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Gold(I)-Catalyzed Intramolecular Hydroarylation of Allenes

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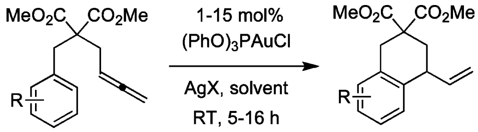
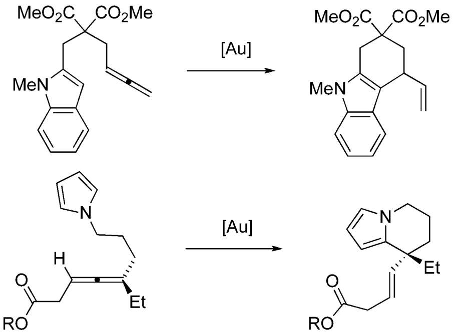


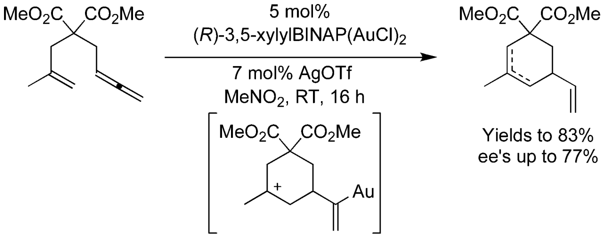
Gold(I) complexes react with 4-allenyl arenes in an *exo* fashion to furnish vinyl-substituted benzocycles. Phosphite gold(I) monocations were found to be optimal, and the catalyst was tolerant of ethers, esters, and pyrroles. Reactions proceeded in unpurified solvent at room temperature.

The Friedel−Crafts reaction has been a part of many successful transformations in organic chemistry.[1] The reaction has been accelerated by strong acids and by stoichiometric and catalytic quantities of various metals. Recent developments on the topic of catalytic cycloarylation reactions include the gold(I)-catalyzed arylation of allenes[2,3] by indoles (Widenhoefer[4]) and pyrroles (Nelson[5]) and the gold(III)-catalyzed hydroarylation of alkynes reported by He[6] (Scheme 1). Hashmi has also shown that intermolecular addition of furans to allenes can be achieved.[7] The mechanisms are presumed to proceed by an initiating allene activation by the electrophilic gold(I) cation.

Related to these first demonstrations is our recent gold(I)-catalyzed cycloisomerization of 1,6-ene-allenes[8] (eq 1). The proposed mechanism paralleled the Nelson/Widenhoefer systems with gold(I) acting as an allene activator for intramolecular attack by the alkene to generate an intermediate carbenium ion. Elimination and protodeauration yielded the vinylcyclohexene with variable regiocontrol.

SCHEME 1. Recent Gold(I)-Catalyzed Allene Arylations[4,5]

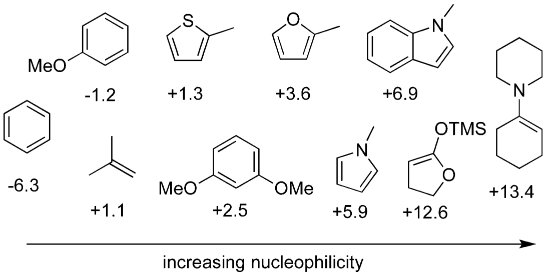




(1)

Arenes exhibit a wide range of π-nucleophilicities as characterized by the Mayr N values,[9] which quantify and rank their rates of reaction with a common electrophile. Comparing these values to the allene activations reported in the literature revealed a focus on alkene ($N = -1.00$ to 1.20) and heteroaromatic (furan/indole/pyrrole; $N = 3.60-7.00$) nucleophiles (Scheme 2).[10]

SCHEME 2. Representative *N* Values[8] for π-Nucleophiles



Since a number of interesting nucleophiles occupy the spectrum between alkenes and N-heterocycles, we initiated efforts to examine arene-allene cycloisomerizations. One expected benefit was the rearomatization-driven regioselective elimination to products. To develop this concept, we began with the relatively activated dimethoxy substrate **2** and the optimum catalyst for the ene-allene cycloisomerization 3,5-xylyl-BINAP-$(AuCl)_2$/$AgBF_4$. Gratifyingly, the desired vinylated product **3** was obtained, but the rate was slower than desired (>16 h for full conversion).

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[1] (a) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley-Interscience: New York, 1963−1965. (b) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem* **2006**, 3527−3544.

[2] For recent reviews on gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936.

[3] For recent examples of gold-catalyzed C-nucleophile additions to allenes, see: (a) Huang, X.; Zhang, L. *Org. Lett.* **2007**, *9*, 4627−4630. (b) Luzung, M.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402−12403. (c) Kim, S. M.; Park, J. H.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6172−6175. (d) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671−7673.

[4] (a) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935−1938. (b) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066−9073.

[5] Liu, Z.; Wasmuth, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352−10353.

[6] Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669−3671.

[7] Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288.

[8] Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6670−6673.

[9] Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

[10] As this manuscript was being completed, Fujii and Ohno reported a $(PR_3)Au(OTf)$ catalyzed, *endo*-selective hydroarylation of allenes (Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821−4824).

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SCHEME 3. Optimized Conditions with Activated Substrate 2

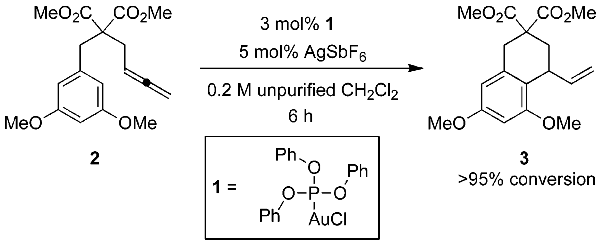


TABLE 1. Optimization of Solvent and Silver Counterion for the Conversion of 2 to 3 (Scheme 3)[a]

entry	solvent[b]	X$^-$	conversion[c] (% **3**)[d]
1	CH$_2$Cl$_2$	OTf	**92**
2	toluene	OTf	52
3	hexane	OTf	73
4	Et$_2$O	OTf	20
5	THF	OTf	36
6	MeNO$_2$	OTf	55
7	CH$_2$Cl$_2$	BF$_4$	100 (75)
8	CH$_2$Cl$_2$	NTf$_2$	79 (80)
9	CH$_2$Cl$_2$	PF$_6$	35 (72)
10	CH$_2$Cl$_2$	SbF$_6$	89 (**88**)
11	CH$_2$Cl$_2$	OTs	51 (58)
12	CH$_2$Cl$_2$	ClO$_4$	92 (76)

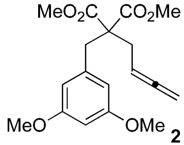
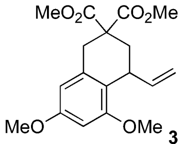
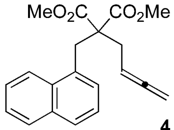
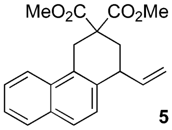
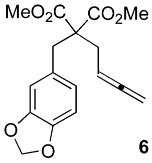
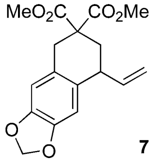
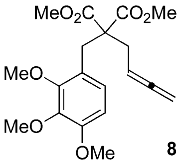
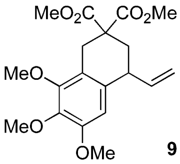
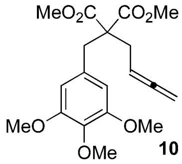
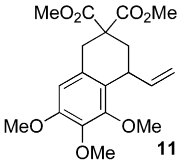
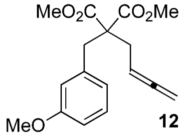
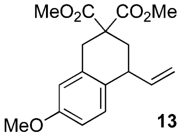
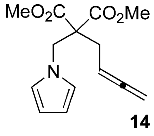
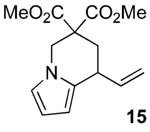
[a] Reaction conditions: 5 mol % of **1**, 7 mol % of AgX, 0.2 M in **2** at rt. [b] Commercial bottles of dichloromethane, hexane, nitromethane, and ether were used without prior purification. [c] As determined by GC integration against remaining SM. [d] Fraction of all products that was the desired cyclic isomer.

To improve the reaction rate, a number of alternative catalysts were examined. The best of these was the triphenylphosphite-derived catalyst[11] **1**, which was an easily prepared, colorless, crystalline material that was bench stable for several weeks.[12] The less basic phosphite ligand[13] generated a catalyst that was significantly more effective (Scheme 3).[14] The reaction produces benzocyclic products that are similar to those reported by Ma[15] from Brønsted activation of allylic alcohols and by Cook[16] utilizing In(III)-mediated atom-transfer cyclization.

As shown in Table 1, dichloromethane in combination with the SbF$_6^-$ counterion was optimum with regard to rate and yield of **3**. Under these conditions, the catalyst load could be reduced to 3 mol % with reasonable reaction times and little change in yield.

Utilizing the standard protocol shown in Scheme 3, a variety of arene nucleophiles were examined (Table 2). Generally speaking, the scope was limited to electron-rich arenes but was tolerant of ethers, acetals, and, not surprisingly, a pyrrole.[5] The naphthalene substrate (Mayr parameter[9] $N = -3.9$) was especially well-behaved. Unfortunately, coordinating aromatics such as triazoles, isoxazoles, and oxazoles were not effective, likely due to nonproductive coordination to the gold(I) catalyst.

TABLE 2. Au-Catalyzed Cyclohydroarylation of Allenes[a]

entry	substrate	Au-loading (mol%)	time (h)	product(s)	yield[b]
1	 **2**	3	6	 **3**	85%
2	 **4**	10	16	 **5**	87%
3	 **6**	3	16	 **7**	93%
4	 **8**	5	16	 **9**	59%
5	 **10**	5	16	 **11**	75%
6	 **12**	10	5	 **13**	60%
7	 **14**	3 1	6 24	 **15**	79% 73%

[a] General Procedure: To a vial charged with **1** and AgSbF$_6$ was added CH$_2$Cl$_2$ by syringe. After stirring 2 min, a white precipitate was observed. Addition of substrate by pipet led to a deeply colored suspension, which was stirred at rt for 4−24 h. [b] Products were directly loaded onto silica gel and eluted with appropriate mixture of hexanes and ethyl acetate; see Supporting Information.

Substrates for this chemistry were obtained from the benzylation of monoallenylmalonate[4b] with base in THF/DMF.[17]

In cases where the arene nucleophile *N* parameter was sufficiently high, the catalyst loading could be lowered to further increase reaction efficiency (Table 3, entry 7). The catalyst was also tolerant of substitution at the allene terminus and variation of the malonate linker (Scheme 4).

To ensure that the above transformations were indeed proceeding by gold catalysis, a series of control experiments were carried out. Interestingly, **3** was obtained from **2** using

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[11] Schneider, D.; Schier, A.; Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **2004**, 1995−2005.

[12] The catalyst can be recrystallized from CH$_2$Cl$_2$/hexanes in a vapor chamber and exhibits a gradual darkening over the course of 1 month.

[13] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348.

[14] A phosphite−Au(I) catalyst for alkyne activation has recently appeared; see: Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269−279.

[15] (a) Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435−3438. (b) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273−6283.

[16] Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311−1314.

[17] Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395−405.

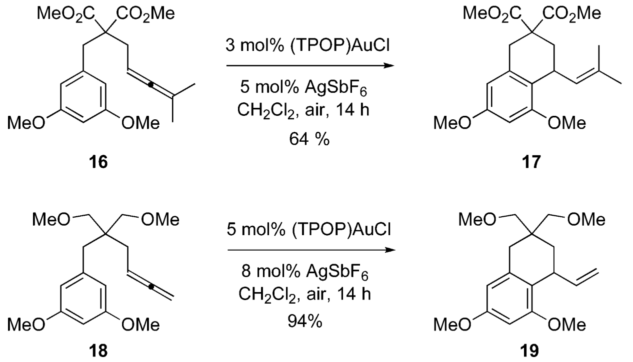
TABLE 3. **Control Experiments[a] Using 2 to Test for Ag^+ or H^+ Background Catalysis**

catalyst	amount	time, temp	products
1	5 mol %	16 h, rt	nr
$AgSbF_6$	5 mol %	16 h, rt	nr
$AgSbF_6$	100 mol %	14 h, 35 °C	90% **3**
TfOH	1 mol %	6 h, rt	<5% conv
TfOH	5 mol %	6 h, rt	30% conv, <1% **3**[c]
$HNTf_2$[b]	1 mol %	6 h, rt	nr
HBF_4•OEt_2	1 mol %	6 h, rt	nr
HBF_4•OEt_2	5 mol %	6 h, rt	nr

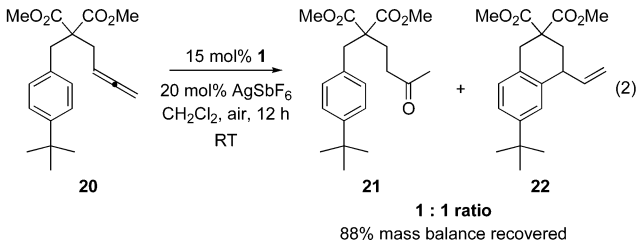
[a] Reaction conditions: 0.2 M **2** in CH_2Cl_2, in air at rt. Conversion was monitored by GC. [b] Tf = trifluoromethanesulfonyl. [c] Six products were observed by GC−MS, the predominant (~30%) being allene hydrolysis to the methyl ketone (*m*/*z* = 352).

stoichiometric amounts of silver but only at higher temperature and longer reaction times (Table 3). Catalytic quantities of triflic acid (5 mol %), $HNTf_2$ (1 mol %), or HBF_4 (1 and 5 mol %) did not produce **3**, ruling out the possibility of a Brønsted pathway. As expected, leaving out the halide abstraction agent did not provide an active catalyst, reinforcing the notion of a $P(OPh)_3Au^+$ active catalyst.

SCHEME 4. Variation in Linker/Allene Substitution



With less activated aryl rings, such as the 4-*tert*-Bu substrate **20**, a major byproduct was allene hydration to methyl ketone **21** (eq 2). The *N* value of ~ −4.0 for a *tert*-butylphenyl group likely represents the lower limit for sufficient π-nucleophilicity to add to the Au^+-activated allene. More electron-deficient arenes (NO_2Ar, BrAr, IAr, etc.) were cleanly converted to the methyl ketone with no trace of cycloisomerized product. A related transformation was recently reported.[18]



Attempts to minimize the allene hydration by using anhydrous CH_2Cl_2 and adding 4 Å MS only led to low conversions (<30%, 72 h). We speculate that the adventitious water acts as a proton shuttle to modulate the rearomatization and protodeauration steps of the mechanism.[19]

In summary, a highly electrophilic phosphite gold(I) catalyst has been applied to the intramolecular allene hydroarylation reaction, producing vinylbenzocycles in good to excellent yields. The catalyst is tolerant of trace water and oxygen, it is bench-stable, and it can be utilized in air with unpurified commercial solvent.

Experimental Section

Representative Cycloisomerization Procedure: To a 5 mL vial charged with a stirbar, **1** (27.2 mg, 0.05 mmol, 1.0 equiv), and $AgSbF_6$ (24.0 mg, 0.07 mmol, 1.4 equiv) was added dichloromethane (1.0 mL) by syringe, at which point a white-gray suspension formed. After 2 min, **2** (168 mg, 0.5 mmol, 10 equiv) was added by pipet. The suspension turned deep green within 20 min. After 6 h, the reaction was loaded directly onto a silica flash column and purified with 1:7 ethyl acetate/hexanes. Yield: 85% of **3** as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 2H), 5.74 (m, 1H), 4.90 (d, 1H, *J* = 10.4 Hz), 4.68 (d, 1H, *J* = 17.2 Hz), 3.77 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.34 (d, 1H, *J* = 16 Hz), 2.99 (d, 1H, *J* = 16.4 Hz), 2.48 (m, 1H), 2.29 (m, 1H). ^{13}C (100 MHz): δ 171.8, 171.7, 159.1, 158.6, 141.3, 135.8, 113.3, 104.3, 97.1, 55.3, 55.2, 52.6, 52.4, 35.4, 35.0, 34.3. HRMS-ESI+: 357.131 calcd for $C_{18}H_{22}O_6 + Na$, found 357.131.

Acknowledgment. Support from the National Institute of General Medicine (GM-60578) is greatly appreciated.

Supporting Information Available: Experimental procedures, ^1H, ^{13}C, and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Hydration of allenyl acetates under solvolysis conditions has been observed: Alameda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2006**, *47*, 913−916.

(19) The Ohno conditions reported in ref 10 include 10% acetic acid to modulate this step; their reported rates are higher than the present results. In a single experiment, we have shown that **2** is converted to **3** (as a mixture of alkene isomers) by 3 mol % of **1**/5 mol % of $AgSbF_6$ in 10:1 DCM/AcOH in <1 h.