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Gold-Catalyzed Addition of Carbon Nucleophiles to Propargyl Carboxylates

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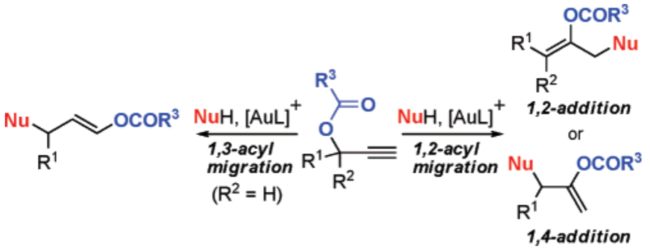
ABSTRACT



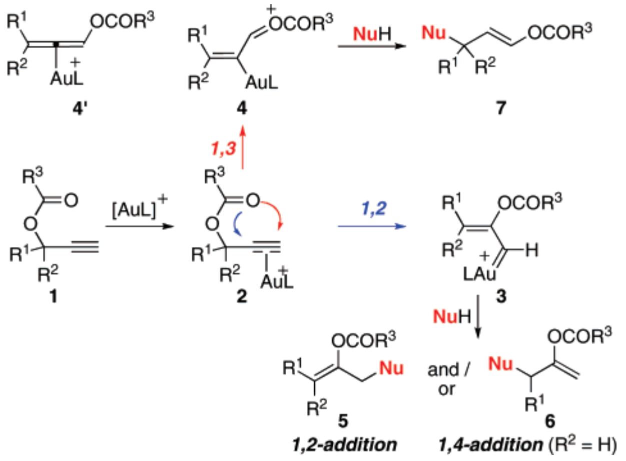
Propargyl carboxylates react with 1,3-dicarbonyl compounds and electron-rich arenes in the presence of Au(I) catalysts to give enol carboxylates via α,β-unsaturated Au(I) carbenes or Au(I)-coordinated allenes formed by 1,2- or 1,3-acyl migration, respectively.

Propargyl esters **1** undergo 1,2- or 1,3-acyl migration with Au(I) complexes via intermediates **2** to form highly reactive α,β-unsaturated Au(I) carbenes **3** or Au(I)-coordinated allenes **4**, respectively (Scheme 1).[1−3] Complexes **4** are usually depicted in a simplified form as Au(I)-coordinated allenes **4′**.[4] Similar pathways take place with other metal catalysts.[1,2,5,6]

Carbenes **3** formed by 1,2-acyl migration of **1** react with alkenes to give cyclopropanes.[3b] Au(I) carbenes formed from 1,6-enynes have also been trapped in cyclopropanation reactions.[7] Recently the Au(I)-catalyzed addition of electron-rich aromatic compounds to 1,6-enynes has been reported.[8] Although the main course of this reaction is the nucleophilic attack at the cyclopropane of intermediate cyclopropyl Au(I) carbenes, we have observed two cases of attack to the carbene with indole as the nucleophile.[8b,9]

Here we report that propargyl esters **1** react with 1,3-dicarbonyl compounds and electron-rich arenes by trapping

Scheme 1



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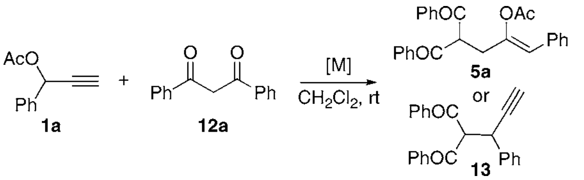
(1) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2−42. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (c) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750−2752. (d) Marco-Contelles, J.; Soriano, E. *Chem.−Eur. J.* **2007**, *13*, 1350−1357. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2006**, 333−346.

(2) (a) Mamane, V.; Grees, T.; Krause, H.; Fürtsner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (b) Fürstner, A.; Hanen, P. *Chem. Commun.* **2004**, 2564−2547. (c) Fürstner, A.; Hanen, P. *Chem.−Eur. J.* **2006**, *12*, 3006−3019. (d) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901−2904.

(3) (a) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5809. (b) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003. (c) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443. (d) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805. (e) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585−4587. (f) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414−8415. (g) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647−3650.

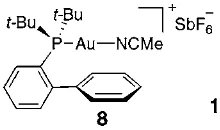
10.1021/ol701706d CCC: $37.00

Table 1. Reaction of **1a** with 1,3-Dicarbonyl Compound **12a**[a]



entry	[M]	time (h)	*Z*/*E* ratio	product (yield, %)
1	AuCl	15	79:21	**5a** (60)
2	$AuCl_3$	1	71:29	**5a** (56) + **13** (6)[b]
3	**8**	1	100:0	**5a** (66)
4[c]	**8**	2.5	100:0	**5a** (88)
5	**9**/Ag(I)	1	100:0	**5a** (50)
6	**10**/Ag(I)	2.5	100:0	**5a** (50) + **13** (36)
7	**11**	15.5	–	**13** (21)
8	$Sc(OTf)_3$	1	–	**13** (98)
9	$Cu(OTf)_2$	1.5	–	**13** (20)[d]

[a] 5 mol % of catalyst. Ag(I) = $AgSbF_6$. [b] The methyl ketone from the hydration of **13** was also obtained (11%).[c] 2 mol % of catalyst. [d] The methyl ketone from the hydration of **13** was also obtained (79%).



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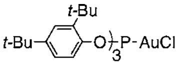

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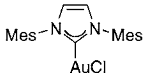
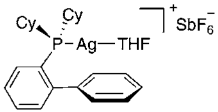
10:





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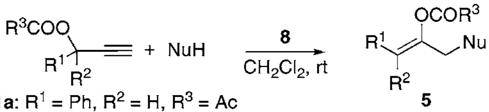
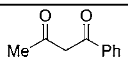
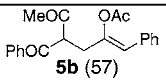
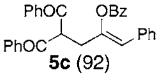
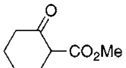
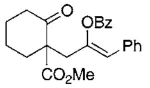
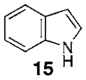
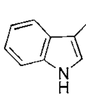
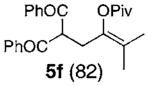
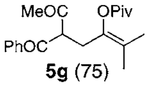
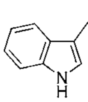
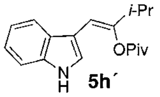
of intermediates **3** or **4** to give adducts **5**, **6**, or **7** depending on the substitution of **1** (Scheme 1). This represents an atom-economical functionalization of carbon nucleophiles under catalytic conditions. These reactions are very different from the addition of carbon nucleophiles to alkynes catalyzed by Lewis acids.[10]

Table 2. Reactions of **1a**–**d** with Carbon Nucleophiles[a]



1a: R^1 = Ph, R^2 = H, R^3 = Ac
1b: R^1 = Ph, R^2 = H, R^3 = Bz
1c: R^1 = R^2 = Me, R^3 = Ac
1d: R^1 = R^2 = Me, R^3 = Piv

entry	1a-d	NuH	time (h)	product (yield, %)
1	**1a**	 **12b**	1.5	 **5b** (57)
2	**1b**	**12a**	1	 **5c** (92)
3[b]	**1b**	 **14a**	1.5	 **5d** (51)
4	**1c**	 **15**	5	 **5e** (68)
5	**1d**	**12a**	0.5	 **5f** (82)
6[c]	**1d**	**12b**	0.75	 **5g** (75)
7	**1d**	**15**	18	 **5h**  **5h´** (61; 1:1.7 **5h**/**5h'**)

[a] 5 mol % of **8**. [b] 2 mol % of **8** and 5 mol % of $Sc(OTf)_3$. [c] 2 mol % of **8**.

We first tested the reaction of propargyl acetate **1a** with 1,3-diketone **12a** in the presence of AuCl, $AuCl_3$, cationic Au(I) complex **8**,[11a] precatalysts **9**[11d] and **10**,[11a,b] and cationic Ag(I) complex **11**[11c] (Table 1). Addition of **12a** to **1a** proceeded at room temperature to give enol acetate **5a** with all the gold catalysts (Table 1, entries 1–6). A mixture of *E* and *Z* isomers was obtained with AuCl and $AuCl_3$ (Table 1, entries 1 and 2), whereas cationic Au(I) catalysts provided pure *Z*-**5a**. The reaction was faster and cleaner with complex **8** (Table 1, entries 3 and 4). With **10** and Ag(I), a mixture of **5a** and the product of nucleophilic substitution **13**[12] was obtained (Table 1, entry 6). Reaction of **1a** with cationic complex **11** or $Sc(OTf)_3$ as catalysts gave acetylene **13**, whereas with $Cu(OTf)_2$, a mixture of **13** and the product of hydration of the alkyne (2-benzoyl-1,3-diphenylpentane-1,4-dione) was obtained (Table 1, entries 7–9). With $AgSbF_6$ (5 mol %), this trione was obtained in 97% yield.[13] Interestingly, propargyl alcohols have been shown to react with allylsilanes in the presence of $AuCl_3$ and other gold catalysts by nucleophilic substitution.[14]

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(4) Structure **4** is more consistent with calculations: Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207–2209.

(5) (a) Maineti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132–2135. (b) Cariou, K.; Maineti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745–9755. (c) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657. (d) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469.

(6) (a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505–8513. (b) Miki, K.; Fujita, M.; Uemura, S.; Ohe, K. *Org. Lett.* **2006**, *8*, 1741–1743.

(7) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029–6032.

(8) (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427–7430. (b) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698–700.

(9) Oxidation of α,β-unsaturated Au(I) carbenes **3** and other Au(I) carbenes with Ph_2SO leads to aldehydes in a process in which the sulfoxide attacks the carbene: Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

(10) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271, and refs therein.

(11) (a) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179. (b) de Fremont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411–2418. (c) Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2672–2676. (d) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029–6032.

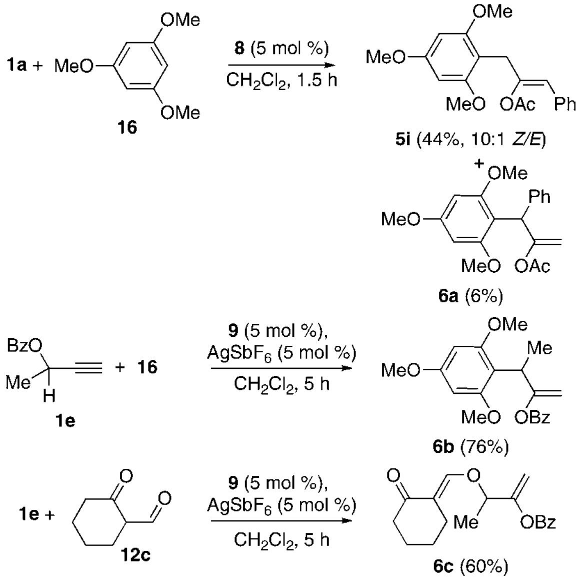
(12) Sanz, R.; Miguel, D.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Org. Lett.* **2007**, *9*, 727–730.

(13) See Supporting Information for details.

Propargyl esters **1a**−**d** react with a variety of carbon nucleophiles with catalyst **8** (Table 2). In the reactions with these substrates, which bear phenyl or *gem*-dimethyl substituents at the propargyl position, products of 1,2-addition via intermediates **3** were obtained. A higher yield was obtained in the reaction of benzoate **1b** (Table 2, entry 2) than that obtained with acetate **1a** under identical conditions (Table 1, entry 2). The addition of β-ketoester **14a** to **1b** had to be carried out in the presence of $Sc(OTf)_3$ (5 mol %) to give adduct **5d** in moderate yield (Table 2, entry 3). In the reaction of **1c** with indole (**15**), the initial product suffered isomerization of the olefin to form **5e** (Table 2, entry 4), whereas **1d** and **15** gave a mixture of **5h**/**5h′** (Table 2, entry 7). *Z*-Isomers **5a**−**e** and **5h** appear to be obtained under kinetically controlled conditions, as their *E*-isomers are slightly more stable (PM3 calculations).

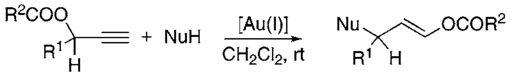
Reaction of **1a** with 1,3,5-trimethoxybenzene (**16**) and catalyst **8** gave the expected product of 1,2-addition to the gold carbene **5i** (44%) along with **6a** (6%), which corresponds to a product of 1,4-addition to intermediate **3** (Scheme 2). A product of this type, **6b**, was obtained in 76% yield from propargyl benzoate **1e** using catalyst **9**. A product of 1,4-addition was also obtained in the reaction between **1e** and keto aldehyde **12c**, although in this case the nucleophile reacts at oxygen to give enol ether **6c** (60%).

Scheme 2

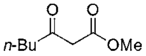
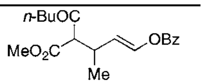
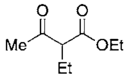
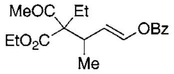
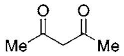
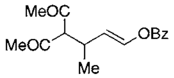
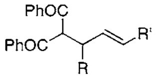
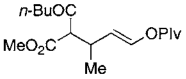
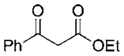
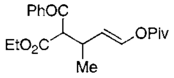
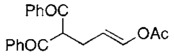


Reactions of **1e**−**g** with diketones **12a** or **12d** or β-ketoesters **14b**−**d** in the presence of **8** or **9** as catalysts afford products resulting from 1,3-acyl migration via intermediates **4** (Table 3). Addition of 5 mol % of $Sc(OTf)_3$ or $Cu(OTf)_2$ led to improved results with β-ketoesters as nucleophiles. In the reaction of **1f** with **12a**, a 1.1:1 mixture of **7d** and **7d′** was obtained (Table 3, entry 5) as a result of nonregioselective attack of the nucleophile to **4**. The trans configurations of **7a**−**g** were assigned on the basis of the observed olefinic ^3J of 12.3−12.6 Hz.[15] It is important to note that in the presence of Sc(III) or Cu(II) as additives the major reaction pathway is dominated by Au(I). Thus, the reaction of **1g** with **14d** did not proceed with $Sc(OTf)_3$ or $Cu(OTf)_2$ (5 mol %) in the absence of Au(I).

Table 3. Reaction of **1a**−**g** with Carbon Nucleophiles[a]

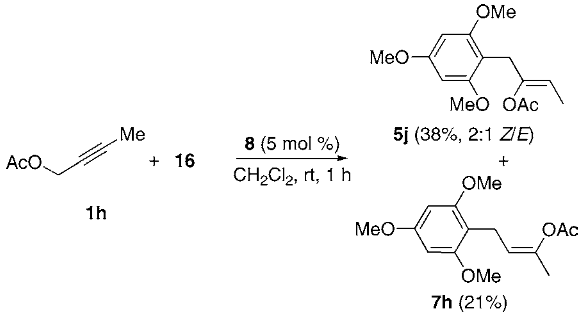


1e: R^1 = Me, R^2 = Bz
1f: R^1 = Me, R^2 = Piv
1g: R^1 = H, R^2 = Ac

entry	1e-g	NuH	[Au]	time(h)	product (yield, %)
1	**1e**	 **14b**	**9**[a]	9	 **7a** (58)
2	**1e**	 **14c**	**9**[a]	9	 **7b** (49)
3	**1e**	 **12d**	**9**[b]	3	 **7c** (46)
4	**1f**	**12a**	**8**[c]	0.5	 **7d**: R = Me, R' = OPiv **7d'**: R = OPiv, R' = Me (1:0.9; 78)
5	**1f**	**14b**	**8**[d]	3	 **7e** (53)
6	**1f**	 **14d**	**8**[d]	3	 **7f** (55)
7	**1g**	**12a**	**8**[c]	4.5	 **7g** (87)

[a] 2 mol % of **9**/$AgSbF_6$ and 5 mol % of $Cu(OTf)_2$. [b] 5 mol % each of **9** and $AgSbF_6$. [c] 2 mol % of **8**. [d] 2 mol % of **8** and 5 mol % of $Sc(OTf)_3$. Compounds **7a**−**c** and **7e**,**f** are 1.1−1.2:1 mixtures of diastereomers.

Scheme 3



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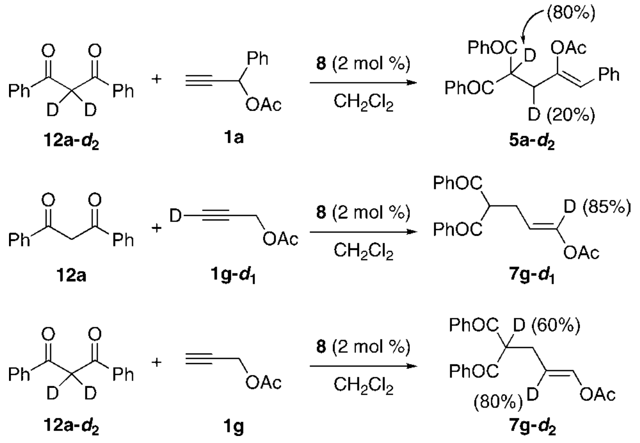
(14) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180−14181.

Reaction of 2-butynyl acetate (**1h**), with a disubstituted alkyne, was examined with arene **16** as the nucleophile (Scheme 3). In this case, reaction with catalyst **8** gave a ca. 2:1 mixture of **5j** and **7h** in a combined 59% yield.

Scheme 4



Experiments with deuterated substrates **12a-d_2** and **1g-d_1** are shown in Scheme 4. These results are consistent with the mechanistic hypotheses shown in Scheme 1 in which the enol of the 1,3-dicarbonyl compound or the arene adds to intermediates **3** or **4**.

Although the factors that control the regioselectivity of the addition are still not totally understood, propargyl carboxylates bearing phenyl or *gem*-dimethyl groups at C-3 lead to products **5** of 1,2-addition to α,β-unsaturated Au(I) carbenes **3**, whereas propargyl carboxylates with a methyl group or no substituents at that position give adducts **6** or **7**. However, substrates **1a** and **1h** also give products of 1,2-addition, **5i** and **5j**, in their reactions with **16** (Schemes 2 and 3), which suggests that a different mechanism takes place in these cases.

In summary, we have found that α,β-unsaturated Au(I) carbenes **3** or Au(I)-coordinated allenes **4** formed from propargyl esters are trapped by 1,3-dicarbonyl compounds and electron-rich arenes. This is a simple procedure for the formation of functionalized enol carboxylates under mild conditions. It is worth noting that in contrast with oxophilic Lewis acids that lead to nucleophilic substitution with propargyl carboxylates Au(I) promotes the nucleophilic addition to these substrates.

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Supporting Information Available: Experimental details, characterization data, and additional results. This material is available free of charge via the Internet at http://pubs.acs.org.

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