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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 cyclopropanations by in-situ generated, reactive α-oxo gold carbene intermediate. The ligand design is based on our previously proposed structure of the carbene intermediate in the presence of a P,N-bidentate ligand, which has a well-organized tris-coordinated gold center, and was implemented by incorporating a C2-symmetric piperidine ring as the nitrogen part. With a range of racemic transformations of α-oxo gold carbene intermediates recently developed, this new class of chiral ligands, as demonstrated in this study, could usher in a new and synthetically valuable phase of exploiting their applications in asymmetric synthesis.

Keywords

gold; carbene; cyclopropanation; asymmetric catalysis; oxidation

Gold-catalyzed intermolecular oxidation of alkyne[1] has become an increasingly popular approach to accessing highly electrophilic α-oxo gold carbene intermediates since our first report in 2010[2] (Scheme 1A). This strategy permits ready explorations of the novel reactive intermediates without using hazardous and potentially explosive diazo ketone precursors.[3],[4] Although various methods[2, 5],[6] have been developed based on this general strategy, a glaring deficiency[7] in this rapidly evolving area is that the only known enantioselective example affords a mere 18% e.e.[8] despite success in a range of other enantioselective gold catalysis.[4h, 9] Herein we report a successful case, where enantioselective intramolecular cyclopropanations are enabled by a newly designed *P,N*-bidentate ligands.

Different from their Rh 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 via the formation of a tris-coordinated gold (i.e., **A**, Scheme 1B) by the coordination of both P and N atoms of the bidentate

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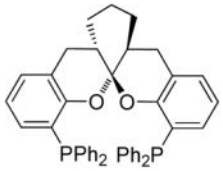
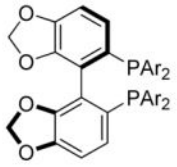
ligand.[5c] As a result, intermolecular trappings of α-oxo gold carbenes have been realized with carboxamides,[5c] MsOH,[12] carboxylic acids,[5a] allyl sulfides,[13] and rather flexibly tethered C-C double bonds[14] (Scheme 1B). Notably, in the last three cases a modified *P*,*N*-bidentate ligand[5a, 14] or a *P*,*S*-bidentate ligand[13] was used as the optimal metal ligand. The structure of α-oxo gold carbene intermediate of type **A** with a tris-coordinated metal center is supported by DFT calculations[5c] and offers a well-organized reaction site for designing chiral ligands for their asymmetric trapping and consequently enantioselective oxidative gold catalysis.

We reasoned that by installing a C_2-symmetric chiral *N*-heterocycle as the *N* component of the bidentate ligand, a largely C_2-symmetric chiral pocket could be created around the gold carbene center (Figure 1A). As such, its enantioselective transformation might be attainable. To reduce it into practice while securing flexibility in accessing a range of ligands, we chose as the chiral *N*-heterocyclic platforms (3*S*,4*S*)-3,4-dihydroxypyrrolidine[15] and (3*R*, 5*R*)-3,5-dihydroxypiperidine,[16] both of which are readily available, and the corresponding *P*,*N*-bidentate ligands with the hydroxyl groups varyingly capped can be easily synthesized (see SI). Some selected examples of the ligands that were prepared during this study are shown in Figure 1B, where **L1** is derived from the chiral pyrrolidine and the rest from the piperidine counterpart.

We chose the cyclopropanation chemistry originally developed by Liu and co-workers[6e] to develop the intended enantioselective oxidative gold catalysis. Specifically, (*E*)-ethyl 3-(2-ethynylphenyl)acrylate (**1a**), readily accessible from 2-bromobenzaldehyde,[6e] was used as the substrate. In Liu's work, 67% of the desired product **3a** was obtained by using the following protocol: 5% $IPrAuNTf_2$ (generated in situ from IPrAuCl/$AgNTf_2$) as the catalyst, 8-methylquinoline *N*-oxide (**2**, 3 equiv.) as the oxidant, DCE as solvent, 80 °C and 3 h. When the ligand **L1** with a pendant bis-TBS-protected (3*S*, 4*S*)-3,4-dihydroxypyrrolidine was used, to our delight, **3a** was formed in 78% yield and with an encouraging enantiomeric excess of 63% (Table 1, entry 1). The shown absolute stereochemistry of the major enantiomer of the product was assigned based on X-ray diffraction studies of it analogs (*vide supra*). Of note is that the reaction conditions, 1.5 equiv of **2** and ambient temperature, are much milder than that using IPr as ligand, which is consistent with our previously observed benefits with using the *P*,*N*-bidentate ligands in α-oxo gold carbene chemistry. [5a, 5c, 12–14]



L10



L11:(R)-DTBM-SEGPHOS

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 conformationally less flexible 6-membered ring, might offer a better platform for ligand development. To this end, the corresponding bis-TBS-derivatized ligand **L2** was applied to the reaction. Indeed, the enantiomeric excess of **3a** was improved to 86%

(entry 2). When the TBS groups of **L2** were replaced with TES groups in the case of **L3**, little change in e.e. was detected (entry 3). However, both the bigger TIPS groups and the much smaller Me groups led to significantly decreased enantioselectivities (entries 4 and 5). Even lower e.e. of **3a** was observed when the HO groups of the ligand piperidine ring were converted into benzoates (i.e., **L6**, entry 6). The substitution of a MeO *para* to the phosphorus in **L2** resulted in the ligand **L7**, which, however, led to essentially the same outcome (entry 7). Interestingly, with one TBS group removed, the resulting ligand **L8** could still enable a fairly good enantioselectivity (entry 8), which is notably better than that by the dimethoxyl ligand **L5**. Finally, the sterically much smaller diphenylphosphine ligand **L9**, though still leading to an efficient intramolecular cyclopropanation, was very poor in realizing alkene facial selectivity during the reaction (entry 9), therefore indicating that importance of the bulky adamantyl groups in enforcing a tight reacting site for the asymmetric cyclopropanation. In contrast to the chiral *P*,*N*-ligands, the spiroketal bisphosphine ligand **L10** (entry 10), which is used successfully in gold-catalyzed, highly enantioselective cyclopropanation reactions with diazooxindole substrates,[4h] and (*R*)-DTBM-SEGPHOS (entry 11), one of the popular ligands for asymmetric gold catalysis,[9a, 9b] could not facilitate the oxidative gold catalysis under the used reaction conditions. The enantiomeric excess of the product was further improved by lowering the reaction temperature to 0°C (entry 12) and further to −20 °C (entry 13), albeit at the expense of yields and reaction times. It is noteworthy that the reaction temperature of the last entry, −20 °C, is much lower than the original 80 °C.[6e]

With the conditions (Table 1, entry 13) optimized to achieve best enantioselectivity, the reaction scope was subsequently examined. As shown in Table 2, entries 1–4, substitutions on the benzene ring could be tolerated. Specifically, a 5-Me group did not affect the reaction outcome much (entry 1), while electron-withdrawing groups such as 5-F (entry 2), 5-CF_3 (entry 3) and 4-Cl (entry 4) resulted in decreased but serviceable yields while the product e.e. remained good to excellent. A 4-MeO group, however, resulted in mostly double oxidation. A better 70% yield was achieved with a naphthalene-based substrate, and the isolated product **3f** had 90% e.e. (entry 5). Somewhat to our surprise, the replacement of the ester group in **1a** with more electron-withdrawing acetyl or benzoyl group afforded a comparable outcome in the former case (entry 6) or a higher yield in the latter case (entry 7), despite the cyclopropanation reaction should prefer more electron-rich double bonds. These results suggest the highly electrophilic nature of even tempered gold carbene intermediates.[5c]

Besides using an arene ring to closely position the ethynyl group and an electron-deficient alkene, cyclic alkenes were also suited for this purpose. As shown in entries 8–10, the reactions were slower, as reflected by higher catalyst loadings (7.5%), higher temperature and longer reaction time, but significantly cleaner, with yields >80%; the enantioselectivities remained good. An acyclic yne-dienoate substrate with the tethering alkene fully substituted reacted equally well, and **3l** was isolated in 81% yield and with 88% e.e. (entry 11); notably, the ones without fully substituted alkene tether led to poor results (data not shown). In comparison to substrates possessing the electron poor alkenes, the reactions of those containing non-electron-deficient alkenes resulted in much higher yields but notably lower

yet still mostly good e.e. (entries 12–14). This phenomenon is expected as more reactive alkenes are capable of trapping the reactive gold carbene more efficiently and a likely earlier and hence less compact cyclopropanation transition state could account for decreased asymmetric induction by the chiral ligand.

With a methyl group substituted β to the carboxylate group of **1a**, the reaction proceeded well, but the e.e. of the product **3p** was very poor (entry 15). In contrast, the regioisomeric substrate **1q**, which has a Me α to the ester group and was prepared as an inseparable geometric mixture (*E*/*Z* = 5:1), was converted to the separable cyclopropane diastereomers **3q** and **3q′** in an almost identical ratio and in a 91% combined yield, indicating that the cyclopropanation is concerted and stereospecific. Moreover, the e.e. of **3q**, which was formed from the (*E*)-isomer, is 92% and better than that from the (*Z*)-isomer. In comparison to **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., avoiding $A^{1,3}$ strain). The beneficial impact of an α-Me group revealed by this case prompted us to examine a related phenone substrate. As shown in entry 17, the oxidative cyclopropanation proceeded in a good 82% isolated yield and with excellent enantioselectivity (93% e.e.).

The absolute stereochemistry of the cyclopropanation products are established based on the single crystal X-ray diffraction studies[17] of both **3e** and **3g**. As shown in Figure 2, both products have the same (1*R*,1a*S*,6a*R*) configurations. By analogy, the absolute configurations of other products are assigned accordingly. The stereochemical outcomes could be rationalized, although in depth DFT calculations are needed to really appreciate the cyclopropanation mechanism and the factors controlling facial selectivity. As outlined in Figure 2B, 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 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.

Notably, this enantioselective oxidative gold catalysis could facilitate access to novel constrained analogs of L-glutamic acid, the principal excitatory amino acid neurotransmitter in human central nervous system. 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 mGluRs (metabotropic glutamate receptors)[18] and has been implicated as a potential treatment of various CNS diseases (Figure 2C),[19] but its asymmetric synthesis has been limited to inefficient resolution,[20] a rather lengthy chiral pool approach,[21] poorly diastereoselective approaches[22] (in one case, separation from four diastereomers[22b]). Since it can be readily accessed from the bicyclic cyclopentenone **4**, which apparently embodies the key feature in the structures prepared in this study, this chemistry would offer asymmetric access to additionally substituted analogs[23] of LY354740.

In summary, we have implemented a first enantioselective oxidative gold catalysis, in which a novel *P*,*N*-bidentate ligand enables in-situ generated, reactive α-oxo gold carbene intermediates to undergo asymmetric intramolecular cyclopropanation. The design of the

ligand relies on our previously proposed structure of the carbene intermediate in the presence of a *P*,*N*-bidentate ligand, which possesses a well-organized tris-coordinated gold center, and was implemented by incorporating a *C2*-symmetric 3,5-bissiloxylated piperidine ring as the nitrogen part. This reaction provides facile access to the bicyclic cyclopropane products with mostly good to excellent enantiomeric excesses. With a large array of racemic transformations of α-oxo gold carbene intermediates recently developed, this new class of chiral ligands, as demonstrated in this study, could usher a new and synthetically highly valuable phase of exploiting synthetic applications of the versatile intermediates in asymmetric synthesis. Our further studies to apply these chiral ligands to oxidative gold catalysis are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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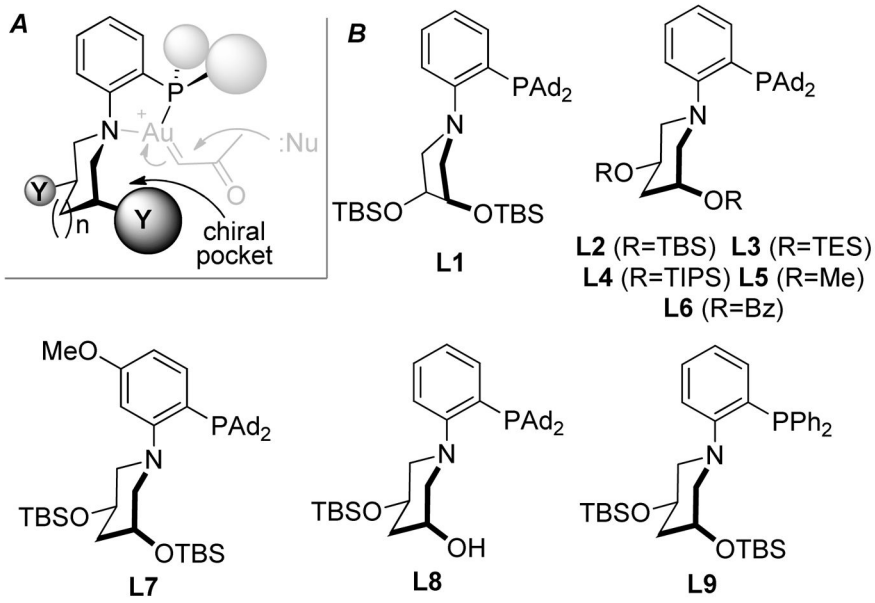


Figure 1.
P,*N*-bidentate ligands: (A) Design; (B) Selected ligands.

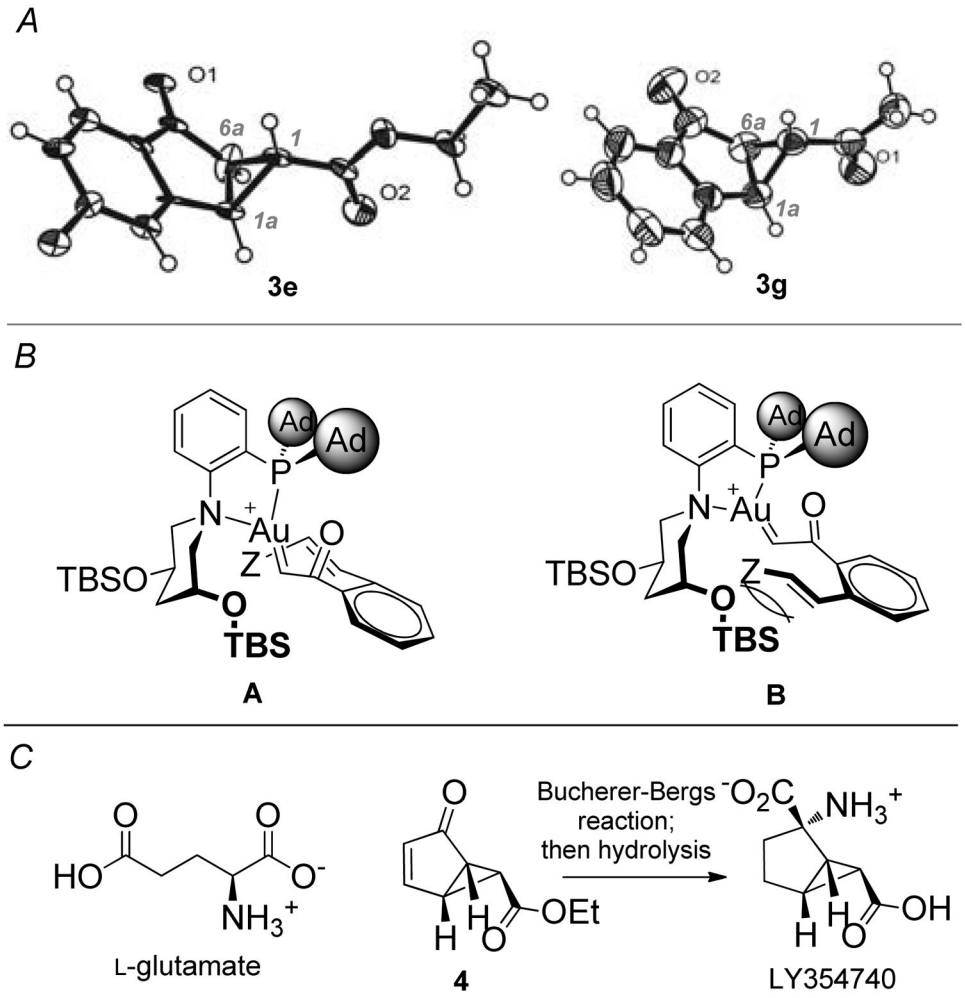
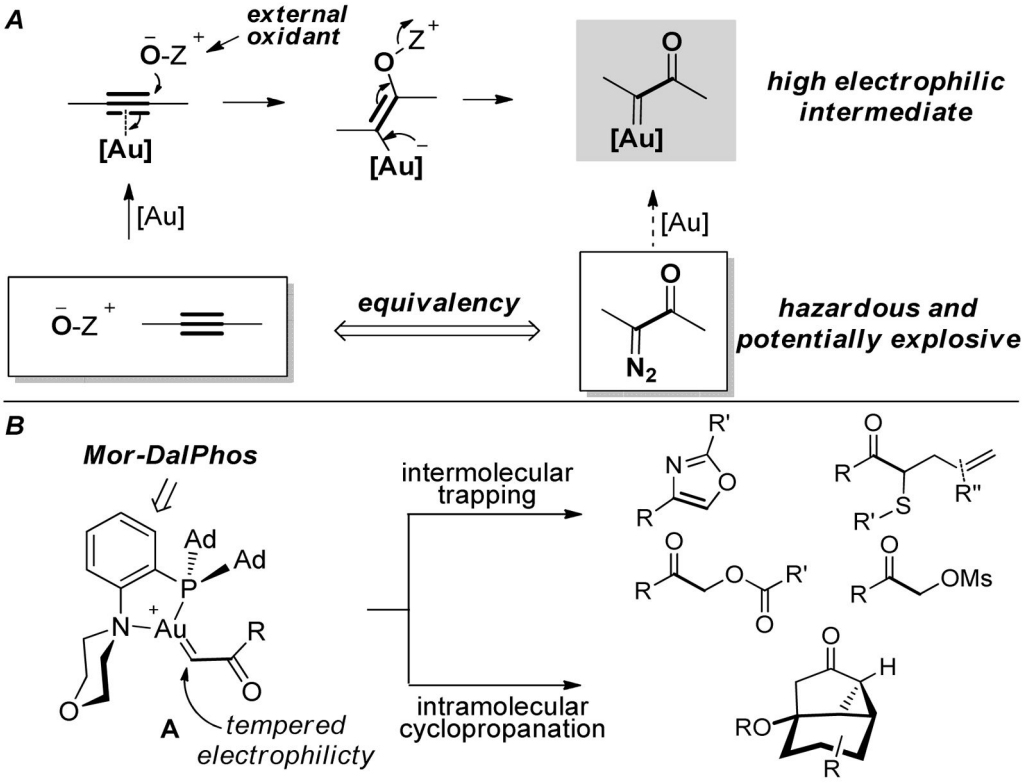


Figure 2.

(A) The structures of **3e** and **3g** with the absolute stereochemistry established via single crystal diffraction studies. (B) The rationale for the observed enantioselectivity. (C) L-Glutamic acid and LY354740



Scheme 1.

(A) Oxidative gold catalysis: a facile, non-diazo access to α-oxo gold carbenes; (B) A *P*,*N*-bidentate ligand tempers carbene reactivities and enables intermolecular trapping and intramolecular cyclopropanation reactions.

Table 1

Ligand optimization and condition study of enantioselective gold catalyzed oxidative cyclopropanation

Entry	L	conditions	Yield[a]	e.e.[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] NMR yield using diethyl phthalate as the internal reference.

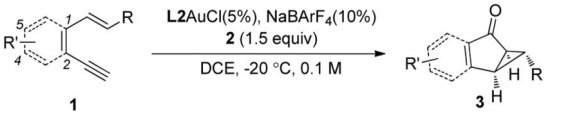
[b] Determined by chiral HPLC.

[c] No desired product was observed from crude NMR.

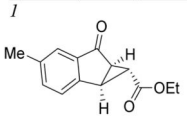
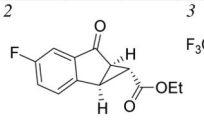
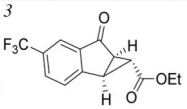
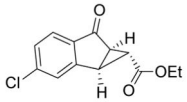
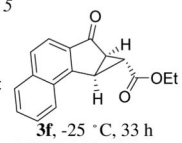
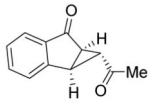
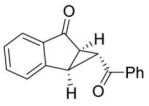
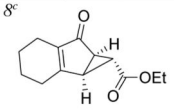
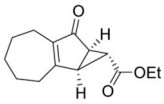
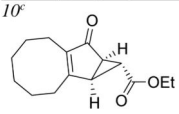
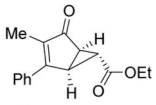
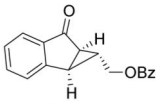
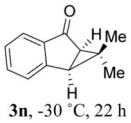
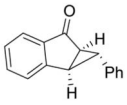
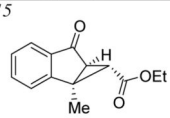
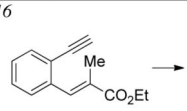
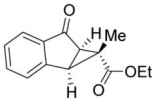
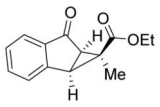
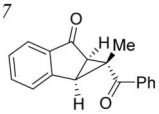
[d] Isolated yield

Table 2

Reaction scope.[a]



1 **3**

1  **3b**, 50 h 60% yield, 90% e.e.	*2*  **3c**, 50 h 51% yield, 87% e.e.	*3*  **3d**, 50 h 50% yield,89% e.e.
4  **3e**, 45 h 54% yield, 94% e.e.	*5*  **3f**, -25 °C, 33 h 70% yield, 90% e.e.	*6*  **3g**, 45 h 62% yield, 92% e.e.
7  **3h**, 50 h 70% yield, 93% e.e.	*8*[c]  **3i**, -10 °C, 72 h 81% yield, 90% e.e.	*9*[c]  **3j**, -10 °C, 72 h 82% yield, 86% e.e.
10[c]  **3k**, -10 °C, 80 h 85% yield, 85% e.e.	*11*[c]  **3l**, -10 °C, 80 h 81% yield, 85% e.e.	*12*  **3m**, 36 h 90% yield, 88% e.e.
13  **3n**, -30 °C, 22 h 90% yield, 63% e.e.	*14*[d]  **3o**, 72 h 88% yield, 87% e.e.	*15*  **3p**, rt, 2 h 78% yield, 11% e.e.
16  **1q** *E*/*Z* = 5:1	 **3q**, 30 h 76% yield, 93% e.e.	 **3q'**, 30 h 15% yield, 87% e.e.
17  **3r**, -20 °C, 46 h 82% yield, 93% e.e.		

[a] Reactions were run in vials.

[b] Isolated yield.

[c] 7.5% **L2**AuCl and 15% NaBARF were used.

[d]The reaction was carried out at 0 °C, toluene as the solvent.