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Author(s)	Sakai, Satoshi; Uchiyama, Kei; Imai, Koji et al.
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Silver-Catalyzed Asymmetric Aldol Reaction of Nonactivated Ketones with α-Isocyanocarboxylic Acid Derivatives Enabled by Prolinol-phosphine-*sec*-amine Chiral Ligand

Satoshi Sakai,[1] Kei Uchiyama,[1] Koji Imai,[1] Kazuna Yato,[1] Mai Onizawa,[1] Kosuke Higashida,[2] Hiroyasu Sato,[3] Yoshitaka Aoyama,[4] Yohei Shimizu,[1,2,5,] Masaya Sawamura[1,2,]**

[1] Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan

[2] Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan

[3] Application Laboratory, Rigaku Corporation, Tokyo 196-8666, Japan

[4] EM Business Unit, SI Business Operations, JEOL Ltd., Tokyo 192-0906, Japan

[5] List Sustainable Digital Transformation Catalyst Collaboration Research Platform, Institute for Chemical Reaction Design and Discovery (ICReDD List-PF), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan

KEYWORDS: asymmetric aldol reaction, ketone, silver catalysis, noncovalent interactions, chiral phosphine

ABSTRACT: The catalytic asymmetric aldol reaction of nonactivated ketones is a formidable challenge in asymmetric catalysis. To this end, we designed and synthesized a prolinol-phosphine-*sec*-amine P,N,N,O-tetradentate chiral ligand that enabled a highly diastereo- and enantioselective silver(I)-catalyzed aldol reaction of nonactivated ketones with isocyanoacetamides, affording enantioenriched α-amino acid derivatives with a tertiary alcohol at the β-position. This stereoselective reaction allowed extremely challenging molecular transformations with sterically demanding dialkyl ketones and alkyl aryl ketones such as *tert*-alkyl methyl ketones, *sec*-alkyl primary alkyl ketones, and *sec*-alkyl aryl ketones. The silver(I) catalyst system was also effective for the enantiocontrolled construction of consecutive tetrasubstituted stereogenic carbon centers through the aldol reaction between simple aryl alkyl ketones and α-alkyl-α-isocyanoaetates. Spectroscopic and microED analysis combined with computational investigations showed that P,N,N,O-tetradentate metal-binding of the chiral ligand allows creation of a metal/organo cooperative asymmetric catalytic space that provides densely accumulated classical and nonclassical hydrogen bonds and complementary London dispersion interactions, stabilizing the transition state of the stereochemistry-determining ring-closing reaction of the oxyanion intermediate.

INTRODUCTION

Catalytic asymmetric aldol reactions are powerful carbon-carbon bond formation reactions that have been studied intensively for decades.[1-3] While there have been numerous reports of catalytic asymmetric aldol reactions using aldehydes as electrophiles, the reaction with ketones remains a formidable challenge for several reasons.[4-13] First, the two carbon substituents of the carbonyl

group must be differentiated. Second, both electronic and steric factors of ketones lead to attenuated reactivity compared to aldehydes. Finally, achieving direct catalytic asymmetric aldol reactions of ketones while avoiding the use of preformed metal enolates is particularly difficult due to their enhanced propensity for retro-aldol reactions,[14] which is more burdensome on reactions involving stabilized carbanions as nucleophiles.

The few successful examples of such direct catalytic asymmetric aldol reactions with nonactivated ketones were those combined with successive cyclization to trap the oxyanion of the aldol adduct, making the reaction irreversible. Using this strategy, Matsunaga and Shibasaki achieved an asymmetric aldol reaction of ketones with isothiocyanato esters promoted by a Mg/Schiff base catalyst to afford cyclic thiocarbamates with high stereoselectivity.[15] This reaction, however, was specifically applicable in cases where the product does not have an α-proton.[16] The asymmetric aldol reaction of aldehydes with isocyanoacetic acid derivatives, originally developed by Ito, Hayashi, and Sawamura with gold or silver catalysts, also proceeded with cyclization, producing chiral oxazolines (Figure 1a).[17-23] Dixon reported a highly stereoselective silver-catalyzed aldol reaction of aryl ketones with isocyanoacetates using a quinine-derived chiral phosphine ligand.[24] Pedro showed the effectiveness of a combination of a silver catalyst and an organocatalyst bearing squaramide and quinoline moieties for the reaction with ketones.[25] These silver-catalyzed asymmetric isocyanoacetate aldol reactions, however, suffer from severe limitation in scope of the dialkyl ketones. Thus, the applicability to this substrate class has only been briefly tested using sterically accessible ketones such as cyclopropyl methyl ketone to give products with low diastereoselectivity.[15,24,25] Dixon's protocol for the reaction of cyclohexyl methyl ketone, as an example of an unbiased dialkyl ketone, with *t*-butyl isocyanoacetate gave the oxazoline product in only 85:15 *dr* (*trans*/*cis*) and 34% *ee* for the *trans* isomer.[24] Hence, the

development of precisely designed catalysts is indispensable to realize reactions that satisfy all the requirements of high reactivity, diastereoselectivity, and enantioselectivity. Ideally, the catalysts should be applicable toward sterically and electronically nonactivated ketones, such as bulky dialkyl ketones, to establish a general route to enantioenriched α-amino acid derivatives with a tertiary alcohol at the β-position.[26]

Enzymes, highly active and selective catalysts in nature, perform complex molecular transformations by precisely controlling the orientations and electronic states of substrates through the synergistic combination of various intermolecular forces such as hydrogen-bonding and van der Waals interactions including London dispersions. Therefore, the development of artificial catalysts comprising these enzyme-like features is an area of active research.[27] However, designing a catalyst with precise multiple intermolecular forces solely with chemical intuition has been challenging. While recent progress in quantum chemical methods has allowed better catalyst design through visualization of intermolecular forces, it is still a formidable task to apply computational results to produce a new catalyst with the desired performance.

Previously, we introduced chiral prolinol-phosphine ligands for the development of a series of transition metal catalyzed enantioselective reactions with carbonyl and carbonyl-related compounds.[28–33] DFT calculations suggested the occurrence of multiple synergistic noncovalent interactions between the prolinol-phosphine ligands and carbonyl compounds including classical O–H···O hydrogen bonds, nonclassical sp^3-C–H···O hydrogen bonds,[34,35] and London dispersion interactions, which establish well-defined stereodiscriminating transition states. Specifically, the silver-catalyzed asymmetric aldol reaction of aldehydes with isocyanoacetic acid derivatives using a chiral prolinol-phosphine ligand yielded chiral oxazolines through C–C bond formation and subsequent cyclization (Figure 1a).[33] In our studies of this silver catalysis, we noted the occurrence

of an additional sp^3-C–H···O hydrogen bond between one of the sp^3-C–H bonds at the C4 position of the pyrrolidine ring of the chiral ligand and the carbonyl group of the isocyanoacetamide donor moiety (highlighted in red, Figure 1b). However, its contribution to the stabilization of the transition state may not be sufficient to influence the stereocontrol.

This computation-based transition state stabilization model encouraged us to develop more efficient silver catalysis systems by introducing reliable polar heteroatom-based hydrogen-bond donor sites such as hydroxy and amino groups at the C4 position of the 2-pyrrolidinemethanol (Figure 1c). Herein, we report a highly efficient silver-catalyzed asymmetric aldol reaction of ketones with isocyanoacetamides as the outcome of computation-guided ligand design based on assembly of multiple intermolecular forces caused by a chiral ligand with a C4-*sec*-amino substituent (Figure 1c, right), highlighting unprecedented applicability toward nonactivated sterically demanding dialkyl ketones and alkyl aryl ketones. A critical importance of a nonclassical sp^2-C–H···O hydrogen bond donated by an aromatic ring in the C4-*sec*-amino substituent is discussed.

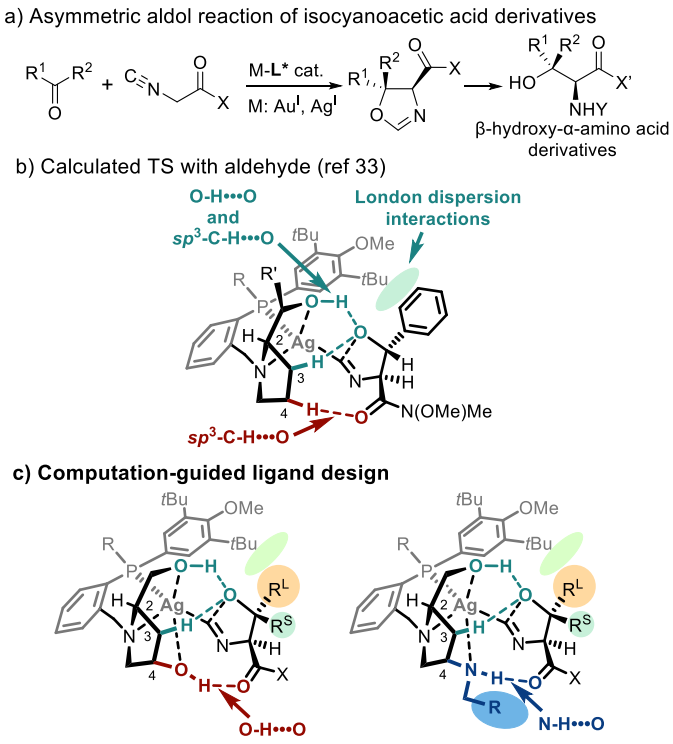


Figure 1. Aldol reactions of isocyanoacetic acid derivatives.

RESULTS AND DISCUSSION

Ligand Optimization. We commenced our investigation by evaluating various chiral prolinol-phosphine ligands (**L**, 2 mol%) in combination with Ag_2CO_3 (1 mol% Ag) for catalytic activity and stereoselectivity in the enantioselective aldol reaction between cyclohexyl methyl ketone **1a**, as an electronically unbiased, sterically demanding dialkyl ketone, and Weinreb-type isocyanoacetamide **2a** in toluene at 25 °C for 8 h (Table 1). To our knowledge, the catalytic asymmetric direct aldol reaction of cyclohexyl methyl ketone (**1a**) has only been described by Dixon and co-workers with only low stereoselectivity (85:15 *dr*, 35% *ee*).[24] The reaction hardly proceeded with the chiral ligand (**L1**) that was optimal in our previous study for the reaction with aldehydes,[30] confirming the inertness of this substrate (entry 1). In this study, however, we noticed that the reaction did proceed slowly with **L2**, which has a primary alcohol pendant on the

pyrrolidine ring instead of the neopentyl-branched secondary alcohol pendant in **L1**, to give 4,4-disubstituted 2-oxazoline-3-carboxamide **3aa** in 17% yield with meaningful stereoselectivity (*trans/cis* 89:11, 30% *ee* for *trans*) (entry 2). Based on this finding and the computation-guided ligand design (Figure 1c), we introduced a hydroxy group at the C4 position of the pyrrolidine ring to obtain *P,N*-diol ligand **L3**. The effect of the additional hydroxy group was significant, giving the product in an increased yield of 55% with a higher diastereoselectivity, albeit with a lower enantioselectivity (*trans/cis* 92:8, 12% *ee*) (entry 3). When the C4 hydroxy group was masked as a MeO group (**L4**), the catalytic activity and stereoselectivity returned to the levels with the original ligand **L2** (entry 4). On the other hand, ligand **L5**, produced by masking the primary alcohol pendant at the pyrrolidine C2 position while maintaining the secondary alcohol at the C4 position, gave very poor catalytic activity in accord with the hydrogen-bonding catalysis model based on the stabilization of the ketone-derived oxyanion (entry 5).

Next, we introduced various *N*-alkylamino groups at the C4 position, expecting additional attractive noncovalent interactions or steric effects that may occur in more cavity-like catalytic environments. To our delight, when an *N*-butylamino group was introduced (**L6**), the yield jumped to 93% with a marked increase in enantioselectivity *(trans/cis* 92:8, 73% *ee*, Table 1, entry 6). An *N*-benzylamino group was a promising platform with **L7**, giving 84% yield, *trans/cis* ratio 93:7, and 76% *ee* (entry 7). The introduction of an electron-donating *p*-OMe substituent to the benzene ring resulted in a negative effect (**L8**, 83% yield, *trans/cis* 92:8, 74% *ee*, entry 8), while an electron-withdrawing *p*-CF_3 group produced a significant improvement in stereoselectivity (**L9**, 84% yield, *trans/cis* 93:7, 85% *ee*, entry 9). Based on these results, we synthesized a chiral ligand (**L10**) with a more electron-deficient *N*-[3,5-bis(trifluoromethyl)phenylmethyl]amino group. To our delight, this ligand gave a quantitative yield and an enantioselectivity as high as 95% *ee* (*trans/cis* 92:8,

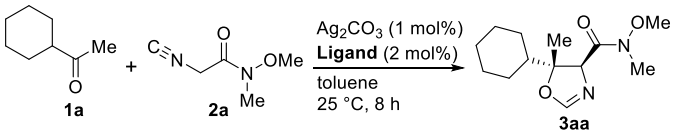
entry 10). The stereoselectivity was slightly improved by changing the solvent from toluene to cyclohexane (95% yield, *trans/cis* 92:8, 96% *ee*, entry 11). This positive effect with the more hydrophobic solvent (cyclohexane) may reflect enhanced hydrogen-bonding effects. In contrast to the favorable effects of the two *m*-CF_3 groups in **L10**, the introduction of two *m*-Me groups had negative effects (vs. **L7**) on both chemical yield and enantioselectivity (**L11**, 80% yield, *trans/cis* 93:7, and 63% *ee*, entry 12), suggesting that the effects of the CF_3 groups in **L9** and **L10** are electronic.[36]

An aniline-type ligand (**L12**) with an electron-withdrawing *N*-3,5-bis(trifluoromethyl)phenyl group on the N–H nitrogen atom, afforded only a low substrate conversion with a low enantioselectivity (51% yield, 31% *ee*, Table 1, entry 13), indicating that enhanced N–H acidity is unfavorable for the enantioselective catalysis. A comparison of the reaction outcomes with the two homologous ligands **L10** and **L12** indicates that the methylene group of the benzylic *N*-substituent of **L10** acts as a hinge to direct the *N*-substituent back to the catalytic environment to allow beneficial attractive interactions with the reacting isocyanoacetamide substrate (*vide infra* for discussion based on computational studies). Introduction of an even stronger hydrogen-bonding site with a carbamate-type ligand (**L13**) resulted in poor catalytic activity with much reduced stereoselectivity (19% yield, *trans*/*cis* 88:12, 4% *ee*, entry 14). The poor performance of the ligands (**L12** and **L13**) with strong N–H acidities may be due to the lack of an N···Ag interaction, the occurrence of which is more probable with the C4-*N*-alkylated ligands (**L6**–**L11**, Figure 1c).

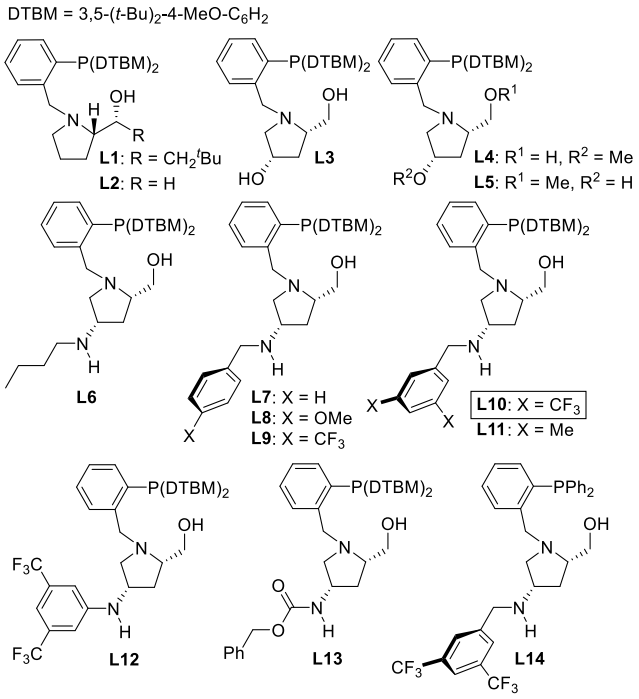
When the sterically demanding *P*-substituents (DTBMs) of **L10** were replaced with simple phenyl groups (**L14**), the chemical yield, diastereoselectivity and enantioselectivity all decreased substantially (64% yield, *trans/cis* 90:10, 85% *ee*, entry 15). Thus, increasing the steric demand of the chiral ligand in the Ar_2P moiety caused favorable effects not only on the stereoselectivity but

also on the rate of the reaction, suggesting the existence of London dispersion interactions between the cyclohexyl group of the ketonic substrate (**1a**) (R^L in Figure 1c) and the DTBM group, which defines the boundary of the catalytic environment.

Table 1. Ligand Optimization.[a]



entry	ligand	NMR yield (%)[b]	*dr* (*trans*/*cis*)	*ee* (%)
1	**L1**	trace	–	–
2	**L2**	17	89:11	30
3	**L3**	55	92:8	12
4	**L4**	18	88:12	34
5	**L5**	6	91:9	9
6	**L6**	93	92:8	73
7	**L7**	84	93:7	76
8	**L8**	83	92:8	74
9	**L9**	84	93:7	85
10	**L10**	>99	92:8	95
11[c]	**L10**	95	93:7	96
12	**L11**	80	93:7	63
13	**L12**	51	92:8	31
14	**L13**	19	88:12	4
15	**L14**	64	90:10	85



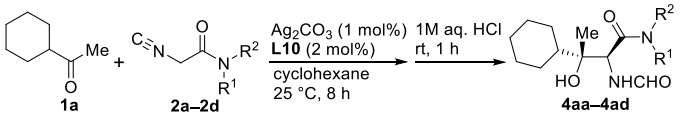
[a]**1a** (0.75 mmol), **2a** (0.5 mmol), Ag_2CO_3 (0.005 mmol), ligand (0.01 mmol), toluene (1 mL), 25 °C, 8 h. [b]Yields and dr were determined by ^1H NMR analysis of crude material using tetrachloroethane as an internal standard. [c]Cyclohexane (1 mL) was used as a solvent instead of toluene.

Effects of Amide Moiety of Isocyanide. With the optimized conditions in hand (Ag-**L10** 2 mol%, cyclohexane, 25 °C, 8 h), effects of the amide moiety of the isocyanides (**2**) were investigated for the reaction with cyclohexyl methyl ketone (**1a**) (Table 2).[37] Since the oxazoline moiety was not stable during the purification by silica gel chromatography, successive hydrolysis was performed to isolate the products as β-hydroxy-α-(*N*-formyl)aminocarboxamides (**4**). The product (**4aa**) from the Weinreb-type isocyanoacetamide (**2a**) was obtained in 98% isolated yield, *dr* 92:8, and 97% *ee* (entry 1). Pyrrolidine (**2b**) and piperidine (**2c**) amides were competent pronucleophiles, being transformed to the corresponding products in good yields with high stereoselectivity (**4ab**: 83% yield, *dr* 95:5, 96% *ee*, entry 2; **4ac**: 77% yield, *dr* 94:6, 92% *ee*, entry 4). A gram-scale reaction between **1a** and **2b** was feasible with reduced catalyst loading, 0.25

mol% of Ag_2CO_3 and 0.5 mol% of **L10**, by extending the reaction time to 96 h (1.62 g of **4ab**, 77% yield, *dr* 93:7, 89% *ee*, entry 3). *N*,*N*-Dimethylamide **2d** afforded **4ad** in excellent enantioselectivity (82% yield, *dr* 96:4, 96% *ee*, entry 5). The reaction with sterically more demanding *N,N*-dibenzylamide **2e** also proceeded, providing **4ae** with high stereoselectivity (48% yield, *dr* 97:3, 89% *ee*, entry 6). An anilide derivative **4af** was applicable without diminishing the reactivity or the stereoselectivity (75% yield, *dr* 96:4, 91% *ee*, entry 7). Overall, the effects of the amide moiety on the reaction outcome were not significant.

When methyl and *t*-butyl 2-isocyanoacetate were employed as the substrates for the reaction with **1a**, dimerization of the isocyanides to form 3-alkoxycarbonylmethyl-5-alkoxycarbonylimidazoles was significant, resulting in low yields of the corresponding oxazolines. Thus, 2-isocyanoacetamides were employed for further study.

Table 2. Scope of Isocyanides (2) for Asymmetric Aldol Reaction of 1a Catalyzed by Ag_2CO_3-L10 System.[a]



entry	R^1, R^2	yield (%)	*dr*	*ee* (%)
1	Me, OMe (**4aa**)	98	92:8	97
2	-$(CH_2)_4$- (**4ab**)	83	95:5	96
3[b]	-$(CH_2)_4$- (**4ab**)	77	93:7	89
4[c]	-$(CH_2)_5$- (**4ac**)	77	94:6	92

5[d]	Me, Me (**4ad**)	82	96:4	96
6[e]	Bn, Bn (**4ae**)	48	97:3	89
7[c]	Me, Ph (**4af**)	75	96:4	91

[a]**1a** (0.75 mmol), **2a** (0.5 mmol), Ag_2CO_3 (0.005 mmol), ligand (0.01 mmol), cyclohexane (1 mL), 25 °C, 8 h. [b]**1a** (11.3 mmol), **2b** (7.5 mmol), Ag_2CO_3 (0.019 mmol), **L10** (0.038 mmol), cyclohexane (3.8 mL), 96 h. [c]48 h. [d]96 h. [e]**1a** (0.45 mmol), **2b** (0.3 mmol), Ag_2CO_3 (0.003 mmol), **L10** (0.006 mmol), cyclohexane (0.6 mL), 48 h.

Scope of Ketones. The scope of ketones (**1b**–**n**) is shown in Scheme 1. Cyclopentyl methyl ketone **1b** reacted smoothly with the pyrrolidine 2-isocyanoacetamide (**2b**) to give **4bb** in 97% yield with α stereoselectivity (*dr* 98:2, 94% *ee*) comparable to **1a**. An isopropyl group was tolerated as an acyclic *sec*-alkyl carbonyl substituent to afford **4cb** in good yield and high stereoselectivity (80% yield, *dr* 94:6, 95% *ee*). The catalytic system accepted methyl ketones with even more sterically demanding substituents such as *tert*-butyl (**1d**) and 1-adamantyl (**1e**) groups, giving the products (**4db** and **4eb**) in good yields with exclusive stereoselectivity (*dr* >99:1, 99% *ee*) with a prolonged reaction time (48 h). X-ray diffraction (XRD) analysis of **4eb** confirmed that the absolute stereochemistry of the product was in accord with the stereocontrol model (Figure 1c), in which the bulky substituent of the ketone is located in proximity to one of the *P*-DTBM substituents of the ligand to acquire better London dispersion interactions. Methyl ketones with primary alkyl substituents such as *n*-hexyl (**1f**), isobutyl (**1g**), and 4-chlorophenylmethyl (**1h**) groups provided the products in high yield and high enantioselectivity, albeit with lower diastereoselectivity (**4fb**: 94% yield, *dr* 69:31, 86% *ee*/86% *ee*; **4gb**: 86% yield, *dr* 59:41, 91% *ee*/94% *ee*; **4hb**: 91% yield, *dr* 72:28, 71% *ee*/62% *ee*).

The scope was not limited to methyl ketones. Ethyl ketones such as ethyl cyclohexyl ketone (**1i**) and ethyl isopropyl ketone (**1j**) underwent smooth reactions with high diastereo- and

enantioselectivities (**4ib**: 88% yield, *dr* 89:11, 99% *ee*/73% *ee*; **4jb**: 86% yield, *dr* 91:9, 98% *ee*/75% *ee*), showing that the catalyst has the ability to recognize structural differences between primary and secondary alkyl groups (Scheme 1).

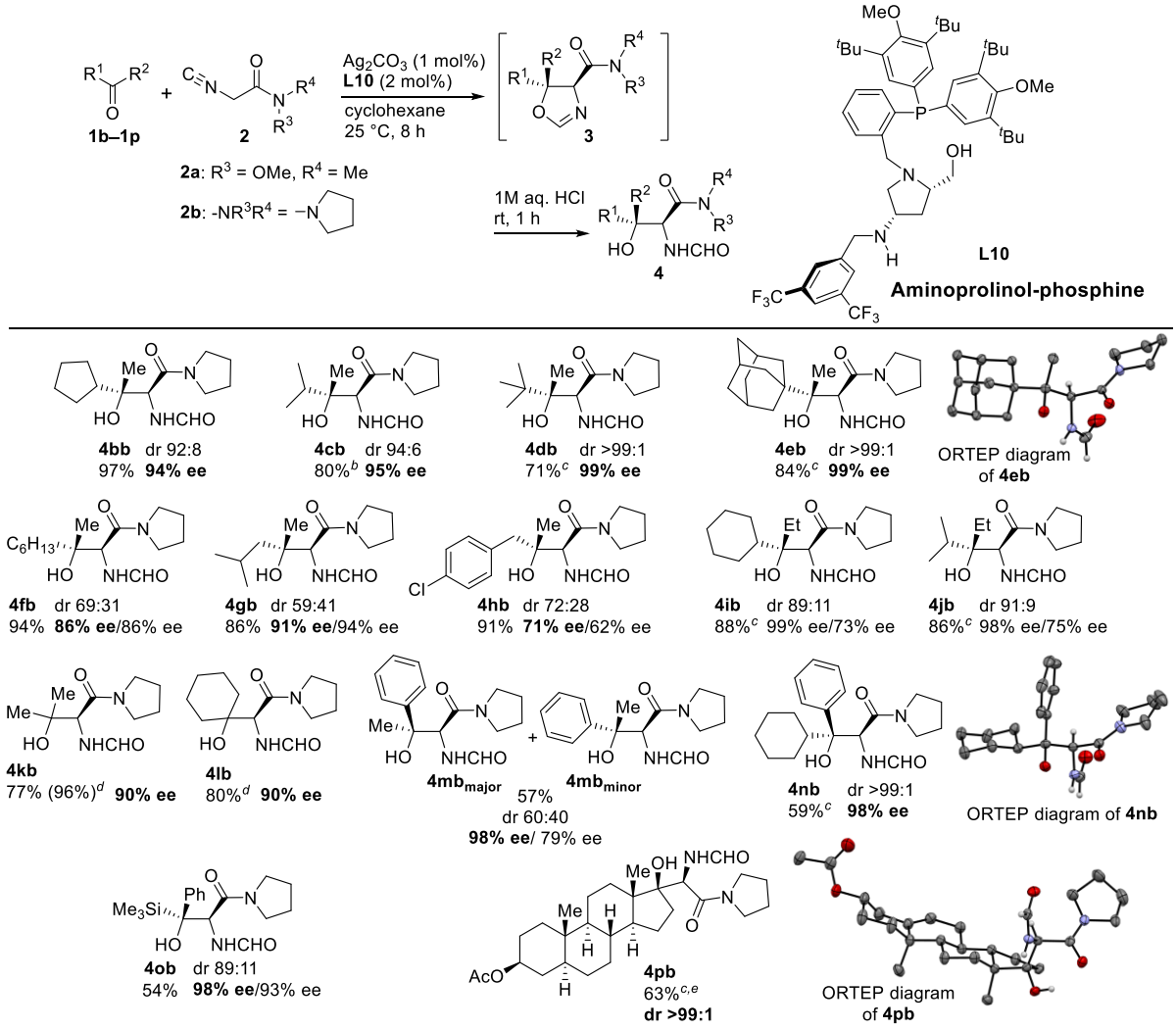
Symmetrical ketones such as acetone **1k** and cyclohexanone **1l** also underwent highly enantioselective reactions under slightly different conditions using the Ag_2O catalyst at 0 °C, affording the corresponding singly stereogenic products **4kb** (77% yield, 90% *ee*) and **4lb** (80% yield, 90% *ee*), respectively (Scheme 1). Thus, the Ag-aminoprolinol-phosphine (**L10**) chiral catalyst has the ability to differentiate the prochiral faces of the isocyanoacetamide enolate in accord with our ligand design based on the ligand-enolate N–H···O hydrogen-bonding (Figure 1c).

Aryl ketones were also examined. The reaction of acetophenone **1m** proceeded in 57% yield with 98% *ee* for the major isomer, but the diastereoselectivity was poor (*dr* 60:40) (Scheme 1). Very interestingly, sterically more demanding cyclohexyl phenyl ketone **1n** was also reactive under the conditions. Notably, the catalyst was able to discriminate two substituents (Cy vs. Ph) with similar steric demands, affording the product (**4nb**) in excellent diastereo- and enantioselectivities (59% yield, *dr* >99:1, 98% *ee*). Based on the absolute configuration of **4nb**, confirmed by XRD analysis, and the transition state model (Figure 1c), the cyclohexyl group is regarded as the larger substituent (R^L in Figure 1c) which has London dispersion interactions with **L10**. We examined the suitability of silyl ketone $PhCOSiMe_3$ (**1o**), expecting the Me_3Si group to be the bulky carbonyl substituent (R^L in Figure 1c). Indeed, the reaction of **1o** with **2b** afforded β-hydroxy-β-trimethylsilyl phenylalanine derivative **4ob** (54% yield, *dr* 89:11, 98% *ee*/93% *ee*) with the expected stereochemistry.

While the reaction between a homochiral natural product dehydroepiandrosterone acetate **1p** and **2a** did not proceed at all with the Ag_2CO_3-**L10** catalyst, a catalyst system with the antipode

(Ag_2CO_3-***ent*-L10**) of **L10** promoted the reaction cleanly to give a single stereoisomer of **4pb** out of the four possible diastereomers (Scheme 1). This indicates that the catalyst precisely recognized the stereochemistry of the chiral substrate for the approach of the nucleophile to the carbonyl group from the side opposite to the adjacent axial Me group.

Scheme 1. Scope of Ketones (1) for Asymmetric Aldol Reaction of 2 Catalyzed by Ag-L10 System.[a]

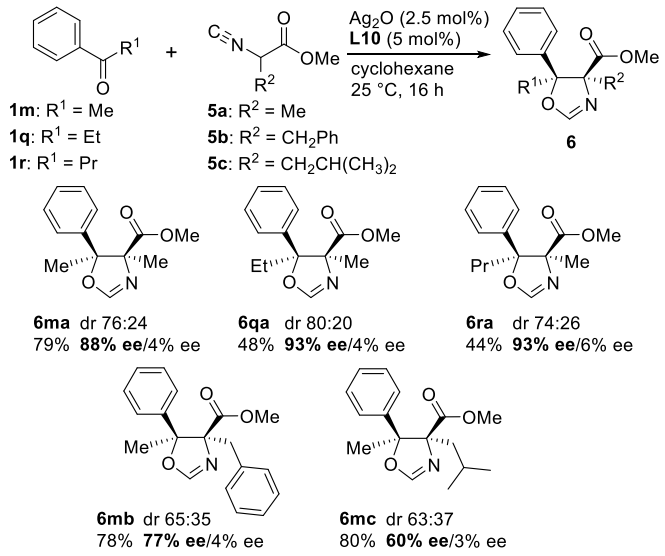


[a]**1** (0.75 mmol), **2** (0.5 mmol), Ag_2CO_3 (0.005 mmol), ligand (0.01 mmol), cyclohexane (1 mL), 25 °C, 8 h. [b]16 h. [c]48 h. [d]Ag_2O was used instead of Ag_2CO_3 in toluene (1 mL) at 0 °C. [e]***ent*-L10** was used instead of **L10**.

Enantiocontrolled Construction of Consecutive Tetrasubstituted Stereogenic Carbon Centers. The Ag-**L10** catalyst system was also effective for the enantiocontrolled construction of consecutive tetrasubstituted stereogenic carbon centers through the aldol reaction between ketones and α-alkyl-α-isocyanoaetates (**5**) (Scheme 2).[15] While a simple symmetrical ketone cyclohexanone (**1l**) reacted with 2-isocyanopropionoate (**5a**) derived from D/L-alanine with moderate enantioselectivity (62% *ee*), the isocyanide (**5a**) did not react with the sterically more demanding cyclohexyl methyl ketone (**1a**) (not shown in Scheme 2). To our delight, however, the alanine-derived isocyanide (**5a**) reacted smoothly with acetophenone (**1m**) under the catalysis of a silver complex prepared from Ag_2O (2.5 mol%) and **L10** (5 mol%) in cyclohexane at 25 °C for 6 h to afford the 4,4,5,5-tetrasubstituted oxazoline **6ma** in 79% yield with a 76:24 diastereomeric ratio. The major diastereomer had a configuration of 4*S*,5*S* with 88% *ee* while the minor diastereomer was nearly racemic (see Supporting Information for configuration determination). Ethyl phenyl ketone (**1q**) and phenyl propyl ketone (**1r**) reacted with **5a** with higher diastereo- and enantioselectivities than acetophenone (**1m**) (**6qa**, *dr* 80:20, 93% *ee*/4% *ee*; **6ra**, 74:26, 93% *ee*/6% *ee*) in line with the trend observed in the reaction of the glycine-derived isocyanoacetamide **2b** with the aromatic ketones (**4m** vs **4n**) (Scheme 1). Isobutyl phenyl ketone (**1u**) was inert for the reaction with **5a**.

Phenylalanine- and leucine-derived isocyanides (**5b**,**c**) also reacted with acetophenone (**1m**) to yield the oxazolines **6mb** and **6mc** with decent enantioselectivities (Scheme 2, **6mb**: 65:35, 77% *ee*/4% *ee*; **6mc**: 63:37, 60% *ee*/3% *ee*).

Scheme 2. Enantioselective Aldol Reaction between Aromatic Ketones (1) and α-Alkyl-α-Isocyanoacetates (5).[a]

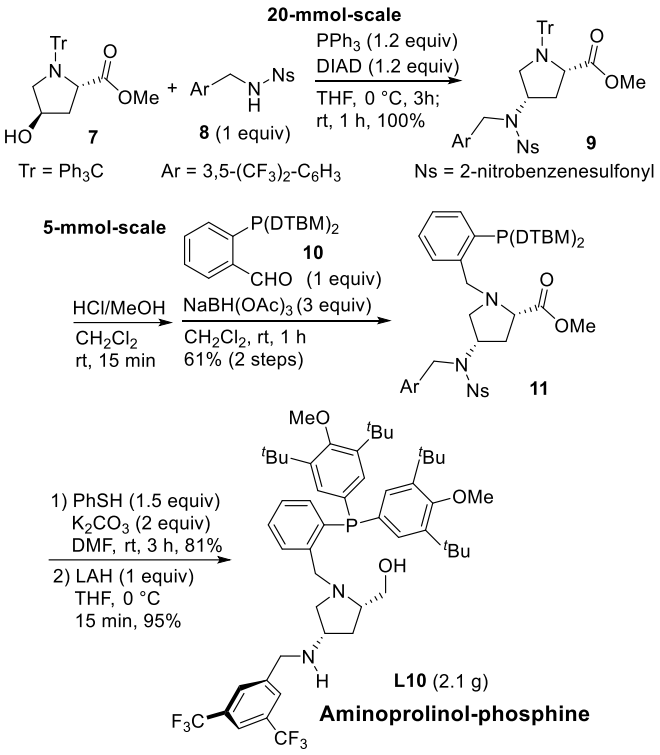


[a] **1** (0.3 mmol), **2** (0.2 mmol), Ag_2O (0.005 mmol), **L10** (0.01 mmol), cyclohexane (1 mL), 25 °C, 16 h.

Ligand Synthesis. Synthesis of the chiral aminoprolinol-phosphine ligand **L10** is outlined in Scheme 3. The amino group at the ring C4 position of the pyrrolidine-2-methanol of **L10** was introduced by Mitsunobu reaction between 4-hydroxyproline derivative **7**[38] and *N*-nosyl-protected benzyl amine **8**, resulting in complete stereoinversion at this position (nosyl: 2-nitrobenzenesulfonyl). The reaction proceeded smoothly, even on a 20-mmol scale, affording the product **9** in quantitative yield. Next, removal of the trityl group under acidic conditions and subsequent reductive amination with 2-diarylphosphinobenzaldehyde **10** on a 5-mmol scale afforded the aminophosphine **11** in 61% yield. Following the two-step transformation, cleavage of the nosyl group with thiophenol and reduction of the ester moiety by lithium aluminum hydride provided 2.1 g of **L10**. The obtained aminoprolinol-phosphine **L10** is an easy-to-handle white

powder that can be weighed under air and stored in a screw-capped vial filled with inert gas at room temperature for at least six months without any loss of purity.

Scheme 3. Synthesis of L10.



Ag–L10 Complexes. To gain information for the coordination of aminoprolinol-phosphine ligand **L10** toward a silver atom, a cationic silver(I)–**L10** complex [Ag-**L10**]$^{+}PF_6^{-}$ was prepared by reacting equimolar amounts of $AgPF_6$ and **L10** in toluene at room temperature for 30 min. After evaporation of the solvent, NMR spectroscopic analysis of a C_6D_6 solution of the crude mixture indicated clean formation of a silver(I) complex [Ag-**L10**]$^{+}PF_6^{-}$. The P–Ag coordination in solution phase was confirmed by the observation of a set of Ag-coupled doublet signals ($J_{P-107Ag}$ = 620 Hz, $J_{P-109Ag}$ = 712 Hz) in the $^{31}P\{^{1}H\}$ NMR spectrum.

Colorless microcrystals of [Ag-**L10**]$^{+}PF_6^{-}$ were obtained by vapor diffusion of hexane into a solution of the complex in 1,4-difluorobenzene. Attempted single-crystal X-ray diffraction analysis was in vain, but microED analysis with a XtaLAB SynergyED® instrument (Rigaku corporation, Tokyo) followed by ab initio structure determination with SHELXT presented a three-dimensional structure of [Ag-**L10**]$^{+}PF_6^{-}$ as shown in Figure 2a (all H atoms are located at the calculated positions). With a major participation of the ring-appended amino group (N_{pend}) in the **L10**–Ag coordination (Ag–N_{pend} 2.34 Å), the cationic silver(I) complex adopts a distorted P,N,N,O-four-coordinate geometry (Ag–P 2.38 Å, Ag–O 2.59 Å, Ag–N_{pyrr} 2.51 Å). The Ag-bound OH group donates a strong hydrogen bond to one of the F atoms of the PF_6^{-} ion (F···H_{calc} 2.16 Å). One of the sp^3-C–H bonds at the ring C3 position of the 2-pyrrolidinemethanol is also located in close proximity to one of the F atoms (F···H_{calc} 2.67 Å).

Geometry optimization of [Ag-**L10**]$^{+}PF_6^{-}$ by a DFT method at the ωB97X-D/6-31G(d),SDD level of theory caused only a subtle structural change, demonstrating the validity of the computational method for the current Ag-prolinol-phosphine systems. The optimized structure is shown in Figure 2b for comparison with the microED structure (Figure 2a). The positions of the PF_6^{-} ion are different, and more C–H···F contacts exist in the DFT structure. This difference is likely due to crystal packing effects in the microED structure. However, geometries around the Ag atom are similar. For instance, the similarity in the coordination of the N_{pend} atom to the Ag atom can be seen by only a slight change in the Ag–N_{pend} length (2.34 Å by microED vs 2.38 Å by DFT). Similarity of the geometries in the periphery of the complex is also to be noted.

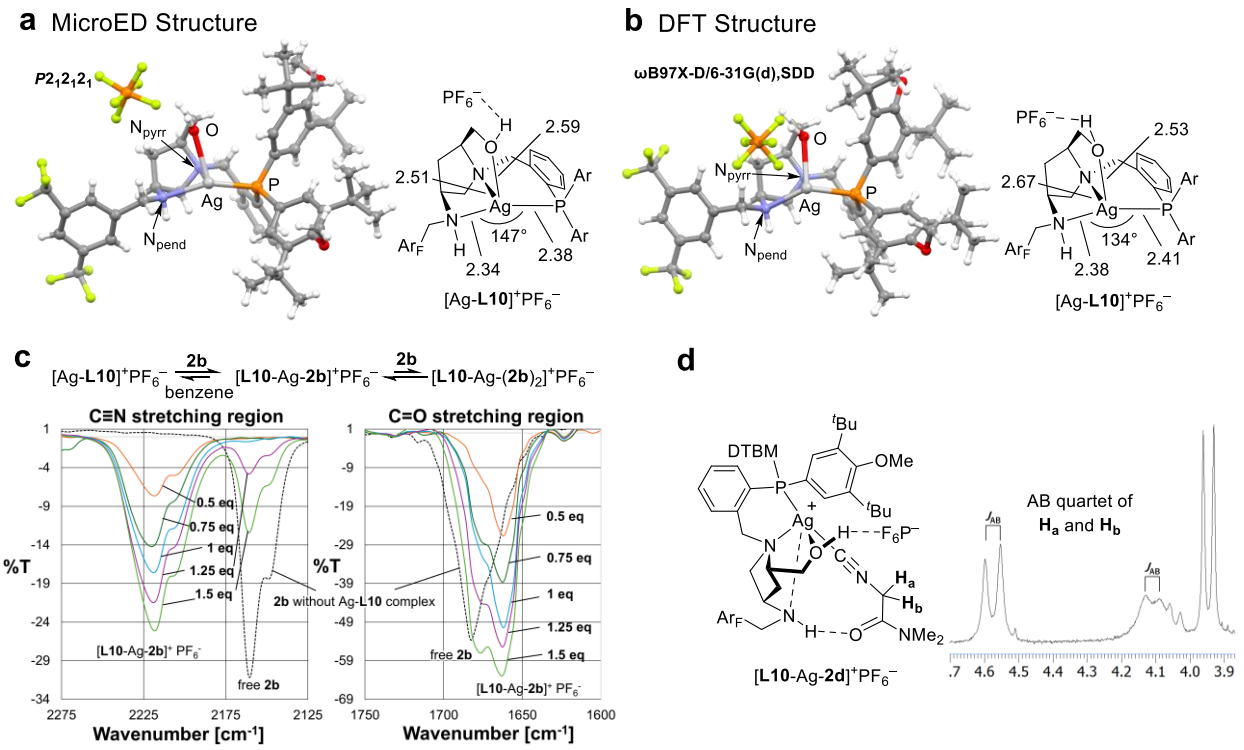


Figure 2. (a) The three-dimensional structure of [Ag-**L10**]$^{+}$PF$_6^{-}$ determined by single crystal microED analysis. Ar = 3,5-*t*-Bu$_2$-4-MeO-C$_6$H$_2$; Ar$_F$ = 3,5-(CF$_3$)$_2$-C$_6$H$_3$. (b) The DFT-optimized structure of [Ag-**L10**]$^{+}$PF$_6^{-}$. (c) The infrared spectra for titration of cationic silver(I)-**L10** complex [Ag-**L10**]$^{+}$PF$_6^{-}$ (0.05 M) with isocyanoacetamide **2b** in benzene for the isocyanide C≡N (left) and the carbonyl C=O (right) stretching vibration regions. The spectra for free **2b** (0.05 M) are shown by black dotted lines. (d) The ^{1}H NMR (C$_6$D$_6$) AB coupling of the diastereotopic methylene protons of isocyanoacetamide **2d** in [**L10**-Ag-**2d**]$^{+}$PF$_6^{-}$ (0.02 M).

Next, we conducted titrations of the cationic silver(I)-**L10** complex [Ag-**L10**]$^{+}$PF$_6^{-}$ with isocyanoacetamide **2b** as observed by IR and NMR spectroscopies to obtain information on the coordination behavior of the isocyanide toward the silver complex. The infrared spectra of the titration of [Ag-**L10**]$^{+}$PF$_6^{-}$ (0.05 M) with **2b** (0.5, 0.75, 1.0, 1.25, and 1.5 mol equiv) in benzene

at rt are shown in Figure 2c.[22] When isocyanide **2b** was no more than 1.0 equivalent (0.5, 0.75, and 1.0 equiv) to [Ag-**L10**]$^{+}PF_6^{-}$, only a single absorption band (ν = 2219 cm^{-1}) with a shoulder of a lower wavenumber (ν = 2206 cm^{-1}) was observed in the isocyanide C≡N stretching vibration region (ν = 2125–2275 cm^{-1}) of the spectra, with no absorption for the free isocyanide observed (Figure 2c, left). In contrast, when the amount of **2b** was further increased so as to be in excess of [Ag-**L10**]$^{+}PF_6^{-}$ (1.25 and 1.5 equiv), the absorption by the free isocyanide was observed with an increase in the intensity upon the increase of the amount of **2b**. The increase in the intensity of the free isocyanide absorption was accompanied by the increase in the intensity of the absorption by the coordinated isocyanide. These observations suggest that isocyanoacetamide **2b** coordinates to silver(I) at the isocyano carbon atom (coordinated: ν = 2219 cm^{-1}, uncoordinated ν = 2161 cm^{-1}) to form cationic isocyanide-Ag 1:1 complex [**L10**-Ag-**2b**]$^{+}$ with a considerably large association constant, and that silver complexes coordinated with two or more isocyanide molecules may also form as minor components when the isocyanide is in excess.

The C=O stretching vibration region of the IR spectra shows a shift of the absorption by the amide carbonyl group of [**L10**-Ag-**2b**]$^{+}$ to a lower wavenumber (ν ~1660 cm^{-1}) relative to the original absorption of **2b** (ν = 1683 cm^{-1}). This shift of the absorption may be attributable to intramolecular hydrogen-bonding between the N–H bond of the ring-appended amino group and the amide carbonyl group of the Ag-coordinated isocyanoacetamide (**2b**) (Figure 2c, right).

Preservation of Ag-**L10** coordination upon addition of one equiv of **2d** to a C_6D_6 solution of [Ag-**L10**]$^{+}PF_6^{-}$ (0.02 M) was confirmed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy in accord with the infrared spectroscopic observation (see Supporting Information in detail). Concerning isocyanide **2d**, a signal for the methylene protons (H_a, H_b) of **2d** appeared as an AB quartet at δ 4.34 ppm with a substantial signal splitting between the diastereotopic protons (Δδ = 0.47 ppm, $J_{H\text{-}H}$ = 18.4 Hz),

reflecting the asymmetric nature of the environment around the isocyanoacetamide molecule, which is created by the silver-coordinated aminoprolinol phosphine chiral ligand (Figure 2d).

The cationic complex [Ag-**L10**]$^{+}PF_6^{-}$ (2 mol%) could be used as a catalyst precursor by the combined use of Cs_2CO_3 (1 mol%) for the reaction between cyclohexyl phenyl ketone (**1n**, 0.3 mmol) and the Weinreb-type isocyanoacetamide (**2a**, 0.2 mmol) in toluene at 25 °C for 8 h (oxazoline **3na**, 48% ^{1}H NMR yield, *dr* >99:1, 94% *ee*). However, attempts to observe silver-**L10** complexes under basic conditions were in vain. For instance, the treatment of a C_6D_6 solution of the cationic complex [Ag-**L10**]$^{+}PF_6^{-}$ with various bases in the presence or absence of isocyanide **2d** resulted in a complex mixture of unidentified compounds, hampering static observation of possible catalytic intermediates.

Reaction Pathways. DFT calculations for the reaction of ketone **1a** with isocyanide **2d** catalyzed by the Ag-**L10** system to produce enantiomeric *trans*-oxazolines **3ad** (Table 2, entry 5) were conducted at the ωB97X-D/6-311+G(d,p),SDD/SMD(toluene)//ωB97X-D/6-31G(d),SDD level of theory.[39,40] Reaction pathway diagrams with relative Gibbs free energies at 25 °C are shown in Figure 3. In the complexes (**Int1-maj** and **Int1-min**) as precursors for the C–C bond forming enolate addition, the carbonyl group of the ketone (**1a**) is bound to the prolinol moiety of the chiral ligand through two hydrogen bonds different in nature: one is a classical/ordinary hydrogen bond (O–H···O) donated by the OH group of the primary alcohol moiety of the ligand and the other is a nonclassical hydrogen bond (sp^3-C–H···O) between the nonpolar sp^3-C–H bond at the pyrrolidine C3 position and the ketonic oxygen atom. The latter is categorized as a kind of van der Waals interaction that occurs between an induced dipole (C–H) and a dipole (O=C). While the quantitative evaluation of the bond energy of this nonclassical hydrogen bond in this large

system is too challenging, it was estimated to be about 10% of ordinary O–H···O hydrogen bonds based on literature values obtained for smaller molecular systems.[28,29,34,35]

The precursor complexes (**Int1-maj**/**min**) undergo enolate addition, producing aldolate intermediates **Int2-maj**/**min** through **TS1-maj**/**min** with relatively low energy barriers. The aldolate intermediates are higher in Gibbs free energy than the precursors **Int1-maj**/**min**, thus these steps are reversible in favor of the starting materials (ΔG = +7.2 and +5.9 kcal/mol, respectively). The successive oxazoline ring formation steps go through transition states (**TS2-maj**/**min**) higher in energy than the transition states of the previous enolate addition steps and are exergonic, affording C2-metalated oxazoline intermediates (**Int3-maj**/**min**). Thus, the ring-forming step should be more important for enantioselection than the enolate addition step.

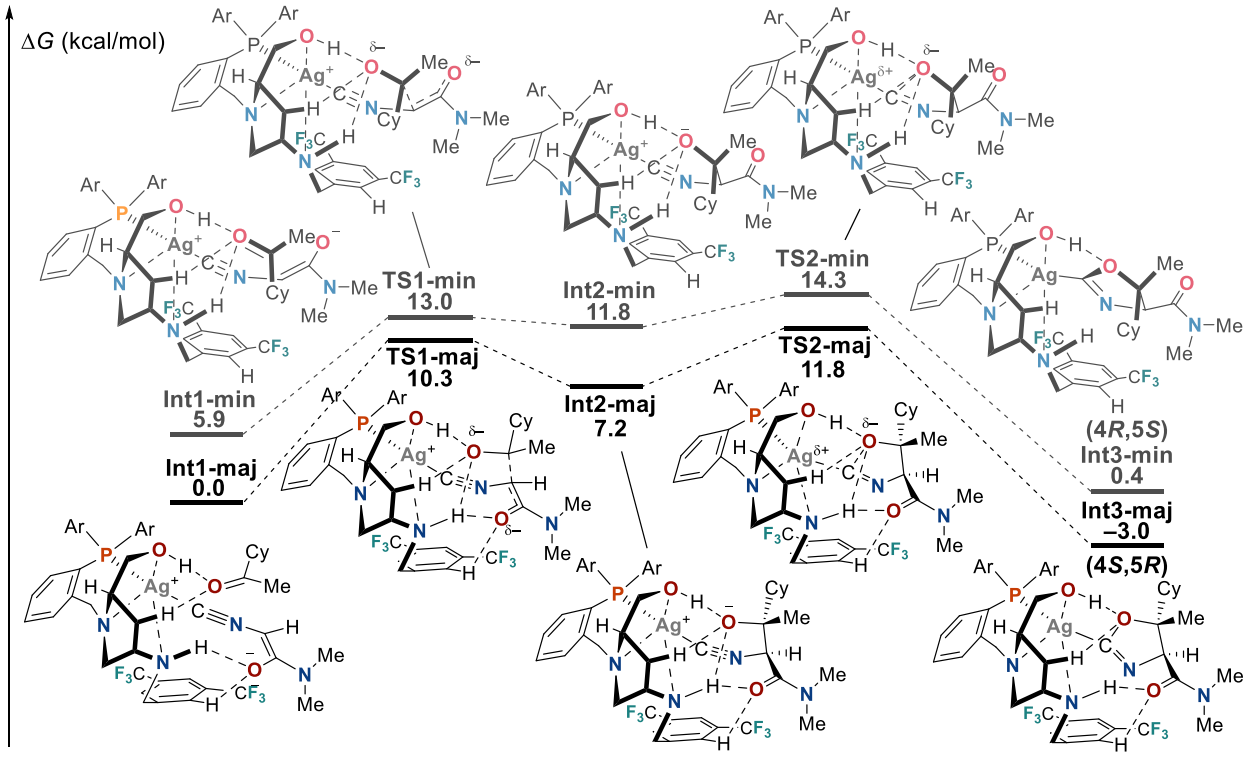


Figure 3. Reaction pathway diagrams for the silver-catalyzed asymmetric aldol reaction between cyclohexyl methyl ketone (**1a**) and *N*,*N*-dimethyl-2-isocyanoacetoamide (**2d**) to form enantiomeric *trans*-oxazolines (**3ad**). The relative free energies at 25 °C are given in kcal/mol.

Mechanism of Enantioselection. The oxazoline ring forming transition state structure (**TS2-maj**) for the most favorable reaction pathway leading to *trans*-(4*S*,5*R*)-**3ad** is shown in Figure 4a alongside that (**TS2-min**) leading to its enantiomer *trans*-(4*R*,5*S*)-**3ad**. Noncovalent interactions between the **L10**-Ag complex and the isocyanide-ketone diad fragments in **TS2-maj** and **TS2-min** were visualized through the independent gradient model based on the Hirshfeld partition (IGMH) method (Figure 4b).[41,42] In accord with the experimentally observed enantioselectivity (96% *ee*, Table 2, entry 5), **TS2-maj** is 2.5 kcal/mol lower in Gibbs free energy than **TS2-min**. As in the case of the reaction with the aldehyde, the oxyanions derived from the ketone in both **TS2-maj** and **TS2-min** are two-point-hydrogen-bonded with **L10** through the Ag-bound OH group and the proximal sp^3-C–H bond at the ring C3-position of 2-pyrrolidinemethanol. In addition to these hydrogen bonds, the newly introduced secondary amino group at the C4-position of 2-pyrrolidinemethanol forms an additional N–H···O hydrogen bond with the oxyanions in both transition states. Notably, the N atoms of the appended amino groups of **TS2-maj**/**min** are coordinated with the Ag atoms (N–Ag: 2.54 and 2.57 Å, respectively), while the coordination of the pyrrolidine N atoms is weakened, causing them to become more electrostatic (N–Ag: 3.05 Å in both **TS2-maj** and **min**). The electron-deficient aromatic rings (**Ar^{CF3}**) in the *N*-benzylic substituents are located underneath the isocyanide-coordinated silver atoms with Ag/π interactions (see IGMH models in SI. Colored isosurfaces for these interactions are not shown in Figure 4b for clarity), creating cavity-like catalytic environments.

In **TS2-maj**, the N–H group of the ring-appended amino group not only binds the ketone-derived oxyanion but also forms an N–H···O hydrogen bond with the amide carbonyl group in line with the ligand design model (Figure 1c), orienting the ring-forming isocyanide-ketone diad in a well-defined manner. The structure of **TS2-maj** clearly shows the role of the electron-deficient aromatic ring $\mathbf{Ar^{CF3}}$. One of the *ortho*-C–H bonds is bound to the amide carbonyl group through an sp^2-C–H···O interaction. As a result of this nonclassical hydrogen bond, the amide carbonyl group is two-point hydrogen-bonded for better and well-defined binding. Both the N–H···O_{amide} hydrogen bond and the sp^2-C–H···O interaction are missing in **TS2-min**. The *c*-Hex substituent of the ketone (***c*-Hex**) is accommodated in a space proximal to a *t*-Bu group (***t*-Bu**) of the *P*-DTBM-substituent of **L10** though a nonclassical sp^3-C–H···O hydrogen bond between ***c*-Hex** and the Ag-bound OH group, as well as by London dispersion interactions between ***c*-Hex** and ***t*-Bu** (Figure 4b). The observation of these attractive interactions caused by the *P*-DTBM substituent is consistent with the experimental result obtained with the simplified *P*-Ph-type ligand **L12**, which showed substantially reduced diastereoselectivity and enantioselectivity (90:10 dr, 85% *ee*, Table 1, entry 15).

In **TS2-min**, the amide carbonyl group points to ***t*-Bu** of the *P*-DTBM substituent, accepting only weak sp^3-C–H···O hydrogen bonds (2.52 and 2.73 Å) (Figure 4a). Although ***c*-Hex** of **TS2-min** interacts with $\mathbf{Ar^{CF3}}$ through London dispersion and sp^3-C–H···F interactions (Figure 4b), their stabilizing effects are not sufficient to compensate for the loss of the N–H···O/sp^2-C–H···O two-point hydrogen bond observed in **TS2-maj**.

From this comparison between **TS2-maj** and **TS2-min**, the two-point hydrogen bond donated by the ring-appended benzylamino group with an electron-deficient aromatic ring to the amide carbonyl group of the isocyanoacetamide substrate **2d**, which selectively occurs in **TS2-maj**, is

thought to be a major source of the enantioselectivity. However, the selective occurrence of weaker attractive interactions such as sp^3-C–H···O hydrogen bonds and London dispersions could also be important contributors. In support of this interpretation, distortion/interaction analysis for **TS2-maj** and **TS2-min** indicated that interaction energies are predominant for the energy difference between the two transition states [$\Delta\Delta E$ (distortion) = +1.70 kcal/mol, $\Delta\Delta E$ (interaction) = –5.29 kcal/mol].[43]

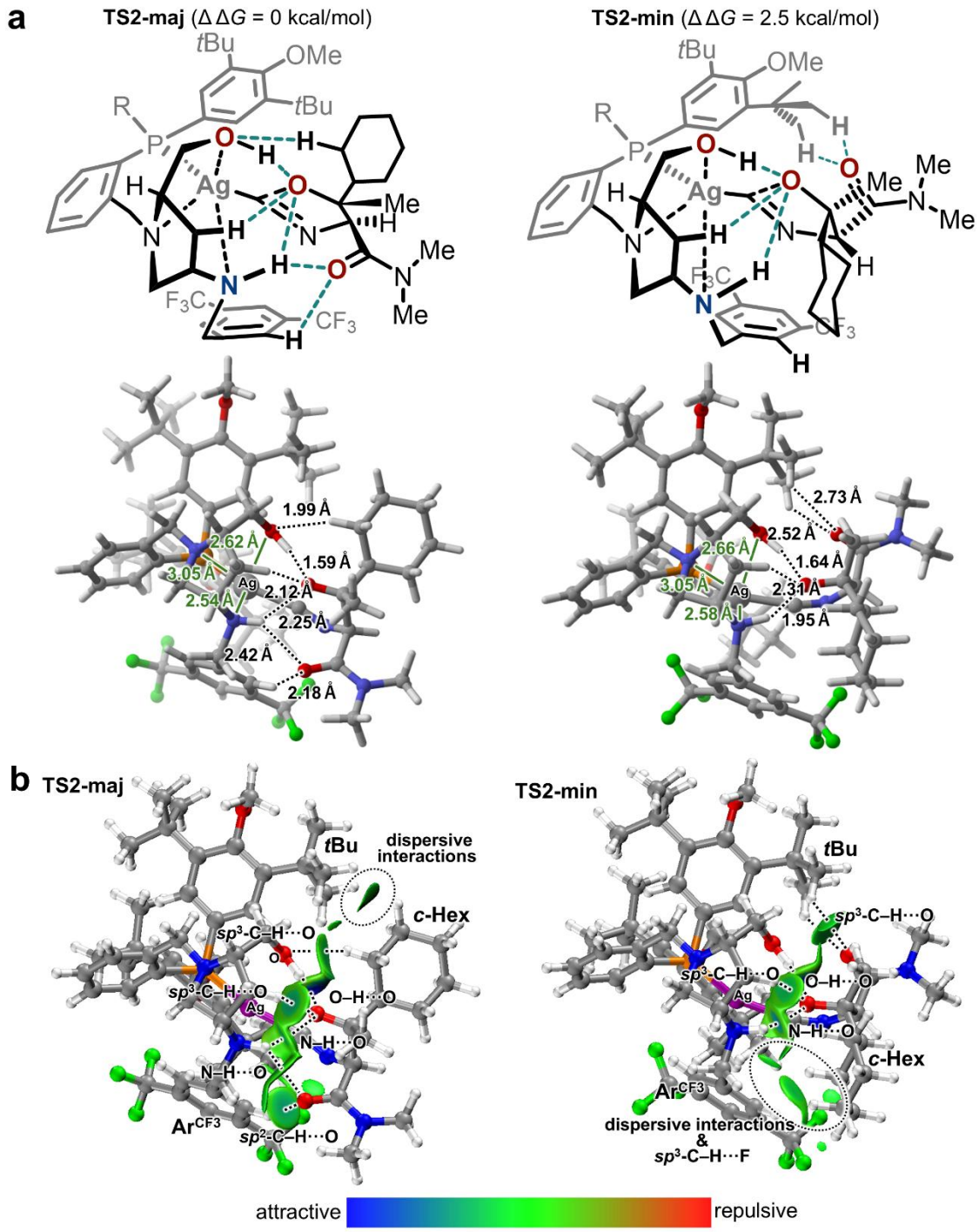


Figure 4. (a) 3D-structures of transition states for enantioselectivity-determining ring-closing steps of silver-catalyzed asymmetric aldol reaction between **1a** and **2d**. (b) IGMH for transition states mapped with colored isosurfaces for δg^{inter} = 0.005 a.u. The color scale for the mapped

function sign(λ_2)ρ is –0.05 < sign(λ_2)ρ < 0.05. Two IGMH fragments were defined for the **L10**-Ag complex and the isocyanide-ketone diad.

CONCLUSIONS

We developed a highly efficient silver-catalyzed asymmetric aldol reaction of nonactivated ketones with isocyanoacetamides through computation-guided design of prolinol-phosphine-based chiral ligands. Ligand optimization based on computational guidance identified a prolinol phosphine with a ring-appended 3,5-bis(trifluoromethyl)benzylamino group (**L10**) that had the best performance for this challenging enantioselective molecular transformation. The reaction with the optimal ligand exhibited unprecedented applicability toward sterically demanding dialkyl ketones and alkyl aryl ketones, owing to the beneficial attractive catalyst-substrate interactions. The catalyst system was also effective for the enantiocontrolled construction of consecutive tetrasubstituted stereogenic carbon centers. Spectroscopic and microED analysis combined with DFT calculations showed that a silver(I) complex coordinated with the aminoprolinol-phosphine ligand creates a metal/organo cooperative asymmetric catalytic space that can cause convergent multiple noncovalent interactions including O–H/N–H-based classical hydrogen bonds, C–H···O nonclassical hydrogen bonds, and London dispersion interactions with the reacting substrates in the stereochemistry-determining transition states. Comparison of the enantiomeric reaction pathways suggested that the two-point hydrogen bond donated by the ring-appended 3,5-bis(trifluoromethyl)benzylamino group to the amide carbonyl group of the isocyanoacetamide, which selectively occurs in **TS2-maj**, is a major cause of the enantioselectivity. Investigations to expand the scope of the isocyanide aldol reaction and related reactions and to uncover further catalytic applications of prolinol-phosphine chiral ligands are ongoing in our laboratory.

EXPERIMENTAL SECTION

General procedure for the silver-catalyzed asymmetric aldol reactions

To a solution of Ag_2CO_3 (1.4 mg, 0.005 mmol) and **L10** (9.0 mg, 0.01 mmol) in cyclohexane (1 mL) in a vial were added isocyanoacetamide **2** (0.5 mmol) and ketone **1** (0.75 mmol) in this order. After stirring at 25 ℃ for 8–96 h, 1M HCl aqueous solution (0.5 mL) was added to the reaction mixture. After stirring at 25 ℃ for 1 h, the aqueous layer was extracted with $CHCl_3$ (1 mL × 5) and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A residue was purified by preparative TLC (EtOAc/MeOH 95:5) to give the product **4**. The ee value was determined by chiral HPLC analysis.

General procedure for ligand optimization (Table 1)

To a solution of Ag_2CO_3 (1.4 mg, 0.005 mmol) and chiral prolinol-phosphine ligand **L** (0.01 mmol) in toluene or cyclohexane (1 mL) in a vial were added isocyanoacetamide **2a** (64.1 mg, 0.5 mmol) and cyclohexylmethylketone **1a** (103 μl, 0.75 mmol) with a micro syringe in this order. After stirring at 25 ℃ for 8 h, the reaction mixture was filtered through a short plug of silica gel (0.5 g) with EtOAc as an eluent and the solvent was removed under reduced pressure to give oxazoline product **3aa**. The ee value was determined by chiral HPLC analysis: CHIRALCEL® IG-3 column (4.6 mm × 250 mm), hexane/2-propanol = 90:10, 1.0 mL/min, 40 ℃, 220 nm UV detector, retention time = 29.7 min [major diastereomer, minor enantiomer, *trans*-(4*R*,5*S*)], 39.7 min [(major diastereomer, major enantiomer, *trans*-(4*S*,5*R*)].

AUTHOR INFORMATION

Corresponding Author

Yohei Shimizu − Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan; Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan; List Sustainable Digital Transformation Catalyst Collaboration Research Platform, Institute for Chemical Reaction Design and Discovery (ICReDD List-PF), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan
Email: shimizu-y@sci.hokudai.ac.jp

Masaya Sawamura − Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan; Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan
Email: sawamura@sci.hokudai.ac.jp

Present Addresses

Kosuke Higashida: Department of Chemistry, Graduate School of Science, Kyoto University
Kitashirakawa Oiwake-cho, Sakyo-ku, Kyoto, 606–8502, Japan

Author Contributions

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ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, HPLC charts, and NMR spectra (PDF), movies for IGMH for transition states (MP4).

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TOC Graphic

