VIP Enantioselective Gold Catalysis

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Enantioselective Alkynylbenzaldehyde Cyclizations Catalyzed by Chiral Gold(I) Acyclic Diaminocarbene Complexes Containing Weak Au–Arene Interactions**

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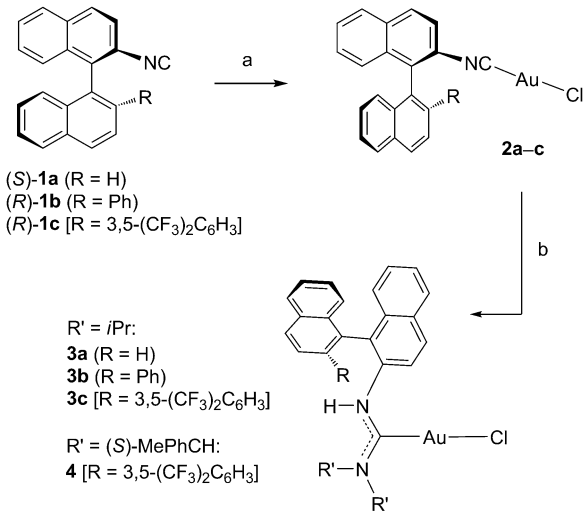
Catalysis with gold(I) has emerged as a powerful tool for the synthesis of complex organic structures, owing to the ability of Au^I to activate a variety of unsaturated bonds toward nucleophilic attack.[1] In efforts to develop enantioselective catalysts, the linear coordination geometry of Au^I presents challenges because of the remoteness of chiral ligand substituents and the inability of substrates to adopt a chelate binding mode that favors asymmetric induction. Nevertheless, high enantioselectivities have been achieved with gold catalysts in an impressive number of reactions.[2] In a few cases, there is evidence that secondary interactions of the ligand help to overcome the inherent difficulty of achieving a chiral environment at a Au^I center.[3] The seminal example of asymmetric gold catalysis utilized the electrostatic attraction between a pendant ammonium group and the substrate to achieve highly enantioselective aldol reactions.[4] For bis(gold) complexes of chiral biaryl diphosphines—currently the most successful chiral catalyst design for Au^I—it has been proposed that π–π interactions of the phosphine substituents play a key role in creating a chiral pocket around the metals.[5] In one intriguing report, interactions of electron-rich aryl groups of chiral phosphoramidite ligands with Au^I were found to greatly enhance the chirality of the substrate binding site.[6] Herein we report that secondary interactions of Au^I with electron-deficient aryl substituents on chiral carbene ligands are associated with highly enantioselective catalysis in a tandem addition/cycloisomerization reaction. These results suggest a new chiral catalyst design motif that could enable further advances in enantioselective applications of Au^I catalysts.

Acyclic diaminocarbene ligands (ADC),[7] also known as nitrogen acyclic carbenes (NAC), are potentially advantageous over the more familiar N-heterocyclic carbenes (NHC) for enantioselective catalysis,[8] because their wide N-C-N angles (116–121°) can place chiral substituents closer to the metal. However, few examples of chiral ADC ligands have appeared despite growing interest in the use of ADC ligands in catalysis.[9,10] Significant asymmetric induction has only been achieved using chelating[11] or bridging[12] chiral bis(ADC) ligands. Only recently has an *ee* value above 90% been reported for a reaction using an ADC/metal catalyst, notably a bis(ADC) digold complex.[12b] Only low *ee* values have been attained with monodentate ADC ligands,[13] and no *ee* value higher than 70% has been reported for a chiral monodentate NHC/Au^I catalyst.[14]

We envisioned creating ADC complexes with chiral groups near the catalytic site by the addition of bulky amines to Au^I complexes of suitably substituted chiral biaryl isocyanides. As no chiral monoisocyanides of this type are known,[15] we devised syntheses of 2-isocyanobinaphthyls **1a–c** (Scheme 1) starting from the corresponding alcohols (see the Supporting Information). Metalation with Au(THT)Cl provided the Au^I complexes **2a–c**, which cleanly converted into enantiomerically pure ADC complexes **3a–c** upon reaction with diisopropylamine.

X-ray crystal structures of **3a–c** revealed that the ADC ligands adopt conformations with the binaphthyl groups *syn* to gold, probably to avoid steric clashes with the *i*Pr groups (Figure 1).[16] ^{1}H NMR spectra indicated static conformations in solution at 25 °C, with no sign of isomerization about the carbene C–N bonds.[10c] Complex **3a** forms dimers with aurophilic contacts of 3.36 Å, but this packing arrangement is sterically prohibited by the 2′-aryl groups in **3b** and **3c**. Two different rotameric forms of the ADC ligand are present in



Scheme 1. Synthesis of chiral gold(I) ADC complexes. Reaction conditions: a) Au(THT)Cl, RT, 9 h, CH_2Cl_2; b) HNR'_2, RT, 2 h, CH_2Cl_2; then 60 °C, 6–8 h, CH_3CN. THT = tetrahydrothiophene.

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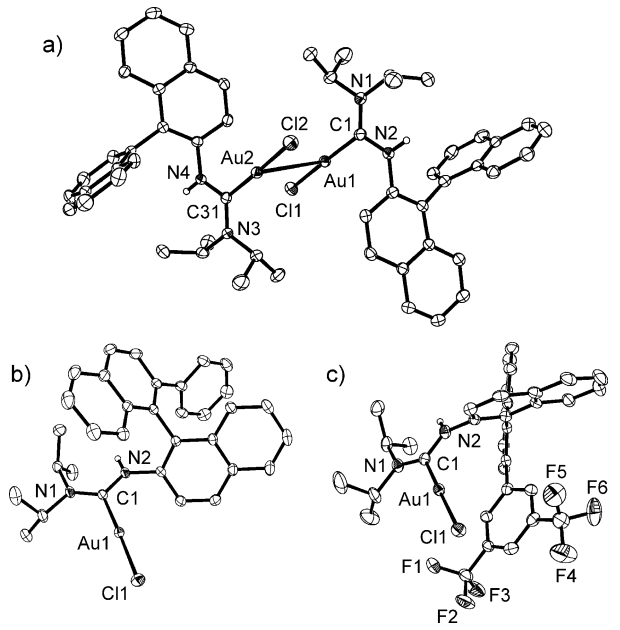
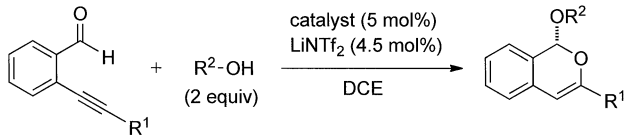


Figure 1. X-ray crystal structures of a) **3a**, b) **3b**, and c) **3c**. Displacement ellipsoids are drawn at the 50% probability level, and non-N–H hydrogen atoms are omitted for clarity. A second, crystallographically nonequivalent complex of **3c** has a similar geometry but is not shown.

Table 1: Catalytic alkynylbenzaldehyde cyclizations.[a]



5a R^1=Ph
5b R^1=*p*-tolyl
5c R^1=*n*Pr

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Entry	5	R^2	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**5a**	*i*Pr	**3a**	37	12[d]	8
2[e]	**5a**	*c*Hex	**3a**	36	31	27
3	**5a**	*i*Pr	**3b**	36	28[d]	61
4[e]	**5a**	*c*Hex	**3b**	36	5[d]	43
5[f]	**5a**	*i*Pr	**3c**	12	68	84
6[e]	**5a**	*c*Hex	**3c**	36	65	98
7[e]	**5b**	*c*Hex	**3c**	37	70	98
8[e]	**5a**	*t*Bu	**3c**	36	66	96
9[e]	**5a**	benzyl	**3c**	28	68	98
10[e]	**5a**	*n*Oct	**3c**	36	87	99
11[e]	**5b**	*n*Oct	**3c**	36	75	99
12[f]	**5c**	*n*Oct	**3c**	37	5[d]	nd[g]
13[e]	**5a**	*n*Bu	**3c**	36	12[d]	nd[g]
14[f]	**5a**	*n*Pr	**3c**	36	5[d]	69
15[f,h]	**5a**	Me	**3c**	24	NR[d,i]	-
16[f,h]	**5b**	Me	**3c**	18	37[d]	56
17[f,h]	**5c**	Me	**3c**	12	NR[d,i]	-
18	**5c**	*n*Oct	**4**	37	86	99
19[e]	**5a**	*n*Bu	**4**	36	59	92
20	**5a**	*n*Pr	**4**	36	67	89
21[h]	**5a**	Me	**4**	24	75	87
22[h]	**5b**	Me	**4**	24	75	92
23[h]	**5c**	Me	**4**	12	26	61
24	**5a**	*i*Pr	**4**	18	70	>99

[a] Reaction conditions: catalyst (5 mol%), $LiNTf_2$ (4.5 mol%), 25°C (except as noted), dichloroethane (DCE, 0.25 M). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] **5** recovered. [e] At 60°C. [f] Yield not improved at 60°C. [g] Not determined. [h] 1.1 equiv MeOH used. [i] No product detected.

the structures of **3b** and **3c**. In **3b**, the binaphthyl group is rotated away from the AuCl unit, thus orienting the 2′-phenyl substituent away from the coordination sphere. However, **3c** adopts a conformation that places the 3,5-$(CF_3)_2C_6H_3$ group directly adjacent to gold; this conformation is unexpected given the larger steric profile of this substituent. The aryl ring centroid is only 3.4 Å from the Au atom of **3c** (3.6 Å for a second, crystallographically independent complex), thus suggesting the presence of a weak gold–π interaction.[17] Although complexes of Au^I with arenes are rare,[18] several reports of ligand aryl groups engaging in similar, longer-range Au–π interactions orthogonal to the two ligation sites have recently appeared.[6,19,20] In the case of **3c**, the presence of the aryl group adjacent to Au creates a significantly more pronounced chiral environment at the metal center compared with **3a** and **3b**.

On the hypothesis that the solid-state structural differences observed in **3a–c** might also be relevant in solution, we investigated whether these differences are reflected in enantioselective catalysis. The tandem acetalization/cycloisomerization of *ortho*-alkynylbenzaldehydes (Table 1), originally reported by Yamamoto using $Pd(OAc)_2$ as a catalyst,[21] gives 1*H*-isochromene derivatives that can have useful medicinal properties.[22] Although several related tandem processes using different nucleophiles are known,[23] including Au^I-catalyzed examples,[23d–h] no enantioselective version of this reaction has appeared.[24]

Initial optimization studies identified $LiNTf_2$ (Tf = trifluoromethanesulfonyl) as a necessary additive to achieve useful activity (see the Supporting Information).[25,26] Under optimized conditions, both yield and enantioselectivity in model cyclizations of substrate **5a** depended strongly on the nature of the R group of the Au^I/carbene catalyst. Complex **3a** gave poor yields and *ee* values of only 8% and 27% using *i*PrOH and cyclohexanol, respectively, as nucleophiles (Table 1, entries 1 and 2). The *ee* values increased to 61% and 43% for catalyst **3b**, but the yield was still low (entries 3 and 4). Only with **3c** [R = 3,5-$(CF_3)_2C_6H_3$] was a good yield and high enantioselectivity attained (entries 5 and 6). With **3c** selected as the most promising catalyst, the scope of enantioselective alkynylbenzaldehyde cyclizations was examined. Good yield and enantiomeric excess of 96% or higher were obtained using tertiary (entry 8), secondary (entries 6 and 7), and larger primary alcohols (entries 9–11) as nucleophiles with alkyne substrates bearing aryl R^1 groups. However, yield and enantioselectivity fell when the alkyne contained *n*-propyl instead of an aryl group (entries 12 and 17) and when alcohols containing shorter *n*-alkyl chains were used (entries 13–17). The use of MeOH resulted in no product formation in two cases (entries 15 and 17).

To address these catalyst limitations, we created a modified version of **3c** using the chiral amine ((*S*)-$PhMeCH)_2NH$ in place of iPr_2NH (**4**; Scheme 1). We hypothesized that the chiral amine substituents might augment the chiral environ-

ment at the metal through steric interactions with the binaphthyl moiety. The X-ray crystal structure of **4** (Figure 2) revealed an Au–arene interaction similar to that seen in **3c** (distance from Au center to ring centroid: 3.6 Å), as well as a short phenyl–binaphthyl contact (C54–C26 3.28 Å), which could sterically hinder rotation away from the Au center. Gratifyingly, catalyst **4** provided cyclization products in good yield and high enantiomeric excess in most of the reactions for which **3c** was ineffective (Table 1, entries 18–22), although an example with small alkyl groups at both R^1 and R^2 was still problematic (entry 23). Significantly higher enantioselectivity was also achieved for a reaction in which comparable yields were obtained using **3c** (entries 5 and 24).

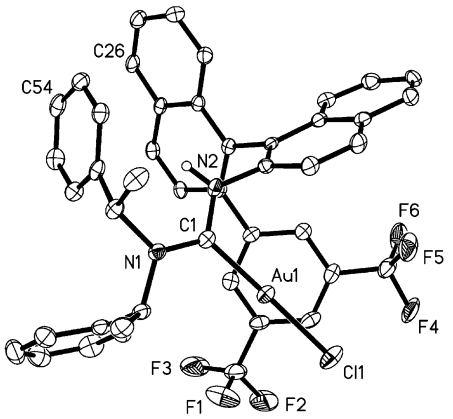
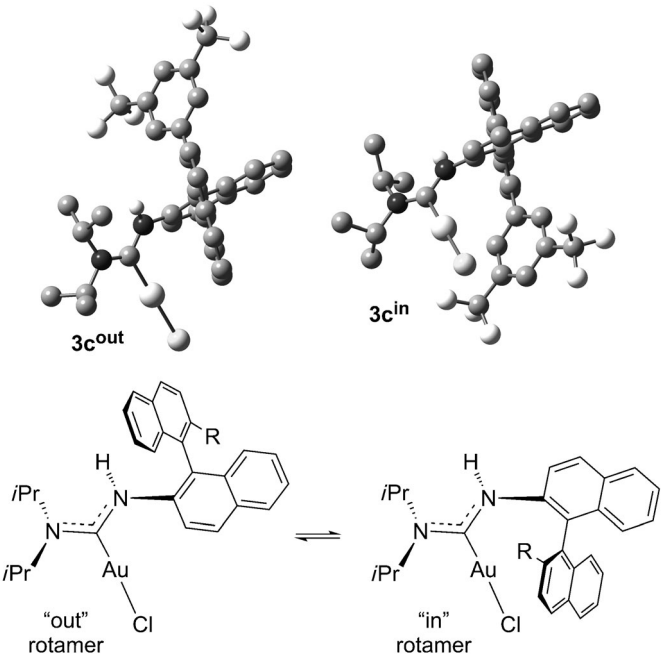


Figure 2. X-ray crystal structure of **4** with 50% probability ellipsoids.

The catalytic results suggest that the Au–arene interactions in **3c** and **4** might enhance both the enantioselectivity and stability of the catalysts. To provide insight into these interactions, DFT calculations were performed on rotamers of **3b** and **3c**.[27] For **3c**, an enthalpic preference of 8 kJ mol^{-1} was calculated for the crystallographically observed "in" rotamer over the "out" rotamer, whereas no significant difference in energy was calculated for **3b** (Figure 3). The 3,5-$(CF_3)_2C_6H_3$ and binaphthyl units of the optimized **3c^{out}** do not show any short contacts with the *i*Pr groups, thus discounting a steric basis for the preference of **3c^{in}**. Interestingly, the preference for the "in" rotamer with the electron-deficient aryl group of **3c**, but not for Ph, suggests an inversion of the electrostatic pairing that underlies typical cation–π interactions.[20a]

In summary, we report a new class of chiral Au^I/ADC catalysts, for which enantioselectivity in alkynylbenzaldehyde cyclization correlates with the presence of Au–arene interactions with an electron-deficient aryl group. The combined structural, catalytic, and DFT results suggest a dynamic chiral pocket in which reversible Au–aryl association, augmented by intra-ligand sterics in the case of **4**, is sufficiently favorable to influence the enantiodetermining step. Although similar interactions of electron-rich aryl groups have been implicated in enantioselective Au^I catalysis in another report,[6] the involvement of electron-deficient aryl substituents hints at a different electrostatic profile in our system, perhaps related to the strong donor ability of the carbene ligand. Future work will seek to better understand these interactions and to exploit them in other catalytic enantioselective reactions that are not currently achievable.



3b (R = Ph): ΔH = –0.7 kJ mol^{-1}
3c [R = 3,5-$(CF_3)_2C_6H_3$]: ΔH = –7.9 kJ mol^{-1}

Figure 3. DFT-calculated relative energies of rotamers of **3b** and **3c**. Optimized geometries of the rotamers of **3c** are shown at the top. The calculated distance between the Au center and the ring centroid for **3c^{in}** is 3.9 Å.

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