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Synthesis of Indenyl Ethers by Gold(I)-Catalyzed Intramolecular Carboalkoxylation of Alkynes

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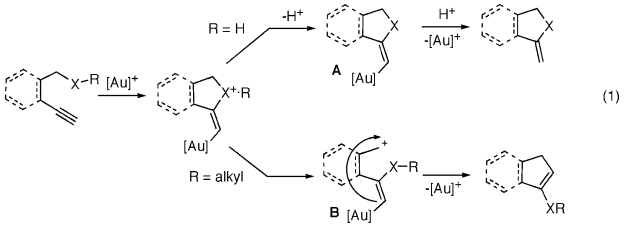
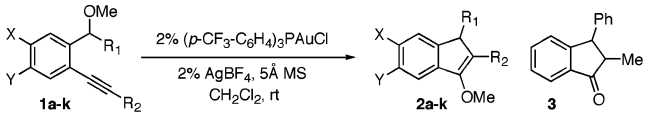
Recently, cationic phosphinegold(I) complexes have been reported to catalyze a variety of transformations involving alkynes. While back-bonding from gold(I) into a cationic intermediate may be essential to some of these transformations,[1] a more conventional reaction pathway relies on the π-acidity of cationic gold(I) complexes to induce a *trans*-addition of a nucleophile generating a vinylgold intermediate (**A**).[2] Trapping of this intermediate with carbon-based electrophiles is challenging, as it undergoes rapid protonation to regenerate the cationic gold(I) catalyst. We hypothesized that protonation of the vinylgold intermediate might be circumvented through intramolecular reaction with an in situ generated electrophile. Toward this goal, we envisioned that a benzylic cation (**B**), a potent electrophile, could be generated by cyclization-induced fragmentation of a C−X bond (eq 1).[3]



(1)

On the basis of this hypothesis, the reaction of gold(I) complexes with benzyl methyl ether **1a** was examined. While no reaction was observed on treatment with neutral Ph_3PAuCl, **1a** was completely consumed on exposure to 2 mol % of Ph_3PAuBF_4, affording a 32% yield of a mixture of enol ether **2a** and indanone **3**.[4] The use of a more electrophilic gold(I) complex, $(p\text{-}CF_3{-}C_6H_4)_3PAuBF_4$,[2f] as a catalyst increased the yield (70%) of cyclized products, however, as a mixture of enol ether **2a** and ketone **3**.[5] Surmising that the ketone arose from hydrolysis of the enol ether with adventitious water, addition of activated molecular sieves produced enol ether **2a** in 81% yield (Table 1, entry 1).[6]

Table 1. Scope of the Gold(I)-Catalyzed Carboalkoxylation

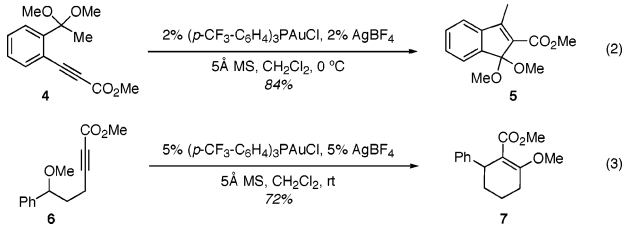


entry	cmpd	X	Y	R_1	R_2	time (h)	yield (%)[a]
1	**a**	H	H	Ph	Me	2	81[b]
2	**b**	H	H	Ph	*n*-Bu	1	96
3	**c**	H	H	Ph	Ph	1.5	95
4	**d**	H	H	Ph	CO_2Me	4	93
5	**e**	CF_3	H	Ph	CO_2Me	24	66[c]
6	**f**	H	MeO	Ph	CO_2Me	2	90
7	**g**	H	H	3-CF_3Ph	CO_2Me	24	41[b,c]
8	**h**	H	H	4-MeOPh	CO_2Me	1.5	99
9	**i**	H	H		Ph	2	92
10	**j**	H	H		CO_2Me	4	83
11	**k**	H	H		CO_2Me	1	99

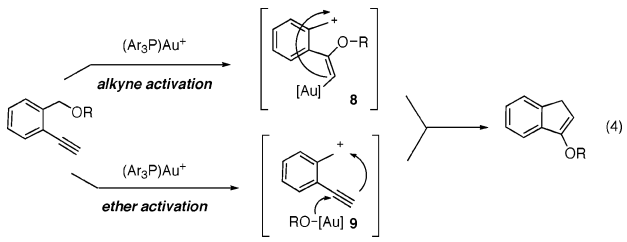
[a] Isolated yields. [b] Conversion by ^{1}H NMR. [c] With 5 mol % of catalyst, 40 °C.

With optimal conditions in hand, we examined the scope of the gold(I)-catalyzed carboalkoxylation. We were pleased to find that the reaction proceeded in high yields with alkyl, phenyl, and ester substituents on the alkyne (entries 2−4). As predicted by the proposed mechanism, the presence of electron-withdrawing groups on the phenyl rings considerably slowed the conversion of **1** to **2** (entries 5 and 7), while functionalization of the latter with electron-donating substituents increased the rate and the yield of the reaction (entries 6 and 8). Additionally, allylic ethers also participated in this gold(I)-catalyzed cyclization (entries 9−11).

On the basis of the requirement for a carbocation-stabilizing substituent at the benzylic position, we reasoned that a carboxonium ion might also be a viable intermediate in this reaction. Accordingly, ketal **4** reacted smoothly to furnish the protected 1-indenone adduct **5** in 84% yield (eq 2).[7] Moreover, the gold(I)-catalyzed reaction was readily extended to the formation of cyclohexene **7** in 72% yield from acyclic benzyl ether **6** (eq 3).



We envisioned two potential mechanisms for these transformations both proceeding through an intermediate carbocation (eq 4). As hypothesized in eq 1, alkyne activation followed by C−O bond scission would generate carbocation **8** which would be trapped by the vinylgold(I) intermediate to give the observed indene adduct. Alternatively, typical Lewis acid activation of the benzylic ether generates carbocation **9** and a gold(I)−alkoxide. Trapping of the cation with the acetylene and (concerted or stepwise) addition of the gold(I)−alkoxide to the alkyne would afford the indenyl ether.



A double label crossover experiment was conducted in order to probe these mechanistic possibilities (eq 5). The lack of observed

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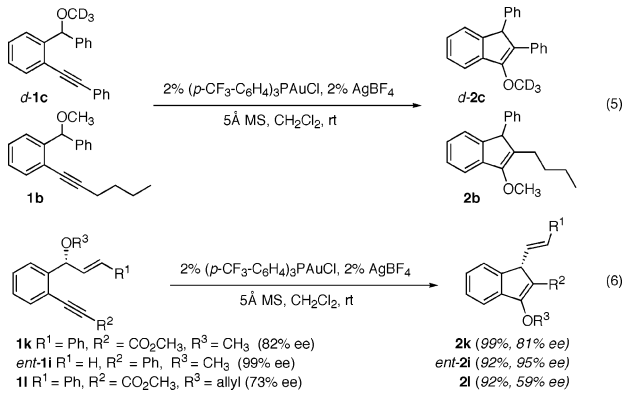
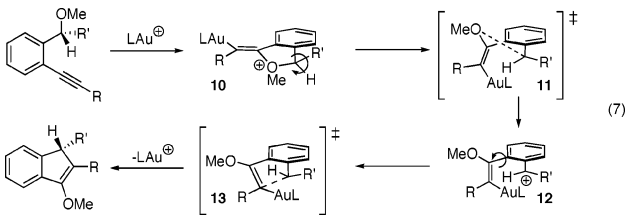
crossover is consistent with a mechanism involving alkyne activation rather than ionization of the benzylic ether; however, a mechanism proceeding through a tight ion pair of **9** could not be excluded. To examine this possibility, enantioenriched **1k** was subjected to the conditions of the gold(I)-catalyzed reaction.[8] At 30% conversion, **1k** was recovered with identical enantiomeric excess further disfavoring a pathway that proceeds through ionization of the methoxy group. Furthermore, we were surprised to find that indene **2k** was also isolated with excellent chirality transfer.[9] A number of allylic ethers underwent the gold(I)-catalyzed rearrangement with only modest deterioration of enantiomeric excess (eq 6).[10]



Given these results, a proposed mechanism is outlined in eq 7. Gold(I)-promoted intramolecular nucleophilic addition of the benzylic ether generates cationic intermediate **10**. Ionization of the C−O proceeds through a transition state (**11**) that maximizes overlap of the forming carbocation with the aromatic π-system and avoids interaction of the benzylic substituent (R′) with the forming enol ether. This pathway allows for the central chirality of the C−O bond to be retained in the axial chirality of carbocation intermediate **12**. Intramolecular addition of the vinylgold(I) moiety to the carbocation, via transition state **13**, transfers the axial chirality to the C−C bond central chirality of the product indene with overall inversion of the stereocenter.[11]



In conclusion, we have reported a gold-catalyzed process ending with the capture of the vinylgold intermediate by a carbon-based electrophile.[12] The gold(I)-catalyzed carboalkoxylation of alkynes proceeds with chirality transfer, providing a rapid entry into functionalized enantioenriched indenyl ethers from readily available benzylic ethers.[13] The resulting enol ethers are well suited for further manipulation, as demonstrated by the diastereoselective formation of a quaternary carbon center via a gold(I)-catalyzed carboalkoxylation/Claisen rearrangement sequence.[9] Further applications and studies on the mechanism of the gold(I)-catalyzed carboalkoxylation reaction are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Catalyst screen, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Reaction of **1a** with 5% $PtCl_2/CO$[3e] (1 atm) at 80 °C in toluene afforded **2a** in 91% yield; however, under identical conditions, a complex mixture was formed in the reaction of **1k**. For additional catalysts examined, see Supporting Information.

(5) Other solvents produced lower yields of cyclized products: toluene, 22%; THF, 0%; acetonitrile, 21%; nitromethane, 6%.

(6) For recent metal-catalyzed synthesis of indanone derivatives, see: (a) Marion, N.; Diez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (b) Shintani, R.; Yashio, K.; Nakamura, T.; Okamoto, K.; Shimada, T.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2772. (c) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872. (d) Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 3248. (e) Kuninobu, Y.; Kawat, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (f) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16043.

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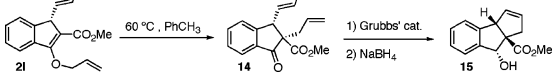
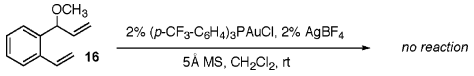
(8) Enantioenriched ethers were prepared from the corresponding alcohols prepared according to **1k** and **1l**: (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. **1i**: (c) Tomita, D.; Wada, R.; Kanai, M. Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.

(9) The absolute configuration of **2l** was assigned using the mandelate ester method on alcohol **15** (see Supporting Information).



(10) Reaction of enantioenriched ether **1c** (89% ee) gave nearly racemic indenyl ether **2c** (9% ee). Similarly, almost racemic **2c** was observed at 50% conversion, while **1c** was recovered without substantial racemization.

(11) A mechanism involving *anti*-addition of an alkyne nucleophile to an allyl or arene−gold(I) complex (as proposed for Pd in ref 7b) would also account for the observed overall inversion. However, this mechanism is not consistent with the observation that, under identical conditions, styrene **16** was recovered unreacted.



(12) For alkylation of a vinylgold(I) species in a gold(I)-catalyzed carbothiolation of alkynes, see: Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

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