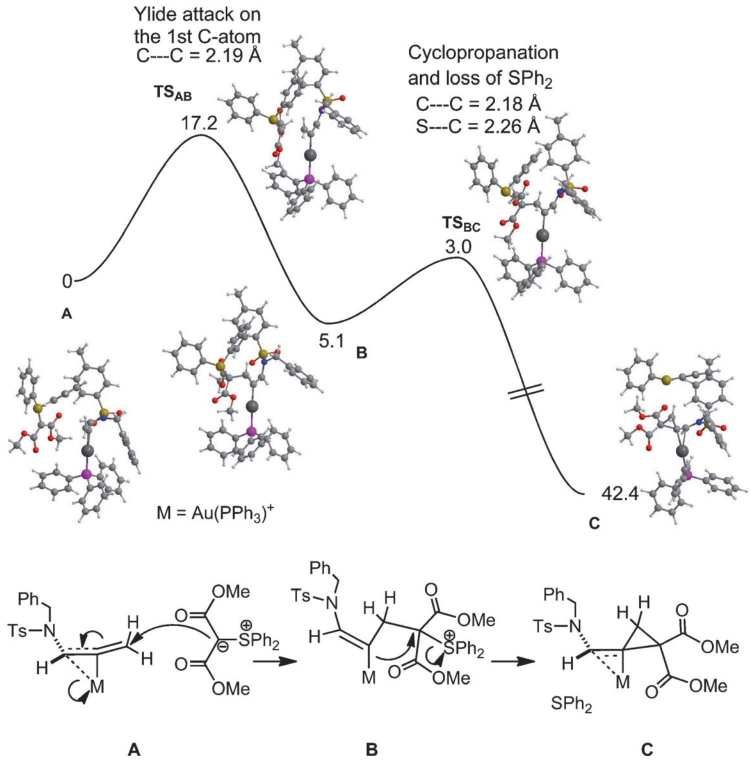


Figure 2. Mechanism and free energy profile (kcal mol^{-1}) calculated by DFT for the gold-catalyzed intermolecular cyclopropanation of sulfonium ylides and allenes.

For comparison, full conversion to **4 f** required 2 h, whereas the analogous allenamide with an unsubstituted aryl ring (**3 a**) only needed 30 min. The use of a sulfur ylide containing a *p*-methoxyphenyl ketone (**4 g**) also markedly slowed down the cyclopropanation process.

The mechanism of this intermolecular alkylidenecyclopropanation was studied by exploratory DFT calculations,[12] using the reaction of the dimethylmalonate ylide (**1 c**) as a case study (Figure 2). The reaction starts with activation of the allene C=C bond through π-coordination to the gold catalyst, as shown in intermediate **A**. From **A**, intermolecular attack of the ylidic carbon atom on the terminal allene C atom results in the gold–vinyl complex **B**. In the subsequent step, loss of SPh$_2$ and nucleophilic attack of the metallic C-sp^2 back onto the original ylidic carbon leads to the formation of complex **C**. Finally, from **C**, ligand exchange with release of the product and addition of a new molecule of allene regenerates the π-complex **A**, thus closing the catalytic cycle in a practically thermoneutral step ($\Delta G = 0.9$ kcal mol^{-1}). Stereochemical constraints force the two consecutive C–C bond formation steps to occur as far away as possible from the N atom and from its bulky substituents, leading to exclusive formation of the *E* isomer of the product. All steps of the mechanism are thermodynamically favorable (Figure 2) and the rate-limiting step is the first one, that is, nucleophilic attack from the ylide to coordinated allene. This mechanism is also consistent with the observed rate enhancement of electron-poor allenamides depicted in Scheme 4, as a more electrophilic complex **A** should lead to a faster nucleophilic attack from the sulfur ylide. However, it provides no explanation for the rate decrease observed in the formation of **4 g** (with the electron-richer ylide). That result suggests that ylide nucleophilicity is not a determining factor for the reaction rate.

In summary, we have developed a gold-catalyzed intermolecular methylenecyclopropanation of allenes with sulfonium ylides. This process allows a direct access to functionalized methylenecyclopropanes and employs stable, readily available and easily handled sulfur ylide substrates, thus providing an interesting and safe alternative to diazo derivatives. The methylenecyclopropane products are formed in good yields and with remarkable *E*-double bond selectivity. Mechanistic studies supported by DFT calculations support a methylenecyclopropanation proceeding by allene activation, in contrast to the usual in situ generated metallocarbene pathways.

Experimental Section

General procedure for the methylenecyclopropanation

A dry Schlenk tube was charged with chloro(triphenylphosphine)gold(I) (0.005 mmol) and silver(I) *p*-toluenesulfonate (0.005 mmol). The resulting mixture was dissolved in dry CH_2Cl_2 (0.25 mL) and stirred at 23 °C. Then ylide (0.100 mmol) and allene (0.100 mmol) were added and the reaction mixture was stirred at 23 °C until complete conversion (as monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel with Hexane/EtOAc as eluent.

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Keywords: alkylidenecyclopropanes · allenes · catalysis · gold · sulfonium ylides

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COMMUNICATION

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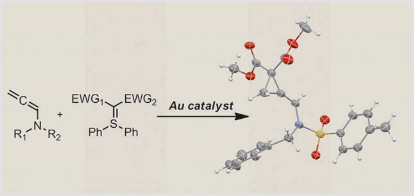

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