

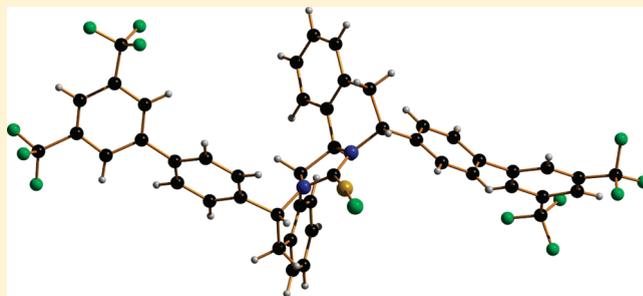
Synthesis of Gold Complexes Bearing Sterically Highly Encumbered, Chiral Carbene Ligands

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S Supporting Information

ABSTRACT: The synthesis of chiral carbene ligands derived from bis(tetrahydroisoquinoline) bearing sterically highly demanding, rigid substituents is described. Their corresponding gold complexes were structurally elucidated and successfully employed as catalysts for the desymmetrization of 1,4-diyne-*amides*.



Since the first reports of N-heterocyclic carbenes¹ (NHCs) this compound class has become a major area of research, focusing on their application as organocatalysts or in catalytically active transition-metal complexes.² Carbene complexes complement and sometimes exceed the properties of catalysts incorporating phosphine ligands with respect to higher thermal stability and resistance toward oxidation. However, while a wealth of chiral phosphines is known and has been successfully employed in highly enantioselective catalytic processes, the applications of related chiral carbene ligands are far more limited in number.^{3,4} This may be explained by the different geometries of the two compound classes. Phosphines with a stereogenic phosphorus atom, which is very close to the metal center, as well as bidentate phosphine ligands with a chiral backbone are readily prepared and the corresponding metal complexes synthesized by simple mixing with a metal salt in the majority of cases. NHC ligands permit the placement of the stereogenic moiety only at some distance from the metal center, causing the catalytically active complex to be spatially more open. In addition, only a few bidentate carbene complexes have been reported for successful application in enantioselective catalysis.⁵

Recently, we reported a gold(I)-catalyzed desymmetrization of 1,4-diyne employing optically active gold carbene complexes.⁶ Gold-catalyzed transformations have attracted increasing interest over the last few years.⁷ Especially, activation of alkynes, allenes, and alkenes followed by nucleophilic addition of O-,⁸ N-,⁹ or C-nucleophiles¹⁰ were found to proceed with high efficiency and under mild reaction conditions. Herein, different phosphine or carbene ligands permit the tuning of the Au(I) catalyst reactivity and selectivity, also with respect to enantioselective transformations. Due to the linear coordination geometry of Au(I) and the assumed anti addition of a nucleophile to the activated multiple bond, ligands bound to the metal center need to exhibit a significant size and steric bulk for effective chiral

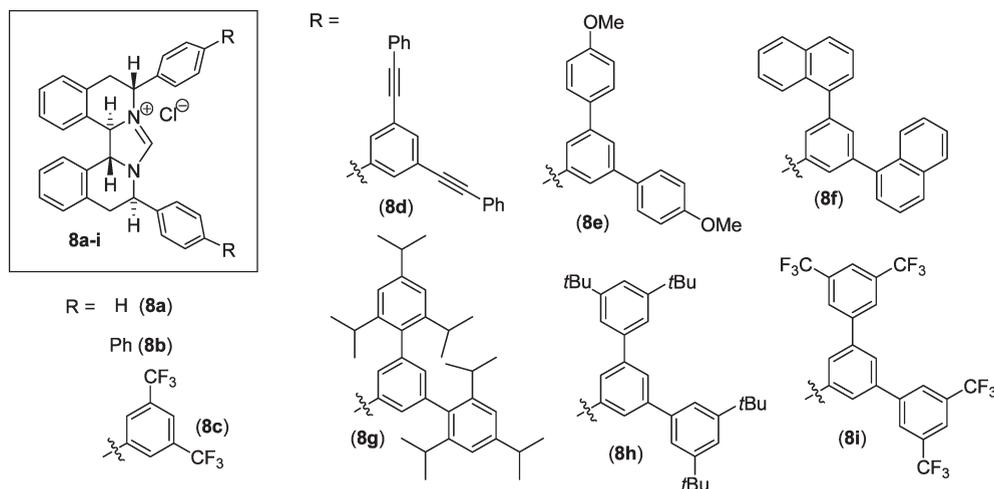
induction. In this paper we describe the synthesis of sterically highly encumbered, chiral carbene ligands derived from bis(tetrahydroisoquinoline)¹¹ and the preparation and structure of the corresponding gold complexes, as well as their application in the desymmetrization of 1,4-diyne-*amides*.

Our synthetic strategy for the preparation of the desired substituted bis(tetrahydroisoquinoline) derivatives was inspired by a ligand synthesis published by Herrmann and co-workers (Chart 1, **8a**).^{11c} An extension of this methodology should allow for a late-stage derivatization of the ligand scaffold in order to easily obtain a variety of structurally diverse compounds which could be screened in the gold-catalyzed desymmetrization. Therefore, the parent phenyl substituent was replaced by a *p*-bromophenyl group. This moiety serves as a convenient handle for cross-coupling, allowing the incorporation of various biaryl substituents which should provide sufficient rigidity in a structurally well-defined scaffold.¹² The synthesis of diamine **5** is depicted in Scheme 1. Phenylacetyl chloride was reacted with bromobenzene under Friedel–Crafts conditions to give ketone **2**.¹³ This was transformed into the secondary amine *rac*-**3** by a reductive amination reaction. It is worth noting that only employment of ammonium acetate and sodium cyanoborohydride in a mixture of methanol and THF proved efficient for this step. Herein, addition of THF was shown to be essential to suppress simple ketone reduction and the formation of the dibenzylamine derivative. Trials to apply Leuckart–Wallach conditions or to reduce the corresponding ketone oxime by hydrogenation or with zinc/formic acid provided no satisfying results. Resolution of the secondary amine *rac*-**3** was achieved by treatment with tartaric acid and fractional crystallization of the corresponding ammonium salt from ethanol/2-propanol.

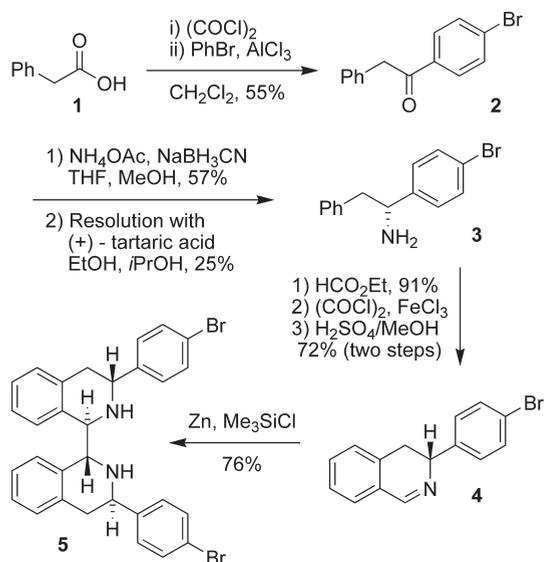
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Chart 1. Sterically Encumbered Carbene Ligand Precursors with Biphenyl or Terphenyl Substitution



Scheme 1. Synthesis of Chiral Bis(tetrahydroisoquinoline) 5



Bischler–Napieralski cyclization of the formylated amine gave the optically active 3-aryldihydroisoquinoline **4** in a yield of 72%.¹⁴ Reductive dimerization with zinc and Me_3SiCl provided chiral diamine **5** as a single diastereomer in 76% yield.¹⁵ Gratifyingly, in this reaction no debromination by zinc was observed.

At this point the stage was set for diversifying the ligand structure by palladium-catalyzed cross-coupling reactions.^{16,17} Suzuki coupling¹⁸ provided access to a variety of different sterically encumbered ligands bearing a biphenyl or terphenyl motif¹⁹ (Scheme 2). Despite the significant size of the substituents, the cross-coupling reactions proceeded in useful yields of 44–84%. Treatment of the diamines **7** with triethyl orthoformate gave the corresponding imidazolium salts **8** as precursors for the carbene ligands (Chart 1).

In order to test the new class of ligands with respect to their behavior in asymmetric catalysis, the corresponding gold complexes were synthesized. It was found that transmetalation from the silver carbene complexes (obtained by using Ag_2O) was

rather slow for the sterically more demanding ligands.²⁰ In contrast, deprotonation of the imidazolium salts **8** with $\text{KO}t\text{Bu}$ and subsequent treatment with Me_2SAuCl led to the desired products **9**, which were stable enough to be purified by silica gel chromatography and were obtained as white solids.²¹

Single crystal X-ray diffraction of the gold complex **9c** permitted structural insight and the determination of the absolute configuration (Figure 1). The tetragonal unit cell has significant size ($a = 26.152(15)$, $c = 12.237(7)$ Å, $V = 8369(7)$ Å³) and contains four pairs of two independent molecules. The Au–C distance (1.995(7) Å) and the linearity of the C–Au–Cl bonds (177.3 and 179.2°) are in good agreement with those in related known complexes.²² The gold atoms form a continuous right-handed helical chain according to Sohnke space group $P4_3$ with Au–Au distances of 3.194(2) and 3.258(2) Å, respectively. These distances are in the typical range for auriphilic interactions found in gold carbene complexes.²³ Interestingly, the trifluoromethyl groups at the ligand substituents are in close proximity in the crystal, presumably by a stabilizing interaction similar to interactions in fluorous phases (Figure 2).²⁴

Mass spectroscopic studies indicated the possibility of the formation of gold bis-carbene complexes. When gold carbene complex **9i** was treated with sodium tetraphenylborate in dichloromethane/methanol and submitted to ESI-MS, the formation of the AuL_2^+ cation with very good agreement of experimental and calculated isotope distributions was observed (Supporting Information). Whether such intermediates play a significant role in catalytic processes in solution, where the chloride ligand is often replaced by a weakly coordinating anion such as tetrafluoroborate, will be the subject of future studies.

The catalytic activity of the new chiral gold carbene complexes was evaluated in the desymmetrization of diynesulfonamide **10**. The cyclization of this compound class had proven difficult with gold phosphine complexes (i.e., $[\text{C}_3\text{P}]\text{AuCl}$), leading to fast catalyst inactivation.^{6b} Gold complexes **9a–i** were premixed with substoichiometric quantities of silver tetrafluoroborate in toluene to form the catalytically active species. We were pleased to find that the catalysts remained active over the course of the reaction and the enamide product **11** was obtained in yields up to 77% (Table 1, entry 6). The highest enantioselectivity (51% ee) was observed with a catalyst bearing the most bulky

Scheme 2. Synthesis of the Carbene Ligand Precursors

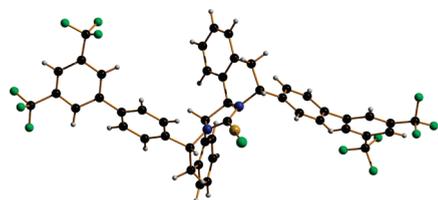
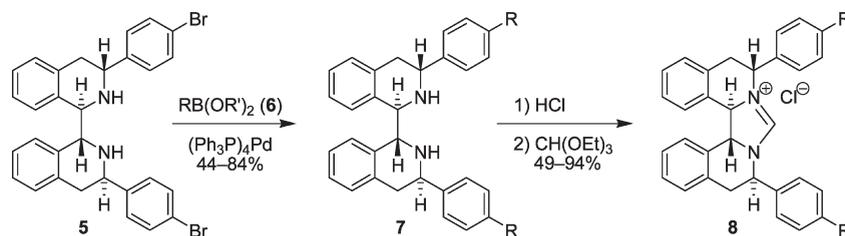
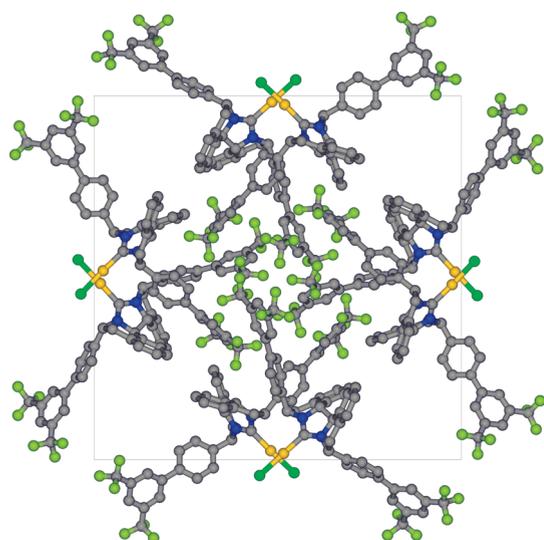
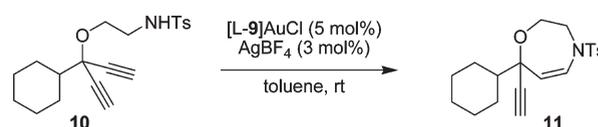
Figure 1. Molecular structure (Diamond 3.1²⁵) of complex 9c.

Figure 2. Unit cell (ViewerLite) of complex 9c, viewed along the 001 axis (hydrogen atoms omitted for clarity).

ligand (9g), which is comparable to the best enantioselectivity of 60% ee that was obtained using the chiral gold phosphine complex [MeOBiPHEP(AuCl)₂]. In this respect it is worth mentioning that examples of gold-catalyzed desymmetrizations of alkynes are very rare.⁶ In these transformations the stereochemical control is quite challenging and only a few examples with moderate enantioselectivities have been reported so far.

Summarizing, a new class of sterically highly encumbered carbene ligands with a tetrahydroisoquinoline backbone and their corresponding gold complexes have been synthesized. Crystal structure analysis of one complex revealed continuous Au^I–Au^I contacts in the solid state. The catalytic activity of the complexes was demonstrated in the desymmetrization reaction of a diynesulfonamide. Herein, catalysts incorporating ligands with high steric demand led to enantioselectivities which were comparable to those of the best

Table 1. Gold-Catalyzed Desymmetrization of Diynesulfonamide 10



entry	gold complex	time/h	yield/%	ee/%
1	9a	20	53	18
2	9b	3	traces	22
3	9c	14	52	45
4	9d	6	36	34
5	9f	7	37	39
6	9g	3	77	51
7	9h	6	50	30
8	9i	14	63	40

gold phosphine catalysts known for this transformation. The straightforward synthesis, the late-stage diversification, and their structural rigidity should cause the depicted ligand class to be candidates also for related transition-metal complexes and applications in asymmetric catalysis when high steric restriction is intended. Studies aiming in this direction are currently in progress, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Text and figures giving experimental procedures, characterization data, and NMR spectra for new compounds and a CIF file giving X-ray crystallographic data for compound 9c. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

[†]Responsible for X-ray crystal structure determination.

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