Asymmetric Catalysis

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Enantioselective Oxidative Gold Catalysis Enabled by a Designed Chiral P,N-Bidentate Ligand**

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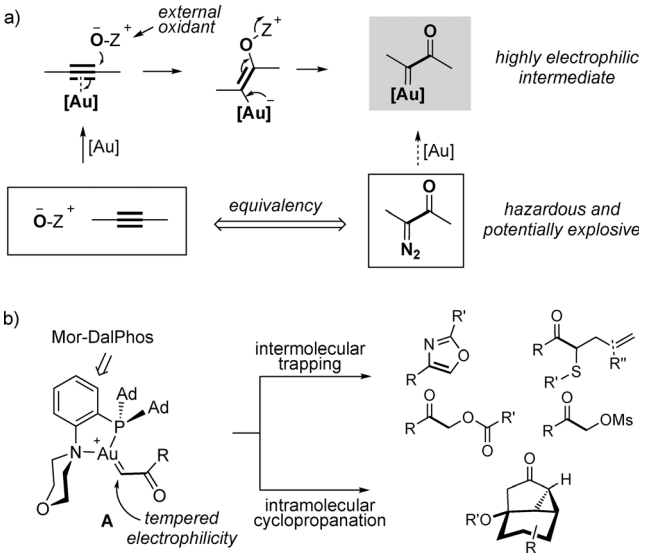
Abstract: *A newly developed P,N-bidentate ligand enables enantioselective intramolecular cyclopropanation by a reactive α-oxo gold carbene intermediate generated in situ. The ligand design is based on our previously proposed structure (with a well-organized triscoordinated gold center) of the carbene intermediate in the presence of a P,N-bidentate ligand. A C_2-symmetric piperidine ring was incorporated in the ligand as the nitrogen-containing moiety. A range of racemic transformations of α-oxo gold carbene intermediates have been developed recently, and this new class of chiral ligands could enable their modification for asymmetric synthesis, as demonstrated in this study.*

The gold-catalyzed intermolecular oxidation of alkynes[1] has become an increasingly popular approach to the formation of highly electrophilic α-oxo gold carbene intermediates since our first report in 2010[2] (Scheme 1a). This strategy permits the ready exploration of these reactive intermediates without the use of hazardous and potentially explosive diazoketone precursors.[3,4] Although various methods[2,5,6] have been developed on the basis of this general strategy, a glaring deficiency[7] in this rapidly evolving area is that the only known enantioselective example afforded the product with just 18% *ee*[8] despite success in a range of other enantioselective gold-catalyzed reactions.[4h,9] Herein we report a successful case of enantioselective intramolecular cyclopropanation enabled by a newly designed chiral P,N-bidentate ligand.

In comparison to their rhodium counterparts,[3] α-oxo gold carbenes tend to be more electrophilic.[10] In 2012, we reported that P,N-bidentate ligands, such as Mor-DalPhos,[11] could temper the electrophilicity of the carbene center through the formation of a triscoordinated gold complex (i.e. **A** in the case of Mor-DalPhos, Scheme 1b) by the coordination of both the P and the N atom of the bidentate ligand.[5c] As a result, the intermolecular trapping of α-oxo gold carbenes is possible with carboxamides,[5c] MsOH,[12] carboxylic acids,[5a] allyl sulfides,[13] and rather flexibly tethered C–C double bonds[14] (Scheme 1b). Notably, in the last three cases, a modified P,N-bidentate ligand[5a,14] or a P,S-bidentate ligand[13] was used as the optimal metal ligand. The structure of α-oxo gold carbene intermediates of type **A** with a triscoordinated metal center is supported by DFT calculations[5c] and offers a well-organized reaction site for the design of chiral ligands for their asymmetric trapping and consequently enantioselective oxidative gold catalysis.



Scheme 1. a) Oxidative gold catalysis: facile access to α-oxo gold carbenes without the use of diazo compounds. b) A P,N-bidentate ligand tempers the reactivity of the carbene and enables intermolecular trapping and intramolecular cyclopropanation reactions. Ad = adamantanyl, Ms = methanesulfonyl.

We reasoned that by installing a C_2-symmetric chiral N heterocycle as the N-containing component of the bidentate ligand, a largely C_2-symmetric chiral pocket could be created around the gold carbene center (Scheme 2a). In this way, its enantioselective transformation might be possible. To reduce this idea to practice while securing flexible access to a range of ligands, we chose (3*S*,4*S*)-3,4-dihydroxypyrrolidine[15] and (3*R*,5*R*)-3,5-dihydroxypiperidine[16] as the chiral N-heterocyclic platforms, both of which are readily available. The corresponding P,N-bidentate ligands with variably capped hydroxy groups were readily synthesized (see the Supporting Information), and selected examples are shown in Scheme 2b.

We chose the cyclopropanation reaction previously developed by Liu and co-workers[6e] to develop the intended enantioselective oxidative gold catalysis. Specifically, ethyl (*E*)-3-(2-ethynylphenyl)acrylate (**1a**), readily accessible from

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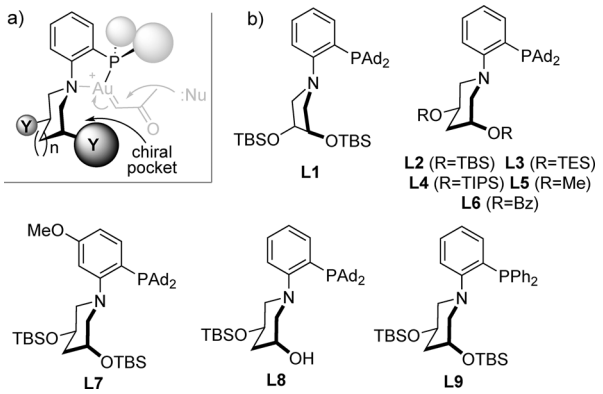
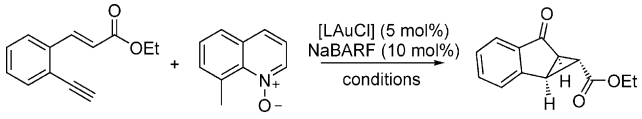


Scheme 2. P,N-bidentate ligands: a) design; b) selected ligands. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

2-bromobenzaldehyde,[6e] was used as the substrate. In the original study[6e] the desired product **3a** was obtained in 67% yield using [IPrAuNTf$_2$] (5 mol%, generated in situ from [IPrAuCl]/AgNTf$_2$; IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as the catalyst, 8-methylquinoline *N*-oxide (**2**, 3 equiv) as the oxidant, and 1,2-dichloroethene (DCE) as the solvent and carrying out the reaction at 80 °C for 3 h. When the ligand **L1** with a bis-TBS-protected (3*S*,4*S*)-3,4-dihydroxypyrrolidine moiety was used, **3a** was formed in 78% yield and with an encouraging 63% *ee* (Table 1, entry 1). The shown absolute configuration of the major enantiomer of the product was assigned on the basis of X-ray diffraction studies of analogues (see below). Notably, the reaction conditions—the use of 1.5 equivalents of **2** at ambient temperature—are much milder than those required for the use of IPr as the ligand, which is consistent with the previously observed benefits of using P,N-bidentate ligands in α-oxo gold carbene chemistry.[5a,c,12–14]

After attempts to improve enantioselectivity by replacing the TBS groups of **L1** with other protecting groups were unsuccessful, we reasoned that (3*R*,5*R*)-3,5-dihydroxypiperidine, which is based on a conformationally more controllable six-membered ring, might offer a better platform for ligand optimization. Thus, the corresponding bis-TBS-substituted ligand **L2** was tested in the reaction. Indeed, the *ee* value of **3a** improved to 86% (Table 1, entry 2). When the TBS groups of **L2** were replaced with TES groups in **L3**, little change in enantioselectivity was detected (Table 1, entry 3). However, the presence of both bigger TIPS groups and much smaller Me groups led to significantly decreased enantioselectivity (Table 1, entries 4 and 5). An even lower *ee* value of **3a** was observed when the HO groups of the ligand piperidine ring were converted into benzoate groups in **L6** (Table 1, entry 6). The introduction of a MeO group *para* to the phosphorus atom in **L2** resulted in the ligand **L7**, the use of which, however, led to essentially the same outcome (Table 1, entry 7). Interestingly, ligand **L8** with one TBS group removed still enabled fairly good enantioselectivity (Table 1, entry 8): notably better than that observed with the dimethoxy ligand **L5**. Finally, the sterically much smaller diphenylphosphine ligand **L9**, although still leading to an efficient

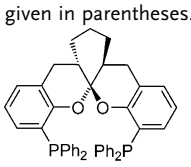
Table 1: Optimization of the reaction conditions for the enantioselective gold-catalyzed oxidative cyclopropanation.[a]



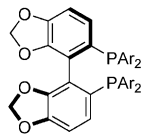
1a **2** (1.5 equiv) **3a**

Entry	L	Conditions	Yield [%][a]	*ee* [%][b]
1	**L1**	DCE, RT, 2 h	78	63
2	**L2**	DCE, RT, 2 h	78	86
3	**L3**	DCE, RT, 2 h	74	85
4	**L4**	DCE, RT, 2 h	73	52
5	**L5**	DCE, RT, 2 h	78	50
6	**L6**	DCE, RT, 2 h	62	23
7	**L7**	DCE, RT, 2 h	78	86
8	**L8**	DCE, RT, 2 h	56	73
9	**L9**	DCE, RT, 2 h	78	3
10	**L10**	DCE, RT, 2 h	NR	–
11	**L11**	DCE, RT, 2 h	–[c]	–
12	**L2**	DCE, 0 °C, 12 h	70	90
13	**L2**	**DCE, −20 °C, 50 h**	**68 (61)**[d]	**94**

[a] The yield was determined by ^{1}H NMR spectroscopy using diethyl phthalate as the internal reference. [b] The *ee* value was determined by HPLC on a chiral stationary phase. [c] No desired product was observed in the crude ^{1}H NMR spectrum. [d] The yield of the isolated product is given in parentheses.



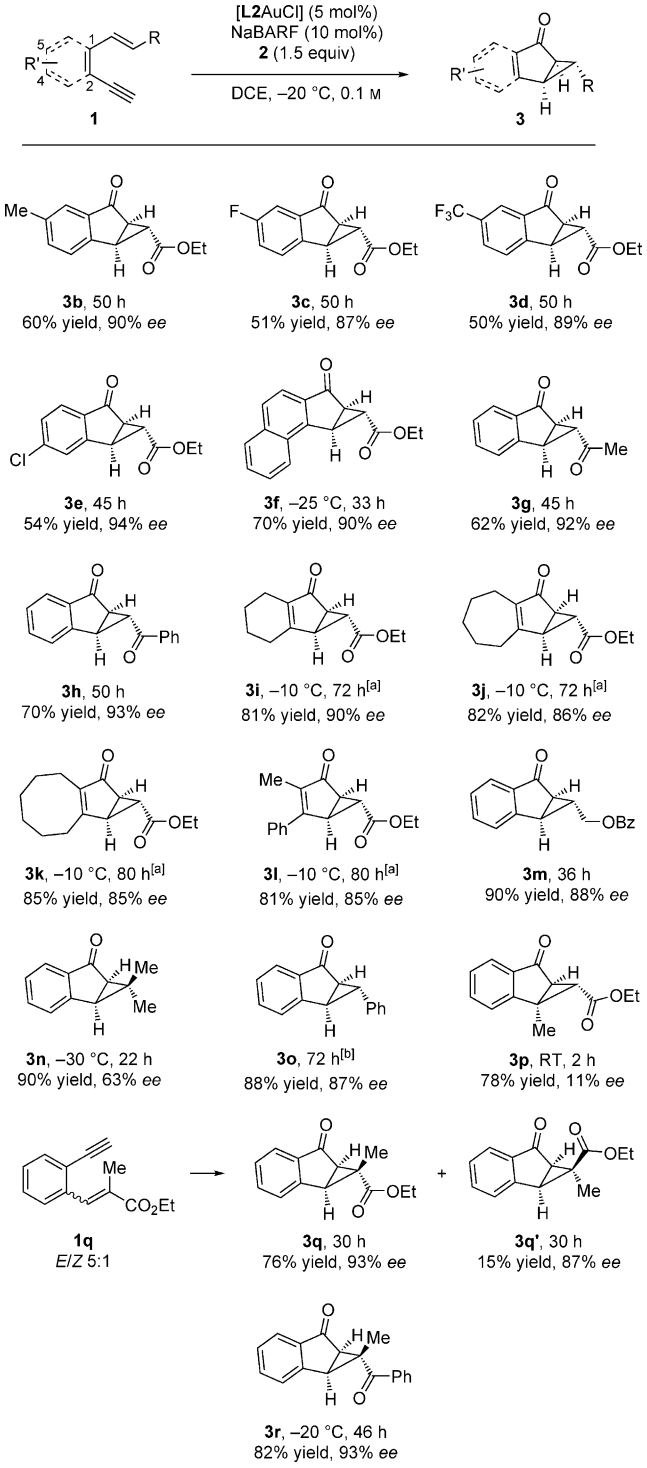
L10



L11: (*R*)-DTBM-segphos

intramolecular cyclopropanation, was very poor in promoting alkene facial selectivity during the reaction (Table 1, entry 9), thus indicating the importance of the bulky adamantyl groups in enforcing a tight reaction site for the asymmetric cyclopropanation. In contrast to the chiral P,N-ligands, the spiroketal bisphosphine ligand **L10** (Table 1, entry 10), which was used successfully in gold-catalyzed, highly enantioselective cyclopropanation reactions with diazooxindole substrates,[4h] and (*R*)-DTBM-segphos (entry 11), a popular ligand for asymmetric gold catalysis,[9a,b] did not facilitate the desired oxidative gold catalysis under the identical reaction conditions used. The *ee* value of the product was further improved by lowering the reaction temperature to 0 °C (Table 1, entry 12) and further to −20 °C (entry 13), albeit at the expense of the yield and reaction time. Notably, the reaction temperature of −20 °C in the last entry is much lower than the originally used 80 °C.[6e]

Having optimized the reaction conditions for the highest possible enantioselectivity (Table 1, entry 13), we subsequently examined the reaction scope (Scheme 3). We found that substituents on the benzene ring were tolerated (products **3b**–**e**). Specifically, a 5-Me group did not affect the reaction outcome significantly (product **3b**). The presence of electron-withdrawing groups, such as 5-F, 5-CF$_3$, and 4-Cl (products **3c**–**e**), resulted in decreased but serviceable yields, whereas the *ee* value of the products remained good to excellent. The presence of a 4-MeO group, however, resulted in mostly



Scheme 3. Reaction scope. Reactions were carried out in vials. Yields given are for the isolated product. [a] The reaction was carried out with [**L2**AuCl] (7.5 mol%) and NaBARF (15 mol%). [b] The reaction was carried out at 0°C. Toluene was used as the solvent. NaBARF = sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

double oxidation. A better 70% yield was observed with a naphthalene-based substrate, and the isolated product **3f** had 90% *ee*. Somewhat to our surprise, the replacement of the ester group in **1a** with a more electron withdrawing acetyl or benzoyl group led to a comparable outcome in the former case (product **3g**) and a higher yield in the latter case (product **3h**), despite the expectation that the cyclopropanation reaction should prefer more electron rich double bonds (see below). These results are indicative of the highly electrophilic nature of the even tempered gold carbene intermediates.[5c]

Besides the use of an arene ring to closely position the ethynyl group and an electron-deficient alkene, cyclic alkenes were also suited for this purpose. Reactions of the corresponding substrates were slower, as reflected by higher catalyst loadings (7.5%), a higher temperature, and a longer reaction times, but significantly cleaner, with yields above 80%, and the enantioselectivity remained good (Scheme 3, products **3i–k**). An acyclic yne–dienoate substrate with a fully substituted tethering alkene reacted equally well, and **3l** was isolated in 81% yield with 88% *ee*. However, reactions of similar substrates with less substituted tethering alkenes led to poor results (data not shown). In comparison to reactions of substrates possessing electron-poor alkenes, reactions of those containing normal alkenes resulted in much higher yields but notably lower yet still mostly good *ee* values (products **3m–o**). This phenomenon is expected, as more reactive alkenes are capable of trapping the reactive gold carbene more efficiently, and an earlier and hence less compact cyclopropanation transition state could account for observed decreased asymmetric induction by the chiral ligand.

When a methyl substituent was present at the β position to the ester group of **1a**, the reaction proceeded well, but the *ee* value of the product **3p** was very poor (Scheme 3). In contrast, the regioisomeric substrate **1q**, which has a α-Me group and was prepared as an inseparable mixture of geometric isomers (*E*/*Z* 5:1), was converted into the separable cyclopropane diastereomers **3q** and **3q′** in an almost identical ratio and in 91% combined yield, thus indicating that the cyclopropanation is concerted and stereospecific. Moreover, the *ee* value of **3q**, which was formed from the *E* isomer, was 93%, and higher than that of **3q′**, formed from the *Z* isomer. In comparison to the reaction of **1a**, the excellent yield in this case could be attributed to the increased electron density of the C–C double bond and the conformation control offered by the Me group (e.g., forcing the diconjugation of the benzene ring and the enoate moiety in order to avoid $A^{1,3}$ strain). The beneficial impact of an α-Me group as revealed by this case prompted us to examine a related phenone substrate. The oxidative cyclopropanation proceeded well to give product **3r** in 82% yield with excellent enantioselectivity (93% *ee*).

The absolute configurations of the cyclopropanation products were established on the basis of single-crystal X-ray diffraction studies[17] of **3e** and **3g**. Both products were found to have the 1*R*,1a*S*,6a*R* configuration (Figure 1a). The stereochemical outcome of the reaction could be rationalized, although in depth DFT calculations might provide detailed understanding of the cyclopropanation mechanism and the factors controlling facial selectivity. As outlined in Figure 1b, the chiral ligand coordinates to the metal center of the α-oxo gold carbene as a bidentate ligand, and the axial TBSO group on the ligand piperidine ring shields the *Re* face of the

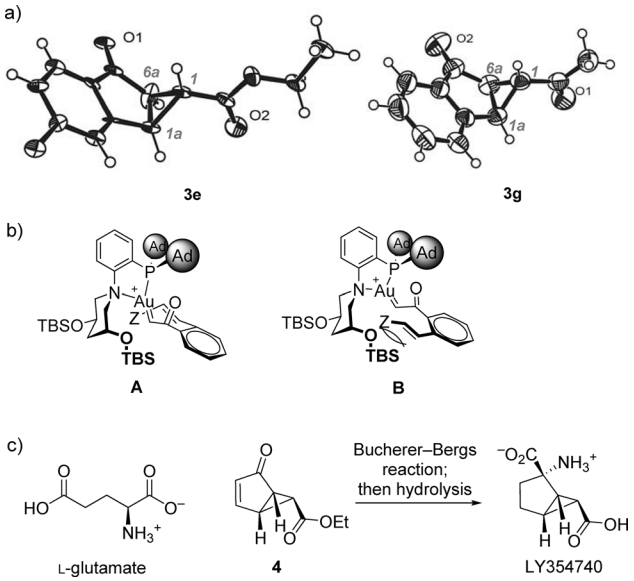


Figure 1. a) Structures of **3e** and **3g** with the absolute configuration established by single-crystal diffraction studies. b) Rationale for the observed enantioselectivity. c) Structures of L-glutamic acid and LY354740 (which can be synthesized from **4**).

carbene center from alkene attack (as in **B**); consequently, its *Si* face is open for the ensuing alkene cyclopropanation (as shown in **A**), thereby leading to the predominant enantiomer.

This enantioselective gold-catalyzed oxidative cyclopropanation could facilitate access to novel constrained analogues of L-glutamic acid, the principal excitatory amino acid neurotransmitter in the human central nervous system (CNS). Structural mimicry of bioactive conformations of this amino acid can lead to high potency and target selectivity. For example, LY354740 is an exceptionally potent agonist for group 2 metabotropic glutamate receptors[18] and has been implicated as a potential agent for the treatment of various CNS diseases (Figure 1c);[19] however, its asymmetric synthesis has been limited to inefficient resolution,[20] a rather lengthy chiral-pool approach,[21] and approaches showing poor diastereoselectivity[22] (in one case, separation from four diastereomers).[22b] Since LY354740 can be readily accessed from the bicyclic cyclopentenone **4**, which is embedded in the structures prepared in this study, this gold catalysis would offer asymmetric access to substituted analogues[23] of LY354740.

In summary, we have described an enantioselective oxidative gold catalysis, in which a novel P,N-bidentate ligand enables reactive α-oxo gold carbene intermediates generated in situ to undergo asymmetric intramolecular cyclopropanation. The design of the ligand relies on our previously proposed structure (with a well-organized tris-coordinated gold center) of the carbene intermediate in the presence of a P,N-bidentate ligand. The ligand was constructed by incorporating a C_2-symmetric 3,5-bissiloxylated piperidine ring as the nitrogen-containing moiety. The gold-catalyzed reaction provides facile access to bicyclic cyclopropane products with mostly good to excellent *ee* values. Since a large array of racemic transformations of α-oxo gold carbene intermediates have recently been developed, this new class of chiral ligands could usher in a new and synthetically highly valuable phase of exploiting these versatile intermediates in asymmetric synthesis.

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