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Gold(I)-Catalyzed Enantioselective Carboalkoxylation of Alkynes

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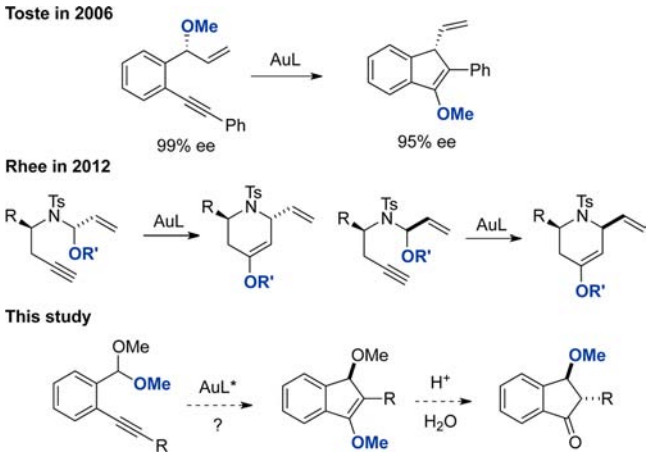
Supporting Information

ABSTRACT: A highly enantioselective carboalkoxylation of alkynes catalyzed by cationic (DTBM-MeO-Biphep)-gold(I) complexes is reported. Various optically active β-alkoxyindanone derivatives were obtained in good yields with high enantioselectivities. Furthermore, this methodology was extended to the enantioselective synthesis of 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 has 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]

Scheme 1. Ether Nucleophiles in Gold(I)-Catalyzed Carboalkoxylation



Acetals are widely used protecting groups for aldehydes because of 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 alkynes using acetals.[1b,c] Inspired by their work, we reasoned that acetals might be better nucleophiles than benzylic ethers for gold-catalyzed carboalkoxylation because of the stronger resonance stabilization of oxocarbenium ions. We also posited that an additional benefit of the increased electronic stabilization could be a reduction of the 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 for their preparation have been reported, and no catalytic enantioselective approaches are available.[7] Herein we report the highly enantioselective gold-catalyzed carboalkoxylation of alkynyl acetals as a concise and convenient means of accessing diverse enantioenriched 3-alkoxyindanones and cyclopentenones. Furthermore, we present evidence 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 dramatically improved the ee to 94% without any loss in yield (entry 5). Other nonpolar solvents were screened. Among them, toluene gave the best results, affording the desired indanone **3** in 88% yield with 94% ee (entry 7). Finally, decreasing the loading of $AgSbF_6$ to 2.5 mol % further increased both the yield and enantioselectivity (92% isolated yield and 95% ee, respectively; 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 with slightly lower enantioselectivity (**3a** vs **3b**). The impact of substituents on the aromatic ring was also investigated. Substrates with an electron-withdrawing group (Cl, F), an electron-donating group (MeO), or two

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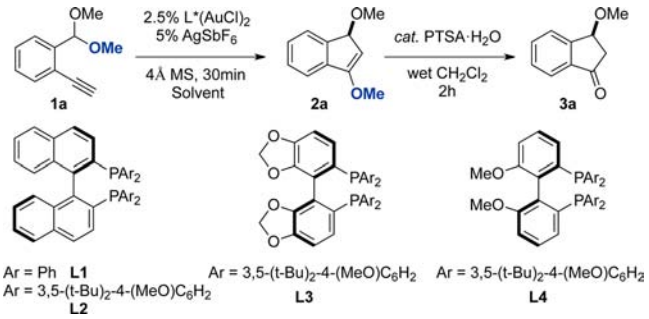
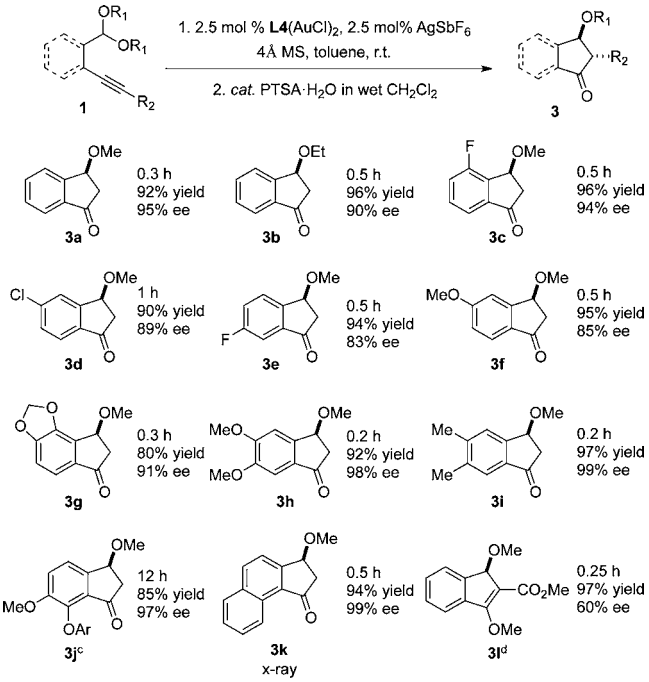
Table 1. Optimization of the Reaction Conditions[a]



entry	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 of **1a**, 10 mg of 4 Å molecular sieves (MS), 1 mL of solvent; (2) 2.5 mol % PTSA·H_2O, 1 mL of CH_2Cl_2, 0.1 mL of H_2O. [b]Isolated yields. [c]Determined by chiral HPLC. Absolute stereochemistries were assigned by analogy to **3k** (see the Supporting Information). [d]2.5 mol % $AgSbF_6$ was used.

Table 2. Substrate Scope of Aryl Acetylenes[a,b]

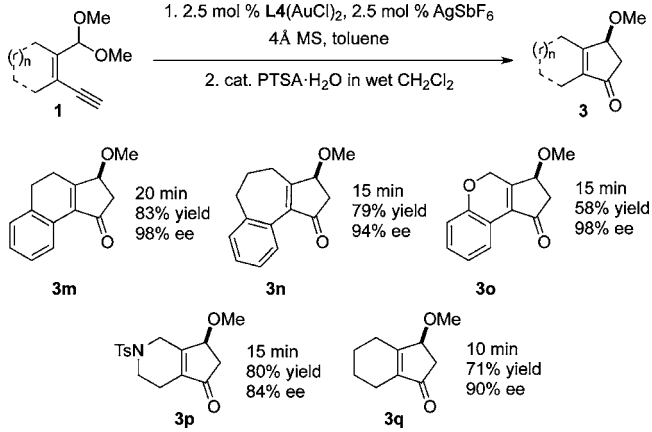


[a]Reaction conditions: (1) 2.5 mol % (*R*)-DTBM-MeO-Biphep-$(AuCl)_2$, 2.5 mol % $AgSbF_6$, 0.2 mmol of **1**, 50 mg of 4 Å MS, 2 mL of toluene; (2) 2.5 mol % PTSA·H_2O, 4 mL of CH_2Cl_2, 0.4 mL of H_2O. [b]Isolated yields are shown; ee's were determined by chiral HPLC. Absolute stereochemistries were assigned by analogy to **3k** (see the Supporting Information). [c]Ar = 4-bromobenzenesulfonyl; 5.0 mol % gold catalyst and 10 mol % $AgSbF_6$ were used. [d]Enol ether hydrolysis was not performed.

substituents on the aryl ring all were well-tolerated (**3c–i**). While the gold-catalyzed reaction to form 7-substituted indanone **3j** required a 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 the reactivities of internal alkynes. Alkynes with phenyl (R_2 = Ph) or alkyl (R_2 = iPr) substitution were unreactive. An electron-withdrawing ester substrate (R_2 = CO_2Me) afforded a nearly quantitative yield of enol ether product (**3l**), but the enantioselectivity was moderate (60% ee).[10]

The possibility of generating 4-methoxycyclopentenones by the gold-catalyzed reaction of simple vinyl actetylenes was also examined (Table 3). Gratifyingly, the reaction displayed high

Table 3. Substrate Scope of Vinyl Acetylenes[a,b]

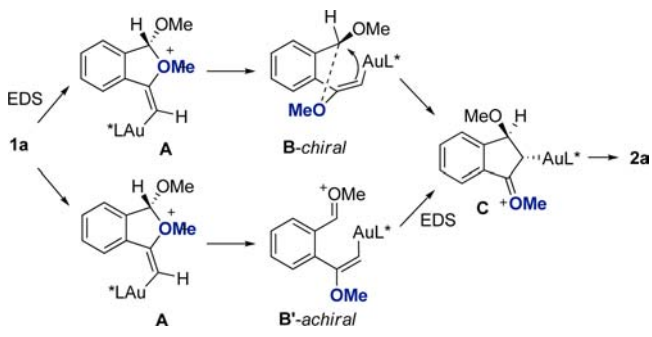


[a]For the reaction conditions see Table 2, footnote *a*. [b]Isolated yields are shown; ee's were determined by chiral HPLC.

enantioselectivities for substrates with different ring sizes. Although the yields for these substrates were slightly lower than for phenyl acetylenes, the rapid assembly 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 (Scheme 2). In the first possibility, coordination of the chiral cationic gold(I) complex to the alkyne moiety would result in 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**

Scheme 2. Two Possible Pathways



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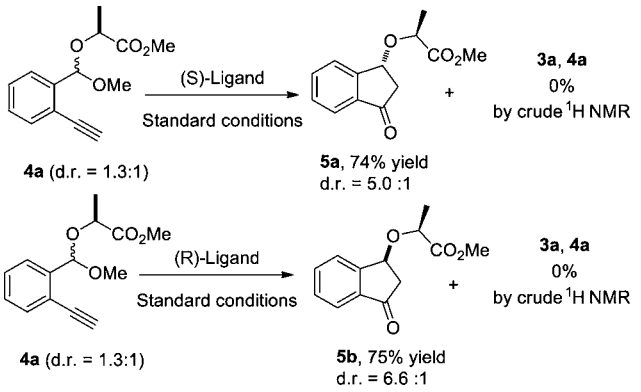
and subsequently **2a**. In this case, the first step would be the enantiodetermining step (EDS). On the other hand, it is possible that oxocarbenium intermediate **B** is sufficiently long-lived to relax to an achiral conformation, **B′-achiral**, that would undergo enantioselective cyclization to afford **C**. In this second possibility, the nucleophilic addition of a vinylgold species to the oxocarbenium intermediate would be the EDS.[5,13−15]

To distinguish between these two plausible mechanisms, the gold-catalyzed reaction of mixed acetal **4a** (dr = 1.3:1) was examined (Scheme 3). We anticipated that the sterically

Scheme 3. Mixed Acetal Study



hindered oxygen atom on the methyl lactate moiety would be unable to participate in nucleophilic attack on the alkyne. If the first mechanism were operative, a kinetic resolution would be expected to occur, returning diastereomerically enriched **4a** and the product **5a** or **5b**. As shown 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 same dr as 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 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 suggested that a vinylgold species and a prochiral oxocarbenium ion 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.

■ ASSOCIATED CONTENT

Supporting Information

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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Notes

The authors declare no competing financial interest.

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(8) For additional conditions examined, see the Supporting Information.

(9) The structure and absolute configuration of **3k** were determined by single-crystal X-ray diffraction (see the Supporting Information). The stereochemistries of the remaining products were assigned by analogy.

(10) In some cases, the obtained enol ether product partially hydrolyzed to the corresponding ketone during the first step.
(11) Vinyl acetylene substrates were prepared from commercially available ketones in four steps (see the Supporting Information for details).
(12) For an example of a gold-catalyzed enantioselective desymmetrization of nucleophiles by alkyne activation, see: (a) Huang, L.; Yang, H.-B.; Zhang, D.-H.; Zhang, Z.; Tang, X.-Y.; Xu, Q.; Shi, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6767. For additional examples of gold-catalyzed reactions involving alkyne activation, see: (b) Mourad, A. K.; Leutzow, J.; Czekelius, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 11149. (c) Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742. (d) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350. (e) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.
(13) For an example of enantioselective trapping of a enamide−gold species generated from an alleneamide, see: (a) Suárez-Pantiga, S.; Hernández-Diaz, C.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11552. For enantioselective trapping of an allylgold intermediate, see: (b) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972.
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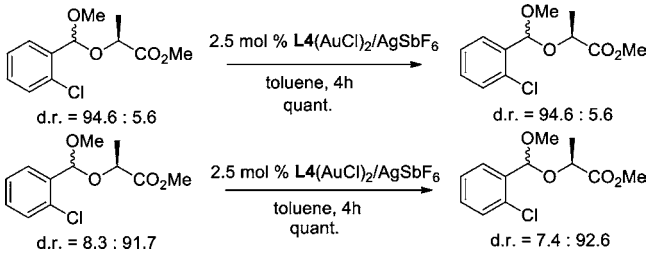
(15) Alternatively, and particularly for the reactions in Table 3, the cyclization event can be viewed as an enantioselective electrocyclization of a gold-substituted pentadienyl cation. For related gold-catalyzed electrocyclizations, see: (a) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5803. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Lee, H. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912. (d) Lin, C.-C.; Teng, T.-M.; Tsai, C.-C.; Liao, H.-Y.; Liu, R. S. *J. Am. Chem. Soc.* **2008**, *130*, 16417. (e) Bhunia, S.; Liu, R. S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (f) Lemiere, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993.
(16) A pathway involving rapid thermodynamic acetal equilibration followed by enantiodetermining cyclization was excluded by the following experiments:



(17) During the preparation of this manuscript, a gold-catalyzed cycloaddition of 2-ethynylbenzyl ethers with organic oxides and α-diazoesters was reported. See: Pawar, P. K.; Wang, C.-D.; Bhunia, S.; Jadhav, A. M.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559.
(18) Trapping of a vinyl gold species has been proposed as the enantiodetermining step in the addition of nucleophiles to allenes. See: (a) Brown, T. J.; Weber, D.; Gagné, M. R.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 9134. (b) Miles, D. H.; Veguillas, M.; Toste, F. D. *Chem. Sci.* **2013**, *4*, 3427. An enantiodetermining rearrangement of a pentadienyl cation is proposed in the following work: (c) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315.