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Gold(I)-Catalyzed Addition of Carboxylic Acids to Alkynes

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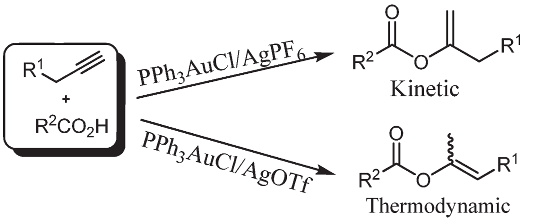
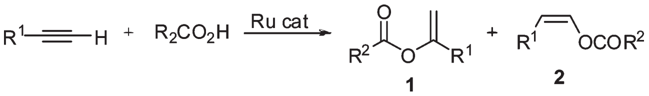
Received August 6, 2010



Au(I)-catalyzed hydroacyloxylation of alkynes with carboxylic acids is described. $PPh_3AuCl/AgPF_6$ catalyst affords the Markonikov addition products, whereas $PPh_3AuCl/AgOTf$ catalyst gives the more stable isomerized products via the Markonikov products.

Gold catalysis has attracted a great deal of recent attention due to its extraordinary versatility in functional group transformations associated with carbon–carbon multiple bonds.[1] Among various useful functionalizations of alkynes, Au(I)-catalyzed nucleophilic additions to alkynes proved to be synthetically useful and include hydroamination,[2] hydroxylation, and hydroalkoxylation.[3] Addition of carboxylic acids to alkynes catalyzed by transition metals is an efficient way to prepare enol esters[4] and has been extensively studied by ruthenium complexes.[5] The electrophilic activation of terminal alkynes by suitable ruthenium complexes together with carboxylic acids has provided an easy access to alk-1-en-2-yl esters **1** and (*Z*)-alk-1-enyl esters **2** derived from the Markovnikov[6] and the *anti*-Markovnikov addition, respectively (Scheme 1).[7]

SCHEME 1. Ru-Catalyzed Addition of Acids to Alkynes



The gold(I)-catalyzed intramolecular addition of carboxylic acids and esters to terminal alkynes, which results in lactones, was reported previously by several groups,[8] but somewhat surprisingly, only one example of the intermolecular version was reported to date.[9] Reaction of acetic acid with 3-hexyne in tetrahydrofuran at 60 °C using (triphenylphosphine)gold(I) pentafluoropropionate and boron trifluoride etherate as a cocatalyst afforded 3-hexene 3-acetate in a very low yield (6.2%) along with 3-hexanone (12.3%).[9] To improve this unsatisfactory result and to determine the scope and limitations of hydroacyloxylation, we have investigated the addition of carboxylic acids to alkynes using gold(I) catalysts along with our recent interest in the functionalization of alkynes.[10]

We initially studied the effectiveness of gold(I) catalysts using 1-hexyne and benzoic acid in toluene (Scheme 2). When 1-hexyne was treated with benzoic acid in toluene in the presence of $Ph_3PAuCl/AgOTf$ catalyst (5 mol %) at room temperature for 15 h, somewhat surprisingly, an *E*- and *Z*-mixture of a more stable enol benzoate **4** was isolated in 87% yield (entry 1). Apparently, the initially formed Markovnikov addition product **3** was isomerized completely to the thermodynamically more stable enol benzoate **4**. $Ph_3PAuCl/AgBF_4$ was

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[1] For reviews on gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Patil, N.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (g) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (h) Skouta, R.; Li, C. J. *Tetrahedron* **2008**, *64*, 4917. (i) Furstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (j) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675.

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[5] For reviews, see: (a) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507. (b) Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, 755. (c) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. (d) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2005**, *45*, 2176.

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[8] (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J. P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Harkat, H.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273. (c) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717.

[9] Roembke, P.; Schmidbaur, H.; Cronje, S.; Raubenheimer, H. *J. Mol. Catal. A* **2004**, *212*, 35.

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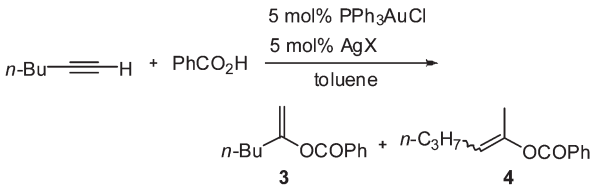
DOI: 10.1021/jo101543q

SCHEME 2. **Au-Catalyzed Addition of Acids to Alkynes**



much less reactive than $Ph_3PAuCl/AgOTf$, and the reaction was very slow at room temperature, yielding a small amount of the product (< 10%) after 15 h. As shown in Table 1, the reaction required heating at 80 °C for 15 h and a 2:1 mixture of **3** and **4** was obtained (entry 2). Interestingly, $Ph_3PAuCl/AgPF_6$ catalyst required heating at 60 °C and afforded only the Markovnikov addition product **3** in 82% yield without any isomerization to **4** (entry 3). In addition, when the reaction was repeated in the presence of allyltrimethylsilane (10 mol %) as an acid scavenger, **3** was isolated in 76% yield (entry 4). $Ph_3PAuCl/AgSbF_6$ and $Ph_3PAuCl/AgNO_3$ catalyst were totally ineffective, and no reaction occurred in refluxing toluene after 15 h (entries 5 and 6). Similarly, Ph_3PAuCl and $AgPF_6$ were also unsuccessful (entries 7 and 8). In addition, to check the possibility of a protic acid catalysis, when the reaction was carried out in the presence of 5 mol % of triflic acid in toluene at 60 °C for 15 h, no reaction took place (entry 9). In addition, in the presence of a trace amount (0.5 mol %) of triflic acid, the reaction did not occur. Furthermore, the reaction did not proceed in the presence of 5 mol % of benzenesulfonic acid (entry 10).

TABLE 1. **Optimization of Reaction**[a]

entry	cat.	temp (°C)	**3** (%)	**4** (%)
1	$PPh_3AuCl/AgOTf$	rt	0	87
2	$PPh_3AuCl/AgBF_4$	80	50	25
3	$PPh_3AuCl/AgPF_6$	60	82	0
4	$PPh_3AuCl/AgPF_6$[b]	60	76	0
5	$PPh_3AuCl/AgSbF_6$	110	0	0
6	$PPh_3AuCl/AgNO_3$	110	0	0
7	PPh_3AuCl	110	0	0
8	$AgPF_6$	110	0	0
9	TfOH	60	0	0
10	$PhSO_2OH$	60	0	0

[a]The reaction was carried out in toluene for 15 h using 5 mol % of catalyst. [b]In the presence of 10 mol % of allyltrimethylsilane.

The influence of solvent was briefly investigated using 5 mol % of $Ph_3PAuCl/AgPF_6$. It was found that the present reaction was very sensitive to solvent, and toluene gave the best result. When the reaction was carried out in dichloromethane, 1,2-dichloroethane, acetonitrile, ethanol, and trifluoroethanol using $Ph_3PAuCl/AgPF_6$ catalyst at 60 °C for 15 h, the reaction did not proceed smoothly to give an observable amount of the desired product. The effectiveness of toluene could be due to stabilization of the cationic complex by the formation of an arene–gold complex.[11] Thus, the remaining reactions were carried out in toluene at 60 °C using 5 mol % of $Ph_3PAuCl/AgPF_6$ to afford the Markovnikov addition product. Furthermore, to prepare the isomerized enol esters, the reaction was carried out in toluene at room temperature using 5 mol % of $Ph_3PAuCl/AgOTf$.

In order to determine the scope and limitations of the method, structurally different alkynes and carboxylic acids were employed under the standard conditions using 5 mol % of $Ph_3P-AuCl/AgPF_6$. As shown in Table 2, several noteworthy features have been found. First, alkyl-substituted terminal alkynes afforded the Markovnikov products exclusively without any anti-Markovnikov products (entries 1–11), but phenylacetylene led to a significant amount of the anti-Markovnikov products **2** together with **1** (entries 12 and 13) Second, diaryl- and arylalkyl-substituted alkynes were slower than terminal alkynes (entries 16–18). In particular, in the case of diphenylacetylene, the reaction was not complete under prolonged reflux (entry 16). Third, the addition of carboxylic acids to conjugated alkyne esters proceeded regio- and stereoselectively via conjugative *trans*-addition (entries 14 and 15). Fourth, aromatic and aliphatic carboxylic acids worked equally well. α,β-Unsaturated carboxylic acids such as acrylic acid and *trans*-cinnamic acid could be successfully employed (entries 10 and 11). Finally, it is noteworthy that the acidity of carboxylic acids influenced the reaction rate considerably. When 4-nitrobenzoic acid was employed, the reaction was complete within 12 h at 60 °C, whereas the reaction using 4-methoxybenzoic acid was required 24 h for completion of the reaction (entries 4 and 6). The reaction using formic acid was complete within 3 h under the same conditions (entry 3). The most notable observation was realized with trifluoroacetic acid. The reaction was much faster and occurred at room temperature within 6 h (entry 7). Furthermore, it is noteworthy that vinyl trifluoroacetate was not further isomerized to the more stable thermodynamic isomer under the present strong acidic conditions.

We briefly studied the hydroacyloxylation using $Ph_3PAuCl/AgOTf$ catalyst (Scheme 3). When the reaction of 1-hexyne with benzoic acid in the presence of 5 mol % catalyst in toluene at room temperature was monitored by ^1H NMR, somewhat surprisingly, the formation of the Markovnikov product **7** was not observed after 2 h, although the reaction was incomplete. Thus, to prove the isomerization of kinetic enol esters to thermodynamic enol esters by $Ph_3PAuCl/AgOTf$ and to determine its efficiency, the isomerization of enol benzoate **3** was initially attempted using 5 mol % of $Ph_3PAuCl/AgOTf$ in deuteriochloroform at room temperature for 6 h, but no reaction took place. However, when the reaction was carried out in

SCHEME 3. **Au-Catalyzed Addition of Acids to Alkynes**

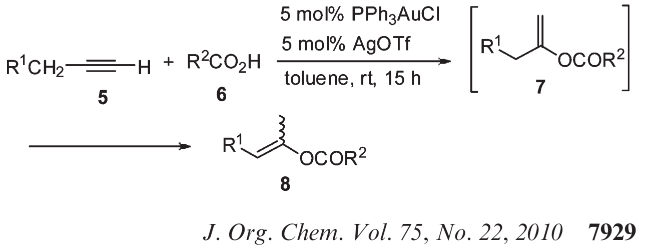


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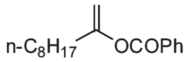
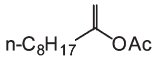
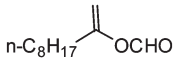
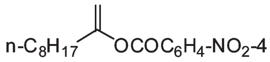
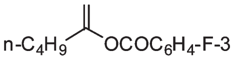
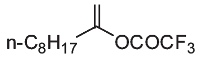
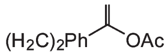
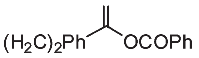
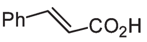
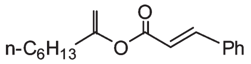
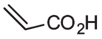
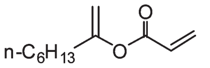
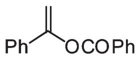
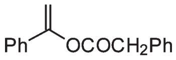
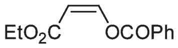
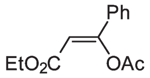
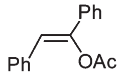
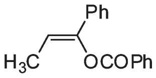
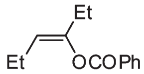
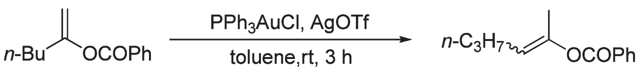
TABLE 2. Addition of Carboxylic Acids to Alkynes with $PPh_3AuCl/AgPF_6$ Catalyst[a]

entry	alkyne	acid	time [h]	temp [°C]	product	yield
1	$n\text{-}C_8H_{17}{-}{\equiv}$	$PhCO_2H$	15	60		90
2	$n\text{-}C_8H_{17}{-}{\equiv}$	AcOH	15	60		82
3	$n\text{-}C_8H_{17}{-}{\equiv}$	HCO_2H	3	60		80
4	$n\text{-}C_8H_{17}{-}{\equiv}$	$4\text{-}NO_2\text{-}C_6H_4CO_2H$	12	60		65
5	$n\text{-}C_4H_9{-}{\equiv}$	$3\text{-}F\text{-}C_6H_4CO_2H$	15	60		75
6	$n\text{-}C_4H_9{-}{\equiv}$	$4\text{-}MeO\text{-}C_6H_4CO_2H$	24	60		63
7	$n\text{-}C_8H_{17}{-}{\equiv}$	CF_3CO_2H	6	rt		82
8	$Ph(CH_2)_2{-}{\equiv}$	AcOH	15	60		75
9	$Ph(CH_2)_2{-}{\equiv}$	$PhCO_2H$	15	60		77
10	$n\text{-}C_6H_{13}{-}{\equiv}$		15	60		78
11	$n\text{-}C_6H_{13}{-}{\equiv}$		15	60		88
12	$Ph{-}{\equiv}$	$PhCO_2H$	15	60		86 (4.9:1)[b]
13	$Ph{-}{\equiv}$	$PhCH_2CO_2H$	15	60		72 (2.5:1)[b]
14	$EtO_2C{-}{\equiv}$	$PhCO_2H$	15	60		80
15	$Ph{-}{\equiv}{-}CO_2Et$	AcOH	15	60		78
16	$Ph{-}{\equiv}{-}Ph$	AcOH	20	110		62 (20)[c]
17	$Ph{-}{\equiv}{-}CH_3$	$PhCO_2H$	20	60		72
18	$Et{-}{\equiv}{-}Et$	$PhCO_2H$	18	60		65

[a] The reaction was carried out with alkyne (1.2 equiv), carboxylic acid (1.0 equiv), and 5 mol % $Ph_3PAuCl/AgPF_6$ in toluene. [b] Ratio of **1** and **2**. [c] Yield of recovered diphenylacetylene.

SCHEME 4. Au(I)-Catalyzed Isomerization

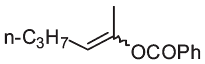
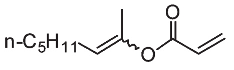
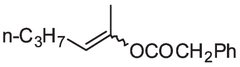
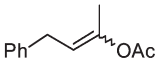


3 **4** (89%, 1:3.4)

toluene, the isomerization proceeded very fast at room temperature and only a small amount of **3** (< 10%) was detected after 2 h (Scheme 4). The results obtained here indicate that the isomerization was sensitive to solvents and occurred very rapidly in toluene. Table 3 summarizes some experimental results obtained in the isomerization of the kinetic enol esters to the more stable isomers using 5 mol % of $Ph_3PAuCl/AgOTf$ in toluene. The reaction proceeded cleanly at room temperature.

In conclusion, we have developed the Au(I)-catalyzed addition of carboxylic acids to alkynes to afford the Markovnikov addition products. Furthermore, $Ph_3PAuCl/AgOTf$ in toluene is effective for the isomerization of kinetic enol esters into thermodynamic isomers.

TABLE 3. $PPh_3AuCl/AgOTf$-Catalyzed Addition of Acids to Alkynes[a]

entry	alkyne **5** (R_1)	acid **6** (R_2)	product **8**	yield [%][b]
1	*n*-C_3H_7	Ph		87 (1:3.1)[c]
2	*n*-C_5H_{11}	$H_2C=CH$		68 (1:2.2)
3	*n*-C_3H_7	$PhCH_2$		86 (1:2.8)
4	$PhCH_2$	Me		82 (1:2.8)

[a] The reaction was carried out using 5 mol % of $PPh_3AuCl/AgOTf$ in toluene at room temperature for 15 h. [b] Isolated yields. [c] Diastereomeric ratio.

Experimental Section

Typical Procedure for $Ph_3PAuCl/AgPF_6$-Catalyzed Addition of Carboxylic Acids to Alkynes. To a suspension of Ph_3PAuCl (10 mg, 0.02 mmol), $AgPF_6$ (5.1 mg, 0.02 mmol), and benzoic acid (50 mg, 0.41 mmol) in toluene (1 mL) was added 1-hexyne (56 μL 0.49 mmol) at room temperature. After being stirred at 60 °C for 15 h, the solvent was removed under reduced pressure, and the reaction mixture was purified by silica gel column chromatography (EtOAc/hexane = 1:10) to give hex-1-en-2-yl benzoate (69 mg, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11−8.03 (m, 2H), 7.59−7.53 (m, 1H), 7.47−7.41 (m, 2H), 4.83 (s, 1H), 4.82 (s, 1H), 2.33 (t, J = 7.6 Hz, 2H), 1.55−1.48 (m, 2H), 1.42−1.33 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 164.9, 156.9, 133.4, 130.0, 128.5, 128.4, 101.4, 33.2, 28.8, 22.2, 13.9; IR (film) 3019.9, 1733.5, 1667.4, 1215.6, 1170.0, 1026.6, 707.4, 665.9 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_2$ M^+ 227.1048, found 227.1047.

Typical Procedure for the Hydroacyloxylation Using $Ph_3PAuCl/AgOTf$ Catalyst. To a suspension of Ph_3PAuCl (6.1 mg, 0.01 mmol), AgOTf (3.1 mg, 0.01 mmol), and benzoic acid (30 mg, 0.24 mmol) in toluene (1 mL) was added 1-hexyne (34 μL, 0.29 mmol) at room temperature. After being stirred for 15 h, the solvent was evaporated under reduced pressure, and the resulting crude product was separated by silica gel column chromatography (EtOAc/hexane = 1:10) to give hex-2-en-2-yl benzoate (diastereomeric ratio 1:3.1, 44 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05−8.12(m, 2H), 7.56−7.59 (m, 1H), 7.25−7.46(m, 2H), 5.23 (t, J = 7.8 Hz, 1H), 5.09 (t, J = 7.3 Hz, 1H), 1.96−1.99(m, 5H), 1.34−1.40 (m, 2H), 0.91 (t, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 164.6, 145.8, 145.2, 133.3, 130.1, 128.6, 128.6, 117.8, 117.4, 28.8, 27.7, 22.9, 22.5, 19.8, 15.5, 13.9; IR (film) 3019.9, 1733.5, 1667.4, 1215.6, 1170.0, 1026.6,707.4, 665.9 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_2M^+$ 205.1229, found 205.1225.

Acknowledgment. We gratefully acknowledge Nanyang Technological University for financial support.

Supporting Information Available: Spectral data for all compounds including copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. A text correction was made to the paragraph above Scheme 3; the new version reposted October 27, 2010.