Synthetic Methods

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Gold-Catalyzed Intermolecular [4+2] and [2+2+2] Cycloadditions of Ynamides with Alkenes**

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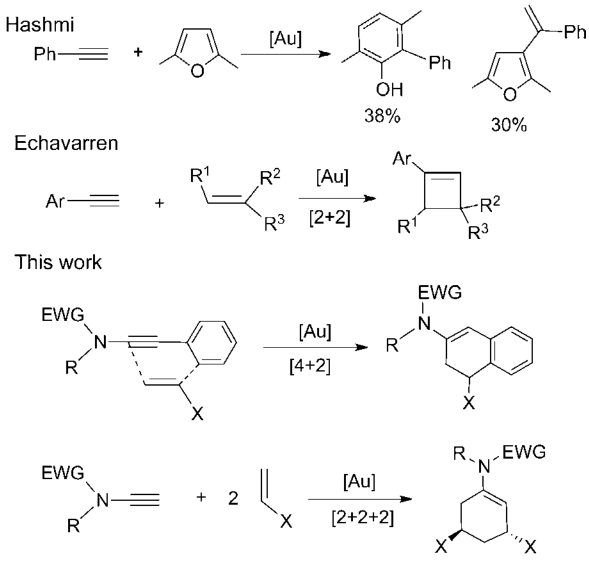
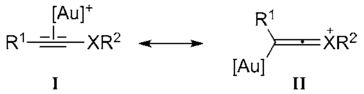
Gold-catalyzed cycloisomerizations of 1,5- and 1,6-enynes represent important advances in modern catalysis.[1] These reactions provide unusual and diverse carbocyclic compounds that are not readily synthesized by common methods. Importantly, such cycloisomerizations allow facile access to naturally occurring compounds.[2,3] As gold-catalyzed enyne cycloisomerizations occur exclusively under intramolecular conditions, little effort has been devoted to the study of intermolecular reactions between alkynes and alkenes.[4,5] Hashmi et al. studied the gold-catalyzed reaction of phenylacetylene with excess 2,5-furan, which gave the desired 2-phenyl-3,5-dimethylphenol in a low yield (Scheme 1).[4] Very recently, Echavarren and co-workers reported the efficient synthesis of cyclobutene derivatives by gold-catalyzed intermolecular [2+2] cycloadditions of phenylacetylenes with alkenes.[5] Intermolecular reactions of alkynes with alkenes can also be performed with nickel and cobalt complexes to give acyclic butene or butadiene derivatives.[6,7] We investigated new intermolecular reactions of alkynes with alkenes catalyzed by gold complexes. Herein, we report [4+2] cycloadditions of 2-arylynamides with alkenes, and [2+2+2] cycloadditions of arylynamides with enol ethers (Scheme 1). To our knowledge, there are no analogous inter- or intramolecular reactions for this type of [2+2+2] cycloaddition.[7]



Scheme 1. Gold-catalyzed intermolecular alkyne/alkene reactions. EWG = electron-withdrawing group.

Recently, there has been considerable interest in the electrophilic activation of ynamides and alkynyl ethers. Such substrates are studied because they are more electrophilic than other, more common alkynes in reactions catalyzed by gold compounds.[8–10] These effects arise from the polarized π-alkyne character of the substrate–catalyst complex (**I**, which can also be drawn as the ketene resonance structure (**II**), Scheme 2) and can control the regioselectivity of reactions.



Scheme 2. Resonance structures of gold–alkyne complexes. XR^2 = OR, NR_2.

Table 1 shows the outcome of the intermolecular [4+2] cycloaddition of ynamide **1a** to 4-methoxyphenylethene (2 equiv) catalyzed by various gold complexes. Echavarren and co-workers have reported intramolecular [4+2] cycloadditions of arylynes with alkenes.[11] The success of this intermolecular reaction relies on a suitable gold catalyst and solvent. The use of [$(PPh_3)AuCl$]/$AgNTf_2$ and [LAuCl]/$AgNTf_2$ (L = $(t\text{Bu})_2$(*o*-biphenyl)P; Tf = trifluoromethanesulfonate) in dichloroethane (DCE) at 25 °C resulted in the recovery of unreacted **1a** in 62 % and 58 % yield, respectively (Table 1, entries 1 and 2). A significant amount of the alkene underwent dimerization during the long reaction time. The use of [(IPr)AuCl]/$AgNTf_2$ (IPr = 1,3-bis(diisopropylphenyl) imidazol-2-ylidene) in DCE gave the desired cycloadduct **2a** in 88 % yield after 1 h. (Table 1, entry 3). Table 1, entries 4 and 5 show the effects of the changing the silver salt on the yield of the reaction. Changing the catalytic system to [(IPr)AuCl]/AgOTf or [(IPr)AuCl]/$AgSbF_6$ reduced the yield of **2a** to 46 % and 57 %, respectively. Degradation of **1a** also occurred in these two reactions. The use of $AgNTf_2$ alone led to complete decomposition of **1a** (Table 1, entry 6). This cycloaddition is sensitive to solvents: Running the reaction in dichloromethane gave **2a** in 62 % yield, whereas no **2a** was formed in nitromethane (Table 1, entries 7 and 8). The initial step in the formation of **2a** is attack of the alkene at the C1 position of the alkyne, because the gold–alkyne complex has a ketene-like character (**II**, Scheme 2). The

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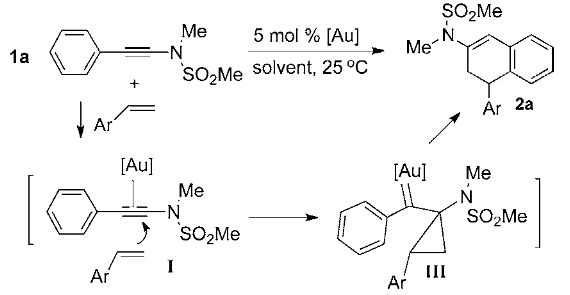
Table 1: [4+2] Cycloadditions of arylynamides and alkenes catalyzed by gold complexes.[a]



Entry	[Au][b]	Solvent	Time [h]	Yield [%]	
				1a[c]	**2a**[c]
1	$[PPh_3AuCl]/AgNTf_2$	DCE	24	62	–
2	$[LAuCl]/AgNTf_2$	DCE	24	58	–
3	$[(IPr)AuCl]/AgNTf_2$	DCE	1	–	88
4	$[(IPr)AuCl]/AgOTf$	DCE	10[d]	–	46
5	$[(IPr)AuCl]/AgSbF_6$	DCE	3[d]	–	57
6	$AgNTf_2$	DCE	10[d]	–	–
7	$[(IPr)AuCl]/AgNTf_2$	CH_2Cl_2	1.5[d]	–	62
8	$[(IPr)AuCl]/AgNTf_2$	CH_3NO_2	24	72%	–

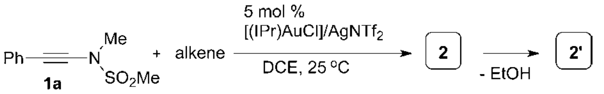
[a] Concentration of **1a** = 0.1 M, Ar = 4-MeOC$_6$H$_4$. [b] IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene, L = P(*t*Bu)$_2$(*o*-biphenyl). [c] Yields are reported after purification. [d] Reaction time corresponds to complete consumption of **1a**.

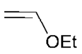
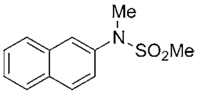
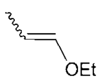
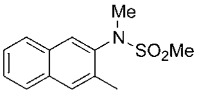
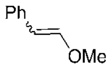
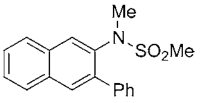
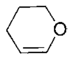
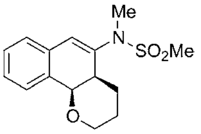
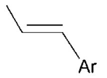
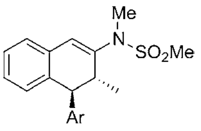
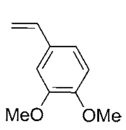
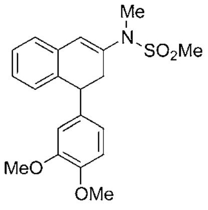
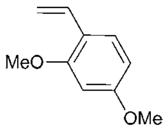
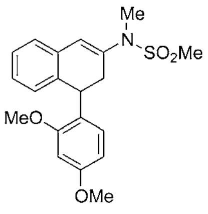
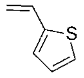
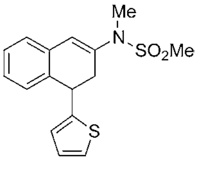
intermediate cyclopropyl gold carbenoid **III** is then attacked by the tethered phenyl group.

To test the scope of the reaction, we examined the cycloaddition of **1a** with various alkenes (Table 2). The reactions were performed with $[(IPr)AuCl]/AgNTf_2$ (5 mol%) in DCE at 25 °C. The cycloadditions of ethoxyethene, 2-methylethoxyethene, (*E*/*Z* = 1:1.2) and 2-phenylethoxyethene (*E*/*Z* = 1.1:1) to **1a** gave 2-aminonaphthalenes **2b′**–**2d′** after the loss of ethanol (Table 2, entries 1–3). In contrast, **2e**, which is derived from a cyclic enol ether, was obtained in 61% yield (Table 2, entry 4). The ^{1}H NMR NOE spectrum of **2e** confirmed its *cis*-fused configuration.[11] The reaction of (*E*)-1-methoxy-4-(prop-1-enyl)benzene with **1a** afforded **2f** in 91% yield (Table 2, entry 5), and the reactions of 2,4-dimethoxyphenylethene, 3,4-dimethoxyphenylethene, and 2-thienylethene with **1a** gave **2g**, **2h**, and **2i** in high yields (Table 2, entries 6–8).

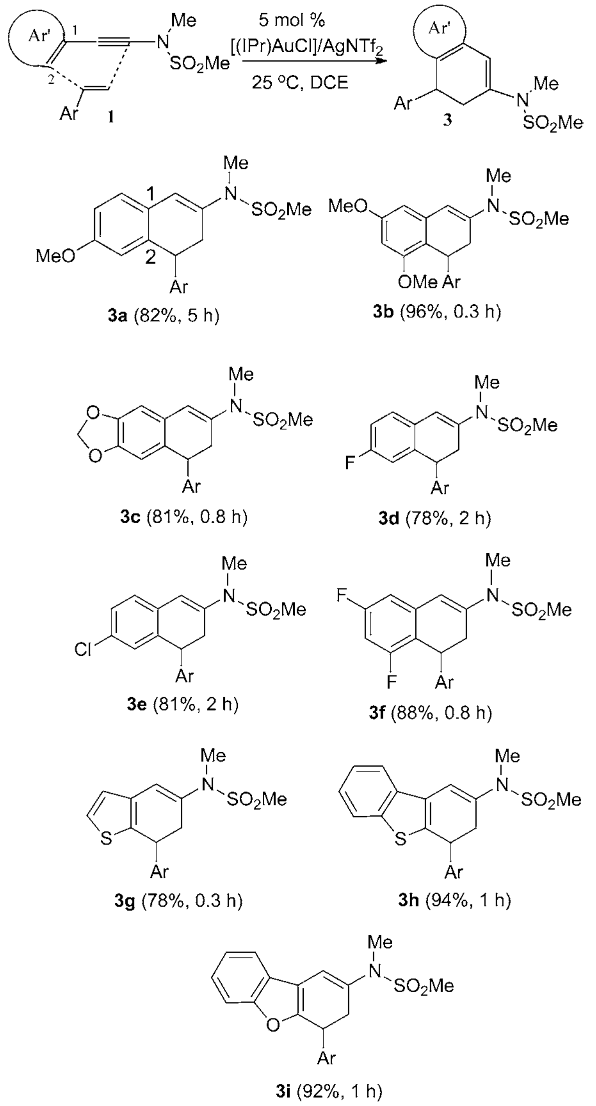
Scheme 3 shows the compatability of the catalytic system with ynamides **1** that have various aryl substituents (Ar′). The reactions were performed with 4-methoxyphenylethene (2 equiv) and $[(IPr)AuCl]/AgNTf_2$ (5 mol%) in DCE at 25 °C. The reactions of ynamide substrates which contain electron-rich Ar′ groups, such as 4-methoxyphenyl, 3,5-dimethoxyphenyl, or benzo[*d*][1,3]dioxole, gave the corresponding products **3a**, **3b**, and **3c** in high yields. We obtained satisfactory yields of products **3d**–**3f** from reactions with ynamide substrates which contain the electron-deficient Ar′ groups 4-fluorophenyl, 4-chlorophenyl, and 3,5-difluorophenyl. The cycloaddition reactions also work well for alkyne substrates that contain 3-thienyl, 3-benzothienyl, and 3-benzofuryl substituents. In these cases, the corresponding products **3g**, **3h**, and **3i** were obtained in 78–94% yields.

Table 2: Scope of [4+2] cycloadditions with various electron-rich alkenes.[a]



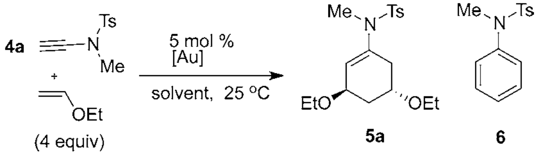
Ent.	Alkene[b]	Time [h]	Product	Yield [%][c]
1)		8	 **2b′**	78
2)	 (*E*/*Z* =1:1.2)	5	 **2c′**	84
3)	 (*E*/*Z* =1.1:1)	1	 **2d′**	81
4)		8	 **2e**	61
5)	 Ar = 4-MeOC$_6$H$_4$	2	 **2f**	91
6)		1	 **2g**	78
7)		0.5	 **2h**	86
8)		5	 **2i**	82

[a] Concentration of **1a** = 0.1 M, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene). [b] 2.0 equiv of alkene were used [c] Product yields are reported after purification.



Scheme 3. Cycloadditions of 4-methoxyphenylethene with various arylynamides. Concentration of substrate = 0.1 M, Ar = 4-MeOC$_6$H$_4$. Reaction times and yields are given in parentheses. Yields are reported after purification.

Table 3: Gold-catalyzed intermolecular [2+2+2] cycloaddition reaction.[a]

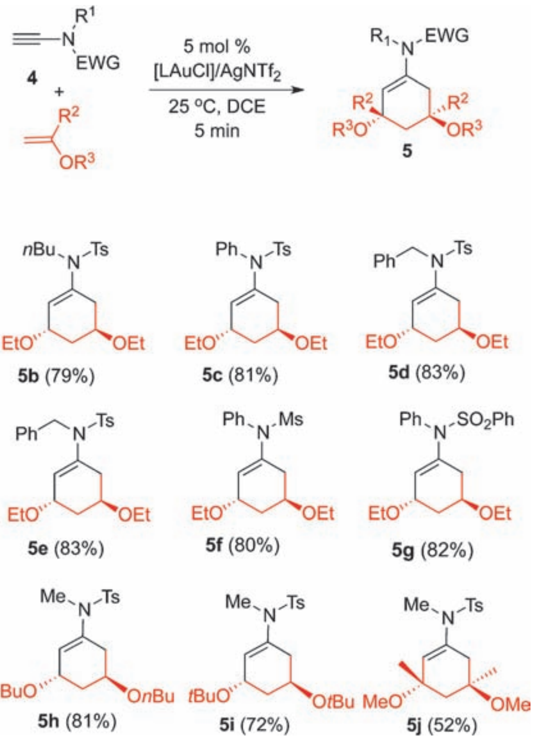


Entry	[Au][b]	Solvent (time)[b]	Product (yields [%])[c]
1	[(IPr)AuCl]/$AgNTf_2$	DCE (12 h)	**4a** (56), **5a** (14)
2	LAuCl/$AgNTf_2$	DCE (5 min)	**5a** (83)
3	LAuCl/$AgSbF_6$	DCE (10 min)	**5a** (70), **6** (10)
4	LAuCl/AgOTf	DCE (10 min)	**5a** (62), **6** (14)
5	PPh^3AuCl/$AgNTf_2$	DCE (15 min)	**5a** (69), **6** (11)
6	LAuCl/$AgNTf_2$	CH_2Cl_2 (8 min)	**5a** (73), **6** (9)
7	LAuCl/$AgNTf_2$	CH_3CN (17 min)	**5a** (33), **6** (18)

[a] Concentration of **4a** = 0.1 M. [b] IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-ylidene, L = P(*t*Bu)$_2$(*o*-biphenyl). [b] Reaction time corresponds to complete consumption of **4a**. [c] Product yields are reported after purification.

We also studied the reaction of terminal ynamide **4a** with ethoxyethene (4 equiv) in dichloroethane at 25 °C (Table 3). In the presence of [(IPr)AuCl]/$AgNTf_2$ (5 mol %), this reaction afforded a 14 % yield of compound **5a** and unreacted **4a** in 56 % yield (Table 3, entry 1). In contrast, the reaction with [LAuCl]/$AgNTf_2$ as the catalyst gave compound **5a** as a single diastereomer in 83 % yield (Table 3, entry 2). The use of other gold catalysts [LAuCl]/$AgSbF_6$, [LAuCl]/AgOTf, and [PPh_3AuCl]/$AgNTf_2$ (Table 3, entries 3–5) resulted in lower yields of compound **5a** because small amounts of by-product **6** were also formed. The undesired product **6** was also obtained in 9 % and 18 % yield with [LAuCl]/$AgNTf_2$ in dichloromethane or acetonitrile, respectively (Table 3, entries 6–7). The stereochemistry of compound **5a** was determined by ^{1}H NMR NOE spectroscopy.[12]

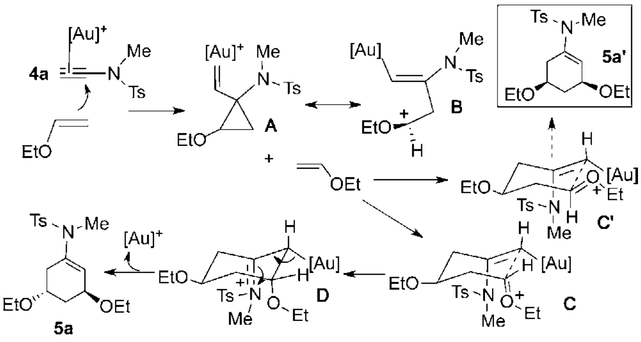
To our knowledge, there is no analogue of the [2+2+2] cycloaddition, even in gold-catalyzed intramolecular enyne cycloisomerizations. The catalytic system is compatible with various substituents on the ynamide group, as well as several different enol ethers (Scheme 4). The cycloadducts **5b**–**5j** were produced with a high diastereoselectively (diastereomer ratio greater than 20:1). Products **5b**–**5g** were obtained in 79–83 % yield from reactions with ynamides that contain different substituents (EWG = methansulfonyl, toluenesulfonyl, or



Scheme 4. Scope of gold-catalyzed [2+2+2] cycloaddition. Concentration of **4** = 0.1 M, EWG = electron-withdrawing group, L = P(*t*Bu)$_2$(*o*-biphenyl). Yields are given in parentheses and are reported after purification.

phenylsulfonyl; R^1 = *n*-butyl, benzyl, or phenyl). Compounds **5h**, **5i**, and **5j** were obtained from the reaction of ynamide **4a** with *n*-butoxyethene, *tert*-butoxyethene, and 1-methyl-1-methoxyethene, respectively. The yields of these reactions were between 52–81 %.

The stereoselectivity of the [2+2+2] cycloaddition is rationalized in Scheme 5. Our calculations indicate that **5a** is slightly more stable than isomer **5a′** by 0.5 kcal mol^{-1}.[13] According to the hypothesis of Echavarren and co-workers,[1a,11] the gold-catalyzed reaction of alkenes with alkynes is more likely to proceed through the intermediate cyclopropyl gold-carbenoid **A** than resonance structure **B** because structure **B** will give a [2+2] cycloadduct.[14] In our experiments we did not obtain any of the [2+2] cycloadducts, which indicates that the role of structure **B** in the reaction is insignificant. We postulate that species **A** reacts further with the second alkene to give an oxonium species that may have two conformations (**C** and **C′**, Scheme 4) in the final cyclization. The product of the reaction is **5a**, which suggests that the steric interactions between the equatorial oxonium moiety and the gold catalyst of conformation **C′** are more hindered than the 1,3-axial interaction between the amino group and the oxonium moiety in conformation **C**. Therefore, the less-hindered conformation will control the stereoselectivity of the cyclization.



Scheme 5. Synthesis of **5a** by [2+2+2] cycloaddition.

In conclusion, prior to this study there were very few examples of gold-catalyzed intermolecular reactions of alkynes with alkenes.[1,4,5] This study describes gold-catalyzed [4+2] cycloadditions of 1-amino-2-aryl-1-ynes with alkenes.[15] The reaction has a wide scope and can accommodate various alkenes, as well as ynamides which are substituted with different aryl groups. The reactions of terminal ynamides with enol ethers resulted in highly stereoselective [2+2+2] cycloadditions.

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[13] Procedures for the calculations are described in the Supporting Information.

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