JOC *Article*

Efficient Functionalization of Aromatic C−H Bonds Catalyzed by Gold(III) under Mild and Solvent-Free Conditions

Zhangjie Shi and Chuan He*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

chuanhe@uchicago.edu

Received February 13, 2004

A gold(III)-catalyzed carbon−carbon bond formation reaction between arenes and electron-deficient alkynes or alkenes is described. Electron-rich arenes can be efficiently functionalized with the alkyne or alkene substrates. This reaction can be run with neat reactants at ambient temperature. Under the "solventless" conditions, clean product was obtained from a reaction of equal molar amounts of arene and alkyne substrates. The mild conditions and potential tolerance to different functional groups make this method practical for arene functionalization and for constructing complicated molecules. Efficient preparation of various coumarins from aryl alkynoates was demonstrated. Preliminary mechanistic studies were performed to probe the pathway of this reaction.

Introduction

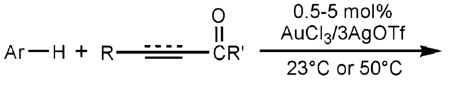
Catalytic functionalization of aromatic C−H bonds to form C−C bonds, if realized under mild and environmentally benign conditions, will provide the most economic way to construct molecules containing arene groups. Although progress has been made in recent years,[1] efficient processes that work at ambient temperature in a typical organic medium or under solvent-free conditions are very limited.

In 1931, Kharasch and Isbell demonstrated that anhydrous gold(III) chloride can react with neat benzene, toluene, or other aromatic compounds to form arylgold(III) complexes at room temperature.[2] Subsequent studies of this chemistry led to the isolation and characterization of several arylgold(III) species generated from the reaction.[3] This auration reaction was shown to proceed in an electrophilic manner.[2,3] In one case, arylgold(III) species were shown to be stabilized by binding to 2,6-lutidine. This lutidine-bound phenylgold(III) complex reacted with phenylacetylene in a stoichiometric manner with heating to give high yields of product diphenylacetylene.[3c] The mechanism of this reaction is not clear.

Hashmi's group discovered that 1 mol % of $AuCl_3$ in acetonitrile catalyzes formation of C−C bonds between 2-methylfuran and methyl vinyl ketone.[4] It was proposed that an arylgold(III) species was likely generated from electrophilic metalation of the 2-methylfuran by $AuCl_3$. Then the arylgold(III) added to methyl vinyl ketone to give the 1,4-addition product. At around the same time that we were investigating these types of reactions, another group discovered hydroarylation of alkyne substrates with $AuCl_3$ plus 2−3 equiv of silver(I) salts.[5] With 1.5 mol % of $AuCl_3/2AgSBF_6$, 10 equiv of mesitylene reacted with 1 equiv of phenylacetylene to yield 1-mesityl-1-phenylethene in 86% yield in nitromethane at 60 °C. It was thought that in this reaction gold(III) merely works as Lewis acid to increase the electrophilicity of the alkyne group. With electron-deficient alkynes, gold(I) salts appeared to be better hydroarylation catalysts.

Results and Discussion

We report here an efficient hydroarylation reaction of alkynes and alkenes to form C−C bonds. The reactions are catalyzed by gold(III) complexes under mild and even solvent-free conditions at ambient temperature (eq 1). No excess amount of arene substrate is required for completion of the reaction. For example, reacting pentamethylbenzene with HC≡CCO_2Et in dichloroethane or with-



(1)

---

[1] (a) Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305−308. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (d) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (e) Weissman, H.; Song, X. P.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337−338. (f) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414−7415. (g) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685−2686. (h) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476−1477. (i) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506−7507. (j) Hennessy, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084−12085. (k) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102−12103. (l) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H. Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102−12103 and references therein.

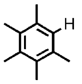
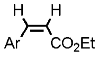
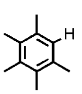
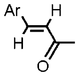
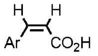
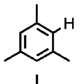
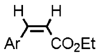
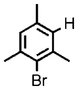
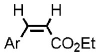
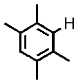
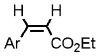
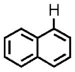
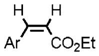
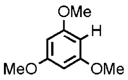
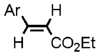
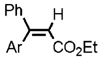
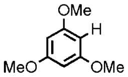
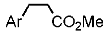
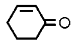
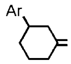
[2] Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053−3059.

[3] (a) Liddle, K. S.; Parkin, C. *J. Chem. Soc., Chem. Commun.* **1972**, 26−28. (b) de Graaf, P. W. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1976**, *105*, 399−406. (c) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330−2334.

[4] (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (b) Dyker, G.; Muth, E.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2003**, *345*, 1247−1252.

10.1021/jo0497353 CCC: $27.50

TABLE 1. Gold-Catalyzed Intermolecular Addition Reactions[f]

Entry	Arene	Substrate	Product	Temp. (°C)	Time (h)	Yield[a] (%)
1[b]		$\equiv$—CO_2Et		23	48(1)	99(99)
2[c]				23	96	99
3		$\equiv$—COMe		23	36	88
4[b]		$\equiv$—CO_2H		23	48(1)	99(99)
5[d]		$\equiv$—CO_2Et		23	48	74
6		$\equiv$—CO_2Et		23	48	75
7[b,d]		$\equiv$—CO_2Et		23	48(16)	97(97)
8		$\equiv$—CO_2Et		50	48	75
9		$\equiv$—CO_2Et		23	48	68
10[e]		Ph—$\equiv$—CO_2Et		23	3	97
11[e]		=—CO_2Me		23	1	99
12[e]				23	3	80

[a] The isolated yields are reported here. [b] Reaction was also performed with neat reactants (2 mmol each) with 2.5 mol % of catalyst; the yield and reaction time are reported in the parentheses. [c] Catalyst loading was 0.5 mol %. [d] A portion of 2:1 arene/alkyne adduct was also formed. [e] The reaction was run with neat reactants. [f] Reactions were typically conducted with 1 mmol of arene, 0.5 mmol of alkyne, and 5 mol % of $AuCl_3$/3AgOTf in dichloroethane.

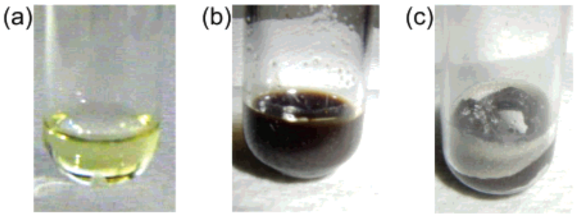
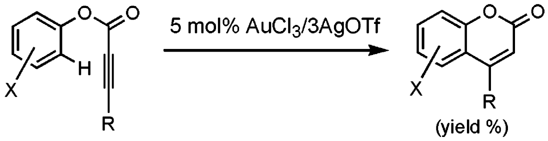
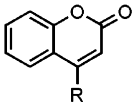


FIGURE 1. Photographs of the gold(III)-catalyzed addition of pentamethylbenzene to ethyl propiolate in the absence of solvents. (a) Equal molar amounts of pentamethylbenzene and ethyl propiolate (2 mmol). (b) The mixture color changed to dark red brown after addition of gold(III) catalyst. (c) Solid product formed after 1 h of reaction at room temperature.

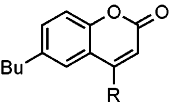
TABLE 2. Gold-Catalyzed Intramolecular Addition Reactions[a]



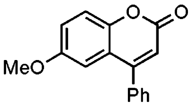
(2)



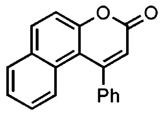
(R = H, **1a**, 84 %; Me, **1b**, 99%; Ph, **1c**, 73%)



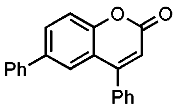
(R = H, **2a**, 99%; Ph, **2b**, 92%)



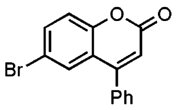
(**3**, 98%)



(**4**, 99%)



(**5**, 82%)



(**6**, 44%)

[a] All reactions were conducted with 0.5 mmol of ester in 2 mL of dichloroethane at 50 °C (reactions for **5** and **6** were run at 70 °C). Isolated yields are reported here.

out any solvent yielded a *cis*-arylalkene product in the presence of $AuCl_3$ pretreated with 3 equiv of AgOTf at room temperature (entry 1 in Table 1). The reaction is quantitative under these conditions and the catalyst loading can be lowered to 0.5 mol % (entry 2 in Table 1). $AuCl_3$ can also catalyze the reaction but gave the product in a lower yield (25%). In the absence of gold, no product was generated. The reaction also works for the alkynes conjugated to CO_2H and COMe (entries 3 and 4 in Table 1). A range of arenes can be activated and converted into products at ambient temperature under air atmosphere in good to excellent yields (Table 1). *trans*-Arylalkene products were obtained in some reactions. Less electron-rich arenes require heating to 50 °C for the completion of the reaction.

The intermolecular addition of arenes to alkynes catalyzed by gold(III) also proceeds under solvent-free conditions. In fact, the reaction proceeds faster under solvent-free conditions. For instance, 2.0 mmol of solid pentamethylbenzene was added into 2.0 mmol of liquid $HC\equiv CCO_2Et$ at room temperature to give a pale yellow solution (Figure 1a). Upon addition of 2.5 mol % of gold(III) catalyst, the solution became dark red brown (Figure 1b). A solid product (99% yield) formed after 1 h of reaction at room temperature (Figure 1c). No impurity peaks were observed from the crude ^1H NMR spectrum of this solid (Figure S1, Supporting Information). Excellent yields were obtained for several substrates that were tested under the solvent-free conditions (Table 1). In several cases, good yields could be obtained only when the reactions were run with neat reactants (entries 10−12 in Table 1). Under such conditions, electron-rich arene substrates can be activated to add to even alkenes in high yields; two examples are shown in Table 1 (entries 11 and 12).

This method can be used to construct molecules such as coumarins (eq 2 in Table 2). Various coumarins were prepared from aryl alkynoates in good to excellent yields. The reaction worked for aryl alkynoates that bear different substituted groups including an electron-withdrawing group (**4** in Table 2), although a higher reaction temperature (70 °C) was required for some of these reactions. It should be noted that similar reactions catalyzed by palladium(II), platinum(II), platinum(IV), and ruthenium(II) have been reported, which may go through different mechanisms.[1a,6]

---

(5) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485−3496.

(6) (a) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264−6267. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. (c) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581−584 and references therein.

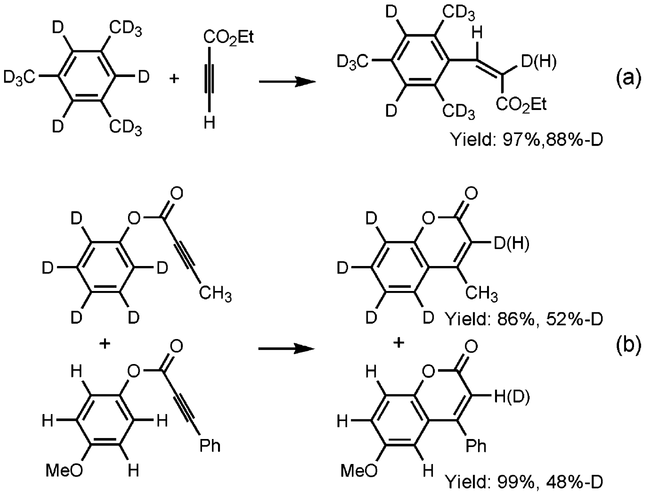


FIGURE 2. Isotope experiments under the conditions of 5 mol % $AuCl_3/3AgOTf$ in dichloroethane at room temperature.

To probe the mechanism, we mixed stoichiometric amounts of gold(III) catalyst with pentamethylbenzene. Immediate darkening of the solution color was observed, accompanied by a disappearance of the aromatic proton signal in the ^1H NMR spectrum (Figure S2, Supporting Information). No immediate change was observed when mixing the gold catalyst with alkyne or alkene substrates. This result may suggest that direct metalation of arene ring might be the first step of the reaction, which was followed by addition of the arylgold(III) to the electron-deficient alkyne substrate. More careful studies are required to fully elucidate the mechanism. It is possible that gold(III) works merely as a Lewis acid in these reactions to activate the alkyne or alkene substrates. Even if an arylgold(III) species was produced as an intermediate in the reaction, the carbon−carbon bond formation reaction could still be aided by Lewis acid-activation of the alkyne or alkene; the metal ions (gold or silver) or the acid released from the auration reaction can serve as the Lewis acid.

To gain further insight of the mechanism, an isotope experiment was performed on the reaction of the deuterium-labeled mesitylene with $HC\equiv CCO_2Et$ (Figure 2A). The result showed that the D (H) incorporated into the vinyl part of the product comes mainly from the aromatic substrate. A reaction with a mixture of two different substrates (Figure 2B), one deuterium-labeled and the other proton-substituted, was also performed. Incorporation of nearly equal amounts of H and D into both products was observed after the two independent intramolecular reactions were completed in the same solution. This result suggests that proton generated from the reaction is liberated into the solution before it is incorporated into the final product.

The results observed so far seem to support the involvement of a direct metalation of electron-rich arene groups by gold(III) species to form arylgold(III) and 1 equiv of acid. Silver salt might help generate a more electrophilic gold(III) species from $AuCl_3$. $AuCl_3$ also worked but gave low yield product. The formed arylgold(III) species could add to electron-deficient alkynes and alkenes to give the final products. This step could be aided by Lewis acid activation of the alkynes and alkenes by metal ions or acid present in the reaction solution. Although we favor this mechanism we cannot exclude the possibility of gold(III) simply works as Lewis acid to activate alkynes and alkenes in the reactions reported here.

Conclusions

In summary, an efficient hydroarylation reaction of electron-deficient alkynes and alkenes is described here. More research efforts are required to fully elucidate the mechanism of these reactions and expand the scope of this chemistry. Nevertheless, the gold(III)-catalyzed reaction presented here offers several advantages; it is atom economic as it can be run with neat reactants and gives clean product, the reaction proceeds efficiently at ambient temperature under air atmosphere, and potentially different functional groups can be tolerated. These features make it a favorable method for constructing complicated molecules in one step. Further exploration of this chemistry by using other electrophiles is in progress.

Acknowledgment. This research was supported by the University of Chicago.

Supporting Information Available: Experimental details; Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0497353