Studies on Modular Ion-Paired Ligands for Palladium-Catalyzed Selective Allylic Alkylations

選択的パラジウム触媒反応におけるイオン対型配位子の多様性と可変性の活用に関する研究

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Chapter 1

General Introduction and Summary

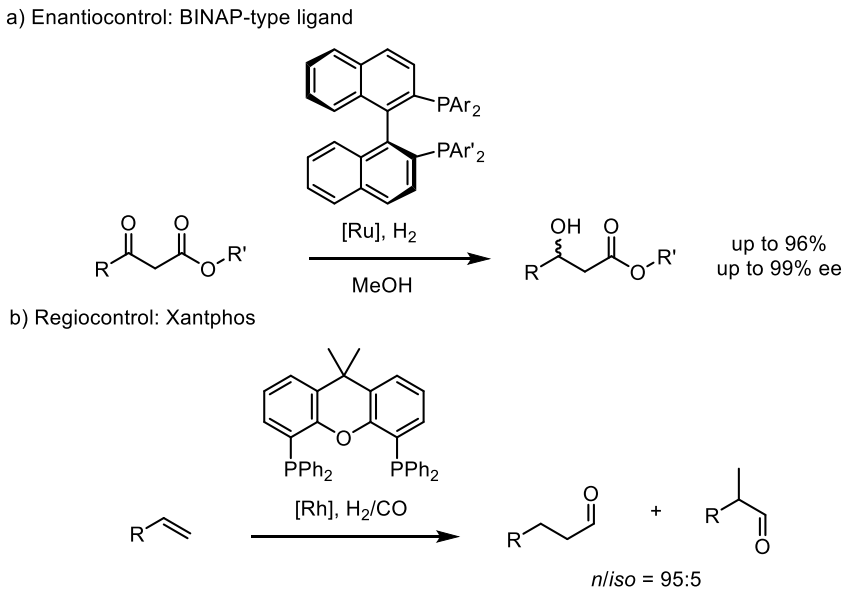
1.1 Conventional chiral ligands

The development of homogeneous catalysis is driven by achieving the target reaction with higher reactivity and selectivity. While enzymatic catalysts are applicable only to the specific substrates, synthetic catalysts have a potential applicability for the wide range of substrate scope. However, there is no general catalyst enabling the control of reactions with a broad substrates. Indeed, for the discovery of effective catalyst for the target reaction, numerous trial-and-error attempts are often required. Additionally, in spite of the great advances in the area of computational and theoretical chemistry, it is formidable task to predict the optimal catalyst.

One of the method for solution of this problem, combinatorial approach enable to speed up the optimization of the best ligand or catalyst for target reaction. Although this strategy has been applied for drug discovery and optimization in the field of pharmaceutical industry, it hasn't been adequate method for screening of the best catalyst. While bidentate ligands is higher selectivity than monodentate ligands for a lot of reactions such as the asymmetric hydrogenation of β-keto esters with ruthenium catalyst (Scheme 1.1 a). However the best ligand has been chosen from variety of ligand library which was constructed a lot of times because it was synthesized multi steps.

For another example of high selectivity by using bidentate ligand, the regioselective hydroformination of terminal alkene with rhodium-xantphos catalyst (Scheme 1.1 b). This type of reaction was achieved few ligands which has wide bite angle such as xantphos. It is more challenging to synthesize non-symmetrically bidentate ligands constructed with two different coordinate sites.

Scheme 1.1 The example of controlling of enantio- or regioselectivity by using conventional chiral ligands

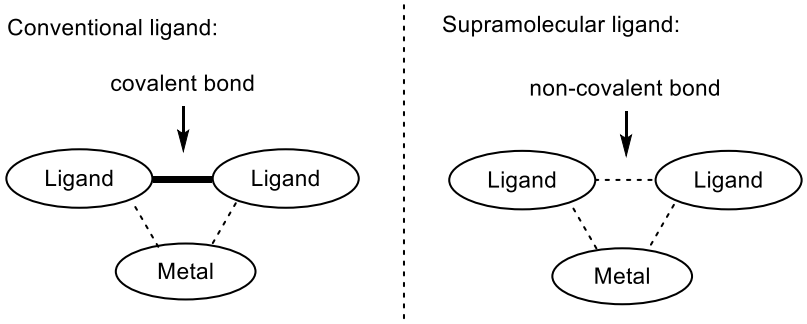


1.2 Supramolecular chiral ligands

To easily construct the complex bidentate ligands, the new approach of catalyst designs were introduced which has supramolecular interactions introduced for catalysts and ligands and various supramolecular catalyst has been synthesized and applied a various reactions (Scheme 1.2).

On the one hand, classical bidentate ligands have only covalent bonds and were constructed by multistep from simple molecules. On the other hands, supramolecular ligand were associated with Supramolecule interaction between simple compounds. This interaction such as hydrogen bond and coordinate bond have reversible coordinations which enable to flexible tuning of the feature of the catalyst. Supramolecular ligand could easily construct from various simple monodentate ligands.

Scheme 1.2 The type of supramolecular catalyst



1.2.1 The type of ligand-ligand interaction

Patureau *et. al.* developed new supramolecular catalyst constructed with sulfonamido-phosphinamide ligands which forms two different tautomers in solvent.[3] When this ligand was mixed with a solution of [Rh(acac)$(CO)_2$], *cis*-bis-phosphorus Rh(acac) complex which had different METAMORPhos tautomers was assembled. Intriguingly, a solution of two different METAMORPhos-type ligands and [Rh(acac)$(CO)_2$] forms hetero complex which could achieve high enantioselective asymmetric hydrogenation of methyl 2-acetamidoacrylate (Fig. 1.1).

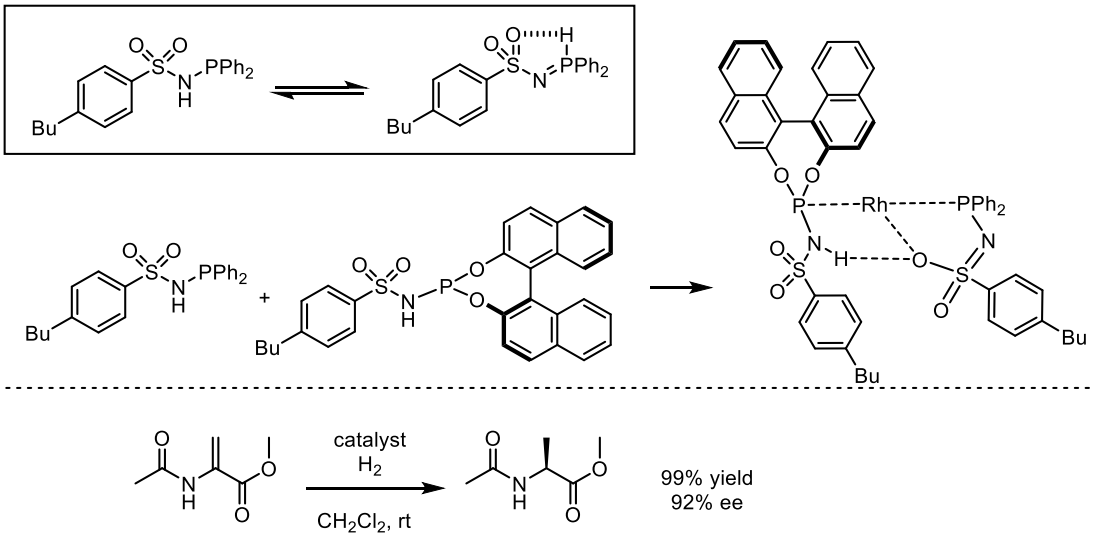


Fig. 1.1 Formation of metal complexes by mixing different METAMORPhos-type ligands and Rh-catalyzed asymmetric hydrogenation.

Breuri *et al*. introduced single hydrogen bonded mododentate ligands which derived from leucine and achiral phosphine.[4] This ligand was constructed with chiral monodentate ligand, LEUPhos and achiral urea-phosphine ligand assembled with hydrogen bond between phosphoraamidite NH unit and urea unit. The rhodium complex could achieve high enantioselective hydrogenation (Fig. 1.2). They calculated the intermediate of reduction step by using DFT. This result suggested that substrate is coordinated with the ester unit of the phosphoramidite unit and this interaction could achieve the high enantioselectivitie.

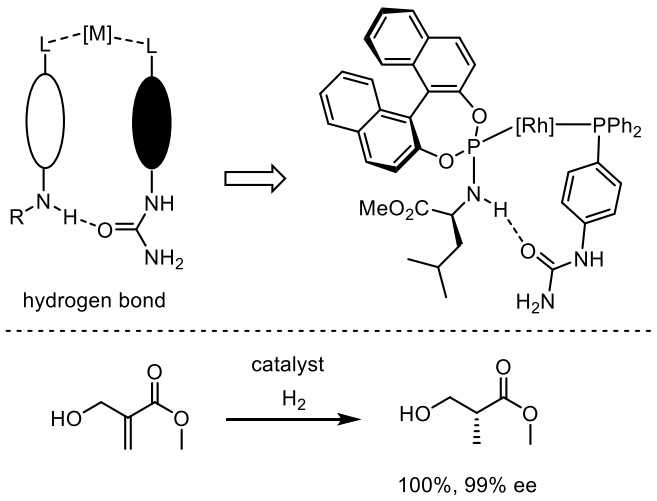


Fig. 1.2 Supramolecular catalyst associated with single hydrogen bond

Another example of the supramolecular catalyst containing single hydrogen bond of urea-functionalized monodentate phosphine was reported. Meeuwissen *et. al.* synthesized the phosphinourea ligand which coordinate with rhodium formed *trans*-coordinating complex of the 2:1 of phosphine to rhodium complex (Fig. 1.3).[5] The different tautomer of phhosphinoureas coordinated to rhodium was observed by NMR, DFT and X-ray analysis. This complex was applied for high regioselective and moderate enantioselective hydroformilation of styrene. This best ligand was determined from 14 combination of ligand library by using combinatorial approach.

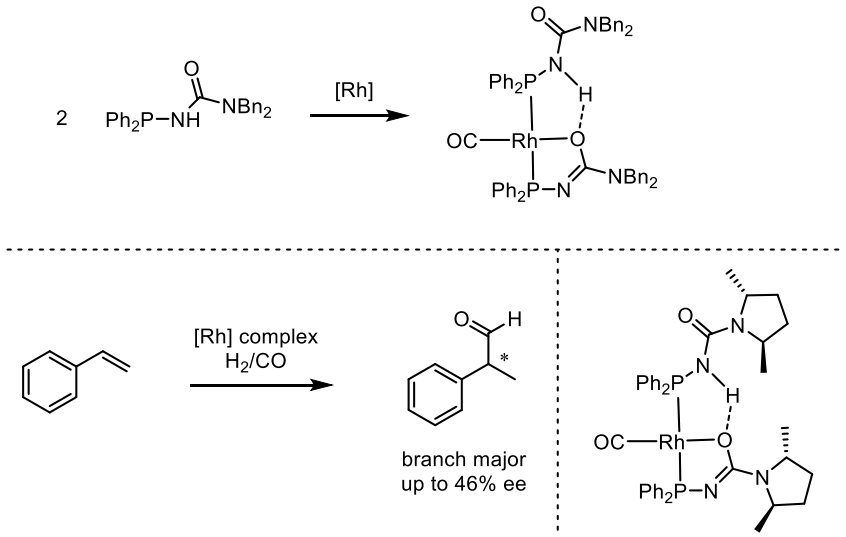


Fig. 1.3 Rhodium complex constructed with two UREAPhos ligands

Breit group synthesized bidentate ligands which were build up with monodentate aminopyridinyl phosphines and isoquinolones based on an adenine-thymine base-pair model (Fig. 1.4).[6] These monodentate ligands form hetero dimer of bidentate ligand. They performed regioselective hydroformination of terminal alkene by using 8 self-assembled ligands and achieved high regioselectivity in favor of linear product.

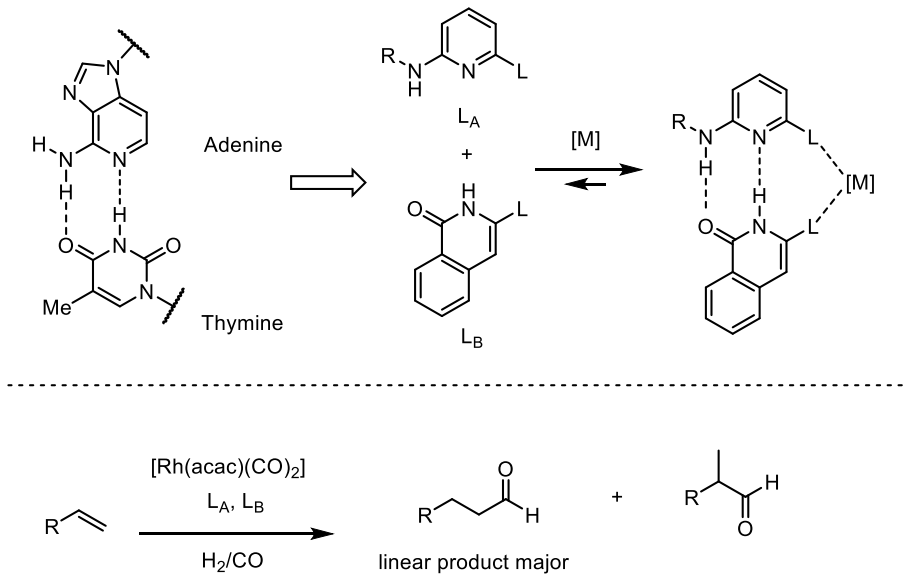


Fig. 1.4 The concept of adenine-thymine base-pair ligand

In previous report, UREAPhos ligand coordinated with anionic rhodium precursor, Reek group introduced new supramolecular catalyst elaborated from UREAPhos ligands associated with two hydrogen bonds and neutral rhodium precursor. This ligand was constructed three parts, urea unit ligand backbone and spacer (Fig. 1.5).[7] They achieved high enantioselective asymmetric hydrogenation of some of valuable compound for industry by using rhodium complex.

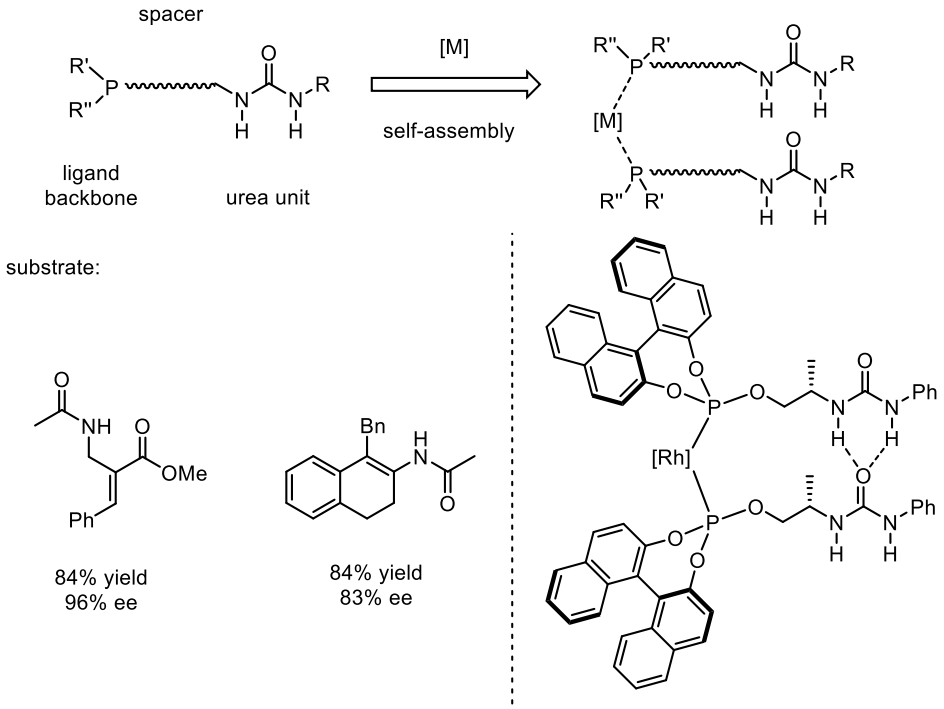


Fig. 1.5 UREAPhos achieving the asymmetric hydrogenation reaction

Breit group synthesize new supramolecular ligand, Supra PhanePhos which has planar chiral PhanePhos-type structure (Fig. 1.6).[8] This ligand has two peptide-like hydrogen bonds and π–π interaction that expected stabilization of assembly. This metal-complex performed high enantioselectivity for asymmetric hydrogenation.of methyl 2-*N*-acetamido acrylate, phenylalanine precursor and dimethyl itaconate.

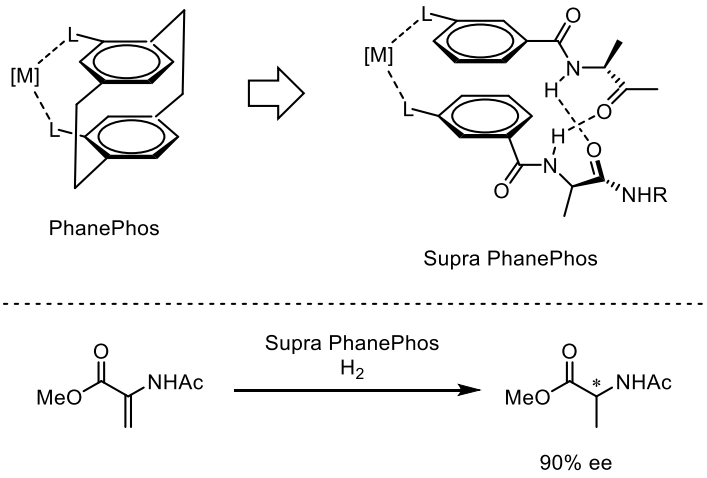


Fig. 1.6 Inducing planar chirality of Supra PhanePhos through self-assembly ligands

Reek group reported palladium-catalyzed kinetic resolution by using supramolecular bidentate ligands which have Lewis Acid-Base interaction such as Zinc(II)porphyrin-pyridine coordinate bond (Fig. 1.7).[9] This complex enable high efficient kinetic resolution of racemic cyclohexenyl acetate by using high-throughput screening from SUPRAPhos library.

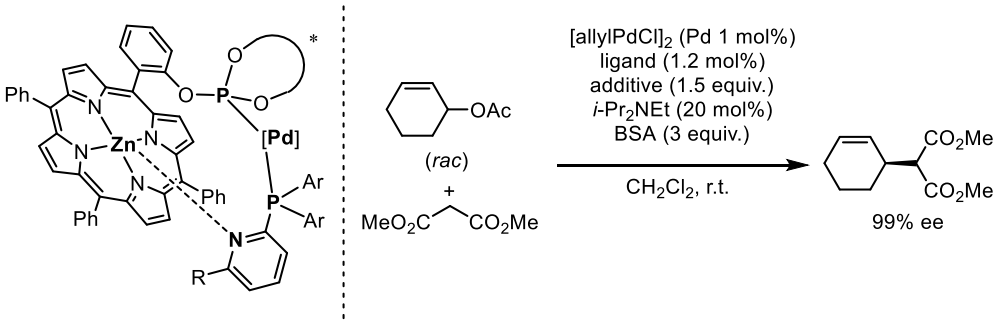


Fig. 1.7 This complex is assembled by pyridine-Zn coordination

Takacs *et al.* synthesized new design of self-assembled bimetallic ligand which contain structural metal and catalytic metal (Fig. 1.8). While structural metal plays a roll of joint between monosubstituted bisoxazoline and TADDOL-derived monophosphates, catalytic metal is reactive site. This ligand enabled to achieve high enantioselective transition metal-catalyzed allylic amination[10] and hydroboration reactions of styrene.[11]

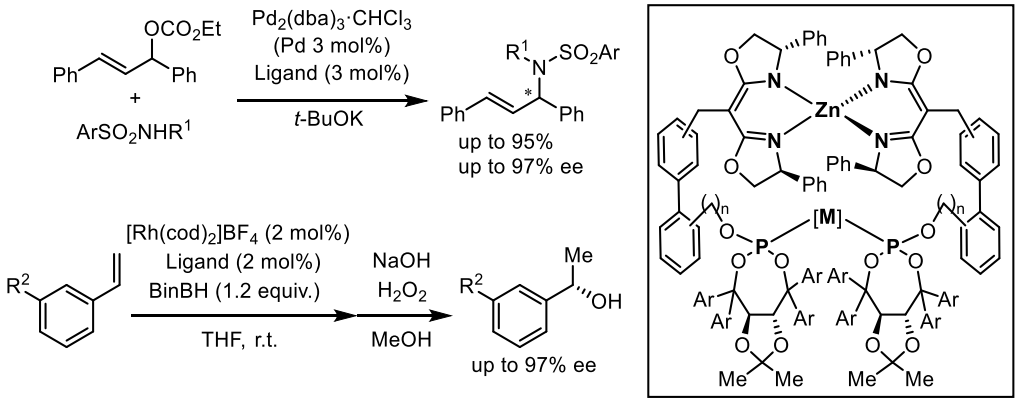


Fig. 1.8 Zn as a structural role and Pd as a catalytic role

1.2.2 The type of ligand-additive intraction

Another approach for construction of supralolecular catalyst, simple monodentate or bidentate ligand with additive which could coordinate with non-covalent bond. This additive enable changing the catalytic properties. While in the Reek's report, two monodentate ligand containing zinc(II)porphyrin or pyridine unit, Bellini *et al.* introduced monodentate chiral ligand associated with two zinc-porphyrin platform as additive (Fig. 1.9).[12] This catalyst achieve more reactivity and selectivity for asymmetric hydroformilation.

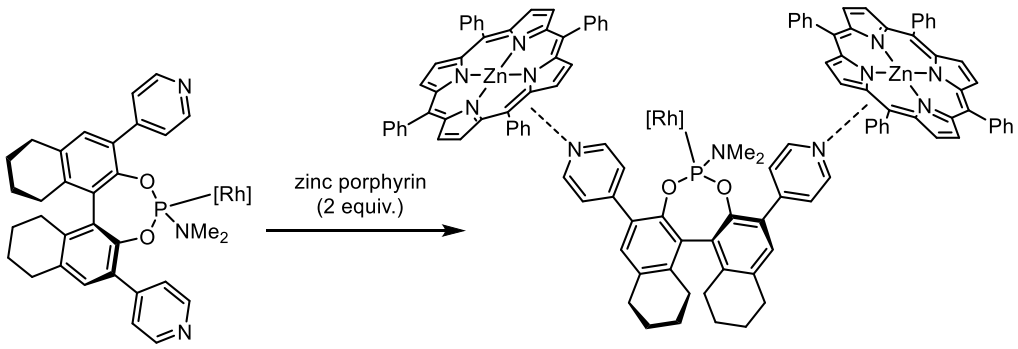


Fig. 1.9 New type of chiral supramolecular catalyst by using ligand-additive strategy.

Reek *et al.* reported supramolecular ligands which was constructed with an achiral bisphosphine ligand and chiral cofactor (Fig. 1.10).[13] As achiral bisphosphine plays a role of the anion receptor, this ligand could connect various chiral anion and form flexible chiral complex. This rhodium complex enable high enantioselective hydrogenation of 2-acetamidoaccrylate.

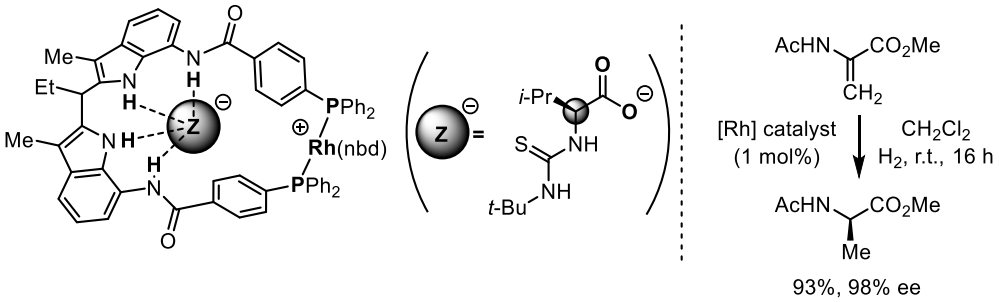


Fig. 1.10 Achiral bidentate ligand and chiral anion assembled by hydrogen bonds.

Generally, to obtain high enantioselectivity for asymmetric transition metal-catalyzed reaction, chiral unit such as BINOL- or TADDOL-derived often coordinate dilectly on metal via covalent bonds. Van Leeuwen group introduced conceptually new supramolecular catalyst constructed from achiral bidentate ligand and simple chiral diol as additive which located on the metal associated with supramolecular interaction (Fig. 1.11).[14] Although there is far from controlling chiral center to the substrate, they achieved Rh-catalyzed asymmetric hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate with high enantioselectivity.

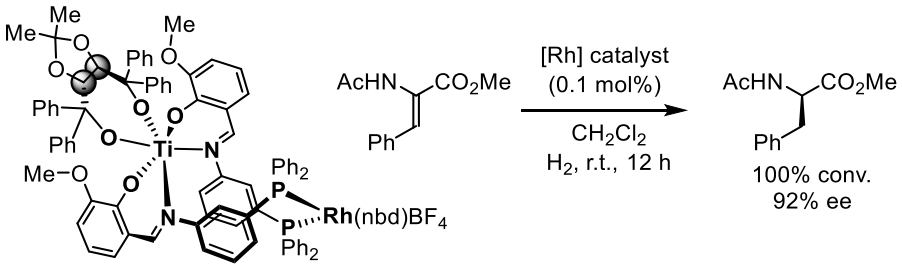
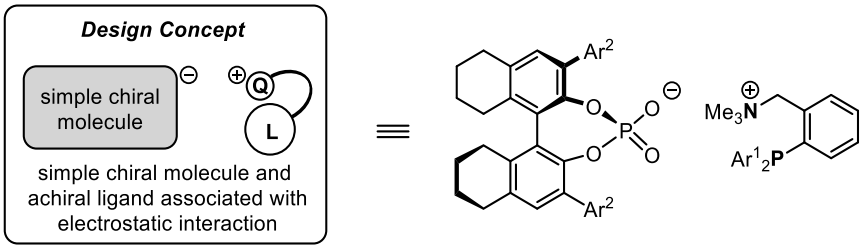


Fig. 1.11 Supramolecular catalyst assembled by heteroatom-Ti coordination

Ooi group recently introduced a conceptually new multicomponent chiral ligand, an ion-paired chiral ligand, assembled from a cationic ammonium-phosphine hybrid ligand and a chiral anion through electrostatic interaction (Scheme 1.3).[15a,b]

Scheme 1.3 Ion-paired chiral ligands constructed from simple compounds



This type of structurally flexible, ion-paired chiral ligand could actually impart notable activity and selectivity to the corresponding palladium complex, enabling the achievement of high asymmetric induction in difficult-to-control C–C bond formations, such as construction of asymmetric tetrasubstituted carbon (Fig. 1.12).

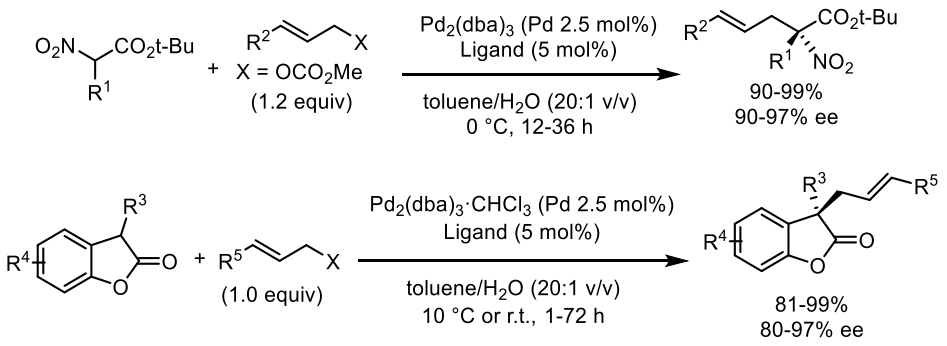


Fig. 1.12 Construction of asymmetric tetrasubstituted carbon by using ion-paired chiral ligands

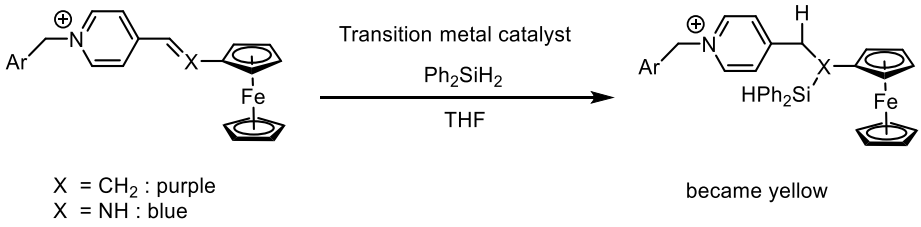
1.3 Combinatorial chemistry

The reactivity and selectivity of homogeneous catalyst for new reaction is not completely predictable. Therefore, the most of target reactions have been discovered by trial-and-error method. As complex catalyst was prepared and assayed for target reaction, advancement is very slow because a lot of times need for synthesizing of catalyst. Rapid screening method is useful for identification of optimal catalyst in the area of chemistry. Combinatorial chemistry includes three steps: (1) The rapid parallel synthesis of compound such as catalysts, ligands, substrates and so on. (2) Parallel screening of these compounds for activity assay (3) Identification of an optimal reaction condition or the best catalyst or ligand. When it became the general methodology, it enables the acceleration of research although this field is still developing step.

1.3.1 High through-put screening

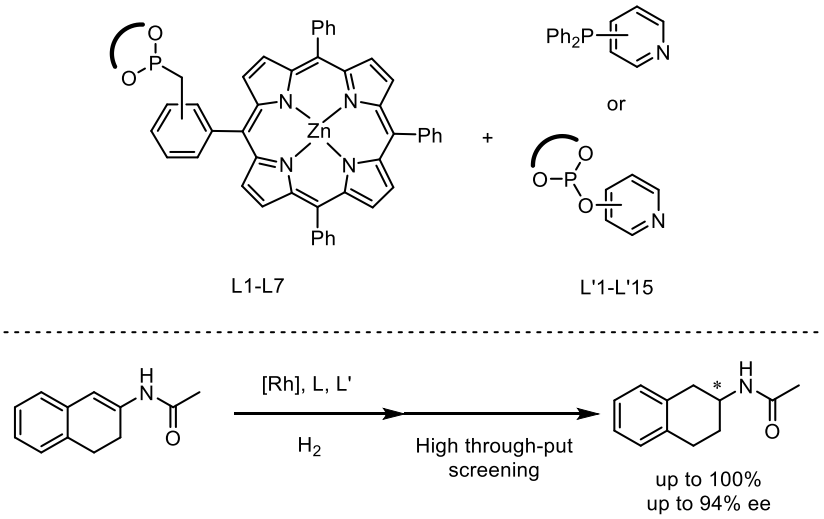
High through-put screening has been applied for rapid catalyst discovery by using IR thermography or laser photoionization. Crabtree group reported high through-put screening of the reactivity of transition metal catalyst for hydrosililation by assaying the color changing of reactive dyes.[16] The structure of dye containing electron donor and acceptor group jointed by electronic connection. When the reaction proceeded and cut the connection, the color of reactive dyes changed dark purple or blue to yellow (Scheme 1.4).

Scheme 1.4 Rapid screening of reaction conditions by using dyes.



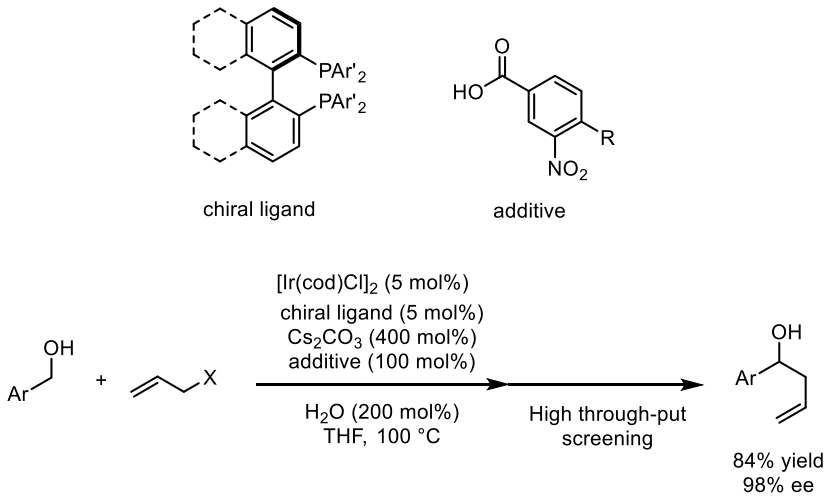
The research group of Reek introduced bidentate ligand associated with the self-assembly of several simple monodentate ligands. This ligand contain bidentate phosphorus-based ligands containing a zinc(II)porphyrin-pyridine coordinate bond. They have synthesized 64 supraphos ligands and shown a combinatorial approach to find the optimal ligand for rhodium-catalyzed asymmetric hydrogenation of *N*-(3,4-dihydro-2-naphthalenyl)acetamide by using automatically screening with 96 reaction plate (Scheme 1.5).[17]

Scheme 1.5 Identification of best ligand from the huge amount of ligand candidate



Krische *et al*. reported high through-put screening of the best condition such as chiral ligand or additive for Iridium catalyzed asymmetric carbonyl allylation (Scheme 1.6). Normally, chiral HPLC and GC were used for determination of enantiomeric excess (ee). They performed these reaction in micro-well plates in a short time and used CD spectrometer for determination of the highest ee of product of C-C coupling of primary alcohols with allyl acetate or chloride from more than 400 examples of reactions.[18]

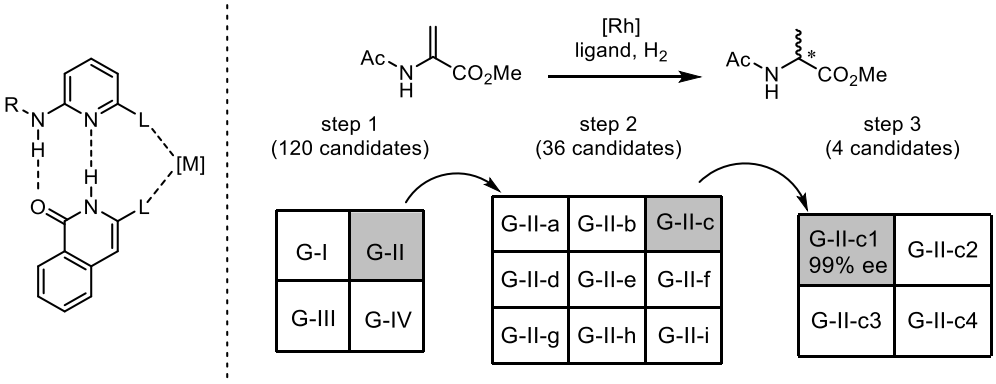
Scheme 1.6 Combinatorial screening from approximately 400 examples.



1.3.2 Iterative deconvolution strategy

Breit *et al*. introduced these supramolecular bidentate ligands which have two hydrogen bonds such as adenine-thymine pair model. They synthesized these 12 ligands having the 2-aminopyridine or 2-aminothiazole backbone and 10 ligands having the isoquinoline or azaindole and identified the optimal ligand from 120 ligand library for asymmetric hydrogenation reaction of several substrates. They used an iterative deconvolution strategy for rapid screening, first of all, ligands were divided into some groups and mixed in a single flask. The groups of which gave the best result were divided and conducted again. Finally, the best catalyst was identified only 17 hydrogenation reactions (Scheme 1.7).[19]

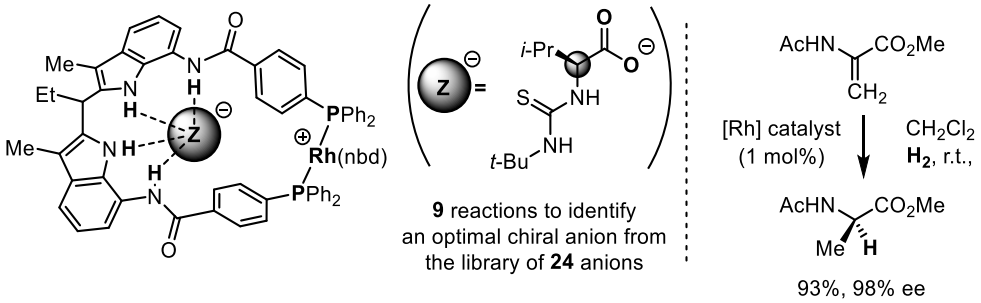
Scheme 1.7 17 Reactions to identify an optimal ligand from the library of 120 ligands



As was mentioned before at Fig 1.10, Reek *et al*. reported new concept of supramolecular ligand. They tried rapid identification of the best chiral cofactor by using deconvolution strategy. In

consequence, only 9 hydrogenation reactions were needed to identify the best one from 24 chiral cofactors (Scheme 1.8).[13]

Scheme 1.8 Combinatorial strategy was applied for hydrogenation by using Reek's supramolecular ligand



However, these approaches are restricted within reactions of narrow limits such as asymmetric hydrogenations.

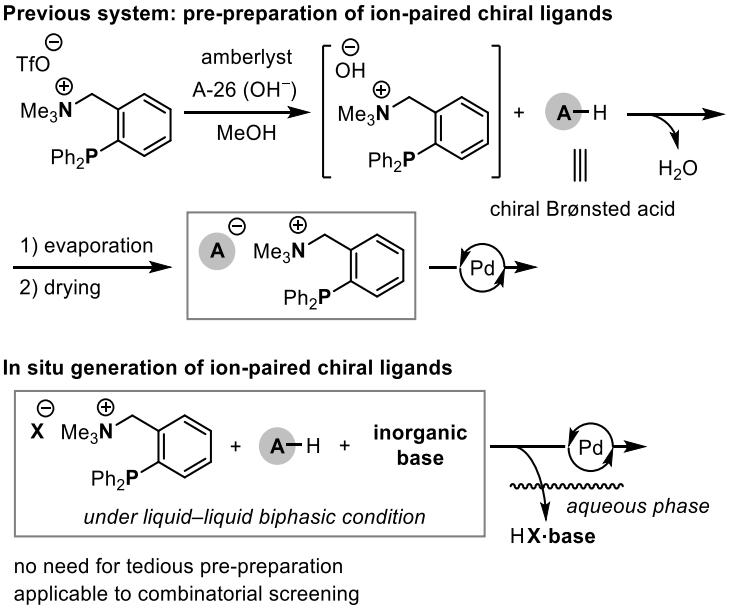
1.4 Rapid Identification of Optimal Ion-Paired Ligand for Asymmetric Allylation (Chapter 3)

The author tried to develop of difficult-to-control C-C bond formations by using the method of combinatorial ligand screening.[20] To apply ion-paired chiral ligand to this screening, the author attempt *in-situ* generation of ion-paired chiral ligand.

1.4.1 *In-situ* generation of ion-paired chiral ligand

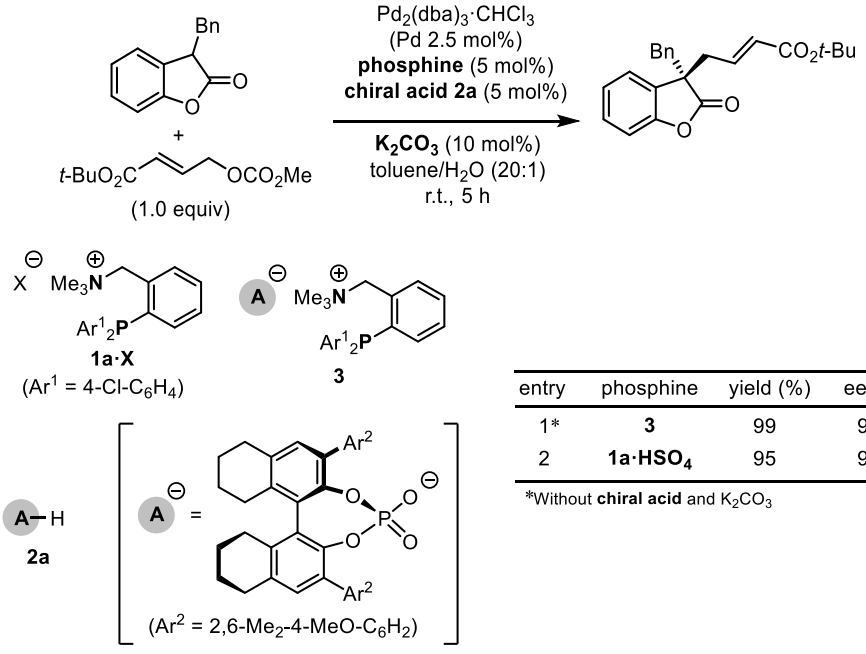
In the previous report, ion-paired chiral ligand had been prepared by ion-exchange process. The author examined *in-situ* generation of ion-paired chiral ligand by using simple achiral ammonium phosphine with chiral Brønsted acids (Scheme 1.9).

Scheme 1.9 Preparation of ion-paired chiral ligand



Asymmetric allylation of benzofuranone with allylic carbonate was selected as a model reaction. As a consequence, phosphinoammonium hydrogen sulfate 1a•HSO_4 was found to be the most effective precursor for the in situ preparation of ion-paired chiral ligand (Scheme 1.10).

Scheme 1.10 *In-situ* generation of ion-paired chiral ligand



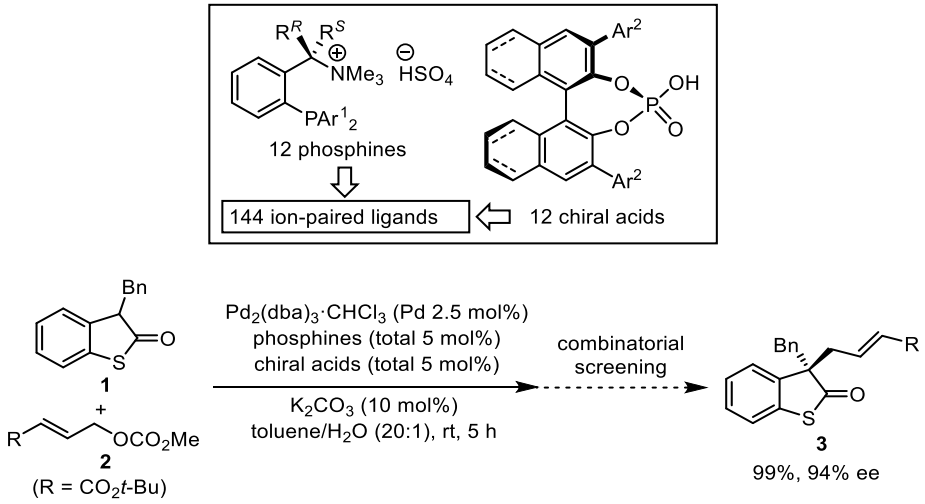
entry	phosphine	yield (%)	ee (%)
1*	**3**	99	92
2	**1a·HSO$_4$**	95	93

*Without **chiral acid** and K_2CO_3

1.4.2 Rapid identification of opimal ligand by using combinatorial strategy

To rapidly discover the most efficient catalyst for the asymmetric allylations of benzothiophenones by using *in-situ* generation method and combinatorial strategy, the author prepared 12 ammonium phosphines and 12 chiral acids and demonstrate rapid identification of the best ligand (Scheme 1.11).

Scheme 1.11 Rapid identification of optimal ion-paired chiral ligand.

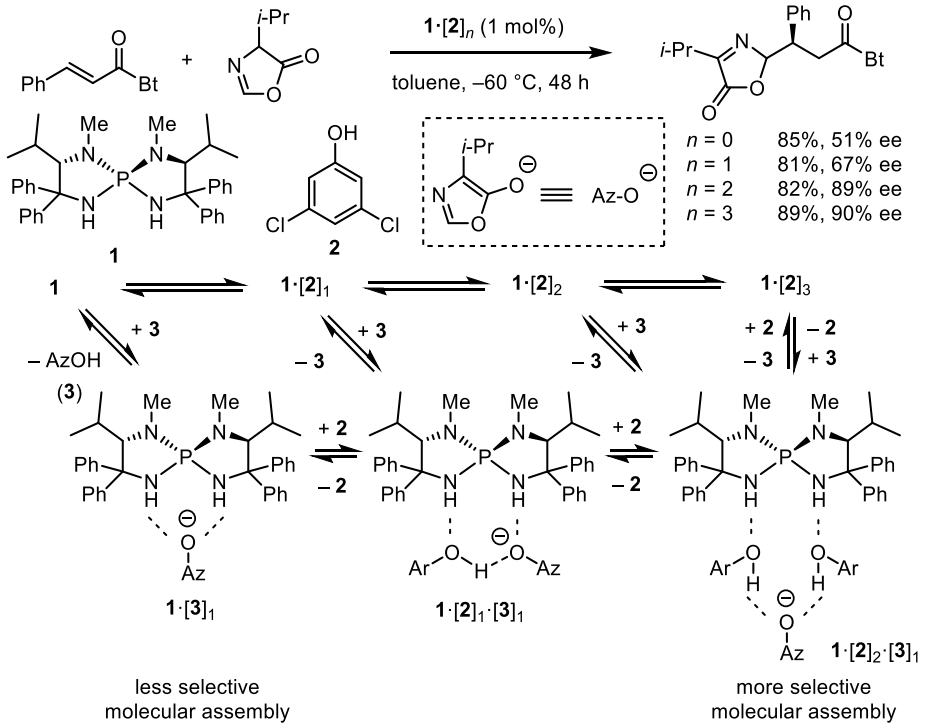


The best ligand could be identified from the library of 144 ion-paired chiral ligands through 16 experiments.

1.5 Changing of the component ratio for supramolecular catalyst

As the author had mentioned about combinatorial screening, the diversity of the catalyst library has been expanded by synthesizing new component. As the available alternative strategy of expansion the supramolecular catalyst library, changing the ratio of component enable construction of the different structure of suplamolecules. There is a few reports of this strategy (Scheme 1.12).[21] Changing the ratio of additive, the different structure of supramolecular catalyst could be generated.

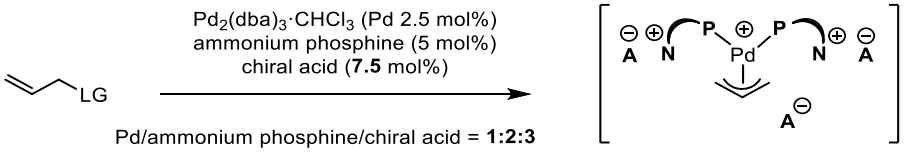
Scheme 1.12 Changing the component ratio of catalyst and additive



1.5.1 Changing of the component ratio for ion-paired chiral ligands (Chapter 4)

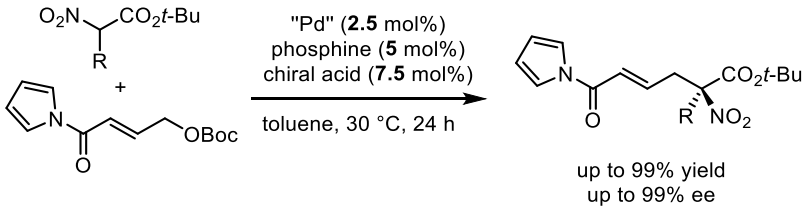
In the previous report, the standard ratio of Pd metal, ammoniumuphosphine and chiral acid is 1:2:2 for Pd catalyzed reaction with ion-paired chiral ligand. Consideration of plausible reactive intermediate, allyl palladium complex has three cations. The author hypothesed when changing the component ratio of 1:2:3, the Pd complex will be formed new complex different from standard ratio (Scheme 1.13).

Scheme 1.13 Changing the component ratio of ion-paired chiral ligand



This new system was applied for asymmetric allylation of nitroester with functionalized allylic carbonate. Pd, ammoniumuphosphine and chiral acid 1:2:3 catalyst system was higher enantioselectivity than Pd, ammoniumuphosphine and chiral acid 1:2:2 catalyst system (Scheme 1.14).

Scheme 1.14 Pd, ammoniumuphosphine and chiral acid 1:2:3 catalyst system was applied for asymmetric allylation



1.6 Conclusion

Up to this day, ion-paired chiral ligand could impart notable activity and selectivity to the corresponding palladium complex and its Pd complex enabled the achievement to the challenging reaction. The author established the new asymmetric palladium-catalyzed reaction by using combinatorial strategy. And the new strategy for increasing the diversity of supramolecular catalyst library was developed. The author hopes that this study will be contributed to the field of supramolecular chemistry.

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Chapter 2

Palladium-Catalyzed Branch-Selective Decarboxylative Allylation Using Ion-Paired Ligands

2.1 Introduction

In metal-catalyzed organic transformations, the structural and electronic properties of ligands are of critical importance for enhancing the reaction efficiency and controlling the selectivity. Accordingly, numerous ligands have been elaborated to date, allowing for the development of a wide variety of valuable synthetic methodologies. For example, Pd-catalyzed allylic alkylation has been established as one of the most powerful and versatile carbon–carbon bond-forming reactions.[1] While the studies in this field has mainly focused on stereocontrol based on the design and applications of chiral ligands,[2,3] regiochemical control also appears crucial in the reaction of non-symmetrical monosubstituted allylic substrates, which, in principle, gives rise to two regioisomeric products: linear and branched isomers. However, less effort has been made to explore the possibility of ligand-enabled regioselectivity dictation primarily because the regiochemical outcome critically depends on the central metals of the catalysts. Pd complexes generally promote allylic alkylations to produce the linear isomer rather than the branched isomer. In fact, branched isomers were only obtained in limited cases, where allylic substrates with directing groups,[4] heteroatom nucleophiles,[5] α-carbanions of imines,[6] or specially designed ligands were employed.[7,8] Therefore, the rational approach to develop Pd-catalyzed branch-selective protocols remains a challenging pursuit.

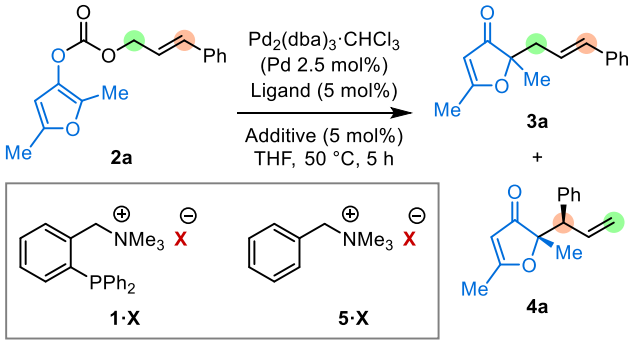
The author have recently introduced ion-paired chiral ligands comprising a cationic ammonium–phosphine hybrid ligand and a chiral anion.[9] The distinct advantage of this novel class of ligands is that the reactivity and selectivity of their metal complexes can be tuned by simply altering the anion component, coupled with structural modification of the phosphinoammonium moiety, thus facilitating the development of unprecedented Pd-catalyzed asymmetric allylation reactions.[10] In continuation of this research program, the author envisioned that the inherent modularity of ion-paired ligands would provide a unique opportunity to address the regioselectivity issue in Pd-catalyzed allylic alkylation. Here, the author report a new system for achieving the Pd-catalyzed branch-selective decarboxylative allylation of allylic enol carbonates,[11,12] which relies on the use of ion-paired ligands with a suitable anion component that plays a dominant role in controlling the regioselectivity.

2.2 Results and Discussion

2.2.1 Optimization of the Reaction Conditions

The author began the author's study by assessing the impact of ligand structure on the regioselectivity of the Pd-catalyzed decarboxylative allylation of furan-3(2*H*)-one-derived cinnamyl enol carbonate **2a**, the product of which is well-known as a basic constituent of natural products and pharmaceuticals.[13] An initial attempt was made by exposing **2a** to a catalytic quantity of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) and PPh_3 (5 mol%) in THF at 50 °C. The expected allyl migration took place cleanly to give a mixture of linear product **3a** and branched product **4a** in a ratio of 7.1:1, revealing the intrinsic regiochemical preference (Table 2.1, entry 1). The tendency toward the favorable formation of **3a** was also observed when ion-paired ligand having bromide ion **1·Br** was applied (entry 2), and switching the anion component of the ligand from bromide ion to chloride ion subtly affect ed the selectivity profile (entry 3). Surprisingly, however, the use of **1·OTf** as the ligand dramatically reversed the regioselectivity, producing branched isomer **4a** exclusively in a quantitative yield with high diastereoselectivity (entry 4).[14] Ligands with other non-coordinating anions such as BF_4 or PF_6 were equally effective in promoting branch-selective allylation with a comparable level of regioselection (entries 5 and 6). Importantly, the reactions performed with PPh_3 as the ligand in combination with benzyltrimethylammonium bromide **5·Br** or tetrafluoroborate **5·BF_4** showed similar regiochemical outcome as that observed in the absence of ammonium salts **5·X** (entries 7 and 8 vs entry 1). These results indicate that the origin of the branch selectivity in the Pd-catalyzed decarboxylative allylation of **2a** is not the mere presence of a requisite anion in the reaction system, but its incorporation as the anion component of ion-paired ligand **1·X** to have a significant effect on the characteristics of the corresponding Pd complex.

Table 2.1 Decarboxylative allylation of furan-3(2*H*)-one-derived cinnamyl enol carbonate **2a**[a]



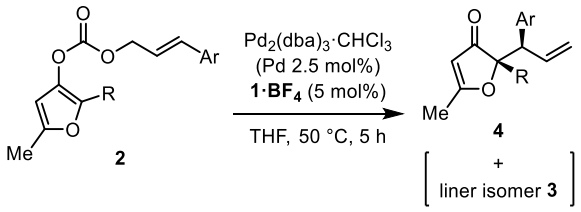
Entry	Ligand	Additive	Yield (%)[b]	**3a**/**4a**[c]	dr of **4a**[c]
1	PPh_3	none	99	7.1:1	nd
2	**1·Br**	none	92	3.2:1	nd
3	**1·Cl**	none	87	2.6:1	nd
4	**1·OTf**	none	99	1:>20	11:1
5	**1·BF_4**	none	99	1:>20	13:1
6	**1·PF_6**	none	99	1:16	11:1
7	PPh_3	**5·Br**	92	6.7:1	nd
8	PPh_3	**5·BF_4**	92	5.9:1	nd

[a] Reactions were carried out with 0.10 mmol of **2a** in the presence of Pd_2dba_3 (Pd 2.5 mol%) and ligand (5 mol%) in THF (0.5 mL) at 50 °C for 5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. nd = not determined.

2.2.2 Generality

Based on the discovery of the anion-dependent regiochemical reversal in Pd/**1·BF_4** complex-catalyzed decarboxylative allylation, we conducted the experiments to probe the substrate scope. As seen in the representative results listed in Table 2, C-2 primary or secondary alkyl-substituted furan-3(2*H*)-one-derived allylic enol carbonates were employable and excellent regio- and diastereoselectivity was uniformly attained (entries 1-2). In contrast, the present catalysis was not robust enough to override the regiochemical preference inherent to C-2 aryl-substituted substrates.[14] With respect to the allylic component, variation in the electronic and steric nature of the aryl substituents has little influence on the regioselectivity (entries 3-5), but the incorporation of fused aromatic substituents slightly decreased the yield of branched isomer (entry 6).[15]

Table 2.2 Scope and limitation of branch-selective allylation of furan-3(2*H*)-one-derived allylic enol carbonate **2**[a]

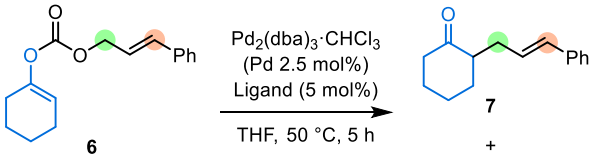


Entry	**4** (R, Ar)	Yield (%)[b]	**3**/**4**[c]	dr of **4**[c]
1	**4b** (Et, Ph)	96	1:17	17:1
2	**4c** (*i*-Pr, Ph)	99	1:>20	>20:1
3	**4d** (Me, 4-Cl-C_6H_4)	70	1:17	8.7:1
4	**4e** (Me, 4-Me-C_6H_4)	70	1:17	13:1
5	**4f** (Me, 2-Me-C_6H_4)	64	1:>20	>20:1
6	**4g** (Me, 2-Naph)	99	1:8.8	7.7:1

[a] Reactions were carried out with 0.10 mmol of **2** in the presence of Pd_2dba_3·$CHCl_3$ (Pd 2.5 mol%) and **1·BF$_4$** (5 mol%) in THF (0.5 mL) at 50 °C for 5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. nd = not determined.

The potential of this new catalytic system was further demonstrated by the reaction of other allylic enol carbonates derived from different ketones such as cyclohexanone derivative **6** (Scheme 2.1). The treatment of **6** with $Pd_2(dba)_3$·$CHCl_3$ and PPh_3 under the conditions identical with those for the reactions of **2** afforded linear isomer **7** as the major product. On the other hand, the replacement of PPh_3 with **1·BF$_4$** resulted in the preferential production of branched isomer **8**, albeit in a moderate yield.

Scheme 2.1 Decarboxylative allylation of cyclohexanone-derived enol carbonate **6**.

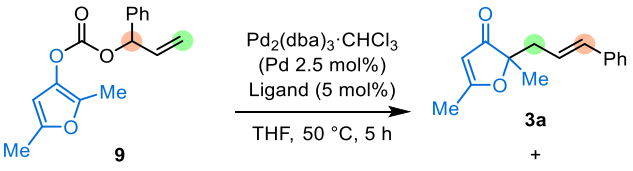


Ligand	**7**/**8**	Yield (%)
PPh_3	2.2:1	99
1·BF$_4$	1:7.0	47 (dr of **8** = 17:1)

2.2.3 Control Experiment

The author next examined the reaction of α-substituted allylic enol carbonate **9** in order to gain insight into the possible reaction pathway. While a 3.1:1 mixture of linear isomer **3a** and branched isomer **4a** was obtained with PPh_3 as the ligand, the employment of ion-paired ligand **1·BF$_4$** led to the predominant formation of the branched isomer (**3a**/**4a** = 1:17). The regiochemical consequence is apparently analogous to that of the reactions with γ-substituted allylic substrate **2a** (Scheme 2.2 vs Table 2.1, entries 1 and 5). This observation suggests that the reactions of **2a** or **9** with PPh_3 or **1·X** as the ligand proceeded via the generation of π-allyl Pd complexes.

Scheme 2.2 Decarboxylative allylation of α-substituted allylic enol carbonate **9**.



Ligand	**3a**/**4a**	Yield (%)
PPh_3	3.1:1	94
1·BF$_4$	1:17	99 (dr of **4a** = 11:1)

2.3 Conclusion

In conclusion, the author have uncovered that ion-paired ligands bearing non-coordinating anions were effective for achieving the branch-selective decarboxylative allylation of allylic enol carbonates. Simply by changing the anion component of the ligand, both the linear and branched isomers were accessible with moderate to excellent regioselectivity. The application of this regiodivergent protocol and mechanistic investigations are currently underway in the author's laboratory.

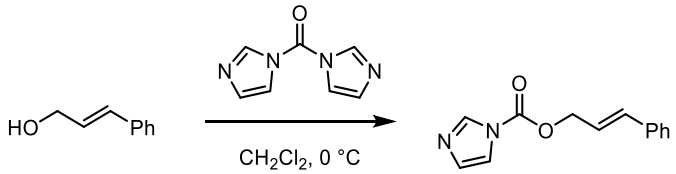
2.4 Experimental section

2.4.1 General information

Infrared spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet m = multiplet) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 600II (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$; 77.16 ppm). The high resolution mass spectra were measured on a Thermo Fisher Scientific Exactive (ESI). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40-50 μm; Kanto CHEMICAL Co., Inc.).

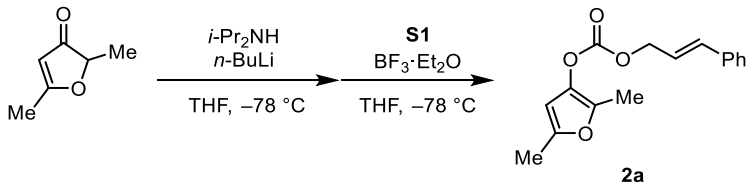
All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. The manipulations for Pd-catalyzed reactions were carried out with standard Schlenk techniques under Ar. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were supplied from Kanto Chemical Co., Inc. as "Dehydrated" and further purified by both A2 alumina and Q5 reactant using a GlassContour solvent dispensing system. Simple chemicals were purchased and used as such.

2.4.2 Representative Procedure for the Synthesis of Furan-3(2*H*)-one-derived Allylic Enol Carbonates 2:



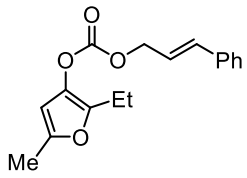
S1

To a solution of 1,1′-carbonyldiimidazole (3.24 g, 20 mmol) in CH_2Cl_2 (90 mL) was slowly introduced a solution of (*E*)-3-phenylprop-2-en-1-ol (2.58 mL, 20 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar. After stirring at the same temperature for 2 h, the solvent was removed *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (hexane/EtOAc = 2:1 as eluent) to afford **S1** (4.06 g, 17.8 mmol, 89% yield) as a colorless oil.

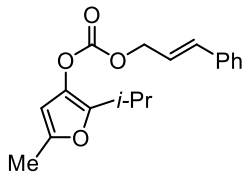


2a

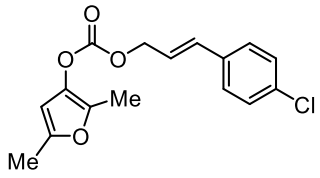
To a solution of *i*-Pr_2NH (0.84 mL, 6.0 mmol) in THF (15 mL) was dropwised a 2.66 M hexane solution of *n*-BuLi (2.2 mL, 5.5 mmol) at 0 °C under Ar, and the solution was stirred for 30 min. After cooling to –78 °C, a solution of 2,5-dimethylfuran-3(2*H*)-one[1] (0.53 mL, 5.0 mmol) in THF (2 mL) was slowly introduced into the flask and the resulting mixture was stirred for 30 min. Then, a solution of **S1** (1.1 g, 5.0 mmol) in THF (2 mL) was added to this mixture followed by the dropwise addition of boron trifluoride etherate (0.63 mL, 5.0 mmol) at –78 °C. The whole mixture was allowed to warm to room temperature and the stirring was maintained for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. Extractive work-up was performed with EtOAc, and the organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification of the crude residue by column chromatography on silica gel (hexane/EtOAc = 30:1 as eluent) gave **2a** (0.82 g, 3.0 mmol, 60% yield) as a colorless oil. **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (2H, m), 7.36-7.27 (3H, m), 6.74 (1H, brd, J = 16.0 Hz), 6.34 (1H, dt, J = 16.0, 6.8 Hz), 6.01 (1H, s), 4.87 (2H, dd, J = 6.8, 1.2 Hz), 2.22 (3H, s), 2.18 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 148.6, 138.3, 136.1, 135.7, 135.1, 128.8, 128.5, 126.8, 122.0, 102.3, 69.4, 14.1, 10.6; IR (film) 2922, 1761, 1449, 1373, 1244, 1138, 1038, 968, 922, 743 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{16}O_4Na^+$ ([M+Na]$^+$) 295.0941. Found 295.0942.



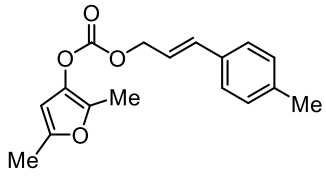
2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (2H, m), 7.36-7.28 (3H, m), 6.74 (1H, brd, J = 16.0 Hz), 6.33 (1H, dt, J = 16.0, 6.4 Hz), 6.00 (1H, s), 4.87 (2H, dd, J = 6.4, 1.6 Hz), 2.56 (2H, q, J = 7.6 Hz), 2.22 (3H, s), 1.17 (3H, t, J = 7.6 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 148.6, 143.3, 136.1, 135.7, 134.2, 128.8, 128.5, 126.9, 122.0, 102.3, 69.4, 18.7, 14.1, 12.3; IR (film) 2974, 1763, 1653, 1449, 1379, 1242, 1034, 966, 781, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{18}O_4Na^+$ ([M+Na]$^+$) 309.1097. Found 309.1098.



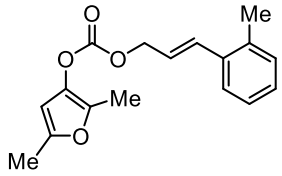
2c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (2H, m), 7.36-7.28 (3H, m), 6.74 (1H, brd, J = 15.6 Hz), 6.33 (1H, dt, J = 15.6, 6.8 Hz), 5.97 (1H, s), 4.87 (2H, d, J = 6.8 Hz), 2.97 (1H, sep, J = 6.8 Hz), 2.22 (3H, s), 1.22 (6H, d, J = 6.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.5, 148.3, 146.4, 136.1, 135.6, 133.3, 128.8, 128.5, 126.9, 122.0, 102.4, 69.3, 25.9, 20.9, 14.1; IR (film) 2970, 1763, 1449, 1381, 1298, 1061, 1028, 968, 920, 746 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{20}O_4Na^+$ ([M+Na]$^+$) 323.1254. Found 323.1252.



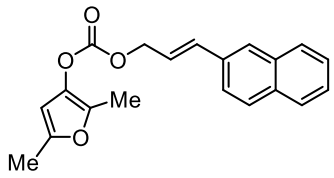
2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (4H, m), 6.69 (1H, brd, J = 16.0 Hz), 6.31 (1H, dt, J = 16.0, 6.6 Hz), 6.01 (1H, s), 4.86 (2H, d, J = 6.6, 1.0 Hz), 2.22 (3H, s), 2.18 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 148.7, 138.3, 135.1, 134.6, 134.3, 134.2, 129.0, 128.1, 122.7, 102.3, 69.1, 14.1, 10.6; IR (film) 2920, 1763, 1657, 1491, 1373, 1236, 1138, 1092, 1038, 968 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{15}O_4ClNa^+$ ([M+Na]$^+$) 329.0551. Found 329.0551.



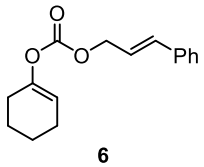
2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, J = 8.4 Hz), 7.14 (2H, d, J = 8.4 Hz), 6.71 (1H, brd, J = 16.0 Hz), 6.28 (1H, dt, J = 16.0, 6.8 Hz), 6.01 (1H, s), 4.85 (2H, dd, J = 6.8, 1.0 Hz), 2.35 (3H, s), 2.21 (3H, s), 2.17 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 148.6, 138.5, 138.3, 135.8, 135.1, 133.3, 129.5, 126.8, 120.9, 102.4, 69.6, 21.4, 14.1, 10.6; IR (film) 2932, 1709, 1558, 1447, 1418, 1296, 1244, 1076, 1028, 968 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{18}O_4Na^+$ ([M+Na]$^+$) 309.1097. Found 309.1098.



2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (1H, m), 7.21-7.13 (3H, m), 6.96 (1H, brd, J = 15.6 Hz), 6.22 (1H, dd, J = 15.6, 6.8 Hz), 6.01 (1H, s), 4.89 (2H, dd, J = 6.8, 1.2 Hz), 2.36 (3H, s), 2.22 (3H, s), 2.19 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 148.6, 138.3, 136.0, 135.2, 135.1, 133.6, 130.5, 128.4, 126.3, 126.1, 123.3, 102.4, 69.6, 19.9, 14.1, 10.6; IR (film) 2920, 1763, 1655, 1449, 1373, 1236, 1036, 966, 922, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{18}O_4Na^+$ ([M+Na]$^+$) 309.1097. Found 309.1098.



2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (4H, m), 7.62-7.60 (1H, m), 7.50-7.44 (2H, m), 6.90 (1H, brd, J = 16.0 Hz), 6.46 (1H, dd, J = 16.0, 6.8 Hz), 6.03 (1H, s), 4.93 (2H, dd, J = 6.8, 0.8 Hz), 2.22 (3H, s), 2.19 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 148.6, 138.3, 135.8, 135.1, 133.6, 133.5, 133.5, 128.5, 128.3, 127.8, 127.3, 126.6, 126.4, 123.6, 122.3, 102.4, 69.5, 14.1, 10.6; IR (film) 2920, 1763, 1653, 1506, 1456, 1373, 1246, 1138, 1038, 964, 781 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{18}O_4Na^+$ ([M+Na]$^+$) 345.1097. Found 345.1097.

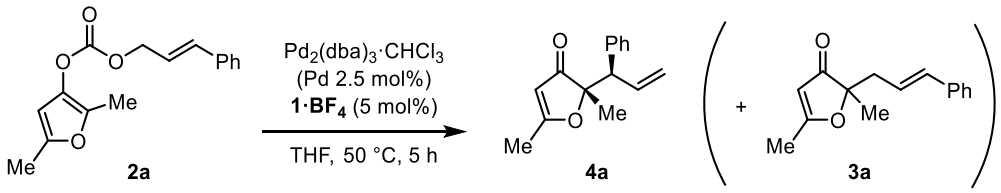


6

6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (2H, m), 7.36-7.31 (2H, m), 7.29-7.25 (1H, m), 6.71 (1H, d, J = 16.0 Hz), 6.31 (1H, dd, J = 16.0, 6.8 Hz), 5.51-5.48 (1H, m), 4.80 (2H, dd, J = 6.8, 1.2 Hz), 2.22-2.19 (2H, m), 2.14-2.09 (2H, m), 1.78-1.72 (2H, m), 1.63-1.56 (2H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.6, 148.8,

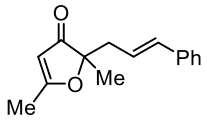
136.2, 135.2, 128.8, 128.4, 126.9, 122.4, 114.3, 68.7, 26.6, 23.7, 22.7, 21.7; IR (film) 2940, 1751, 1449, 1381, 1246, 1233, 1152, 1026, 966, 781 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{18}O_3Na^+$ ($[M+Na]^+$) 281.1148. Found 281.1151.

2.4.3 General Procedure for Branch-Selective Allylation of Furan-3(2*H*)-one-derived Allylic Enol Carbonate 2:

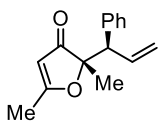


To a Schlenk flask was added $Pd_2(dba)_3{\cdot}CHCl_3$ (1.3 mg, 1.3 □mol) and **1·BF$_4$** (2.1 mg, 5.0 □mol), and the flask was evacuated and refilled with Ar three times. After the addition of THF (0.50 mL), the resulting catalyst mixture was degassed by alternating vacuum evacuation/Ar backfill at –78 °C. The mixture was warmed up to 50 °C and enol carbonate **2a** (27.2 mg, 0.1 mmol) was successively added. After stirring for 5 h at the same temperature, the reaction mixture was cooled to room temperature. Filtration through the short silica-gel pad with the aid of EtOAc and concentration of the filtrate were performed. The resulting crude residue was purified by column chromatography on silica gel (hexane/ EtOAc = 10:1 as eluent) to furnish **4a** (22.8 mg, 0.099 mmol, 99% yield, **3a**:**4a** = 1:>20, dr = 13:1) as a yellow liquid.

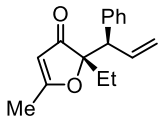
2.4.4 Characterization Data for the Allylated Product 3a, 4 and 8:



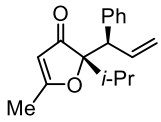
3a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (4H, m), 7.23-7.19 (1H, m), 6.46 (1H, brd, J = 15.6 Hz), 6.05 (1H, ddd, J = 15.6, 8.2, 7.4 Hz), 5.39 (1H, s), 2.62 (1H, ddd, J = 14.6, 7.4, 1.2 Hz), 2.57 (1H, ddd, J = 14.6, 8.2, 1.2 Hz), 2.20 (3H, s), 1.40 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.8, 188.7, 137.3, 134.5, 128.7, 127.6, 126.4, 122.6, 103.3, 90.8, 40.3, 21.4, 17.0; IR (film) 2978, 1699, 1601, 1387, 1346, 1161, 1114, 966, 799, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{16}O_2Na^+$ ($[M+Na]^+$) 251.1043. Found 251.1049.



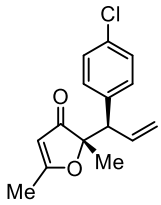
4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (4H, m), 7.28-7.24 (1H, m), 5.98 (1H, ddd, J = 16.8, 10.2, 8.8 Hz), 5.39 (1H, s), 5.07 (1H, brd, J = 16.8 Hz), 5.04 (1H, d, J = 10.2 Hz), 3.61 (1H, d, J = 8.8 Hz), 2.23 (3H, s), 1.18 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.8, 189.0, 139.1, 134.9, 129.3, 128.6, 127.2, 118.4, 104.3, 92.8, 56.1, 21.2, 17.0; IR (film) 1699, 1601, 1435, 1387, 1344, 1155, 957, 922, 795, 750 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{16}O_2Na^+$ ($[M+Na]^+$) 251.1043. Found 251.1042.



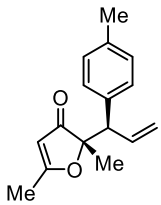
4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (4H, m), 7.27-7.22 (1H, m), 6.03 (1H, ddd, J = 17.2, 10.2, 9.0 Hz), 5.40 (1H, s), 5.07 (1H, brd, J = 17.2 Hz), 5.04 (1H, brd, J = 10.2 Hz), 3.62 (1H, d, J = 9.0 Hz), 2.22 (3H, s), 1.73 (1H, dq, J = 14.6, 7.4 Hz), 1.52 (1H, dq, J = 14.6, 7.4 Hz), 0.69 (3H, t, J = 7.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.4, 189.8, 139.2, 134.9, 129.2, 128.5, 127.1, 118.3, 106.3, 95.9, 56.1, 28.2, 16.7, 7.1; IR (film) 2938, 1701, 1603, 1452, 1387, 1346, 1159, 951, 924, 752 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{18}O_2Na^+$ ([M+Na]$^+$) 265.1199. Found 265.1205.



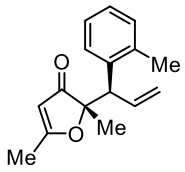
4c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (5H, m), 6.26 (1H, ddd, J = 17.2, 10.2, 9.2 Hz), 5.22 (1H, s), 5.10 (1H, brd, J = 17.2 Hz), 5.09 (1H, d, J = 10.2 Hz), 3.83 (1H, d, J = 9.2 Hz), 2.10 (3H, s), 2.09 (1H, sept, J = 6.8 Hz), 0.92 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.3, 189.3, 139.2, 135.0, 129.3, 128.2, 127.0, 118.1, 106.8, 96.7, 53.8, 32.0, 16.5, 16.1, 15.7; IR (film) 2972, 1695, 1607, 1456, 1387, 1342, 1144, 966, 932, 743 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{21}O_2^+$ ([M+H]$^+$) 257.1536. Found 257.1536.



4d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz), 5.95 (1H, ddd, J = 17.2, 10.2, 8.8 Hz), 5.38 (1H, s), 5.06 (1H, brd, J = 10.2 Hz), 5.06 (1H, brd, J = 17.2 Hz), 3.60 (1H, d, J = 8.8 Hz), 2.22 (3H, s), 1.18 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.5, 189.0, 137.6, 134.4, 133.1, 130.6, 128.7, 118.8, 104.4, 92.4, 55.5, 21.2 17.0; IR (film) 2980, 1701, 1603, 1491, 1387, 1344, 1155, 1092, 957, 791 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{15}O_2ClNa^+$ ([M+Na]$^+$) 285.0653. Found 285.0654.

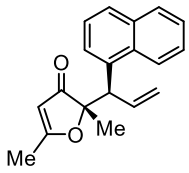


4e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 8.0 Hz), 5.95 (1H, ddd, J = 17.2, 10.2, 9.0 Hz), 5.39 (1H, s), 5.06 (1H, brd, J = 17.2 Hz), 5.02 (1H, brd, J = 10.2 Hz), 3.58 (1H, d, J = 9.0 Hz), 2.33 (3H, s), 2.23 (3H, s), 1.17 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.0, 189.0, 136.8, 136.1, 135.1, 129.3, 129.1, 118.2, 104.3, 93.0, 55.7, 21.2, 21.2, 17.0; IR (film) 2922, 1699, 1603 1514, 1387, 1344, 1155, 957, 920, 787 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{19}O_2^+$ ([M+H]$^+$) 243.1380. Found 243.1380.

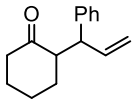


4f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 7.6 Hz), 7.22-7.12 (3H, m), 5.85 (1H, ddd, J = 17.4, 10.0, 8.4 Hz), 5.43 (1H, s), 5.01 (1H, brd, J = 17.4 Hz), 5.00 (1H, brd, J = 10.0 Hz), 3.97 (1H, d, J = 8.4 Hz), 2.37 (3H, s), 2.25 (3H, s), 1.19 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.1, 189.0, 137.4, 136.8, 135.1, 130.7, 128.6, 126.9, 126.3, 118.2, 104.2, 93.5, 50.7, 20.8, 20.2, 17.0; IR (film) 2976, 1701, 1603, 1435, 1387, 1344,

1155, 957, 922, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{18}O_2Na^+$ ([M+Na]$^+$) 265.1199. Found 265.1206.



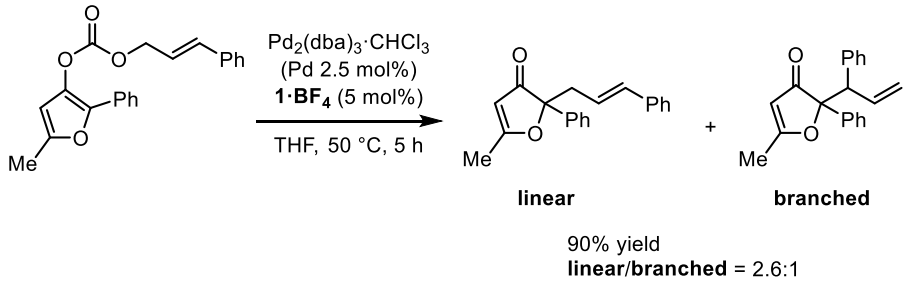
4g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.75 (4H, m), 7.54-7.40 (3H, m), 6.07 (1H, ddd, J = 17.2, 10.2, 8.8 Hz), 5.40 (1H, s), 5.10 (1H, brd, J = 17.2 Hz), 5.07 (1H, brd, J = 10.2 Hz), 3.80 (1H, d, J = 8.8 Hz), 2.24 (3H, s), 1.21 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.8, 189.1, 136.7, 134.8, 133.6, 132.7, 128.3, 128.2, 128.0, 127.7, 127.2, 126.2, 125.9, 118.7, 104.4, 92.9, 56.3, 21.3, 17.0; IR (film) 2978, 1699, 1601, 1437, 1387, 1344, 1157, 955, 926, 797 cm^{-1}; HRMS (ESI) Calcd for $C_{19}H_{18}O_2Na^+$ ([M+Na]$^+$) 301.1199. Found 301.1198.



8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.15 (5H, m), 5.88 (1H, ddd, J = 17.2, 10.0, 8.8 Hz), 5.09 (1H, brd, J = 17.2 Hz), 5.06 (1H, brd, J = 10.0 Hz), 3.81 (1H, app t, J = 8.8 Hz), 2.82-2.76 (1H, m), 2.38-2.31 (1H, m), 2.30-2.20 (1H, m), 2.17-2.12 (1H, m), 2.02-1.95 (1H, m), 1.95-1.86 (1H, m), 1.80-1.58 (3H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.8, 143.4, 139.4, 128.5, 128.0, 126.4, 116.4, 55.4, 49.5, 42.5, 31.7, 28.5, 24.5; IR (film) 2930, 1703, 1603, 1449, 1387, 1344, 1155, 957, 920, 754 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{18}ONa^+$ ([M+Na]$^+$) 237.1250. Found 237.1257.

2.4.5 Decarboxylative Allylation of C-2 Aryl-Substituted Substrate:

A reaction of C-2 phenyl-substituted furan-3(2*H*)-one-derived allylic enol carbonate preferentially gave linear product (Scheme S1).



Scheme S1. An attempted reaction of C-2 aryl-substituted substrate.

2.4.6 Crystallographic Structure Determination:

Recrystallization of 4g: A single crystal of **4g** was obtained from a solution of hexane and diethyl ether at room temperature. The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 103 K on a Brucker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on *F2* by using SHELXTL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in calculated positions. The crystallographic data are summarized in Table S1 and ORTEP diagram is shown in Figure S1.

Table S1. Crystal data and structure refinement for **4g** (CCDC-1455361).

Empirical formula	$C_{19}H_{18}O_2$	
Formula weight	278.33	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 14.959(2) Å	α = 90°.
	b = 6.2782(9) Å	β = 93.428(3)°.
	c = 16.175(2) Å	γ = 90°.
Volume	1516.4(4) $Å^3$	
Z	4	
Density (calculated)	1.219 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	

F(000)	592
Crystal size	0.70 x 0.20 x 0.15 mm^3
Theta range for data collection	1.80 to 28.28°.
Index ranges	-14<=h<=19, -7<=k<=8, -21<=l<=21
Reflections collected	10502
Independent reflections	3750 [R(int) = 0.0395]
Completeness to theta = 28.28°	99.6 %
Absorption correction	Empirical
Max. and min. transmission	0.9884 and 0.9476
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3750 / 0 / 192
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1367
R indices (all data)	R1 = 0.0603, wR2 = 0.1143
Largest diff. peak and hole	0.359 and -0.236 e.$Å^{-3}$

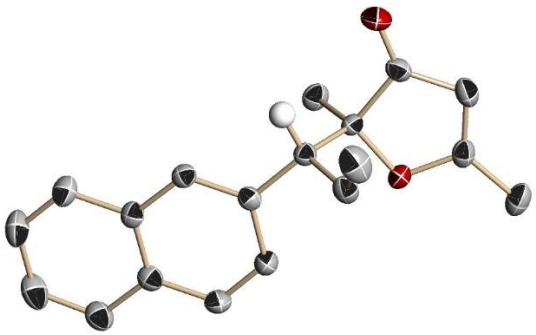


Figure S1. Molecular structure of **4g**. All calculated hydrogen atoms except for one attached to stereogenic center are omitted for clarity. red = oxygen, black = carbon, white = hydrogen.

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14) For detail, see the Supporting Information.

15) The relative stereochemistry of major diastereomer of **4g** was established by X-ray crystallographic analysis (CCDC-1455361), and the stereochemistry of the remaining examples were assumed by analogy.

Chapter 3

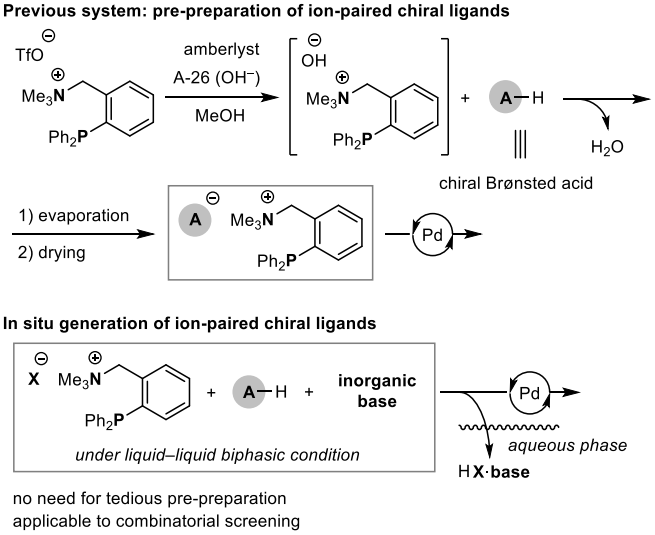
In-Situ Generation of Ion-Paired Chiral Ligands: Rapid Identification of Optimal Ligand for Palladium-Catalyzed Asymmetric Allylation

3.1 Introduction

The discovery of a molecular catalyst that exerts high activity and stereoselectivity for target asymmetric transformation is often essential in various synthetic endeavors in academia and industry; yet it is usually a laborious task, relying to a great extent on trial and error. Despite rapid advances in theoretical chemistry, the rational design of chiral catalysts remains a formidable challenge because of the very small energy differences in the competing transition states leading to different enantiomers.[1,2] In addition, the reactivity and selectivity profiles of catalytic asymmetric reactions are sensitive to both the steric and electronic nature of reactants; thus, an optimal catalyst for a particular substrate is not necessarily effective for other substrates with similar structures. Accordingly, a truly combinatorial approach to significantly accelerate the catalyst discovery process is much sought after.[3-5] As a means for addressing this important issue, supramolecular chiral ligands and catalysts, spontaneously assembled from relatively simple molecular components through noncovalent interactions, have been introduced and successfully applied to the synthetically useful bond-forming reactions.[6-9] The inherent modularity of supramolecular catalysts would allow the expeditious construction of structurally diverse and meaningful catalyst libraries. However, this possibility has rarely been exploited in the actual evaluation of the combinatorially formed mixtures of individual catalysts for rapidly identifying the best one. The pioneering study by Breit and the recent Reek's contribution provide the only examples reported to date, which specifically focused on the identification of optimal bidentate ligands for asymmetric hydrogenation.[10] This situation is largely due to the deficiency of reliable methods for generating sufficient libraries of chiral catalysts within a short time frame for efficient high-throughput screening; hence, the full potential of this powerful approach is yet to be realized, particularly in terms of solving synthetic problem such as the development of difficult-to-control asymmetric carbon–carbon bond formations.

Here, the author report a new system for the combinatorial rapid ligand identification and its viability in developing an unprecedented palladium-catalyzed asymmetric allylic alkylation protocol. The author's strategy is based on the establishment of a method for *in-situ* generation of ion-paired chiral ligands of type **3**[11] (see Scheme for Table 3.1) from simple salts of ammonium phosphines and axially chiral phosphoric acids[12-16] under phase-transfer conditions (Scheme 3.1). This method obviates the pre-preparation of the individual ion-paired ligands by the ion-exchange technique and thus enables its application to combinatorial ligand screening in palladium catalysis for achieving a highly enantioselective allylation of benzo[b]thiophen-2(3*H*)-ones.

Scheme 3.1 Preparation of ion-paired chiral ligands



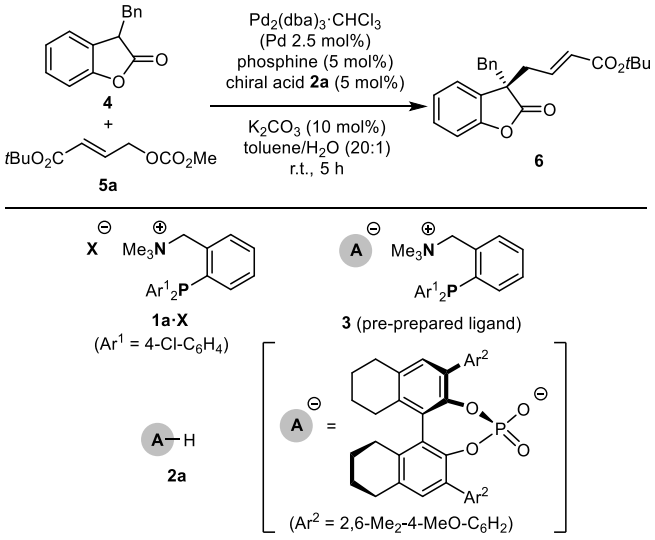
3.2 Result and Discussion

3.2.1 Optimization of the reaction conditions

The conception of devising a practical method for the *in-situ* generation of ion-paired chiral ligand **3** and its analogues arose from the author's continued effort for taking full advantage of this multicomponent ligand, consisting of readily accessible ammonium phosphines and chiral phosphate ions, in synthetic reaction development. Because **3** was recently identified as an effective chiral ligand for the palladium-catalyzed, highly enantioselective bond formation between 3-benzylbenzofuranone **4** and allylic carbonate **5a** by testing a series of each pre-prepared ion-paired ligand, The author considered this allylation as an ideal benchmark to evaluate the feasibility of the *in-situ* generation of **3** through ion metathesis under phase-transfer conditions. After reconfirming the performance of pre-prepared **3** (entry 1 in Table 1), the initial trial was carried out by simply stirring an equimolar mixture of **4** and **5a** with $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%), bromide salt of ammonium phosphine **1a·Br** (5 mol%), and chiral phosphoric acid **2a** (5 mol%) in toluene and an aqueous solution of K_2CO_3 (10 mol%) as the acid scavenger to facilitate the expected ion exchange at room temperature. Although the reaction proceeded smoothly, allylated product **6** was obtained with a negligible degree of enantioselectivity (entry 2). The observed lack of selectivity could be ascribed to the inefficiency of the ion exchange process between **1a·Br** and **2a**; thus, the reaction was mostly catalyzed by the palladium-**1a·Br** complex. The author reasoned that the properties, such as basicity and hydrophilicity, of the anion moiety (**X**) would affect the capability of **1a·X** both as an achiral ligand for palladium (nonstereoselective background reaction) and as a precursor for the generation of **3** through the

requisite ion exchange with **2a** under liquid–liquid biphasic conditions (stereoselective reaction).[17,18] In fact, while the change of **1a·Br** to ammonium phosphine with more lipophilic iodide ion (**1a·I**) failed to improve the reaction outcome (entry 3), the employment of hydrophilic acetate salt **1a·OAc** yielded **6** quantitatively with dramatic enhancement of enantioselectivity (entry 4). Eventually, hydrogensulfate salt **1a·HSO4** was found to be the most suitable precursor for the *in-situ* generation of ion-paired chiral ligand **3**, allowing the isolation of **6** in 95% yield with 93% ee (entry 5). It should be noted that the attempted reaction with tris(4-chlorophenyl)phosphine as an achiral ligand instead of **1a·X** under otherwise identical conditions afforded racemic **6** (entry 6), corroborating that the combined use of ammonium phosphine and the chiral acid is crucial for the stereocontrol.

Table 3.1 *In-situ* generation of ion-paired chiral ligand for Pd-catalyzed asymmetric allylation.[a]



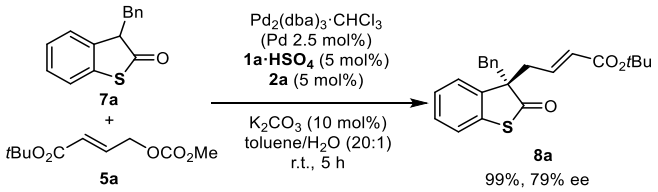
Entry	Phosphine	Yield [%][b]	ee [%][c]
1[d]	**3**	99	92
2	**1a·Br**	78	–11
3	**1a·I**	26	–5
4	**1a·OAc**	99	90
5	**1a·HSO$_4$**	95	93
6	P(4-Cl-C$_6$H$_4$)$_3$	40	<1

[a] Unless otherwise noted, reactions were carried out with 0.10 mmol of **4** and 0.10 mmol of **5a** in the presence of $Pd_2(dba)_3·CHCl_3$ (Pd 2.5 mol%), phosphine (5 mol%), **2a** (5 mol%), and K_2CO_3 in toluene (1.0 mL)/H_2O (0.05 mL) at room temperature. [b] Isolated yield of **6**. [c] Enantiomeric excess of **6** was determined by chiral HPLC analysis. [d] The reaction was carried out without chiral acid **2a** and K_2CO_3.

Having established the system for the *in-situ* generation of ion-paired chiral ligands, the author pursued its utilization for combinatorial ligand screening, particularly for the development of a new

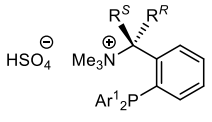
asymmetric palladium-catalyzed reaction. As a target transformation, the author selected the asymmetric allylation of a sulfur analogue of benzofuran-2(3*H*)-one, 3-substituted benzo[b]thiophen-2(3*H*)-one,[19,20] considering not only the relevance of C(3)-quaternary benzothiophenones as a core structure of potent pharmaceuticals,21 but also the presumed difficulty in rigorous stereocontrol using the ligand effective for the benzofuranone allylation despite the structural similarity. As anticipated, exposure of 3-benzylbenzothiophenone **7a** to the optimized conditions for the allylation with *in-situ* generated ion-paired ligand **3** resulted in the quantitative formation of the desired product **8a**, albeit with a markedly lower level of enantioselection (Scheme 3.2). This observation represents an obstacle often encountered in expanding the scope of the asymmetric catalysis of prominent ligand-transition metal complexes and emphasizes the importance of a high-throughput screening strategy as a viable solution to surmount it.

Scheme 3.2 Asymmetric allylation of 3-benzylbenzothiophenone **7a** with **5a** under the conditions optimized for the reaction of **4** with in situ-generated **3**.

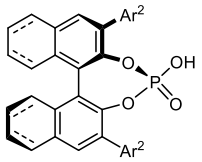


To rapidly identify an optimal ion-paired chiral ligand for the palladium-catalyzed asymmetric allylation of benzothiophenones **7** by exploiting the *in-situ* generation system, the author decided to adopt the iterative deconvolution strategy.[10a] For this purpose, the author prepared 12 ammonium phosphines (**1a**-**1l**) as a form of hydrogensulfate and 12 chiral phosphoric acids (**2a**-**2l**), from which 144 combinations of ion pairs could be generated (Figure 3.1). The 12 phosphines and 12 chiral acids were then divided into three groups (**1a**-**1d**, **1e**-**1h**, and **1i**-**1l**) and two groups (**2a**-**2f** and **2g**-**2l**), respectively. Each group of four ammonium phosphines **1·HSO4** and each group of six chiral acids **2** were mixed in a single flask and subjected to the reaction of **7a** with **5a**, where a total of 5 mol% phosphines and the same amount of a mixture of acids were used as the precursors of ion-paired chiral ligands. All six experiments were performed by combining the groups of phosphines with those of acids, and the results are summarized in Figure 3.2, Step 1. The catalyst activity was sufficient in all the cases, and the highest enantioselectivity was attained in the reaction with a mixture of the group of phosphines **1e**-**1h** and the group of acids **2g**-**2l**. With this information in hand, the author further divided phosphines **1e**-**1h** and acids **2g**-**2l** each into two groups as shown in Figure 3.2, Step 2. The similar experiments were then repeated by combining each group of two phosphines with each group of two acids, which revealed the combination of the group of ammonium phosphines **1g**, **1h** and the group of phosphoric acids **2g**-**2i** as the optimal candidate for ligand precursors. Finally, the author evaluated the performance of the remaining six combinations of each ligand component (Figure 3.2,

Step 3) and found that the combination of **1h·HSO4** and **2h** allowed the generation of the ion-paired ligand that exerted excellent catalytic activity and stereocontrolling ability in this asymmetric allylation, leading to produce **8a** quantitatively with 94% ee.



1·HSO4



2: octahydrobinaphthyl (**H8**) or binaphthyl (**B**)

1	R^S	R^R	Ar^1
1a	H	H	4-Cl-C_6H_4
1b	H	H	4-MeO-C_6H_4
1c	H	H	4-F-C_6H_4
1d	H	H	4-CF_3-C_6H_4
1e	H	Me	4-Cl-C_6H_4
1f	H	Me	4-MeO-C_6H_4
1g	H	Me	4-F-C_6H_4
1h	H	Me	4-CF_3-C_6H_4
1i	Me	H	4-Cl-C_6H_4
1j	Me	H	4-MeO-C_6H_4
1k	Me	H	4-F-C_6H_4
1l	Me	H	4-CF_3-C_6H_4

2		Ar^2
2a	**H8**	2,6-Me_2-4-MeO-C_6H_2
2b	**H8**	2,6-Et_2-4-MeO-C_6H_2
2c	**H8**	2,4,6-$(MeO)_3$-C_6H_2
2d	**H8**	2,4,6-Me_3-C_6H_2
2e	**H8**	4-Ph-C_6H_4
2f	**H8**	β-Naph
2g	**B**	2,6-Me_2-4-MeO-C_6H_2
2h	**B**	2,6-Et_2-4-MeO-C_6H_2
2i	**B**	2,4,6-$(MeO)_3$-C_6H_2
2j	**B**	2,4,6-Me_3-C_6H_2
2k	**B**	4-Ph-C_6H_4
2l	**B**	β-Naph

Figure 3.1 Library of ammonium phosphines **1** and chiral acids **2**.

In general, a mixture of monodentate phosphines could generate the corresponding palladium complexes coordinated by two different monodentate phosphines, namely, heterocomplexes, as well as homo-complexes bearing the same two phosphines. Because these hetero-complexes would exhibit different stereoselectivity from the homo-complexes,[22] it was uncertain if the iterative deconvolution of the *in-situ* prepared, monodentate ion-paired ligands led to the identification of the best combination of ammonium phosphine and chiral phosphoric acid. Therefore, although the optimal ligand system was identified from the above 16 experiments, there remained the possibility that the best of all the possible 144 combinations could be a different combination. To assess the validity of the iterative deconvolution, the author carried out 144 reactions of **7a** with **5a** using all the possible combinations of ammonium phosphines **1·HSO4** and phosphoric acids **2** individually (Figure 3.3).[23] The results from these evaluations confirmed that the combination of **1h·HSO4** and **2h** was indeed the precursor of the most effective ligand in terms of both reactivity and stereoselectivity.

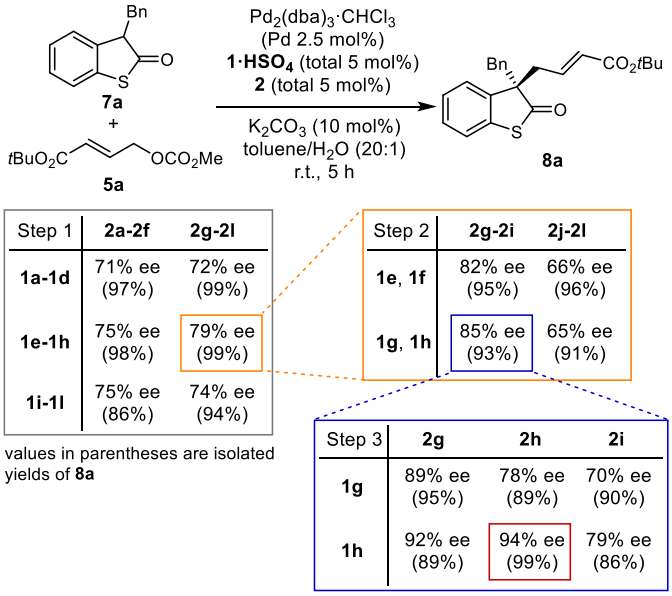


Figure 3.2 Combinatorial screening of ligand libraries.

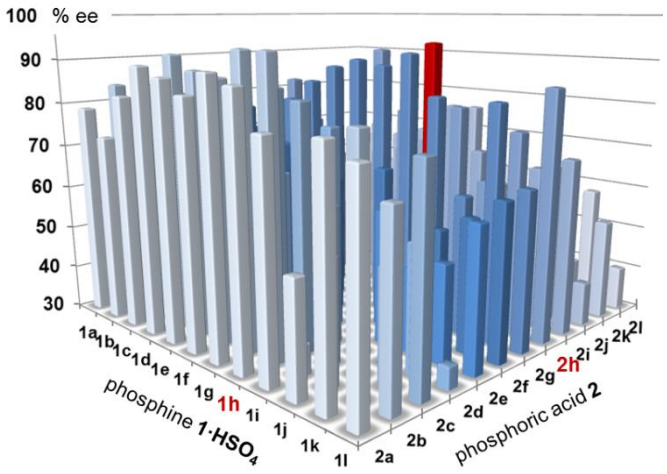


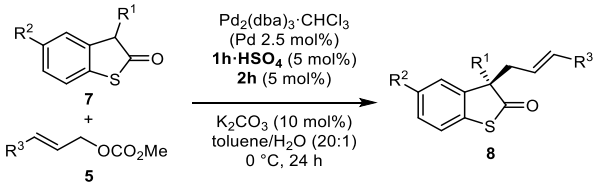
Figure 3.3 Individual evaluations of all possible 144 combinations

3.2.2 Generality

After a brief adjustment in the reaction temperature, which showed that even higher enantioselectivity could be attained at 0 °C (entry 1 in Table 3.2), further experiments were conducted to probe the substrate scope of the present asymmetric allylation of benzothiophenones **7** using the newly identified, optimal combination of ammonium phosphine **1h·HSO4** with chiral acid **2h**. Significant structural variations in the 3-alkyl substituents of benzothiophenones were well tolerated, and the corresponding allylated products were obtained with uniformly high enantioselectivities

(entries 2-7). Benzothiophenones possessing methyl or chlorine at the C-5 position also appeared to be good substrates (entries 8 and 9). In addition, synthetically satisfactory levels of enantiocontrol were feasible with allylic carbonate having different electron-withdrawing groups such as methyl ester or phenyl ketone (entries 10 and 11).

Table 3.2 Substrate scope.[a]



Entry	**7** (R^1, R^2)	**5** (R^3)	**8**	Yield [%][b]	ee [%][c]
1	**7a** (Bn, H)	**5a** (CO_2tBu)	**8a**	95	97
2	**7b** (Me, H)	**5a**	**8b**	89	93
3	**7c** (*n*Bu, H)	**5a**	**8c**	89	94
4	**7d** (*i*Pr, H)	**5a**	**8d**	93	97
5	**7e** (*i*Bu, H)	**5a**	**8e**	92	95
6	**7f** (CH_2CO_2Me, H)	**5a**	**8f**	91	92
7	**7g** [$(CH_2)_3$Ph, H]	**5a**	**8g**	99	95
8	**7h** (Bn, Me)	**5a**	**8h**	91	96
9	**7i** (Bn, Cl)	**5a**	**8i**	96	95
10	**7a**	**5b** (CO_2Me)	**8j**	92	93
11[d]	**7a**	**5c** (COPh)	**8k**	99	89

[a] Unless otherwise noted, the reactions were carried out with 0.10 mmol of **7** and 0.10 mmol of **5** in the presence of $Pd_2(dba)_3$·$CHCl_3$ (Pd 2.5 mol%), **1h·HSO₄** (5 mol%), **2h** (5 mol%), and K_2CO_3 in toluene (1.0 mL)/H_2O (0.05 mL) at 0 °C. [b] Isolated yield of **8**. [c] Enantiomeric excess of **8** was determined by chiral HPLC analysis. The absolute configuration of **8a** was established to be *R* by X-ray diffraction analysis, and the stereochemistry of the remaining examples were assumed by analogy. [d] Performed at –5 °C.

3.3 Conclusion

In conclusion, the author established a method for the *in-situ* generation of ion-paired chiral ligands from simple salts of ammonium phosphines and chiral Brønsted acids under phasetransfer conditions. This method was successfully utilized for the combinatorial ligand screening in palladium catalysis, which enabled the rapid identification of the optimal ion-paired ligand for achieving the first highly enantioselective allylation of benzothiophenones. The author believe that the author's approach based on the inherently combinatorial nature of the ion-paired chiral ligands paves the way for the development of hitherto difficult, transition-metal-catalyzed asymmetric bond-forming reactions.

3.4 Experimental section

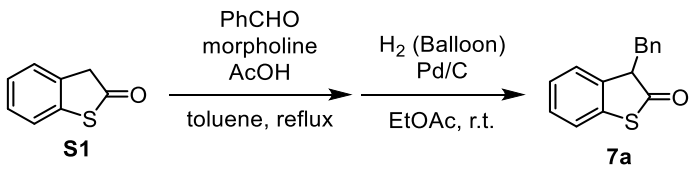
3.4.1 General information

Infrared spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet and m = multiplet) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$; 77.16 ppm). ^{31}P NMR spectra were recorded on a JEOL JNM-ECS400 (162 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from H_3PO_4 (0.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were measured on a Thermo Fisher Scientific Exactive (ESI). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on PSQ60AB (spherical, 40-50 μm; FUJI SILYSIA CHEMICAL Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns (φ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALCEL OZ-3 (OZ3), CHIRALPAC IC-3 (IC3) and CHIRALPAC AD-3 (AD3)) with hexane (H) and isopropyl alcohol (IPA) as eluent.

All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. The manipulations for Pd-catalyzed reactions were carried out with standard Schlenk techniques under Ar. Toluene was supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by both A2 alumina and Q5 reactant using a GlassContour solvent dispensing system. Allylic carbonates **5** were synthesized from the corresponding allylic alcohols. Other simple chemicals were purchased and used as such.

3.4.2 Experimental procedures and characterization

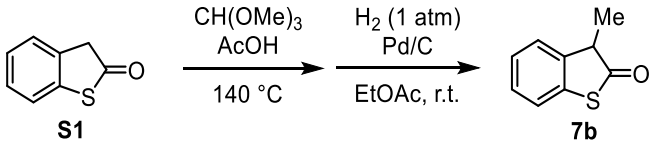
3.4.2.1 Representative procedures for synthesis of benzothiophenones 7:



S1 **7a**

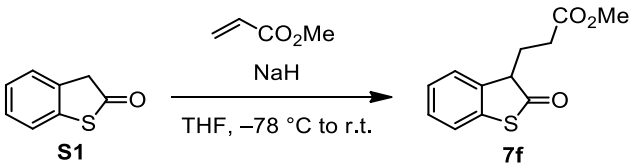
To a solution of **S1** (891 mg, 3.74 mmol) in toluene (10 mL) were added benzaldehyde (0.76 mL, 7.48 mmol), morpholine (0.032 mL, 0.37 mmol), and acetic acid (0.021 mL, 0.37 mmol) , and whole reaction mixture was refluxed with stirring for 12 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of EtOAc, and then concentrated. The resulting residue was dissolved in EtOAc (10 mL), and the

flask was degassed by alternating vacuum evacuation/Ar backfill. After successive addition of 10% Pd/C (400 mg) at 0 °C, the reaction flask was evacuated again and refilled with H_2 three times. The resulting suspension was stirred for 12 h at room temperature. After flushing the remaining H_2 out with Ar, the mixture was filtered to remove Pd/C and the filtercake was rinsed with EtOAc. The filtrate was evaporated and the residue was purified by silica gel column chromatography (H/EtOAc = 30:1 as eluent) to give **7a** (737 mg, 3.07 mmol, 82% yield) as an off-yellow oil. Benzothiophenones (**7c**, **7d**, **7e**, **7g**, **7h** and **7i**) were synthesized by following the same procedure. **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28-7.18 (5H, m), 7.12 (1H, ddd, J = 7.8, 6.8, 1.9 Hz), 7.08-7.05 (2H, m), 6.90 (1H, d, J = 7.8 Hz), 4.07 (1H, dd, J = 7.8, 4.8 Hz), 3.42 (1H, dd, J = 14.0, 4.8 Hz), 3.16 (1H, dd, J = 14.0, 7.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 136.7, 136.2, 136.1, 129.7, 128.5, 128.5, 127.0, 125.9, 125.5, 123.1, 58.3, 38.9; IR (film) 3063, 3028, 2922, 1703, 1466, 1449, 1022, 748, 737, 696 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{15}H_{11}O_1S_1^-$ ([M–H]$^-$) 239.0525. Found 239.0531.



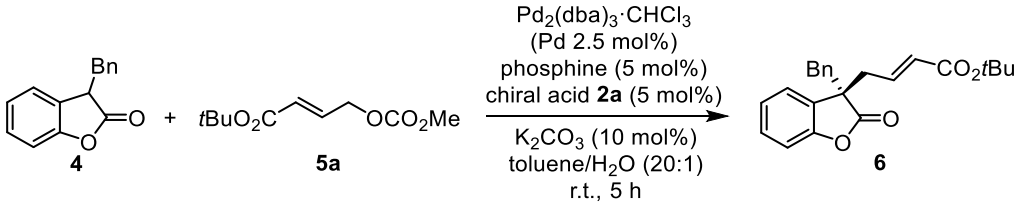
S1 **7b**

A round-bottomed flask was charged with **S1** (751mg, 5.0 mmol) and trimethyl orthoformate (2.5 mL, 15 mmol) in acetic acid (1.9 mL, 20 mmol). The solution was stirred at 140 °C in an oil bath for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Extractive work-up was conducted with EtOAc three times, and the combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated. To a solution of the resulting residue in EtOAc (3 mL) was added 10% Pd/C (87 mg) at 0 °C under Ar, the reaction flask was evacuated again and refilled with H_2 three times. The resulting suspension was stirred for 12 h at room temperature. After flushing the remaining H_2 out with Ar, the mixture was filtered to remove Pd/C and the filtercake was rinsed with EtOAc. The filtrate was evaporated and the residue was purified by silica gel column chromatography (H/EtOAc = 10:1 as eluent) to give **7b** (95 mg, 0.58 mmol, 71% yield) as a colorless oil. **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, d, J = 7.8 Hz), 7.32-7.22 (3H, m), 3.83 (1H, q, J = 7.8 Hz), 1.55 (3H, d, J = 7.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0, 138.3, 135.5, 128.5, 126.4, 124.6, 123.1, 52.2, 17.4; IR (film) 2978, 2932, 1711, 1468, 1445, 1101, 1005, 924, 750, 696 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_9H_7O_1S_1^-$ ([M–H]$^-$) 163.0223. Found 163.0211.



A dried two neck flask was charged with NaH (67 mg, 1.68 mmol) in THF (2 mL) under Ar. To this suspention was dropwised a solution of **S1** (253 mg, 1.68mmol) in THF (2 mL) at 0 ºC, and the resulting mixture was stirred for 30 min at the same temperature. The reaction solution was then slowly transferred via cannula into a cooled solution of methyl acrylate (0.076 mL, 0.84 mmol) in THF (2 mL) at –78 °C. After stirring for 15 min, the reaction mixture was allowed to warm gradually to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). Extractive work-up was conducted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10:1 H/EtOAc) to afford **7f** (79 mg, 0.33 mmol, 40% yield) as a red liquid. **7f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, J = 7.3 Hz), 7.33-7.26 (2H, m), 7.24 (1H, dd, J = 8.2, 1.2 Hz), 3.90 (1H, dd, J = 6.0, 4.1 Hz), 3.63 (3H, s), 2.51-2.2.40 (2H, m), 2.34-2.23 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 173.2, 136.1, 135.9, 128.7, 126.5, 124.9, 123.2, 55.7, 51.8, 29.5, 27.6; IR (film) 2951, 1732, 1703, 1593, 1447, 1437, 1211, 1175, 1009, 748 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{12}H_{11}O_3S_1^-$ ([M–H]$^-$) 235.0423. Found 235.0427.

3.4.2.2 General procedure for *in-situ* generation of ion-paired chiral ligand

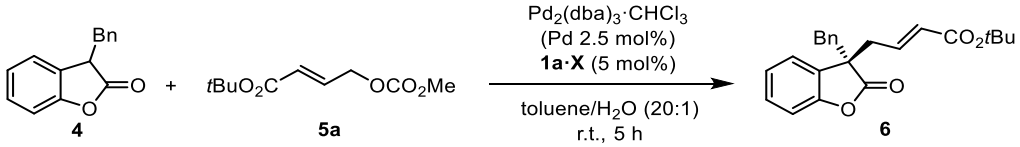


To a Schlenk flask were added 3-benzylbenzofuranone **4** (22.4 mg, 0.1 mmol), $Pd_2(dba)_3$·$CHCl_3$ (1.29 mg, 0.0013 mmol), ammonium phosphine **1a·HSO$_4$** (2.5 mg, 0.005 mmol), chiral phosphoric acid **2a** (3.12 mg, 0.005 mmol) and K_2CO_3 (1.38 mg, 0.01 mmol) and the flask was degassed by alternating vacuum evacuation/Ar backfill. Then, toluene (1 mL) was added, and the resulting catalyst mixture was evacuated and refilled with Ar three times. After addition of H_2O (0.05 mL), allylic carbonate **5a** (21.6 mg, 0.1 mmol) was successively introduced at room temperature. After stirring for 5 h at the same temperature, the reaction mixture was directly subjected to the purification by column chromatography on silica gel (H/EtOAc = 10:1 as eluent) to afford **6** (34.6 mg, 0.095 mmol, 95% yield) as a colorless liquid.

3.4.2.3 Additional control experiments

To verify the activity of the catalyst prepared from $Pd_2(dba)_3{\cdot}CHCl_3$ and precursors 1a·X, the reactions of 4 with 5a were conducted under the similar conditions described in Table 1 without chiral acid 2a and K_2CO_3. The results were summarized in Table S1. The reason why the reaction using 1a·I solely as a ligand showed higher conversion than that of the reaction with 1a·I, 2a, and K_2CO_3 (Table 3.3, entry 2 vs Table 3.1, entry 3) is unclear at present. While bond formation did not take place at all when $1a{\cdot}HSO_4$ was used as a ligand (entry 4), an attempted reaction with the same ligand in the absence of H_2O furnished allylated benzofuranone 6 in moderate yield (entry 5). These results suggested that $1a{\cdot}HSO_4$ would dissolve in water and thus could not form the corresponding Pd complex without ion-exchange event.

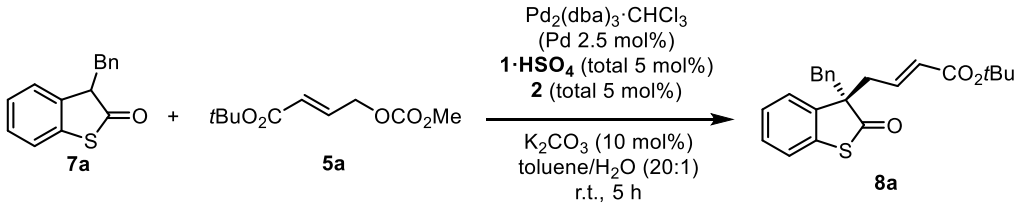
Table 3.3 Palladium-catalyzed allylation of 4 with 5a using achiral 1a·X as a ligand.[a]



entry	phosphine	yield [%][b]
1	**1a·Br**	62
2	**1a·I**	88
3	**1a·OAc**	90
4	**$1a{\cdot}HSO_4$**	0
5[c]	**$1a{\cdot}HSO_4$**	47

[a] Reactions were carried out with 0.10 mmol of 4 and 0.10 mmol of 5a in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%) and 1a·X (5 mol%) in toluene (1.0 mL)/H_2O (0.05 mL) at room temperature. [b] Isolated yield of 6. [c] The reaction was conducted without H_2O.

3.4.2.4 General procedure for asymmetric allylation – combinatorial catalyst screening



To a Schlenk flask were added 3-benzylbenzothiophenone **7a** (the amount is shown below), $Pd_2(dba)_3{\cdot}CHCl_3$, ammonium phosphines **$1{\cdot}HSO_4$**, chiral phosphoric acids **2** and K_2CO_3, and the flask was degassed by alternating vacuum evacuation/Ar backfill. Then, toluene was added, and the

resulting catalyst mixture was evacuated and refilled with Ar three times. After addition of H_2O, allylic carbonate **5a** was successively introduced at room temperature. After stirring for 5 h at the same temperature, the reaction mixture was directly subjected to the purification by column chromatography on silica gel (H/EtOAc = 10:1 as eluent) to afford **8a** as a colorless liquid.

Step 1:

benzothiophenone **7a**	0.4 mmol	1.0 equiv
allylic carbonate **5a**	0.4 mmol	1.0 equiv
$Pd_2(dba)_3{\cdot}CHCl_3$	0.0052 mmol	2.5 mol%
4 × ammonium phosphine **1·HSO₄** e	ach 0.005 mmol	5 mol%
6 × phosphoric acid **2**	each 0.0033 mmol	5 mol%
K_2CO_3	0.04 mmol	10 mol%
toluene 4.0 mL, H_2O 0.2 mL		

Step 2:

benzothiophenone **7a**	0.2 mmol	1.0 equiv
allylic carbonate **5a**	0.2 mmol	1.0 equiv
$Pd_2(dba)_3{\cdot}CHCl_3$	0.0026 mmol	2.5 mol%
2 × ammonium phosphine **1·HSO₄**	each 0.005 mmol	5 mol%
3 × phosphoric acid **2**	each 0.0033 mmol	5 mol%
K_2CO_3	0.02 mmol	10 mol%
toluene 2.0 mL, H_2O 0.1 mL		

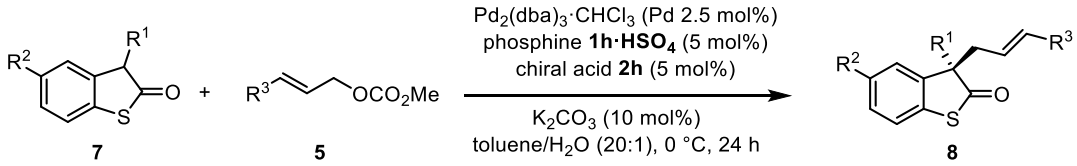
Step 3:

benzothiophenone **7a**	0.1 mmol	1.0 equiv
allylic carbonate **5a**	0.1 mmol	1.0 equiv
$Pd_2(dba)_3{\cdot}CHCl_3$	0.0013 mmol	2.5 mol%
ammonium phosphine **1·HSO₄**	0.005 mmol	5 mol%
phosphoric acid **2**	0.005 mmol	5 mol%
K_2CO_3	0.02 mmol	10 mol%
toluene 1.0 mL, H_2O 0.05 mL		

Table 3.4. The results of all possible 144 combinations of 1·HSO_4 and 2

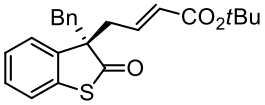
XX% ee (yield)	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l
2a	79% ee (99%)	73% ee (99%)	83% ee (92%)	90% ee (91%)	88% ee (94%)	85% ee (96%)	90% ee (96%)	88% ee (99%)	80% ee (88%)	55% ee (86%)	81% ee (92%)	78% ee (99%)
2b	84% ee (94%)	74% ee (99%)	85% ee (93%)	92% ee (94%)	89% ee (96%)	88% ee (92%)	94% ee (99%)	94% ee (97%)	80% ee (88%)	57% ee (94%)	82% ee (90%)	70% ee (93%)
2c	70% ee (94%)	60% ee (90%)	76% ee (90%)	58% ee (89%)	67% ee (92%)	43% ee (86%)	86% ee (95%)	84% ee (83%)	64% ee (85%)	22% ee (88%)	55% ee (85%)	77% ee (84%)
2d	65% ee (94%)	52% ee (90%)	50% ee (90%)	68% ee (89%)	74% ee (99%)	66% ee (88%)	52% ee (98%)	78% ee (82%)	65% ee (85%)	13% ee (99%)	58% ee (85%)	35% ee (89%)
2e	56% ee (91%)	54% ee (93%)	62% ee (99%)	64% ee (90%)	71% ee (96%)	60% ee (88%)	65% ee (96%)	67% ee (86%)	60% ee (87%)	49% ee (96%)	52% ee (84%)	62% ee (92%)
2f	56% ee (86%)	77% ee (84%)	61% ee (92%)	68% ee (83%)	69% ee (90%)	62% ee (90%)	66% ee (96%)	67% ee (81%)	42% ee (83%)	56% ee (91%)	60% ee (80%)	65% ee (81%)
2g	70% ee (95%)	77% ee (90%)	79%ee (99%)	84% ee (93%)	88% ee (90%)	90% ee (88%)	89% ee (95%)	92% ee (89%)	83% ee (89%)	62% ee (96%)	83% ee (95%)	66% ee (90%)
2h	72% ee (99%)	83% ee (96%)	73% ee (92%)	87% ee (95%)	88% ee (99%)	92% ee (91%)	78% ee (89%)	94% ee (99%)	80% ee (93%)	64% ee (89%)	76% ee 95%)	86% ee (99%)
2i	74% ee (83%)	57% ee (93%)	67% ee (99%)	85% ee (99%)	65% ee (97%)	67% ee (88%)	70% ee (90%)	79% ee (86%)	69% ee (93%)	57% ee (83%)	67% ee (80%)	70% ee (90%)
2j	59% ee (88%)	61% ee (92%)	57% ee (89%)	71% ee (94%)	69% ee (97%)	71% ee (82%)	71% ee (90%)	78% ee (87%)	60% ee (88%)	39% ee (96%)	66% ee (87%)	40% ee (89%)
2k	50% ee (99%)	54% ee (92%)	31% ee (91%)	47% ee (91%)	52% ee (99%)	54% ee (90%)	59% ee (95%)	47% ee (93%)	35% ee (94%)	47% ee (90%)	42% ee (94%)	53% ee (90%)
2l	62% ee (74%)	65% ee (82%)	58% ee (83%)	62% ee (80%)	58% ee (85%)	64% ee (88%)	50% ee (80%)	61% ee (84%)	57% ee (86%)	61% ee (80%)	58% ee (82%)	40% ee (93%)

3.4.2.5 General procedure for asymmetric allylation of benzothiophenones 7

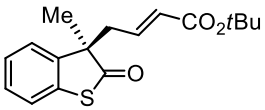


To a Schlenk flask were added benzothiophenone **7a** (22.4 mg, 0.1 mmol), $Pd_2(dba)_3·CHCl_3$ (1.29 mg, 0.0013 mmol), ammonium phosphine **1h·HSO_4** (2.5 mg, 0.005 mmol), chiral phosphoric acid **2h** (3.12 mg, 0.005 mmol) and K_2CO_3 (1.38 mg, 0.01 mmol), and the flask was degassed by alternating vacuum evacuation/Ar backfill. Then, toluene (1 mL) was added, and the resulting catalyst mixture was evacuated and refilled with Ar three times. After addition of H_2O (0.05 mL), allylic carbonate **5a** (21.6 mg, 0.1 mmol) was successively introduced at 0 ºC. After stirring for 24 h at the same temperature, the reaction mixture was directly subjected to the purification by column chromatography on silica gel (H/EtOAc = 10:1 as eluent) to afford **8a** (36.1 mg, 0.095 mmol, 95% yield) as a colorless liquid.

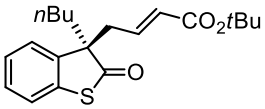
3.4.2.6 Characterization data for the alkylated product 8:



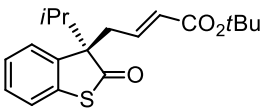
8a: $[\alpha]_D^{21}$ = –27.8 (*c* = 0.94, $CHCl_3$) for 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.29-7.16 (4H, m), 7.13-7.04 (3H, m), 6.79 (1H, dd, *J* = 8.2, 1.8 Hz), 6.43 (1H, ddd, *J* = 15.6, 8.4, 6.8 Hz), 5.73 (1H, d, *J* = 15.6 Hz), 3.24 (1H, d, *J* = 13.3 Hz), 3.07 (1H, d, *J* = 13.3 Hz), 2.92 (1H, dd, *J* = 14.2, 8.4 Hz), 2.76 (1H, dd, *J* = 14.2, 6.8 Hz), 1.40 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 165.2, 140.1, 137.9, 135.7, 134.6, 130.1, 128.8, 128.0, 127.2, 127.0, 126.2, 125.0, 123.2, 80.5, 64.6, 46.0, 41.7, 28.2; IR (film) 2978, 2930, 1705, 1653, 1368, 1152, 980, 922, 735, 700 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{23}H_{24}O_3S_1Na^+$ ([M+Na]$^+$) 403.1338. Found 403.1340.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.3 min (minor), 11.7 min (major).



8b: $[\alpha]_D^{21}$ = –50.5 (*c* = 1.0, $CHCl_3$) for 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* = 7.3, 1.8 Hz), 7.29 (1H, dt, *J* = 7.3, 1.8 Hz), 7.26 (1H, dt, *J* = 7.3, 1.8 Hz), 7.18 (1H, dd, *J* = 7.3, 1.8 Hz), 6.47 (1H, ddd, *J* = 15.6, 8.6, 7.0 Hz), 5.70 (1H, dd, *J* = 15.6, 1.4 Hz), 2.74 (1H, ddd, *J* = 14.2, 8.6, 1.4 Hz), 2.63 (1H, ddd, *J* = 14.2, 7.0, 1.4 Hz), 1.46 (3H, s), 1.42 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 165.3, 140.5, 140.4, 134.4, 128.7, 127.1, 126.7, 124.2, 123.3, 80.5, 59.2, 42.4, 28.2, 25.3; IR (film) 2976, 2930, 1707, 1653, 1368, 1337, 1155, 984, 955, 758 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{17}H_{20}O_3S_1Na^+$ ([M+Na]$^+$) 327.1025. Found 327.1024.; HPLC IC3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 18.0 min (major), 29.0 min (minor).

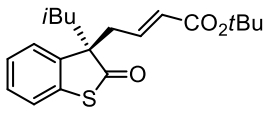


8c: $[\alpha]_D^{21}$ = +41.4 (*c* = 1.0, $CHCl_3$) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* = 7.4, 1.8 Hz), 7.30 (1H, dt, *J* = 7.4, 1.8 Hz), 7.27 (1H, dt, *J* = 7.4, 1.8 Hz), 7.15 (1H, dd, 7.4, 1.8 Hz), 6.44 (1H, ddd, *J* = 15.8, 8.6, 6.9 Hz), 5.68 (1H, brd, *J* = 15.8 Hz), 2.71 (1H, ddd, *J* = 14.1, 8.6, 0.9 Hz), 2.60 (1H, ddd, *J* = 14.1, 6.9, 1.4 Hz), 2.01 (1H, dt, *J* = 12.9, 4.4 Hz), 1.79 (1H, dt, *J* = 12.9, 4.4 Hz), 1.41 (9H, s), 1.28-1.05 (3H, m), 0.92-0.78 (1H, m), 0.77 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 165.3, 140.2, 139.2, 135.6, 128.6, 127.0, 126.6, 124.2, 123.3, 80.4, 63.6, 42.8, 39.7, 28.2, 26.1, 22.9, 13.8; IR (film) 2959, 2932, 1703, 1653, 1368, 1254, 1153, 980, 920, 743 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{20}H_{26}O_3S_1Na^+$ ([M+Na]$^+$) 369.1495. Found 369.1494.; HPLC IC3, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 210 nm, 15.8 min (major), 16.5 min (minor).

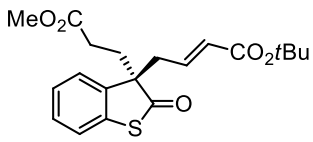


8d: $[\alpha]_D^{21}$ = +97.1 (*c* = 1.0, $CHCl_3$) for 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.6, 1.4 Hz), 7.30 (1H, dt, *J* = 7.6, 1.4 Hz), 7.25 (1H, dt, *J* = 7.6, 1.4 Hz), 7.17 (1H, dd, *J* = 7.6, 1.4 Hz), 6.35 (1H, ddd, *J* = 15.6, 8.7, 6.7 Hz), 5.68 (1H, dt, *J* = 15.6, 1.4 Hz), 2.83 (1H, ddd, *J* = 14.1, 8.7, 1.4 Hz), 2.71 (1H, ddd,

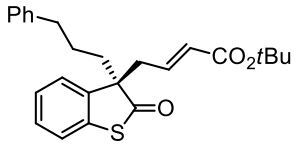
J = 14.1, 6.7, 1.4 Hz), 2.19 (1H, sep, *J* = 7.1 Hz), 1.39 (9H, s), 0.95 (3H, d, *J* = 7.1 Hz), 0.94 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8, 165.3, 140.9, 138.6, 136.1, 128.5, 126.9, 126.3, 124.7, 123.1, 80.4, 66.2, 39.6, 38.2, 28.2, 17.4, 16.9; IR (film) 2974, 2934, 1703, 1653, 1368, 1327, 1152, 982, 910, 750 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{19}H_{24}O_3S_1Na^+$ ([M+Na]$^+$) 355.1338. Found 355.1337.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.0 min (minor), 10.9 min (major).



8e: $[\alpha]_D^{21}$ = +28.9 (*c* = 0.75, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 7.6, 1.6 Hz), 7.30 (1H, dt, *J* = 7.6, 1.6 Hz), 7.27 (1H, dt, *J* = 7.6, 1.6 Hz), 7.15 (1H, dd, *J* = 7.6, 1.6 Hz), 6.44 (1H, ddd, *J* = 15.6, 8.6, 7.0 Hz), 5.66 (1H, dt, *J* = 15.6, 1.4 Hz), 2.64 (1H, ddd, *J* = 13.9, 8.6, 1.4 Hz), 2.52 (1H, ddd, *J* = 13.9, 7.0, 1.4 Hz), 2.01 (1H, dd, *J* = 14.1, 8.0 Hz), 1.84 (1H, dd, *J* = 14.1, 5.5 Hz), 1.49-1.35 (1H, m), 1.42 (9H, s), 0.75 (3H, d, *J* = 6.7 Hz), 0.64 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 165.3, 139.9, 139.1, 135.4, 128.6, 127.2, 126.4, 124.7, 123.3, 80.5, 63.2, 47.6, 44.7, 28.2, 25.5, 24.1, 23.6; IR (film) 2959, 2932, 1705, 1653, 1468, 1368, 1333, 1153, 982, 743 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{20}H_{26}O_3S_1Na^+$ ([M+Na]$^+$) 369.1495. Found 369.1495.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 8.0 min (minor), 8.7 min (major).

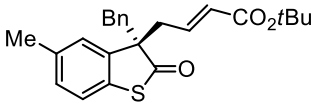


8f: $[\alpha]_D^{21}$ = +59.6 (*c* = 0.97, $CHCl_3$) for 92% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, dd, *J* = 7.3, 1.6 Hz), 7.32 (1H, dt, *J* = 7.3, 1.6 Hz), 7.29 (1H, dt, *J* = 7.3, 1.6 Hz), 7.18 (1H, dd, *J* = 7.3, 1.6 Hz), 6.42 (1H, ddd, *J* = 15.6, 8.7, 7.1 Hz), 5.70 (1H, dt, *J* = 15.6, 1.5 Hz), 3.56 (3H, s), 2.75 (1H, ddd, *J* = 14.1, 8.7, 1.5 Hz), 2.63 (1H, ddd, *J* = 13.9, 7.1, 1.5 Hz), 2.36-2.15 (3H, m), 1.96-1.84 (1H, m), 1.41 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 172.8, 165.1, 139.5, 137.7, 135.5, 129.1, 127.5, 126.9, 124.4, 123.5, 80.6, 62.7, 51.8, 42.5, 34.2, 28.8, 28.2; IR (film) 2978, 2953, 1738, 1703, 1655, 1447, 1368, 1152, 984, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{20}H_{24}O_5S_1Na^+$ ([M+Na]$^+$) 399.1237. Found 399.1226.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 19.7 min (minor), 23.2 min (major).

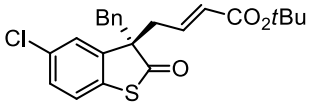


8g: $[\alpha]_D^{21}$ = +24.9 (*c* = 0.82, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.6, 1.6 Hz), 7.28 (1H, dt, *J* = 7.6, 1.6 Hz), 7.26-7.20 (3H, m), 7.17-7.12 (1H, m), 7.07 (1H, dd, *J* = 7.6, 1.6 Hz), 7.02 (1H, d, *J* = 8.2 Hz), 7.02 (1H, d, *J* = 8.2 Hz), 6.41 (1H, ddd, *J* = 15.7, 8.6, 7.0 Hz), 5.67 (1H, dt, *J* = 15.7, 1.4 Hz), 2.70 (1H, ddd, *J* = 14.1, 8.6, 1.4 Hz), 2.57 (1H, ddd, *J* = 14.1, 7.0, 1.4 Hz), 2.54 (1H, ddd, *J* = 14.4, 8.7, 6.4 Hz), 2.43 (1H, ddd, *J* = 14.4, 8.7, 6.4 Hz), 2.06 (1H, ddd, *J* = 13.3, 12.8, 4.5 Hz), 1.82 (1H, ddd, *J* = 13.3, 12.8, 4.5 Hz), 1.54-1.42 (1H, m), 1.41 (9H, s), 1.25-

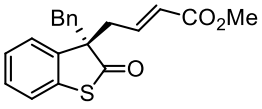
1.14 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 165.3, 141.4, 140.1, 138.8, 135.5, 128.7, 128.4, 128.4, 127.1, 126.7, 126.0, 124.1, 123.4, 80.5, 63.5, 42.8, 39.3, 35.8, 28.2, 25.6; IR (film) 2976, 2934, 2361, 1703, 1601, 1368, 1150, 982, 746, 698 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{25}H_{28}O_3S_1Na^+$ ([M+Na]$^+$) 431.1651. Found 431.1650.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 9.5 min (minor), 10.6 min (major).



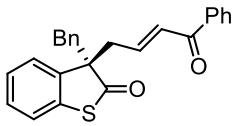
8h: $[\alpha]_D^{21}$ = –39.1 (*c* = 1.0, $CHCl_3$) for 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.05 (5H, m), 6.99 (1H, s), 6.79-6.77 (2H, m), 6.42 (1H, ddd, *J* = 15.6, 8.7, 6.7 Hz), 5.74 (1H, d, *J* = 15.6 Hz), 3.21 (1H, d, *J* = 13.3 Hz), 3.06 (1H, d, *J* = 13.3 Hz), 2.89 (1H, dd, *J* = 14.2, 8.7 Hz), 2.74 (1H, dd, *J* = 14.2, 6.7 Hz), 2.38 (3H, s), 1.41 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 165.3, 140.3, 137.8, 136.1, 134.7, 132.2, 130.2, 129.6, 127.9, 127.1, 127.0, 125.7, 122.9, 80.5, 64.5, 46.1, 41.6, 28.2, 21.5; IR (film) 2976, 2920, 1697, 1653, 1325, 1150, 978, 922, 731, 700 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{24}H_{26}O_3S_1Na^+$ ([M+Na]$^+$) 417.1495. Found 417.1491.; HPLC AD3, H/IPA = 19:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.4 min (minor), 14.1 min (major).



8i: $[\alpha]_D^{19}$ = –42.6 (*c* = 1.0, $CHCl_3$) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, dd, *J* = 8.0, 1.8 Hz), 7.17 (1H, d, *J* = 1.8 Hz), 7.15-7.08 (3H, m), 7.12 (1H, dd, *J* = 8.0, 1.8 Hz), 6.81 (2H, m), 6.42 (1H, ddd, *J* = 15.6, 8.7, 6.6 Hz), 5.75 (1H, brd, *J* = 15.6 Hz), 3.25 (1H, d, *J* = 13.3 Hz), 3.05 (1H, d, *J* = 13.3 Hz), 2.93 (1H, ddd, *J* = 14.2, 8.7, 0.9 Hz), 2.74 (1H, ddd, *J* = 14.2, 6.6, 1.4 Hz), 1.41 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 165.1, 139.7, 139.4, 134.1, 132.3, 130.1, 129.1, 128.1, 127.5, 127.3, 125.3, 124.2, 80.7, 64.9, 46.1, 41.5, 28.2, one peak for aromatic carbon was not found probably due to overlapping; IR (film) 2978, 2927, 1709, 1655, 1456, 1368, 1152, 980, 922, 700 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{23}H_{23}O_3Cl_1S_1Na^+$ ([M+Na]$^+$) 437.0949. Found 437.0948.; HPLC OD3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.2 min (major), 13.5 min (minor).

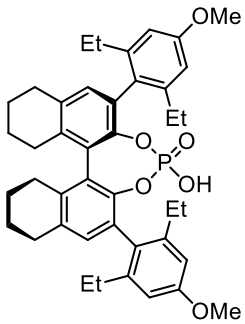


8j: $[\alpha]_D^{21}$ = –27.0 (*c* = 0.96, $CHCl_3$) for 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (2H, m), 7.21-7.17 (2H, m), 7.14-7.05 (3H, m), 6.79 (2H, d, *J* = 7.3 Hz), 6.53 (1H, ddd, *J* = 15.8, 8.3, 7.3 Hz), 5.79 (1H, d, *J* = 15.8 Hz), 3.64 (3H, s), 3.25 (1H, d, *J* = 13.3 Hz), 3.08 (1H, d, *J* = 13.3 Hz), 2.96 (1H, dd, *J* = 14.2, 8.3 Hz), 2.79 (1H, dd, *J* = 14.2, 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 166.3, 141.7, 137.7, 135.7, 134.5, 130.2, 128.9, 128.0, 127.1, 126.3, 125.1, 125.0, 123.3, 64.6, 51.6, 46.2, 41.7; IR (film) 3030, 2949, 1703, 1659, 1437, 1325, 1275, 1167, 737, 700 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{20}H_{18}O_3S_1Na^+$ ([M+Na]$^+$) 361.0869. Found 361.0862.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 17.7 min (minor), 22.2 min (major).

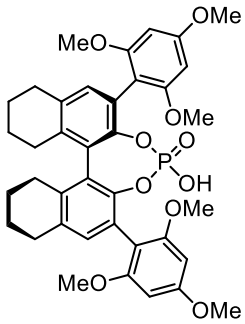


8k: $[\alpha]_D^{21}$ = +17.1 (*c* = 1.0, $CHCl_3$) for 89% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (2H, m), 7.51 (1H, t, *J* = 7.8 Hz), 7.39 (2H, t, *J* = 7.8 Hz), 7.33-7.24 (3H, m), 7.21 (1H, dd, *J* = 7.8, 1.7 Hz), 7.16-7.07 (3H, m), 6.83-6.81 (2H, m), 6.76 (1H, d, *J* = 15.6 Hz), 6.53 (1H, ddd, *J* = 15.6, 8.2, 7.1 Hz), 3.30 (1H, d, *J* = 13.3 Hz), 3.14 (1H, d, *J* = 13.3 Hz), 3.08 (1H, dd, *J* = 14.2, 8.2 Hz), 2.90 (1H, dd, *J* = 14.2, 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 190.7, 141.4, 137.9, 137.5, 135.7, 134.5, 132.9, 130.3, 130.2, 128.9, 128.7, 128.6, 128.0, 127.1, 126.4, 125.2, 123.3, 65.0, 46.2, 42.4; IR (film) 3061, 3030, 2920, 1703, 1670, 1622, 1447, 1281, 922, 698 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{25}H_{20}O_2S_1Na^+$ ($[M+Na]^+$) 407.1076. Found 407.1063.; HPLC OZ3, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 27.9 min (minor), 44.2 min (major).

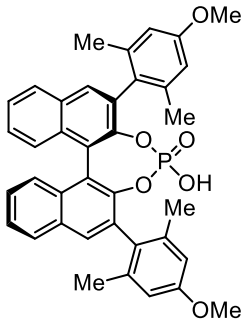
3.4.2.6 Characterization data for chiral phosphoric acids 2



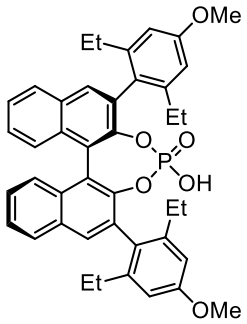
2b: $[\alpha]_D^{21}$ = –35.2 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (2H, s), 6.58 (2H, s), 6.57 (2H, s), 3.69 (6H, s), 2.87-2.69 (6H, m), 2.43-2.19 (10H, m), 1.90-1.80 (6H, m), 1.71-1.64 (2H, m), 1.11 (6H, t, *J* = 7.6 Hz), 0.97 (6H, t, *J* = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.5, 144.0, 143.9 (d, J_{P-C} = 8.6 Hz), 136.5, 134.4, 132.5, 129.6 (d, J_{P-C} = 3.9 Hz), 128.0, 126.9, 110.9, 110.6, 55.0, 29.4, 27.9, 27.1, 26.9, 23.0, 22.9, 15.6, 14.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 2.1; IR (film) 2959, 2930, 1601, 1578, 1190, 1157, 1016, 953, 901, 748 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{42}H_{48}O_6P_1^-$ ($[M-H]^-$) 679.3179. Found 679.3179.



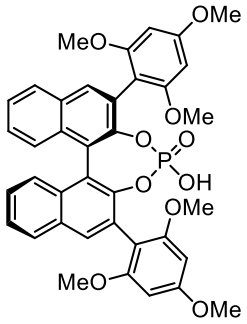
2c: $[\alpha]_D^{20}$ = –69.6 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (2H, s), 6.08 (4H, s), 3.72 (6H, s), 3.55 (6H, s), 3.53 (6H, s), 2.87-2.79 (4H, m), 2.78-2.71 (2H, m), 2.39-2.30 (2H, m), 1.86-1.74 (6H, m), 1.71-1.61 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 158.8, 158.7, 144.7 (d, J_{P-C} = 8.7 Hz), 136.6, 134.2, 133.0, 126.7, 124.1 (d, J_{P-C} = 2.9 Hz), 107.8, 91.2, 90.7, 56.0, 55.9, 55.3, 29.4, 28.1, 22.9, 22.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.1; IR (film) 2934, 2837, 1585, 1454, 1414, 1204, 1123, 1016, 903, 725 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{38}H_{40}O_{10}P_1^-$ ($[M-H]^-$) 687.2354. Found 687.2363.



2g: $[\alpha]_D^{21}$ = –60.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.2 Hz), 7.79 (2H, s), 7.50 (2H, t, *J* = 7.6 Hz), 7.39-7.30 (4H, m), 6.56 (2H, d, *J* = 2.3 Hz), 6.49 (2H, d, *J* = 2.3 Hz), 3.39 (6H, s), 2.12 (6H, s), 1.99 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 145.7 (d, $J_{P\text{-}C}$ = 8.7 Hz), 138.5 (d, $J_{P\text{-}C}$ = 2.9 Hz), 132.8, 132.1, 132.0, 131.6, 128.6, 128.3, 127.2, 126.5, 125.8, 122.3, 113.0, 112.8, 54.9, 21.5, 20.8, one peak for aromatic carbon was not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.1; IR (film) 2955, 2920, 1605, 1312, 1194, 1150, 1020, 905, 750, 729 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{38}H_{32}O_6P_1^-$ ([M−H]$^-$) 615.1931. Found 615.1932.



2h: $[\alpha]_D^{21}$ = –23.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.5 Hz), 7.81 (2H, s), 7.50 (2H, ddd, *J* = 8.5, 6.4, 2.2 Hz), 7.36-7.30 (4H, m), 6.62 (2H, d, *J* = 2.5 Hz), 6.56 (2H, d, *J* = 2.5 Hz), 3.58 (6H, s), 2.39-2.20 (8H, m), 1.11 (6H, t, *J* = 7.7 Hz), 0.98 (6H, t, *J* = 7.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 146.1 (d, $J_{P\text{-}C}$ = 8.7 Hz), 144.9, 144.4, 132.4 (d, $J_{P\text{-}C}$ = 2.9 Hz), 132.4, 132.3, 131.2, 128.3, 127.9, 127.3, 126.3, 125.7, 122.3, 110.8, 110.7, 55.1, 27.2, 27.0, 15.6, 14.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.8; IR (film) 2963, 2932, 1601, 1578, 1192, 1148, 1018, 995, 962, 748 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{42}H_{40}O_6P_1^-$ ([M−H]$^-$) 671.2557. Found 671.2558.



2i: $[\alpha]_D^{21}$ = –93.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, *J* = 8.6 Hz), 7.89 (2H, s), 7.46-7.42 (4H, m), 7.29-7.24 (2H, m), 6.15 (2H, d, *J* = 1.8 Hz), 6.11 (2H, d, *J* = 1.8 Hz), 3.75 (6H, s), 3.59 (6H, s), 3.54 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 159.2, 158.8, 146.4 (d, $J_{P\text{-}C}$ = 10.6 Hz), 133.4, 132.2, 131.5, 128.5, 127.6, 127.0 (d, $J_{P\text{-}C}$ = 2.9 Hz), 126.0, 125.3, 121.9 (d, $J_{P\text{-}C}$ = 1.9 Hz), 107.7, 91.3, 91.2, 56.2, 56.1, 55.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.3; IR (film) 2938, 2837, 1609, 1585, 1410, 1225, 1204, 1123, 1018, 750 cm^{-1}; HRMS (ESI, negative ion mode) Calcd for $C_{38}H_{32}O_{10}P_1^-$ ([M−H]$^-$) 679.1728. Found 679.1740.

3.4.2.7 Crystallographic structure determination

Recrystallization of 8a: A single crystal of **8a** was obtained from a solution of hexane and diethyl ether at room temperature. The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 103 K on a Brucker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-

matrix least squares on *F2* by using SHELXTL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in calculated positions. The crystallographic data are summarized in Table 3.5 and ORTEP diagram is shown in Fig. 3.4.

Table 3.5. Crystal data and structure refinement for **8a**.

Empirical formula	C23 H24 O3 S	
Formula weight	380.48	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.5465(17) Å	α = 90°.
	b = 7.844(2) Å	β = 90°.
	c = 38.945(10) Å	γ = 90°.
Volume	1999.9(9) $Å^3$	
Z	4	
Density (calculated)	1.264 Mg/m^3	
Absorption coefficient	0.182 mm^{-1}	
F(000)	808	
Crystal size	0.3 x 0.4 x 0.8 mm^3	
Theta range for data collection	2.09 to 29.14°.	
Index ranges	-8<=h<=8, -10<=k<=10, -44<=l<=53	
Reflections collected	12232	
Independent reflections	5092 [R(int) = 0.0215]	
Completeness to theta = 29.14°	94.8 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5092 / 0 / 247	
Goodness-of-fit on F^2	0.662	
Final R indices [I>2sigma(I)]	R1 = 0.0235, wR2 = 0.0420	
R indices (all data)	R1 = 0.0559, wR2 = 0.0426	
Absolute structure parameter	0.00(5)	
Largest diff. peak and hole	0.168 and -0.182 e.$Å^{-3}$	

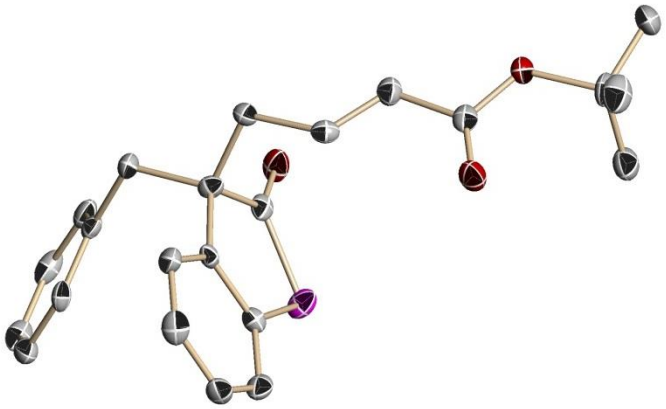


Figure 3.4 Molecular structure of **8a**. All calculated hydrogen atoms are omitted for clarity. purple = sulfur, red = oxygen, black = carbon.

References and Notes

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2) a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071; b) C. Jaekel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912.

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1a·X, see Table S1 in the Supporting Information.

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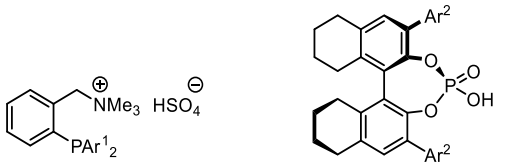
Chapter 4

Change of the Component Ratio for Ion-Paired Chiral Ligands: Enhancement of Stereocontrolling Ability of Their Palladium Complexes

4.1 Introduction

Increasing attention has recently directed toward supramolecular chiral catalysts, which are assembled from small molecules through non-covalent interactions and act as single chiral catalysts.[1,2] One of advantages of these supramolecular catalysts over the conventional catalysts is the facile and rapid access to sufficiently large libraries based on the combination of catalyst components, thus facilitating the realization of highly stereoselective transformations. In general, the increase of the diversity of supramolecular catalysts is achieved by the preparation of a multitude of components. An alternative strategy is to change the structure of assembled supramolecules by using the different ratio of components.[3] Although the employment of such strategy together with a wide array of catalyst components should considerably expand the catalyst libraries, the successful example in this direction has been scarcely reported.



1·HSO$_4$ (Ar^1 = 4-CF$_3$C$_6$H$_4$) **2a** (Ar^2 = 2,4,6-Me$_3$C$_6$H$_2$) **2b** (Ar^2 = 4-*t*Bu-2,6-Me$_2$C$_6$H$_2$)

Figure 4.1 Components of ion-paired chiral ligands in this study

Recently, the author have introduced a new class of supramolecular chiral ligand, ion-paired chiral ligand, comprising a cationic ammonium–phosphine hybrid ligand and a chiral anion.[4] This supramolecular chiral ligand can be generated from hydrogen sulfate salt of ammonium phosphine of type **1·HSO$_4$** and chiral Brønsted acid, such as phosphoric acid **2** (Figure 4.1),[4d] and its palladium complex exhibited the excellent stereocontrolling ability in asymmetric allylic alkylations. In the previous studies on ion-paired chiral ligand,[5] the combined use of Pd metal, ammonium phosphine, and chiral acid in the ratio of 1:2:2 was the standard catalytic system. However, upon consideration of the plausible structure of intermediary π-allyl palladium complex, one more chiral anion can be involved in the bond-forming event as a counter ion of cationic allyl-Pd (Figure 4.2).[6,7] Here, the author report the discovery that the component ratio of ion-paired chiral ligands could significantly affect the stereocontrolling ability of their Pd complexes in asymmetric allylic alkylations. In particular, the author achieved highly enantioselective allylation of α-nitrocarboxylates with functionalized allylic carbonate using supramolecular Pd complexes generated from Pd metal, ammonium phosphine, and chiral acid in the ratio of 1:2:3.

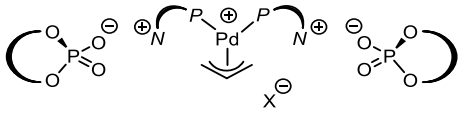


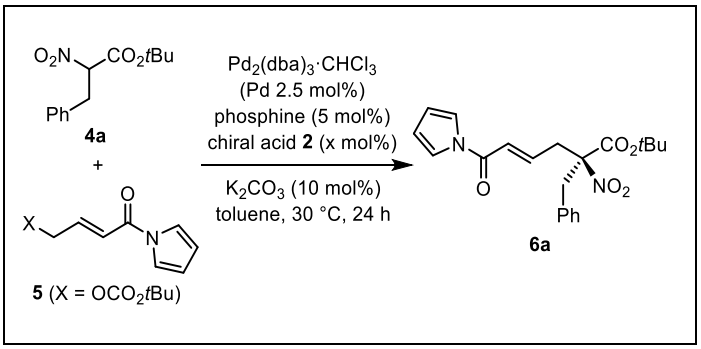
Figure 4.2 Plausible reactive intermediate in Pd-catalyzed allylic alkylations using ion-paired chiral ligands.

4.2 Result and Discussion

4.2.1 Optimization of the reaction conditions

Initially, the author's study focused on the examination of the hypothesis that the component ratio of ion-paired chiral ligands could affect the catalytic performance of their Pd complexes. For this purpose, the author chose the reaction of α-nitrocarboxylate **3a**[8] with the synthetically attractive functionalized allylic carbonate **4** as a model reaction,[9,10] because the use of 1:2:2 Pd/ammonium phosphine/chiral acid–catalyst system failed to achieve the satisfactory level of stereochemical control in this reaction despite the tremendous screening of catalyst components. For instance, the reaction of **3a** with **4** under the influence of $Pd_2(dba)_3 \cdot CHCl_3$ (Pd 2.5 mol%), ammonium phosphine **1·HSO₄** (5 mol%), and chiral phosphoric acid **2a** (5 mol%) proceeded to give the corresponding allylated product **5a** with moderate enantioselectivity (Table 4.1, entry 1). While the screening of a wide array of ammonium phosphines and chiral phosphoric acids led to the identification of **1·HSO₄** and **2b** as the optimal combination, the enantioselectivity remained below 90% ee (entry 2). Therefore, the author next examined the catalytic system with higher amount of chiral phosphoric acid. When the reaction conducted with 7.5 mol% of chiral acid **2b** under otherwise identical conditions, to the author's delight, **5a** was isolated quantitatively with excellent enantioselectivity (entry 3). Further increase of the amount of **2b** did not induce the further selectivity enhancement (entry 4), indicating that three molecules of chiral phosphate ion would involve in stereo-determining step. To confirm the importance of the ammonium−phosphine hybrid ligand for asymmetric induction, the author also attempted the reaction with tris(4-trifluoromethylphenyl)phosphine as a ligand in the presence of either 5 or 7.5 mol% of chiral phosphoric acid **2b**, which gave rise to racemic **5a** (entries 5 and 6).

Table 4.1 Asymmetric Allylation of α-Nitrocarboxylate **4a** with Allylic Carbonate **5**.[a]



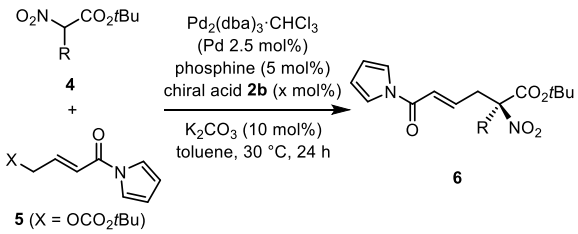
entry	phosphine	**2**	mol% of **2**	yield (%)[b]	ee (%)[c]
1	**1·HSO₄**	**2a**	5	98	52
2	**1·HSO₄**	**2b**	5	99	89
3	**1·HSO₄**	**2b**	7.5	99	98
4	**1·HSO₄**	**2b**	8.75	97	98
5	$P(4\text{-}CF_3C_6H_4)_3$	**2b**	5	99	<1
6	$P(4\text{-}CF_3C_6H_4)_3$	**2b**	7.5	99	<1

[a] Reaction conditions: **4a** (0.1 mmol), **5** (0.12 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (Pd 2.5 mol%), **1·HSO₄** (5 mol%), **2**, K_2CO_3 (10 mol%), toluene (1 mL), 30 °C, 24 h, under Ar. [b] Isolated yield. [c] Determined by HPLC with chiral column.

4.2.2 Generality

Based on the experimental validation of the superior performance of 1:2:3 Pd/ammonium phosphine/chiral acid–catalyst system over 1:2:2 system, the author then examined its generality in Pd-catalyzed asymmetric allylations of α-nitrocarboxylates **4** with allylic carbonate **5** (Table 4.2). Noteworthy is that 1:2:3 catalyst system exhibited higher stereocontrolling ability than 1:2:2 system for all substrates, giving rise to the corresponding allylated products with uniformly excellent enantioselectivities. For examples, the reactions of nitrocarboxylates having α-methyl or α-ethyl substitutent under the influence of 1:2:2 catalyst system proceeded to afford the products **6b** and **6c** with nearly 90% ee (entries 1 and 3). In contrast, the use of 1:2:3 catalyst system resulted in the production of almost enantiomerically pure **6b** and **6c** (entries 2 and 4). Similar selectivity enhancement and excellent enantioselectivities were generally observed in the reactions of other alkyl, allyl, or benzylic substituted α-nitrocarboxylates, when the 1:2:3 catalyst system were employed (entries 5-20). These results clearly demonstrated the importance of the components ratio of ion-paired chiral ligands on the stereocontrolling ability of their Pd complexes.

Table 4.2 Substate Scope with Different Component Ratio of Ion-Paired Chiral Ligand



entry	**4**	R	mol% of **2b**	yield (%)[b]	ee (%)[c]
1	**4b**	Me	5	99	92
2			7.5	95	99
3	**4c**	Et	5	86	91
4			7.5	83	98
5	**4d**	*n*-Hex	5	93	93
6			7.5	90	94
7	**4e**	$CH_2CH=CH_2$	5	99	96
8			7.5	98	99
9	**4g**	$CH_2(4\text{-}MeO)C_6H_4$	5	84	96
10			7.5	91	98
11	**4h**	$CH_2(4\text{-}CF_3)C_6H_4$	5	85	87
12			7.5	99	96
13	**4i**	$CH_2(4\text{-}Br)C_6H_4$	5	96	99
14			7.5	96	99
15	**4j**	$CH_2(3,5\text{-}Me_2)C_6H_3$	5	92	93
16			7.5	98	98
17	**4k**	CH_2(2-thienyl)	5	99	94
18			7.5	99	98

[a] Standard reaction conditions: **4** (0.1 mmol), **5** (0.12 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (Pd 2.5 mol%), **1·HSO$_4$** (5 mol%), **2b** (5 or 7.5 mol%), K_2CO_3 (10 mol%), toluene (1 mL), 30 °C, 24 h, under Ar. [b] Isolated yield. [c] Determined by HPLC with chiral column. [d] 40 °C, 24 h.

4.3 Conclusion

In conclusion, the author revealed that changing the ratio of components of ion-paired chiral ligands, which are ammonium–phosphine hybrid ligand and chiral phosphoric acid, actuary affected the stereocontroling ability of their Pd complexes in asymmetric allylation of α-nitrocarboxylates. The exploitation of this strategy with a diverse array of catalyst components would offer a new yet powerful tool for the development of hitherto difficult asymmetric transformations. Investigations for catalyst structure and further applications are currently underway in the author's laboratory.

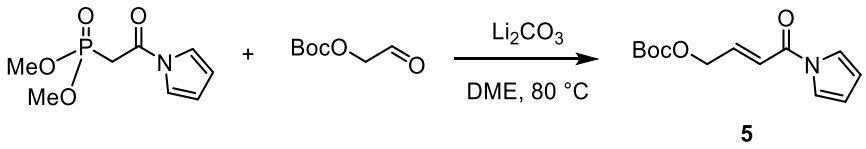
4.4 Experimental section

4.4.1 General information

Infrared spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet and br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$; 77.16 ppm). ^{31}P NMR spectra were recorded on a JEOL JNM-ECS400 (162 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from H_3PO_4 (0.0 ppm) resonance as the external standard. ^{19}F NMR spectra were recorded on a JEOL JNM-ECS400 (376 MHz) spectrometer. Chemical shifts are reported in ppm from benzotrifluoride (–64.0 ppm) resonance as the external standard. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were measured on a Thermo Fisher Scientific Exactive (ESI). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on silica gel 60 (spherical, 40-50 μm; Kanto CHEMICAL Co., Inc.). Enantiomeric excesses were determined by HPLC analysis using chiral columns (φ 4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALPAC IC-3 (IC3), CHIRALPAC IC (IC), CHIRALPAC AD-3 (AD3), CHIRALCEL OX-3 (OX3), CHIRALPAC AS-3 (AS3), CHIRALPAC IF-3 (IF3) and CHIRALPAC ID-3 (ID3)) with hexane (H) and isopropyl alcohol (IPA) as eluent.

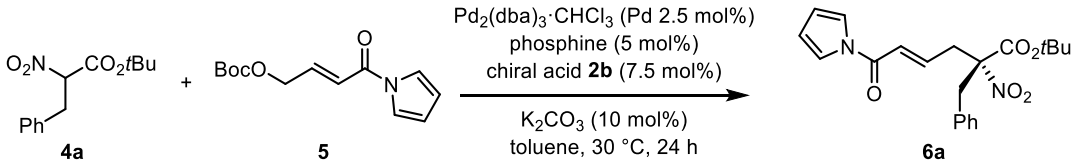
All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. The manipulations for Pd-catalyzed reactions were carried out with standard Schlenk techniques under Ar. Toluene was supplied from Kanto Chemical Co., Inc. as “Dehydrated” and further purified by both A2 alumina and Q5 reactant using a Glass Contour solvent dispensing system. Simple chemicals were purchased and used as such.

4.4.2 Representative procedures for synthesis carbonate 5



To a suspension of Li_2CO_3 (2.96 g, 40.0 mmol) in 1,2-dimethoxyethane (40 ml) was added dimethyl [2-oxo-2-(1*H*-pyrrol-1-yl)ethyl]phosphonate (4.34 g, 20.0 mmol) and the resulting reaction mixture was stirred at 80 °C for 12 h. Then, *tert*-butyl (2-oxoethyl) carbonate (6.41 g, 40.0 mmol) was introduced into the reaction flask and the stirring was kept for further 18 h at the same temperature. The reaction was cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl. Extractive work-up was performed with EtOAc, and the organic extracts were washed with brine and dried over Na_2SO_4. The evaporation of solvents and the purification of the crude product was purified by column chromatography (Hex/EtOAc = 20:1 as eluent) to give **5** as a colorless oil (3.58 g, 71% yield). **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, t, J = 2.3 Hz), 7.23 (1H, dt, J = 15.6, 4.4 Hz), 6.80 (1H, dt, J = 15.6, 2.1 Hz), 6.34 (2H, t, J = 2.3 Hz), 4.85 (2H, dd, J = 4.4, 2.1 Hz), 1.52 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 153.0, 144.1, 120.0, 119.5, 113.7, 83.2, 65.3, 27.9; IR (film) 2980, 1742, 1699, 1585, 1470, 1344, 1275, 1252, 1159, 1126 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{13}H_{17}O_4NNa^+$ ([M+Na]$^+$) 274.1050. Found 274.1049.

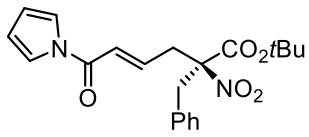
4.4.3 General procedure for asymmetric allylation of nitroester 6



To a Schlenk flask were added $Pd_2(dba)_3$·$CHCl_3$ (1.3 mg, 0.0013 mmol), ammonium phosphine **1·HSO$_4$** (2.8 mg, 0.005 mmol), chiral phosphoric acid **2b** (5.1 mg, 0.0075 mmol) and K_2CO_3 (1.4 mg, 0.010 mmol), and the flask was degassed by alternating vacuum evacuation/Ar backfill. After the addition of toluene (1.0 mL), the resulting catalyst mixture was evacuated and refilled with Ar three times. The reaction flask was then warmed up to 30 °C, and nitroester **4a** (25.1 mg, 0.10 mmol) and allylic carbonate **5** (30.2 mg, 0.12 mmol) was successively introduced. After stirring for 24 h at the same temperature, the reaction mixture was cooled to room temperature. Filtration through the short silica-gel pad with the aid of EtOAc and

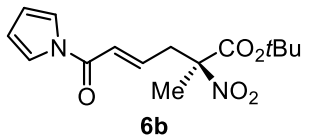
concentration of the filtrate were performed. The reaction mixture was purified by column chromatography on silica gel (Hex/EtOAc = 20:1 as eluent) to afford **6a** (38.4 mg, 0.099 mmol, 99% yield, 99% ee) as a colorless liquid.

4.4.4 Characterization data for the alkylated product 6



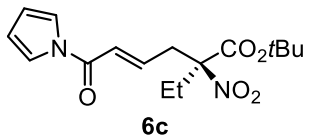
6a

6a: $[\alpha]_D^{24}$ = –3.08 (*c* = 1.0, CH_3OH) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 2.3 Hz), 7.35-7.30 (3H, m), 7.13 (1H, dt, *J* = 15.2, 7.6 Hz), 7.16-7.11 (2H, m), 6.64 (1H, dt, *J* = 15.2, 1.5 Hz), 6.34 (2H, t, *J* = 2.3 Hz), 3.65 (1H, d, *J* = 14.4 Hz), 3.50 (1H, d, *J* = 14.4 Hz), 3.03 (1H, ddd, *J* = 15.5, 7.6, 1.5 Hz), 2.99 (1H, ddd, *J* = 15.5, 7.6, 1.5 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 161.8, 142.6, 132.8, 130.1, 129.0, 128.3, 124.7, 119.4, 113.9, 95.7, 85.5, 40.3, 36.6, 27.8; IR (film) 2980, 1744, 1699, 1553, 1468, 1352, 1296, 1283, 1152, 743 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{21}H_{24}O_5N_2Na^+$ ([M+Na]$^+$) 407.1577. Found 407.1581.; HPLC OX3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.4 min (major), 13.5 min (minor).



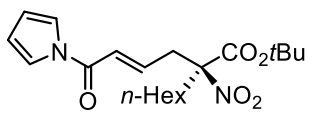
6b

6b: $[\alpha]_D^{24}$ = +5.28 (*c* = 0.97, CH_3CN) for 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 2.2 Hz), 7.08 (1H, dt, *J* = 15.0, 7.6 Hz), 6.58 (1H, dt, *J* = 15.0, 1.2 Hz), 6.34 (2H, t, *J* = 2.2 Hz), 3.20 (1H, ddd, *J* = 14.8, 7.6, 1.2 Hz), 3.11 (1H, ddd, *J* = 14.8, 7.6, 1.2 Hz), 1.81 (3H, s), 1.49 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.4, 161.8, 142.4, 125.0, 119.4, 113.9, 92.1, 85.1, 39.6, 27.8, 21.6; IR (film) 2980, 1744, 1699, 1553, 1468, 1350, 1294, 1157, 1125, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{15}H_{20}O_5N_2Na^+$ ([M+Na]$^+$) 331.1264. Found 331.1263.; HPLC IC3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 19.3 min (*S*), 20.6 min (*R*).



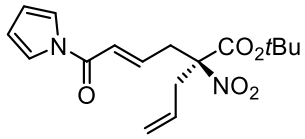
6c

6c: $[\alpha]_D^{24}$ = –7.47 (*c* = 0.98, CH_3OH) for 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 2.3 Hz), 7.04 (1H, dt, *J* = 15.2, 7.8 Hz), 6.66 (1H, dt, *J* = 15.2, 1.4 Hz), 6.34 (2H, t, *J* = 2.3 Hz), 3.18 (1H, ddd, *J* = 15.2, 7.8, 1.4 Hz), 3.14 (1H, ddd, *J* = 15.2, 7.8, 1.4 Hz), 2.38 (1H, dq, *J* = 14.8, 7.6 Hz), 2.22 (1H, dq, *J* = 14.8, 7.6 Hz), 1.49 (9H, s), 0.98 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 161.8, 142.5, 124.6, 119.4, 113.8, 95.9, 84.9, 36.6, 27.8, 27.5, 8.1; IR (film) 2980, 1742, 1699, 1549, 1468, 1352, 1288, 1252, 1125, 741 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{16}H_{22}O_5N_2Na^+$ ([M+Na]$^+$) 345.1421. Found 345.1422.; HPLC IC, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 14.7 min (major), 15.6 min (minor).



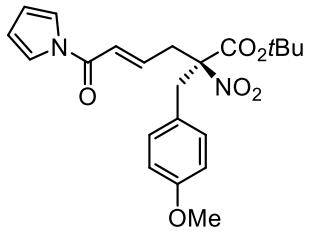
6d

6d: $[\alpha]_D^{24}$ = +13.3 (*c* = 1.0, CH_3CN) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, t, *J* = 2.2 Hz), 7.04 (1H, dt, *J* = 15.2, 7.8 Hz), 6.64 (1H, brd, *J* = 15.2 Hz), 6.33 (2H, t, *J* = 2.2 Hz), 3.18 (1H, ddd, *J* = 15.2, 7.8, 1.0 Hz), 3.13 (1H, ddd, *J* = 15.2, 7.8, 1.0 Hz), 2.27-2.11 (2H, m), 1.48 (9H, s), 1.37-1.22 (8H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 161.8, 142.6, 124.6, 119.4, 113.8, 95.6, 84.9, 37.1, 34.1, 31.5, 29.2, 27.8, 23.6, 22.6, 14.1; IR (film) 2932, 1744, 1701, 1553, 1468, 1352, 1294, 1153, 1126, 743 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{20}H_{30}O_5N_2Na^+$ ($[M+Na]^+$) 401.2047. Found 401.2040.; HPLC OX3, Hex/IPA = 97:3, flow rate = 0.5 mL/min, λ = 210 nm, 14.8 min (minor), 16.0 min (major).



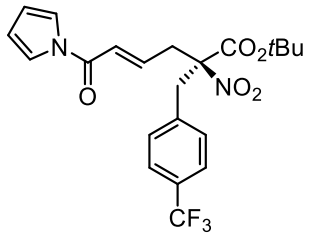
6e

6e: $[\alpha]_D^{24}$ = +11.9 (*c* = 0.98, CH_3OH) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 2.4 Hz), 7.05 (1H, dt, *J* = 15.2, 7.8 Hz), 6.65 (1H, dt, *J* = 15.2, 1.2 Hz), 6.34 (2H, d, *J* = 2.4 Hz), 5.64 (1H, ddt, *J* = 16.3, 10.4, 7.7 Hz), 5.27 (1H, dd, *J* = 10.4, 1.2 Hz), 5.26 (1H, dd, *J* = 16.3, 1.2 Hz), 3.18 (1H, ddd, *J* = 15.2, 7.8, 1.2 Hz), 3.12 (1H, ddd, *J* = 15.2, 7.8, 1.2 Hz), 3.02 (1H, dd, *J* = 14.7, 7.7 Hz), 2.92 (1H, dd, *J* = 14.7, 7.7 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.4, 161.8, 142.3, 129.2, 124.9, 122.1, 119.4, 113.9, 94.6, 85.3, 38.8, 36.9, 27.8; IR (film) 2982, 1744, 1699, 1553, 1468, 1352, 1296, 1152, 1126, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{17}H_{22}O_5N_2Na^+$ ($[M+Na]^+$) 357.1421. Found 357.1414.; HPLC OD3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 10.6 min (minor), 11.6 min (major).



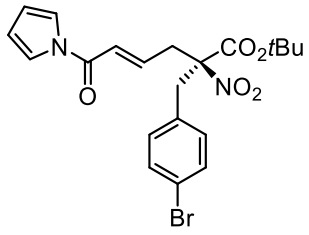
6f

6f: $[\alpha]_D^{24}$ = –2.93 (*c* = 0.87, CH_3OH) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 2.3 Hz), 7.12 (1H, dt, *J* = 15.4, 7.4 Hz), 7.04 (2H, dt, *J* = 8.8, 2.5 Hz), 6.84 (2H, dt, *J* = 8.8, 2.5 Hz), 6.63 (1H, dt, *J* = 15.4, 1.5 Hz), 6.34 (2H, t, *J* = 2.3 Hz), 3.79 (3H, s), 3.59 (1H, d, *J* = 14.4 Hz), 3.43 (1H, d, *J* = 14.4 Hz), 3.03 (1H, ddd, *J* = 15.4, 7.4, 1.5 Hz), 2.98 (1H, ddd, *J* = 15.4, 7.4, 1.5 Hz), 1.49 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 161.8, 159.6, 142.8, 131.2, 124.6, 124.6, 119.4, 114.4, 113.9, 95.9, 85.4, 55.4, 39.6, 36.6, 27.8; IR (film) 2359, 2342, 1744, 1699, 1555, 1352, 1298, 1254, 1152, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{22}H_{26}O_6N_2Na^+$ ($[M+Na]^+$) 437.1683. Found 437.1676.; HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 16.9 min (major), 23.7 min (minor).



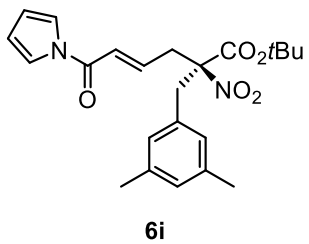
6g

6g: $[\alpha]_D^{24}$ = –3.52 (*c* = 1.0, CH_3CN) for 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.2 Hz), 7.34 (2H, t, *J* = 2.4 Hz), 7.27 (2H, d, *J* = 8.2 Hz), 7.12 (1H, dt, *J* = 15.1, 7.5 Hz), 6.66 (1H, dt, *J* = 15.1, 1.3 Hz), 6.35 (2H, t, *J* = 2.4 Hz), 3.69 (1H, d, *J* = 14.4 Hz), 3.56 (1H, d, *J* = 14.4 Hz), 3.05 (1H, ddd, *J* = 15.4, 7.5, 1.3 Hz), 2.99 (1H, ddd, *J* = 15.4, 7.5, 1.3 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3, 161.7, 142.1, 137.1, 130.7 (q, $J_{F\text{-}C}$ = 32.4 Hz), 130.6, 126.0, 125.0, 124.1 (q, $J_{F\text{-}C}$ = 277.7 Hz), 119.4, 114.0, 95.4, 86.0, 40.1, 36.8, 27.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6; IR (film) 2980, 1746, 1699, 1557, 1352, 1325, 1165, 1153, 1126, 1069, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{22}H_{23}O_5N_2F_3Na^+$ ($[M+Na]^+$) 475.1451. Found 475.1447.; HPLC AS3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.9 min (major), 14.3 min (minor).



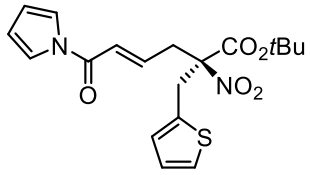
6h

6h: $[\alpha]_D^{24}$ = –8.47 (*c* = 0.82, CH_3CN) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, dt, *J* = 8.4, 2.8 Hz), 7.34 (2H, t, *J* = 2.3 Hz), 7.10 (1H, dt, *J* =15.2, 7.5 Hz), 7.05 (2H, dt, *J* = 8.4, 2.8 Hz), 6.64 (1H, brd, *J* = 15.2 Hz), 6.35 (2H, t, *J* = 2.3 Hz), 3.60 (1H, d, *J* = 14.8 Hz), 3.45 (1H, d, *J* = 14.8 Hz), 3.03 (1H, ddd, *J* = 15.4, 7.5, 1.4 Hz), 2.97 (1H, ddd, *J* = 15.4, 7.5, 1.4 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3, 161.7, 142.2, 132.2, 131.8, 131.8, 124.8, 122.6, 119.4, 113.9, 95.4, 85.8, 39.7, 36.6, 27.8; IR (film) 2980, 1744, 1699, 1553, 1468, 1352, 1298, 1288, 1152, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{21}H_{23}O_5N_2BrNa^+$ ($[M+Na]^+$) 485.0683. Found 485.0677.; HPLC IC3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 14.4 min (major), 15.6 min (minor).



6i

6i: $[\alpha]_D^{24}$ = +10.5 (*c* = 0.99, CH_3CN) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 2.4 Hz), 7.14 (1H, dt, *J* = 15.2, 7.6 Hz), 6.93 (1H, s), 6.73 (2H, s), 6.63 (1H, dt, *J* = 15.2, 1.4 Hz), 6.34 (2H, t, *J* = 2.4 Hz), 3.54 (1H, d, *J* = 14.4 Hz), 3.44 (1H, d, *J* = 14.4 Hz), 3.01 (2H, dd, *J* = 7.6, 1.4 Hz), 2.28 (6H, s), 1.49 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 161.8, 142.9, 138.5, 132.6, 129.9, 127.9, 124.6, 119.4, 113.8, 95.9, 85.3, 40.0, 36.7, 27.8, 21.4; IR (film) 2978, 2926, 1746, 1699, 1553, 1468, 1350, 1292, 1153, 743 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{23}H_{28}O_5N_2Na^+$ ($[M+Na]^+$) 435.1890. Found 435.1891; HPLC AD3, Hex/IPA = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 12.4 min (minor), 13.7 min (major).

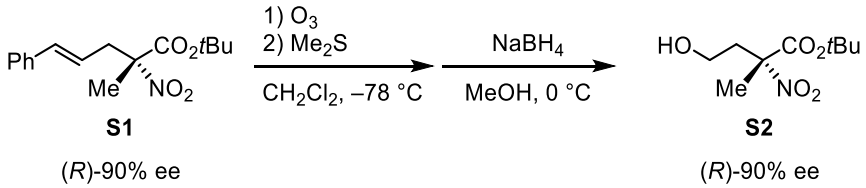


6j

6j: $[\alpha]_D^{24}$ = +16.4 (*c* = 0.98, $CHCl_3$) for 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, t, *J* = 2.3 Hz), 7.25 (1H, dd, *J* = 5.4, 1.2 Hz), 7.08 (1H, dt, *J* = 14.8, 7.6 Hz), 6.97 (1H, dd, *J* = 5.4, 3.0 Hz), 6.87 (1H, brd, *J* = 3.0 Hz), 6.68 (1H, dt, *J* = 14.8, 1.3 Hz), 6.34 (2H, t, *J* = 2.3 Hz), 3.85 (1H, d, *J* = 15.6 Hz), 3.70 (1H, d, *J* = 15.6 Hz), 3.12 (2H, dd, *J* = 7.6, 1.2 Hz), 1.49 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2, 161.7, 142.2, 133.7, 128.7, 127.5, 126.2, 125.1, 119.4, 113.9, 95.3, 85.8, 36.7, 34.6, 27.8; IR (film) 2980, 1744, 1699, 1555, 1352, 1296, 1287, 1152, 745 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{19}H_{22}O_5N_2SNa^+$ ($[M+Na]^+$) 413.1142. Found 413.1144.; HPLC ID3, Hex/IPA = 19:1, flow rate = 0.5 mL/min, λ = 210 nm, 35.3 min (minor), 39.1 min (major).

4.4.5 Determination of the absolute configuration

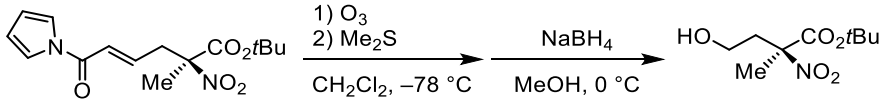
Absolute configuration of allylated product **6b** was determined after the derivatization into *tert*-butyl 4-hydroxy-2-methyl-2-nitrobutanoate **S2**. Comparison of the optical rotation and HPLC spectra to authentic sample, which was prepared by the following procedure, revealed that the absolute configuration of **6b** was S.



Alkylated nitroester (*R*)-**S1** (29.1 mg, 0.10 mmol, 90% ee), of which the absolute configuration was established in our previous report, was dissolved in dichloromethane (3.0 mL). After cooling to –78 °C in a dry ice/methanol bath, ozone was bubbled into the reaction mixture until the solution turned blue. The solution was then purged with argon. Dimethyl sulfide (74.0 □L, 1.0 mmol) was successively added dropwise and the resulting mixture was warmed to room temperature. After stirring for 8 h at room temperature, all volatiles was removed in vacuo. The crude product was dissolved in methanol (2.0 mL), and the solution was cooled to 0 °C. Sodium borohydride (18.9 mg, 0.50 mmol) was added and the reaction mixture stirred at 0 °C for 1 h. The reaction was quenched by the addition of 1N HCl *aq*, and the aqueous phase was extracted with $CHCl_3$. The combined organics were dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (Hex/EtOAc = 2:1 as eluent) to yield a colorless oil **S2** (19.4 mg, 89% yield, 90% ee). **S2**: $[\alpha]_D^{24}$ = –4.42 (*c* = 0.99, CH_3OH) for 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (2H, dt, *J* = 6.4, 1.6 Hz), 2.47 (2H, t, *J* = 6.4 Hz), 1.81 (3H, s), 1.75 (1H, brd, *J* = 1.6 Hz), 1.48 (9H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 92.2, 84.5, 58.2, 38.9, 27.7, 21.7; IR (film) 2980, 1744, 1553, 1387, 1352, 1258, 1157, 1136, 1051, 841 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_9H_{18}O_5N^+$ ($[M+H]^+$) 220.1179. Found 220.1178.;

HPLC IF3, Hex/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 7.8 min (*R*), 11.6 min (*S*).

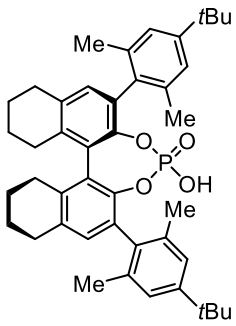
Allylated producted **6b** was also converted into **S2** by the same procedure.



6b
98% ee

S2
(*S*)-98% ee

4.4.6 Characterization Data for Chiral Phosphoric Acid 2b



2b

2b: $[\alpha]_D^{24}$ = –90.2 (*c* = 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (2H, s), 6.90 (2H, s), 6.88 (2H, s), 2.81-2.68 (6H, m), 2.26 (2H, dt, *J* = 16.4, 5.5 Hz), 2.13 (6H, s), 1.99 (6H, s), 1.84-1.79 (6H, m), 1.68-1.63 (2H, m), 1.13 (18H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.4, 143.4 (d, $J_{P\text{-}C}$ = 8.7 Hz), 136.1, 136.1, 135.8, 134.8, 133.1, 131.8, 130.3 (d, $J_{P\text{-}C}$ = 2.9 Hz), 126.8, 124.7, 123.6, 34.0, 31.3, 29.2, 27.7, 22.8, 22.8, 21.4, 20.8; ^{31}P NMR (135 MHz, $CDCl_3$) δ 4.5; IR (film) 2949, 2936, 1256, 1171, 1020, 966, 955, 903, 866, 756 cm^{-1}; HRMS (ESI, positive ion mode) Calcd for $C_{44}H_{53}O_4PNa^+$ ($[M+Na]^+$) 699.3574. Found 699.3572.

References and Notes

1) *Supramolecular Catalysis*; van Leeuwen, P. W. N. M. ,Ed.; Wiley-VCH: Weinheim, **2008**.

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List of Publications

Publications Related to the Thesis

(1) Ohmatsu, K.; Hara, Y.; Ooi, T. *Chem*. *Sci*. **2014**, *5*, 3645.

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