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Chiral carbene approach to gold-catalyzed asymmetric cyclization of 1,6-enynes

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ABSTRACT

Chiral C_2-symmetric *N*-heterocyclic carbenes (NHCs) were tested for their stereocontrolling abilities in gold(I)-catalyzed asymmetric cyclization of 1,6-enynes giving the corresponding cyclopentane derivatives with moderate enantioselectivity of up to 59%.

Gold(I) complexes with phosphanes or *N*-heterocyclic carbenes (NHCs)[1] have emerged as attractive homogeneous catalysts that activate C–C multiple bonds.[2] Several chiral phosphane–Au(I) complexes have been reported to enantioselectively catalyze coupling of aldehydes with isocyanoacetates,[3] cyclization of 1,6-enynes,[4] nucleophilic addition to allenes,[5] and cyclopropanation of alkenes.[2b,6] To date, however, there are no reports of a chiral NHC–Au(I) complex acting as a chiral catalyst.[7] The scarcity of enantioselective Au(I)-catalyzed transformations is probably due to the linear coordination geometry of Au(I),[8,9] in which a reacting multiple bond coordinates at the side of Au(I) opposite to a chiral ligand; thus, the reaction site is far away from the chiral environment (Fig. 1).

We developed a chiral C_2-symmetric NHC for asymmetric Cu(I)-catalyzed conjugate addition of Grignard reagents to 3-substituted cyclohexenones, where high enantioselectivity and the sense of asymmetric induction were correlated with the X-ray structures of NHC–AuCl complexes **1a** and **1b** (Fig. 2).[10–12] The most recent successful Cu(I)-catalyzed asymmetric arylation of allylic bromides with aryl-Grignard reagents was also indebted to the copper counterparts of **1c** and **1d**.[13] As part of our continuing studies, we applied **1a**–**d** to Au(I)-catalyzed asymmetric cyclization of 1,6-enynes. We describe herein a chiral C_2-symmetric NHC–Au(I)-catalyzed asymmetric cyclization of 1,6-enynes to give the corresponding cyclopentane products with moderate ee of up to 59%.[4,14]

Asymmetric cyclization of enyne **2a**[4] in methanol was successfully catalyzed by 6 mol % each of *N*-aryl-NHC–AuCl **1a**[10a] and silver hexafluoroantimonate at room temperature for 1 h to give **3a**[15] in 94% isolated yield (Table 1, entry 1). The enantioselectivity, however, was poor; only 5% ee by chiral HPLC (DAICEL ChiralPack AD, 2-propanol/hexane = 1/19).[4a] The *N*-mesitylmethyl version **1b**[10a] gave **3a** in 93% yield, but also with poor enantioselectivity of 4% (entry 2).

The extremely poor enantioselectivity exhibited by gold complexes **1a** and **1b** was likely due to the absence of a stereocontrolling group around the Au coordination site. In fact, previously described X-ray structures[10a] indicated that the aryl group on the nitrogen of **1a** and **1b** was fixed to the direction against the Au–Cl bond, probably due to a π–π interaction between the phenyl group on the chiral carbon and the aryl group on the nitrogen. Furthermore, the relatively long bond length between the carbene carbon and Au, 1.967 and 1.968 Å as well as 2.286 and 2.268 Å for Au–Cl of **1a** and **1b**, respectively, indicated the need for a mechanism to enable the substituents on the NHC nitrogen to overlay the Au–Cl bond.

Based on the expectation that one of the two aryl groups of a diarylmethyl group on the NHC nitrogen should be fixed by the

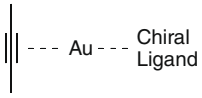

Figure 1. Linear coordination of triple bond–gold–chiral ligand.

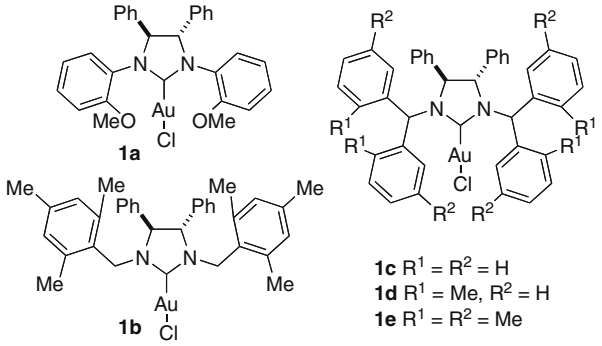

Figure 2. Chiral NHC–AuCl catalyst precursors **1**.

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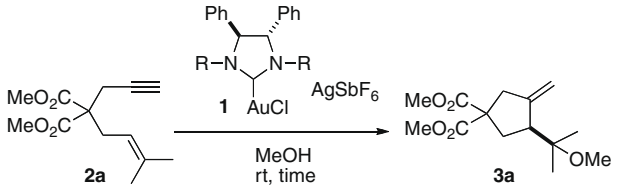
Table 1
Chiral NHC–Au(I) **1**-catalyzed cyclization of enyne **2a**[a]



Entry	NHC–AuCl **1**	Time (h)	Yield (%)	ee (%)
1	**1a**	1	94	5[b]
2	**1b**	2.5	93	4[b]
3	**1c**	1	95	8
4	**1d**	1	95	32
5	**1e**	1	95	56

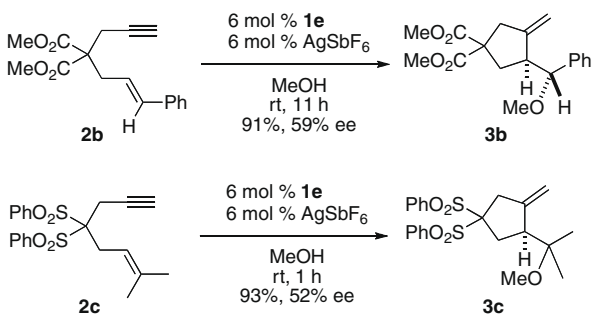
[a] The reaction was conducted with 6 mol % each of **1** and silver hexafluoroantimonate.
[b] The antipode was obtained.

π–π interaction and hence a free aryl group overlays the Au–Cl bond, **1c** and **1d**[13] bearing a diarylmethyl group on nitrogen were tested. Although the improvement was very slight (8% ee) with **1c** bearing a diphenylmethyl substituent (entry 3), this substituent became the basis for further improvement. Attaching one methyl group on the phenyl ring of **1c** would bring a methyl group to the direction of Au–Cl bond realizing more steric control. In fact, **1d** with the *ortho*-methyl group on the phenyl group significantly improved the enantioselectivity to 32% ee (entry 4). Further introduction of a second methyl group on the 5-position of the phenyl group was then examined as shown in **1e** with expectation of much more efficient steric bulk.

The new NHC–AuCl complex **1e** bearing bis(2,5-dimethylphenyl)methyl substituents was synthesized as an air-stable colorless amorphous of mp 135–138 °C and $[\alpha]_D^{25}$ −236 (*c* 0.96, $CHCl_3$) starting from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine via bis(2,5-dimethylphenyl)methylation with the corresponding bromide in the presence of sodium carbonate in *N*,*N*-dimethylpropylene urea at 120 °C,[16] imidazolium salt formation with orthoformate and ammonium tetrafluoroborate,[17] and finally, treatment with sodium *t*-butoxide and a gold chloride–SMe_2 complex in THF.[10a] To our delight **1e** gave the best enantioselectivity of 56% among examined (entry 5).

The obtained NHC–AuCl **1e** could generally be applied to a catalytic asymmetric enyne cyclization of enynes **2b** and **2c** in methanol at room temperature for 11 h and 1 h to give the corresponding cyclopentanes **3b** with 59% ee and **3c** with 52% ee, respectively, in high chemical yields (Scheme 1).

The sense of the asymmetric induction by **1e**–$AgSbF_6$ catalyst is predictable based on a model structure (Fig. 3). One aryl group of the bis(2,5-dimethylphenyl)methyl substituent would be fixed by



Scheme 1. Enyne cyclization of **2** catalyzed by NHC–Au(I) **1e**–$AgSbF_6$.

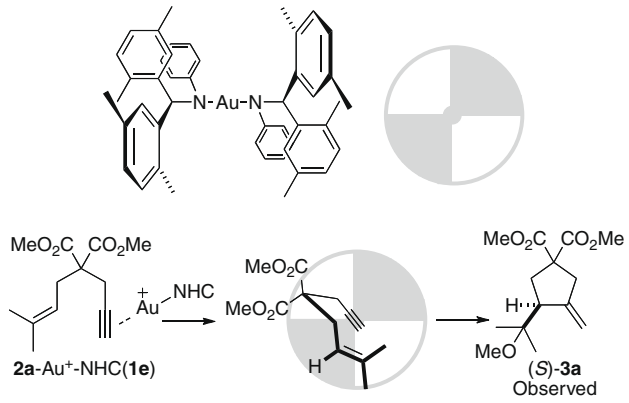


Figure 3. Perspective view of **1e** and stereochemical model for cyclization.

a π–π interaction with the phenyl group on the chiral carbon. Looking through the structure of **1e** from the chlorine to the Au, the appearance of the aryl rings on the right-upside and left-downside shows the presence of a steric barrier there. The coordination of the C–C triple bond of **2a** to the Au(I) triggers the cyclization by placing residues in the vacant space as shown to give (*S*)-**3a**[18] with the observed absolute configuration.

In summary, we developed a chiral C_2-symmetric NHC–Au(I) catalyst based on the use of an *N*-bis(2,5-dimethylphenyl)methyl substituent endowing a chiral environment around Au(I). The validity of the concept was evidenced by the moderate enantioselectivity and predictable absolute configuration in the *first* chiral NHC–Au(I)-catalyzed asymmetric cyclization of 1,6-enynes. The results described here provide a basis for the design of much more efficient chiral NHC–Au(I) catalysts.

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