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Chiral (Acyclic Diaminocarbene)Gold(I)-Catalyzed Dynamic Kinetic Asymmetric Transformation of Propargyl Esters

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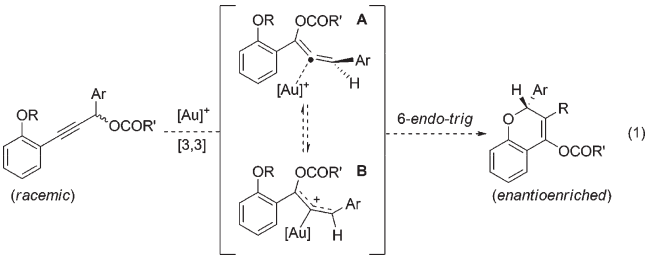
Supporting Information

ABSTRACT: A highly enantioselective transformation catalyzed by chiral (acyclic diaminocarbene)gold(I) complexes is reported. The enantioselective synthesis of 2-substituted chromenyl pivalates from racemic phenol-substituted propargyl pivalates was developed. Rearrangement of the substrates in the presence of cationic gold gave allene intermediates, whose cyclization resulted in formation of enantioenriched product through a dynamic kinetic asymmetric transformation.

Gold(I)-catalyzed nucleophilic addition to allenes has been studied intensively in recent years as an atom-economical approach to the synthesis of heterocyclic compounds.[1] While several examples of enantioselective reactions catalyzed by cationic gold(I) complexes bearing phosphorus ligands are now known,[2−4] these complexes are not universally applicable in gold-catalyzed transformations. Notably, gold(I)−carbene complexes can catalyze reactions with reactivity and selectivity dramatically different from those observed when the phosphine-ligated complexes are employed as catalysts.[5,6] However, transformations using chiral cationic gold(I)−carbene complexes as catalysts have generally proceeded with low to moderate levels of enantioselectivity.[7] Herein, we report a highly enantioselective synthesis of substituted chromenyl pivalates catalyzed by a gold(I)−carbene complex.



The gold-catalyzed rearrangement of propargylic esters to allenes through formal [3,3] sigmatropic rearrangement is well-known.[8] We envisioned a scenario in which the intermediate gold(I)−allene complex formed in such a rearrangement could be trapped by a pendant phenol nucleophile to give a 6-*endo*-trig cyclization intermediate (eq 1). In previously reported gold-catalyzed transformations involving allenes, both chirality transfer and loss of chirality have been observed, depending on both the substitution pattern of the allene and the nature of the gold catalyst.[9] In the case of propargylic esters, the donating oxygen substituent of the product allene greatly stabilizes the planar allyl cation-like form **B**, resulting in relatively shallow barriers to loss of configuration.[9b] We hypothesized that chiral ligands for gold that provided access to this achiral intermediate could be employed in a dynamic kinetic asymmetric transformation.[10]

To test our hypotheses, we surveyed gold(I)−phosphine complexes that were previously used successfully in asymmetric allene additions. Encouragingly, when propargyl ester **1a** was treated with (*R*)-DTBM-Segphos$(AuCl)_2$ or (*R*)-DTBM-MeO-Biphep$(AuCl)_2$ in the presence of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF), the desired adduct **2a** was formed with moderate enantioselectivity (Table 1, entries 1 and 2).

We posited that the modest enantioselectivity in these transformations might be the result of a slow gold-promoted equilibration of the allene enantiomers through **B** whose rate could be enhanced by electron-rich ligands for gold. In accord with this hypothesis, phosphoramidite catalyst **L3**·(AuCl),[3c] which we have successfully applied in gold-catalyzed reactions of allenes, catalyzed the formation of **2a** with poor enantioselectivity. Therefore, we hypothesized that electron-donating carbene ligands would be ideal for this transformation; however, chiral NHC complex **L4**·(AuCl)[7b] afforded product **2a** with poor enantioselectivity (entry 4).

Inspired by the success with 3,3′-modified BINOL-derived phosphoramidite ligands in gold catalysis,[3] we considered acyclic carbene ligands[11] based on 3,3′-functionalization of BINAM. Although initial experiments with the reported[7a] acyclic carbene **A1**·$(AuCl)_2$ as a catalyst resulted in disappointing enantioselectivities, we found that complex **A2**·$(AuCl)_2$ with phenyl substituents at the 3,3′-positions of the BINAM scaffold gave improved enantioselectivities (entry 6). We investigated the effect of 3,3′-substitution on reactivity and enantioselectivity in more detail. Of the substitution patterns surveyed, only 4-substitution of the 3,3′-aryl group resulted in improved enantioselectivities, while the electronics of the substituents appeared to be unimportant (entries 10−12). Further optimization of 4-trifluoromethylphenyl-substituted catalyst **A8** (Figure 1) with respect to the counterion revealed that using AgOTf in place of NaBARF resulted in further improvements in yield and enantioselectivity (entry 13).[12] Finally, lowering the reaction temperature to 0 °C afforded **2a** in 85% yield and 91% enantiomeric excess (entry 14).

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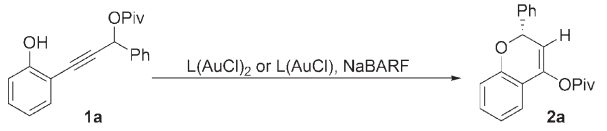
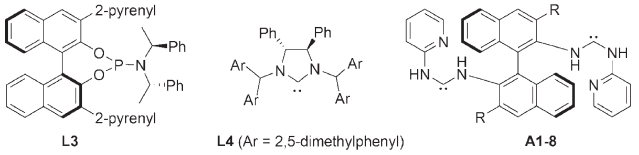
Table 1. Au(I) Catalyst Screen



entry[a]	precatalyst[e]	R	% ee[f] (% yield[h])
1	**L1**·$(AuCl)_2$	—	52
2	**L2**·$(AuCl)_2$	—	60
3[b]	**L3**·(AuCl)	—	0
4[b]	**L4**·(AuCl)	—	7
5	**A1**·$(AuCl)_2$	H	22
6	**A2**·$(AuCl)_2$	Ph	56
7	**A3**·$(AuCl)_2$	3,5-$(MeO)_2C_6H_3$	7
8	**A4**·$(AuCl)_2$	2,6-$(MeO)_2C_6H_3$	—[g]
9	**A5**·$(AuCl)_2$	2-Naph	50
10	**A6**·$(AuCl)_2$	4-^{t}BuC_6H_4	63
11	**A7**·$(AuCl)_2$	4-MeOC_6H_4	68
12	**A8**·$(AuCl)_2$	4-$CF_3C_6H_4$	73 (56)
13[c]	**A8**·$(AuCl)_2$	4-$CF_3C_6H_4$	85 (78)
14[d]	**A8**·$(AuCl)_2$	4-$CF_3C_6H_4$	91

[a] Conditions: CH_2Cl_2 (0.05 M), 5 mol % precatalyst, 10 mol % NaBARF for 16 h at room temperature. [b] With 5 mol % NaBARF used. [c] With 10 mol % AgOTf used in place of NaBARF. [d] With 10 mol % AgOTf used in place of NaBARF, in $CDCl_3$ (0.1 M) at 0 °C in 85% isolated yield. [e] **L1** is (*R*)-DTBM-Segphos, and **L2** is (*R*)-DTBM-MeO-Biphep. [f] Determined by chiral HPLC. [g] Low yield of **2a**; enantioselectivity not determined. [h] Determined by ^{1}H NMR with *m*-dinitrobenzene as the internal standard.



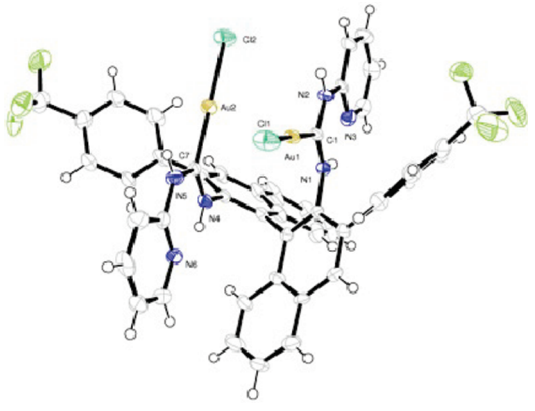
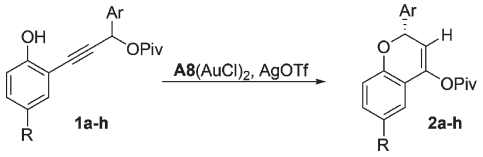


Figure 1. X-ray structure of **A8**.

Under these conditions, we examined the scope of the gold-catalyzed kinetic dynamic asymmetric transformation (Table 2). Steric bulk at the *ortho* and *para* positions of the propargyl aryl ring was tolerated (entries 3−5). Moreover, electron-withdrawing substituents on the aryl moiety also furnished the desired adducts with good yields and enantioselectivities (entries 2 and 6). Good yields and enantioselectivities were also obtained from the gold-catalyzed rearrangement of substrates with further substitution on the phenol (entries 7 and 8).[13]

Table 2. Enantioselective Synthesis of Chromenyl Pivalate from Phenols



entry[a,b]	1	R	Ar	% yield[c]	% ee[d]
1	**1a**	H	Ph	85	91
2	**1b**	H	*p*-BrC_6H_4	86	86
3	**1c**	H	2-Naph	68	84
4	**1d**	H	*o*-MeC_6H_4	77	84
5	**1e**	H	*p*-^{i}PrC_6H_4	73	89
6	**1f**	H	*p*-$CF_3C_6H_4$	76	88
7	**1g**	Me	Ph	85	90
8	**1h**	Br	Ph	83	83

[a] Conditions: $CDCl_3$ (0.1 M), 5 mol % **A8**·$(AuCl)_2$, 10 mol % AgOTf for 4 h at 0 °C. [b] Absolute stereochemistry assigned by analogy to **4e** (Table 3). [c] Isolated yield of product after column chromatography. [d] Determined by chiral HPLC.

We next looked at alkylated phenols, to explore the possibility of generating 3-substituted chromenes. Carbodemetalation of the vinylgold intermediate by a stabilized carbocation lost from the oxonium moiety would result in formal 1,3-migration of an electron-rich alkyl group and formation of a carbon−carbon bond. Gratifyingly, *p*-methoxybenzylether **3a** reacted smoothly under the standard conditions to afford 3-substituted product **4a** in excellent yield and enantioselectivity (entry 1). A variety of other electron-rich arylmethyl phenyl ethers, including those derived from N-, O-, and S-heterocycles, similarly underwent cyclization and O-to-C transfer to provide the products in excellent enantioselectivity and yield (Table 3).[14,15]

To gain a better mechanistic understanding of the reaction, the gold-catalyzed rearrangement of enantioenriched **1a** (60% ee) was examined. When the reaction was halted at 70% conversion, starting material was reisolated in a diminished 17% ee and product **2a** in 88% ee (eq 2). This observation suggests either racemization of starting material via **B** (eq 1) or selective reactivity of the enantiomers of **1a**, resulting in kinetically resolved starting material. To distinguish between these possibilities, the **A8**·$(AuCl)_2$-catalyzed reaction of racemic **1a** was conducted until 60% conversion had been reached (eq 2). Under these conditions, the recovered starting material **1a** was isolated in 47% ee (enriched in the opposite enantiomer) and the product **2a** in 90% ee. These results imply a kinetic resolution of the starting material and a relatively slow equilibration between the starting material and the intermediate gold-coordinated allene. Enantiodetermining cyclization onto the rapidly interconverting isomers of **A** and/or **B** then accounts for the observed *dynamic* kinetic resolution.

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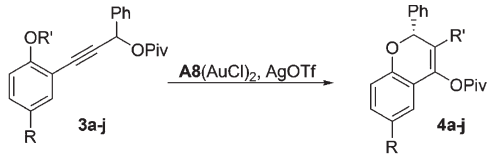
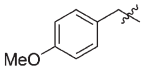
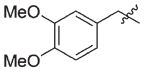
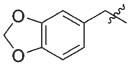
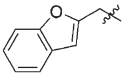
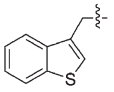
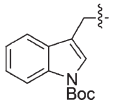
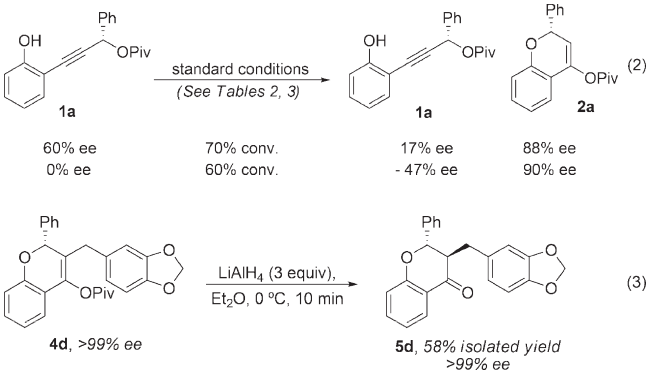
Table 3. Enantioselective Synthesis of Chromenyl Pivalate from Phenol Ethers



entry[a,b]	3	R	R'	% yield[b]	% ee[d]
1	**3a**	H		92	>99
2	**3b**	Me		75	>99
3[c]	**3c**	Me		62	99
4	**3d**	H		91	>99
5	**3e**	H		59	99
6[c]	**3f**	H		75	>99
7	**3g**	H		75	97
8	**3h**	H		73	99
9[c]	**3i**	H		73	96
10	**3j**	H		94	95

[a] Conditions: $CDCl_3$ (0.1 M), 5 mol % **A8**·$(AuCl)_2$, 10 mol % AgOTf for 4 h at 0 °C. [b] Isolated yield of product after column chromatography. [c] At room temperature. [d] Determined by chiral HPLC.



In summary, we report the application of modular 3,3′-substituted BINAM-derived acyclic diaminocarbene ligands to a highly enantioselective gold(I)-catalyzed reaction. The chiral acyclic carbenegold(I) catalyzed dynamic kinetic asymmetric transformation allows for the enantioselective synthesis of chromenyl pivalates from racemic propargyl pivalates. These adducts serve as useful precursors to enantioenriched chromanones. For example, treatment of **4d** with $LiAlH_4$ at 0 °C provided chromanone **5d** as a single diastereomer in >99% ee (eq 3).[16,17] The chiral carbene catalysts offer better enantioselectivity and reactivity than phosphine− and phosphoramidite−gold(I) catalysts that have previously been developed for enantioselective gold catalysis. Finally, we demonstrate that the generation of configurationally labile intermediates from propargyl esters is a promising strategy for asymmetric gold catalysis.

■ ASSOCIATED CONTENT

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

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(12) Replacing the NaBARF with silver salts in the (phosphine)gold(I)-catalyzed reactions (Table 1, entries 1 and 2) resulted in diminished yield and no improvement in enantioselectivity.

(13) Substrates with electron-donating substituents on the propargyl aryl ring could not be prepared or gave poor yields because of extensive decomposition of starting material. When the propargyl aryl ring was replaced with a cyclohexyl group, the product mixture consisted of a 3:1 mixture of benzofuran product (from 5-*endo*-dig cyclization of the starting propargyl ester) and the desired chromenyl pivalate. Substrate **1a** with an additional methyl group at the propargylic position gave desired product in only 11% ee.

(14) Gold-catalyzed reactions terminated by a carbodeauration: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (b) Dube, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (c) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649. (d) Renault, J.; Qian, Z.; Uriac, P.; Gouault, N. *Tetrahedron Lett.* **2011**, *52*, 2476. For a review of reactions of organogold compounds with electrophiles, see:(e) Hashmi, A. S. K.; Ramamurthi, T. D.; Toss, M. H.; Tsang, A. S.-K.; Graf, K. *Aust. J. Chem.* **2010**, *63*, 1619.

(15) A crossover experiment performed using a 1:1 mixture of **3b** and **3d** gave no crossover products, as observed by ^{1}H NMR and HRMS (ESI). This is consistent with direct intramolecular alkyl migration or migration via a contact ion pair and is consistent with previous reports.[14]

(16) The structure and absolute configuration of **4e** were determined by single-crystal X-ray diffraction (see the Supporting Information). The stereochemistry of the remaining products was assigned by analogy.

(17) The relative configuration was assigned by analogy to *trans*-2-phenyl-3-propylchromanone: Saito, A.; Kasai, J.; Odaira, Y.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 5644.