Enantioselective Cyanation of Ketones and α,β-Unsaturated Carbonyl Compounds Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxides

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Contents

Chapter 1

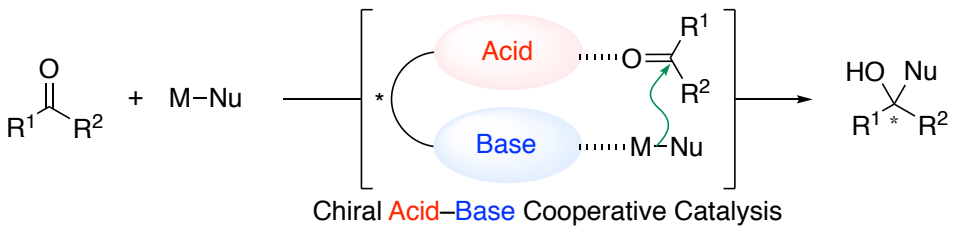
Introduction and General Summary

1-1. Introduction

Cyanation of carbonyl compounds is one of the most important reactions for constructing a carbon–carbon bond. The corresponding cyanated compounds can be easily transformed to carboxylic acids, esters, amides, amines, and so on. In particular, chiral α-cyanohydrins, which are obtained by the enantioselective cyanation of aldehydes, are versatile intermediates for many pharmaceuticals, natural products, and agrochemicals.[1] Indeed, catalytic enantioselective cyanations of aldehydes have been used over the past two decades and have been well summarized in several reviews.[1,2] However, the enantioselective cyanation of ketones in place of aldehydes is still challenging, since ketones are less reactive and more difficult to enantiocontrol than aldehydes due to steric and electronic reasons. Therefore, while many chiral Lewis acid and/or Lewis base catalysts have been developed for the enantioselective cyanation of aldehydes, neither chiral Lewis acid or Lewis base catalysts alone have been used for the enantioselective cyanation of ketones.

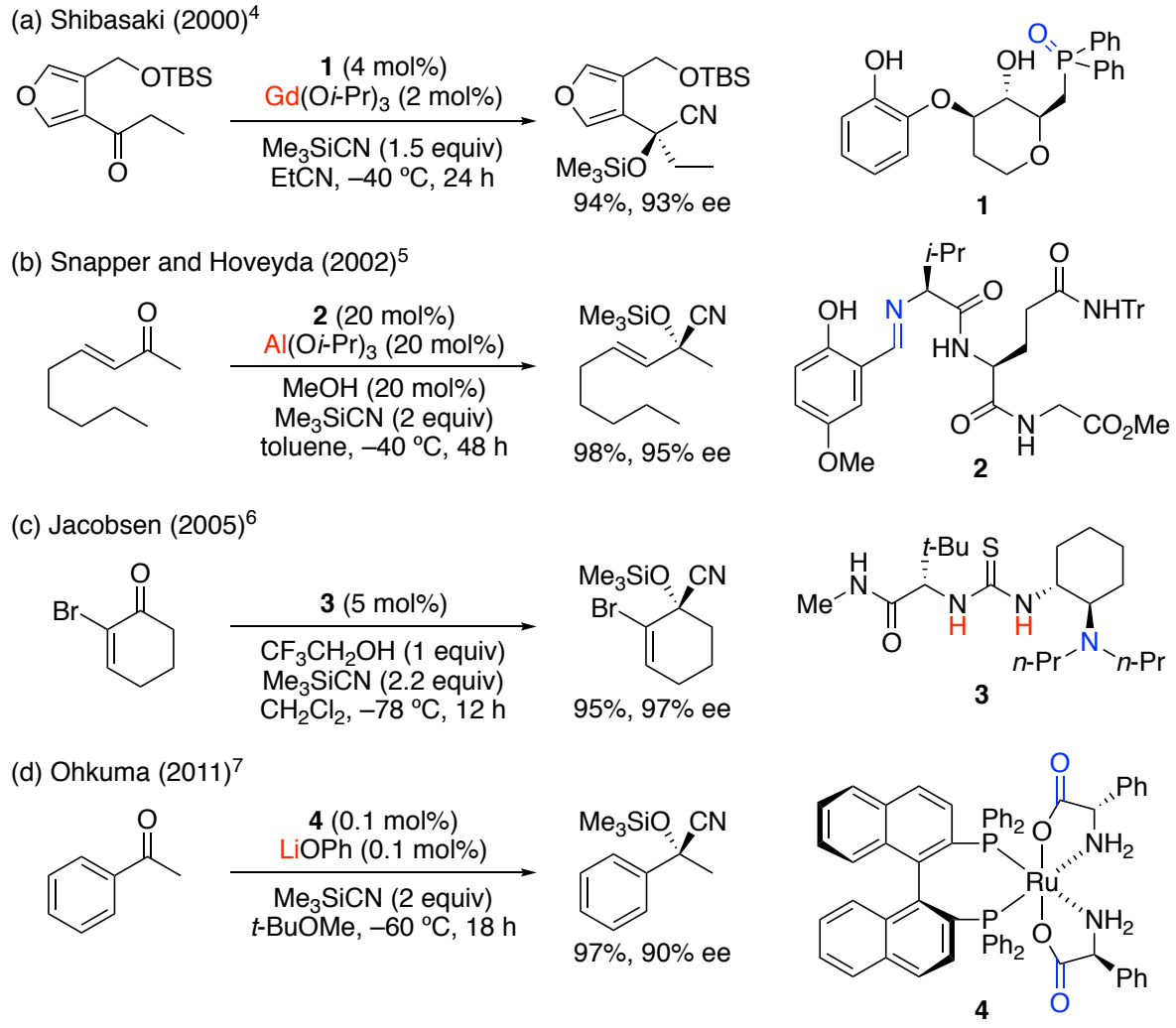
In this regard, Shibasaki provided the pioneering concept of acid–base bifunctional catalysis for many enantioselective reactions. In particular, they focused on the dual activation of both carbonyl compounds and cyanating reagents through acid–base cooperative catalysis (Scheme 1).[3] By taking advantage of Shibasaki's report of the enantioselective cyanosilylation of ketones in 2000 (Scheme 2a),[4] a few research groups later developed their original chiral acid–base bifunctional catalysts.

Scheme 1. Concept of Acid–Base Bifunctional Catalysis for Enantioselective Reactions



For example, in 2002, Snapper and Hoveyda reported that chiral Al(III)–peptide **2**-derived catalyst was effective in enantioselective cyanosilylation (Scheme 2b).[5] Remarkably, high enantioselectivities were achieved even for aliphatic ketones. In 2005, Jacobsen developed chiral thiourea–amine-derived catalyst **3** for enantioselective cyanosilylation (Scheme 2c).[6] Mechanistic studies involving kinetic studies, control experiments, and density functional theory calculations have revealed that *in situ*-generation of HCN from trimethylsilyl cyanide and isopropanol was crucial for this reaction. In particular, chiral

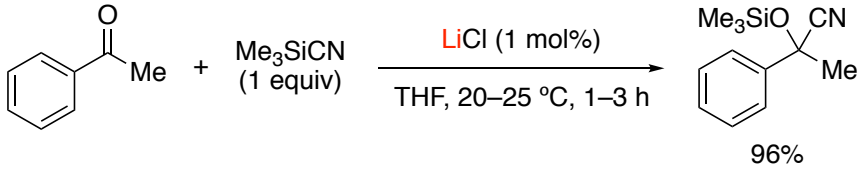
Scheme 2. Previous Acid–Base Bifunctional Catalysts for the Enantioselective Cyanosilylation of Ketones



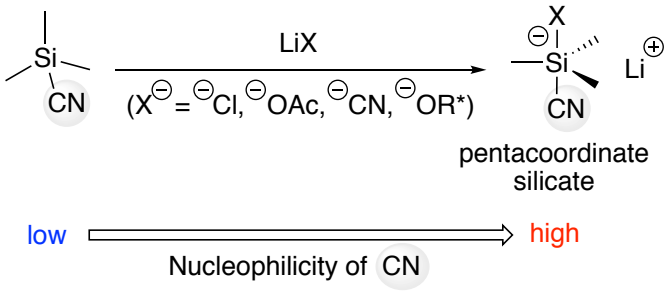
Ru(II)/(*S*)-BINAP/phenylglycine-derivative **4**–Li(I) combined catalyst, which was developed by Ohkuma, exhibited excellent catalytic activities for the enantioselective cyanosilylation of ketones with an extremely low catalyst loading (Scheme 2d).[7]

In this regard, the use of highly reactive pentacoordinate silicates should make it unnecessary to use chiral strong Lewis acid catalysts[8], such as Gd[4] catalysts, to promote the cyanation of ketones. For instance, Ohkuma previously reported that a small amount of lithium chloride (1 mol%) could promote the cyanosilylation of ketones with trimethylsilyl cyanide (Scheme 3).[9] It is well known that trimethylsilyl cyanide can be activated into a pentacoordinate silicate by the use of achiral basic lithium salts (LiX) (Scheme 4).[10,11]

Scheme 3. Synthesis of Achiral Cyanohydrin Derivatives with the Use of Pentacoordinate Silicate



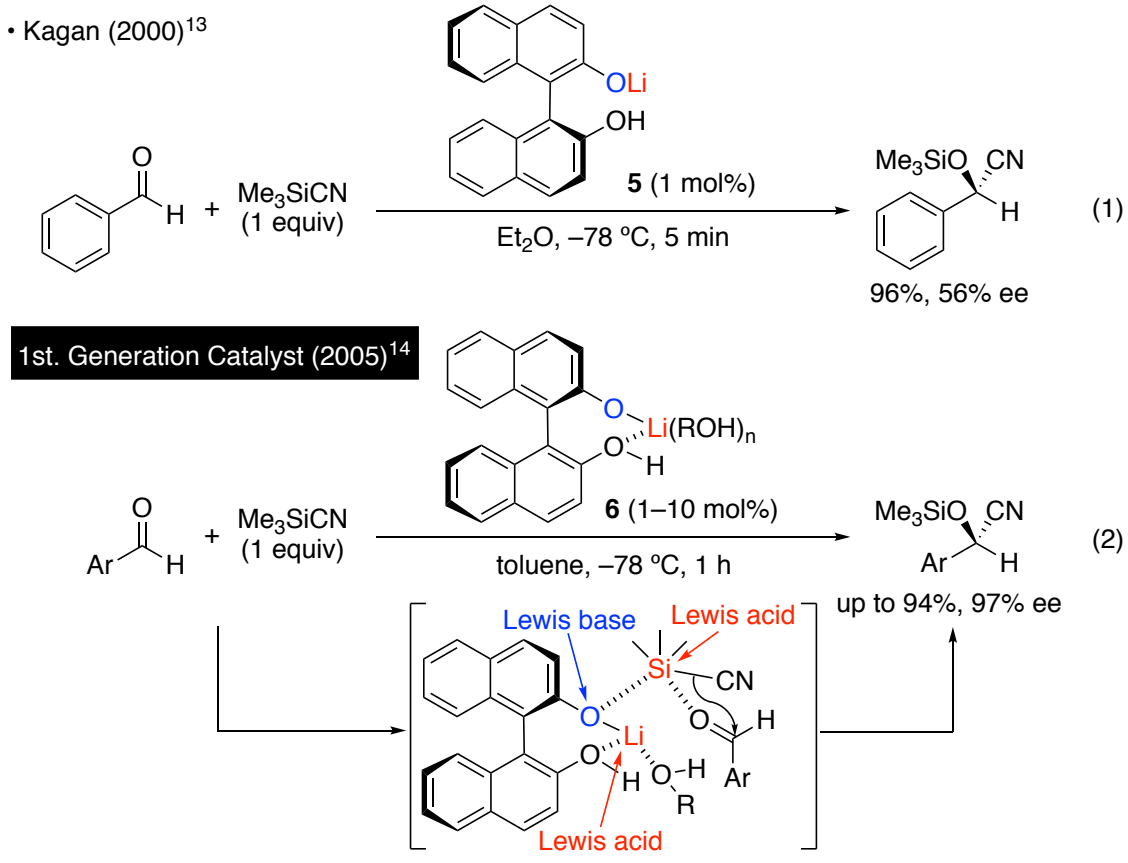
Scheme 4. Activation of Trimethylsilyl Cyanide by Basic Additives



In this context, chiral Li(I) catalysts, which are prepared from an appropriate Li(I) source and chiral ligands, might be promising chiral acid–base bifunctional catalysts.[3] The use of more abundant Li(I) salt catalysts might be more desirable, for environmental and economic

reasons, than less abundant lanthanoid and late transition metal salts.[12] Furthermore, because of its stronger covalent property compared to other alkali metals, the Li(I) center may form a more stable complex with anionic ligands. Actually, a few chiral acid–base bifunctional Li(I) catalysts have been used in the catalytic enantioselective cyanation of carbonyl compounds. In a pioneering work, Kagan developed chiral Li(I)–BINOLate catalyst **5** for the enantioselective cyanosilylation of aldehyde (Scheme 5, Eq. 1).[13] With catalyst **5**, the reaction proceeds smoothly, although the enantioselectivities are still moderate. Based Kagan's work,[13] our laboratory developed chiral Li(I)–BINOLate catalyst **6** as a 1st-generation catalyst for the enantioselective cyanosilylation of aldehydes (Scheme 5, Eq. 2).[14] In the latter case, the Lewis-basic phenolic hydroxyl group of binaphthol more

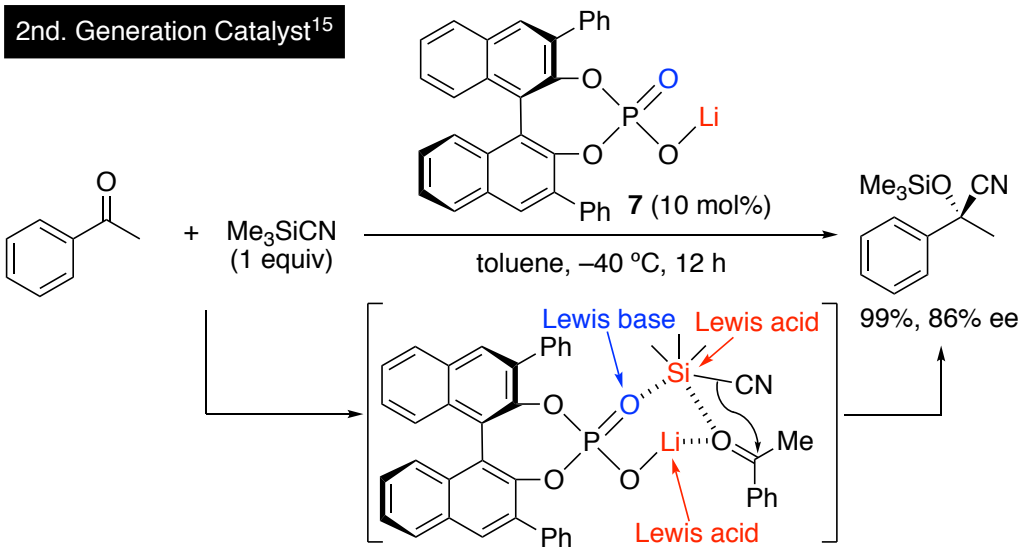
Scheme 5. Chiral Li(I) Catalysts **5** and **6** for the Enantioselective Cyanosilylation of Aldehydes



efficiently activates the silyl group because monomeric catalysts are generated *in situ*. As a result, both the Lewis-acidic silyl group and Li(I) ion could activate the carbonyl group. Moreover, they found that either water or alcohol could dramatically activate the reaction due to the ligand effect to prevent the association of chiral Li(I)–BINOLate catalyst. However, this catalytic system could not be applied to the enantioselective cyanosilylation of less reactive ketones.[15]

Later, as a 2nd-generation catalyst for the enantioselective cyanosilylation of ketones, our laboratory developed chiral phosphoric acid lithium salt catalyst **7** (Scheme 6).[15] The phosphoryl group can act as a Lewis base to activate the silyl group as well as the phenolic hydroxyl group of **6**, and form a six-membered chelation ring with Li(I) ion. Thus, a few aryl methyl ketones can be doubly activated by a silyl group and Li(I) center, and be transformed to the corresponding cyanohydrins in moderate to good enantioselectivities (≤86% ee).

Scheme 6. Chiral Li(I) Catalyst **7** for the Enantioselective Cyanosilylation of Ketones



1-2. Chiral Li(I) Phosphoryl Phenoxide Catalysts for the Enantioselective Cyanosilylation of Ketones

To further develop a highly efficient enantioselective cyanosilylation of ketones, the author decided to continue developing acid–base bifunctional chiral Li(I) catalysts through the use of highly reactive pentacoordinate silicates (Figure 1). Unfortunately, catalysts **6** and **7** did not show sufficient enantioselectivities or substrate scope in the enantioselective cyanosilylation of ketones. Even for an enzyme, excellent catalytic activity can not be realized unless the necessary functional groups and metal ion are arranged in the required positions. Therefore, the author simply designed catalyst **8** as a 3rd-generation catalyst. Catalyst **8** is combined with a phenoxide, which is similar to the 1st-generation catalyst **6**, and a phosphoryl moiety, which is similar to the 2nd-generation catalyst **7**. As a result, a favored six-membered ring, which would be formed by the Li(I) center, phosphoryl group, and phenoxide, might be the

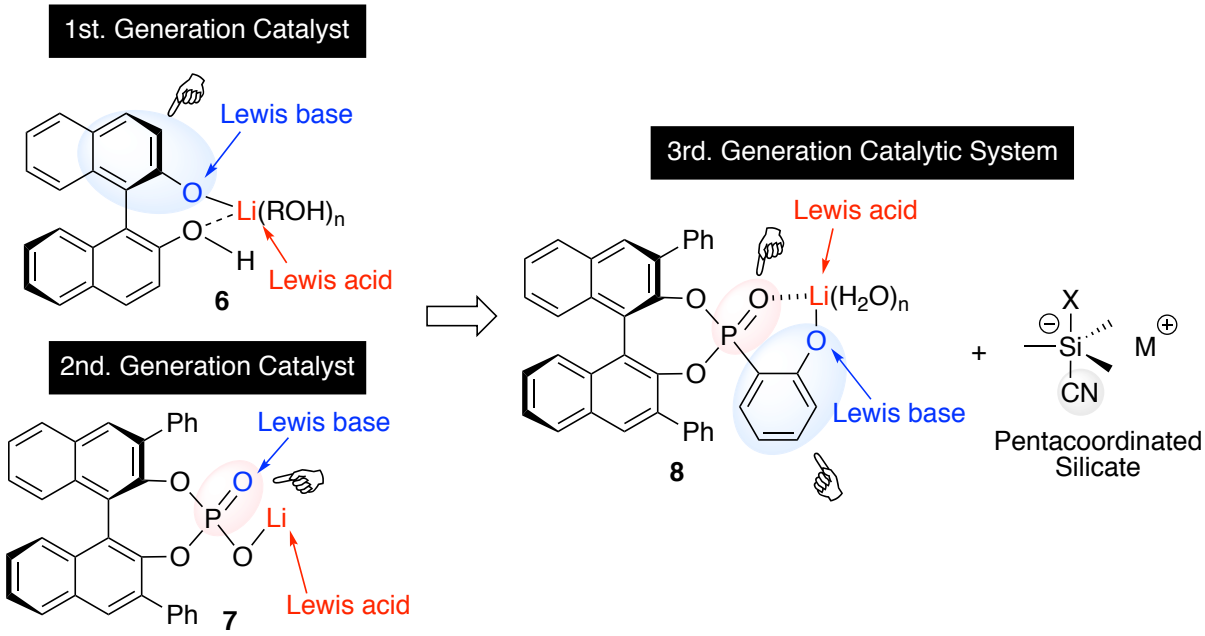
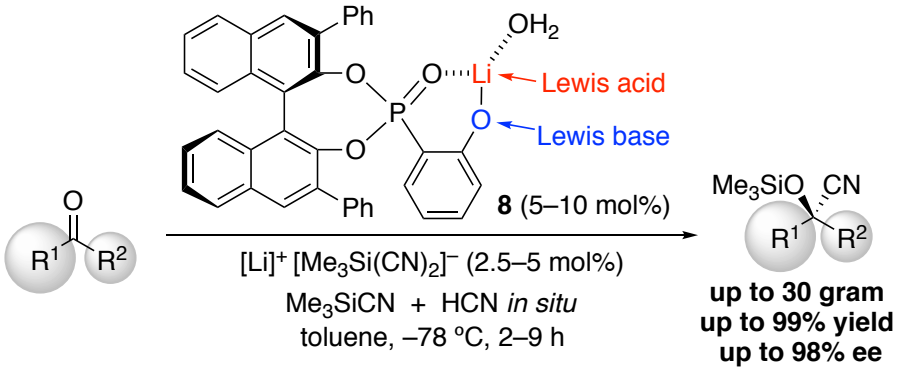


Figure 1. Design of Lewis Acid–Lewis Base Cooperative Catalyst **8** with the Use of Pentacoordinate Silicate

key for stabilizing the catalyst structure. Moreover, the combined use of highly reactive pentacoordinate silicate should help to improve the reactivity. Chapter 2 describes how the author developed Lewis acid–Lewis base cooperative chiral Li(I) phosphoryl phenoxide catalyst **8** for the enantioselective cyanosilylation of ketones (Scheme 7).[16] The reaction proceeded smoothly within a short time (2–9 h). Various functional groups such as halogen, nitrile, ester, and alkyne were tolerable, and the corresponding products were obtained in high yields with high enantioselectivities. This robust catalytic system was used in a 30g-scale reaction. Moreover, a key intermediate of (+)-13-hydroxyisocyclocelabenzine[17] was successfully synthesized in an optically pure form (Figure 2). An extremely reactive pentacoordinate silicate would be generated *in situ* from trimethylsilyl cyanide and lithium cyanide based on the results of an ESI-MS analysis, NMR study, and control experiments.

Scheme 7. Chiral Li(I) Catalyst **8** for the Enantioselective Cyanosilylation of Ketones



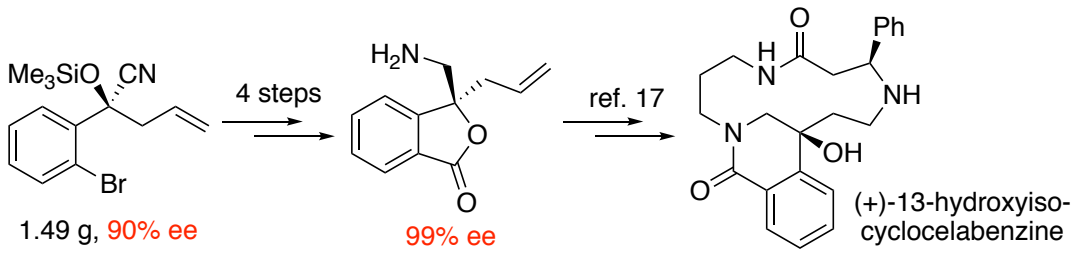
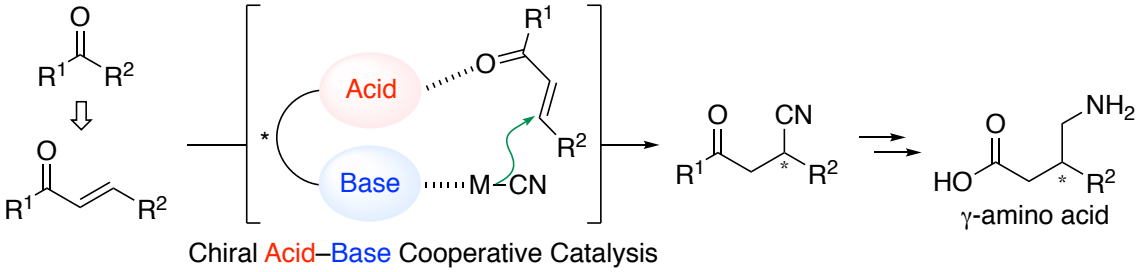


Figure 2. Transformation to the Intermediate of (+)-13-Hydroxyisocyclocelabenzine

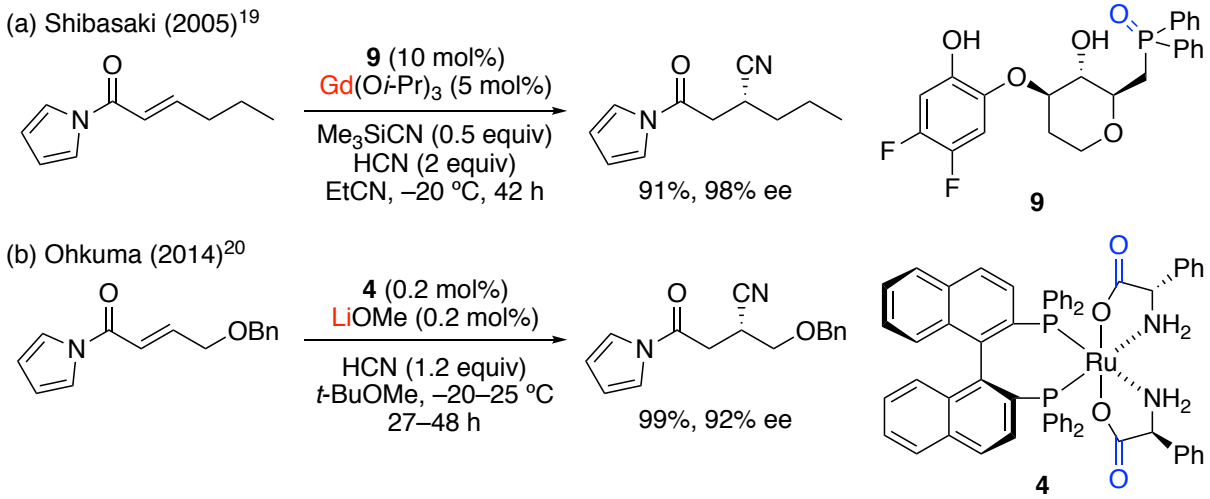
1-3. Chiral Li(I) Phosphoryl Phenoxide Catalysts for the Enantioselective Conjugate Cyanation of α,β-Unsaturated *N*-Acylpyrroles

Optically active β-cyano carbonyl compounds, which are obtained by the enantioselective 1,4-cyanation of α,β-unsaturated carbonyl compounds, are intermediates for various natural products and medicines, including the well-known γ-aminobutyric acid (GABA).[18] Acid-base bifunctional catalysts also show high performance in the enantioselective 1,4-cyanation of α,β-unsaturated carbonyl compounds, which is sometimes more difficult than the 1,2-cyanation of ketones, not only due to the low reactivity, but also because of the difficulty of enantioface discrimination at the remote β-position (Scheme 8).[2] To the best of my knowledge, only two acid–base bifunctional catalysts, including the chiral D-glucose-

Scheme 8. Enantioselective 1,4-Cyanation of α,β-Unsaturated Carbonyl Compounds



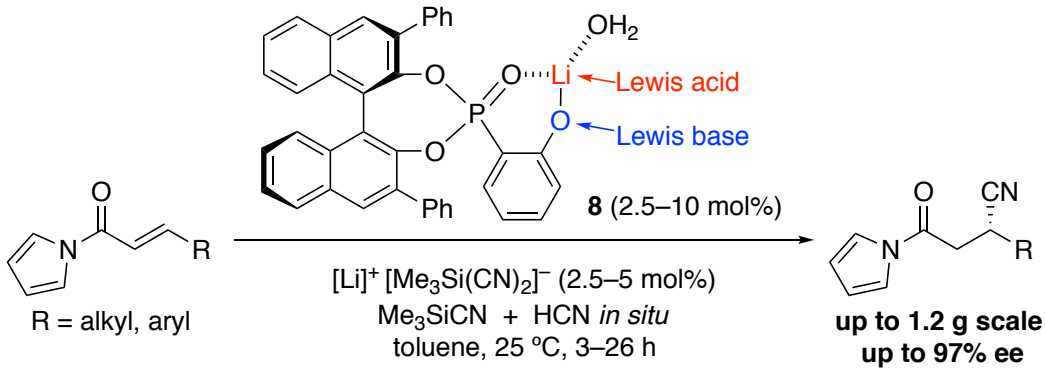
Scheme 9. Previous Acid–Base Bifunctional Catalysts for Enantioselective 1,4-Cyanations



derivative **9**–Gd(III) catalyst developed by Shibasaki (Scheme 9a),[19] and the chiral Ru(II)/(*S*)-BINAP/phenylglycine-derivative **4**–Li(I) combined catalyst developed by Ohkuma (Scheme 9b),[20] have been shown to be effective for both the enantioselective cyanosilylation of ketones and the enantioselective 1,4-cyanation of α,β-unsaturated *N*-acylpyrroles.

Due to the great success of the enantioselective cyanosilylation of ketones (Chapter 2) with the combined use of chiral Lewis acid–Lewis base cooperative Li(I) phosphoryl phenoxide **8** and the highly reactive pentacoordinate silicate, the author considered whether or not this catalytic system might be applied to the 1,4-hydrocyanation of α,β-unsaturated carbonyl compounds instead of ketones. Chapter 3 describes the development of chiral Li(I) phosphoryl phenoxide catalyst **8** for the enantioselective conjugate hydrocyanation of α,β-unsaturated *N*-acylpyrroles (Scheme 10).[21] This reaction was useful for a variety of *N*-acylpyrroles, such as heteroaryl- and halogen-substituted substrates. Moreover, a gram-scale synthesis and transformations to bioactive compounds such as (*R*)-succinate, (*R*)-baclofen, (*S*)-pregabalin, and (*S*)-paraconic acid, which is a synthetic intermediate of A-factor,[22] were demonstrated (Figure 3).

Scheme 10. Chiral Li(I) Catalyst **8** for the Enantioselective Conjugate Cyanation of α,β-Unsaturated *N*-Acylpyrroles



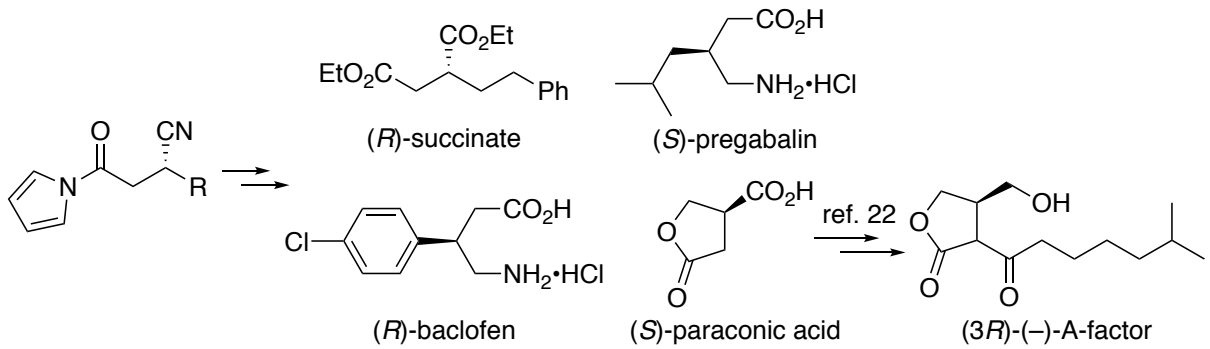


Figure 3. Transformations to Bioactive Compounds

1-4. Conclusion

In summary, the author has developed the enantioselective cyanosilylation of ketones and the conjugate hydrocyanation of α,β-unsaturated *N*-acylpyrroles catalyzed by Lewis acid–Lewis base coorperative chiral Li(I) phosphoryl phenoxide catalyst **8**. With this catalytic system, chiral (*R*)-BINOL-derived ligand **8**, Me_3SiCN, water, and *n*-BuLi or LiOH as the Li(I) source can be used to prepare both active Li(I) catalysts and active Li(I) silicates(IV) *in situ*. Catalyst **8** showed high catalytic activity, high enantioselectivity, and a broad substrate scope. The present method is practical and scalable, and total syntheses of several bioactive compounds were demonstrated.

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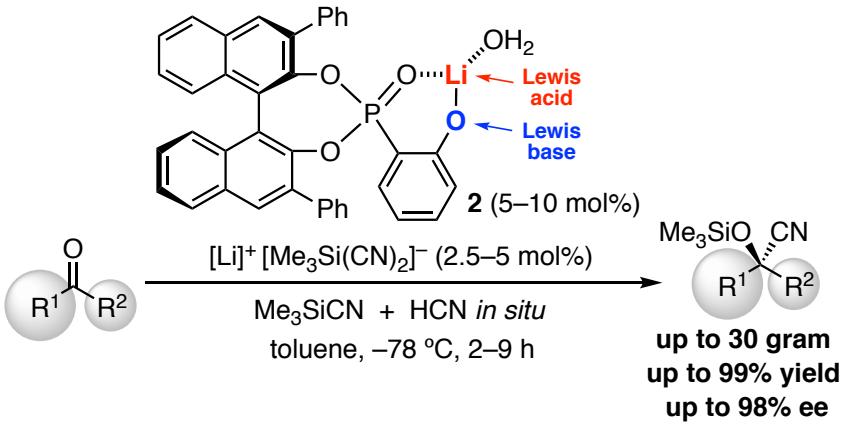
Chapter 2

Chiral Lithium(I) Phosphoryl Phenoxide Catalysts for Enantioselective Cyanosilylation of Ketones

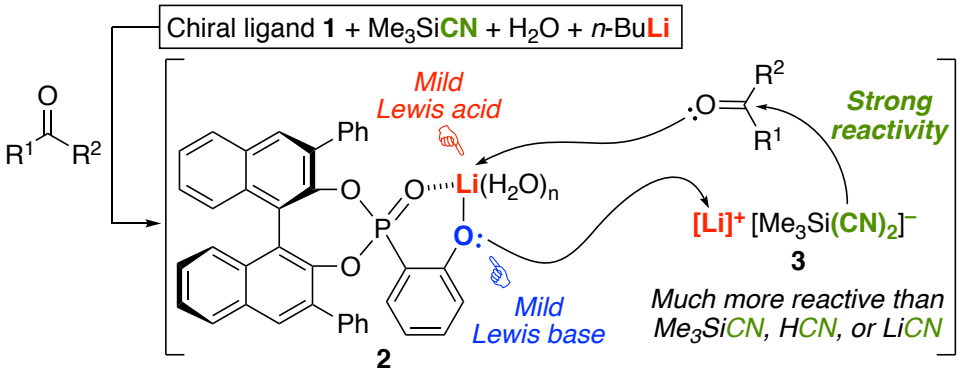


Abstract: A highly enantioselective cyanosilylation of ketones was developed with the use of a chiral lithium(I) phosphoryl phenoxide aqua complex as a simple acid–base cooperative catalyst. Pentacoordinate silicate generated *in situ* from Me_3SiCN/LiCN acts as an extremely reactive cyano-reagent. A 30 gram scale reaction and a transformation to the key intermediate of (+)-13-hydroxyisocyclocelabenzine were demonstrated.

2-1. Introduction

Optically active cyanohydrins are important compounds since they can readily provide α-hydroxy carboxylic acids, β-hydroxy amines, etc. which are used in many pharmaceuticals.[1] However, the catalytic enantioselective cyanosilylation of ketones is still challenging, since ketones are inherently much less reactive than aldehydes due to steric and electronic constraints.[2] Therefore, there might be room for some improvement with regard to the substrate scope, reaction time (typically 24–48 h), and reaction scale even in reports of the excellent results with ketones.[3] To overcome the difficulties of the enantioselective cyanosilylation of unreactive simple ketones, we assumed that the extraordinary activation of trimethylsilyl cyanide reagent by some achiral additives should be effective. This strategy is highly promising since it might not depend on the use of chiral strong Lewis acid catalysts to activate substrates, and even chiral weak Lewis acid catalysts might be possible. In this regard, we envisioned that extremely active lithium(I) dicyanotrimethylsilicate(IV) **3**[4] *in situ* might be suitable with the use of chiral lithium(I) phosphoryl phenoxide aqua complex **2** as a newly designed mild Lewis acid–Lewis base cooperative catalyst for the cyanosilylation of ketones (Scheme 1).[5–7] As a great advantage of this catalytic system, we can simply use chiral

Scheme 1. Acid–Base Combined Catalytic System with Reactive Lithium(I) Dicyanotrimethylsilicate(IV) **3**

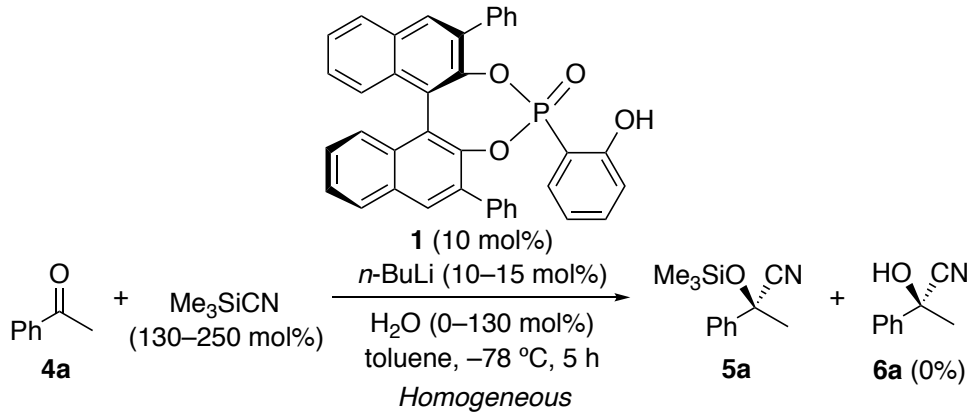


(*R*)-BINOL (1,1'-bi-2-naphthol)-derived ligand **1**, Me_3SiCN, water, and *n*-BuLi or LiOH as the same lithium(I) source to prepare both active lithium(I) catalysts and active lithium(I) silicates(IV) *in situ*.

2-2. Results and Discussion

We initially examined the reaction of acetophenone **4a** with the use of **1** (10 mol%), *n*-BuLi (10 mol%), Me_3SiCN (130 mol%), and H_2O (0–130 mol%) in toluene at –78 °C for 5 h (Table 1, entries 1–6). The reaction was sluggish in the absence of water (entry 1). In contrast, the reactions were promoted in the presence of water, and the highest enantioselectivity (92% ee) of **5a** was observed with the use of 60 mol% of H_2O (entry 4). The yield was improved with the use of 250 mol% of Me_3SiCN and 120 mol% of H_2O (entry 7). Finally, the use of 15 mol% of *n*-BuLi provided **5a** in 94% yield with 91% ee (entry 8). LiOH in place of *n*-BuLi could be used without problems (entry 9), although we have conventionally used *n*-BuLi as common catalytic lithium(I) source in the cyanosilyation.[7] Water might be essential for the generation of active monomeric species,[7,8] and we observed lithium(I) aqua complex **2** as a major peak in ESI-MS analysis (eq 1, also see the Experimental Section). Most of the remaining water might soon be used to give HCN (and Me_3SiOH) *in situ* since the reactions were operated under the homogeneous reaction conditions. It is noted that *the active cyanide reagent in this reaction might not be HCN* (entry 6) and OH-free cyanohydrin **6a** was not obtained in any of the cases (entries 1–11). Moreover, Me_3SiOH and $(Me_3Si)_2O$ generated *in situ* had almost no influence on the results (entries 10 and 11).

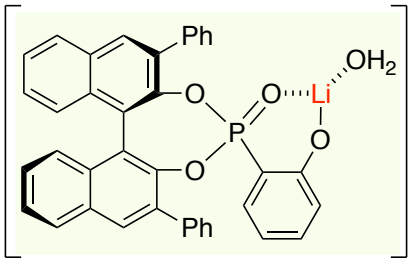
Table 1. Optimization of the Reaction Conditions[a]



Entry	*n*-BuLi (mol%)	Me_3SiCN (mol%)	H_2O (mol%)	Me_3SiOH (mol%)	$(Me_3Si)_2O$ (mol%)	**5a**, yield [%]	**5a**, ee [%]
1	10	130	0	0	0	23	44
2	10	130	20	0	0	44	69
3	10	130	40	0	0	51	86
4	10	130	60	0	0	35	92
5	10	130	80	0	0	25	91
6	10	130	130	0	0	0	–
7	10	250	120	0	0	68	90
8	**15**	**250**	**120**	**0**	**0**	**94**	**91**
9	**15**[b]	**250**	**120**	**0**	**0**	**98**	**90**
10	15	250	120	50	0	90	91
11	15	250	120	0	50	91	89

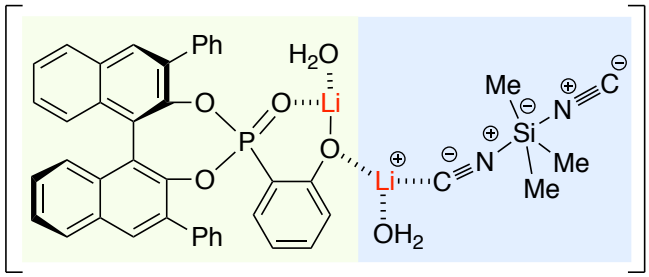
[a] The reaction was carried out with **4a** (0.5 mmol), Me_3SiCN (130 or 250 mol%), **1** (10 mol%), *n*-BuLi (10 or 15 mol%), and H_2O (0–130 mol%) in toluene at –78 °C for 5 h. The OH-free cyanohydrin **6a** was not obtained in any of the cases. [b] LiOH was used in place of *n*-BuLi.

ESI-MS (positive) analysis:

1 (1 equiv) —[*n*-BuLi (1.5 equiv), H_2O (2 equiv), toluene, rt, 10 min]→ 

2

Calcd for [**2**+Li]$^+$ 607.1834, found 607.1840. (1)

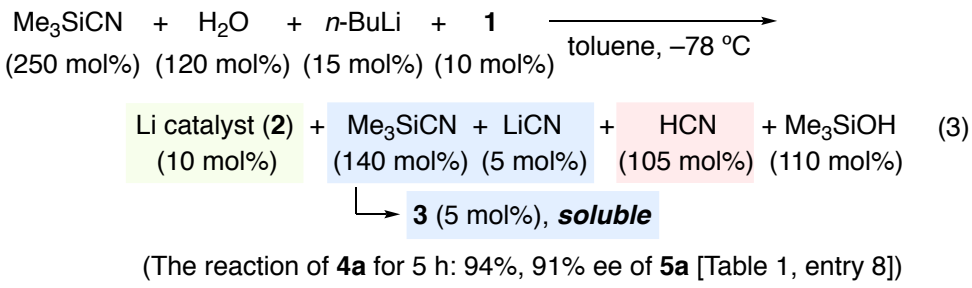
1 (1 equiv) —[1) *n*-BuLi (1.5 equiv), H_2O (3 equiv), toluene, rt, 1 h; 2) $[Li]^+[Me_3Si(CN)_2]^-$ (**3**) (10 equiv) in THF]→ 

2 + **3** + H_2O

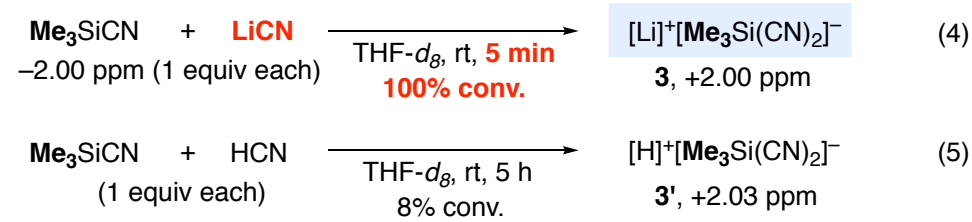
Calcd for [**2**+**3**+H_2O+Li]$^+$ 757.2635, found 757.2639 (2)

For the mechanistic aspect, our catalytic system should include multiple cyano-sources *in situ*, such as Me_3SiCN, LiCN, HCN, and their relevant combinations (eq 3). In particular, based on the screening of the reaction conditions for **4a** in Table 1, a catalytic amount of LiCN *in situ* should play a key role (entry 8 v.s. entry 7).[9,10] To identify a possible active reagent in the system, we thus performed a ^{13}C NMR analysis of a 1:1 molar ratio of Me_3SiCN (–2.00 ppm) and LiCN in tetrahydrofuran-d_8 (eq 4, also see the Experimental Section). As a result, pentacoordinate silicate $[Li]^+[Me_3Si(CN)_2]^-$ (**3**)[4] was instantly observed as a sole peak at +2.00 ppm. Ionic LiCN is essential for generation of the silicate, since a 1:1 molar ratio of Me_3SiCN and HCN gave $[H]^+[Me_3Si(CN)_2]^-$ (**3'**) in 8% conversion even after 5 h (eq 5, also see the Experimental Section). Based on these results, *a catalytic amount (5 mol%) of highly nucleophilic* ***3*** *in situ* might be an active reagent in eq 3.[10,11]

Overall, the monomeric lithium(I) aqua complex **2** (eq 1) and the highly nucleophilic pentacoordinate silicate **3** (eq. 4) might associate through the acid–base cooperative interaction. In this regard, we could observe **2**+**3**-combined complex in ESI-MS analysis (eq 2, also see the Experimental Section).



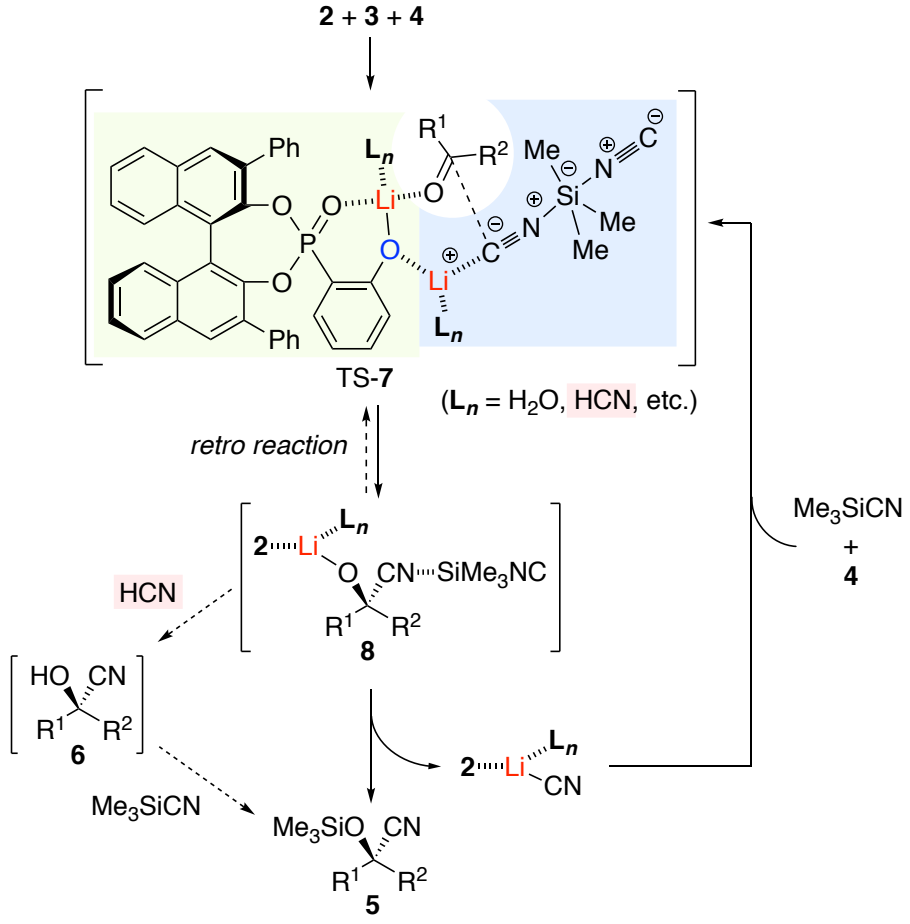
^{13}C NMR analysis:



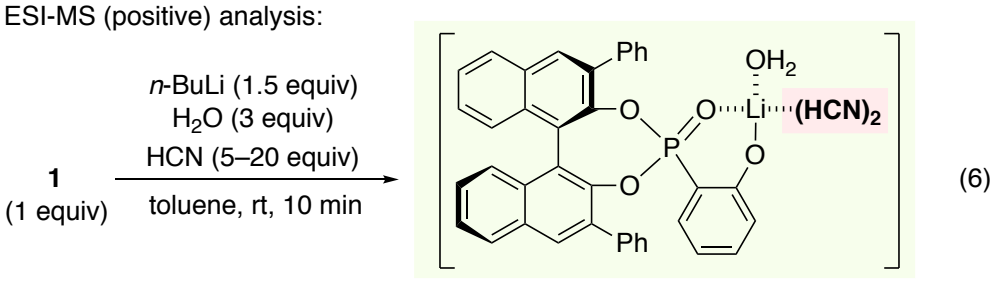
We show a possible catalytic cycle in Scheme 2. A transition state (TS)-**7**[12] might involve the **2**+**3**-combined complex, as shown in eq 2, and ketone **4**. After cyanation,[13] product **5** would be provided *via* lithium(I) cyanohydrin **8**. We could not detect OH-free cyanohydrin **6** directly even by *in situ*-IR analysis (see the Experimental Section), although we cannot completely rule out transient generation of **6** by protonation[14,15] in a large amount of HCN buffer and subsequent quick silylation[16] of **6**. Instead, it is likely that HCN would act as coordinating ligand(s) for the lithium(I) center of catalyst **2** and/or **3**, and the corresponding lithium(I)-L_n (L_n = H_2O and HCN) solvates might promote releasing **5** and the active species (e.g., L_n···**2**···LiCN) to regenerate TS-**7**. To support this assumption, we could detect **2**·$(HCN)_2$ in ESI-MS analysis when a large amount of HCN (10~20 equiv)[17] was used in the presence of **2** (eq 6, also see the Experimental Section). Accordingly, in the presence of

much more excess amount of HCN (totally 205 mol% *in situ*), we demonstrated a scalable reaction of **4a** (18.0 g, 150 mmol). As a result, *with the use of 5 mol% (half-size) of the catalyst in shorten reaction time (3 h), ca. 30 gram of* ***5a*** *was obtained with 90% ee after extraction, concentration, and filtration without silica gel column chromatography* (eq 7). Moreover, ligand **1** was easily recovered in 98% (>99% purity) after the precipitation by hexane and 1 *M* aqueous HCl-washing.

Scheme 2. Possible Catalytic Cycles



ESI-MS (positive) analysis:

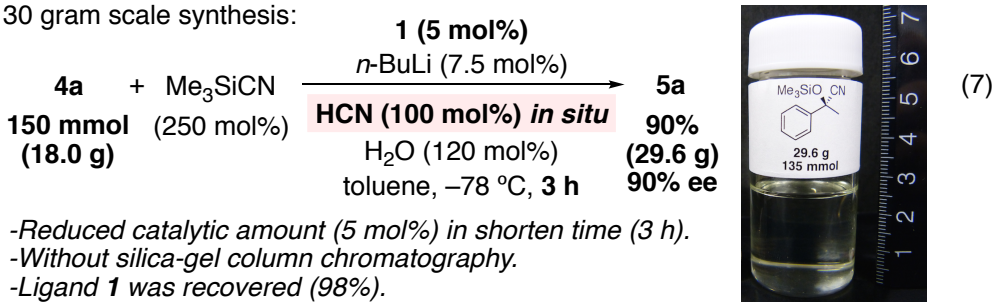


(6)

2 + 2HCN

Calcd for [**2**+2HCN+H]$^+$ 655.1969, found 655.1968.

30 gram scale synthesis:

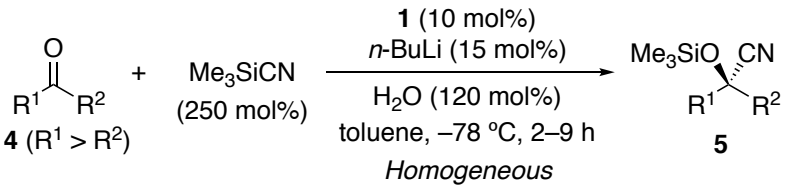


(7)

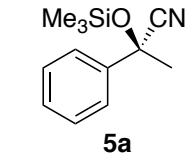
-Reduced catalytic amount (5 mol%) in shorten time (3 h).
-Without silica-gel column chromatography.
*-Ligand **1** was recovered (98%).*

With the optimized reaction conditions in hand (Table 1, entry 8), we examined the scope of ketones **4** (Scheme 3). *ortho*-, *meta*-, or *para*-Substituted acetophenones could be used successfully, and the corresponding products **5b**–**m** were obtained in high yields with high enantioselectivities (87–98% ee).[18] In particular, electron-withdrawing groups could generally promote the reactions, while an electron-donating group, such as a methyl group, surprisingly decreased the reactivity with recovery of the starting ketone **4j**.[19] Whereas sterically hindered *ortho*-substituted ketones are often problematic for use in conventional catalysts,[1–3] they could be used in our catalytic system (see **5b**–**f**). Moreover, our catalyst could be used for unprecedented carbonyl- and cyano-substituted ketones (see **5f**, **5h**, and **5l**), which might deactivate relatively strong Lewis acid catalysts.[1–3] Coordinating 2-furyl and 3-thienyl ketones, **4o** and **4p**, also could be used without serious problems. Cyclohexyl methyl ketone **4q**, as a simple aliphatic ketone, showed moderate enantioselectivity (**5q**, 78% ee). In sharp contrast, acyclic and cyclic α,β-unsaturated aliphatic ketones **4r**–**t** provided the

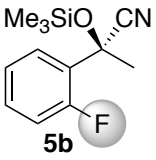
Scheme 3. Substrate Scope in the Catalytic Enantioselective Cyanosilylation of Ketones **4**[a]



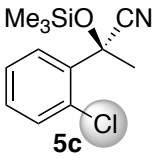
Product **5**, yield, enantioselectivity, and reaction time:



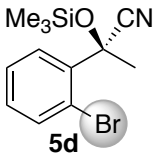
94%, 91% ee (5 h)



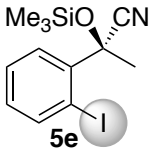
99%, 90% ee (4 h)



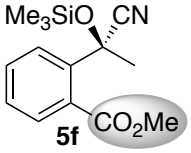
51%, 88% ee (7 h)
90%, 90% ee (6 h)[b]



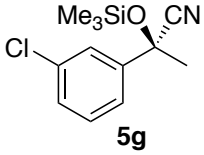
99%, 90% ee (3 h)[b]
91%, 92% ee (6 h)[c]



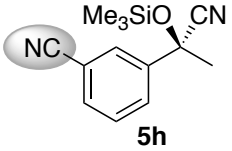
94%, 91% ee (7 h)



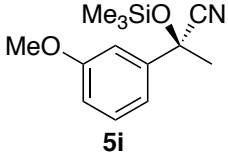
94%, 90% ee (8 h)



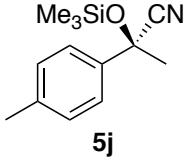
98%, 93% ee (8 h)



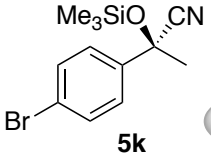
57%, 97% ee (5 h)
99%, 98% ee (3 h)[d]



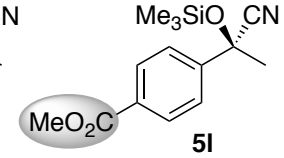
80%, 91% ee (8 h)



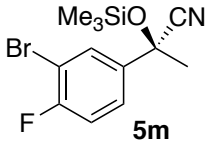
13%, 87% ee (4 h)
15%, 86% ee (10 h)



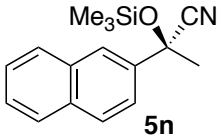
99%, 94% ee (4 h)
99%, 94% ee (6 h)[c]



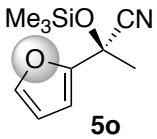
48%, 94% ee (9 h)
99%, 95% ee (2 h)[b]



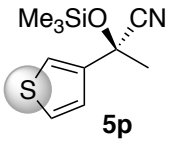
97%, 94% ee (2 h)[b]



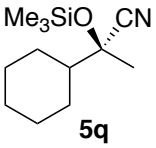
90%, 87% ee (5 h)[b]



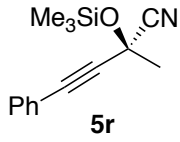
75%, 91% ee (5 h)



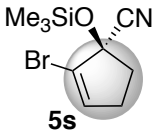
97%, 93% ee (5 h)[d]



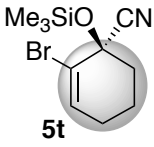
88%, 78% ee (6 h)



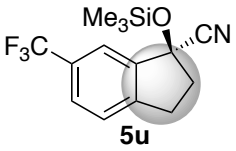
95%, 90% ee (7 h)



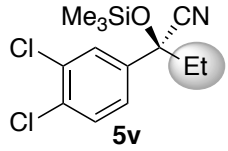
90%, 90% ee (9 h)



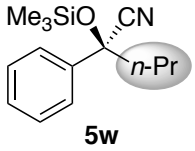
91%, 83% ee (6 h)



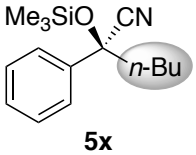
94%, 94% ee (4 h)



94%, 90% ee (6 h)



82%, 90% ee (9 h)



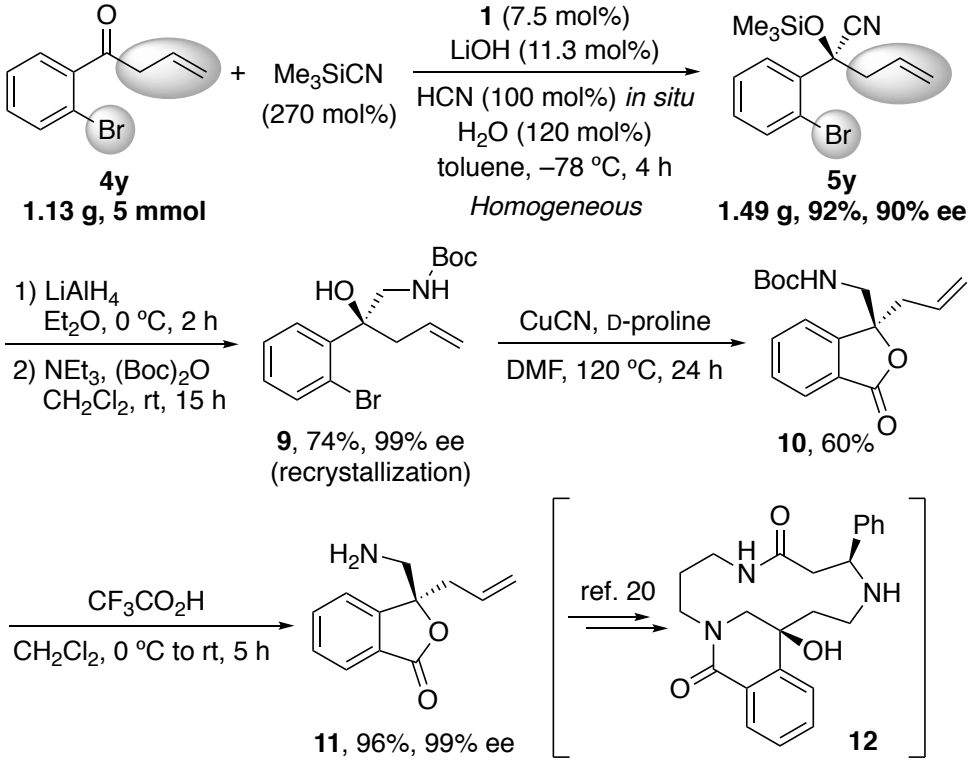
96%, 91% ee (7 h)[d]

[a] Unless otherwise noted, the reaction was carried out with **4** (0.5 mmol), Me_3SiCN (250 mol%), **1** (10 mol%), *n*-BuLi (15 mol%), and H_2O (120 mol%) in toluene at –78 °C. [b] 270 mol% of Me_3SiCN was used. [c] The reaction was carried out with **4** (1 mmol), Me_3SiCN (250 mol%), **1** (5 mol%), *n*-BuLi (7.5 mol%), and H_2O (120 mol%) in toluene at –78 °C for 6 h. [d] 300 mol% of Me_3SiCN was used.

corresponding products **5r**–**t** in high yields with good to high enantioselectivities (83–90% ee). Remarkably, our catalyst could be used for other non-methyl ketones, such as 1-indanone, propiophenone, butyrophenone, and valerophenone derivatives, and the desired products **5u**–**x** were obtained with high enantioselectivities (90–94% ee). Overall, our catalytic system features a much shorter reaction time (2–9 h) than conventional systems.[1–3] It is noted again that cyanohydrins **6** were not obtained in any cases of Scheme 3.

To demonstrate the synthetic utility of our catalytic system, we performed a transformation to obtain the key intermediate of (+)-13-hydroxyisocyclocelabenzine **12**,[20] which is a spermidine alkaloid with antibacterial and antitumor activities (Scheme 4). Bulky allyl 2-bromophenyl ketone **4y** was selected as a starting ketone. Fortunately, with the use of of LiOH and **1** (7.5 mol%)- derived catalyst in the enantioselective cyanosilylation of **4y** on a 1.13 g scale, **5y** was obtained in 92% yield (1.49 g) with 90% ee. Compound **5y** was then

Scheme 4. Transformation to the key Intermediate **11** of (+)-13-Hydroxyisocyclocelabenzine



transformed to **9** by reduction with $LiAlH_4$ and Boc-protection (Boc = *tert*-butoxycarbonyl). A single recrystallization of **9** increased the enantiopurity to 99% without a serious loss of yield. Finally, the optically pure key intermediate **11** was obtained after a Cu(I)-promoted lactonization to **10** and deprotection of the *N*-Boc moiety.

2-3. Conclusion

In summary, we have developed a highly enantioselective cyanosilylation of ketones with the use of a chiral lithium(I) phosphoryl phenoxide complex as an acid–base cooperative catalyst. Extremely reactive pentacoordinate silicate generated *in situ* from Me_3SiCN and LiCN acts as a key cyano-reagent. In particular, our robust catalytic system was scalable up to 30 gram-cyanohydrin synthesis without any serious problems. Also, the key intermediate of (+)-13-hydroxyisocyclocelabenzine was successfully synthesized in an optically pure form.

2-4. References.

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(7) We previously developed a chiral lithium(I) binaphtholate aqua complex for aldehydes and a chiral lithium(I) phosphate for a very limited numbers of ketones. The reactions scarcely proceed with these catalysts (<15% yield with <10% ee) under the conditions as in entry 8 of Table 1 (see the Experimental Section). Therefore, this catalytic system with silicate **3** turned out to be different from our previous catalytic systems with Me_3SiCN. a) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776; b) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776.

(8) A positive nonlinear effect, which supports the notion that the catalysts have oligomeric structures, was observed between **1** and **5a** (see the Experimental Section).

(9) Shibasaki reported a role of catalytic amount of LiCN in the cyano-ethoxycarbonylation and cyano-phosphorylation of aldehydes with the use of chiral YLi_3tris(binaphthoxide) complexes. a) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.*

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(10) We used *a catalytic amount* of isolated LiCN in a model reaction of **4a** with Me_3SiCN in toluene at –78 °C (See the Experimental Section in detail). As a result, a positive effect of LiCN on both yield and enantioselectivity was observed against the control experiment without LiCN. However, isolated LiCN was hardly-soluble and caused overall lower efficiency under heterogeneous conditions, particularly in the yield, than soluble LiCN *in situ*-prepared from Me_3SiCN, *n*-BuLi, and H_2O under homogeneous conditions.

(11) Investigation of the reactions of aldehydes also supports that **3** might be more active than other reagents *in situ*. See the Experimental Section.

(12) Possible transition states, which might explain the absolute stereochemistry of **5**, are shown in the Experimental Section.

(13) The retro reaction of 3°-cyanohydrin **8** to TS-**7** might be possible. Therefore, the reaction of **8** with HCN buffer would also provide a slight bias on the equilibrium between TS-**7** and **8**.

(14) On the basis of pK_a values in water (HCN = 9.1, Me_3SiOH = 12.7, H_2O = 15.8), HCN might act as a proton source. a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456; b) Delak, K. M.; Sahai, N. *Chem. Mater.* **2005**, *17*, 3221.

(15) Oguni reported a chiral titanium(IV)-catalyzed cyanosilylation of aldehydes, in which Me_3SiCN and HCN coexist. In their report, silyl-protected cyanohydrin could be obtained from titanium(IV)-cyanohydrins by HCN, followed by silylation with Me_3SiCN. Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135.

(16) In a control experiment, isolated cyanohydrin **6a** was quickly trimethylsilylated within 1

min under the standard reaction conditions. See the Experimental Section in detail.

(17) A large amount of HCN (i.e., 105 mol% under optimized conditions) is necessary to promote reaction. A control experiment with 45 mol% of HCN showed significantly slow conversion (5 h, 41% yield with 89% ee). In contrast, another control experiment with 205 mol% of HCN showed fast conversion (2 h, 95% yield with 91% ee). See the Experimental Section in detail.

(18) For some ketones, the use of 270 or 300 mol% of Me_3SiCN gave better yields than the use of 250 mol% of Me_3SiCN.

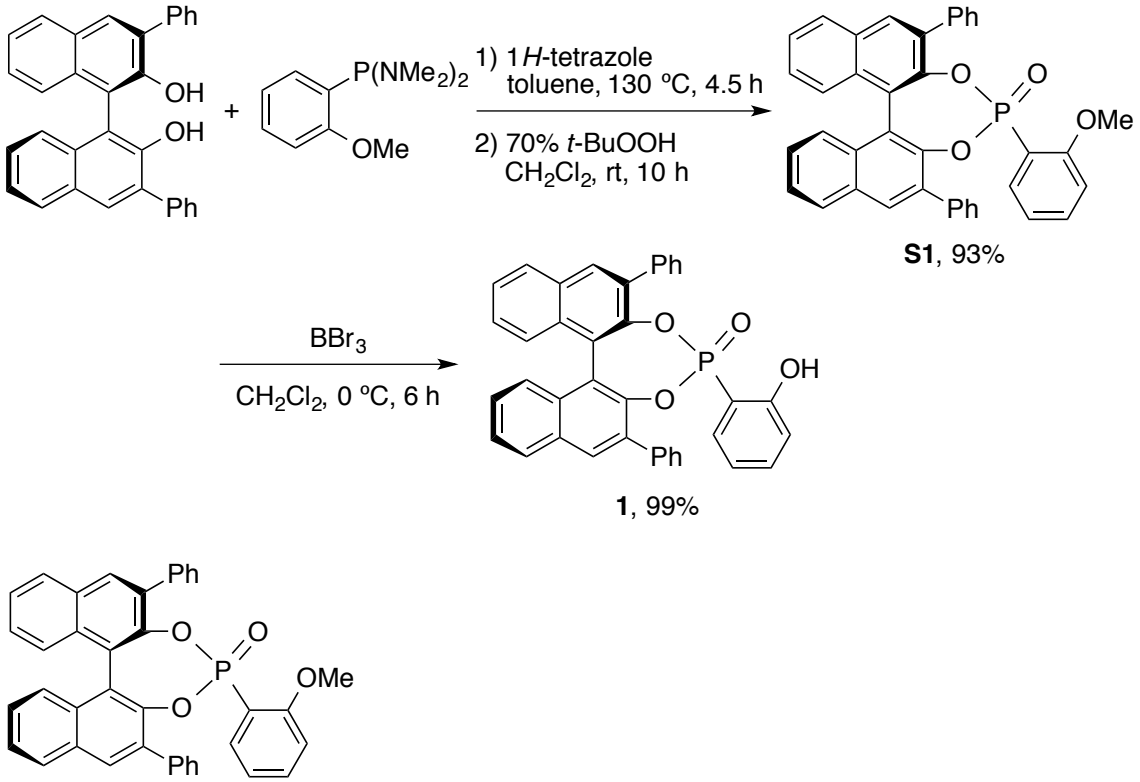
(19) During the reaction, inactive silylated ligand **13** was partially detected (see the Experimental Section) particularly when unreactive ketones such as **4j** were used. A routine workup/purification procedure always recovered **1** 90–95%, which could be reused after it was washed with 1 *M* aqueous HCl.

(20) Li, Y.; Linden, A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 579.

2-5. Experimental Section.

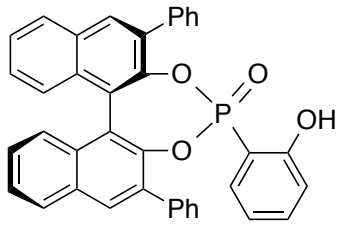
2-5-1. General Methods. ^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard (H_3PO_4 at 0 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). Optical rotations were measured on Rudolph Autopol IV digital polarimeter. The products were purified by column chromatography on silica gel (E. Merck Art. 9385; Kanto Chemical Co., Inc. 37560). High resolution mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700, Bruker Daltonics micrOTOF-QII). Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 Plus instrument with a flame-ionization detector and a capillary column of CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; CHROMPACK; GL Science Inc.) or CHIRALDEX B-DM, G-TA (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL, CHIRALPAK; AD-H, AD-3, AS-H, AS-3, OD-H, OD-3, OJ-H, and OZ-H. X-ray analysis was performed by Rigaku PILATUS-200K. *In situ*-IR analysis was performed by Mettler-Toledo ReactIR 15. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. In experiments that required dry solvents such as toluene, diethyl ether, dichloromethane, and trimethylsilyl cyanide [**Caution!** Highly toxic.] were distilled in prior to use.

2-5-2. Preparation of chiral ligand 1.



(11b*R*)-4-(2-Methoxyphenyl)-2,6-diphenyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (S1): Compound **S1** was prepared based on the reported procedures.[1,2] (*R*)-3,3'-Diphenyl-1,1'-binaphthol[3] (1.75 g, 4.0 mmol) was added to a solution of *N*,*N*,*N'*,*N'*-tetramethyl-1-(2-methoxyphenyl)phosphanediamine[1,4] (1.18 g, 5.2 mmol) and 1*H*-tetrazole (841 mg, 12.0 mmol) in toluene (80 mL). The mixture was heated at reflux temperature for 4.5 h, and then cooled to room temperature. The resulting mixture was concentrated under reduced pressure. To the resultant residue, dichloromethane (40 mL) and *tert*-butyl hydroperoxide (ca. 70% aqueous solution, 1.7 mL, 12 mmol) were slowly added at room temerature, and the mixture was stirred for 10 h. Water (60 mL) was then carefully added to the mixture, and the resulting mixture was extracted with chloroform (50 mL × 3). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 20:1 then chloroform), to give (*R*)-**S1** as a white solid (2.19 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 6.48 (t, *J* = 7.8 Hz, 1H),

6.58 (td, J = 7.8, 4.1 Hz, 1H), 7.16-7.54 (m, 16H), 7.78 (s, 1H), 7.85-7.91 (m, 3H), 7.99 (d, J = 8.2 Hz, 1H), 8.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.1, 110.4, 110.5, 112.3 (d, J = 193 Hz), 119.3, 119.5, 122.9, 123.2, 125.7, 125.8, 126.3, 126.4, 126.9, 127.0, 127.1, 127.5, 127.8 (2C), 128.1 (2C), 128.3, 128.4, 129.6 (2C), 130.1 (2C), 130.7, 131.4, 131.5, 131.6, 132.1 (d, J = 18 Hz), 134.1, 134.7, 134.8, 136.6, 137.2, 143.8 (d, J = 9.5 Hz), 145.2 (d, J = 10.5 Hz), 161.8. ^{31}P NMR (161 MHz, $CDCl_3$) δ 24.5. IR (KBr) 3054, 2934, 1590, 1480, 1407, 1296, 1139 cm^{-1}. M.p. 326–331 °C (decomposition). $[\alpha]_D^{23}$ = –202.8 (*c* 1.00, $CHCl_3$). HRMS(FAB+) calcd for $C_{39}H_{28}O_4P$ $[M+H]^+$ 591.1725, found 591.1746.



(11b*R*)-4-(2-Hydroxyphenyl)-2,6-diphenyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (1): In a flask purged with nitrogen, boron tribromide (4.8 mL, 4.8 mmol) was added to a solution of **S1** (2.19 g, 3.71 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at that temperature for 6 h. Water (50 mL) was then carefully added, and the resulting mixture was extracted with chloroform (50 mL × 3). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 8:1 to 4:1). The combined filtrates are washed with 1 *M* aqueous HCl, and concentrated under reduced pressure to give (*R*)-**1** as a white solid (2.14 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (ddd, J = 13.8, 7.8, 1.3 Hz, 1H), 6.45 (m, 1H), 6.61 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 6.9 Hz, 2H), 7.18 (t, J = 7.3 Hz, 2H), 7.21-7.30 (m, 2H), 7.33-7.47 (m, 7H), 7.55 (t, J = 7.8 Hz, 2H), 7.77 (d, J = 7.3 Hz, 2H), 7.93 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H), 9.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) Some peaks overlapped. δ 105.7 (d, J = 183 Hz), 117.5 (d, J = 12.4 Hz), 118.8 (d, J = 14.3 Hz), 122.6 (d, J = 7.6 Hz), 126.2 (2C), 126.7, 126.8, 126.9 (2C), 127.4, 127.7, 127.9 (2C), 128.2 (2C), 128.4, 128.6, 129.1 (2C), 129.9 (2C), 130.9, 131.5, 131.6, 131.7, 131.8 (2C), 131.9,

134.2, 135.6, 135.7, 136.7, 143.0 (d, J = 10.5 Hz), 144.3 (d, J = 9.5 Hz), 161.5 (d, J = 6.8 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.7. IR (KBr) 3224, 3053, 1611, 1572, 1466, 1406, 1244, 1191, 1135, 1085 cm^{-1}. M.p. 175–176 °C (decomposition). $[\alpha]_D^{23}$ = –299.6 (*c* 1.00, $CHCl_3$). HRMS(FAB+) calcd for $C_{38}H_{26}O_4P$ $[M+H]^+$ 577.1569, found 577.1558. **Crystal data of 1:** Compound **1** was recrystallized in benzene for X-ray analysis. Formula $C_{44}H_{31}O_4P$, colorless, crystal dimensions 0.40 × 0.40 × 0.30 mm^3, orthorhombic, space group $P2_12_12$ (#18), a = 24.598(3) Å, b = 10.7512(12) Å, c = 12.3961(14) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V = 3278.2(6) $Å^3$, Z = 4, ρ_{calc} = 1.326 g cm^{-3}, F(000) = 1368, μ(MoKα) = 0.130 mm^{-1}, T = 123 K. 23562 reflections collected, 8153 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 28.35 °), and 446 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Flack x = –0.01(6). R_1 = 0.0332 and wR_2 = 0.0857. GOF =1.027. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1059249. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

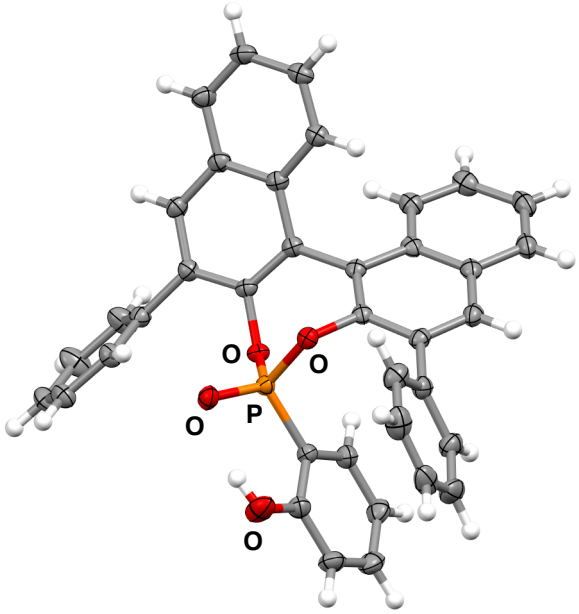
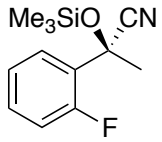


Figure S1. OPTEP drawing of (*R*)-**1**.

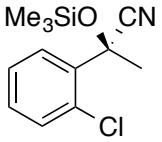
2-5-3. General procedure for catalytic enantioselective cyanosilylation of ketones (Scheme 3).

Chiral ligand **1** (28.8 mg, 0.05 mmol, 10 mol%) and water (10.8 μL, 0.6 mmol) were placed in a Schlenk tube under a nitrogen atmosphere and dissolved in dry toluene (2 mL). To a stirred solution was added *n*-BuLi (1.60 *M* in *n*-hexane, 46.9 μL, 0.075 mmol, 15 mol%) at room temperature, and the solution was stirred for 1 h. Ketone **4** (0.50 mmol) was then added at room temperature and the mixture was stirred at –78 ºC for 10 min. Trimethylsilyl cyanide (157 μL, 1.25 mmol) was added dropwise at –78 ºC, and the mixture was stirred at –78 ºC for 2–9 h. The resulting mixture was quenched with water (3 mL) at –78 ºC, extracted with ethyl acetate (10 mL × 2), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 30:1 to 10:1) to give the desired product (**5**). Usually, ligand **1** was recovered (90–95%) by the same chromatography. If the ligand is to be reused, washing with 1 *M* aqueous HCl is needed to remove the metal salts. The enantiomeric purity of **5** was determined by chiral GC or HPLC analysis.

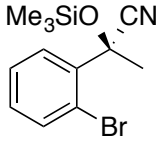
(*S*)-2-Phenyl-2-((trimethylsilyl)oxy)propanenitrile (5a):[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.86 (s, 3H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.6, 71.6, 121.6, 124.6 (2C), 128.6 (3C), 141.9. IR (neat) 2961, 1448, 1254, 1154, 1118, 1076 cm^{-1}. $[\alpha]_D^{22}$ = –21.6 (*c* 1.00, $CHCl_3$, 91% ee). [lit. $[\alpha]_D^{20}$ = +18.5 (*c* 1.15, $CHCl_3$, for *R* enantiomer with 81% ee)].[5] GC analysis; CHIRALDEX G-TA, 80 °C, 100 kPa, t_R = 13.6 min (minor, *R*), 15.0 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{17}NNaOSi$ $[M+Na]^+$ 242.0972, found 242.0979.



(*S*)-2-(2-Fluorophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5b):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.94 (s, 3H), 7.09 (dd, J = 11.4, 8.7 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.35 (m, 1H), 7.58 (td, J = 7.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 30.8, 68.3, 116.4 (d, $J_{C–F}$ = 21.9 Hz), 120.6, 124.2 (d, $J_{C–F}$ = 3.8 Hz), 126.6, 128.7 (d, $J_{C–F}$ = 10.5 Hz), 130.6 (d, $J_{C–F}$ = 8.6 Hz), 159.3 (d, $J_{C–F}$ = 249.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –112.2. IR (neat) 2961, 1486, 1448, 1255, 1161, 1129, 1103 cm^{-1}. $[\alpha]_D^{25}$ = –12.4 (*c* 1.00, CH_2Cl_2, 90% ee). [lit. $[\alpha]_D^{27}$ = –16.2 (*c* 1, CH_2Cl_2, for *S* enantiomer with 86% ee)].[6] GC analysis; CHIRALDEX G-TA, 70 °C, 100 kPa, t_R = 33.6 min (minor, *R*), 36.6 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{16}FNNaOSi$ $[M+Na]^+$ 260.0877, found 260.0877.



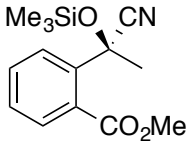
(*S*)-2-(2-Chlorophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5c):[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.00 (s, 3H), 7.26-7.35 (m, 2H), 7.42 (m, 1H), 7.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2 (3C), 29.8, 70.2, 120.4, 126.9, 127.0, 129.9, 131.2, 131.5, 138.0. IR (neat) 2960, 1468, 1432, 1255, 1218, 1159, 1117, 1089, 1040 cm^{-1}. $[\alpha]_D^{28}$ = –2.0 (*c* 1.00, $CHCl_3$, 90% ee). [lit. $[\alpha]_D^{20}$ = +2.3 (*c* 1.69, $CHCl_3$, for *R* enantiomer with 85% ee)].[7] GC analysis; CHIRALDEX B-DM, 65 °C, 130 kPa, t_R = 126.3 min (major, *S*), 130.7 min (minor, *R*). HRMS (ESI+) calcd for $C_{12}H_{16}ClNNaOSi$ $[M+Na]^+$ 276.0582, found 276.0583.



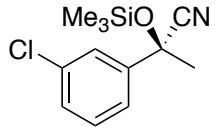
(*S*)-2-(2-Bromophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5d):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 2.03 (s, 3H), 7.21 (td, J = 7.4, 1.8 Hz, 1H), 7.37 (td, J = 7.4, 1.4 Hz, 1H), 7.64 (dd, J = 7.8, 1.4 Hz, 1H) , 7.73 (dd, J = 7.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 1.2 (3C), 29.9, 71.4, 120.1, 120.4, 127.3, 127.6, 130.1, 135.2, 139.2. IR (neat) 2959, 1463, 1428, 1371, 1254, 1215, 1160, 1129, 1109, 1024 cm^{-1}. $[\alpha]_D^{27}$ = –1.2 (*c* 1.00, CH_2Cl_2, 90% ee). [lit. $[\alpha]_D^{20}$ = –17.5 (*c* 1, CH_2Cl_2, for *S* enantiomer with 79% ee)].[6] GC analysis; CHIRALDEX B-DM, 90 °C, 110 kPa, t_R = 57.7 min (major, *S*), 59.3 min (minor, *R*). HRMS (ESI+) calcd for $C_{12}H_{16}BrNNaOSi$ $[M+Na]^+$ 320.0077, found 320.0076.

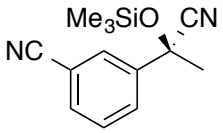
(*S*)-2-(2-Iodophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5e): ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 9H), 2.05 (s, 3H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H) , 7.72 (d, *J* = 7.8 Hz, 1H) , 8.01 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2 (3C), 30.0, 73.0, 92.6, 120.3, 127.0, 128.2, 130.1, 141.1, 142.8. IR (neat) 2959, 1457, 1422, 1371, 1254, 1214, 1159 cm^{-1}. $[\alpha]_D^{24}$ = –8.0 (*c* 1.00, $CHCl_3$, 91% ee). HPLC analysis; AS-3, *n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, t_R = 4.2 min (major, *S*), 5.1 min (minor, *R*). HRMS (ESI+) calcd for $C_{12}H_{16}INNaOSi$ $[M+Na]^+$ 367.9938, found 367.9940.



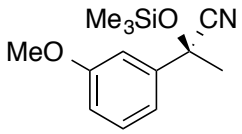
Methyl (*S*)-2-(1-cyano-1-((trimethylsilyl)oxy)ethyl)benzoate (5f): ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 9H), 2.07 (s, 3H), 3.90 (s, 3H), 7.38 (td, *J* = 7.3, 0.9 Hz, 1H), 7.49 (td, *J* = 7.8, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.69 (dd, *J* = 7.8, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (3C), 32.5, 52.3, 71.9, 121.3, 125.8, 128.3, 129.5, 130.5, 130.6, 140.3, 169.3. IR (neat) 2955, 1732, 1433, 1265, 1163, 1122, 1064 cm^{-1}. $[\alpha]_D^{28}$ = –22.4 (*c* 1.00, $CHCl_3$, 90% ee). HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, t_R = 11.5 min (minor, *R*), 12.9 min (major, *S*). HRMS (ESI+) calcd for $C_{14}H_{19}NNaO_3Si$ $[M+Na]^+$ 300.1026, found 300.1025.



(*S*)-2-(3-Chlorophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5g):[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.84 (s, 3H), 7.30-7.38 (m, 2H), 7.42 (m, 1H), 7.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.5, 71.0, 121.1, 122.8, 124.9, 128.8, 130.0, 134.7, 144.1. IR (neat) 2961, 1597, 1577, 1415, 1255, 1223, 1159, 1124 cm^{-1}. $[\alpha]_D^{21}$ = –22.0 (*c* 1.00, $CHCl_3$, 93% ee). [lit. $[\alpha]_D^{24}$ = –19.3 (*c* 1.28, $CHCl_3$, for *S* enantiomer with 91% ee)].[8] GC analysis; CHIRALDEX G-TA, 90 °C, 100 kPa, t_R = 22.1 min (minor, *R*), 24.3 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{16}ClNNaOSi$ $[M+Na]^+$ 276.0582, found 276.0579.



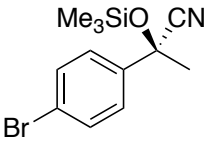
(*S*)-3-(1-Cyano-1-((trimethylsilyl)oxy)ethyl)benzonitrile (5h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 1.86 (s, 3H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.4, 70.7, 113.0, 118.2, 120.7, 128.2, 129.0, 129.6, 132.3, 143.8. IR (neat) 2961, 2232, 1424, 1255, 1172, 1120 cm^{-1}. $[\alpha]_D^{26}$ = –28.0 (*c* 1.00, $CHCl_3$, 98% ee). GC analysis; CHIRALDEX G-TA, 100 °C, 100 kPa, t_R = 58.4 min (minor, *R*), 65.5 min (major, *S*). HRMS (ESI+) calcd for $C_{13}H_{16}N_2NaOSi$ $[M+Na]^+$ 267.0924, found 267.0924.



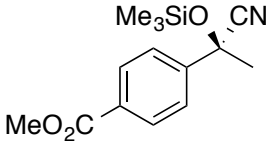
(*S*)-2-(3-Methoxyphenyl)-2-((trimethylsilyl)oxy)propanenitrile (5i):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.85 (s, 3H), 3.83 (s, 3H), 6.88 (dd, *J* = 8.3, 2.8 Hz, 1H), 7.08 (t, *J* = 2.3 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.5, 55.3, 71.5, 110.5, 113.8, 116.9, 121.5, 129.7, 143.6, 159.7. IR (neat) 2960, 1602, 1488, 1433, 1263, 1157, 1118, 1000 cm^{-1}. $[\alpha]_D^{30}$ = –20.8 (*c* 1.00, $CHCl_3$, 91% ee). [lit. $[\alpha]_D^{25}$ = –21.8 (*c* 1.0, $CHCl_3$, for *S* enantiomer with 97% ee)].[9] GC analysis;

CHIRALDEX G-TA, 80 °C, 80 kPa, t_R = 85.2 min (minor, *R*), 90.5 min (major, *S*). HRMS (ESI+) calcd for $C_{13}H_{19}NNaO_2Si$ $[M+Na]^+$ 272.1077, found 272.1081.

(*S*)-2-(*p*-Tolyl)-2-((trimethylsilyl)oxy)propanenitrile (5j):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.84 (s, 3H), 2.34 (s, 3H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.1 (3C), 21.1, 33.5, 71.5, 121.7, 124.6 (2C), 129.2 (2C), 138.5, 139.1. IR (neat) 2960, 1512, 1448, 1408, 1371, 1254, 1231, 1155, 1116 cm^{-1}. $[\alpha]_D^{24}$ = –17.6 (*c* 1.00, $CHCl_3$, 86% ee). [lit. $[\alpha]_D^{25}$ = –24.0 (*c* 1.0, $CHCl_3$, for *S* enantiomer with 96% ee)].[9] GC analysis; CHIRALDEX G-TA, 100 °C, 50 kPa, t_R = 18.2 min (minor, *R*), 19.1 min (major, *S*). HRMS (ESI+) calcd for $C_{13}H_{19}NNaOSi$ $[M+Na]^+$ 256.1128, found 256.1125.

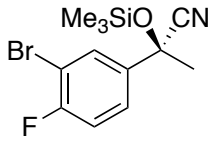


(*S*)-2-(4-Bromophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5k):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.83 (s, 3H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.5, 71.1, 121.2, 122.7, 126.4 (2C), 131.8 (2C), 141.2. IR (neat) 2960, 1487, 1396, 1255, 1226, 1158, 1120, 1078 cm^{-1}. $[\alpha]_D^{22}$ = –16.0 (*c* 1.00, $CHCl_3$, 94% ee). [lit. $[\alpha]_D^{25}$ = –20.1 (*c* 1.18, $CHCl_3$, for *S* enantiomer with 93% ee)].[9] GC analysis; CHIRALDEX G-TA, 90 °C, 100 kPa, t_R = 48.0 min (minor, *R*), 54.2 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{16}BrNNaOSi$ $[M+Na]^+$ 320.0077, found 320.0078.

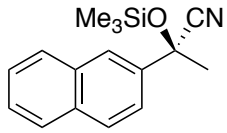


Methyl (*S*)-4-(1-cyano-1-((trimethylsilyl)oxy)ethyl)benzoate (5l): ^{1}H NMR (400 MHz,

$CDCl_3$) δ 0.19 (s, 9H), 1.86 (s, 3H), 3.93 (s, 3H), 7.61 (d, J = 8.2 Hz, 2H), 8.07 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.4, 52.2, 71.2, 121.1, 124.6 (2C), 129.9 (2C), 130.4, 146.7, 166.3. IR (neat) 2956, 1725, 1611, 1436, 1408, 1281, 1117 cm^{-1}. $[\alpha]_D^{31}$ = –33.5 (*c* 1.00, $CHCl_3$, 95% ee). HPLC analysis; OZ-H, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, t_R = 14.8 min (minor, *R*), 17.1 min (major, *S*). HRMS (ESI+) calcd for $C_{14}H_{19}NNaO_3Si$ $[M+Na]^+$ 300.1026, found 300.1026.

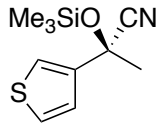


(*S*)-2-(3-Bromo-4-fluorophenyl)-2-((trimethylsilyl)oxy)propanenitrile (5m): ^1H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.83 (s, 3H), 7.15 (t, J = 8.2 Hz, 1H), 7.47 (m, 1H), 7.73 (dd, J = 6.4, 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 33.5, 70.4, 109.3 (d, J_{C-F} = 21.0 Hz), 116.6 (d, J_{C-F} = 22.9 Hz), 120.9, 125.4 (d, J_{C-F} = 7.6 Hz), 130.0, 139.6 (d, J_{C-F} = 3.8 Hz), 159.0 (d, J_{C-F} = 248.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.0. IR (neat) 2961, 1493, 1394, 1254, 1217, 1159, 1120 cm^{-1}. $[\alpha]_D^{30}$ = –19.9 (*c* 1.00, $CHCl_3$, 94% ee). GC analysis; CHIRALDEX G-TA, 100 °C, 100 kPa, t_R = 24.1 min (minor, *R*), 26.1 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{15}BrFNNaOSi$ $[M+Na]^+$ 337.9983, found 337.9983.

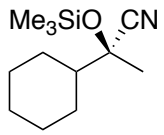


(*S*)-2-(Naphthalen-2-yl)-2-((trimethylsilyl)oxy)propanenitrile (5n):[7] ^1H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.94 (s, 3H), 7.48-7.56 (m, 2H), 7.61 (dd, J = 8.7, 1.8 Hz, 1H), 7.81-7.92 (m, 3H), 8.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.1 (3C), 33.5, 71.8, 121.6, 122.3, 123.7, 126.6, 126.7, 127.6, 128.4, 128.7, 132.8, 133.3, 139.2. IR (neat) 2960, 1254, 1188, 1115, 1000 cm^{-1}. $[\alpha]_D^{23}$ = –13.2 (*c* 1.00, $CHCl_3$, 87% ee). [lit. $[\alpha]_D^{20}$ = +12.6 (*c* 1.99, $CHCl_3$, for *R* enantiomer with 94% ee)].[7] HPLC analysis; OJ-H, *n*-hexane/*i*-PrOH = 99.5/0.5, 0.5 mL/min, t_R = 14.0 min (minor, *R*), 18.4 min (major, *S*). HRMS (ESI+) calcd for $C_{16}H_{19}NNaOSi$ $[M+Na]^+$ 292.1128, found 292.1127.

(*R*)-2-(Furan-2-yl)-2-((trimethylsilyl)oxy)propanenitrile (5o):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.95 (s, 3H), 6.39 (dd, *J* = 3.2 , 1.8 Hz, 1H), 6.50 (d, *J* = 3.2 Hz, 1H), 7.44 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.5 (3C), 28.9, 65.9, 108.1, 110.7, 120.2, 143.1, 151.6. IR (neat) 2962, 1255, 1162, 1114 cm^{-1}. $[\alpha]_D^{24}$ = –30.4 (*c* 1.00, $CHCl_3$, 91% ee). [lit. $[\alpha]_D^{25}$ = –30.9 (*c* 1.0, $CHCl_3$, for *R* enantiomer with 97% ee)].[9] GC analysis; CHIRALDEX G-TA, 80 °C, 100 kPa, t_R = 6.8 min (major, *R*), 8.4 min (minor, *S*). HRMS (ESI+) calcd for $C_{10}H_{15}NNaO_2Si$ $[M+Na]^+$ 232.0764, found 232.0762.

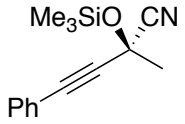


(*S*)-2-(Thiophen-3-yl)-2-((trimethylsilyl)oxy)propanenitrile (5p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.89 (s, 3H), 7.14 (dd, *J* = 5.5, 1.4 Hz, 1H), 7.34 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.41 (dd, *J* = 2.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (3C), 32.3, 68.4, 121.4, 121.9, 124.9, 127.1, 143.1. IR (neat) 2960, 1415, 1254, 1192, 1145, 1117, 1001 cm^{-1}. $[\alpha]_D^{22}$ = –25.2 (*c* 1.00, $CHCl_3$, 93% ee). GC analysis; CHIRALDEX B-DM, 85 °C, 100 kPa, t_R = 15.7 min (major, *S*), 16.4 min (minor, *R*). HRMS (ESI+) calcd for $C_{10}H_{15}NNaOSSi$ $[M+Na]^+$ 248.0536, found 248.0535.

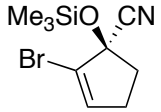


(*S*)-2-Cyclohexyl-2-((trimethylsilyl)oxy)propanenitrile (5q):[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 9H), 1.02-1.31 (m, 5H), 1.47 (m, 1H), 1.52 (s, 3H), 1.69 (m, 1H), 1.78-1.87 (m, 3H), 1.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2 (3C), 25.9, 26.0 (2C), 26.2, 27.0, 27.2, 48.5, 73.0, 121.8. IR (neat) 2933, 2857, 1453, 1375, 1253, 1181, 1134, 1102 cm^{-1}. $[\alpha]_D^{26}$ = –10.4 (*c* 1.00, $CHCl_3$, 78% ee). [lit. $[\alpha]_D^{25}$ = +15.1 (*c* 1.52, $CHCl_3$, for *R* enantiomer with 90% ee)].[10] GC analysis; CHIRALDEX G-TA, 75 °C, 100 kPa, t_R = 21.1 min (minor, *R*),

22.9 min (major, *S*). HRMS (ESI+) calcd for $C_{12}H_{23}NNaOSi$ $[M+Na]^+$ 248.1441, found 248.1441.



(*S*)-2-Methyl-4-phenyl-2-((trimethylsilyl)oxy)but-3-ynenitrile (5r): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9H), 1.95 (s, 3H), 7.32-7.42 (m, 3H), 7.46 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 32.5, 60.7, 85.9, 86.1, 119.5, 120.9, 128.5 (2C), 129.5, 131.7 (2C). IR (neat) 2962, 2240, 1491, 1254, 1139, 1110 cm^{-1}. $[\alpha]_D^{23}$ = –7.7 (*c* 1.00, $CHCl_3$, 90% ee). GC analysis; CHIRALDEX G-TA, 75 °C, 100 kPa, t_R = 111.5 min (major, *S*), 118.8 min (minor, *R*). HRMS (ESI+) calcd for $C_{14}H_{17}NNaOSi$ $[M+Na]^+$ 266.0972, found 266.0972.

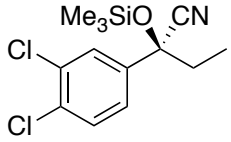


(*R*)-2-Bromo-1-((trimethylsilyl)oxy)cyclopent-2-enecarbonitrile (5s): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.27 (m, 1H), 2.41-2.59 (m, 2H), 2.73 (m, 1H), 6.20 (t, J = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2 (3C), 30.0, 40.1, 79.7, 119.5, 122.8, 136.8. IR (neat) 2959, 1315, 1254, 1184, 1151, 1105 cm^{-1}. $[\alpha]_D^{21}$ = +2.8 (*c* 1.00, $CHCl_3$, 90% ee). GC analysis; CHIRALDEX G-TA, 90 °C, 100 kPa, t_R = 17.4 min (minor, *S*), 19.6 min (major, *R*). HRMS (ESI+) calcd for $C_9H_{14}BrNNaOSi$ $[M+Na]^+$ 281.9920, found 281.9921.

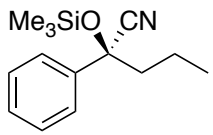
(*R*)-2-Bromo-1-((trimethylsilyl)oxy)cyclohex-2-enecarbonitrile (5t):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 1.80-1.89 (m, 2H), 2.09-2.22 (m, 3H), 2.35 (m, 1H), 6.32 (t, J = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2 (3C), 18.1, 27.2, 39.0, 70.8, 120.1, 121.8, 135.2. IR (neat) 2958, 1254, 1184, 1134, 1026 cm^{-1}. $[\alpha]_D^{22}$ = +18.8 (*c* 1.00, $CHCl_3$, 83% ee). [lit. $[\alpha]_D^{25}$ = +20.3 (*c* 1.0, $CHCl_3$, for *R* enantiomer with 97% ee)].[9] GC analysis; CHIRALDEX

G-TA, 90 °C, 100 kPa, t_R = 41.4 min (minor, *S*), 44.9 min (major, *R*). HRMS (ESI+) calcd for $C_{10}H_{16}BrNNaOSi$ $[M+Na]^+$ 296.0077, found 296.0076.

(*S*)-6-(Trifluoromethyl)-1-((trimethylsilyl)oxy)-2,3-dihydro-1*H*-indene-1-carbonitrile (5u): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 2.47 (ddd, *J* = 14.2, 7.8, 6.4 Hz, 1H), 2.79 (ddd, *J* = 13.2, 7.3, 5.0 Hz, 1H), 3.06 (m, 1H), 3.15 (m, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.1 (3C), 29.3, 42.8, 76.0, 120.3, 121.2 (d, $J_{C–F}$ = 3.8 Hz), 123.9 (d, $J_{C–F}$ = 277.5 Hz), 125.7, 127.0 (d, $J_{C–F}$ = 3.8 Hz), 130.1 (q, $J_{C–F}$ = 32.4 Hz), 143.2, 146.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.1. IR (neat) 2961, 1439, 1333, 1256, 1236, 1161, 1130, 1095 cm^{-1}. $[\alpha]_D^{30}$ = –29.6 (*c* 1.00, $CHCl_3$, 94% ee). GC analysis; CHIRALDEX G-TA, 80 °C, 80 kPa, t_R = 77.9 min (minor, *R*), 83.7 min (major, *S*). HRMS (ESI+) calcd for $C_{14}H_{16}F_3NNaOSi$ $[M+Na]^+$ 322.0845, found 322.0844.

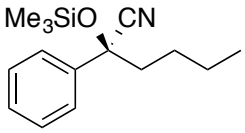


(*S*)-2-(3,4-Dichlorophenyl)-2-((trimethylsilyl)oxy)butanenitrile (5v): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.87-2.06 (m, 2H), 7.35 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (3C), 8.5, 39.1, 75.1, 120.0, 124.5, 127.2, 130.5, 132.8, 132.9, 141.3. IR (neat) 2972, 1697, 1470, 1381, 1255, 1207, 1116, 1030 cm^{-1}. $[\alpha]_D^{29}$ = –15.2 (*c* 1.00, $CHCl_3$, 90% ee). GC analysis; CHIRALDEX B-DM, 90 °C, 100 kPa, t_R = 121.7 min (major, *S*), 126.5 min (minor, *R*). HRMS (ESI+) calcd for $C_{13}H_{17}Cl_2NNaOSi$ $[M+Na]^+$ 324.0349, found 324.0345.



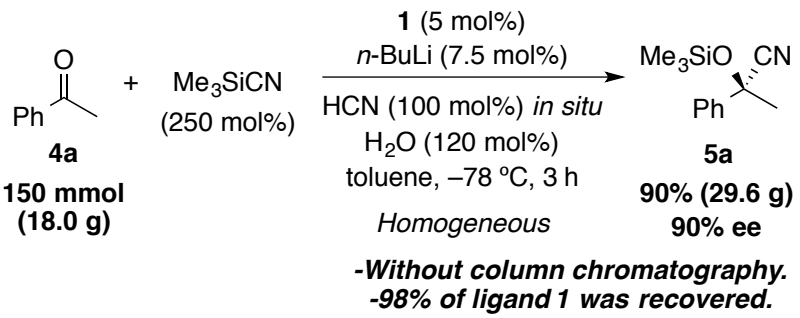
(*S*)-2-Phenyl-2-((trimethylsilyl)oxy)pentanenitrile (5w):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ

0.13 (s, 9H), 0.90 (t, J = 7.4 Hz, 3H), 1.35 (m, 1H), 1.53 (m, 1H), 1.87 (ddd, J = 12.0, 8.7, 5.0 Hz, 1H), 1.94-2.04 (ddd, J = 13.3, 12.2, 5.0 Hz, 1H), 7.31-7.42 (m, 3H), 7.48-7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (3C), 13.6, 17.7, 48.1, 75.5, 121.0, 125.0 (2C), 128.4 (2C), 128.5, 141.1. IR (neat) 2963, 1449, 1254, 1209, 1102, 1041 cm^{-1}. $[\alpha]_D^{25}$ = –15.2 (*c* 1.00, $CHCl_3$, 90% ee). GC analysis; CHIRALDEX G-TA, 60 °C, 60 kPa, t_R = 176.0 min (minor, *R*), 187.6 min (major, *S*). HRMS (ESI+) calcd for $C_{14}H_{21}NNaOSi$ $[M+Na]^+$ 270.1285, found 270.1281.

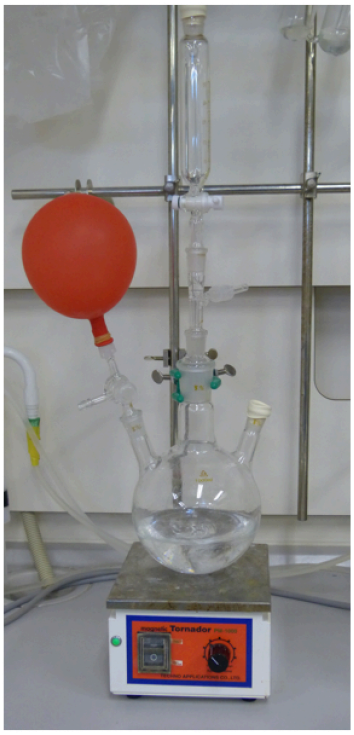


(*S*)-2-Phenyl-2-((trimethylsilyl)oxy)hexanenitrile (5x):[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H), 1.25-1.39 (m, 3H), 1.50 (m, 1H), 1.92 (m, 1H), 2.03 (m, 1H), 7.33-7.44 (m, 3H), 7.53 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (3C), 13.8, 22.2, 26.4, 45.8, 75.6, 121.0, 125.0 (2C), 128.4 (2C), 128.5, 141.1. IR (neat) 2959, 1449, 1254, 1103 cm^{-1}. $[\alpha]_D^{24}$ = –13.6 (*c* 1.00, $CHCl_3$, 91% ee). Ee value was determined after convesion to the corresponding benzoyl amide ([1] $LiAlH_4$, THF; [2] benzoyl chloride, 1 *M* NaOH aq.). HPLC analysis; AS-H, *n*-hexane/*i*-PrOH = 9/1, 1.0 mL/min, t_R = 27.0 min (major, *S*), 34.9 min (minor, *R*). [lit. AS-H, *n*-hexane/*i*-PrOH = 9/1, 1.5 mL/min, t_R = 15.3 min (major, *S*), 21.0 min (minor, *R*)].[11] HRMS (ESI+) calcd for $C_{15}H_{23}NNaOSi$ $[M+Na]^+$ 284.1441, found 284.1441

2-5-4. Gram scale reaction of 4a (Eq 7).



Chiral ligand **1** (4.32 g, 7.5 mmol, 5 mol%) and water (3.24 mL, 180 mmol) were placed in a 1L round-bottom flask under a nitrogen atmosphere and dissolved in dry toluene (450 mL). To a stirred solution was added *n*-BuLi (1.57 *M* in *n*-hexane, 7.16 mL, 11.3 mmol, 7.5 mol%) at room temperature, and the solution was stirred for 2 h. Acetophenone (**4a**) (17.5 mL (18.0 g), 150 mmol) and HCN solution, which was prepared with trimethylsilyl cyanide (18.8 mL, 150 mmol) and *i*-PrOH (11.5 mL, 150 mmol) in toluene (150 mL) in advance, were added at room temperature and the mixture was stirred at –78 ºC for 20 min. Trimethylsilyl cyanide (46.9 mL, 375 mmol) was added dropwise at –78 ºC, and the mixture was stirred at –78 ºC for 3 h. The resulting mixture was quenched with water (200 mL) at –78 ºC, extracted with ethyl acetate (100 mL × 3), and washed with brine (100 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was diluted with *n*-hexane. White solid precipitated, and it was filtrated. The filtrate was evaporated, and the volatiles were completely removed under reduced pressure (<5 Torr) to give the desired product (**5a**) in 90% yield (29.6 g, >99% purity). The enantiomeric purity of **5a** was determined by chiral GC analysis (90% ee). The white precipitation was dissolved in toluene, and the solution was washed with 1 *M* aqueous HCl. The organic phase was concentrated under reduced pressure, and ligand **1** was obtained (4.23 g, 98%, >99% purity).

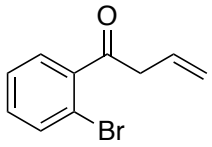


Preparation of catalyst at rt.

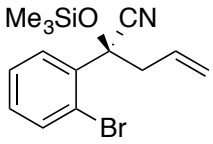
Drop of Me_3SiCN to 1-L flask at –78 °C.

Obtained product **5a** (29.6 g).

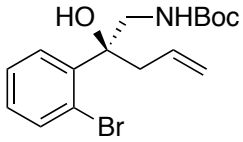
2-5-5. Transformation to the key intermediate 11 of (+)-13-hydroxyisocyclocelabenzine 12 (Scheme 4).



1-(2-Bromophenyl)but-3-en-1-one (4y):[12] To a suspension of *N,O*-dimethylhydroxylamine hydrochloride salt (2.19 g, 22.5 mmol) in dichloromethane (25 mL) at 0 ºC was added 2-bromobenzoyl chloride (1.96 mL, 15.0 mmol). To the suspension was added triethylamine (4.19 mL, 30.0 mmol). The mixture was then allowed to warm to room temperature and stirred for 24 h. The resulting mixture was quenched with water (10 mL), extracted with EtOAc (10 mL × 2), and washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 5:1 to 2:1) to give the Weinreb amide (3.64 g, 99% yield). To a solution of the Weinreb amide (3.64 g, 14.9 mmol) in THF (50 mL) at 0 ºC was slowly added allylmagnesium chloride (2.02 *M* in THF, 11.1 mL, 22.5 mmol), and the mixture was stirred at 0 ºC for 5.5 h. The resulting mixture was quenched with water (10 mL), extracted with EtOAc (10 mL × 2), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 10:1) to give the desired product (**4y**) (3.05 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, *J* = 6.9 Hz, 2H), 5.17-5.27 (m, 2H), 6.01 (m, 1H), 7.30 (m, 1H), 7.34-7.41 (m, 2H), 7.61 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.8, 118.2, 118.9, 127.1, 128.2, 129.7, 131.3, 133.2, 140.8, 201.3. IR (neat) 3080, 1702, 1587, 1428, 1323, 1209, 1054, 1026, 1001 cm^{-1}. HRMS (ESI+) calcd for $C_{10}H_9BrNaO$ $[M+Na]^+$ 246.9729, found 246.9730.



(*S*)-2-(2-Bromophenyl)-2-((trimethylsilyl)oxy)pent-4-enenitrile (5y): Chiral ligand **1** (216 mg, 0.375 mmol, 7.5 mol%) and water (108 μL, 6.0 mmol) were placed in a Schlenk tube under a nitrogen atmosphere and dissolved in dry toluene (15 mL). To a stirred solution was added LiOH (13.5 mg, 0.565 mmol, 11.3 mol%) at room temperature and the solution was stirred for 2 h. Then the mixture was allowed to cool at –78 ℃ and stirted for 5 min. Ketone **4y** (1.13 g, 5.0 mmol) and HCN solution, which was prepared with trimethylsilyl cyanide (625 μL, 5.0 mmol) and *i*-PrOH (382 μL, 5.0 mmol) in toluene (4 mL) in advance, were then added at –78 ºC and the mixture was stirred at –78 ºC for 10 min. Trimethylsilyl cyanide (1.69 mL, 13.5 mmol) was added dropwise at –78 ºC, and the mixture was stirred at –78 ºC for 4 h. The resulting mixture was quenched with water (10 mL) at –78 ºC, extracted with ethyl acetate (10 mL × 2), and washed with brine (10 mL × 2). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was diluted with *n*-hexane. White solid precipitated, and it was filtrated. The filtrate was evaporated to give the mixture of desired product **5y** (93%) and recovered ketone **4y** (7%), and **5y** was obtained after neutral silica gel column chromatography (eluent: hexane:EtOAc = 50:1) in 92% yield (1.49 g). The enantiomeric purity was determined by chiral HPLC analysis (90% ee). The white precipitation was dissolved in toluene, and the solution was washed with 1 *M* aqueous HCl. The organic phase was concentrated under reduced pressure, and ligand **1** was obtained (205 mg, 95%, >99% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 2.98 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.11 (dd, *J* = 14.2, 7.2 Hz, 1H), 5.10-5.22 (m, 2H), 5.69 (m, 1H), 7.21 (td, *J* = 7.8, 1.4 Hz, 1H), 7.36 (td, *J* = 7.8, 1.4 Hz, 1H), 7.64 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0 (3C), 45.3, 75.1, 119.3, 119.9, 120.4, 127.4, 128.5, 130.1, 130.6, 135.3, 137.5. IR (neat) 2959, 1462, 1428, 1254, 1105, 1024 cm^{-1}. $[\alpha]_D^{28}$ = –3.2 (*c* 1.00, $CHCl_3$, 86% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, t_R = 8.1 min (minor, *R*), 8.7 min (major, *S*). HRMS (ESI+) calcd for $C_{14}H_{18}BrNNaOSi$ $[M+Na]^+$ 346.0233, found 346.0232.



***tert*-Butyl (*S*)-(2-(2-bromophenyl)-2-hydroxypent-4-en-1-yl)carbamate (9):** To a suspension of lithium aluminium hydride (68.3 mg, 1.8 mmol) in ether (1 mL) at 0 ºC was slowly added a solution of **5y** (146 mg, 0.45 mmol) in ether (0.5 mL), and the mixture was stirred at 0 ºC for 2 h. The resulting mixture was quenched with saturated aqueous Na_2SO_4 solution at 0 ºC, and then Na_2SO_4 and ether were added. After filtration, the organic phase was concentrated under reduced pressure. To a solution of the obtained product in dichloromethane (1 mL) at room temperature was added triethylamine (97 μL, 0.675 mmol). The mixture was allowed to cool at 0 ºC and a solution of di-*tert*-butyl dicarbonate (147 mg, 0.675 mmol) in dichloromethane (0.5 mL) was added to a mixture. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. The resulting mixture was quenched with saturated aqueous NH_4Cl solution (3 mL), extracted with chloroform (5 mL × 2), and washed with water (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 9:1 to 2:1) to give the desired product (**9**) (119.2 mg, 74% yield). The enantiomeric purity was determined by chiral HPLC analysis. Recrystallization from benzene at 0 ºC gave **9** with the enhanced enantioselectivity (>99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.67 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.09 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.74 (dd, *J* = 14.7, 6.4 Hz, 1H), 3.98 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.69 (s, 1H), 4.81 (br, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 5.67 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (3C), 41.7, 48.7, 78.3, 80.0, 118.3, 119.6, 127.4, 128.8, 130.1, 133.2, 134.5, 142.6, 157.9. IR (KBr) 3429, 2978, 1687, 1589, 1367, 1280, 1252, 1168, 1019 cm^{-1}. M.p. 78–80 °C. $[\alpha]_D^{23}$ = +54.8 (*c* 1.00, $CHCl_3$, >99% ee). HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 9/1, 0.5 mL/min, t_R = 14.6 min (minor), 15.9 min (major). HRMS (ESI+) calcd for $C_{16}H_{22}BrNNaO_3$ $[M+Na]^+$ 378.0675, found 378.0674.

Crystal data of 9: Compound **9** was recrystallized from hexane–ether at room temperature for 1 day. Formula $C_{16}H_{22}BrNO_3$, colorless, crystal dimensions 0.35 × 0.20 × 0.20 mm^3, monoclinic, space group $P2_1$ (#4), a = 9.389(4) Å, b = 7.785(3) Å, c = 11.611(5) Å, α = 90.00°, β = 98.908(8)°, γ = 90.00°, V = 838.5(6) $Å^3$, Z = 2, ρ_{calc} = 1.411 g cm^{-3}, F(000) = 368, μ(MoKα) = 2.460 mm^{-1}, T = 123 K. 7014 reflections collected, 3559 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 27.604°), and 213 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0378 and wR_2 = 0.0735. GOF = 0.887. Flack x parameter = 0.026(11). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1059250. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

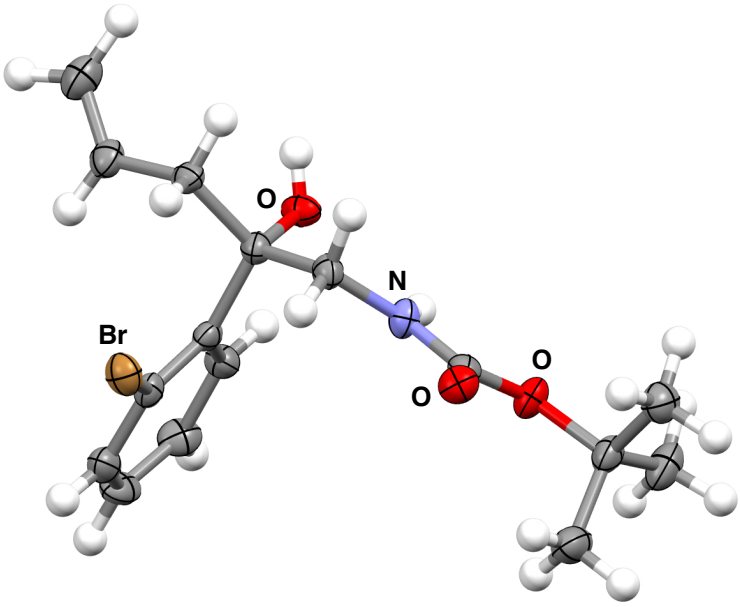
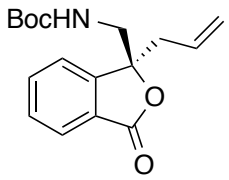
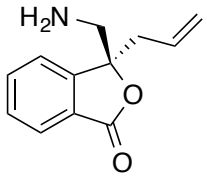


Figure S2. OPTEP drawing of **9**.



***tert*-Butyl (*S*)-((1-allyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl)carbamate (10):** On the basis of a literature procedure.[13] To a suspension of **9** (107 mg, 0.30 mmol) and L-proline (138 mg, 1.2 mmol) in well-degassed DMF, CuCN (107 mg, 1.2 mmol) was added. The mixture was then allowed to heat at 120 ºC and stirred for 36 h. The resulting mixture was quenced with 1 *M* aqueous KCN solution (2 mL), extracted with chloroform (5 mL × 2), and washed with water (10 mL). The combined extracts was dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: hexane:EtOAc = 9:1 to 3:1) to give the desired product (**10**) (52.9 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 2.66-2.80 (m, 2H), 3.65 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.73 (dd, *J* = 14.7, 7.3 Hz, 1H), 4.72 (br, 1H), 5.03-5.13 (m, 2H), 5.51 (m, 1H), 7.47-7.54 (m, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (3C), 40.2, 46.3, 79.6, 89.0, 120.6, 122.5, 125.3, 127.0, 129.3, 129.9, 133.8, 149.3, 155.5, 169.7. IR (KBr) 3368, 1760, 1686, 1523, 1277 cm^{-1}. M.p. 103–104 °C. $[\alpha]_D^{24}$ = –48.4 (*c* 1.00, $CHCl_3$, >99% ee). HRMS (ESI+) calcd for $C_{17}H_{21}NNaO_4$ $[M+Na]^+$ 326.1363, found 326.1366.

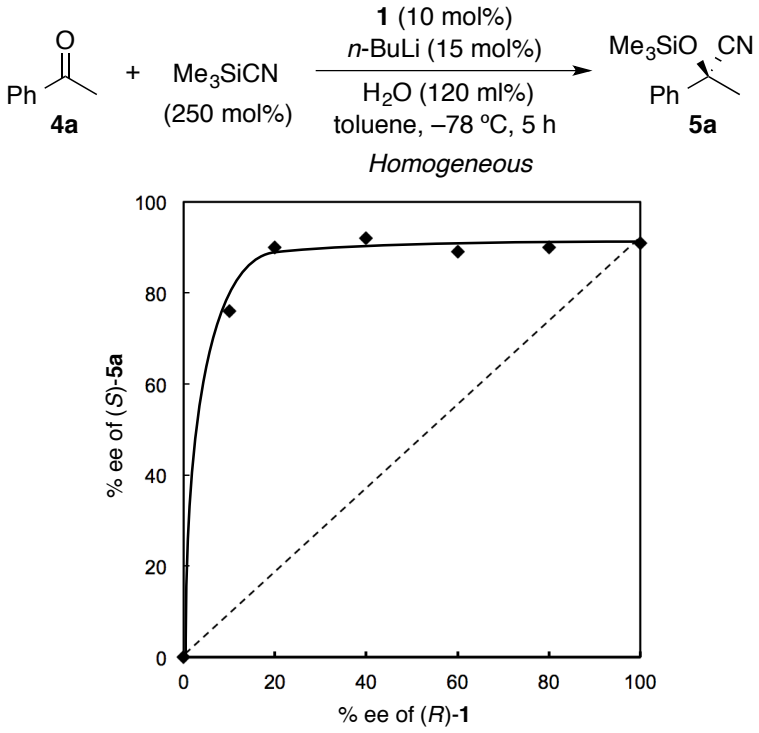


(*S*)-3-Allyl-3-(aminomethyl)isobenzofuran-1(3*H*)-one (11):[14] To a solution of **10** (91.0 mg, 0.30 mmol) in dichloromethane (3 mL) at 0 ºC was added trifluoroacetic acid (115 μL, 1.5 mmol), and the mixture was stirred at room temperature for 5 h. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with chloroform (5 mL × 2), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified

by neutral silica gel column chromatography (eluent: $CHCl_3$:MeOH = 20:1 to 10:1) to give the desired product (**11**) (58.8 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (br, 2H), 2.69 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.78 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.10 (m, 1H), 3.22 (m, 1H), 5.00-5.12 (m, 2H), 5.55 (m, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 48.8, 89.8, 120.2, 121.4, 125.7, 127.4, 129.3, 130.3, 134.1, 150.1, 169.9. IR (neat) 3395, 2915, 1759, 1613, 1466, 1286, 1085 cm^{-1}. $[\alpha]_D^{26}$ = –8.6 (*c* 1.00, $CHCl_3$, >99% ee). HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 9/1, 1.0 mL/min, t_R = 17.9 min (major, *S*) (and 20.0 min (minor, *R*)). HRMS (ESI+) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$ 204.1019, found 204.1022.

2-5-6. Non-linear effect between the ee (%) of (*R*)-1 and the ee (%) of (*S*)-5a.

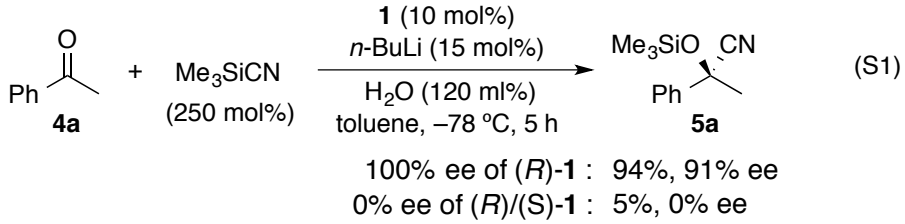
A non-linear effect was examined in the reaction of acetophenone (**4a**) (0.50 mmol) with trimethylsilyl cyanide (250 mol%) in the presence of (*R*)-**1** (10 mol%, 0% ee to 100% ee), *n*-BuLi (15 mol%), and water (120 mol%) in toluene at –78 °C for 5 h. As shown in Scheme S1, a remarkable positive non-linear effect was observed. This non-linear relationship



Scheme S1. Plot of ee of (*S*)-**5a** vs. ee of (*R*)-**1**.

strongly suggests that hetero-$(R)_n/(S)_m$ oligomeric lithium(I) complexes might be involved under the reaction conditions with the use of <100% ee of (*R*)-**1**.

As expect, the 1:1 ratio of (*R*)/(*S*)-**1**-derived catalyst (i.e., 0% ee catalyst) showed almost no catalytic activity (5% yield, 0% ee), while (*R*)-100% ee catalyst showed much higher catalytic activity (94%, 91% ee) (Eq. S1). These results strongly suggest that hetero-(*R*)/(*S*)-**1** dimer (or oligomers) might be inactive species and extremely stable. Totally, the remaining (*R*)-enriched monomeric lithium(I) complexes, such as **2** observed in ESI-MS analysis, etc., should be active species and promote the reaction. These observations clearly rationalize the strong positive non-linear effect.



(S1)

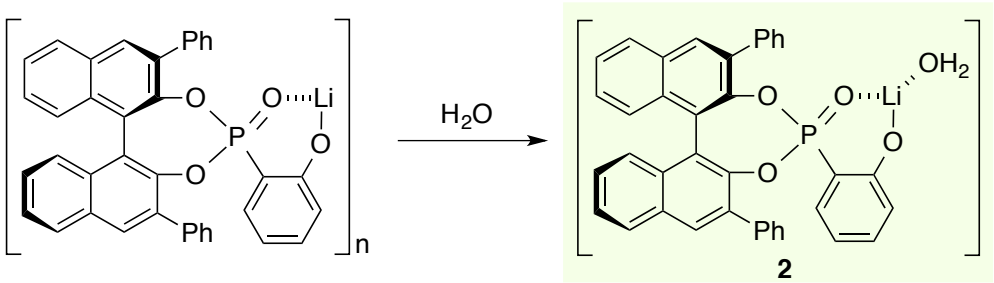
2-5-7. ESI-MS analysis of catalyst 2.

In the absence of water: To a solution of (*R*)-**1** (14.4 mg, 0.025 mmol) in toluene (5 mL) was added *n*-BuLi (1.63 *M* in *n*-hexane, 15.4 μL, 0.025 mmol) in a well-dried pyrex Schlenk tube at room temperature. After 10 min, 100 μL of the resulting mixture was diluted with toluene (400 μL) in a well-dried test tube (final concentration: 1.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The spectrum is shown in Figure S3. Moreover, correlation of theoretical and observed ion distribution for the peaks (*m/z* = 589.1728, 1171.3322, 1753.4855) is shown in Figure S5.

In the presence of water: To a mixture of (*R*)-**1** (28.8 mg, 0.05 mmol) and H_2O (1.8 μL, 0.1 mmol) in toluene (10 mL) was added *n*-BuLi (1.63 *M* in *n*-hexane, 46.2 μL, 0.075 mmol) in a well-dried pyrex Schlenk tube at room temperature. After 10 min, 100 μL of the resulting mixture was diluted with toluene (400 μL) in a well-dried test tube (final concentration: 1.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The

spectrum is shown in Figure S4. Moreover, correlation of theoretical and observed ion distribution for the peaks (*m/z* = 607.1836, 1207.3492, 1807.5325) is shown in Figure S6.

The ESI-MS analysis in Figures S3 and S4 clearly suggests that water can promote the dissociation of dimeric and trimeric lithium(I) complexes into monomeric species (Scheme S2), which are suggested to be an active species by the remarkable positive non-linear effect in Scheme S1. Overall, water is necessary to both coordinate to the Li(I) center and generate a large amount of HCN *in situ* from Me_3SiCN.



Scheme S2. Dissociation of oligomeric lithium(I) complexes into monomeric species by water

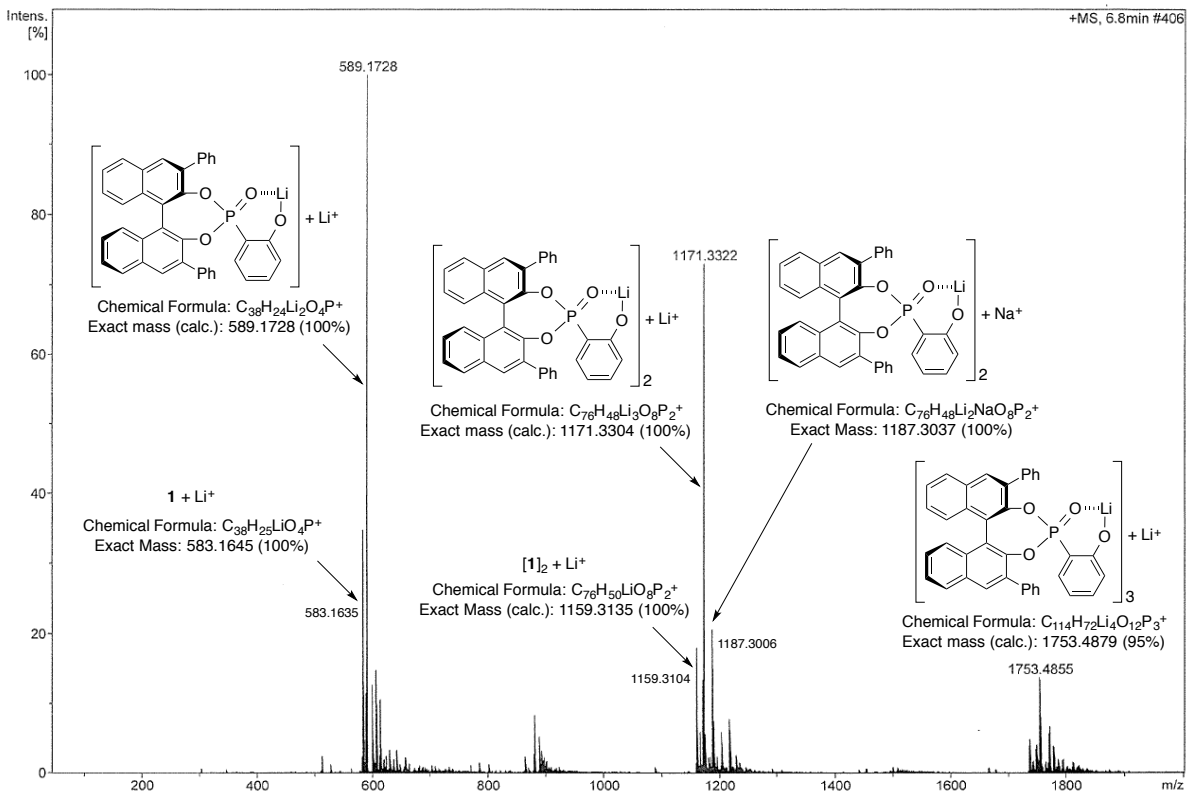


Figure S3. ESI-MS spectrum of (*R*)-**1**:*n*-BuLi = 1:1 in dry toluene.

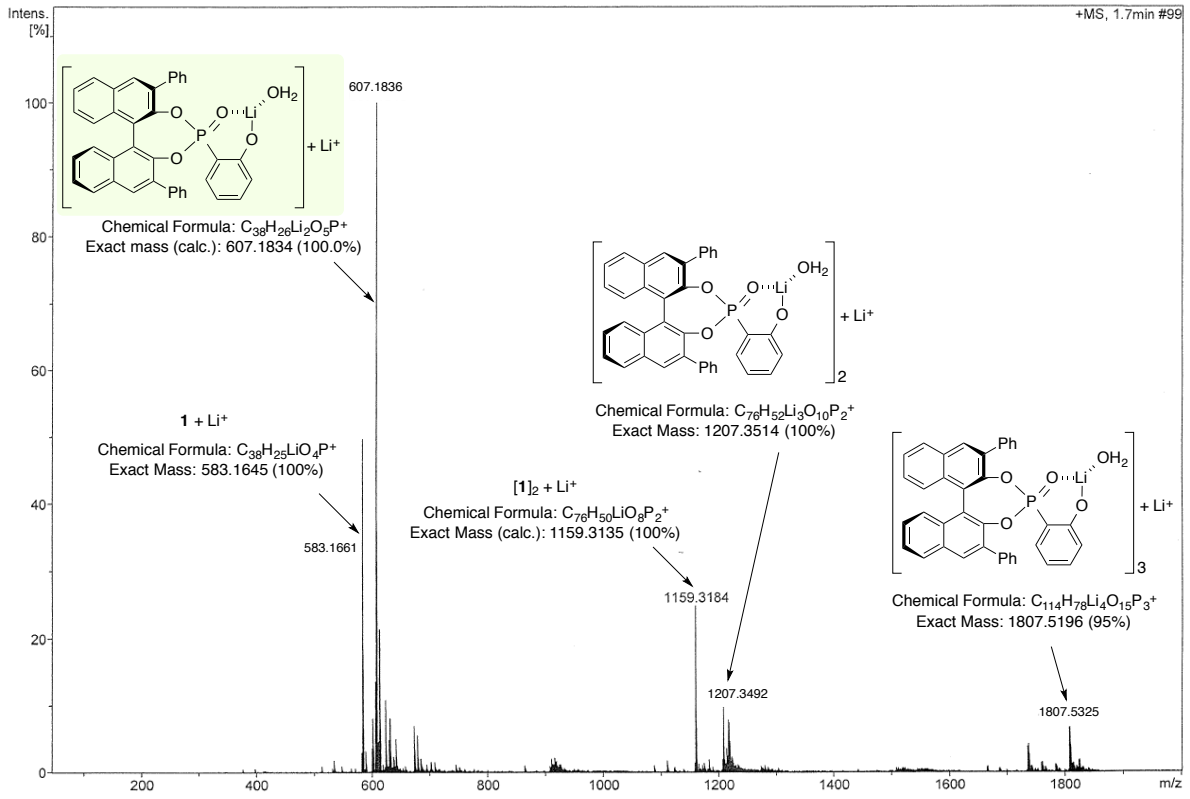
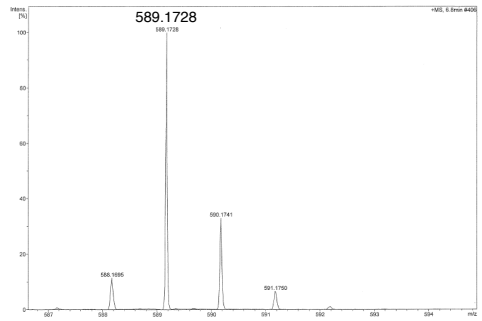
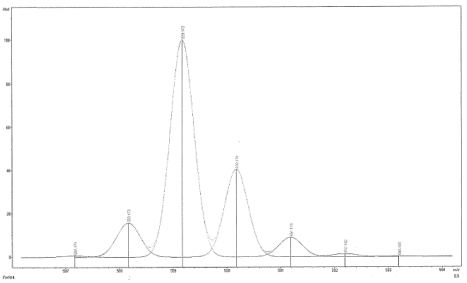


Figure S4. ESI-MS spectrum of (*R*)-**1**:*n*-BuLi = 1:1.5 in toluene–H_2O.

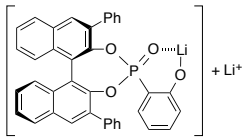
Chemical Formula: $C_{38}H_{24}Li_2O_4P^+$, Exact mass (calc.): 589.1728 (100%)

observed (close-up) **theoretical**



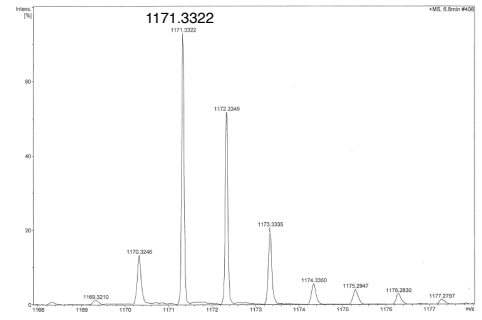


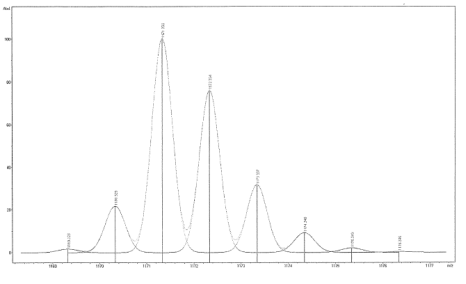
#	m/z	Abundance
1	587.170917	0.631
2	588.171840	15.631
3	589.172842	100.000
4	590.176139	40.280
5	591.179286	8.852
6	592.182263	1.378
7	593.185179	0.168



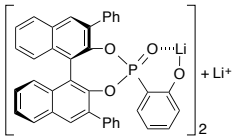
Chemical Formula: $C_{76}H_{48}Li_3O_8P_2^+$, Exact mass (calc.): 1171.3304 (100%)

observed (close-up) **theoretical**



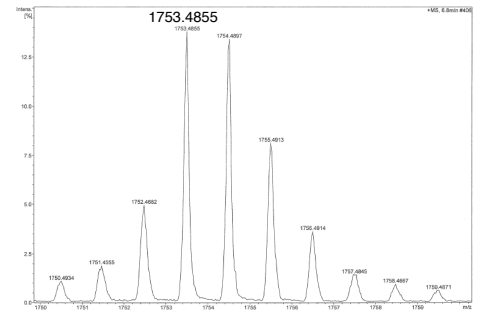


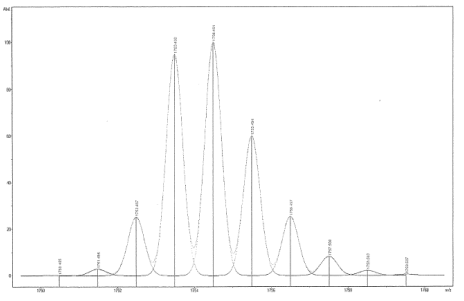
#	m/z	Abundance
1	1169.328197	1.708
2	1170.329186	21.735
3	1171.330356	100.000
4	1172.333521	75.966
5	1173.336706	31.635
6	1174.339935	9.200
7	1175.342906	2.076
8	1176.345926	0.386



Chemical Formula: $C_{114}H_{72}Li_4O_{12}P_3^+$, Exact mass (calc.): 1753.4879 (95%)

observed (close-up) **theoretical**





#	m/z	Abundance
1	1750.484547	0.149
2	1751.485530	2.845
3	1752.486502	25.033
4	1753.487951	94.825
5	1754.490967	100.000
6	1755.494123	59.965
7	1756.497279	25.224
8	1757.500407	8.219
9	1758.503493	2.196
10	1759.506557	0.499

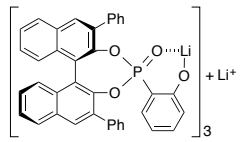
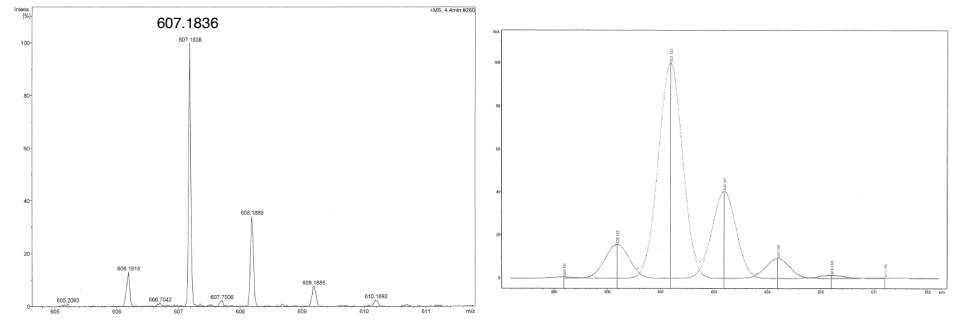


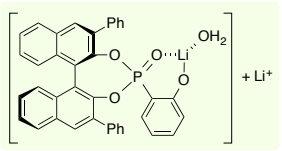
Figure S5. Theoretical and observed ion distribution for the major peaks in dry toluene (Enlarged version of Figure S3).

Chemical Formula: $C_{38}H_{26}Li_2O_5P^+$, Exact mass (calc.): 607.1834 (100.0%)

observed (close-up) **theoretical**

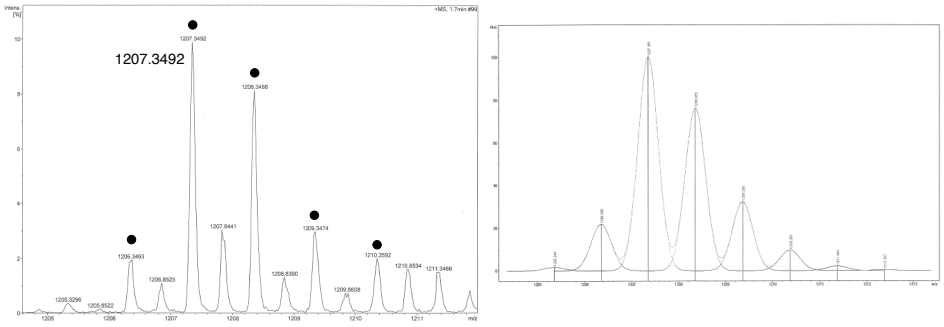


#	m/z	Abundance
1	605.181481	0.631
2	606.182405	15.630
3	607.183407	100.000
4	608.186706	40.369
5	609.189787	9.081
6	610.192729	1.466
7	611.195591	0.188

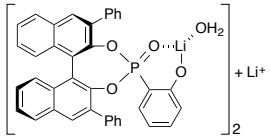


Chemical Formula: $C_{76}H_{52}Li_3O_{10}P_2^+$, Exact Mass (calc.): 1207.3514 (100%)

observed (close-up) **theoretical**

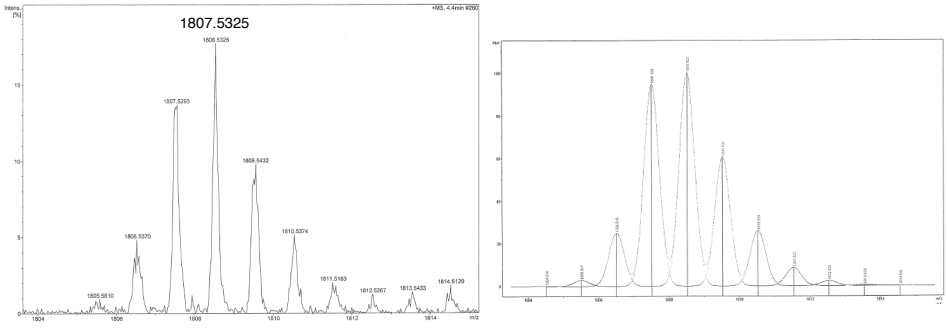


#	m/z	Abundance
1	1205.349327	1.707
2	1206.350316	21.730
3	1207.351486	100.000
4	1208.354653	76.152
5	1209.357813	32.128
6	1210.360905	9.548
7	1211.363930	2.217
8	1212.366901	0.426



Chemical Formula: $C_{114}H_{78}Li_4O_{15}P_3^+$, Exact mass (calc.): 1807.5196 (95.0%)

observed (close-up) **theoretical**



#	m/z	Abundance
1	1804.516241	0.149
2	1805.517224	2.836
3	1806.518297	24.957
4	1807.519648	94.578
5	1808.522664	100.000
6	1809.525804	60.534
7	1810.528932	25.867
8	1811.532023	8.603
9	1812.535074	2.361
10	1813.538086	0.553
11	1814.541064	0.114

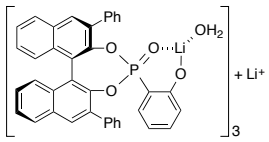


Figure S6. Theoretical and observed ion distribution for the major peaks in wet toluene (Enlarged version of Figure S4).

2-5-8. ESI-MS analysis of catalyst 2 with HCN.

To a mixture of (*R*)-**1** (11.5 mg, 0.02 mmol) and H_2O (1.1 μL, 0.06 mmol) in toluene (5 mL) was added *n*-BuLi (1.63 *M* in *n*-hexane, 18.4 μL, 0.03 mmol) in a well-dried pyrex Schlenk tube at room temperature and the solution was stirred for 1 h. HCN solution, which was prepared from Me_3SiCN (50.0 μL, 0.4 mmol) and *i*-PrOH (30.8 μL, 0.4 mmol) in toluene (1 mL) in advance, was then added. After 10 min, 100 μL of the resulting mixture was diluted with toluene (300 μL) in a well-dried test tube (final concentration: 1.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The spectrum is shown in Figure S7. Moreover, correlation of theoretical and observed ion distribution for the peaks (*m/z* = 655 and 679) is shown in Figure S8.

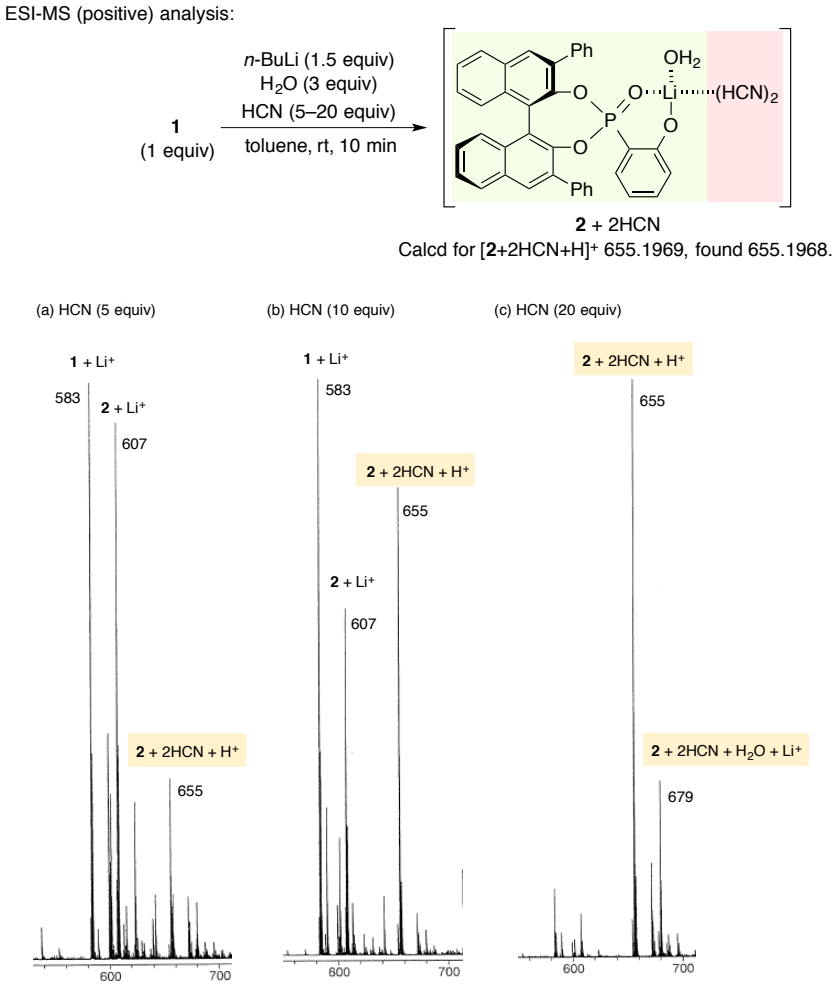


Figure S7. ESI-MS spectrum of catalyst **2** with HCN in toluene.

(a) 5 equiv of HCN was used. (b) 10 equiv of HCN was used. (c) 20 equiv of HCN was used.

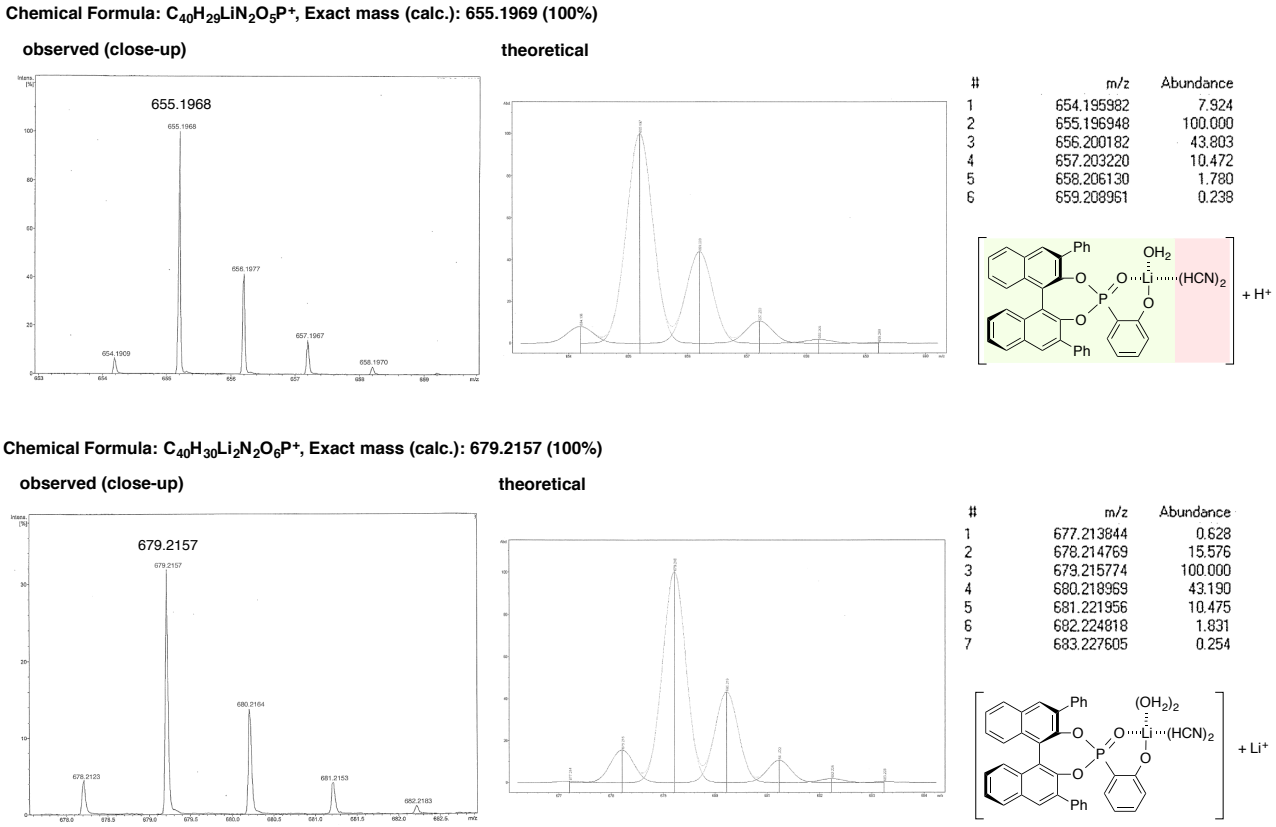


Figure S8. Theoretical and observed ion distribution for the major peaks for catalyst **2** with HCN (Enlarged version of Figure S7).

The ESI-MS analysis in Figures S7 and S8 clearly suggests that HCN can coordinate to catalyst **2**. The population of **2**–HCN complexes (*m*/*z* = 655 and 679) increased as HCN increased from 5 to 20 equiv. Overall, efficiency of the coordination of HCN to catalyst **2** was not good, since more than 10 equiv of HCN was needed to give significant amount of **2**–HCN complexes (*m*/*z* = 655 and 679) as shown in Figures S7b and S7c. This tendency would agree with the yields of the probe reaction with the use of HCN *in situ* (45, 105, and 205 mol%).

2-5-9. ESI-MS analysis of catalyst 2 with $[Li]^+[Me_3Si(CN)_2]^-$ 3.

To a mixture of (*R*)-**1** (11.5 mg, 0.02 mmol) and H_2O (1.1 μL, 0.06 mmol) in toluene (4 mL) was added *n*-BuLi (1.63 *M* in *n*-hexane, 18.4 μL, 0.03 mmol) in a well-dried pyrex Schlenk tube at room temperature and the solution was stirred for 1 h. $[Li]^+[Me_3Si(CN)_2]^-$ (0.2 mmol) solution, which was prepared from Me_3SiCN (25.0 μL, 0.2 mmol) and LiCN (6.6 mg, 0.2 mmol) in THF (1 mL) in advance, was then added. As soon as possible, 100 μL of the resulting mixture was diluted with toluene (300 μL) in a well-dried test tube (final concentration: 1.0 m*M*), and passed through a membrane filter (200 mm mesh) just before injection. The spectrum is shown in Figure S9. Moreover, correlation of theoretical and observed ion distribution for the peaks (*m/z* = 757) is shown in Figure S10.

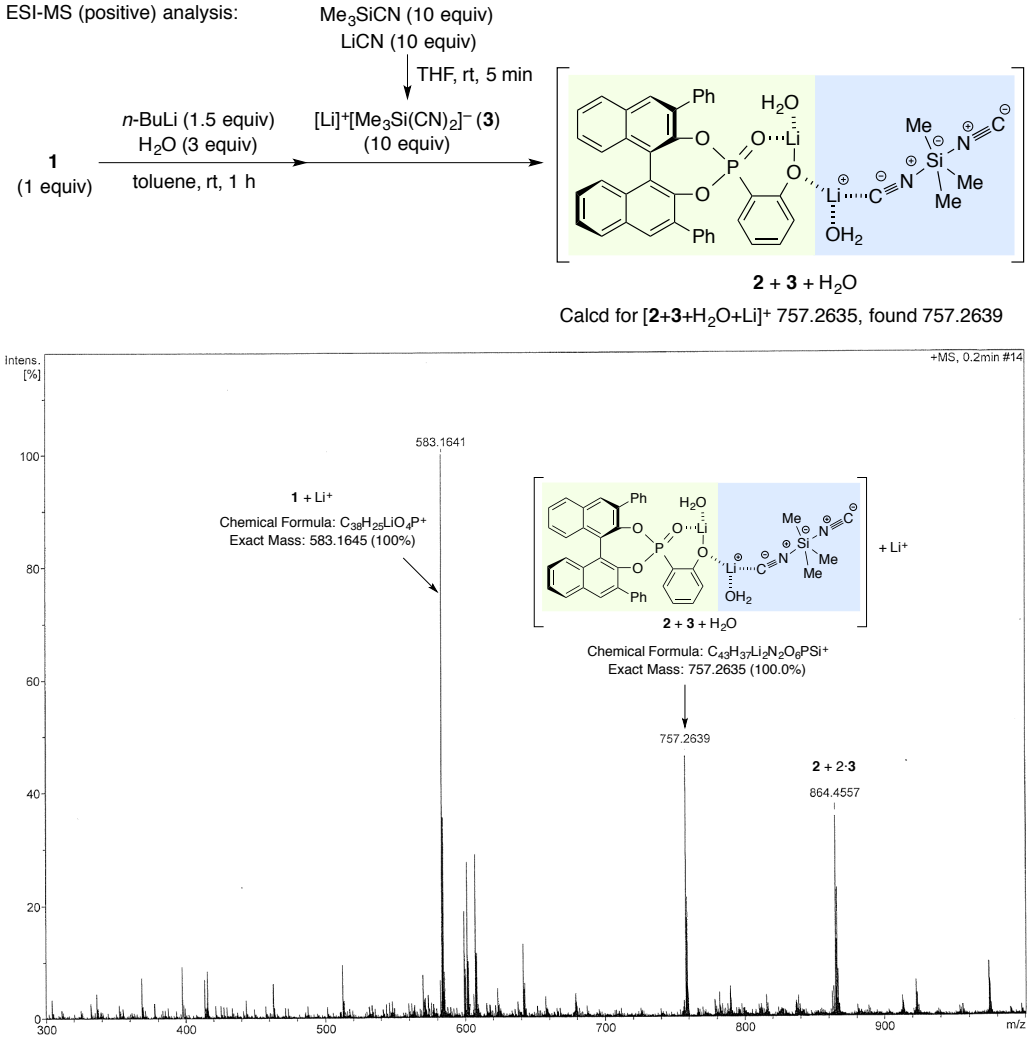


Figure S9. ESI-MS spectrum of catalyst **2** with $[Li]^+[Me_3Si(CN)_2]^-$ **3** in toluene and THF.

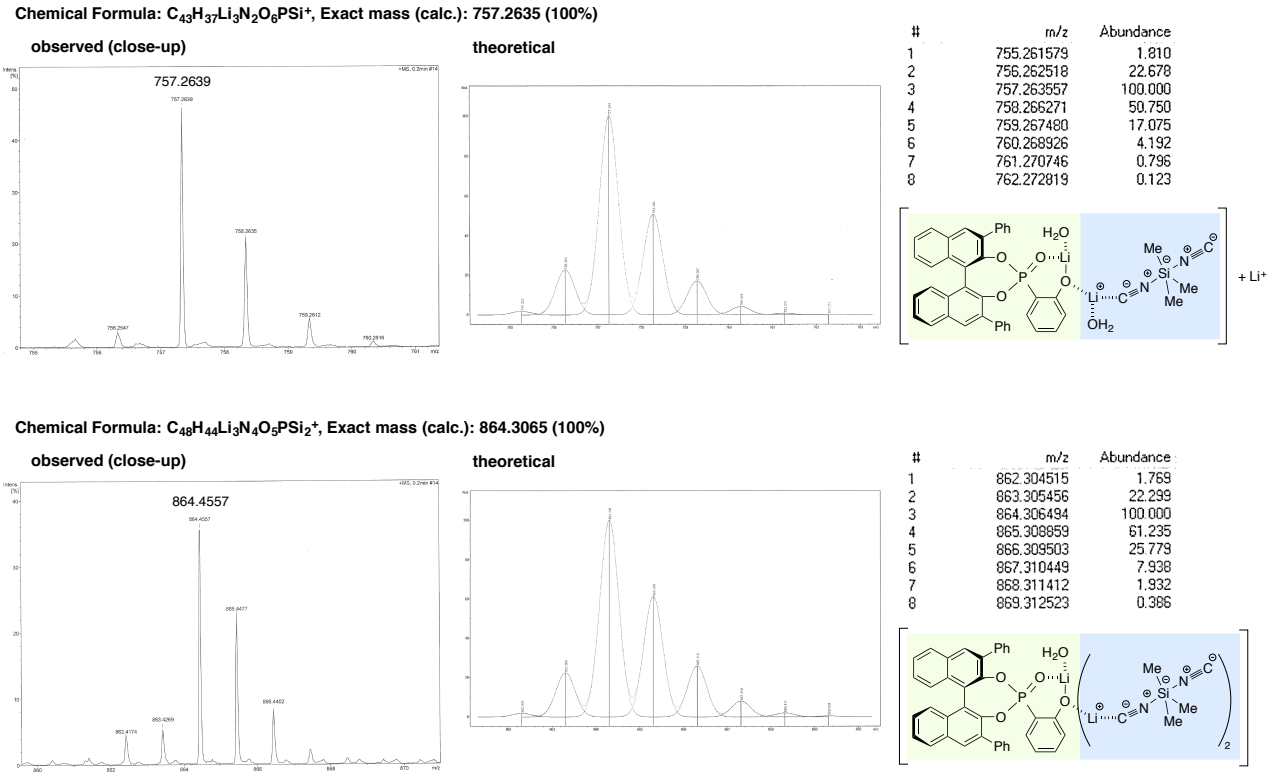


Figure S10. Theoretical and observed ion distribution for the major peak for catalyst **2** with $[Li]^+[Me_3Si(CN)_2]^-$ **3** (Enlarged version of Figure S9).

The ESI-MS analysis in Figures S9 and S10 clearly suggests that $[Li]^+[Me_3Si(CN)_2]^-$ can coordinate to catalyst **2**. This information about the complex **2**+**3** strongly supports thinking the possible transition states. Also see the Section 18 (page S37).

2-5-10. ^{1}H- and ^{31}P-NMR analysis of 1–Li(I) complexes.

To support the former ESI-MS analysis, we performed a ^{1}H NMR (toluene-d_8) analysis of **1**–Li(I) complexes (Figure S11). The spectrum of ligand **1** is shown in Figure S11a. A 1:1 molar ratio of **1** and *n*-BuLi without water gives the corresponding Li(I) complexes, which have broad spectra, as shown in Figure S11b. Based on the ESI-MS analysis, the Li(I) complexes in Figure S11b might be oligomers with similar structures. Moreover, a 1:1:1 molar ratio of **1**, *n*-BuLi, and D_2O gives the Li(I) aqua complexes along with a change in the chemical shifts from dry conditions, as shown in Figure S11c. Further addition of D_2O (total of 3 equiv) did not affect the spectra (Figure S11d). This result supports those of the ESI-MS analysis on the crucial point that the monomeric Li(I) aqua complex might involve one water molecule.

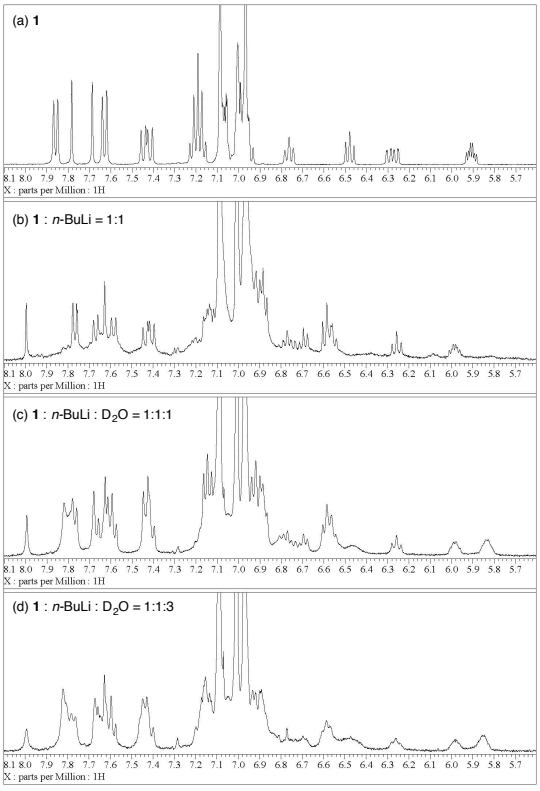


Figure S11. ^{1}H NMR (toluene-d_8) experiment of **1**–Li complexes. (a) Ligand **1** in toluene-d_8 (b) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) in toluene-d_8. (c) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) + D_2O (1 equiv) in toluene-d_8. (d) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) + D_2O (3 equiv) in toluene-d_8.

In addition to ^{1}H NMR analysis, ^{31}P NMR (toluene-d_8) analysis of **1**–Li(I) complexes was also performed (Figure S12). The spectrum of ligand **1** (+28.07 ppm) is shown in Figure S12a. A somewhat broad peak at +34.67 ppm was observed with downfield shift from free ligand **1** when a 1:1 molar ratio of **1** and *n*-BuLi were used (Figure S12b). Moreover, almost the same chemical shift at +34.69 ppm was observed when a 1:1:1 and 1:1:3 molar ratio of **1**, *n*-BuLi, and D_2O were used (Figures S12c and S12d). These results in ^{31}P NMR analysis have a good correlation to those in ^{1}H NMR analysis, which were shown in Figure S11.

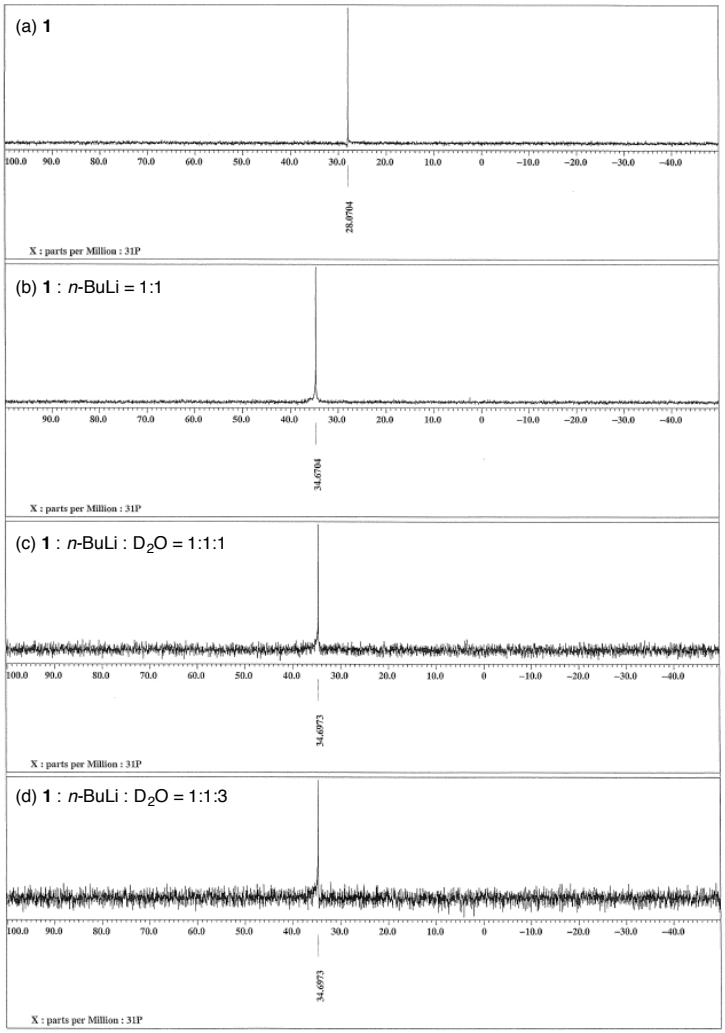


Figure S12. ^{31}P NMR (toluene-d_8) experiment of **1**–Li complexes. (a) Ligand **1** in toluene-d_8 (b) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) in toluene-d_8. (c) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) + D_2O (1 equiv) in toluene-d_8. (d) Ligand **1** (1 equiv) + *n*-BuLi (1 equiv) + D_2O (3 equiv) in toluene-d_8.

2-5-11. ^{13}C-NMR analysis of cyano-reagents (Eqs. 4 and 5).

To determine a possible active reagent in our catalytic system, we examined the ^{13}C NMR (tetrahydrofuran-d_8) analysis. Me_3SiCN shows –2.00 ppm (Figure S13a). A 2:1 molar ratio of Me_3SiCN and *i*-PrOH, to examine Me_3SiCN (1 equiv) and HCN (1 equiv), showed two new peaks of Me_3SiO*i*-Pr at +0.26 ppm (37%) and $[H]^+[Me_3Si(CN)_2]^-$ (**3'**) at +2.03 ppm (8%) in addition to Me_3SiCN at –1.95 ppm (55%) (Figure S13b). The ratio of the peaks did not change for 5 h due to the arrival of an equilibrium. In sharp contrast, a 1:1 molar ratio

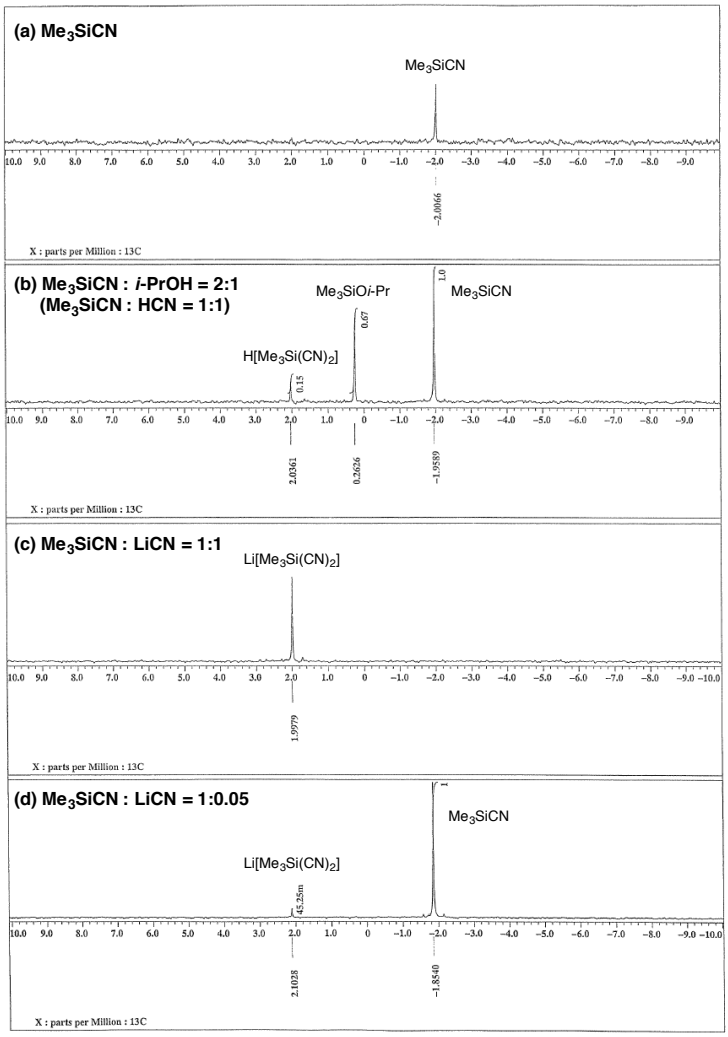
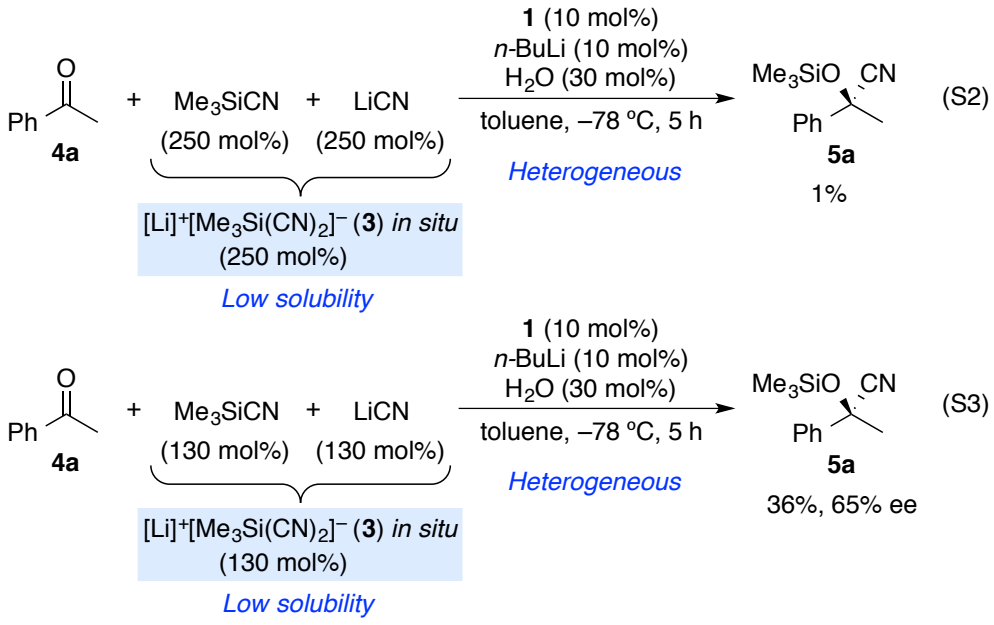


Figure S13. ^{13}C NMR (THF-d_8) experiment of cyano reagents. (a) Me_3SiCN in THF-d_8. (b) Me_3SiCN (2 equiv) + *i*-PrOH (1 equiv) in THF-d_8. Correspondingly, Me_3SiCN (1 equiv) + HCN (1 equiv) in THF-d_8. (c) Me_3SiCN (1 equiv) + LiCN (1 equiv) in THF-d_8. (d) Me_3SiCN (1 equiv) + LiCN (0.05 equiv) in THF-d_8.

of Me_3SiCN and LiCN showed a sole peak of pentacoordinate silicate $[Li]^+[Me_3Si(CN)_2]^-$ (**3**) at +2.00 ppm within 5 min (Figure S13c). These results in Figures S13a and S13b mean that ionic LiCN (*but not HCN*) should be essential for generation of the pentacoordinate silicate. Moreover, a 1:0.05 molar ratio of Me_3SiCN and LiCN also showed a peak of **3** (4.3%, i.e., 86% conversion based on LiCN) within 5 min (Figure S13d). Therefore, LiCN might readily convert to **3** under the standard reaction conditions.

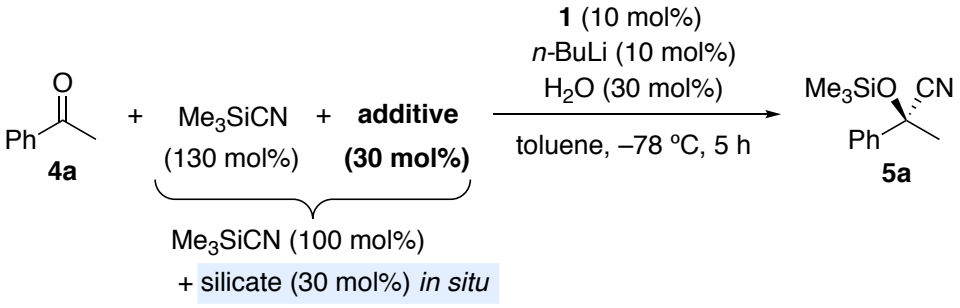
In this regard, we examined the effect of the pentacoordinate silicate **3** more directly in the reaction of **4a**. First, we used *the stoichiometric amount of the silicate 3*, which were prepared *in situ* from Me_3SiCN and LiCN (Eqs. S2 and S3). LiCN was prepared from LiH and acetone cyanohydrin and isolated in advance. However, unexpectedly, the reactions were sluggish, partially due to the low solubility of a stoichiometric amount of **3** in toluene. Therefore, we could not evaluate the real activity of silicate **3** under the stoichiometric reaction conditions.



Next, to clarify the effect of the *catalytic amount of possible silicates*, the standard reaction was conducted *under the unoptimized conditions (control reaction conditions)* with the use of **1** (10 mol%), *n*-BuLi (10 mol%), H_2O (30 mol%), and Me_3SiCN (130 mol%), and **5a** was obtained in 57% yield with 87% ee (Table S1, entry 1). With the use of HCN (30 mol%)

which would partially provide $[H]^+[Me_3Si(CN)_2]^-$ (**3'**) *in situ*, the yield increased although the enantioselectivity did not change (72% yield and 86% ee) (entry 2). With the use of 30 mol% of LiCN, which would generate 30 mol% of $[Li]^+[Me_3Si(CN)_2]^-$ **3** *in situ* (low solubility), both the yield and enantioselectivity increased (72% yield and 92% ee) (entry 3). Moreover, the use of 30 mol% of LiOH was also effective (entry 4). With the use of 30 mol% of *n*-Bu_4NCN which would provide $[n\text{-}Bu_4N]^+[Me_3Si(CN)_2]^-$ *in situ* (completely soluble), the reaction was sluggish (entry 5). These results in Table S1 suggest that the lithium(I) cation should be important for the silicates.

Table S1. Effect of catalytic amount of possible silicates.



entry	**additive**	*conditions*	**5a**	
			yield (%)	ee (%)
1 (control)	–	*Homogeneous*	57	87
2[a]	HCN	*Homogeneous*	72	86
3[b]	**LiCN**	*Heterogeneous*	**72**	**92**
4[b]	**LiOH**	*Heterogeneous*	**80**	**90**
5[c]	*n*-Bu_4NCN	*Homogeneous*	8	5

[a] Formaly, $[H]^+[Me_3Si(CN)_2]^-$ (**3'**) (soluble) might be provided *in situ*.

[b] Formaly, $[Li]^+[Me_3Si(CN)_2]^-$ (**3**) (partially soluble) might be provided *in situ*.

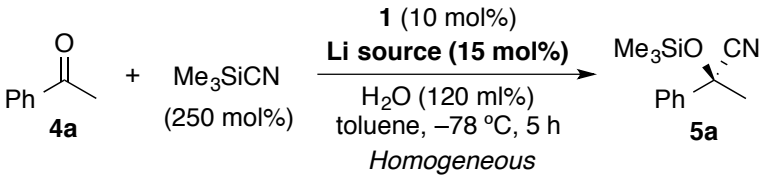
[c] Formaly, $[n\text{-}Bu_4N]^+[Me_3Si(CN)_2]^-$ (soluble) might be provided *in situ*.

2-5-12. Control experiments with the use of other lithium(I) sources.

We have conventionally used *n*-BuLi as lithium(I) source for the catalyst. However, as another useful lithium(I) source in place of *n*-BuLi, LiOH showed almost the same catalytic

activity to that of *n*-BuLi (Table S2, entry 1 and entry 2). In contrast, LiOAc was not effective, and the reaction scarcely proceeded (entry 3).

Table S2. Other lithium(I) sources.



entry	Li source	5a	
		yield (%)	ee (%)
1	***n*-BuLi**	**94**	**91**
2	**LiOH**	**96**	**90**
3	LiOAc	2	–

2-5-13. *In situ*-IR analysis under the optimized reaction conditions.

We performed the *in situ*-IR analysis for monitoring the reaction under the optimized reaction conditions. Peaks at 1677 cm^{-1} for **4a** and 1995 cm^{-1} for **5a** were selected. Results are shown in Figure S14 (3D view and 2D view). Moreover, OH-free cyanohydrin **6a** was not observed during the reaction monitoring.

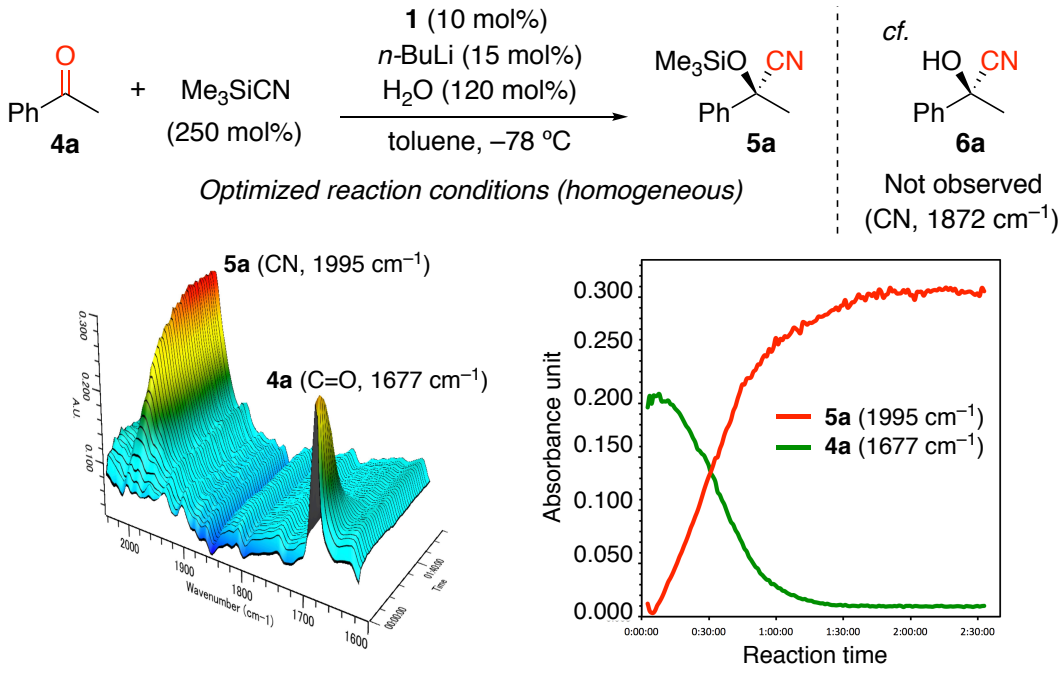
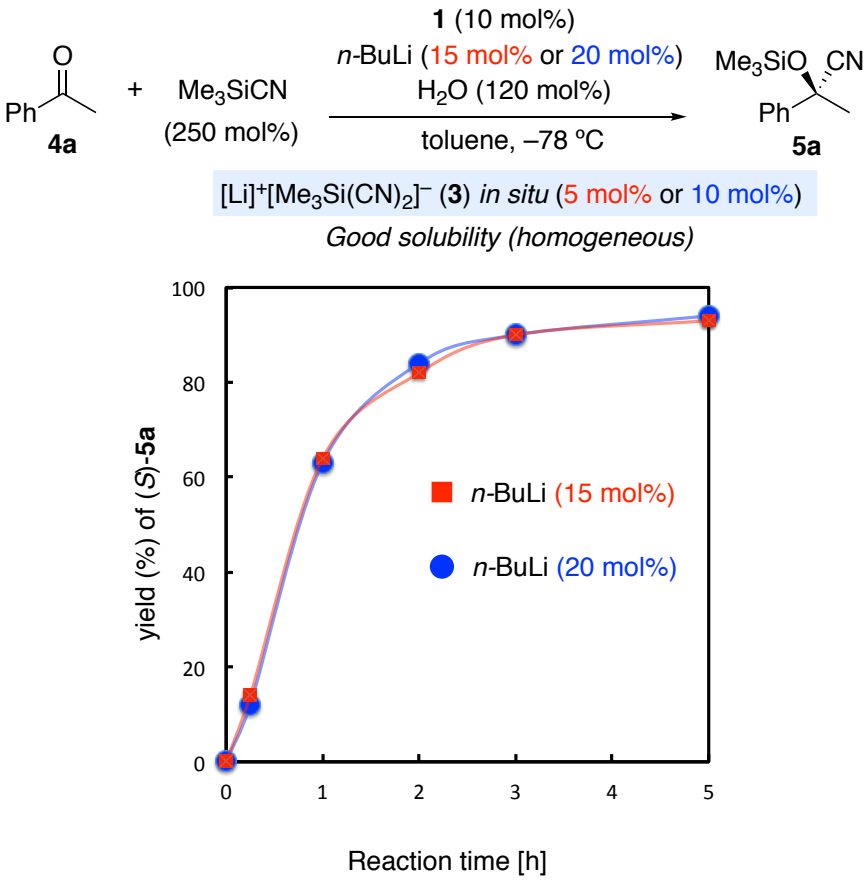


Figure S14. *In situ*-IR analysis (3D view and 2D view)

2-5-14. 15 or 20 mol% of $[Li]^+[Me_3Si(CN)_2]^-$ (3) under the optimized reaction conditions.

We investigated the yield of (*S*)-**5a** under the optimized conditions with the use of 15 or 20 mol% of *n*-BuLi [By the usual method and not by the *in situ*-IR] (Scheme S3). As a result, almost the same values of the yield were observed under the conditions with the use of 15 or 20 mol% of *n*-BuLi. These results strongly suggest that turnover number of the reation might not depend on the amount of $[Li]^+[Me_3Si(CN)_2]^-$ (**3**) (5 or 10 mol%, respectively).

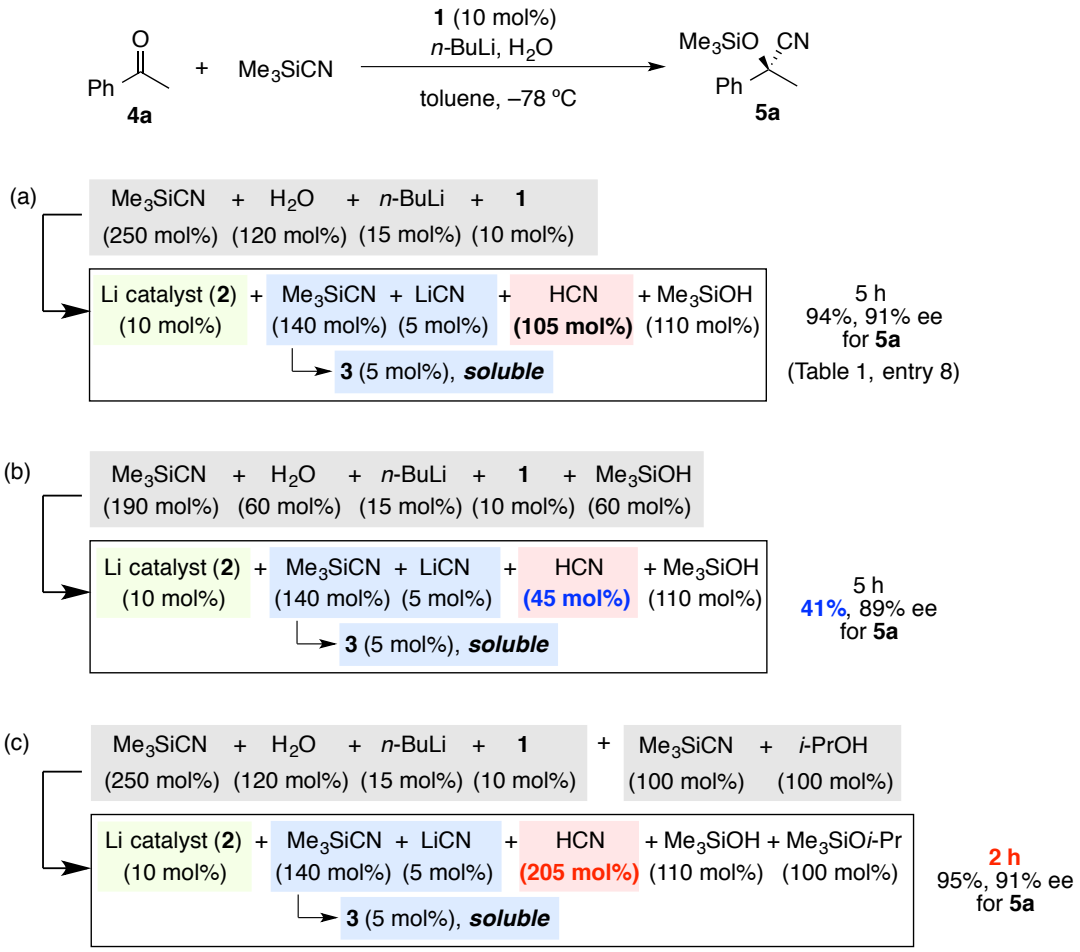


Scheme S3. The yield of (*S*)-**5a** under optimized conditions.

2-5-15. Effect of HCN.

We next examined whether or not the total amount of HCN affects the yield (or reactivity) and enantioselectivity in the probe reaction of **4a** (Scheme S4). We show the standard reaction conditions (105 mol% of HCN) and the corresponding result (5 h, 94% yield with 91% ee for **5a**) in Scheme S4a. When HCN *in situ* was decreased (45 mol%), the reaction proceeded slowly, and **5a** was obtained in 41% yield with 89% ee for 5 h (Scheme S4b). In

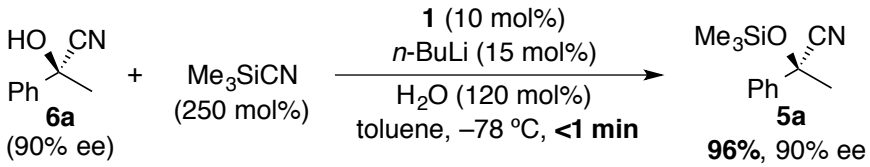
sharp contrast, when HCN *in situ* was increased (205 mol%), the reaction was facilitated, and **5a** was obtained in 95% yield with 91% ee for 2 h (Scheme S4c). Therefore, the total amount of HCN affected the yield, and the excess amount of HCN was significantly effective to promote the reaction. These results strongly support the previous ESI-MS analysis of catalyst **2** with HCN as shown in Figure S7, since **2**–HCN complex was clearly observed with the use of 20 equiv of HCN (i.e., 200 mol% of HCN for 10 mol% of **2**) in Figure S7c.



Scheme S4. Trace experiment of (*S*)-**5a** under optimized conditions. (a) HCN *in situ* was 105 mol% (standard conditions). (b) HCN *in situ* was 45 mol%. (c) HCN *in situ* was 205 mol%.

2-5-16. Trimethylsilylation of cyanohydrin 6a.

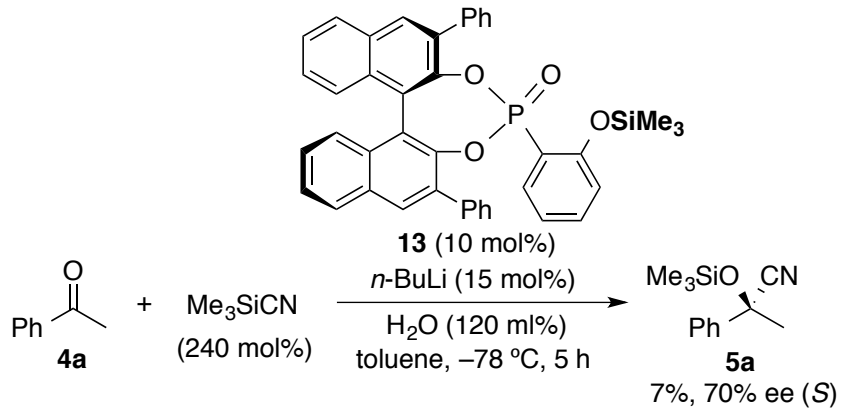
We could not detect OH-free cyanohydrin **6a** directly even by *in situ*-IR analysis. However, we cannot completely rule out transient generation of **6a** by protonation in a large amount of HCN buffer and subsequent quick silylation of **6a**. In a control experiment, isolated cyanohydrin **6a** (90% ee) was quickly trimethylsilylated *within 1 min* under the standard reaction conditions without epimerization (90% ee) (Scheme S5).



Scheme S5. Trimethylsilylation of cyanohydrin **6a**.

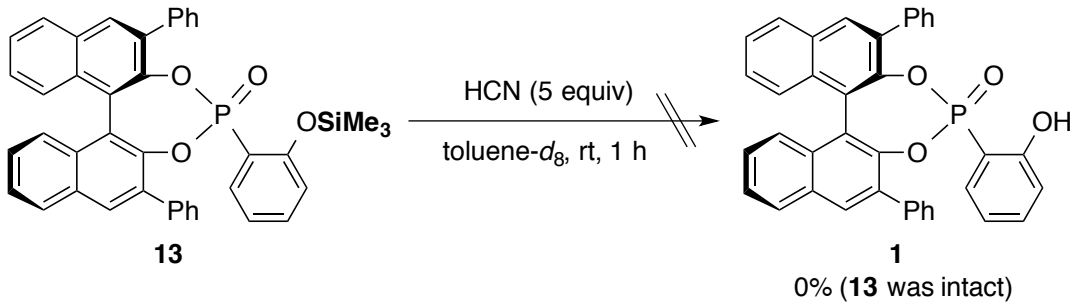
2-5-17. Control experiment with inactive catalyst 13.

To determine whether or not the trimethylsilylated ligand (**13**) would still be active under the reaction conditions, we examined the reaction of **4a** with the use of **13**, which was prepared in advance, under the standard conditions (Scheme S6). As a result, the reaction was sluggish, and the product **5a** was obtained in only 7% yield with 70% ee. This result means that **13** might be an inactive species which would induce low catalytic activity in the reaction.

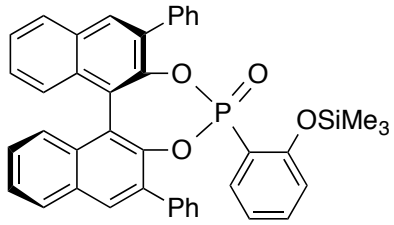


Scheme S6. Control experiment for the inactive catalyst **13**.

Moreover, **13** was intact in the presence of an excess amount of HCN even at room temperature (Scheme S7). Therefore, HCN did not act as proton source (i.e., protone buffer) to regenerate **1** *in situ*.



Scheme S7. Compound **13** in the presence of excess HCN.



(11b*R*)-2,6-Diphenyl-4-(2-((trimethylsilyl)oxy)phenyl)dinaphtho[2,1-d:1',2'-f][1,3,2] dioxaphosphepine 4-oxide (13): ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.15 (s, 9H), 6.43 (t, *J* = 7.8 Hz, 1H), 6.59 (td, *J* = 7.8, 4.6 Hz, 1H), 7.15-7.25 (m, 16H), 7.79 (s, 1H), 7.84 (d, *J* = 6.8 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 8.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.03 (3C), 114.9, 116.7, 119.6, 119.7, 120.3, 120.5, 123.1, 125.6, 125.8, 126.2, 126.4, 127.1 (3C), 127.4, 127.8 (2C), 128.1 (2C), 128.3, 128.3, 129.5 (2C), 130.0 (2C), 130.7, 131.4, 131.5, 132.0, 132.3, 134.3, 134.6, 134.7, 136.6, 137.2, 134.7 (d, *J* = 11.5 Hz), 145.1 (d, *J* = 12.4 Hz), 158.3. ^{31}P NMR (161 MHz, $CDCl_3$) δ 25.2. IR (KBr) 3056, 1593, 1476, 1302, 1251 cm^{-1}. M.p. 158–161 °C (decomposition). $[\alpha]_D^{27}$ = –172.4 (*c* 1.00, $CHCl_3$). HRMS(ESI+) calcd for $C_{41}H_{33}NaO_4PSi$ $[M+Na]^+$ 671.1778, found 671.1778.

2-5-18. Possible transition states.

A plausible transition state (TS-**S2**) for ketones is shown in Figure S15. In TS-**S2**, ketone **4** ($R^1 > R^2$) can be activated at the Lewis acidic Li(I) center. The bulky R^1 moiety would be extended outside of the catalyst. Moreover, attractive bonding between the Lewis basic phenoxide oxygen of the catalyst and the Li(I)-ion of the pentacoordinate silicate $[Li]^+[Me_3Si(CN)_2]^-$ (**3**) might be possible. Olah previously reported that ab initio calculations show that the pentacoordinate silicate has two *N*-bonded diaxial cyano groups with the lowest energy.[15] Consequently, the *re*-face attack of cyanide would preferentially lead to the (*S*)-isomer (**5**). On the other hand, the *si*-face attack in TS-**S3** would be disfavored due to significant steric repulsion between bulky R^1 and the interior of the caytalyst.

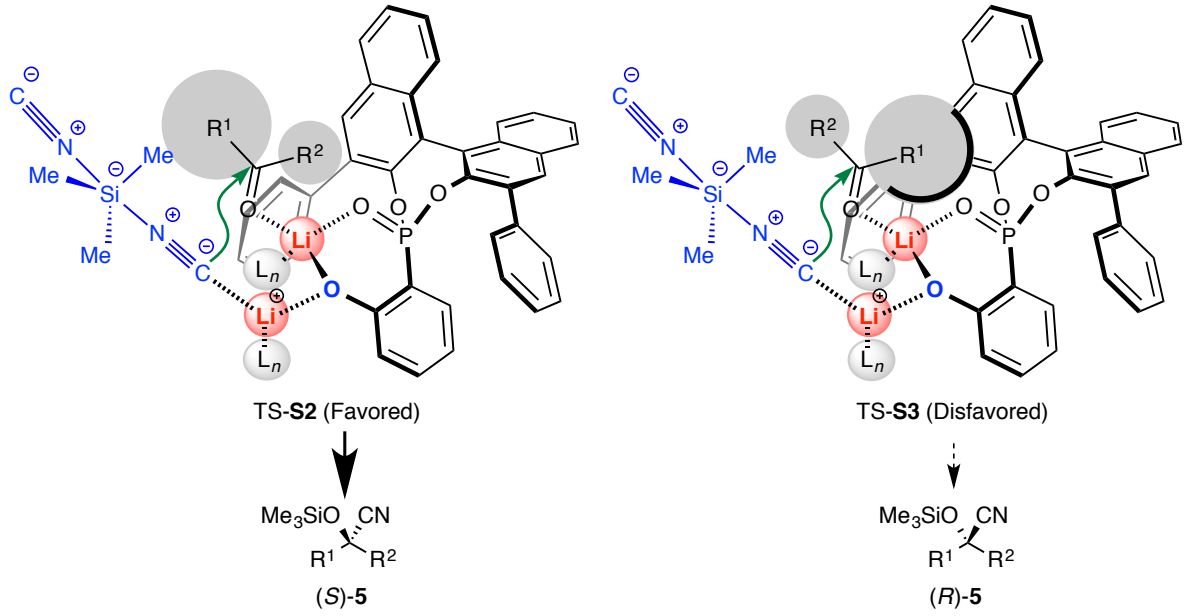
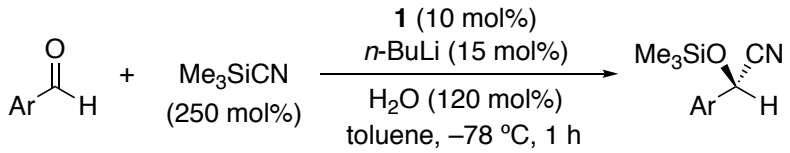


Figure S15. Possible transition states for ketones (L_n = H_2O, HCN, solvent, etc.).

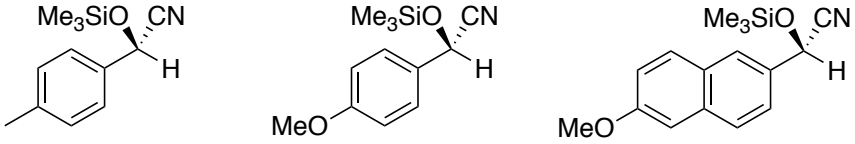
2-5-19. Reaction of aldehydes.

Interestingly, our catalytic system was not effective for aldehydes, and the enantioselectivities were generally low. However, detailed investigations indicated that less reactive aldehydes such as 4-methoxybenzaldehyde and 6-methoxy-2-naphthaldehyde showed higher enantioselectivities than more reactive aldehydes such as 4-methylbenzaldehyde (Scheme S8).[16] While the optimized reaction conditions in our catalytic system should

include multiple cyano-sources *in situ*, highly reactive aldehydes would not be able to discriminate among these mixed cyano-reagents, which might trigger uncontrollable reaction pathways. Therefore, *the most reactive cyano-reagent (i.e., $[Li]^+[Me_3Si(CN)_2]^-$ (**3**)) might predominantly be used for less reactive ketones.* The tendency is summarized in Table S3.



Product, yield, and enantioselectivity.



>99% [48%]^b, 57% ee | 91% [13%]^b, 71% ee | 93% [3%]^b, 85% ee

Scheme S8. Cyanosilylation of aldehydes.[a]

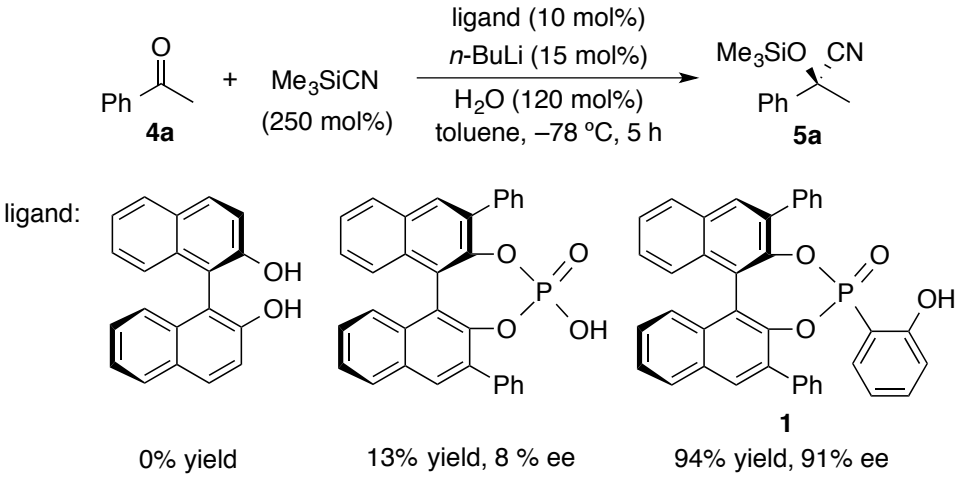
[a] The reaction was carried out with aldehyde (0.5 mmol), Me_3SiCN (250 mol%), **1** (10 mol%), *n*-BuLi (15 mol%), and H_2O (120 mol%) in toluene at –78 °C for 1 h. [b] Yield when the reaction time was 5 min.

Table S3. Summary for the reaction of aldehydes and ketones.

Reagent / Substrate	Me_3SiCN, HCN, or LiCN	$[Li]^+[Me_3Si(CN)_2]^-$ (in the presence of Me_3SiCN, HCN, and LiCN)
Reactive aldehyde	**High conversion** Low ee	**High conversion** Low ee
Less reactive aldehyde	Moderate conversion Low ee	**High conversion** Moderate ee
Ketone	Low conversion Low ee	**High conversion High ee**

2-5-20. Control experiments with our previous catalysts.

We examined the probe reaction with the use of our previous catalysts such as a chiral lithium(I) binaphtholate aqua complex[17] and a chiral lithium(I) phosphate[5] (Scheme S9). However, the reactions scarcely proceed with these catalysts (<15% yield with <10% ee) under the same optimized conditions as in entry 8 of Table 1. Therefore, this catalytic system with silicate **3** turned out to be different from our previous catalytic systems with Me_3SiCN.



Scheme S9. Control experiments with previous catalysts

2-5-21. References.

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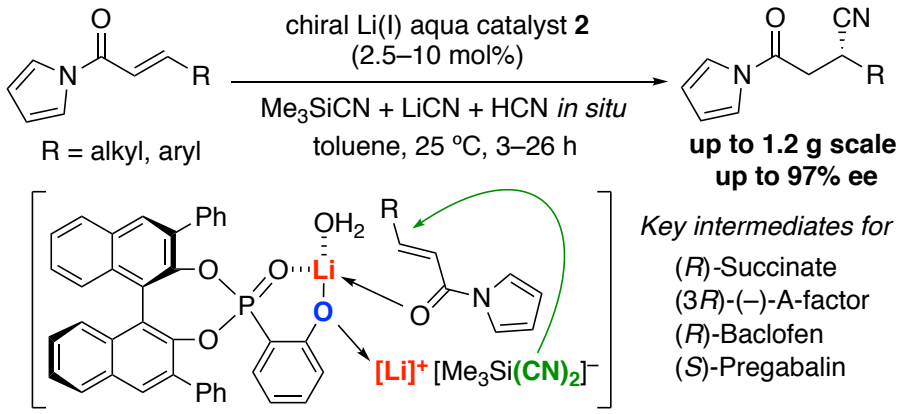
Chapter 3

Chiral Lithium(I) Phosphoryl Phenoxide Catalysts for Enantioselective Conjugate Hydrocyanation of α,β-Unsaturated *N*-Acylpyrroles



ABSTRACT: Enantioselective conjugate hydrocyanation of α,β-unsaturated *N*-acylpyrroles with the combined use of Me_3SiCN, LiCN, and HCN has been developed in the presence of a chiral lithium(I) phosphoryl phenoxide catalyst. This reaction is useful for a variety of *N*-acylpyrroles, including previously unreported substrates, such as heteroaryl and halogen-substituted *N*-cinnamoylpyrroles. A gram-scale reaction and subsequent transformations to a (*R*)-succinate, (*S*)-paraconic acid, and (*R*)-baclofen demonstrate an entry for the practical synthesis of optically active β-substituted γ-aminobutyric acids (GABA).

3-1. Introduction

Catalytic enantioselective cyanation of α,β-unsaturated carboxylic acid derivatives is one of the most useful synthetic methods for obtaining optically active β-substituted γ-aminobutyric acids (GABA). Due to the great importance of GABA-derived natural products, pharmaceuticals, and agro-chemicals,[1] considerable attention has been devoted to this catalysis,[2] particularly since Jacobsen reported the first catalytic enantioselective cyanation of α,β-unsaturated imides with the use of chiral salen-Al(III) catalysts.[3] By taking advantage of the comparable development of chiral catalysts for the cyanation of aldehydes, ketones, imines, and nitroolefins,[2,4,5] chiral Al(III),[3,6] Al(III)/Er(III),[7] Gd(III),[8] Na(I),[9] Sr(II),[10] Ru(II)/Li(I),[11] Mg(II),[12] and Ti(IV)[13] complexes and chiral phase transfer catalysts (PTC)[14] have been shown to be effective for the cyanation of α,β-unsaturated carboxylic acid derivatives. In these reports, the combined use of trimethylsilyl cyanide (Me_3SiCN) and alcohols/phenols (i.e., *in situ* generation of HCN), ethyl cyanoformate, acetone cyanohydrin, KCN, and $K_4[Fe(CN)_6]$[15] were used as cyanide sources. In this regard, we have recently developed the catalytic enantioselective cyanosilylation of ketones with the combined use of Me_3SiCN, LiCN, and HCN in the presence of chiral lithium(I) phosphoryl phenoxide (*R*)-**2** (Figure 1).[16,17a] Indeed, highly nucleophilic lithium(I) dicyanotrimethylsilicate(IV) **3** would be readily generated *in situ* from Me_3SiCN and LiCN,[16,17a] and the catalytic activity of Li(I) aqua complex (*R*)-**2** as an acid–base cooperative catalyst[18] was dramatically increased in the presence of HCN. In this context, we are currently interested in whether or not our catalytic system can be applied to the enantioselective conjugate hydrocyanation of α,β-unsaturated carboxylic acid derivatives instead of ketones (Figure 1). From the viewpoint of poor abundances of lanthanoid and late transition metals in the Earth's crust (worldwide mining production per year; Er:[7] 500 tons, Gd:[8] 400 tons, Ru:[11] 12 tons),[19] a sole use of the lightest Li

(39,000 tons)-catalysts might be helpful in environmental and economical reasons.

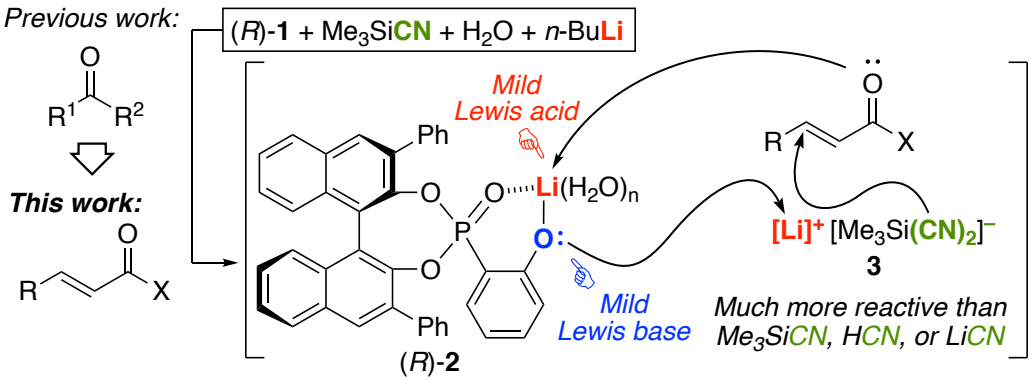


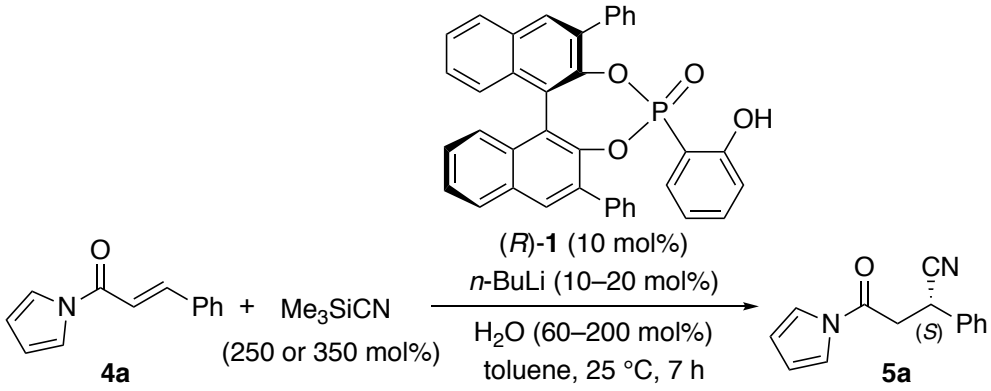
Figure 1. Outline of Conjugate Hydrocyanation by Using Chiral Li(I) Catalyst (*R*)-**2** and Extremely Reactive Cyano Sources.

3-2. Results and Discussion

We initially examined the reaction of highly synthetically useful α,β-unsaturated *N*-acylpyrrole **4a**[20], unlike less practical chalcones or phenyl vinyl ketone derivatives, through the use of chiral BINOL (1,1'-bi-2-naphthol)-derived lithium(I) phosphoryl phenoxide (*R*)-**2** (10 mol%) in toluene at 25 °C for 7 h (Table 1, also see the Experimental Section). Fortunately, under the same reaction conditions as in our previous report[17a] (with 15 mol% of *n*-BuLi, 250 mol% of Me_3SiCN, and 120 mol% of H_2O), the corresponding product **5a** was obtained in 67% yield with 91% ee (entry 2). The yield was slightly improved when 350 mol% of Me_3SiCN was used (entry 3). 60 mol% of water increased the yield but decreased the enantioselectivity to 66% ee (entry 4). On the other hand, the reaction did not proceed when 200 mol% of H_2O was used, where the majority of Me_3SiCN would be converted to HCN (entry 5). The use of 20 mol% of *n*-BuLi was highly effective for improving the yield, and **5a** was obtained in 90% yield with 91% ee and (*R*)-**1** was fully recovered through the workup procedure (entry 6). In contrast, shortage of Li(I)-source for **3** greatly decreased the

yield (entry 1, also see the Experimental Section). Further investigation of the reaction temperature at 15 °C decreased the yield to 52% (entry 7). The use of extra HCN (100 mol%), which was prepared in advance from Me_3SiCN and 2-propanol, was not effective,[21] and the yield was slightly decreased (entry 8). Moreover, racemic **1** showed significantly low catalytic activity (entry 9), which indicates the hetero-dimerization of (*R*)-**2**/(*S*)-**2**[17a] (Also

Table 1. Optimization of the Reaction Conditions[a]



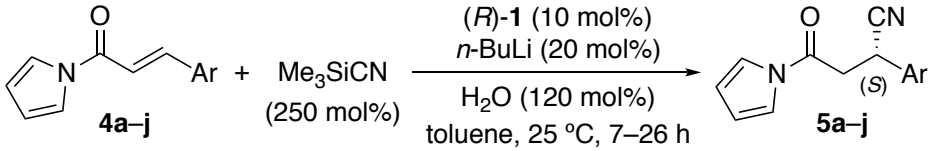
Entry	*n*-BuLi (mol%)	Me_3SiCN (mol%)	H_2O (mol%)	**5a**, yield [%]	**5a**, ee [%]
1	10	250	120	7	53
2	15	250	120	67	91
3	15	350	120	85	90
4	15	250	60	97	66
5	15	250	200	0	–
6	**20**	**250**	**120**	**90**	**91**
7[b]	20	250	120	52	89
8[c]	20	250	120	76	90
9[d]	20	250	120	14	0

[a] The reaction was carried out with **4a** (0.30 mmol), Me_3SiCN (250 or 350 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (10–20 mol%), and H_2O (60–200 mol%) in toluene at 25 °C for 7 h unless otherwise noted. [b] Reaction temperature was 15 °C. [c] Extra HCN (100 mol%) was added. [d] Racemic **1** was used instead of (*R*)-**1**.

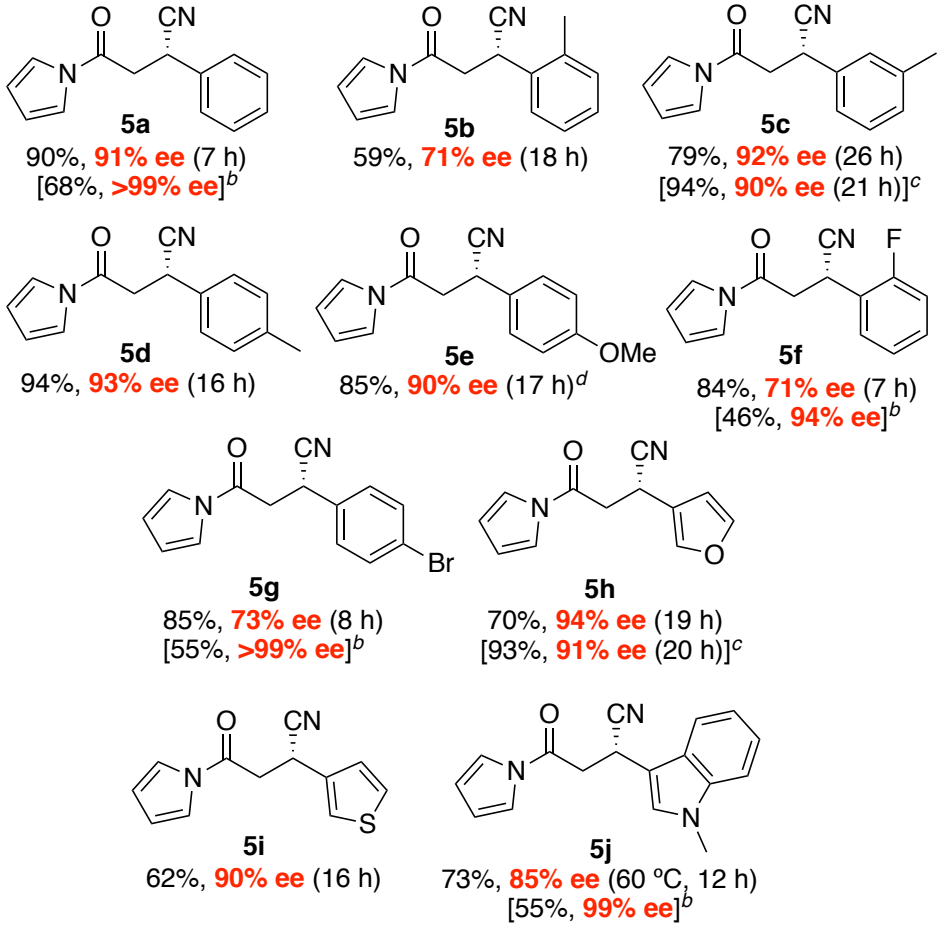
see the positive non-linear effect in the Experimental Section). Overall, the present reaction system with the use of chiral Li(I) catalyst **2** and $[Li]^+[Me_3Si(CN)_2]^-$ **3** was effective for the catalytic enantioselective cyanation of α,β-unsaturated *N*-acylpyrrole **4a**.

With the optimized reaction conditions in hand, we next examined the scope of *N*-(3-aryl)acryloylpyrroles **4a–j** (Scheme 1). We first investigated *o*-, *m*-, and *p*-tolyl-substituted substrates (**4b–d**). As a result, *m*-tolyl **5c** and *p*-tolyl **5d** were obtained with 92% ee and 93% ee, respectively, whereas *o*-tolyl **5b** was obtained in only moderate yield (59%) and enantioselectivity (71% ee). Substrate **4e** with a *p*-anisyl moiety as an electron-donating group gave the corresponding product **5e** in 85% yield with 90% ee. On the other hand, substrates **4f** and **4g** with haloaryl moieties as electron-withdrawing groups gave the corresponding products **5f** with 71% ee and **5g** with 73% ee, respectively. Although the enantioselectivities of **5f** and **5g** were moderate, to the best of our knowledge, this is the first example of the use of halogen-substituted *N*-cinnamoylpyrroles in enantioselective conjugate hydrocyanation.[8a,b,11b,14a] Moreover, previously non-applicable substrates **4h** with 3-furyl, **4i** with 3-thienyl, and **4j** with 3-inolyl moieties as heteroaryl groups gave products **5h** with 94% ee, **5i** with 90% ee, and **5j** with 85% ee. Fortunately, recrystallization of the products **5a**, **5f**, **5g**, and **5j** with moderate enantio-purities increased these values to 94–99% ee without any serious loss of yield (see the results in brackets *b* in Scheme 1). During this crystallization, a crystal of **5g** that was suitable for X-ray analysis was obtained, and the absolute stereochemistry of **5g** was determined to be *S*-configuration (See the Experimental Section).

Scheme 1. Substrate Scope of *N*-Cinnamoylpyrroles



Product **5**, yield, enantioselectivity, and reaction time:[a]

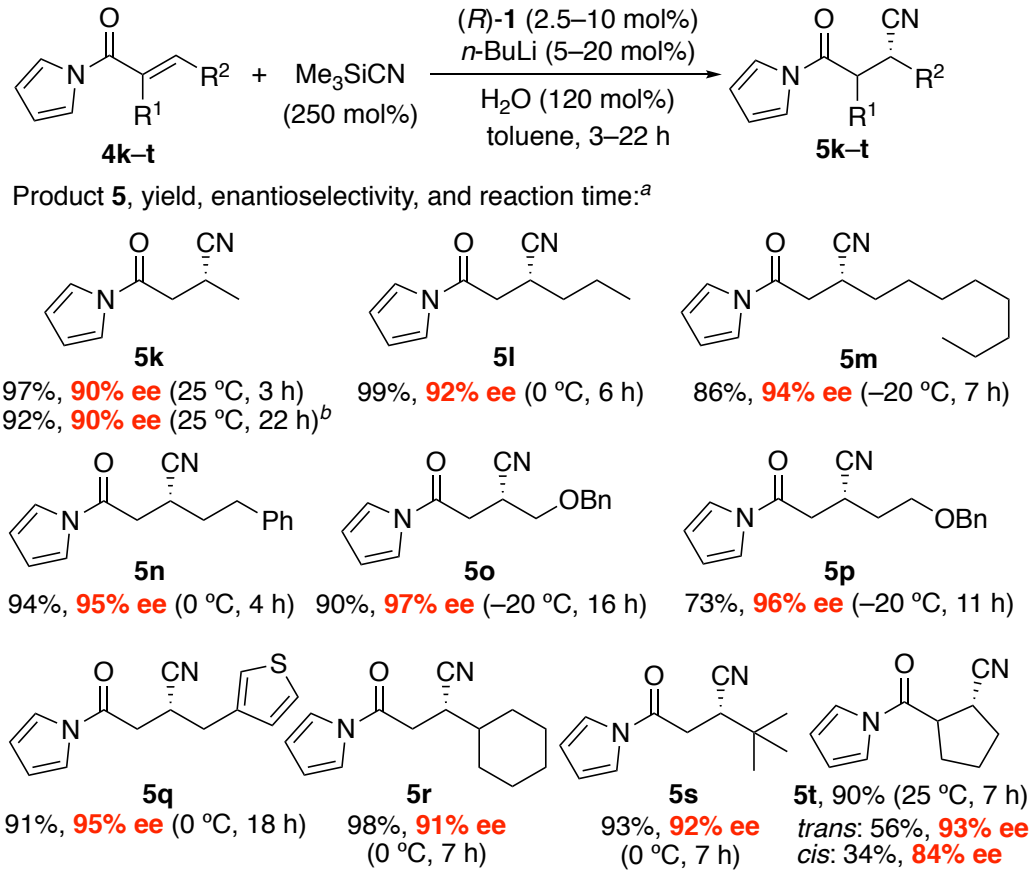


[a] The reaction was carried out with **4** (0.30 mmol), Me$_3$SiCN (250 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (20 mol%), and H$_2$O (120 mol%) in toluene at 25 °C for 7–26 h unless otherwise noted. (*R*)-**1** could be fully recovered (>99%) in all the cases through the routine purification on silica gel column chromatography. [b] Yield and enantio-purity after a recrystallization. [c] 270 mol% of Me$_3$SiCN was used. [d] 300 mol% of Me$_3$SiCN was used.

Encouraged by the relatively wide scope of *N*-(3-aryl)acryloylpyrroles **4a–j** in Scheme 1, we next examined *N*-(3-alkyl)acryloylpyrroles **4k–t** (Scheme 2). Compared to **4a–j**, **4k–t** showed better reactivity, and sometimes the reaction could be conducted at –20 or 0 °C. As

a result, substrates **4k**–**n** with simple *n*-alkyl chains gave the corresponding products **5k**–**n** in high yields with high enantioselectivities (90–95% ee). Although we consistently used 10 mol% of catalyst due to an experimental reason in a small scale, **5k** was obtained indeed in 92% yield with 90% ee even with the use of 2.5 mol% of catalyst. A benzyloxy group could be used in the alkyl chains (i.e., **4o** and **4p**), and the corresponding products **5o** and **5p** were obtained with high enantioselectivities. Substrate **4q** with a terminal thienyl moiety gave **5q** in 91% yield with 95% ee. Substrates **4r** and **4s** with sterically hindered cyclohexyl and

Scheme 2. Substrate Scope of α,β-Unsaturated *N*-(3-Alkyl)acylpyrroles

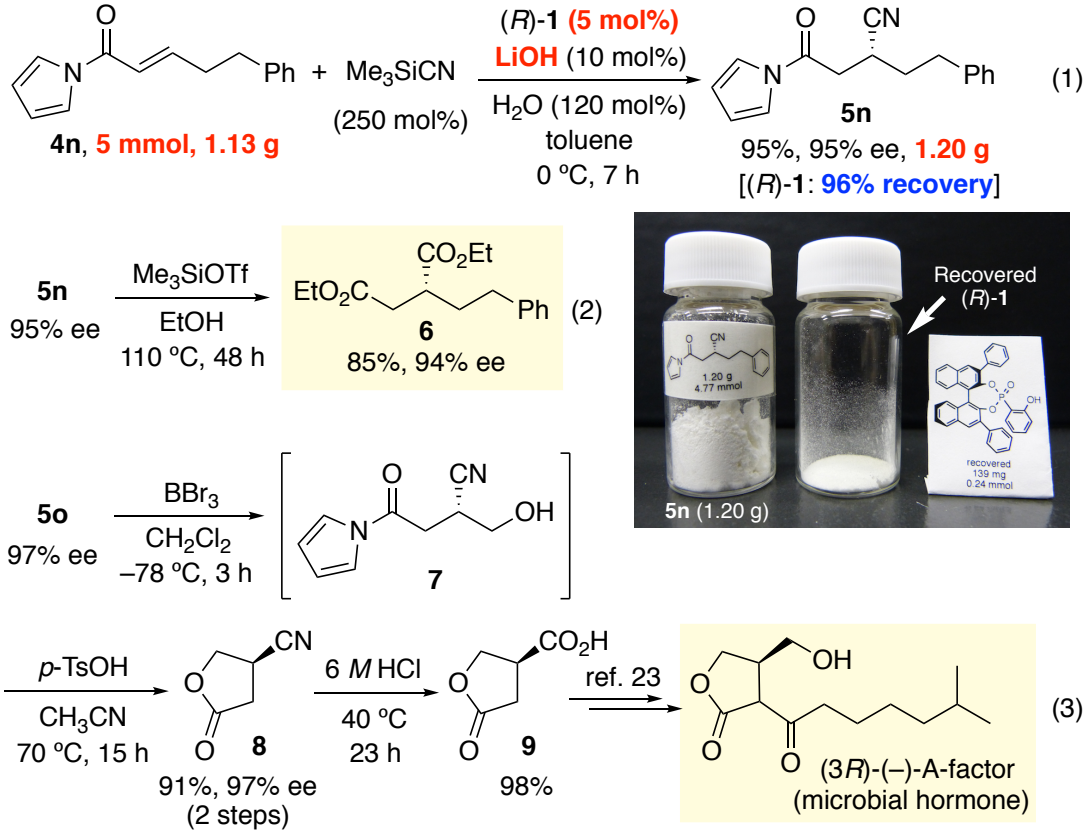


[a] The reaction was carried out with **4** (0.30 mmol), Me_3SiCN (250 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (20 mol%), and H_2O (120 mol%) in toluene at –20, 0, or 25 °C for 3–22 h unless otherwise noted. (*R*)-**1** could be fully recovered (>99%) in all the cases through the routine purification on silica gel column chromatography. [b] 2.5 mol% of catalyst was used.

tert-butyl moieties gave **5r** and **5s** in high yields with 91–92% ee. Moreover, α,β-disubstituted substrate **4t** could be used, and the corresponding **5t** was obtained with high enantioselectivities. The lack of diastereoselectivity in **5t** might be due to non-stereoselective protonation of the lithium(I) enolate intermediates.[8a,b]

To demonstrate the synthetic utility of the present catalysis, we conducted a >1 g-scale synthesis of **5n** (Scheme 3, eq. 1). The reaction proceeded smoothly at 0 °C with the use of 1.13 g (5 mmol) of **4n**. In such a large scale, we could easily reduce (*R*)-**1** to 5 mol%, and, moreover, LiOH instead of *n*-BuLi could be used. Consequently, 1.20 g of **5n** was obtained in 95% yield with 95% ee. It is noted that chemically stable and non-polar (*R*)-**1**, unlike the regarded catalysts such as unstable chiral salens, polar sugar-derivatives and amino acids,[2] could be almost recovered (96%) without any practical difficulties through the routine purification on silica gel column chromatography, although our catalyst's turnover number was not extremely high. **5n** (95% ee) was transformed to synthetically useful 2-alkyl-substituted succinic acid diester **6**, which is usually difficult to synthesize by asymmetric hydrogenation, unlike 2-aryl-substituted succinic acid derivatives,[22] in 85% yield without epimerization by using Me_3SiOTf in ethanol at 110 °C (Scheme 3, eq. 2). Moreover, compound **5o** (97% ee) was transformed to γ-butyrolactone **8** (97% ee) through removal of the Bn moiety by treatment with BBr_3 and then cyclization under acidic conditions (Scheme 3, eq. 3). Hydrolysis of **8** provided biologically active (*S*)-(–)-paraconic acid **9** in 98% yield, which is a key intermediate of microbial hormone (3*R*)-(–)-A-factor.[23] To the best of our knowledge, this is the first example for the catalytic asymmetric synthesis of paraconic acid **9**.[24]

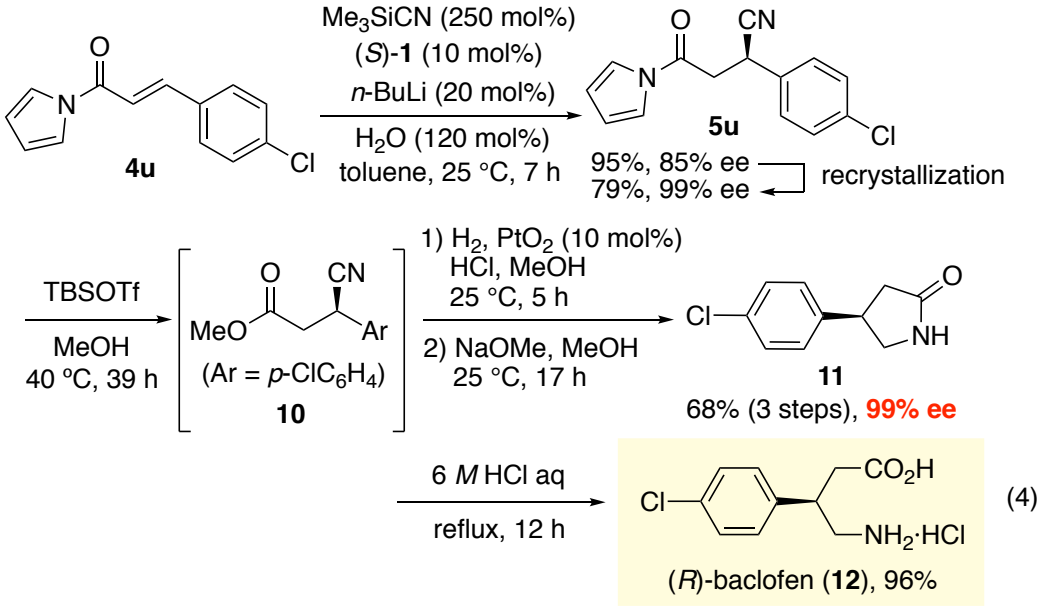
Scheme 3. Synthesis of Succinic Acid Diester **6** and (*S*)-(–)-Paraconic Acid **9**



Moreover, we synthesized (*R*)-baclofen **12**,[25,26] an inhibitory neurotransmitter as a GABA receptor agonist marketed by Novartis and Daiichi-Sankyo (Scheme 4, eq. 4). By taking advantage of our catalyst over halogen-substituted *N*-cinnamoylpyrroles, substrate **4u** was used in the presence of (*S*)-**1**. Fortunately, the corresponding product **5u** was obtained in 95% yield with 85% ee, even though **4u** is a previously disfavoured chloro-substituted *N*-cinnamoylpyrrole.[11b] Recrystallization of **5u** improved the optical purity up to 99% ee. Subsequently, non-epimerized TBSOTf-catalyzed esterification of **5u** gave **10**, followed by PtO_2-catalyzed hydrogenation of **10** and cyclization under basic conditions to give **11** in 68% yield in three steps (Also see the Experimental Section for other reaction conditions.). Finally, hydrolysis of **11** provided (*R*)-baclofen **12** in 96% yield. Moreover, a key intermediate of (*S*)-pregabalin,[3,8a,8b] which is an anticonvulsant GABA receptor agonist by

Pfizer, was synthesized from substrate **4v** in 82% yield with 90% ee (Scheme 4, eq. 5). In this case, recrystallization of **5v** also improved the optical purity up to >99% ee.

Scheme 4. Synthesis of GABA, (*R*)-Baclofen **12**, and (*S*)-Pregabalin



Although further investigation of the actual catalysts is required to fully understand the reaction mechanism,[27] a postulated monomeric structure was considered as a working model, as shown in Figure 2. In TS-**13**, attractive bonding between the Lewis basic phenoxide oxygen of the catalyst and the Li(I)-ion of the pentacoordinate silicate **3** might be possible. In this regard, Olah previously reported that ab initio calculations show that the

pentacoordinate silicate has two *N*-bonded diaxial cyano groups with the lowest energy.[28] More importantly, *trans*-coordination of amide to an acid center (i.e., *trans*-N–C=O···Li) is more likely than *cis*-coordination (i.e., *cis*-N–C=O···Li) due to steric and electronic constraints.[29] In fact, the reactivity of (*Z*)-**4n** was quite low (eq. 6), and this result might strongly support the *trans*-coordination of amide to the lithium(I) center. Overall, the *re*-face attack to **4a** by **3** via TS-**13** would preferentially lead to (*S*)-product **5a** after protonation of the corresponding lithium(I) enolate intermediate **14** with HCN (Also see the Experimental Section).

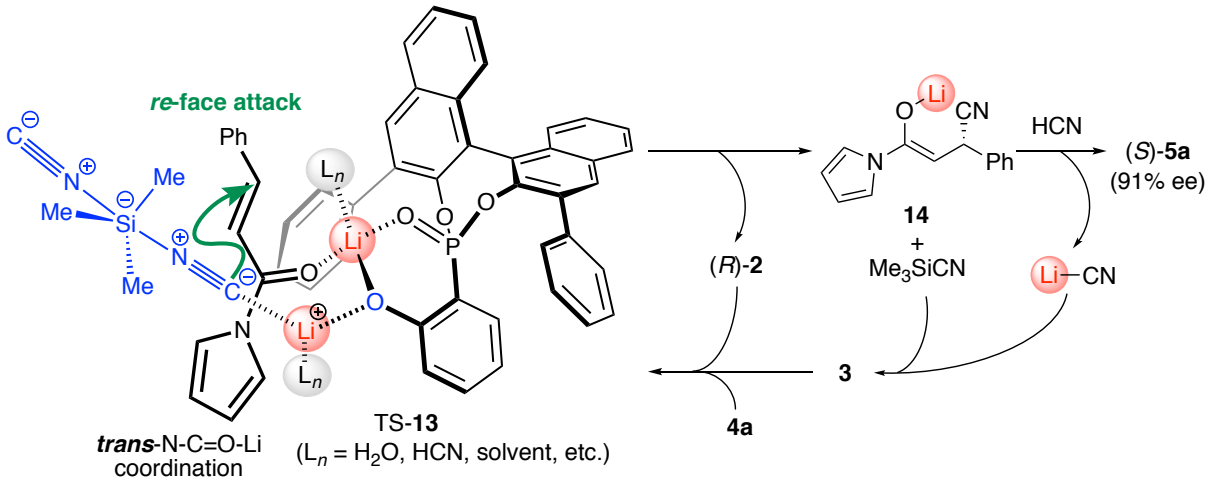
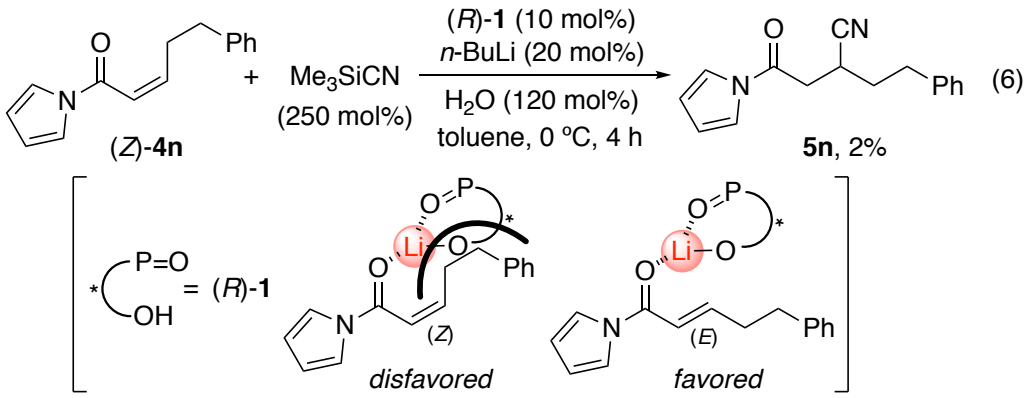


Figure 2. Possible Transition state **13** to (*S*)-**5a**



3-3. Conclusion

In summary, we have developed the enantioselective conjugate hydrocyanation of α,β-unsaturated *N*-acylpyrroles with the use of highly practical and heavy metal-free chiral lithium(I) phosphoryl phenoxide catalyst. A mixture of Me_3SiCN, LiCN, and HCN is a key to promote the reaction. A variety of *N*-acryloylpyrroles were used, some of which have been unsuitable for use with previous catalysts. A gram-scale reaction and transformations of (*R*)-succinic acid derivative, (*S*)-paraconic acid, (*R*)-baclofen, and a key intermediate of (*S*)-pregabalin were demonstrated. Overall, a variety of optically active β-substituted GABA compounds would be accessed much more easily with this powerful conjugate hydrocyanation.

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(17) a) Hatano, M.; Yamakawa, K.; Kawai, T.; Horibe, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 4021. Also see our relevant reports for asymmetric cyanosilylation with chiral Li(I) catalysts. b) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776; c) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776.

(18) Reviews on acid–base combination chemistry, see: a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, *2005*, 1491; b) Ishihara, K.; Sakakura, A.; Hatano, M.

Synlett **2007**, *2007*, 686; c) Ishihara, K. *Proc. Jpn. Acad. Ser. B* **2009**, *85*, 290; d) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117; e) Kumagai, N.; Kanai, M.; Sasai, H. *ACS Catal.* **2016**, *6*, 4699.

(19) a) *CRC Handbook of Chemistry and Physics*, 97th ed, Haynes, W. M. CRC Press, Boca Raton, FL, 2017. b) *Geoscience news and information* (http://geology.com/metals/)

(20) a) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3188; b) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559; c) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. For a review, see: d) Goldys, A. M.; McErlean, C. S. P. *Eur. J. Org. Chem.* **2012**, 1877. Also see, refs. 8a, 8b, 11b, and 14a.

(21) In our previous study in ref. 17a, use of additional HCN was effective for increasing the catalytic activity. In contrast, no significant positive effect on either the yield or enantioselectivity of the product was observed, although the reason for this finding is still not clear.

(22) Recent reports on asymmetric hydrogenation to provide 2-alkyl-substituted succinic acid diesters: a) Bernasconi, M.; Müller, M.-A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5385; b) Wang, M. H.; Cohen, D. T.; Schwamb, C. B.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 5891.

(23) a) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919. See a review: b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43.

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has been limited to one report. c) Parsons, P. J.; Lacroutsa, P.; Bussb, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 437.

(25) a) Olpe, H. R.; Demiéville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133; b) Bowery, N. G. *Trends Pharm. Sci.* **1982**, *3*, 400; c) Allan, R. D.; Bates, M. C.; Drew, C. A.; Duke, R. K.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511; d) Kerr, D. I. B.; Ong, J. *Med. Res. Rev.* **1992**, *12*, 593; e) Ong, J.; Kerr, D. I. S.; Doo-lette, D. J.; Duke, R. K.; Mewett, K. N.; Allen, R. D.; Johnson, G. A. R. *Eur. J. Pharm.* **1993**, *233*, 169.

(26) Baclofen has not been synthesized by enantioselective conjugate hydrocyanation. See the selected papers for catalytic asymmetric synthesis of baclofen. a) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213; b) Schoenfelder, A.; Mann A.; Coz, S. L. *Synlett* **1993**, *1993*, 63; c) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79; d) Corey, E. J.; Zhang, F.-Y.*Org. Lett.* **2000**, *2*, 4257; e) Becht, J.-M.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, *2003*, 2805; f) Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275; g) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; h) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825; i) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307; j) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788; k) Jensen, K. L.; Poulsen, P. H.; Donslund, B. S.; Morana, F.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 1516; l) Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 13688; m) Leyva-Pérez, A.; García-García, P.; Corma, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 8687. Also see a review: n) Ramesh, P.; Suman, D.; Reddy, K. S. N. *Synthesis* **2018**, *50*, 211.

(27) Possible active species in the enantioselective cyanosilylation of ketones have been

discussed in our previous paper, see ref. 17a. Moreover, in this reaction, we also found a positive non-linear effect of **1** and **5a**, which supports the notion that the active species might be monomeric structures in this reaction. The preliminary results are shown in the Experimental Section.

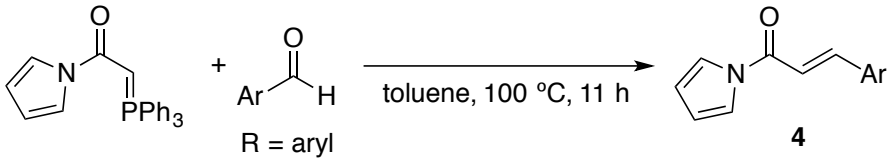
(28) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1990**, *55*, 2016.

(29) In previous reports, Lewis acids (LA) have been considered to coordinate α,β-unsaturated *N*-acylpyrroles in a *trans*-N‐C=O···LA manner. a) Ohshima, T.; Nemoto, T.; Tosaki, S.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 10485; b) Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2016**, *22*, 15192. Also see a review: c) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2015**, *115*, 9922.

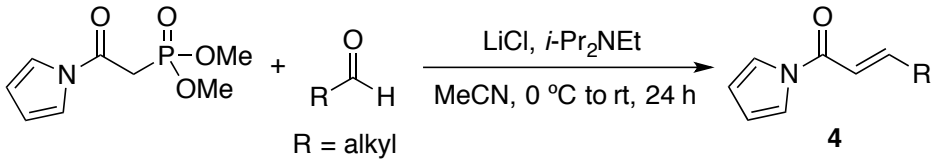
3-5. Experimental Section

3-5-1. General methods. ^{1}H NMR spectra were measured on a JEOL ECS400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the external standard ($CFCl_3$ at 0 ppm). Optical rotations were measured on Rudolph Autopol IV digital polarimeter. The products were purified by column chromatography on silica gel (E. Merck Art. 9385; Kanto Chemical Co., Inc. 37560). High resolution mass spectral analyses were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-T100GCV (EI), Bruker Daltonics micrOTOF-QII (ESI)). Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. X-ray analysis was performed by Rigaku PILATUS-200K. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL, CHIRALPAK; AD-3, AS-3, OD-3, OJ-H, and IA-3. Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 instrument with a flame-ionization detector and a capillary column of CHIRALDEX B-DM and G-TA (i.d., 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60GF254 0.25 mm) were used. Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. In experiments that required dry solvents such as toluene, diethyl ether, dichloromethane, and trimethylsilyl cyanide [**Caution!** Highly toxic] were distilled in prior to use.

3-5-2. Preparation of α,β-unsaturated *N*-acylpyrroles 4

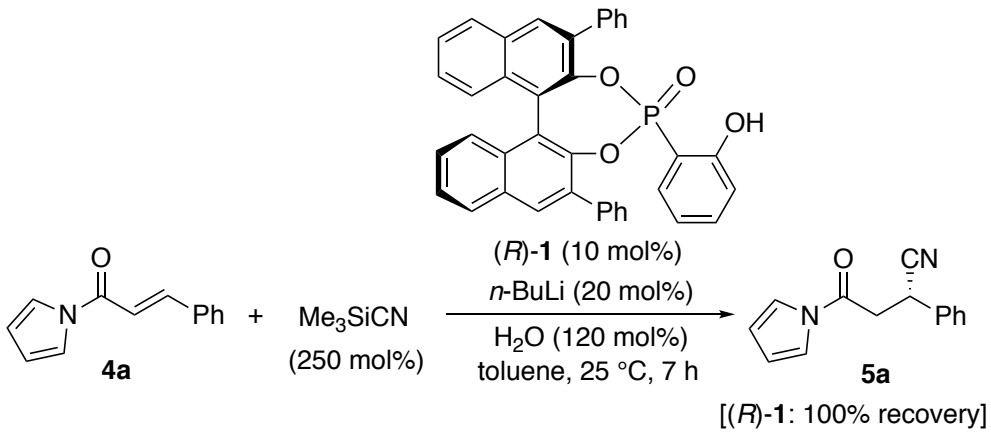


Compounds **4** (Ar = aryl) were prepared on the basis of a literature procedure.[1] To a solution of ylide[1] (960 mg, 2.6 mmol) in toluene (5 mL) was added aromatic aldehyde (2.0 mmol). The mixture was heated to 100 °C and stirred for 11 h. After cooling to room temperature, volatiles were removed under reduced pressure. The resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 6:1) to give the desired products **4** in 31–99% yields (Colorless solid for **4a**–**i** and **4u**; yellow solid for **4j**).

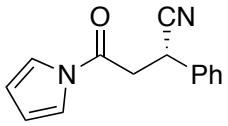


Compounds **4** (R = alkyl) were prepared on the basis of a literature procedure.[2] Lithium chloride (170 mg, 4.0 mmol) in a 50 mL flask was dried by a heat gun under reduced pressure. Phosphonate[2] (478 mg, 2.2 mmol) in acetonitrile (13 mL) and *N*,*N*-diisopropylethylamine (686 mL, 4.0 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 20 min, and then aliphatic aldehyde (2.0 mmol) was added. The mixture was stirred at room temperature for 24 h, and water (10 mL) was added. The mixture was extracted with ethyl acetate (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 10:1) to give the desired products **4** in 90–99% yields (Colorless oil for **4k**–**m** and **4v**; pale yellow solid for **4n** and **4q**; colorless solid for **4r**; pale yellow oil for **4o**, **4p**, **4s**, and **4t**).

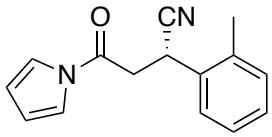
3-5-3. Representative procedure for catalytic enantioselective conjugate hydrocyanation of α,β-unsaturated *N*-acylpyrroles (Schemes 1 and 2)



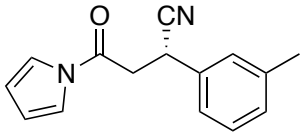
Chiral ligand (*R*)-**1**[3] (17.3 mg, 0.030 mmol, 10 mol%) and water (6.5 mL, 0.36 mmol) were placed in a Schlenk tube under a nitrogen atmosphere and dissolved in dry toluene (1.2 mL). To a stirred solution was added *n*-BuLi (1.63 *M* in *n*-hexane, 36.8 μL, 0.060 mmol, 20 mol%) at 25 °C, and the solution was stirred for 1 h. Substrate **4a** (59.2 mg, 0.30 mmol) was then added at 25 °C. Trimethylsilyl cyanide (93.8 mL, 0.75 mmol) was added dropwise at 25 °C, and the mixture was stirred for 7 h. The resulting mixture was quenched with water (2 mL), extracted with ethyl acetate (5 mL × 2), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1) to give the desired product **5a** in 90% yield (60.7 mg) as colorless solid. The enantiomeric purity of **5a** was determined by HPLC analysis. Chiral ligand (*R*)-**1** could be recovered as some metal salts of (*R*)-**1** through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 10:1) quantitatively. When the recovered ligand would be reused for the catalysis, the further purification with washing 1 *M* HCl aq. is necessary in toluene solution. The organic phase was then concentrated under reduced pressure, and ligand (*R*)-**1** was fully recovered (>99% purity) as colorless solid.



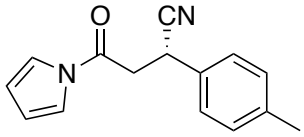
(*S*)-4-Oxo-2-phenyl-4-(1*H*-pyrrol-1-yl)butanenitrile (5a):[4] 90%, 91% ee (TMSCN 250 mol%, 25 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.33 (*n*-hexane:EtOAc = 4:1). Colorless solid. Compound **5a** was recrystallized from *i*-PrOH/*n*-hexane at room temperature (68%, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.57 (dd, *J* = 17.4, 8.2 Hz, 1H), 4.55 (dd, *J* = 7.8, 6.0 Hz, 1H), 6.32 (t, *J* = 2.3 Hz, 2H), 7.26 (br, 2H), 7.34-7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 40.5, 113.9 (2C), 118.8 (2C), 119.9, 127.4 (2C), 128.7, 129.3 (2C), 134.3, 165.9. IR (KBr) 3141, 2244, 1715, 1473, 1282, 1128 cm^{-1}. M.p. 154-155 °C. $[\alpha]_D^{26}$ = –19.6 (*c* 1.00, $CHCl_3$, 91% ee) [lit.[4] $[\alpha]_D^{23}$ = –19.9 (*c* 0.985, $CHCl_3$, for *S* enantiomer with 92% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 28.6 min (major), 38.4 min (minor). HRMS (ESI+) calcd for $C_{14}H_{12}N_2NaO$ $[M+Na]^+$ 247.0842, found 247.0840.



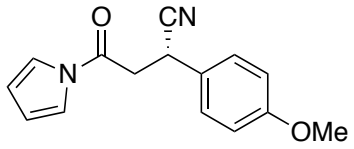
(*S*)-4-Oxo-4-(1*H*-pyrrol-1-yl)-2-(*o*-tolyl)butanenitrile (5b): 59%, 71% ee (TMSCN 250 mol%, 25 °C, 18 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.30 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.28 (dd, *J* = 17,4, 5.5 Hz, 1H), 3.55 (dd, *J* = 17.4, 9.2 Hz, 1H), 4.69 (dd, *J* = 9.2, 5.5 Hz, 1H), 6.33 (t, *J* = 2.3 Hz, 2H), 7.22-7.30 (m, 5H), 7.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 29.4, 39.3, 114.1 (2C), 119.0 (2C), 120.2, 127.3, 127.6, 128.9, 131.6, 132.6, 135.4, 166.2. IR (KBr) 2928, 2244, 1717, 1471, 1407, 1369, 1280, 1122 cm^{-1}. M.p. 76-78 °C. $[\alpha]_D^{26}$ = –38.0 (*c* 1.00, $CHCl_3$, 71% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 17.0 min (major), 26.1 min (minor). HRMS (ESI+) calcd for $C_{15}H_{14}N_2NaO$ $[M+Na]^+$ 261.0998, found 261.0997.



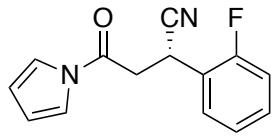
(*S*)-4-Oxo-4-(1*H*-pyrrol-1-yl)-2-(*m*-tolyl)butanenitrile (5c): 76%, 92% ee (TMSCN 250 mol%, 25 °C, 26 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.31 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.33 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.55 (dd, *J* = 17.4, 8.2 Hz, 1H), 4.50 (dd, *J* = 8.2, 6.0 Hz, 1H), 6.31 (t, *J* = 2.8 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.19-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 32.4, 40.7, 114.1 (2C), 119.0 (2C), 120.2, 124.6, 128.2, 129.4, 129.5, 134.3, 139.4, 166.2. IR (KBr) 2930, 2245, 1716, 1473, 1403, 1374, 1296, 1279, 1129, 1068, 1130 cm^{-1}. M.p. 140-143 °C. $[\alpha]_D^{26}$ = –19.6 (*c* 1.00, $CHCl_3$, 92% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 13.0 min (major), 15.0 min (minor). HRMS (ESI+) calcd for $C_{15}H_{14}N_2NaO$ $[M+Na]^+$ 261.0998, found 261.0998.



(*S*)-4-Oxo-4-(1*H*-pyrrol-1-yl)-2-(*p*-tolyl)butanenitrile (5d): 94%, 93% ee (TMSCN 250 mol%, 25 °C, 16 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.31 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.33 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.54 (dd, *J* = 17.4, 8.2 Hz, 1H), 4.50 (dd, *J* = 7.8, 6.4 Hz, 1H), 6.31 (t, *J* = 2.3 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.26 (br, 2H), 7.32 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 32.0, 40.6, 114.0 (2C), 118.8 (2C), 120.1, 127.3 (2C), 130.0 (2C), 131.3, 138.7, 166.0. IR (KBr) 2931, 2245, 1716, 1474, 1293, 1281 1129 cm^{-1}. M.p. 166-170 °C. $[\alpha]_D^{26}$ = –20.8 (*c* 1.00, $CHCl_3$, 93% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 13.5 min (major), 14.9 min (minor). HRMS (ESI+) calcd for $C_{15}H_{14}N_2NaO$ $[M+Na]^+$ 261.0998, found 261.0998.

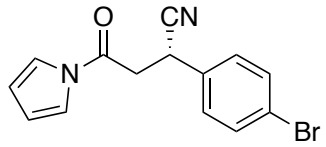


(*S*)-2-(4-Methoxyphenyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5e):[4] 85%, 90% ee (TMSCN 300 mol%, 25 °C, 17 h). Column chromatography (eluent: *n*-hexane:EtOAc = 7:1 to 2:1). Rf = 0.23 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.53 (dd, *J* = 17.4, 7.8 Hz, 1H), 3.81 (s, 3H), 4.49 (t, *J* = 6.9 Hz, 1H), 6.31 (t, *J* = 2.3 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.26 (br, 2H), 7.35 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 40.6, 55.3, 113.9 (2C), 114.7 (2C), 118.8 (2C), 120.2, 126.2, 128.6 (2C), 159.7, 166.0. IR (KBr) 3140, 2245, 1711, 1511, 1474, 1406, 1373, 1286, 1253, 1032 cm^{-1}. M.p. 116-118 °C. $[\alpha]_D^{26}$ = –22.5 (*c* 1.00, $CHCl_3$, 90% ee) [lit.[4] $[\alpha]_D^{25}$ = –16.5 (*c* 1.080, $CHCl_3$, for *S* enantiomer with 90% ee)] HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 9/1, 230 nm, 1.0 mL/min, t_R = 25.7 min (minor), 27.4 min (major). HRMS (ESI+) calcd for $C_{15}H_{14}N_2NaO_2$ $[M+Na]^+$ 277.0947, found 277.0944.



(*S*)-2-(2-Fluorophenyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5f): 84%, 71% ee (TMSCN 250 mol%, 25 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.29 (*n*-hexane:EtOAc = 4:1). Colorless solid. Compound **5f** was recrystallized from EtOAc/*n*-hexane at room temperature (46%, 94% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.55 (dd, *J* = 17.4, 8.7 Hz, 1H), 4.73 (dd, *J* = 8.3, 5.5 Hz, 1H), 6.32 (t, *J* = 2.3 Hz, 2H), 7.26 (br, 2H), 7.14 (m, 1H), 7.22 (td, *J* = 6.4, 1.3 Hz, 1H), 7.38 (m, 1H), 7.56 (td, *J* = 7.8, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 38.5, 114.1 (2C), 116.2 (d, J_{C-F} = 21.0 Hz), 118.8, 118.9 (2C), 121.3 (d, J_{C-F} = 15.3 Hz), 125.1 (d, J_{C-F} = 2.9 Hz), 129.7 (d, J_{C-F} = 2.9 Hz), 130.9 (d, J_{C-F} = 8.6 Hz), 160.0 (d, J_{C-F} = 250 Hz), 165.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.6. IR (KBr) 3141, 2940, 2243, 1713, 1493, 1472, 1405, 1372, 1320, 1274, 1240, 1121, 1067 cm^{-1}. M.p. 121-127 °C (decomposition). $[\alpha]_D^{23}$ = –26.7 (*c* 1.00, $CHCl_3$, 71% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240

nm, 1.0 mL/min, t_R = 13.1 min (major), 15.9 min (minor). HRMS (ESI+) calcd for $C_{14}H_{11}FN_2NaO$ $[M+Na]^+$ 265.0748, found 265.0748.



(*S*)-2-(4-Bromophenyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5g): 85%, 73% ee (TMSCN 250 mol%, 25 °C, 8 h). Column chromatography (eluent: *n*-hexane:EtOAc = 7:1 to 2:1). Rf = 0.25 (*n*-hexane:EtOAc = 4:1). Colorless solid. Compound **5g** was recrystallized from *i*-PrOH/CH_2Cl_2 at room temperature (55%, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (dd, *J* = 16.9, 6.4 Hz, 1H), 3.55 (dd, *J* = 17.4, 7.3 Hz, 1H), 4.52 (t, *J* = 6.9 Hz, 1H), 6.32 (t, *J* = 2.3 Hz, 2H), 7.24 (br, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 40.2, 114.1 (2C), 118.8 (2C), 119.5, 122.8, 129.2 (2C), 132.5 (2C), 133.3, 165.7. IR (KBr) 2933, 2246, 1708, 1473, 1290, 1129 cm^{-1}. M.p. 134-137 ºC. $[\alpha]_D^{27}$ = –21.2 (*c* 1.00, $CHCl_3$, 73% ee). HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 4/1, 230 nm, 1.0 mL/min, t_R = 14.6 min (minor), 17.2 min (major). HRMS (ESI+) calcd for $C_{14}H_{11}BrN_2NaO$ $[M+Na]^+$ 324.9947, found 324.9942.

Crystal data of 5g (Figure S1): Compound **5g** was recrystallized from *i*-PrOH/CH_2Cl_2 at room temperature for 1 day. Formula $C_{14}H_{11}BrN_2O$, colorless, crystal dimensions 0.35 × 0.25 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$ (#19), *a* = 5.1494(9) Å, *b* = 10.5103(18) Å, *c* = 23.635(4) Å, a = 90.00°, b = 90.00°, g = 90.00°, *V* = 838.5(6) $Å^3$, *Z* = 4, r_{calc} = 1.574 g cm^{-3}, F(000) = 608, m(MoKa) = 3.202 mm^{-1}, *T* = 93 K. 10436 reflections collected, 2875 independent reflections with $I > 2s(I)$ ($2q_{max}$ = 27.495°), and 203 parameters were used for the solution of the structure.

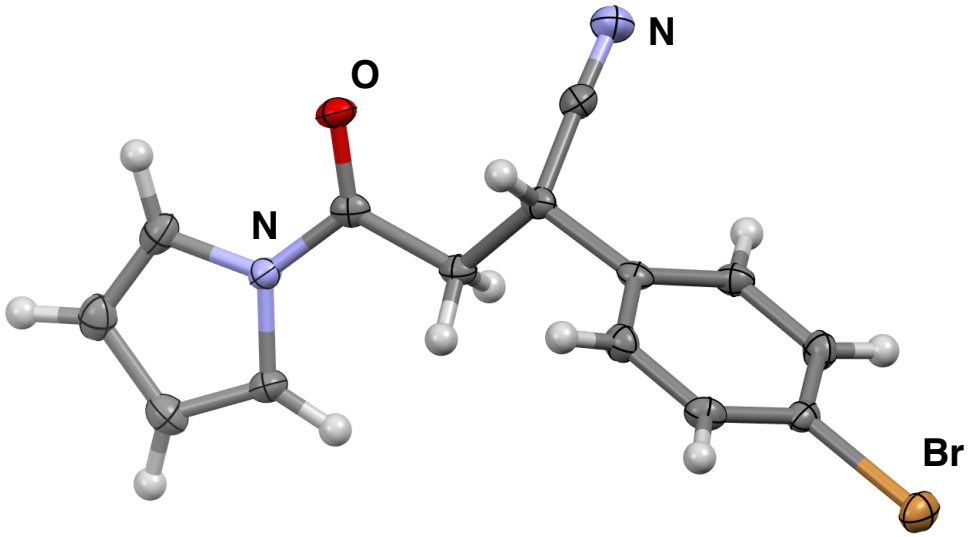
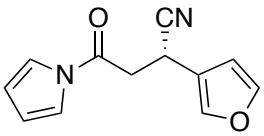


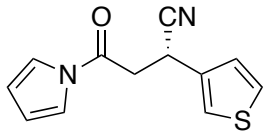
Figure S1. OPTEP drawing of **5g**

The non-hydrogen atoms were refined anisotropically. R_1 = 0.0188 and wR_2 = 0.0391. GOF = 0.967. Flack x parameter = 0.002(4). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1522874. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk; Web page: http://www.ccdc.cam.ac.uk/pages/Home.aspx].

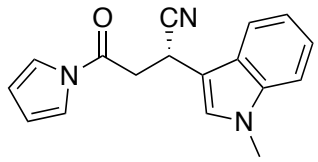


(*S*)-2-(Furan-3-yl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5h): 70%, 94% ee (TMSCN 250 mol%, 25 °C, 19 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.32 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (dd, *J* = 17.0, 6.9 Hz, 1H), 3.50 (dd, *J* = 17.4, 6.9 Hz, 1H), 4.50 (t, *J* = 6.9 Hz, 1H), 6.34 (t, *J* = 2.3 Hz, 2H), 6.45 (d, *J* = 0.9 Hz, 1H), 7.26 (br, 2H), 7.44 (t, *J* = 1.8 Hz, 1H), 7.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 39.3, 109.3, 114.2 (2C), 119.0 (2C), 119.4, 119.5, 140.6,

144.4, 166.1. IR (KBr) 2904, 2249, 1707, 1472, 1413, 1376, 1302, 1263, 1122, 1027 cm^{-1}. M.p. 90-92 °C. $[\alpha]_D^{26}$ = +10.0 (*c* 1.00, $CHCl_3$, 94% ee). HPLC analysis; AS-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 26.7 min (major), 32.9 min (minor). HRMS (ESI+) calcd for $C_{12}H_{10}N_2NaO_2$ $[M+Na]^+$ 237.0634, found 237.0632.

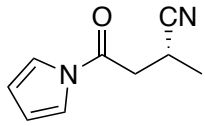


(*S*)-4-Oxo-4-(1*H*-pyrrol-1-yl)-2-(thiophen-3-yl)butanenitrile (5i): 62%, 90% ee (TMSCN 250 mol%, 25 °C, 16 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.29 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.54 (dd, *J* = 16.9, 7.3 Hz, 1H), 4.66 (t, *J* = 6.9 Hz, 1H), 6.33 (t, *J* = 2.3 Hz, 2H), 7.12 (dd, *J* = 4.1, 2.3 Hz, 1H), 7.26 (br, 2H), 7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 39.7, 114.0 (2C), 118.8 (2C), 119.7, 123.5, 126.2, 127.6, 134.0, 165.9. IR (KBr) 2938, 2237, 1707, 1471, 1405, 1372, 1291, 1122, 1067 cm^{-1}. M.p. 109-111 °C. $[\alpha]_D^{24}$ = –5.6 (*c* 1.00, $CHCl_3$, 90% ee). HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 12.8 min (minor), 15.1 min (major). HRMS (ESI+) calcd for $C_{12}H_{10}N_2NaOS$ $[M+Na]^+$ 253.0406, found 253.0405.

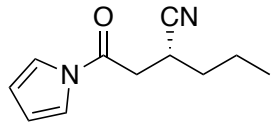


(*S*)-2-(1-Methyl-1*H*-indol-3-yl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5j): 73%, 85% ee (TMSCN 250 mol%, 60 °C, 12 h). Column chromatography (eluent: *n*-hexane:EtOAc = 3:1 to 1:1). Rf = 0.32 (*n*-hexane:EtOAc = 1:1). Yellow solid. Compound **5j** was recrystallized from CH_2Cl_2/*n*-hexane at room temperature (55%, 99% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 3.51 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.59 (dd, *J* = 17.4, 7.8 Hz, 1H), 3.79 (s, 3H), 4.81 (dd, *J* = 7.3, 6.4 Hz, 1H), 6.30 (t, *J* = 2.3 Hz, 2H), 7.17-7.22 (m, 2H), 7.26 (br, 2H), 7.30 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 32.9, 39.3, 107.1, 109.9 (2C), 113.8 (2C), 118.2, 118.8, 120.0, 120.1, 122.5, 125.2,

127.6, 137.2, 166.4. IR (KBr) 2930, 2240, 1721, 1474, 1408, 1373, 1322, 1285, 1256, 1129, 1071 cm^{-1}. M.p. 122-126 °C (decomposition). $[\alpha]_D^{27}$ = –32.8 (*c* 1.00, $CHCl_3$, 85% ee). HPLC analysis; IA-3, *n*-hexane/*i*-PrOH = 1/1, 240 nm, 0.5 mL/min, t_R = 14.7 min (minor), 15.7 min (major). HRMS (ESI+) calcd for $C_{17}H_{15}N_3NaO$ $[M+Na]^+$ 300.1107, found 300.1106

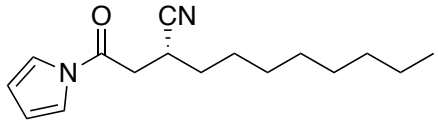


(*R*)-2-Methyl-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5k):[5] 97%, 90% ee (10 mol%-catalysts: TMSCN 250 mol%, 25 °C, 3 h), 92%, 90% ee (2.5 mol%-catalysts: TMSCN 350 mol%, 25 °C, 22 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.33 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.9 Hz, 3H), 3.06 (dd, *J* = 17.0, 6.9 Hz, 1H), 3.24-3.40 (m, 2H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.29 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.0, 38.2, 113.9 (2C), 118.8 (2C), 121.8, 166.3. IR (neat) 3417, 2939, 2244, 1717, 1471, 1407, 1372, 1293, 1115, 1047 cm^{-1}. $[\alpha]_D^{27}$ = +8.3 (*c* 1.00, $CHCl_3$, 90% ee) [lit.[5] $[\alpha]_D^{23}$ = –8.94 (*c* 0.57, $CHCl_3$, for *S* enantiomer with 97% ee)]. HPLC analysis; OJ-H, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 31.7 min (major), 42.0 min (minor). HRMS (ESI+) calcd for $C_9H_{10}N_2NaO$ $[M+Na]^+$ 185.0685, found 185.0687.

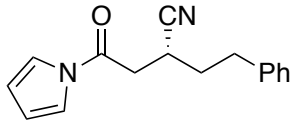


(*R*)-2-(2-Oxo-2-(1*H*-pyrrol-1-yl)ethyl)pentanenitrile (5l):[4] 99%, 92% ee (TMSCN 250 mol%, 0 °C, 6 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.35 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.3 Hz, 3H), 1.47-1.76 (m, 4H), 3.08 (dd, *J* = 19.3, 9.2 Hz, 1H), 3.22-3.32 (m, 2H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.29 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 20.3, 26.6, 33.7, 36.9, 113.8 (2C), 118.8 (2C), 121.0, 166.5. IR (neat) 3147, 2962, 2242, 1716, 1471, 1408, 1374,

1285, 1120 ,1074 cm^{-1}. $[\alpha]_D^{26}$ = +16.4 (*c* 1.00, $CHCl_3$, 92% ee) [lit.[4] $[\alpha]_D^{24}$ = +19.1 (*c* 0.858, $CHCl_3$, for *R* enantiomer with 98% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 9.1 min (major), 10.2 min (minor). HRMS (ESI+) calcd for $C_{11}H_{14}N_2NaO$ $[M+Na]^+$ 213.0998, found 213.1004.

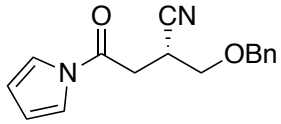


(*R*)-2-(2-Oxo-2-(1*H*-pyrrol-1-yl)ethyl)decanenitrile (5m): 86%, 94% ee (TMSCN 250 mol%, –20 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.38 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.20-1.42 (m, 10H), 1.44-1.66 (m, 2H), 1.71 (q, *J* = 7.3 Hz, 2H), 3.02-3.12 (m, 1H), 3.21-3.30 (m, 2H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.29 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 26.8, 27.0, 28.9, 29.1, 29.2, 31.7, 31.8, 36.9, 113.8 (2C), 118.8 (2C), 121.1, 166.5. IR (KBr) 3146, 2924, 2851, 2243, 1720, 1471, 1406, 1373, 1321, 1276, 1113, 1071 cm^{-1}. M.p. 56-60 °C. $[\alpha]_D^{27}$ = +14.2 (*c* 1.00, $CHCl_3$, 85% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 10.6 min (major), 12.6 min (minor). HRMS (ESI+) calcd for $C_{16}H_{24}N_2NaO$ $[M+Na]^+$ 283.1781, found 283.1776.

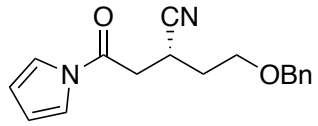


(*R*)-4-Oxo-2-phenethyl-4-(1*H*-pyrrol-1-yl)butanenitrile (5n):[6] 94%, 95% ee (TMSCN 250 mol%, 0 °C, 4 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.31 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (q, *J* = 7.3 Hz, 2H), 2.79-2.88 (m, 1H), 2.93-3.12 (m, 2H), 3.19-3.30 (m, 2H), 6.32 (t, *J* = 1.8 Hz, 2H), 7.20-7.35 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 33.1, 33.3, 36.8, 113.9 (2C), 118.8 (2C), 120.7, 126.5, 128.3 (2C), 128.7 (2C), 139.5, 166.3. IR (KBr) 2920, 2244, 1710, 1471, 1402, 1376, 1277, 1122, 1072 cm^{-1}. M.p. 92-94 °C. $[\alpha]_D^{26}$ = +23.0 (*c* 1.00, $CHCl_3$, 95% ee) [lit.[6] $[\alpha]_D^{23}$ = –21.7 (*c* 0.88, $CHCl_3$, for *S* enantiomer with 95% ee)]. HPLC

analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 22.9 min (major), 25.6 min (minor). HRMS (ESI+) calcd for $C_{16}H_{16}N_2NaO$ $[M+Na]^+$ 275.1155, found 275.1150.

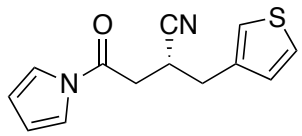


(*R*)-2-((Benzyloxy)methyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5o):[6] 90%, 97% ee (TMSCN 250 mol%, –20 °C, 16 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 3:1). Rf = 0.24 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (dd, *J* = 17.4, 6.9 Hz, 1H), 3.33 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.50 (m, 1H), 3.69-3.78 (m, 2H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 6.33 (t, *J* = 2.3 Hz, 2H), 7.24-7.38 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 33.6, 67.8, 73.4, 113.9 (2C), 118.9 (2C), 119.5, 127.7 (2C), 128.1, 128.5 (2C), 136.9, 166.5. IR (neat) 2870, 2248, 1717, 1471, 1408, 1372, 1319, 1291, 1110 cm^{-1}. $[\alpha]_D^{25}$ = –8.8 (*c* 1.00, $CHCl_3$, 97% ee) [lit.[6] $[\alpha]_D^{22}$ = +7.87 (*c* 0.34, $CHCl_3$, 92% ee)]. HPLC analysis; IA-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 10.4 min (major), 12.0 min (minor). HRMS (ESI+) calcd for $C_{16}H_{16}N_2NaO_2$ $[M+Na]^+$ 291.1104, found 291.1100.

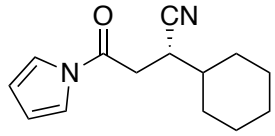


(*R*)-2-(2-(Benzyloxy)ethyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5p): 73%, 96% ee (TMSCN 250 mol%, –20 °C, 11 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 3:1). Rf = 0.24 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (q, *J* = 6.0 Hz, 2H), 3.18 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.25 (dd, *J* = 17.4, 6.8 Hz, 1H), 3.52 (quint, *J* = 6.8 Hz, 1H), 3.65-3.75 (m, 2H), 4.52 (s, 2H), 6.31 (t, *J* = 2.8 Hz, 2H), 7.24 (br, 2H), 7.27-7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 31.5, 36.6, 66.7, 73.2, 113.7 (2C), 118.8 (2C), 120.7, 127.7 (2C), 127.8, 128.4 (2C), 137.7, 166.5. IR (KBr) 2865, 2241, 1703, 1474, 1409, 1375, 1298, 1273, 1092 cm^{-1}. M.p. 64-67 °C. $[\alpha]_D^{27}$ = +7.8 (*c* 1.00, $CHCl_3$, 75% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min,

t_R = 17.6 min (minor), 38.5 min (major). HRMS (ESI+) calcd for $C_{17}H_{18}N_2NaO_2$ $[M+Na]^+$ 305.1260, found 305.1259.

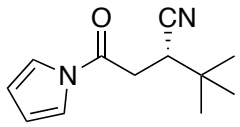


(*R*)-4-Oxo-4-(1*H*-pyrrol-1-yl)-2-(thiophen-3-ylmethyl)butanenitrile (5q): 91%, 95% ee (TMSCN 250 mol%, 0 °C, 18 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.32 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (dd, *J* = 17.9, 6.9 Hz, 1H), 3.11 (d, *J* = 6.9 Hz, 2H), 3.19 (dd, *J* = 17.4, 6.9 Hz, 1H), 3.53 (quin, *J* = 6.8 Hz, 1H), 6.33 (t, *J* = 2.3 Hz, 2H), 7.05 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.16 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.26 (br, 2H), 7.34 (dd, *J* = 5.0, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 31.7, 35.7, 114.0 (2C), 118.8 (2C), 120.8, 123.4, 126.7, 127.9, 135.9, 166.3. IR (neat) 3146, 3105, 2927, 2244, 1713, 1470, 1408, 1372, 1328, 1289, 1121, 1075, 1049 cm^{-1}. $[\alpha]_D^{27}$ = –4.4 (*c* 1.00, $CHCl_3$, 94% ee). HPLC analysis; AS-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 25.5 min (major), 30.5 min (minor). HRMS (ESI+) calcd for $C_{13}H_{12}N_2NaOS$ $[M+Na]^+$ 267.0563, found 267.0562.

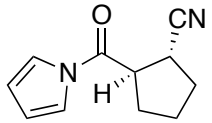


(*S*)-2-Cyclohexyl-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5r):[6] 98%, 91% ee (TMSCN 250 mol%, 0 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.30 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.36 (m, 5H), 1.58-1.73 (m, 2H), 1.74-1.93 (m, 4H), 3.11 (m, 1H), 3.17-3.27 (m, 2H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.30 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.7, 25.8, 28.9, 31.3, 33.0, 34.5, 38.7, 113.8 (2C), 118.8 (2C), 120.2, 166.8. IR (KBr) 2931, 2238, 1713, 1472, 1405, 1373, 1321, 1285, 1114 cm^{-1}. M.p. 110-112 °C. $[\alpha]_D^{28}$ = –2.8 (*c* 1.00, $CHCl_3$, 91% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 12.2 min (major), 14.0 min (minor). HRMS (ESI+) calcd for $C_{14}H_{18}N_2NaO$ $[M+Na]^+$ 253.1311, found

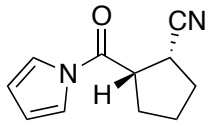
253.1313.



(*S*)-2-(*tert*-Butyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5s):[4] 93%, 92% ee (TMSCN 250 mol%, 0 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.32 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.02-3.21 (m, 3H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.32 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (3C), 32.9, 33.1, 38.4, 113.8 (2C), 118.9 (2C), 120.4, 167.1. IR (KBr) 2972, 2239, 1714, 1470, 1407, 1375, 1328, 1293, 1270, 1122, 1073 cm^{-1}. M.p. 125-129 °C. $[\alpha]_D^{27}$ = –38.4 (*c* 1.00, $CHCl_3$, 92% ee) [lit.[4] $[\alpha]_D^{25}$ = –34.5 (*c* 1.048, $CHCl_3$, for *S* enantiomer with 90% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 9.5 min (minor), 12.0 min (major). HRMS (ESI+) calcd for $C_{12}H_{16}N_2NaO$ $[M+Na]^+$ 227.1155, found 227.1149.

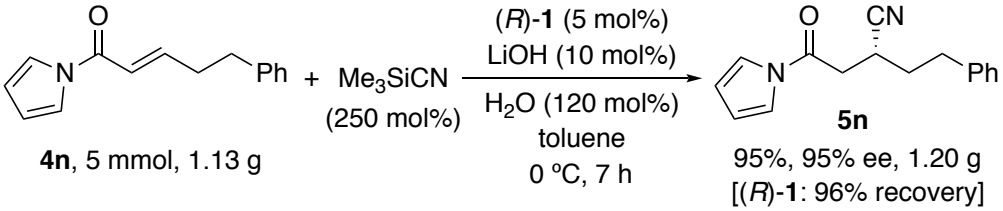


(1*R*,2*R*)-2-(1*H*-Pyrrole-1-carbonyl)cyclopentane-1-carbonitrile (*trans*-5t):[4] 56%, 93% ee (TMSCN 250 mol%, 25 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.38 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.99 (m, 3H), 2.06 (m, 1H), 2.23-2.39 (m, 2H), 3.52 (q, *J* = 6.8 Hz, 1H), 3.71 (td, *J* = 9.6, 6.4 Hz, 1H), 6.35 (t, *J* = 2.8 Hz, 2H), 7.32 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 30.7, 31.5, 31.7, 48.2, 113.9 (2C), 119.2 (2C), 121.7, 170.1. IR (neat) 3147, 2967, 2877, 2241, 1711, 1599, 1470, 1375, 1292, 1121, 1074 cm^{-1}. $[\alpha]_D^{26}$ = –123.6 (*c* 1.00, $CHCl_3$, 93% ee) [lit.[4] $[\alpha]_D^{25}$ = –119.8 (*c* 1.595, $CHCl_3$, for (1*R*,2*R*)-enantiomer with 86% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 7.6 min (major), 8.4 min (minor). HRMS (ESI+) calcd for $C_{11}H_{12}N_2NaO$ $[M+Na]^+$ 211.0842, found 211.0840.



(1*R*,2*S*)-2-(1*H*-Pyrrole-1-carbonyl)cyclopentane-1-carbonitrile (*cis*-5t):[4] 34%, 84% ee (TMSCN 250 mol%, 25 °C, 7 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.29 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (m, 1H), 2.00-2.38 (m, 5H), 3.10 (q, *J* = 7.8 Hz, 1H), 3.73 (q, *J* = 7.8 Hz, 1H), 6.34 (t, *J* = 2.8 Hz, 2H), 7.32 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 29.5, 30.9, 32.5, 45.8, 113.8 (2C), 119.1 (2C), 119.6, 169.2. IR (KBr) 2957, 2240, 1713, 1470, 1375, 1279, 1126, 1076 cm^{-1}. M.p. 54-65 °C (decomposition). $[\alpha]_D^{26}$ = +23.6 (*c* 1.00, $CHCl_3$, 84% ee) [lit.[4] $[\alpha]_D^{26}$ = +21.1 (*c* 1.265, $CHCl_3$, for (1*R*,2*S*)-enantiomer with 84% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm 1.0 mL/min, t_R = 8.5 min (minor), 9.6 min (major). HRMS (ESI+) calcd for $C_{11}H_{12}N_2NaO$ $[M+Na]^+$ 211.0842, found 211.0841.

3-5-4. Gram scale synthesis of 5n (Eq. 1)



4n, 5 mmol, 1.13 g

95%, 95% ee, 1.20 g
[(*R*)-**1**: 96% recovery]

Chiral ligand (*R*)-**1** (144.1 mg, 0.25 mmol, 5 mol%) and lithium hydroxide monohydrate (21.0 mg, 0.50 mmol, 10 mol%) dissolved in water (108 mL, 6.0 mmol) were placed in a Schlenk tube under a nitrogen atmosphere and dissolved in dry toluene (20 mL), and the solution was stirred for 2 h. Substrate **4n** (1.13 g, 5.0 mmol) was then added at 25 °C and the mixture was stirred at 0 °C for 20 min. Trimethylsilyl cyanide (1.56 mL, 12.5 mmol) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 7 h. The resulting mixture was quenched with water (10 mL) at 0 °C extracted with ethyl acetate (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 4:1) to give the desired product **5n** in 95% yield (1.20 g). The enantiomeric purity of **5n** was determined by HPLC analysis. Chiral ligand (*R*)-**1** could be recovered as some metal salts of (*R*)-**1** through the same silica gel column chromatography (eluent: $CHCl_3$:MeOH = 10:1) almost quantitatively. When the recovered ligand would be reused for the catalysis, the further purification with washing 1 *M* HCl aq. is necessary in toluene solution. The organic phase was then concentrated under reduced pressure, and ligand (*R*)-**1** was obtained (138.8 mg, 96%, >99% purity) as colorless solid (Figure S2).

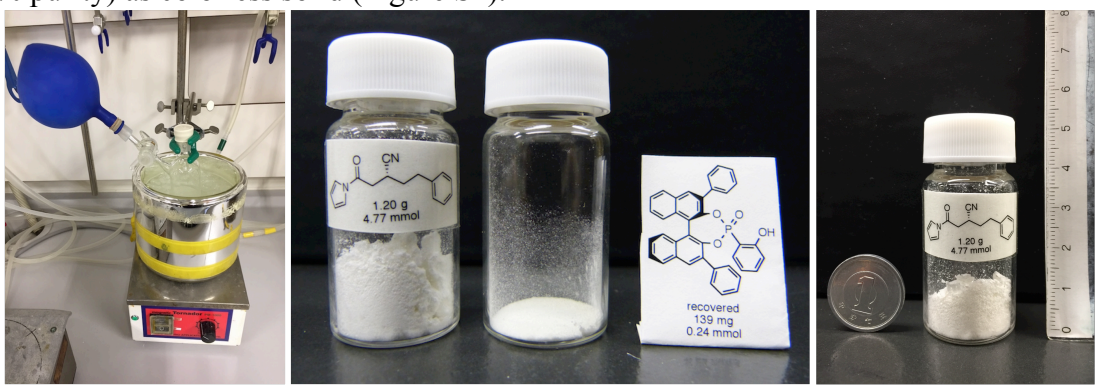
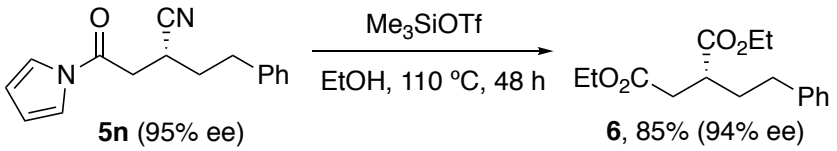


Figure S2. Gram scale synthesis of **5n**.

3-5-5. Transformation of products 5n to optically active succinic acid diester 6 (Eq. 2)

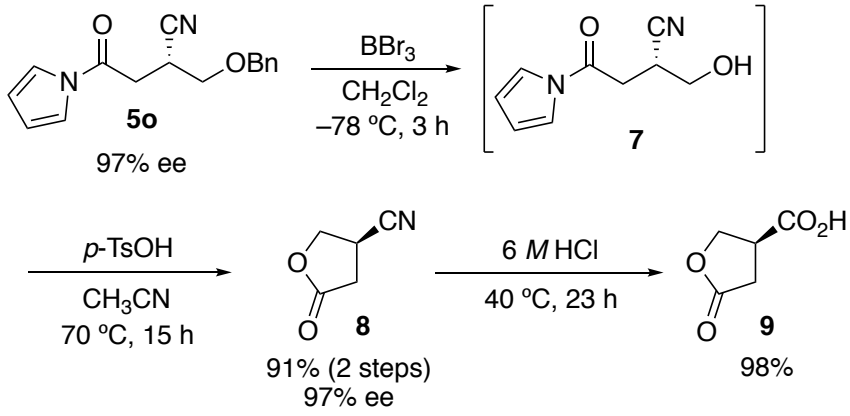


5n (95% ee) **6**, 85% (94% ee)

On the basis of a literature procedure.[7] To a suspension of **5n** (37.8 mg, 0.15 mmol) in ethanol (1.5 mL), trimethylsilyl triflate (136 mL, 0.75 mmol) was added dropwise at room temperature. The mixture was then allowed to heat at 110 °C and stirred for 10 h. Monitoring the reaction by TLC, the mixture was cooled to room temperature, and trimethylsilyl triflate (136 mL, 0.75 mmol) was added dropwise. The mixture was then allowed to heat at 110 °C and stirred for 30 h. Monitoring the reaction by TLC, the mixture was cooled to room temperature, and trimethylsilyl triflate (136 mL, 0.75 mmol) was added dropwise. The mixture was then allowed to heat at 110 °C and stirred for 8 h. Monitoring the reaction by TLC, the resulting mixture was quenched with water (5 mL) at 0 °C, filtered through celite pad, extracted with ethyl acetate (10 mL × 3), and washed with brine (10 mL). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 10:1) to give the desired product **6** as pale blown oil in 85% yield (35.3 mg). The enantiomeric purity of **6** was determined by HPLC analysis.

Diethyl (*R*)-2-phenethylsuccinate (6):[8] Pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.82 (m, 1H), 1.99 (m, 1H), 2.47 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.57-2.69 (m, 2H), 2.75 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.88 (m, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 4.17 (qd, *J* = 6.9, 2.3 Hz, 2H), 7.15-7.24 (m, 3H), 7.25-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 33.2, 33.6, 36.2, 40.9, 60.6, 60.7, 126.0, 128.3 (2C), 128.4 (2C), 141.2, 171.8, 174.7. IR (neat) 2981, 1733, 1455, 1374, 1259, 1175, 1031 cm^{-1}. $[\alpha]_D^{27}$ = +29.7 (*c* 1.00, $CHCl_3$, 94% ee). HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min, t_R = 8.1 min (major), 10.3 min (minor). HRMS (ESI+) calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$ 301.1410, found 301.1410.

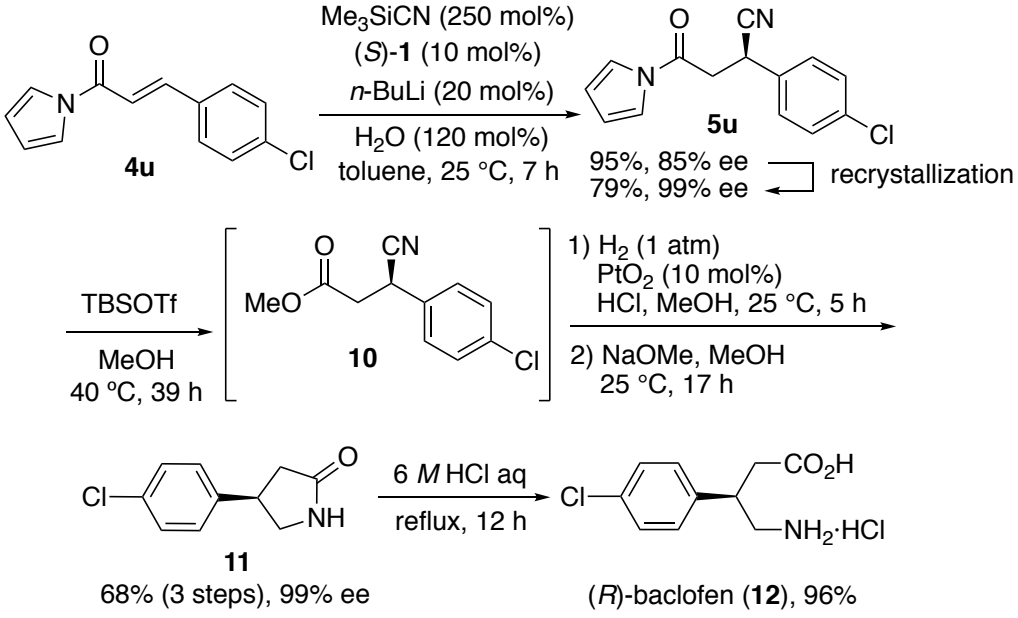
3-5-6. Trnasformation of products 5o to optically active (*S*)-(–)-paraconic acid 9 (Eq. 3)



(*R*)-5-Oxotetrahydrofuran-3-carbonitrile (8): To a solution of **5o** (61.0 mg, 0.23 mmol, 97% ee) in dichloromethane (2.3 mL), boron tribromide (1 *M* in dichloromethane, 340 mL, 0.34 mmol) was added at –78 °C.[9] The mixture was stirred at –78 °C for 3 h, and then purified by frash neutral silica gel column chromatography (eluent: $CHCl_3$:EtOAc = 3:1) to give the desired compound **7**. Compound **7** was immediately used without further purification. To a solution of **7** in acetonitrile (5 mL), *p*-toluenesulfonic acid anhydrate (58.7 mg, 0.34 mmol) was added, and the mixture was stirred at 70 °C for 12 h. Monitoring the reaction by TLC, *p*-toluenesulfonic acid anhydrate (58.7 mg, 0.34 mmol) was added, and the mixture was stirred at 70 °C for additional 3 h. The mixture was allowed to cool to room temperature, and diluted with water (10 mL). The mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: $CHCl_3$:EtOAc = 3:1) to give the desired product **8** as colorless oil in 91% yield (23.4 mg). The enantiomeric purity of **8** was determined by chiral GC analysis ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (dd, J = 17.9, 8.3 Hz, 1H), 2.95 (dd, J = 17.9, 9.2 Hz, 1H), 3.55 (quintet, J = 7.8 Hz, 1H), 4.47 (dd, J = 9.6, 6.9 Hz, 1H), 4.60 (dd, J = 9.2, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 31.7, 68.3, 117.7, 172.4. IR (neat) 3544, 2957, 2251, 1790, 1416, 1382, 1335, 1170, 1040 cm^{-1}. $[\alpha]_D^{22}$ = –26.8 (*c* 1.00, $CHCl_3$, 97% ee). GC analysis; CHIRALDEX G-TA, 100 °C to 115 °C (+5 °C/min), 110 kPa, t_R = 37.6 min (major), 43.3 min (minor). HRMS (EI) calcd for $C_5H_5NO_2$ $[M]^+$ 111.0320, found 111.0317.

(*S*)-(–)-Paraconic acid (9):[10] A solution of **8** (14.0 mg, 0.126 mmol) in 6 *M* HCl (1 mL) was allowed to heat at 40 °C and stirred for 23 h. The resulting mixture was allowed to cool to room temperature, and then concentrated under reduced pressure. The resultant residue was diluted with chloroform (10 mL), and was dried over $MgSO_4$, and then was concentrated under reduced pressure to give the desired product **9** as colorless viscous oil in 98% yield (16.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (dd, *J* = 17.8, 9.6 Hz, 1H), 2.91 (dd, *J* = 17.9, 6.9 Hz, 1H), 3.52 (m, 1H), 4.50 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.54 (dd, *J* = 9.2, 8.2 Hz, 1H) [CO_2H was not oberved]. ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 39.7, 68.9, 175.4, 176.4. IR (neat) 3500, 2923, 1770, 1732, 1384, 1193, 1032 cm^{-1}. $[\alpha]_D^{24}$ = –49.2 (*c* 1.00, MeOH, 97% ee (*S*)) [lit.[11] $[\alpha]_D^{25}$ = –35 (*c* 0.002, MeOH, for *S* enantiomer), $[\alpha]_D^{25}$ = +40.0 (*c* 0.001, MeOH, for *R* enantiomer)]. HRMS (ESI–) calcd for $C_5H_5NaO_4$ $[M–H]^-$ 129.0193, found 129.0189.

3-5-7. Synthesis of (*R*)-(–)-baclofen 12 (Eq. 4)



(*R*)-2-(4-Chlorophenyl)-4-oxo-4-(1*H*-pyrrol-1-yl)butanenitrile (5u):[6] 95%, 85% ee (TMSCN 250 mol%, 25 °C, 18 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.31 (*n*-hexane:EtOAc = 4:1). Compound **5u** was recrystallized from dichloromethane/*n*-hexane at room temperature (99% ee). Colorless solid. ^{1}H NMR (400

MHz, $CDCl_3$) δ 3.34 (dd, *J* = 17.4, 6.9 Hz, 1H), 3.55 (dd, *J* = 17.4, 7.3 Hz, 1H), 4.53 (t, *J* = 6.9 Hz, 1H), 6.32 (t, *J* = 2.3 Hz, 2H), 7.24 (br, 2H), 7.39 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 40.4, 114.2 (2C), 118.8 (2C), 119.5, 128.9 (2C), 129.6 (2C), 132.8, 134.8, 165.7. IR (KBr) 2934, 2245, 1710, 1473, 1406, 1374, 1315, 1290, 1130, 1094 cm^{-1}. M.p. 145-150 °C. $[\alpha]_D^{22}$ = +18.4 (*c* 1.00, $CHCl_3$, 99% ee) [lit.[6] $[\alpha]_D^{22}$ = +8.50 (*c* 0.39, $CHCl_3$, for *S* enantiomer with 41% ee)]. HPLC analysis; AS-3, *n*-hexane/*i*-PrOH = 4/1, 240 nm, 1.0 mL/min, t_R = 22.4 min (minor), 27.5 min (major). HRMS (ESI+) calcd for $C_{14}H_{11}ClN_2NaO$ $[M+Na]^+$ 281.0452, found 281.0457.

(*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (11):[12] To a suspension of **5u** (37.0 mg, 0.145 mmol) in methanol (0.75 mL), *t*-$BuMe_2SiOTf$ (TBSOTf) (333 mL, 1.45 mmol) was added at 25 °C.[7] The mixture was stirred at 40 °C for 39 h, and then directly purified by frash neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 2:1) to give the desired compound **10**, which involved inpurities such as an diester via overreaction of the CN moiety. The mixture of **10** was subsequently used without further purification. To a solution of **10** in methanol (1.2 mL), platinum(IV) oxide (3.3 mg, 0.0145 mmol) and 3 *M* HCl in methanol (290 mL, 0.87 mmol) were added, and the mixture was stirred at 25 °C under a hygrogen atmosphere (760 Torr, balloon) for 5 h.[13] Platinum(IV) oxide was removed by filteration, and then the filtrate was concentrated under reduced pressure. To a solution of crude material in methanol (1.5 mL), sodium methoxide (157 mg, 2.9 mmol) was added, and the mixture was stirred at 25 °C for 17 h, and saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resultant residue was purified by neutral silica gel column chromatography (eluent: *n*-hexane:EtOAc = 3:1 to $CHCl_3$:MeOH = 12:1) to give the desired product **11** (19.3 mg, 68% yield in 3 steps). The enantiomeric purity of **11** was determined by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (dd, *J* = 17.0, 8.7 Hz, 1H), 2.74 (dd, *J* = 16.9, 8.7 Hz, 1H), 3.38 (dd, *J* = 7.3, 9.2 Hz, 1H), 3.68 (quint, *J* = 8.2 Hz, 1H), 3.79 (t, *J* = 8.3 Hz, 1H), 6.03 (br, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9,

39.6, 49.4, 128.1 (2C), 129.0 (2C), 132.9, 140.6, 177.6. IR (KBr) 3197, 1688, 1492, 1346, 1259, 1090, 1013 cm^{-1}. M.p. 105-110 °C. $[\alpha]_D^{26}$ = –28.2 (*c* 0.78, EtOH, 99% ee) [lit.[14] $[\alpha]_D^{30}$ = –39.7 (*c* 1.00, $CHCl_3$, for *S* enantiomer with >99% ee)]. HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 9/1, 220 nm, 1.0 mL/min, t_R = 10.1 min (major), 11.8 min (minor). HRMS (ESI+) calcd for $C_{10}H_{11}ClNO$ $[M+H]^+$ 196.0524, found 196.0520.

(*R*)-(–)-Baclofen (12):[14] A suspension of **11** (23.7 mg, 0.121 mmol) in 6 *M* HCl aqueous solution (1 mL) was allowed to heat at 100 °C and stirred for 24 h. The resulting mixture was filtered through celite pad, and concentrated under reduced pressure to give the desired product **12** in 96% yield (29.1 mg). ^1H NMR (400 MHz, D_2O) δ 2.73 (m, 1H), 2.83 (dd, *J* = 16.0, 3.7 Hz, 1H), 3.22 (m, 1H), 3.30-3.46 (m, 2H), 7.27-7.38 (m, 2H), 7.41 (d, *J* = 6.9 Hz, 2H) [NH_2·HCl and CO_2H were not observed.]. ^{13}C NMR (100 MHz, D_2O) δ 38.5, 39.8, 44.0, 129.5 (2C), 129.7 (2C), 133.6, 138.3, 175.7. IR (KBr) 2915, 1718, 1495, 1413, 1198, 1094 cm^{-1}. M.p. 185-189 °C $[\alpha]_D^{25}$ = –3.1 (*c* 0.65, H_2O, 99% ee) [lit.[14] $[\alpha]_D^{30}$ = –3.79 (*c* 0.65, H_2O, for *R* enantiomer with >99% ee)]. HRMS (ESI+) calcd for $C_{10}H_{13}ClNO_2$ $[M+H]^+$ 214.0629, found 214.0639.

We summarized the transformation of **5u** to **10** or **11** in Eqs. S1–S5 and Table S1. Compound **5u** was easily epimerized under basic conditions. Therefore, regarded reaction conditions with *n*-Bu_4CN[15] and NaOMe gave the corresponding racemic product **10** (Eqs. S1 and S2). $CoCl_2$ or $NiCl_2$ with $NaBH_4$[12,16] gave the corresponding product **11** with a significant loss of enantio-purity (Eqs. S3 and S4). Moreover, common reduction process with H_2 on Pd/C gave an unexpected Cl-reduced product **S1** (Eq. S5). In contrast, acid-treatment to **5u** in methanol generally worked well, and **10** was obtained without epimerization (Table S1). In particular, TBSOTf was better than TMSOTf,[17] **10** was ultimately obtained in 76% yield when 10 equiv of TBSOTf was used (entry 4). In all cases, the generation of undesired diester **S2** (22–32% yields) could not be avoided.

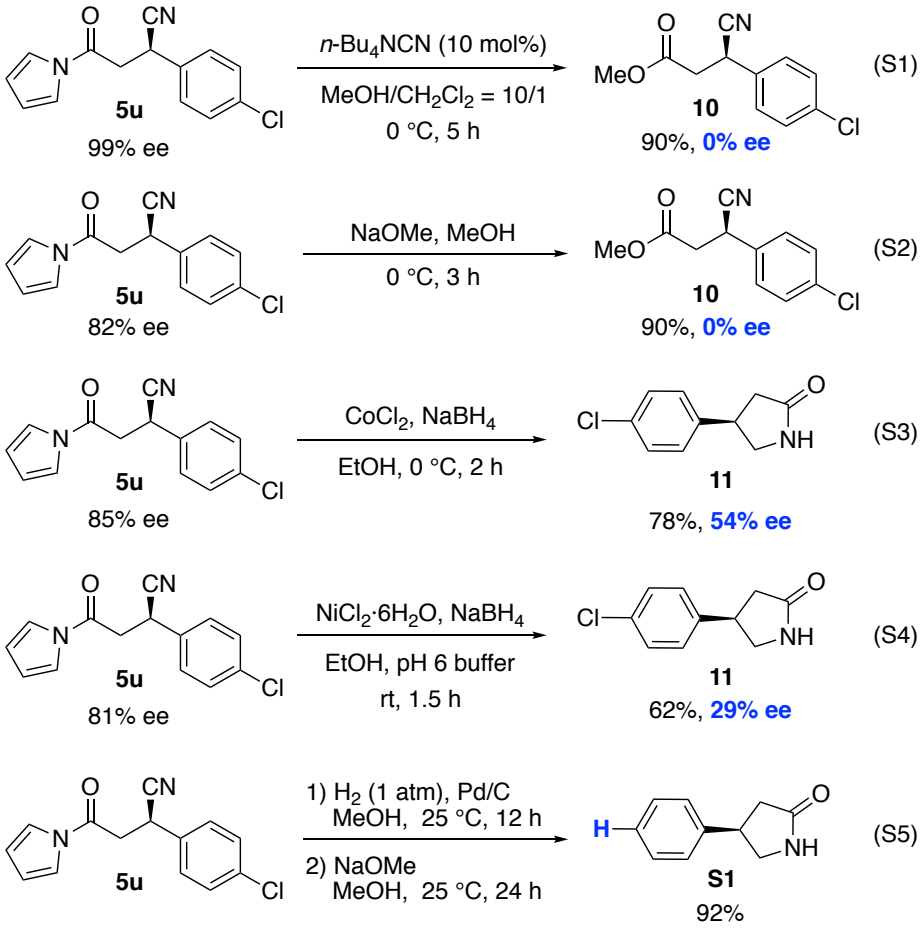
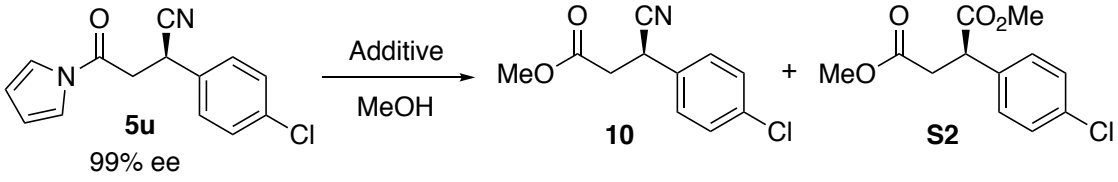
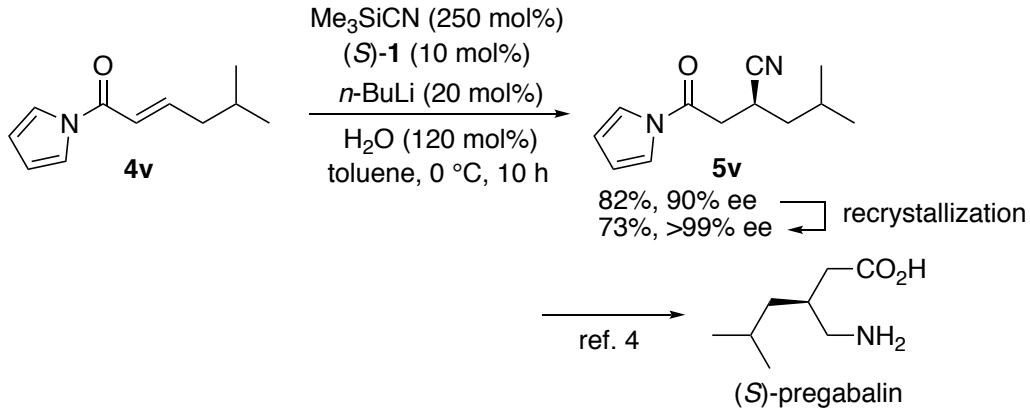


Table S1. Screening of reaction conditions of **5u**



entry	Additive (equiv)	Conditions	yield (%) of **10**	yield (%) of **S2**
1	TMSOTf (7.5)	60 °C, 25 h	58 (99% ee)	22
2	TMSOTf (15)	60 °C, 31 h	54 (99% ee)	23
3	TBSOTf (7.5)	60 °C, 21 h	64 (99% ee)	32
4	**TBSOTf (10)**	40 °C, 39 h	**76** (99% ee)	24

3-5-8. Synthesis of (*S*)-pregabalin (Eq. 5)

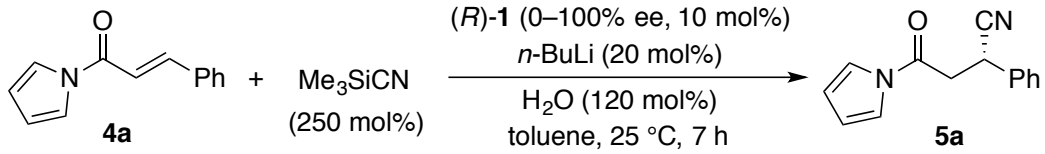


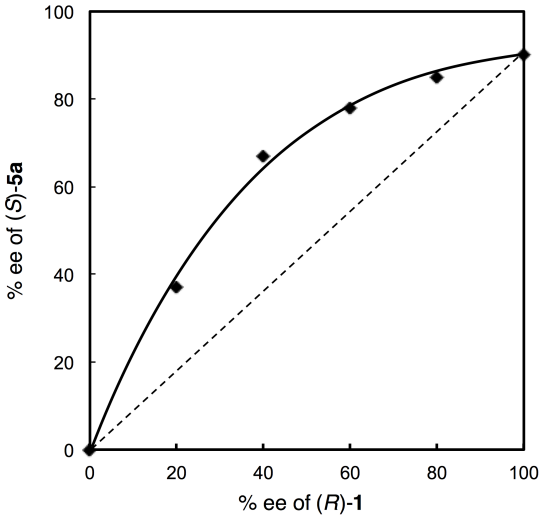
(*S*)-4-Methyl-2-(2-oxo-2-(1*H*-pyrrol-1-yl)ethyl)pentanenitrile (5v):[4] 82%, 90% ee (TMSCN 250 mol%, 0 °C, 10 h). Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.36 (*n*-hexane:EtOAc = 4:1). Compound **5v** was recrystallized from dichloromethane/*n*-hexane at room temperature (>99% ee). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.45 (m, 1H), 1.71 (m, 1H), 1.92 (m, 1H), 3.05 (m, 1H), 3.22 (d, *J* = 6.9 Hz, 1H), 3.30 (m, 1H), 6.34 (t, *J* = 2.3 Hz, 2H), 7.29 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 22.8, 25.0, 26.1, 37.3, 40.7, 113.8 (2C), 118.8 (2C), 121.1, 166.5. IR (KBr) 2967, 2240, 1727, 1473, 1378, 1290, 1072 cm^{-1}. M.p. 64-67 °C. $[\alpha]_D^{22}$ = –26.2 (*c* 1.00, $CHCl_3$, 90% ee). [lit.[4] $[\alpha]_D^{22}$= +26.2 (c 0.940, $CHCl_3$, for *R* enantiomer with 97% ee)]. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 240 nm, 1.0 mL/min, t_R = 10.6 min (minor), 13.0 min (major). HRMS (ESI+) calcd for $C_{12}H_{16}N_2NaO$ $[M+Na]^+$ 227.1155, found 227.1153.

3-5-9. Non-linear effect between the ee (%) of (*R*)-1 and the ee (%) of (*S*)-5a

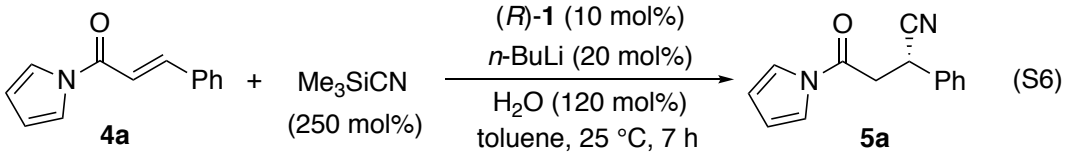
As shown in Scheme S1, a non-linear effect was examined in the reaction of *N*-acylpyrrole **4a** (0.30 mmol) with trimethylsilyl cyanide (250 mol%) in the presence of (*R*)-**1** (10 mol%, 0% ee to 100% ee), *n*-BuLi (20 mol%), and water (120 mol%) in toluene at 25 °C for 7 h. This non-linear relationship strongly suggests that inactive hetero-$(R)_n/(S)_m$ oligomeric lithium(I) complexes might be involved under these reaction conditions with the use of <100% ee of (*R*)-**1**.

Scheme S1. Plot of ee of (*S*)-**5a** vs. ee of (*R*)-**1**





As expected, a 1:1 ratio of (*R*)/(*S*)-**1**-derived catalyst (i.e., 0% ee catalyst) showed low catalytic activity (14% yield, 0% ee), while (*R*)-100% ee catalyst showed higher catalytic activity (90%, 90% ee) (Eq. S6). These results strongly suggest that hetero-(*R*)/(*S*)-**1**-derived Li(I)-dimer (or oligomers) might be stable and inactive. Overall, the remaining (*R*)-enriched monomeric lithium(I) complexes should be the active species and promote the reaction. These observations can clearly explain the strong positive non-linear effect.



100% ee of (*R*)-**1** : 90%, 91% ee
0% ee of (*R*)/(S)-**1** : 14%, 0% ee

3-5-10. Possible transition states

Plausible transition states for α,β-unsaturated *N*-acylpyrroles are shown in Figure S3. In this reaction, α,β-unsaturated *N*-acylpyrrole **4a** can be activated at the Lewis acidic Li(I) center in TS-**13** or TS-**13'**. TS-**13** shows favored *trans*-coordination of amide to an acid center (i.e., *trans*-N–C=O···Li), whereas TS-**13'** shows disfavored *cis*-coordination (i.e., *cis*-N–C=O···Li).

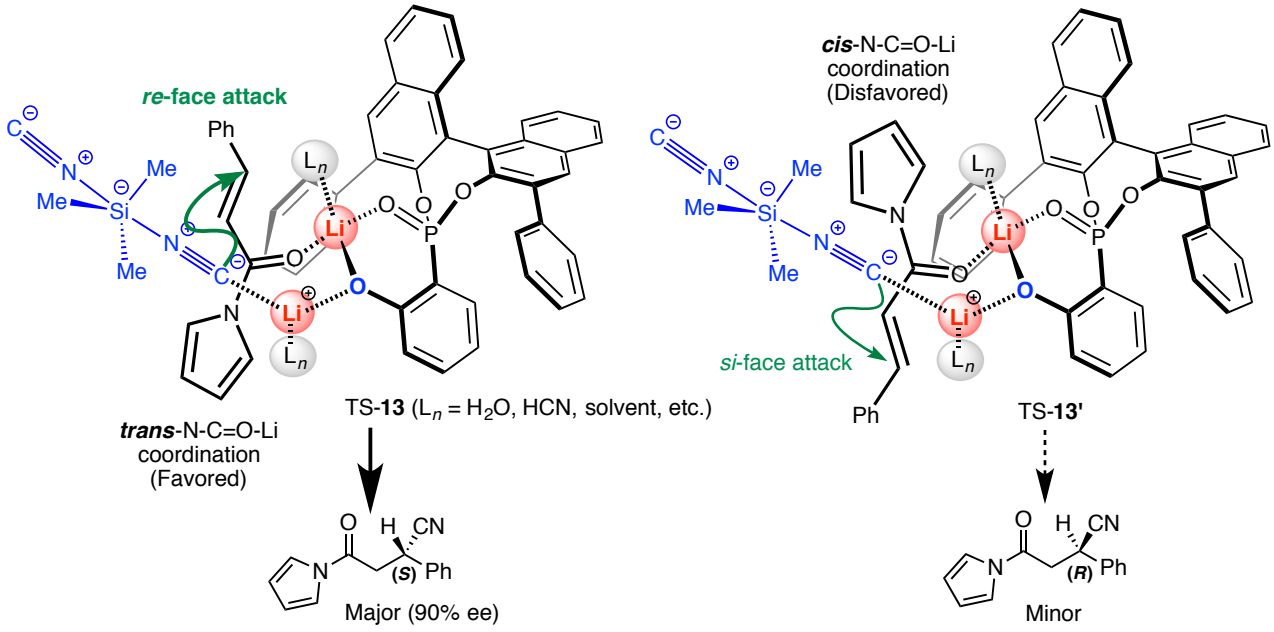
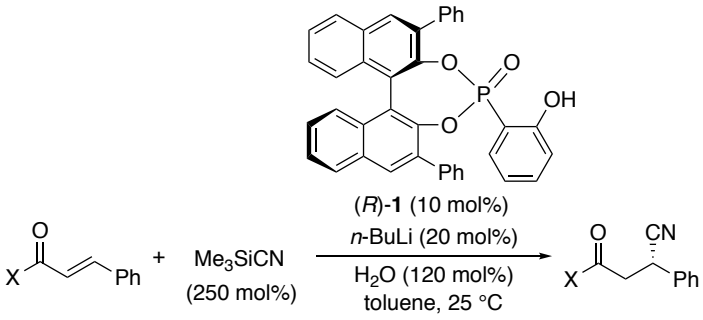


Figure S3. Possible transition states for *N*-cinnamoylpyrrole **4a**

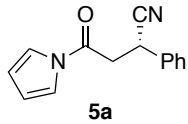
3-5-11. Optimization of the substrates

Optimization of the substrates are summarized in Table S2. In our catalysis, the *N*-acylpyrrole moiety was essential both to promote the reacton and to induce the enantioselectivity.

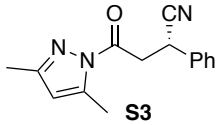
Table S2. Optimization of the substrates[a]



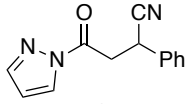
Product, yield, enantioselectivity, and reaction time:[a]



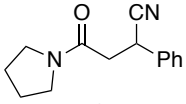
5a
90%, 90% ee (7 h)



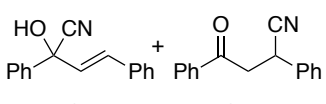
S3
38%, 70% ee (6 h)[b]



S4
32%, 0% ee (12 h)

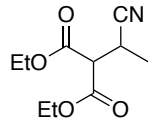


S5
0% (12 h)

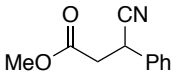


S6
24%, 1% ee

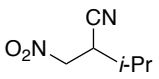
S7
70%, 58% ee (20 h)



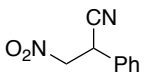
S8
98%, 0% ee (9 h)



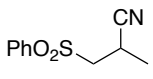
S9
0% (14 h)



S10
98%, 0% ee (7 h)

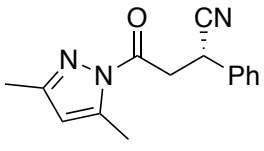


S11
0% (19 h)



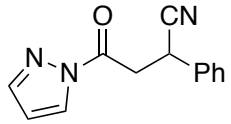
S12
40%, 19% ee (8 h)

[a] The reaction was carried out with substrate (0.30 mmol), Me_3SiCN (250 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (20 mol%), and H_2O (120 mol%) in toluene at 25 °C unless otherwise noted. [b] 15 mol of *n*-BuLi was used.

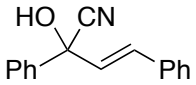


(*S*)-4-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-oxo-2-phenylbutanenitrile (S3):[18] Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.38 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR and ^{13}C NMR data were consistent with previously reported

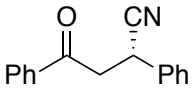
values.[18] HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 9/1, 1.0 mL/min, t_R = 31.3 min (major), 39.6 min (minor).



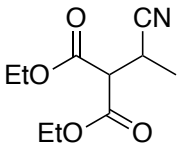
Oxo-2-phenyl-4-(1*H*-pyrazol-1-yl)butanenitrile (S4): Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.31 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) d 3.70 (dd, *J* = 17.9, 6.4 Hz, 1H), 3.89 (dd, *J* = 17.9, 8.7 Hz, 1H), 4.52 (dd, *J* = 8.2, 6.4 Hz, 1H), 6.47 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.34-7.46 (m, 5H), 7.70 (s, 1H), 8.25 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) d 32.4, 40.0, 110.3 119.8, 127.5 (2C), 128.5, 128.6, 129.3 (2C), 134.3, 144.7, 167.7. IR (KBr) 3130, 2246, 1732, 1422, 1389, 1321, 1255, 1203, 1095, 1035 cm^{-1}. M.p. 93-96 °C. HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 9/1, 1.0 mL/min, t_R = 16.4 min and 18.0 min. HRMS (ESI+) calcd for $C_{13}H_{11}N_3NaO$ $[M+Na]^+$ 248.0794, found 248.0791.



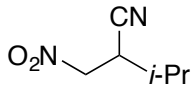
2-Hydroxy-2,4-diphenylbut-3-enenitrile (S6):[19] Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.36 (*n*-hexane:EtOAc = 4:1). Colorless oil. ^{1}H NMR and ^{13}C NMR data were consistent with previously reported values.[19] HPLC analysis; IA-3, *n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, t_R = 8.5 min (major), 10.9 min (minor).



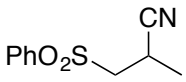
(*S*)-4-Oxo-2,4-diphenylbutanenitrile (S7):[18] Column chromatography (eluent: *n*-hexane:EtOAc = 10:1 to 5:1). Rf = 0.28 (*n*-hexane:EtOAc = 4:1). Colorless solid. ^{1}H NMR and ^{13}C NMR data were consistent with previously reported values.[18] HPLC analysis; OD-3, *n*-hexane/*i*-PrOH = 7/3, 1.0 mL/min, t_R = 12.8 min (major, *S*), 15.6 min (minor, *R*).



Diethyl 2-(1-cyanoethyl)malonate (S8):[20] Column chromatography (eluent: *n*-hexane:EtOAc = 15:1). Rf = 0.42 (*n*-hexane:EtOAc = 9:1). Colorless oil. ^{1}H NMR and ^{13}C NMR data were consistent with previously reported values.[20] GC analysis; CHIRALDEX B-DM, 100 ºC, 100 kPa, t_R = 17.4 min, 18.7 min.



3-Nethyl-2-(nitromethyl)butanenitrile (S10):[21] Column chromatography (eluent: *n*-hexane:EtOAc = 15:1). Rf = 0.45 (*n*-hexane:EtOAc = 9:1). Colorless oil. ^{1}H NMR and ^{13}C NMR data were consistent with previously reported values.[21] HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 98/2, 1.0 mL/min, t_R = 22.0 min, 25.6 min.

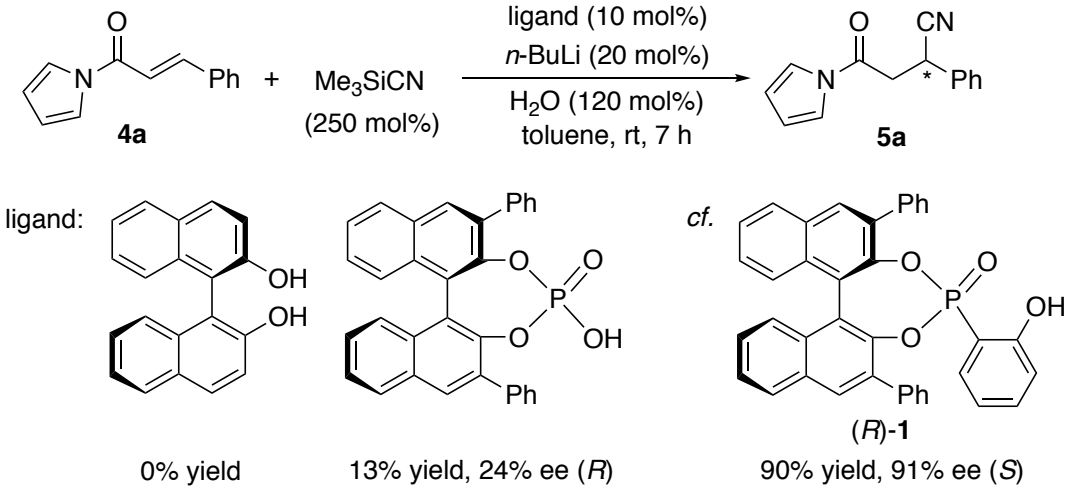


2-Phenyl-3,3-bis(phenylsulfonyl)propanenitrile (S12):[22] Column chromatography (eluent: *n*-hexane:EtOAc = 3:1 to 1:1). Rf = 0.28 (*n*-hexane:EtOAc = 2:1). Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) d 1.52 (d, *J* = 7.3 Hz, 3H), 3.17-3.30 (m, 2H), 3.47 (dd, *J* = 13.3, 6.4 Hz, 1H), 7.63 (t, *J* = 8.2 Hz, 2H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.96 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) d 18.3, 20.8, 58.3, 119.7, 128.2 (2C), 129.7 (2C), 134.6, 138.3. IR (KBr) 2994, 2939, 2243, 1450, 1315, 1293, 1183, 1147 cm^{-1}. M.p. 76–77 °C. $[a]_D^{27}$ = –2.4 (*c* 1.00, $CHCl_3$, 23% ee). HPLC analysis; AD-3, *n*-hexane/*i*-PrOH = 1/1, 0.7 mL/min, t_R = 14.3 min (minor), 15.6 min (major). HRMS (ESI+) calcd for $C_{10}H_{11}NNaO_2S$ $[M+Na]^+$ 232.0403, found 232.0398.

3-5-12. Control experiments with our previous catalysts

We examined a probe reaction with the use of our previous catalysts such as a chiral lithium(I) binaphtholate aqua complex[23] and a chiral lithium(I) phosphate[24] (Scheme S2). However, the reactions scarcely proceeded with these catalysts (<15% yield) under the same optimal conditions as in entry 5 of Table 1. Therefore, this catalytic system with silicate $[Li]^+[Me_3Si(CN)_2]^-$ **3** turned out to be different from our previous catalytic systems with Me_3SiCN.

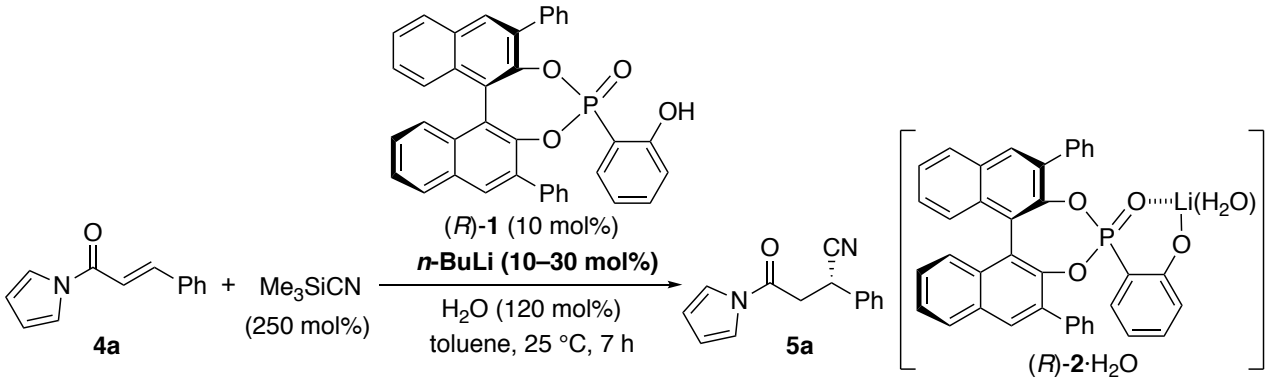
Scheme S2. Control experiments with previous catalysts



3-5-13. Control experiments of cyanation of *N*-acylpyrrole 4a and acetophenone S13

To confirm lithium(I) dicyanotrimethylsilicate(IV), $[Li]^+[Me_3Si(CN)_2]^-$ **3**, would be essential or not, a present probe reaction was carried out in the absence or presence of **3** (i.e., 0, 5, 10, and 20 mol% of LiCN) (Table S3, also see Table 1 in the paper). As a result, in the absence of **3**, the reaction itself hardly proceeded (entry 1). This result strongly suggests that Me_3SiCN, HCN, and/or the combined reagent Me_3SiCN/HCN would not be effective in this present reaction. Moreover, we have already confirmed that the combined use of Me_3SiCN and HCN in the absence of $Li(I)^+$ almost did not provide the corresponding silicate(IV), such as $[H]^+[Me_3Si(CN)_2]^-$.[3] In contrast, the reaction was facilitated more smoothly in the presence of 10 mol% of **3** (entry 3) than 5 mol% of **3** (entry 2). However, 20 mol% of **3** provided an insoluble black material probably due to undesired side reactions, and the yield and enantioselectivity were decreased (entry 4).

Table S3. Conjugate hydrocyanation to *N*-acylpyrrole **4a**[a]

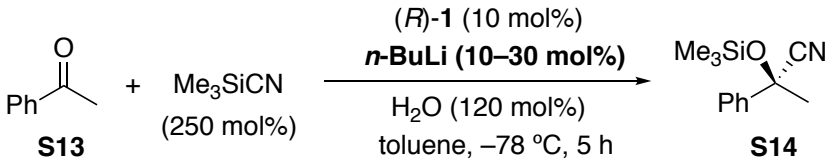


entry	*n*-BuLi	Theoretical amount (mol%) of					5a	5a
	(mol%)	(*R*)-**2**·H_2O	LiCN	Me_3SiCN	HCN	Me_3SiOH	yield (%)	ee (%)
1	10	10	0	140	110	110	7	53
2	15	10	5	140	105	110	67	91
3	**20**	**10**	**10**	**140**	**100**	**110**	**90**	**91**
4	30	10	20	140	90	110	65	60

[a] The reaction was carried out with **4a** (0.30 mmol), Me_3SiCN (250 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (10–30 mol%), and H_2O (120 mol%) in toluene at 25 °C for 7 h.

Next, to consider the cyanation of *N*-acylpyrrole **4a**, and we carried out the cyanosilylation of acetophenone **S13** according to the previous report (Table S4).[3] As a result, in the absence of **3**, the reaction proceeded, and **S14** was obtained in 68% yield with 90% ee (entry 1). Since acetophenone **S13** is much more reactive (reaction temperature is –78 °C) than *N*-acylpyrrole **4a** (reaction temperature is 25 °C), we cannot completely deny the participation of Me_3SiCN, HCN, and/or the combined reagent Me_3SiCN/HCN. However, in the presence of only 5 mol% of **3**, the reaction was greatly promoted, and **S14** was obtained in more improved yield (94%) with 91% ee (entry 2). The reaction was also greatly promoted in the presence of 10 mol% and 20 mol% of **3**, although the enantioselectivity was gradually decreased (entries 3 and 4).

Table S4. Cyanosilylation to acetophenone **S13**.[a]



entry	***n*-BuLi**	Theoretical amount (mol%) of					**S14**	**S14**
	(mol%)	(*R*)-**2**·H_2O	LiCN	Me_3SiCN	HCN	Me_3SiOH	yield (%)	ee (%)
1	10	10	0	140	110	110	68	90
2	**15**	**10**	**5**	**140**	**105**	**110**	**94**	**91**
3	20	10	10	140	100	110	93	89
4	30	10	20	140	90	110	97	84

[a] The reaction was carried out with **S13** (0.30 mmol), Me_3SiCN (250 mol%), (*R*)-**1** (10 mol%), *n*-BuLi (10–30 mol%), and H_2O (120 mol%) in toluene at –78 °C for 5 h.

Overall, between the conjugate hydrocyanation to *N*-acylpyrrole **4a** and the previous cyanosilylation of acetophenone **S13**, the optimum reaction conditions were practically same except for the reaction temperature. *In both reactions, the use of lithium(I) dicyanotrimethylsilicate(IV), $[Li]^+[Me_3Si(CN)_2]^-$* ***3*** *was quite effective.* In particular, shortage or lack of **3** decreased the yield. Moreover, the use of the more than optimal amount of **3** decreased the enantioselectivity.

3-5-14. References

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Research Achievement

Publications

(1) "Enantioselective Cyanosilylation of Ketones with Extremely Reactive Lithium(I) Dicyanotrimethylsilicate(IV) Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide"
Hatano, M.; Yamakawa, K.; Kawai, T.; Horibe, T.; Ishihara K. *Angew. Chem. Int. Ed.* **2016**, *55*, 4021–4025. (Cover picture に採用)
紹介記事: *Synfacts* (Lautens, M.; Yamamoto, K. *Synfacts*, **2016**, *12*, 0395.)
化学工業日報(2016 年 2 月 9 日、第 5 面)、
中日新聞(2016 年 3 月 4 日、第 6 面)

(2) "Enantioselective Conjugate Hydrocyanation of α,β-Unsaturated *N*-Acylpyrroles Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide"
Hatano, M.; Yamakawa, K.; Ishihara, K. *ACS. Catal.* **2017**, *7*, 6686–6690.
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(3) "Understanding and Interrupting the Fischer Azaindolization Reaction"
Simmons, B. J.; Hoffmann, M.; Champagne, P. A.; Picazo, E.; Yamakawa, K.; Morrill, L. A.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2017**, *139*, 14833–14836.

Conference Presentation

- Oral Presentation

(1) 「ケトンの高エナンチオ選択的シアノシリル化反応に有効なキラルリチウム(I)ホスホリルフェノキシド触媒」
○ 山川勝也、河合知明、堀部貴大、波多野学、石原一彰
日本化学会第 93 春季年会、2E4-10、滋賀、2013 年 3 月、A 講演

(2) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いるケトンの高エナンチオ選択的シアノシリル化反応」
○ 山川勝也、波多野学、石原一彰
日本化学会第 94 春季年会、3B8-08、愛知、2014 年 3 月、A 講演

(3) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いるケトンのエナンチオ選択的シアノシリル化反応」
○ 山川勝也、波多野学、石原一彰
日本化学会第 95 春季年会、1E2-28、千葉、2015 年 3 月、A 講演

(4) 「高活性シリカートを鍵とするキラルリチウム(I)ホスホリルフェノキシド触媒を用いるケトンの不斉シアノシリル化反応」
○ 山川勝也、波多野学、石原一彰
第 46 回中部化学関係学協会支部連合秋季大会、1A05、三重、2015 年 11 月、口頭発表

(5) 「高配位シリカートを鍵とするキラルリチウム(I)ホスホリルフェノキシド触媒を用いるケトンのエナンチオ選択的シアノシリル化反応」
○ 山川勝也、波多野学、石原一彰
日本化学会第 96 春季年会、3B1-28、京都、2016 年 3 月、B 講演

(6) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いるα,β-不飽和 N-アシルピロールのエナンチオ選択的共役シアノ化反応」
○ 山川勝也、波多野学、石原一彰
日本化学会第 97 春季年会、4E6-26、神奈川、2017 年 3 月、A 講演

(7) 「キラルπ-銅(II)触媒を用いるアシルピラゾールのエナンチオ選択的α-ハロゲン化反応」
○ 西村和揮、王彦兆、小倉義浩、山川勝也、石原一彰

日本化学会第 97 春季年会、1E6-41、神奈川、2017 年 3 月、A 講演

(8) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いるα,β-不飽和-*N*-アシルピロールのエナンチオ選択的共役シアノ化反応」
○ 山川勝也、波多野学、石原一彰
第 111 回有機合成シンポジウム、2-7、岡山、2017 年 6 月

(9) 「Enantioselective Cyanation of Ketones and α,β-Unsaturated Carbonyl Compounds Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide」
○ 山川勝也、波多野学、石原一彰
日本化学会第 98 春季年会、千葉、2018 年 3 月発表予定、B 講演

(10) 「キラルπ-カチオン触媒によるアシルピラゾールのエナンチオ選択的α-フッ素化反応」
○ 西村和揮、Yanzhao Wang、小倉義浩、山川勝也、石原一彰
日本化学会第 98 春季年会、千葉、2018 年 3 月発表予定、A 講演

• Poster Presentation

(1) 「ケトンの高エナンチオ選択的シアノシリル化反応に有効なキラルリチウム(I)ホスホリルフェノキシド触媒」
○ 山川勝也、波多野学、石原一彰
第 46 回有機金属若手の会　夏の学校、宮城、2013 年 7 月

(2) 「 Chiral Lithium(I) Phosphoryl Phenoxide-Catalyzed Highly Enantioselective Cyanosilylation of Ketones」
○ 山川勝也、波多野学、石原一彰
IGER Annual meeting 2013、G-26、愛知、2014 年 1 月

(3) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いたケトンの高エナンチオ選択的シアノシリル化反応」
○ 山川勝也、波多野学、石原一彰
第 49 回天然物化学談話会、P16、岡山、2014 年 7 月

(4) 「キラルリチウム(I)ホスホリルフェノキシド触媒を用いるケトンの高エナンチオ選択的シアノシリル化反応」

○ 山川勝也、波多野学、石原一彰
第 5 回 CSJ 化学フェスタ 2015、P3-032、東京、2015 年 10 月

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○ 山川勝也、波多野学、石原一彰
名古屋大学グリーン自然科学国際教育研究プログラム・分子科学研究所リトリート研修「分子研・知られざる有機合成の世界」、P15、愛知、2015 年 11 月

(6) 「Enantioselective Cyanosilylation of Ketones with Extremely Reactive Hypervalent Silicate Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide」
○ 山川勝也、波多野学、石原一彰
IGER Annual meeting 2016、G10、愛知、2016 年 1 月

(7) 「Chiral Lithium(I) Phosphoryl Phenoxide Catalysts for Enantioselective Conjugate Cyanation of α,β-Unsaturated *N*-Acylpyrroles」
○ 山川勝也、波多野学、石原一彰
IGER/ITbM Chemistry Workshop 2016 ~Student-Centered Symposium of Forefront Chemistry~、P10、愛知、2016 年 12 月

(8) 「Chiral Lithium(I) Phosphoryl Phenoxide Catalysts for Enantioselective Conjugate Cyanation of α,β-Unsaturated *N*-Acylpyrroles」
○ 山川勝也、波多野学、石原一彰
IGER Annual meeting 2017、G10、愛知、2017 年 1 月

(9) 「Chiral Lithium(I) Phosphoryl Phenoxide Catalyst for Enantioselective Conjugate Cyanation」
○ 山川勝也、波多野学、石原一彰
The 8th International Meeting on Halogen Chemistry、P-85、愛知、2017 年 9 月

(10) 「キラルリチウム(I)ホスホリルフェノキシド触媒とリチウム(I)ジシアノシリカート(IV)を用いるケトン及びα,β-不飽和カルボニル化合物の不斉シアノ化反応」
○ 山川勝也、波多野学、石原一彰
第 35 回メディシナルケミストリーシンポジウム、1P-100、愛知、2017 年 10 月

(11) 「Enantioselective Hydrocyanation of Ketones and α,β-Unsaturated *N*-Acylpyrroles Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide」
○ 石原一彰、波多野学、山川勝也
ICCEOCA-12/ARNCEOCA-3、PO-B19、China、2017 年 11 月

(12) 「キラルπ-銅(II)触媒によるアシルピラゾールのエナンチオ選択的α-ハロゲン化反応」
○ 西村和揮、Yanzhao Wang、小倉義浩、山川勝也、石原一彰
IGER/ITbM Chemistry Workshop 2017、P30、愛知、2017 年 11 月

(13) 「Enantioselective Cyanation of Ketones and α,β-Unsaturated Carbonyl Compounds Catalyzed by Chiral Lithium(I) Phosphoryl Phenoxide」
○ 山川勝也、波多野学、石原一彰
IGER Annual meeting 2018、愛知、2018 年 1 月

- **Award**

(1) 第 46 回中部化学関係学協会支部連合秋季大会 VIP 賞 (有機合成化学協会、平成 27 年 11 月、1A05、三重)

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Katsuya Yamakawa