Published in final edited form as:
J Am Chem Soc. 2013 August 28; 135(34): 12600–12603. doi:10.1021/ja407150h.

Gold(I)-Catalyzed Enantioselective Carboalkoxylation of Alkynes

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Abstract

A highly enantioselective carboalkoxylation of alkynes catalyzed by cationic (DTBM-MeO-Biphep) gold(I) complexes is reported. Various optically active beta-alkoxy indanone derivatives were obtained in good yields and high enantioselectivities. Furthermore, this methodology was extended to enantioselective syntheses 3-methoxycyclopentenones. The reaction is proposed to proceed through an enantioselective cyclization of intermediates containing vinylgold(I) and prochiral oxocarbenium moieties.

Gold(I)-catalyzed carboalkoxylation of alkynes affords a direct and atom-economical synthetic approach to diversified cyclic enol ethers bearing stereogenic centers at the β position.[1,2] We[2a] and Rhee[2d] reported that carboalkoxylation occurs with efficient chirality transfer from enantioenriched benzylic ethers (Scheme 1a) and N,O-acetals (Scheme 1b), respectively. Despite the intensive development of homogeneous gold(I) catalyzed enantioselective reactions, enantioselective carboalkoxylation of alkynes posed an unsolved challenge.[3] This could be attributed in part to the low reactivity of the ether C-O bond, which necessitates the use of highly electrophilic catalytic systems and precludes many others developed for enantioselective gold catalysis. In addition, our group's previous work pertaining to chirality transfer suggested that initial desymmetrization of sterically modest ether linkages might be required.[2a,4]

Acetals are widely used protecting groups for aldehydes due to their chemical inertness under many reaction conditions. Nevertheless, the use of transition metal catalysts affords the opportunity to use them as reactive functionalities.[5] In 2004, Yamamoto reported the palladium and platinum catalyzed carboalkoxylation of alkyne using acetals.[1b,1c] Inspired by their work, we reasoned that acetals might be better nucleophiles than benzylic ethers for gold-catalyzed carboalkoxylation, due to the stronger resonance stabilization of oxocarbenium ions. We also posited that an additional benefit of the increased electronic stabilization could be a reduction of chirality transfer efficiency, which would provide additional opportunities for enantioinduction. Hydrolysis of the initially formed enol ether product would provide enantioselective access to 3-alkoxyindanones and cyclopentenones (Scheme 1c). The prevalence of these structural motifs in natural products and bioactive molecules makes them valuable targets for enantioselective synthesis.[6] However, few methods have been reported for their preparation, and no catalytic enantioselective approaches are available.[7] Herein, we report the highly enantioselective gold-catalyzed carboalkoxylation of alkynylacetals as a concise and convenient means of accessing diverse enantioenriched 3-alkoxyindanone and cyclopentenones. Furthermore, we present evidence

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The authors declare no competing financial interest.

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

for trapping of the vinylgold intermediate as the enantiodetermining step, in contrast to our previous work with benzylic ethers.

We began our investigation by examining the carboalkoxylation of alkyne **1a** with cationic gold(I) catalysts bearing different chiral bisphosphine ligands (Table 1).[8] Although these catalyst systems all gave good yields, only DTBM-MeO-Biphep$(AuCl)_2$/$AgSbF_6$ induced any significant enantioselectivity. (entry 4). To our delight, simply changing the solvent from CH_2Cl_2 to CCl_4, the ee improved dramatically to 94% without any loss in yield (entry 5). Other nonpolar solvents were screened. Among them, toluene gave the best result and the desired indanone **3** was obtained in 88% yield and 94% ee (entry 7). Finally, decreasing the loading of $AgSbF_6$ to 2.5 mol % further increased both yield and enantioselectivity to 92% isolated yield and 95% ee. (entry 8).

With these optimized conditions in hand, we next investigated the scope of the gold(I)-catalyzed enantioselective carboalkoxylation reaction of alkynes (Table 2). Changing from a dimethyl acetal to a diethyl acetal produced the corresponding indanone in slightly lower enantioselectivity (**3a** vs. **3b**). The impact of substituents on the aromatic ring was also investigated. Substrates with electron-withdrawing group (Cl, F), electron-donating group (MeO) and two substituents on the aryl ring all were well-tolerated (**3c**–**3i**). While the gold-catalyzed reaction to form 7-substituted indanone **3j** required prolonged reaction time, excellent enantioselectivity was still obtained. On the other hand, the reaction of a naphthalene-derived substrate proceeded smoothly under the standard reaction conditions (**3k**).[9] We next explored reactivities of internal alkynes. Phenyl (R2 = Ph) and alkyl (R2 = iPr) substituted of the alkynes were unreactive. Electronic-withdrawing ester substrate (R2 = CO2Me) afforded nearly quantitative yield of enol-ether product (**3l**) but the enantioselectivity was moderate (60% ee).[10]

We next explored the possibility of generating 4-methoxylcyclopentenones from the gold-catalyzed simple vinyl acetylenes (Table 3). Gratifyingly, the reaction displayed high enantioselectivities for different ring size substrates. Although the yields for these substrates were slightly lower compared to phenyl acetylenes, the rapid assemble of various bicyclic cyclopentenones from easily prepared substrates[11] greatly expands the synthetic versatility of the gold-catalyzed reaction.

We envisioned two possible pathways to explain the origin of the enantioinduction. In the first possibility, coordination of chiral cationic gold(I) to the alkyne moiety results in a desymmetrizing alkoxylation of the triple bond.[12] In analogy to the previously studied chirality transfer of benzyl ethers,[2a] the resulting intermediate **A** bearing a chiral acetal-derived cation would undergo rearrangement through chirality-preserving intermediate **B**-*chiral* to provide **C** and subsequently **2a**. In this case the first step would be the enantiodetermining step (EDS). On the other hand, it is possible that oxocarbenium intermediate **B** is sufficiently long lived to relax to an achiral conformation, **B′**-*achiral,* that would undergo enantioselective cyclization to afford **C**. In this second possibility, the nucleophilic addition of a vinylgold species to the oxocarbenium intermediate would be enantiodetermining.[5,13–15]

In order to distinguish between these two plausible mechanisms, the gold-catalyzed reaction of mixed acetal **4a** (d.r. = 1.3:1) was examined (Scheme 3). We anticipated that the sterically-hindered oxygen atom on the methyl lactate moiety would be unable to participate in nucleophilic attack of the alkyne. If the first mechanism were operative, a kinetic resolution would be expected to occur, to return diastereomerically enriched **4a** and the product **5a** or **5b**. As showed in scheme 3, the gold-catalyzed reaction of mixed acetal **4a** selectively gave the cyclized products **5a/5b** and **3a** and **4a** were not detected in the crude

reaction mixtures; therefore, if the chirality transfer pathway were operative, the products (**5a**/**5b**) would be expected to form in approximately the dr of the starting material. However, epimers **5a** and **5b** were formed with similar diastereoselectivity using (*S*) and (*R*) catalysts, respectively. The observation that the catalyst controls the diastereoselectivity in this process, irrespective of the the dr of the starting acetal, is more consistent with the second mode of enantioinduction presented.[16]

In conclusion, we have developed the first gold-catalyzed enantioselective carboalkoxylation of alkynes, including phenyl acetylenes and vinyl acetylenes, which allowed a variety of highly enantioenriched 3-methoxyindanones and cyclopentenones to be prepared.[17] Mechanistic studies suggest that a vinylgold species and a prochiral oxocarbenium are involved the enantioselectivity determining cyclization. Despite the prevalence of vinylgold intermediates in gold-catalyzed reactions of allenes and alkynes,[18] this reaction constitutes a rare example of enantioselective carbon-carbon bond formation from this organometallic species.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge NIHGMS (RO1 GM073932) for financial support. W. Z. is grateful to Shanghai Institute of Organic Chemistry (SIOC) and Zhejiang Medicine for a joint postdoctoral fellowship. We thank Yi-Ming Wang for helpful discussions and proofreading this manuscript.

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8. For additional conditions examined see Supporting Information.
9. The structure and absolute configuration of 3k were determined by single-crystal X-ray diffraction (see the Supporting Information). The stereochemistry of the remaining products was assigned by analogy.
10. In some cases, the obtained enol ether product partly hydrolyzed to ketone during the first step.
11. Vinyl acetylene substrates were prepared from commercially available ketones in four steps, see supporting information for details.
12. For an example of a gold-catalyzed enantioselective desymmetrization of nucleophiles by alkyne activation see: Huang L, Yang HB, Zhang DH, Zhang Z, Tang XY, Xu Q, Shi M. Angew Chem Int Ed. 2013; 52:6767.For additional examples of gold-catalyzed reactions involving alkyne activation, see: Mourad AK, Leutzow J, Czekelius C. Angew Chem Int Ed. 2012; 51:11149.Brazeau JF, Zhang S, Colomer I, Corkey BK, Toste FD. J Am Chem Soc. 2012; 134:2742. [PubMed: 22296571] Cera G, Chiarucci M, Mazzanti A, Mancinelli M, Bandini M. Org Lett. 2012; 14:1350. [PubMed: 22335367] Sethofer SG, Mayer T, Toste FD. J Am Chem Soc. 2010; 132:8276. [PubMed: 20518531]
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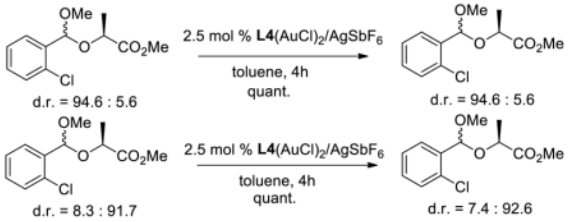
15. Alternatively, and particularly for the reactions in Table 3, the cyclization event can be viewed as a enantioselective electrocyclization of a gold-substituted pentadienyl cation. For related gold-catalyzed electrocyclizations see: Shi X, Gorin DJ, Toste FD. J Am Chem Soc. 2005; 127:5803.Zhang L, Wang S. J Am Chem Soc. 2006; 128:1442. [PubMed: 16448102] Lee HH, Toste FD. Angew Chem Int Ed. 2007; 46:912.Lin CC, Teng TM, Tsai CC, Liao HY, Liu RS. J Am Chem Soc. 2008; 130:16417. [PubMed: 18998692] Bhunia S, Liu RS. J Am Chem Soc. 2008; 130:16488. [PubMed: 19554723] Lemiere G, Gandon V, Cariou K, Hours A, Fukuyama T, Dhimane AL, Fensterbank L, Malacria M. J Am Chem Soc. 2009; 131:2993. [PubMed: 19209868]
16. A pathway involving rapid thermodynamic acetal equilibration followed by enantiodetermining cyclization was excluded by the following experiments:



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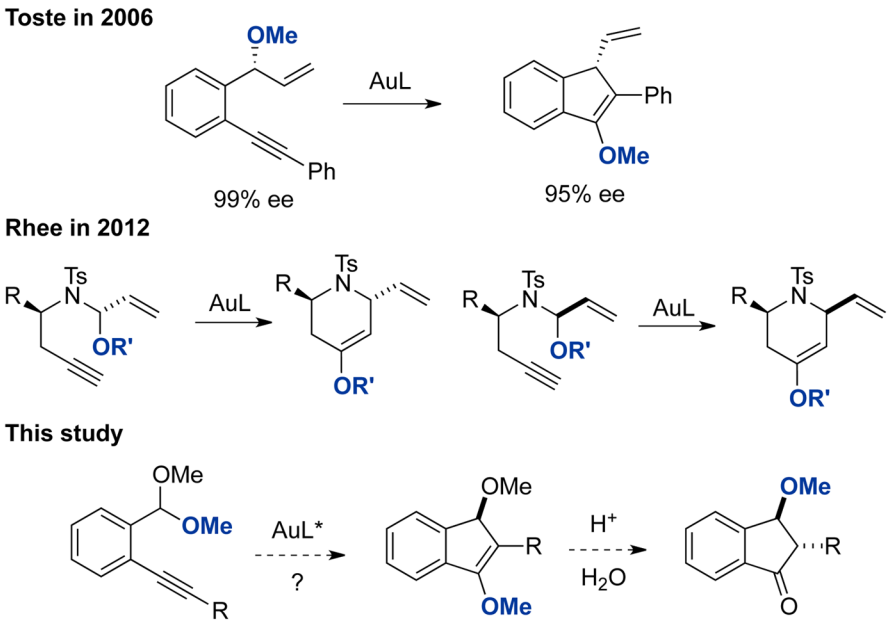
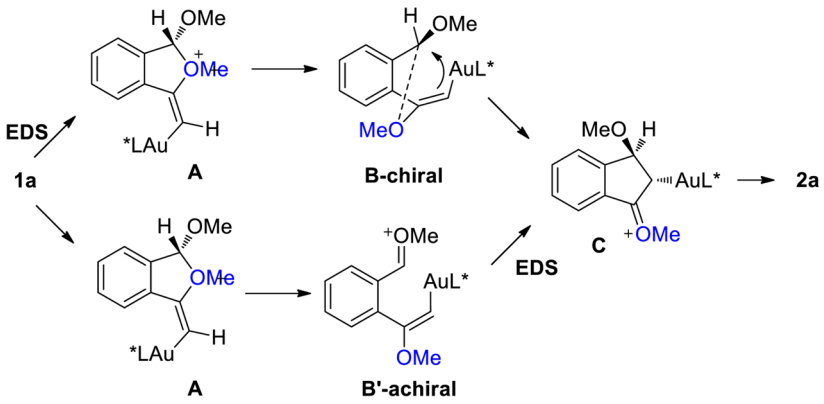
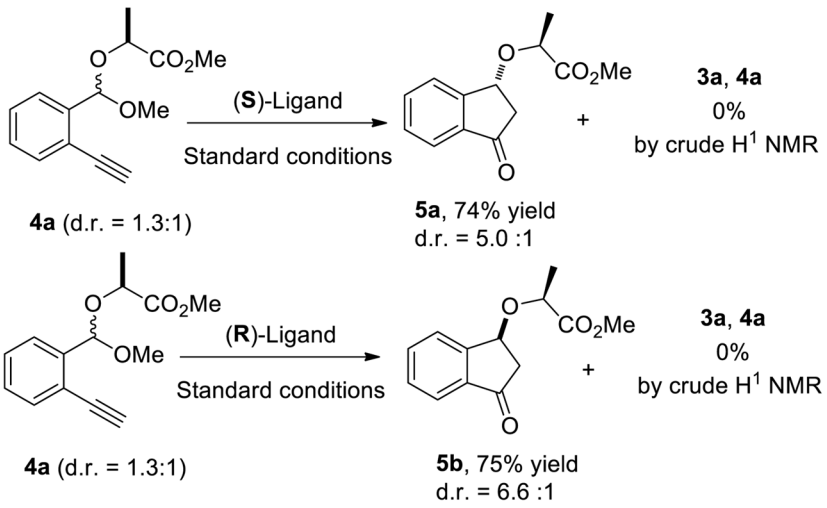
J Am Chem Soc. 2012; 134:9134. [PubMed: 22621418] Miles DH, Veguillas M, Toste FD. Chem Sci. 2013; 4:3427.An enantiodeterming rearrangement of a pentadienyl cation is proposed in: Sethofer SSG, Staben ST, Hung OY, Toste FD. Org Lett. 2008; 10:4315. [PubMed: 18759435]



Scheme 1.
Ether nucleophiles in gold(I)-catalyzed carboalkoxylation



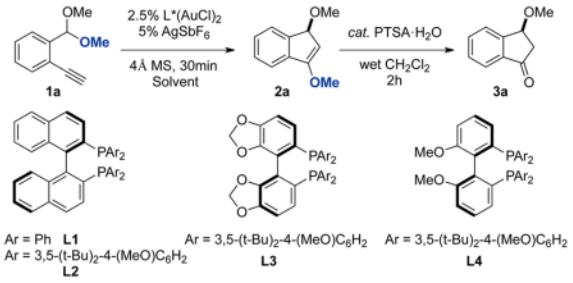
Scheme 2.
Two Possible Pathways



Scheme 3.
Mixed Acetal Study.

Table 1

Optimization of the Reaction Conditions



entry[a]	L	Solvent	yield (%)[b]	ee (%)[c]
1	L1	CH_2Cl_2	75	8
2	L2	CH_2Cl_2	77	2
3	L3	CH_2Cl_2	71	5
4	L4	CH_2Cl_2	74	24
5	L4	CCl_4	74	94
6	L4	Benzene	80	89
7	L4	Toluene	88	94
8[d]	L4	Toluene	92	95

[a] Reaction conditions: 1) 2.5 mol % gold catalyst, 5 mol % $AgSbF_2$, 0.05 mmol **1a**, 10 mg 4Å molecular sieve, 1 mL solvent. 2) 2.5 mol % PTSA • H_2O, 1 mL CH_2Cl_2, 0.1 mL H_2O.

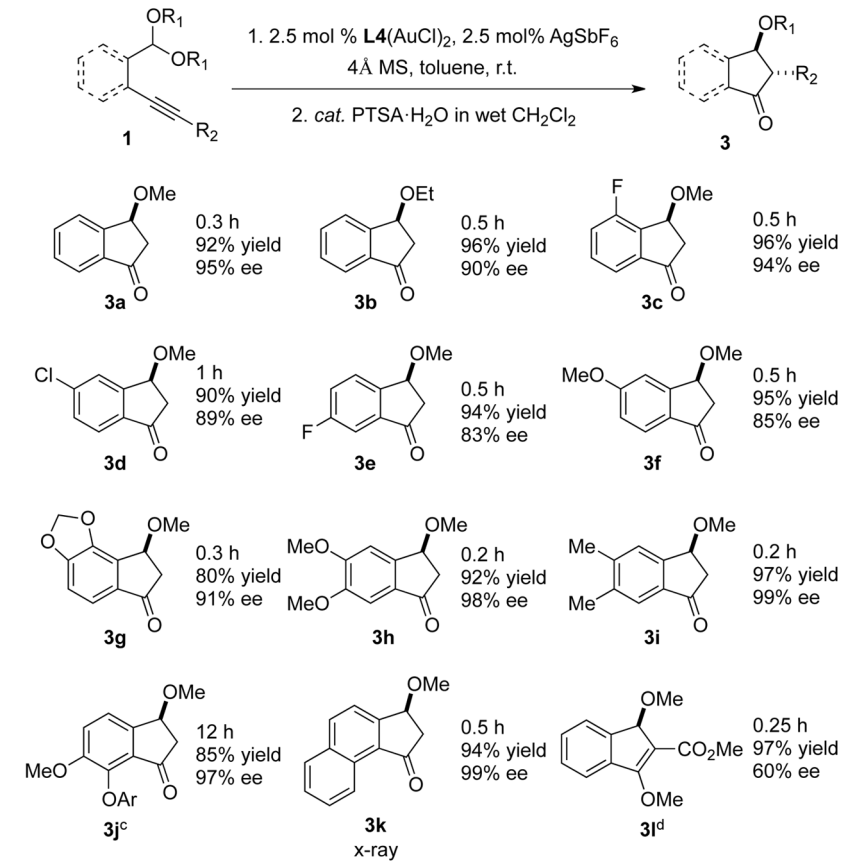
[b] Isolated yields.

[c] Determined by chiral HPLC. Absolute stereochemistry assigned by analogy to **3k**, see the Supporting Information.

[d] 2.5 mol % $AgSbF_6$ was used.

Table 2

Substrate scope for aryl acetylenes[a,b]



[a]Reaction conditions: 1) 2.5 mol % (R)-DTBM-MeO-Biphep(AuCl)2, 2.5 mol % $AgSbF_6$, 0.2 mmol **1**, 50 mg 4Å molecular sieve, 2 mL toluene. 2) 2.5 mol % PTSA • H_2O, 4 mL CH2Cl2, 0.4 mL H2O.

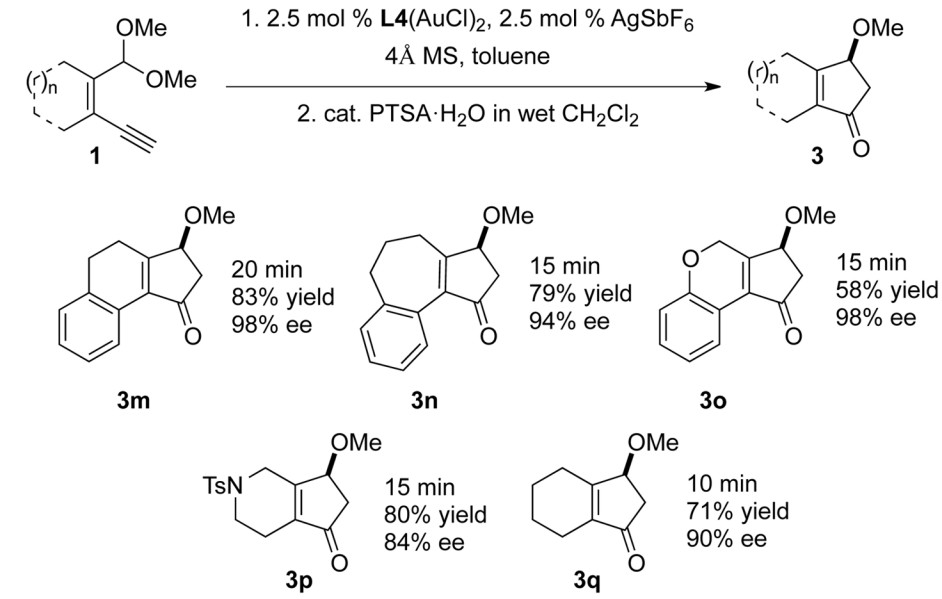
[b]Isolated yields. ee was determined by chiral HPLC. Absolute stereochemistry assigned by analogy to **3k**, see the Supporting Information.

[c]Ar = 4-bromobenzenesulfonyl, 5.0 mol % gold catalyst and 10 mol % $AgSbF_6$ was used.

[d]Enol ether hydrolysis was not performed.

Table 3

Substrate Scope for vinyl acetylenes[a,b]



[a]Reaction conditions see table 2.

[b]Isolated yields. ee was determined by chiral HPLC.