Gold(I)-Catalyzed Intermolecular [2+2] Cycloadditions between Allenamides and Alkenes

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Gold(I)-catalyzed intermolecular (2 + 2) cycloadditions between allenamides and alkenes

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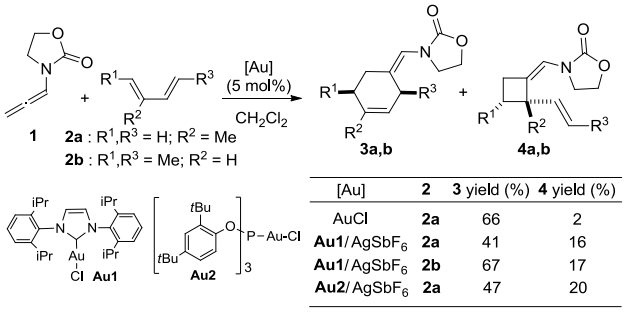
Abstract. 3-(Propa-1,2-dien-1-yl)oxazolidin-2-one works as an efficient two-carbon partner in a variety of intermolecular (2 + 2) gold-catalyzed cycloadditions to alkenes. The transformation represents a simple and practical entry to highly substituted cyclobutane derivatives and take place with complete regio- and stereocontrol.

Keywords: Gold, Allenamides, Cycloaddition, Enamides, cyclobutanes.

Along the last decade, homogeneous gold (I or III) catalysis has experienced an extraordinary development.[1] The singular characteristics of gold complexes, such as their high carbophilicity and low propensity to participate in typical metal redox processes, has allowed the development of a variety of powerful and unique transformations. Particularly relevant in terms of versatility and synthetic potential are the cycloadditions between π-unsaturated systems and allenes.[2] Indeed, a variety of new gold-catalyzed intramolecular (4 + 3) and (4 + 2) cycloadditions of allenes and dienes,[3,4] as well as (3 + 2) and (2 + 2) annulations to alkenes,[5,6] have been recently developed.

In contrast to these intramolecular cases, more challenging intermolecular cycloadditions are extremely scarce.[7,8] In this context, we recently disclosed the first gold-catalyzed intermolecular cycloaddition of non-activated 1,3-dienes (4C) and allenamides (2C),[7a] a type of allenic scaffold which is particularly versatile.[9] This (4 + 2) cycloaddition takes place with good yield and high selectivity using AuCl or the cationic gold(I) complex **Au1**/$AgSbF_6$ as catalysts. However, in a number of cases, in addition to the (4 + 2) adducts (**3a,b**), we also observed cyclobutane side products arising from a competitive (2 + 2) cycloaddition between the allene and one of the carbon-carbon double bonds of the diene (**4a,b**, Scheme 1).[10]



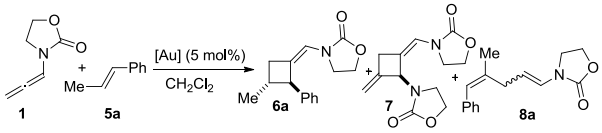
[Au]	2	3 yield (%)	4 yield (%)
AuCl	**2a**	66	2
Au1/$AgSbF_6$	**2a**	41	16
Au1/$AgSbF_6$	**2b**	67	17
Au2/$AgSbF_6$	**2a**	47	20

Scheme 1. Previously reported (4 + 2) cycloadditions of allenamides and dienes. Isolation of (2 + 2) side adducts.

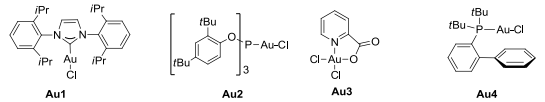
On these bases, and considering the synthetic and medicinal relevance of the cyclobutane framework,[11] we decided to specifically pursue the development of a gold-catalyzed intermolecular (2 + 2) cycloaddition.[12] Herein, we demonstrate that the allenamide **1** participates in a variety of (2 + 2) cycloadditions with different type of alkenes, in particular with enamides and styrene derivatives, to provide excellent yields of (2 + 2) adducts of type **6**, with complete regio-, chemo- and stereoselectivity. Our technology represents a significant addition to the armoury of catalytic cycloaddition methods and provides a particularly practical, powerful and versatile manner to construct highly functionalized cyclobutanes.

In order to assess the viability of a robust and selective (2 + 2) process, we decided to check reaction conditions using as cycloaddition partners the allenamide **1** and a challenging 1,2-disubstituted alkene, namely *trans*-methylstyrene **5a** (Table 1). Unfortunately, using the optimal conditions developed for the (4 + 2) cycloaddition, we observed the formation of a relatively complex mixture of products (Table 1, entries 1-2). Nonetheless, in this mixture we could identify traces of the desired (2 + 2) adduct **6a**, together with the homodimer **7** and the acyclic hydroalkenylation product **8a**.[13] The picolinic acid gold(III) derivative **Au3** or the biaryl phosphine-based catalyst **Au4**/$AgSbF_6$, also failed to give the desired adduct, but selectively produced the allene homodimer **7** in 64% and 34% yield, respectively (Table 1, entries 3-4).[14] Conversely, the π-acidic cationic phosphite gold(I) catalyst **Au2**/$AgSbF_6$ selectively provided the desired (2 + 2) cycloadduct **6a** in a moderate 51% yield (Table 1, entry 5). Gratifyingly, running the reaction in presence of 4Å molecular sieves, and adding the allenamide to the reaction mixture over a period of one hour, led to a significant increase in the efficiency of the process, which now provided **6a** in a good 80% yield (Table 1, entry 6). Moreover, the catalyst loading could be reduced without affecting the rate and efficiency of the reaction (Table 1, entry 7). It is important to note that the cycloaddition process took place with complete selectivity, since no other regio- or stereoisomers could be detected by ^{1}H-NMR analysis of the crude reaction mixtures.

Table 1. Preliminary Screening of catalytic activity between **1** and **5a**.[a]



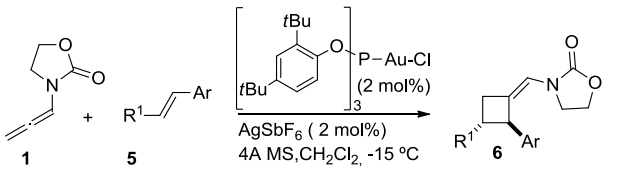
Entry	[Au]	Temp (°C)	**6a** (% yield)	**7** (% yield)	**8a** (% yield)
1	AuCl	rt	-	-	-
2	**Au1**/$AgSbF_6$	-15°C	-	-	-
3	**Au3**	rt	4	64	8
4	**Au4**/$AgSbF_6$		5	34	0
5	**Au2**/$AgSbF_6$	-15°C	51	0	0
6[b]	**Au2**/$AgSbF_6$	-15°C	80	0	0
7[b,c]	**Au2**/$AgSbF_6$	-15°C	79	0	0

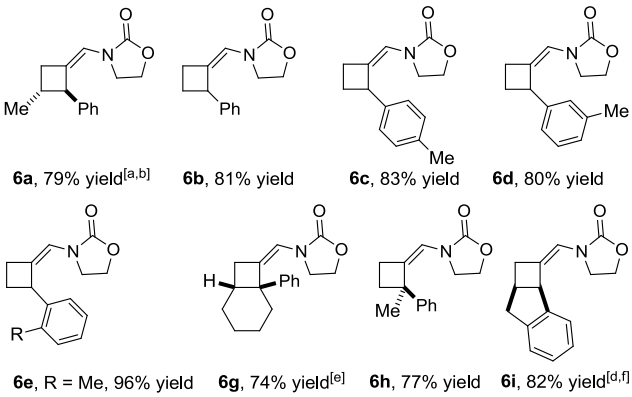


[a] Allene **1** (1 equiv) was added dropwise to a mixture of **5a** (3 equiv) and the gold(I) catalyst (5 mol%) in CH_2Cl_2 (0.1 M) at -15 ºC, unless otherwise noted; >99% conversions (^{1}H-NMR). Yields indicated correspond to isolated products. [b] Allenamide **1** was added dropwise over 1h. [c] Reaction carried out with 2 mol% catalyst.

Once established an optimum catalytic system, the versatility and scope of the process was evaluated. As shown in Scheme 2, allenamide **1** also undergoes the cycloaddition reaction with styrene to provide, after just 5 min, the corresponding (2 + 2) adduct **6b** in 81% yield. Methyl substituents at the *para*, *meta*, and *ortho* positions of the phenyl ring of **5** were perfectly tolerated, so the corresponding (2 + 2) adducts (**6c**-**6e**) could be isolated in good to excellent yields (80 – 96% yield). The presence of a bromine atom at the aromatic ring is also compatible with the reaction conditions, although the adduct **6f** was isolated in a modest 42% yield.

Importantly, the cycloaddition also proceeded with a 1,1-disubstituted alkenes such as 1-phenyl-1-cyclohexene and α-methyl styrene to selectively afford, in 74 and 77% yield, the (2 + 2) cycloadducts **6g** and **6h**, which incorporate one quaternary stereocenter. Interestingly, the cycloaddition with the *cis*-styrene (*Z*)-**5a** led a 15% yield of a 1 : 1.2 mixture of **6a** and its *syn* isomer **6a'**.[15] However, the cycloaddition with 1*H*-indene provided the (2 + 2) adduct **6i** in an excellent 82% yield. The stereochemical identity of all these adducts (**6a**-**6i**) was determined by NMR analysis. Additionally, the structure of **6a** and **6i** could be further confirmed by X-ray diffraction analysis (Figure 1).[16]





[a] Allene **1** (1 equiv) was added dropwise over a period of 1 hour to a mixture of **5** (3 equiv), gold(I) catalyst (2 mol%) and 4A MS, in CH_2Cl_2 (0.1 M) at -15 ºC, unless otherwise noted; >99% conversions (^{1}H-NMR). [b] Isolated yields of **6**. [c] Additionally, a 29% yield of the homodimer **7** was also isolated. [d] 5 mol % of catalyst was employed in the reaction. [e] Additionally, a 10 % of an hydrofunctionalization product (**8g**) was also isolated. [f] Reaction carried out at rt.

Scheme 2. (2+ 2) cycloaddition of allenamide **1** and styrene derivatives.

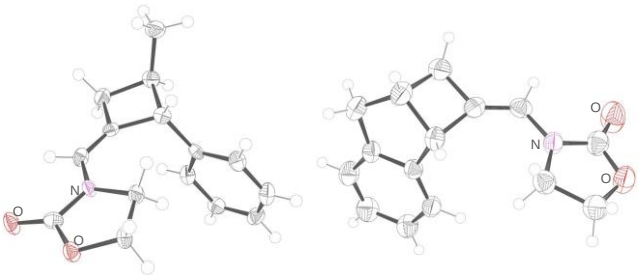


Figure 1. X-ray structures of adducts **6a** and **6i**.[16]

The requirement of an aromatic substituent at the alkene was next investigated. Initially, we tested the feasibility of the cycloaddition of **1** with methylene cyclohexene (Table 2, entry 1). Unfortunately, although the desired cycloadduct **6j** was detected, the major product of the reaction was the acyclic compound **8j**, formally resulting from the hydrofunctionalization of the allenamide unit with the alkene.[13] Both, **6j** and **8j**, were isolated as an inseparable 1: 6 mixture in a global 78% yield.

The observation of allenamide cyclodimerization side reactions (**7**) suggested the possibility of using enamides as alkene components. Gratifyingly, enamides **5k**-**5n** are excellent cycloaddition partners, providing the corresponding cyclobutanic adducts with complete selectivity and excellent yields (entries 2 - 7).[17] Remarkably, as can be deduced from entries 3 -6, both (*E*) and (*Z*) isomers of enamides **5l** and **5m** provided, with comparable efficiencies, a single stereoisomer of the cycloadducts **6l** and **6m**, both featuring a *trans* disposition of the methyl and carbamoyl groups. These results clearly point out to a reaction mechanism involving carbocationic intermediates, as this could explain the observed loss of stereochemical information of the starting *Z*-enamides. Finally, the phenylenamide derivative **5n** also participated in the reaction, leading to cycloadduct **6n**, which was obtained with complete regio- and stereoselectivity and good yield (entry 7).

It was recently reported that indoles react with allenamides such as **1** in the presence of $[Ph_3PAu]^+$ complexes to provide hydrofunctionalization products of type **8o**-**p**.[13b] In consonance, under our catalytic conditions, indole **5o** reacted to provide the hydrofunctionalization product **8o** in 75% yield. However, the reaction of its *N*-Boc-analog **5p** afforded a low but promising 33% yield of the desired (2 + 2) cycloadduct **6p**. On the other hand, the reaction with a cyclic enamide such as **5q** proceeded with excellent yield and complete selectivity to provide the 4,6-fused byciclic system **6q** in 94% yield. The stereochemical assignment of **6k** as well as that of **6q** could be successfully confirmed by X-ray analysis (Figure 2).[18]

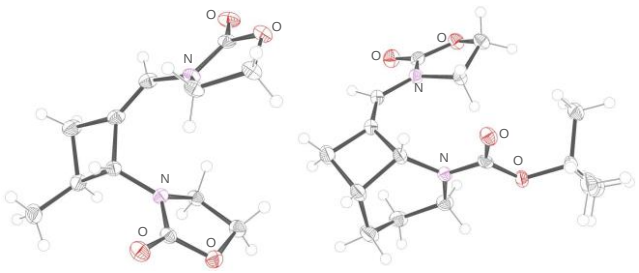
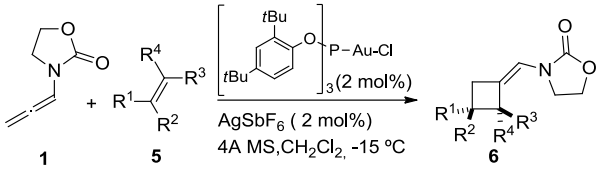
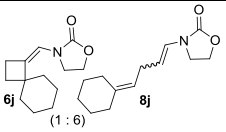
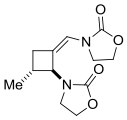
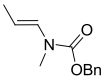
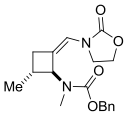
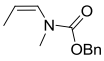
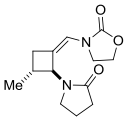
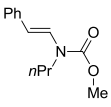
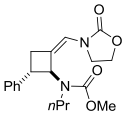
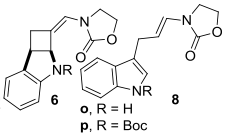
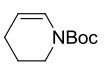
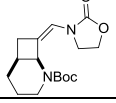


Figure 2. X-ray structures of adducts **6k** and **6q**.[18]

Table 2. Scope of the cycloaddition with other alkenes.[a]

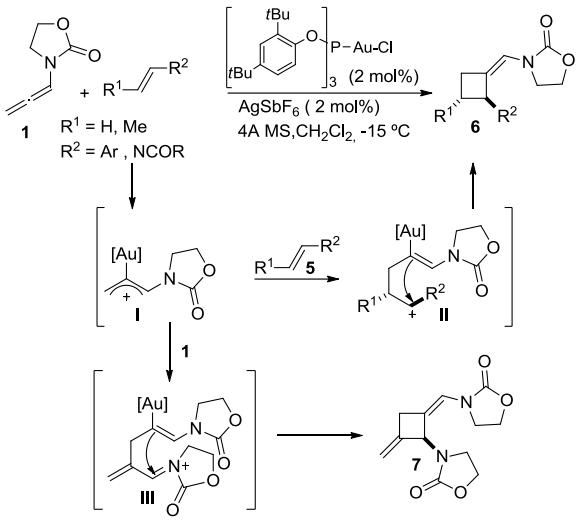


Entry	Alkene	**5**	Products	**6**, Yield , %[b]
1		**5j**		**6j+8j**, 78
2		**5k**		**6k**, 76
3		(*E*)-**5l**		**6l**, 91
4		(*Z*)-**5l**		**6l**, 96
5		(*E*)-**5m**		**6m**, 73
6		(*Z*)-**5m**		**6m**, 71
7		**5n**		**6n**, 78
8		**5o,** R=H		**6o**, 0; **8o** 75
9		**5p,**R=Boc		**6p**, 33;**8p** 21
10		**5q**		**6q**, 94

[a] Allene **1** (1 equiv) was added dropwise over 1h to a mixture of **5** (3 equiv) and the gold(I) catalyst (2 mol%) in CH_2Cl_2 (0.1 M) at -15 ºC, unless otherwise noted; >99% conversions (^{1}H-NMR). [b] Isolated yields.

From a mechanistic perspective the reaction might proceed through a stepwise cationic pathway such as that shown in Scheme 3, at least in the case of the enamides partners. Thus, activation of the allene by the Au catalyst would afford an Au-allyl cation species of type **I**.[3,4,7] Nucleophilic intermolecular interception of **I** by the alkene would provide a second cationic intermediate **II**. This would be the regioselectivity-determining step, with the formation of the more stabilized bencylic or imonium cation being favoured. At this point, rotation around the sigma C-C bond result in the loss of the stereochemical information coming from the alkene. Finally, a ring closing process through attack of the vinyl gold species to the stabilized cation, and elimination of the Au complex, would yield the final (2 + 2) adduct of type **6**. Alternatively, when the metal allyl cation intermediate **I** is attacked by another unit of allenamide **1**, a second cationic intermediate of type **III** could be formed. After a ring closing process, this intermediate could give rise the homodimer adduct **7**, observed in certain cases.

We are currently further investigating the mechanistic aspects of the cycloaddition by theoretical and experimental means, and seeking an explanation for the different behaviour of (*Z*) and (*E*)-**5a**.



Scheme 3. Mechanistic rationale for the (2 + 2) cycloadditions of allenamide **1** and alkenes

In conclusion, we have developed an efficient (2 + 2) catalytic cycloaddition methodology that provides synthetically appealing cyclobutane derivatives in a highly or completely selective manner. Work to develop enantioselective variants and to gain a deeper mechanistic understanding is underway.

Experimental Section

Representative procedure for the (2 +2) cycloaddition of 1 with 5a.

To a cooled solution (-15 °C) of *trans*-β-methylstyrene (**5a,** 162 µl, 1.25 mmol), $AgSbF_6$ (2.86 mg, 8.31 µmol) and **Au2** (7.31 mg, 8.31 µmol) in a dried Schlenk tube, was slowly added a solution of allenamide **1** (52 mg, 0.426 mmol) in CH_2Cl_2 (1 mL), over 1 hour. The mixture was additionally stirred at -15 °C for 5 min and filtered through a short pad of florisil®, eluting with Et_2O. The solvent was evaporated and the crude mixture was chromatographed to give **6a** (80 mg, 0.30 mmol) in 79% yield.

Acknowledgements

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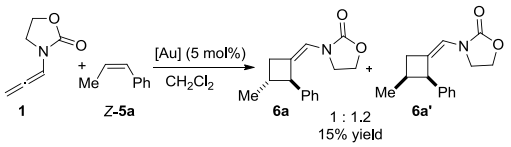
[15] This reaction provided a complex mixture of products together with a 15% yield of a 1:1.2 mixture of **6a** and **6a'**.



[16] CCDC 863034 (**6a**) and CCDC 863036 (**6i**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Cycloaddition of allenamide **5k** could be carried out using 1.5 equiv of enamide, albeit **6k** is isolated in a slightly lower yield (56%). Additionally, performing the addition of the enamide in one portion did not significantly affect the efficiency of the reaction, since **6k** could be isolated in a comparable 63% yield.

[18] CCDC 863038 (**6k**) and CCDC 863037 (**6q**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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