Development of Palladium-Catalyzed [3 + 2] Cycloadditions for Stereoselective Construction of Contiguous All-Carbon Quaternary Stereocenters Using Chiral Ammonium-Phosphine Hybrid Ligands

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Contents

		Page
Chapter 1	**General Introduction and Summary**	**1**
Chapter 2	**Ligand-Enabled Multiple Absolute Stereocontrol in Metal-Catalyzed Cycloaddition for Construction of Contiguous All-Carbon Quaternary Stereocenters**	**16**
Chapter 3	**Multiple Absolute Stereocontrol in Pd-Catalyzed [3 + 2] Cycloaddition of Oxazolidinones with Trisubstituted Alkenes Using Chiral Ammonium-Phosphine Hybrid Ligand**	**50**
Chapter 4	**Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand**	**67**
List of Publications		**87**
Acknowledgements		**88**

Chapter 1 General Introduction and Summary

In this chapter, the author described about the synthetic methods for the construction of contiguous all-carbon quaternary stereocenters. Carbon atom has four valences and easily binds to various atoms. When carbon atom binds to four different carbon substituents, such carbon is called all-carbon quaternary stereocenter. All-carbon quaternary stereocenters are frequently found in organic compounds such as pharmaceutical agents and natural products, and these structural motifs would play important roles for the expression of their biological activities. While the development of the methodology for the catalytic asymmetric synthesis of chiral molecules bearing one all-carbon quaternary stereocenter has been successfully achieved in past decades, synthetic protocols for the construction of more complex contiguous all-carbon quaternary stereocenters has remained forefront of research.

1.1 Contiguous All-Carbon Quaternary Stereocenters

The contiguous array of two all-carbon quaternary stereocenters is often found in a variety of complex natural products such as (−)-Communesin-(F), (−)-Perophoramidine, and (+)-Chimonanthine (Figure 1). The interesting biological activities and unique structural frameworks of these compounds have attracted many scientists. In the past decade, the stereoselective construction of such frameworks has been realized by diastereoselecive reactions of chiral substrates. On the other hand, successful methods for the catalytic asymmetric access to contiguous all-carbon quaternary stereocenters have been scarcely reported because of the formidable difficulty in the catalytic control of the asymmetric construction of these complex molecular structures with high levels of enantio- and diastereoselectivity.[1]

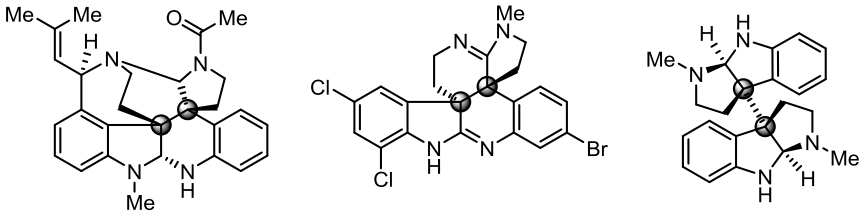


Figure 1. Representative natural products bearing contiguous all-carbon quaternary stereocenters

1.2 How to Achieve the Stereoselective Construction of Contiguous All-Carbon Quaternary Stereocenters

In general, the chemical transformations for the construction of contiguous all-carbon quaternary stereocenters can be classified into two general schemes. One is the asymmetric addition reaction to tetrasubstituted alkenes (Figure 2a), in which resulting relative stereochemistry of two chiral stereocenters heavily depends on the starting alkenes. Accordingly, in order to achieve precise stereocontrol, a geometrically pure alkene as a starting material is required. However, the lack of the general approach for the selective preparation of tetrasubstituted alkene obstructs the developments of this type of transformations.[2] The other one is the asymmetric bond-forming reaction of trisubstitued carbon nucleophiles with trisubstitued carbon electrophiles (Figure 2b). While the complicated preparation of substrates is not necessary for this type of transformations, the realization of bond connection between sterically congested prochiral carbon reactants with rigorous and simultaneous stereocontrol is very challenging task in terms of reactivity as well as stereoselectivity.

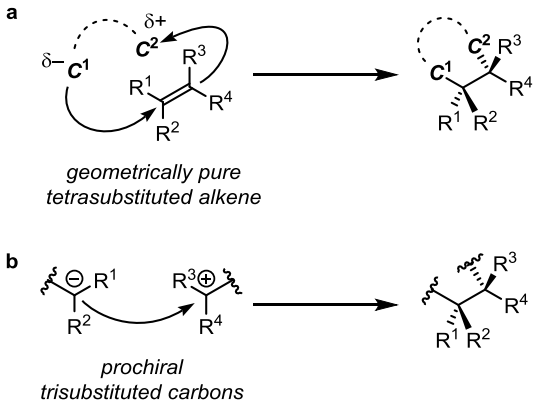


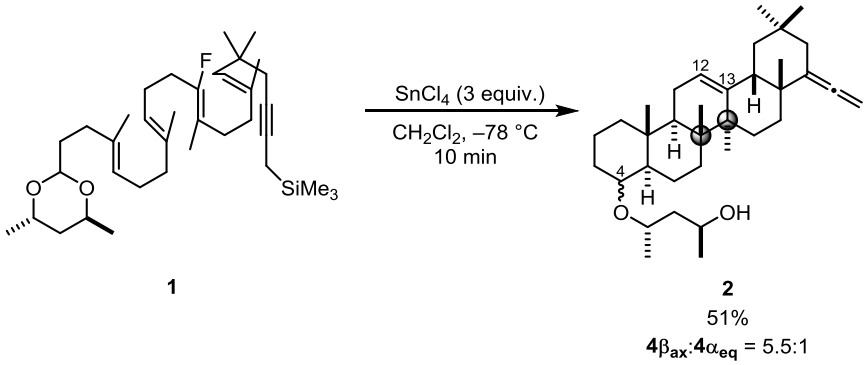
Figure 2. Two types of stereoselective transformations for the construction of contiguous all-carbon quaternary stereocenters

1.3 Diastereoselective Construction of Contiguous All-Carbon Quaternary Stereocenters

Many of previously reported successful examples are diastereoselective reactions under the substrate control. In addition, these reactions were accomplished by intramolecular reaction such as polyene cyclizations[3,4], [3,3]-sigmatropic rearrangements[5-9], and intramolecular cycloaddition[10] in order to acquire the reactivity for the bond formation between sterically congested carbons.

1.3.1 Polyene Cyclization

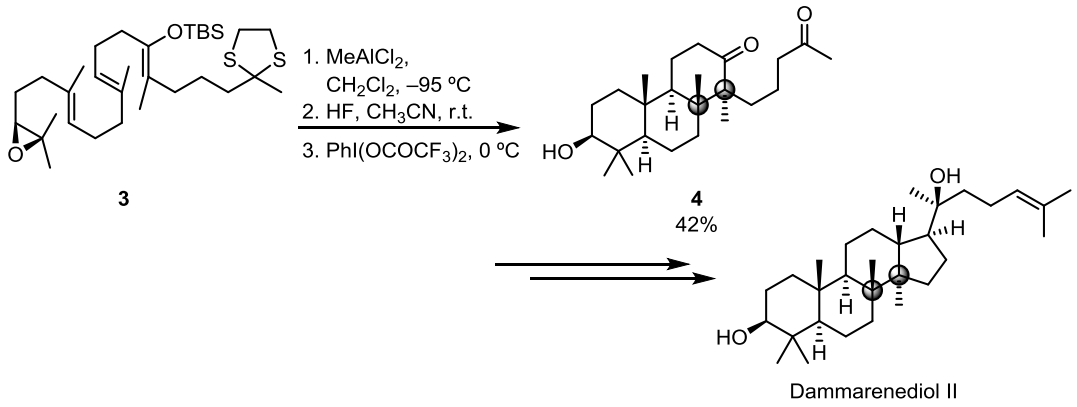
In 1994, Johnson *et al.* reported the non-enzymatic polyene cyclization (Scheme 1).[3] The treatment of $SnCl_4$ as a Lewis acid to acetal **1** caused a smooth cyclization to give a complex mixture of C-4 isomeric pentacyclic alcohol **2** having contiguous all-carbon quaternary stereocenters in 51% yield. Fluoropentacyclic alcohols were not observed in this cyclization. This reaction proceeded regiospecific dehydrofluorinative cyclization to generate C-12–C-13 double bond and $SnCl_4$ was expected to accelerate HF elimination.



1 **2**
51%
$4\beta_{ax}$:$4\alpha_{eq}$ = 5.5:1

Scheme 1. Lewis acid induced defluorinative polyene cyclization

After two years from Johnson's report, Corey *et al.* presented Lewis acid-catalyzed diastereoselective polyene cyclization reaction for asymmetric total synthesis of Dammarenediol II (Scheme 2).[4] They used chiral epoxy triene **3** as substrate for inducing successful cyclization to give a tricyclic alcohol **4**.

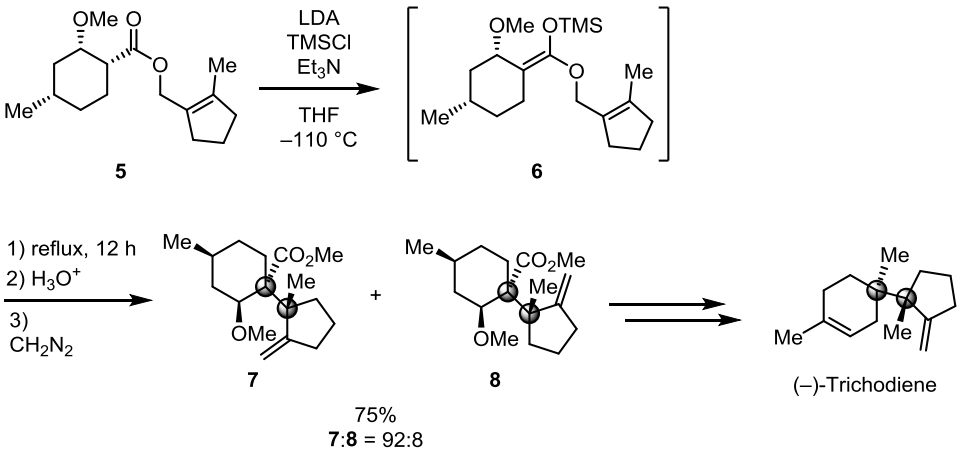


3 **4**
42%
Dammarenediol II

Scheme 2. Lewis acid catalyzed polyene cyclization reaction and total synthesis of Dammarenediol II

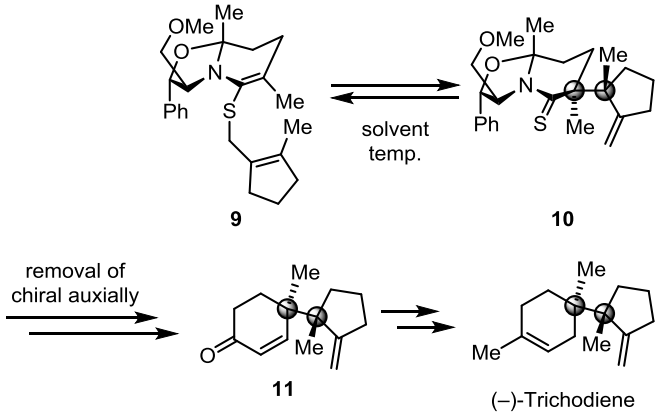
1.3.2 Sigmatropic Rearrangement

In 1993, Gilbert *et al.* published a paper entitled enantioselective total synthesis of (–)-Trichodiene (Scheme 3).[5] In this study, the key reaction was Ireland−Claisen rearrangement of ketene silyl acetal **6** to construct vicinal quaternary stereocenters.



Scheme 3. Ireland−Claisen rearrangement of the ketene silyl acetal and total synthesis of (–)-Trichodiene

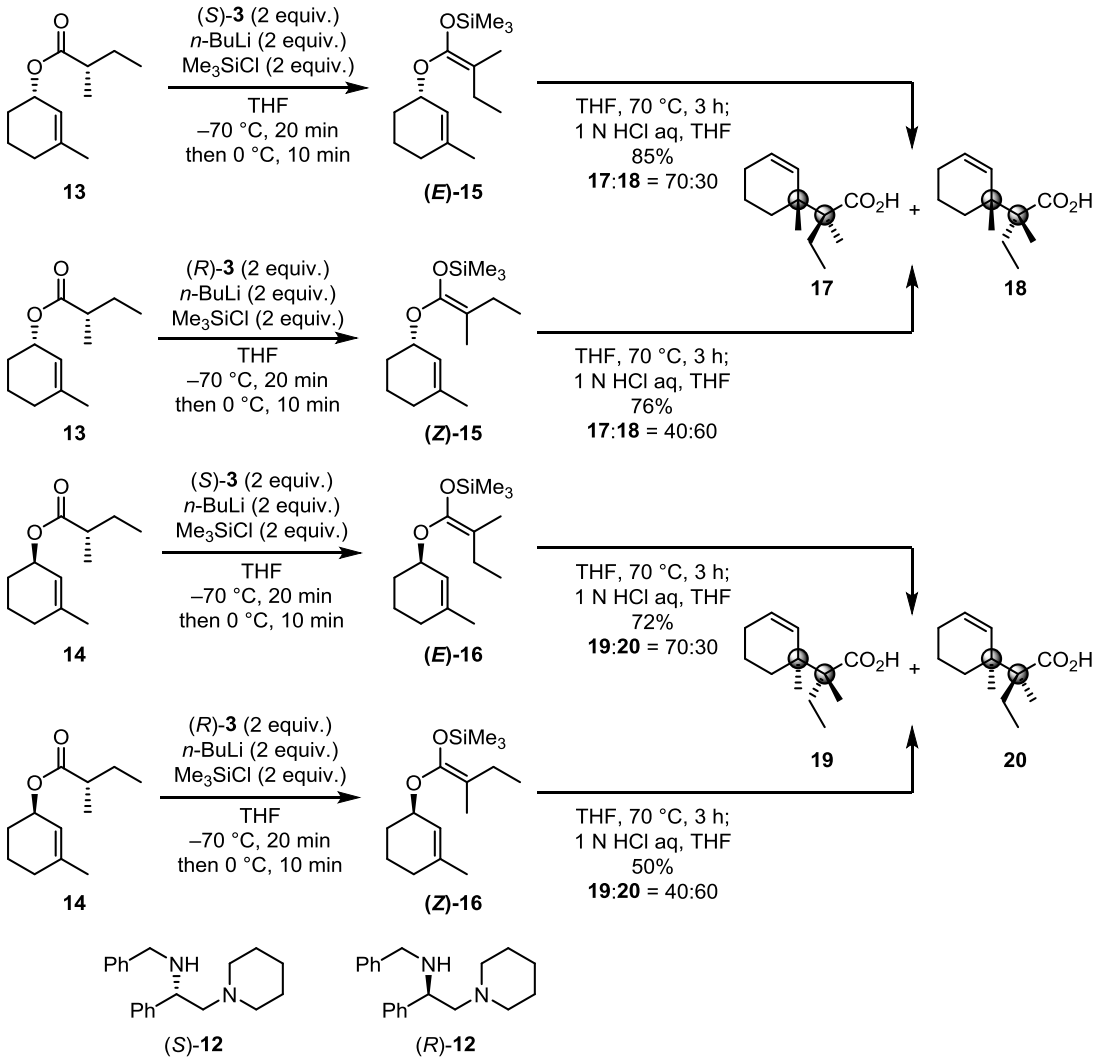
In 1998, Meyers *et al.* also reported asymmetric synthesis of (–)-Trichodiene (Scheme 4).[6a] Their strategy for the construction of contiguous all-carbon quaternary stereocenters was the exploitation of thio-Claisen rearrangement of *S*-allylthioenamine **10** derived from chiral thiolactam **9**. They found that the [3,3]-sigmatropic rearrangement of **9** to give **10** was reversible, and equilibrium ratio was dependent on the solvent. They revealed that the screening of solvents as well as the examination of the effect of reaction temperature allowed them to identify the optimal condition; nearly a 1:2 ratio of **9**:**10** was obtained in DMF at 90 °C after 72 h. It should also be noted that the chiral auxiliary of enamine **9** was readily prepared from (1*S*,2*S*)-(+)-2-amino-1-phenyl 1,3-propanediol.[6b]



solvent	temp. (°C)	ratio of **9**:**10**
xylenes	140	100:0
MeCN	80	65:35
DME	83	60:40
dioxane	101	60:40
Bu_2O	140	60:40
HMPA	100	48:52
DMF	90	36:64
DMSO	80	decomposition
H_2O:EtOH (3:1)	90	decomposition
EtOH	78	decomposition

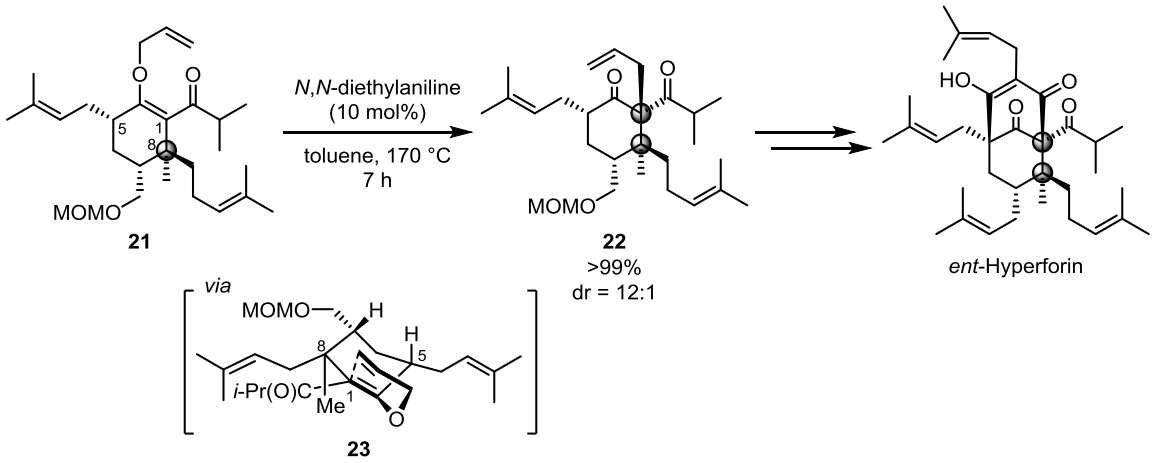
Scheme 4. Thio-Claisen rearrangement of *S*-alkylthioenamine and asymmetric total synthesis of (–)-Trichodiene

In 2010, Zakarian group reported highly diastereoselective Ireland−Claisen rearrangement of α,α-disubstituted enolates **(*E*)-15** generated from esters of cyclic alcohols **13** (Scheme 5.).[7a] The key point for achieving high diastereoselectivity was selective formation of geometrically pure enolate from α-branched esters based on the use of Koga-type chiral base such as **12**.[7b] They also succeeded to demonstrate stereo-divergent synthesis of **17**, **18**, **19**, and **20** by the appropriate choice of substrates or chiral bases.



Scheme 5. Stereo-divergent synthesis of **17**, **18**, **19**, and **20**

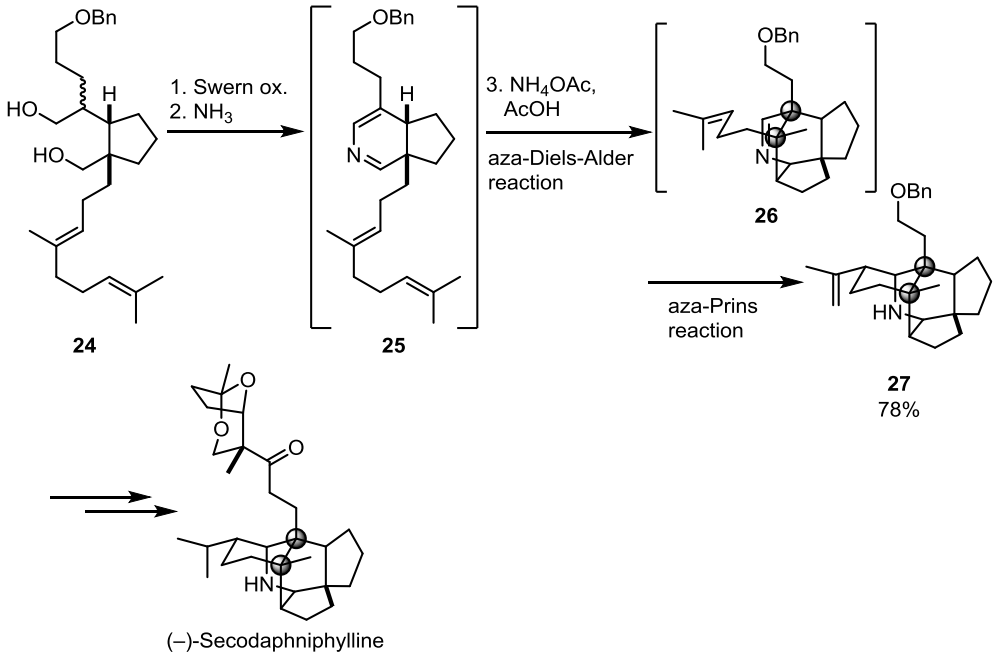
In 2010, Shibasaki and Kanai *et al.* reported catalytic asymmetric total synthesis of *ent*-Hyperforin (Scheme 6).[8a] In this study, they examined the Claisen rearrangement of *O*-allyl β-ketoester **21** in the presence of 10 mol% of *N*,*N*-diethylaniline, resulting in the production of α-allylated β-ketoester **22** bearing vicinal quaternary stereocenters with high diastereoselectivity.[8b]



Scheme 6. Construction of α-allylated β-ketoester by a Claisen rearrangement and total synthesis of *ent*-Hyperforin

1.3.3 Intramolecular Cycloaddition

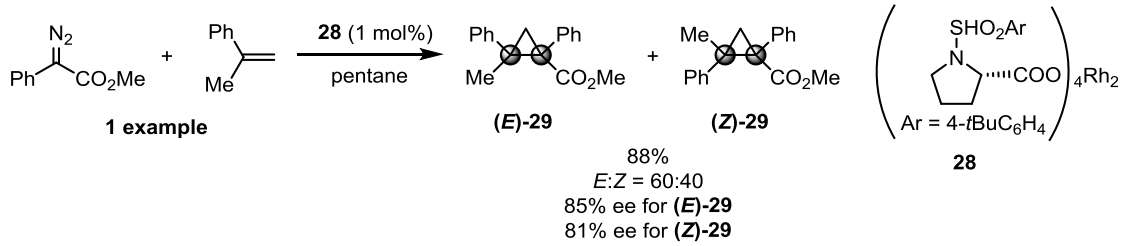
In 1990, Heathcock *et al.* reported asymmetric total synthesis of (–)-Secodaphniphyline (Scheme 7).[9] They obtained tetracyclic compound **27** through aza-Diels–Alder reaction of 2-aza diene **25** under the acidic condition followed by aza-Prins reaction.



Scheme 7. Asymmetric total synthesis of (–)-Secodaphniphylline

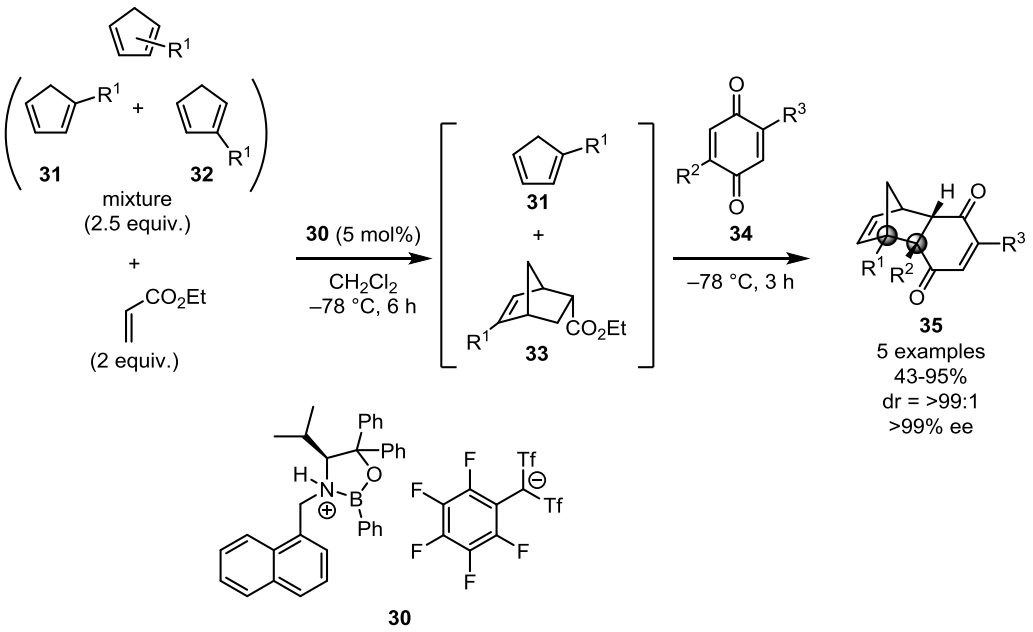
1.4 Catalytic Asymmetric Construction of Contiguous All-Carbon Quaternary Stereocenters

A pioneering work for the catalytic asymmetric construction of contiguous all-carbon quaternary stereocenters was accomplished by Doyle *et al.* in 1996.[10] They reported enantioselective intermolecular cyclopropanation reaction of α-methyl styrene with methyl phenylziazoacetate catalyzed by chiral rhodium(II) complex **28** to give densely substituted chiral cyclopropane **29** albeit with very low diastereoselectivity (Scheme 8). Since this type of cycloadditions would proceeded through the stepwise mechanism, the bond-forming step for the construction of contiguous all-carbon quaternary stereocenters could be also regarded as intramolecular reaction.



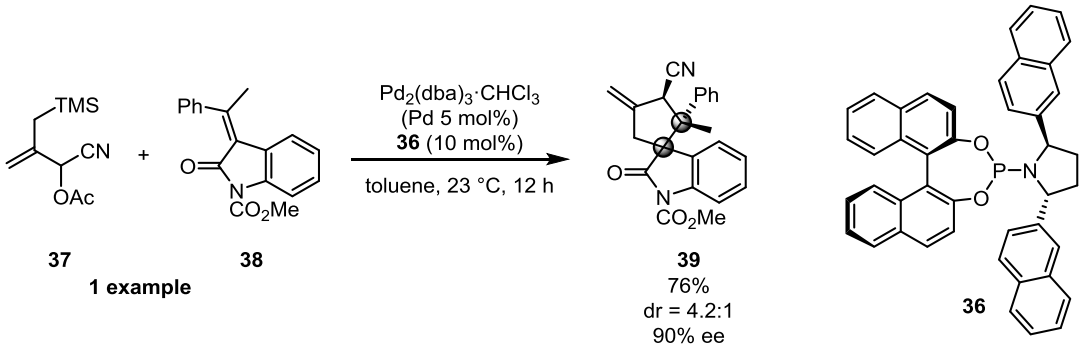
Scheme 8. Chiral Rhodium(II) catalyzed cycropropanation of α-methyl styrene

Since then, Yamamoto *et al.* disclosed region-, diastereo-, and enantioselective Diels–Alder reaction catalyzed by a chiral oxazaborolidinium ion **30** as a Lewis Acid (Scheme 9).[11] They found that the reaction of mixture of 1-substituted cyclopentadiene **31** and 2-substituted one **32** with ethyl acrylate under the influence of **30** proceeded, resulting in the production of cycloadduct **33** as a single regioisomer derived from **32**. They conceived to utilize the observed regio-discrimination by catalyst **30** for the reaction of **31** with the more reactive dienophile **34**. They employed excess ethyl acrylate to consume all **32**, and subsequently added **34**. The reaction proceeded regioselectively, resulting in the production of cycloadduct **35** as a sole regioisomer derived from 1-substituted cyclopentadiene **31** in good-to-high yield and excellent stereoselectivity.



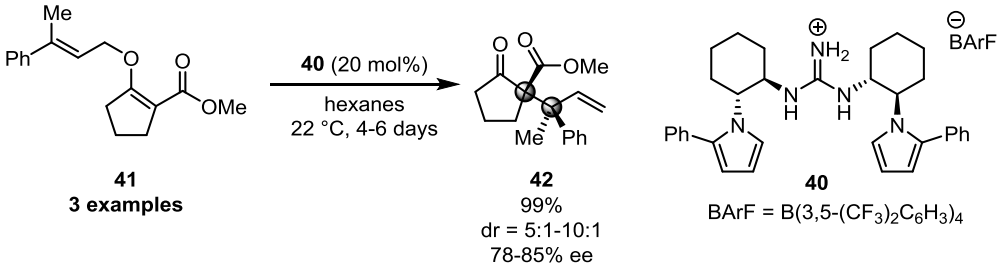
Scheme 9. Chiral oxazaborolidinium ion catalyzed Diels–Alder reactions

After the report of Yamamoto *et al.*, Trost *et al.* reported enantioselective construction of contiguous all-carbon quaternary stereocenters through palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane **37** with β,β-disubstituted α-methlene oxindole **38** (Scheme 10).[12] Under the influence of BINOL-derived chiral phosphoramidite **36**, the spirocyclic oxindolic cyclopentane **39** was obtained with high enantio- and moderate diastereoselectivity.



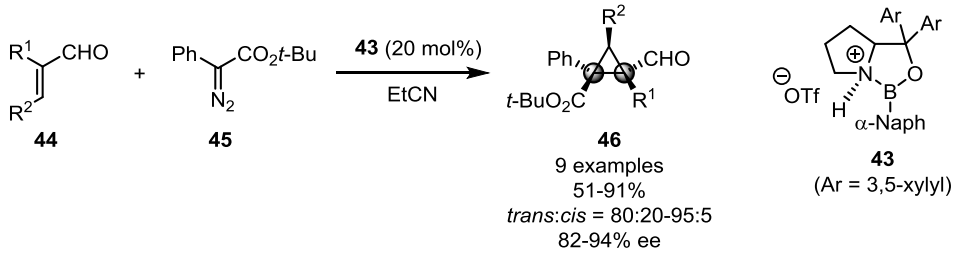
Scheme 10. Palladium catalyzed cycloaddition reaction

In 2010, Jacobsen reported chiral Brønsted acid-catalyzed asymmetric Claien rearrangement of *O*-allyl β-ketoesters **41** to construct all-carbon quaternary stereocenters, where acidic chiral guanidinium salt **40** was found to be the optimal catalyst (Scheme 11).[13] However, this catalytic system requires quite long reaction time (4-6 days). In addition, substrate scope was narrow (only 3 examples), and enantioselectivity was not so high (78-85% ee).



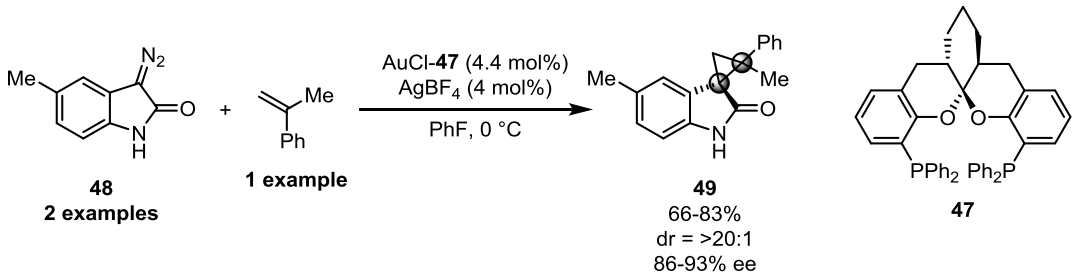
Scheme 11. Chiral guanidinium salt-catalyzed Claisen rearrangement

Ryu and coworkers reported oxazaborolidinium ion catalyzed cyclopropanation of α-substituted acroleins **44** with *t*-butyl diazoacetates **45**. This reaction initiated by Michael addition of **45** to **44** followed by ring closure to give cyclopropane **46** with good-to-high enantio- and diastereoselectities (Scheme 12).[14]



Scheme 12. Asymmetric cyclopropanation of α-substituted acroleins with *t*-butyl diazoacetates

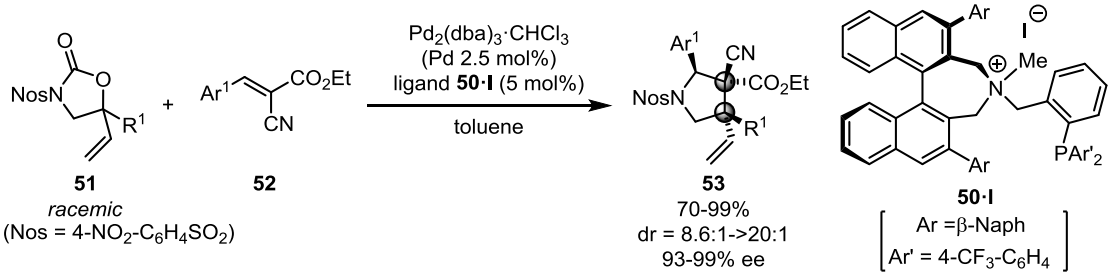
Zhou *et al.* developed highly stereoselective olefin cyclopropanation of diazooxindoles **48** with α-methyl styrene (Scheme 13)[15] catalyzed by a chiral gold complex. A spiroketal bisphosphine ligand **47** derived chiral gold catalyst was effective for the synthesis of spirocyclopropyloxindoles **49** although substrate scope was quite narrow (2 examples for diazooxindoles).



Scheme 13. Gold-catalyzed highly stereoselective olefin cyclopropanation

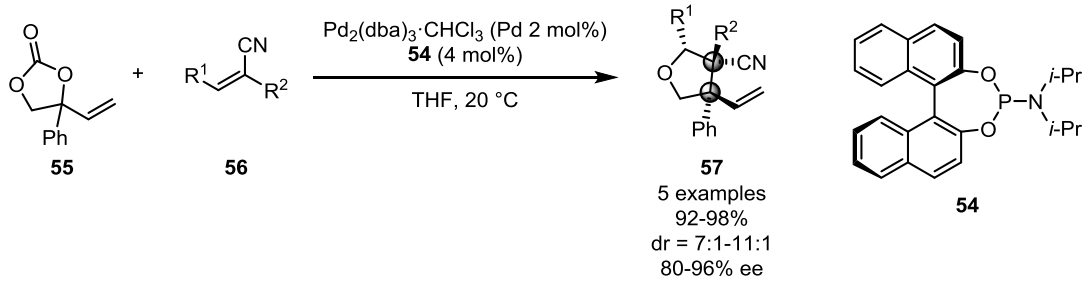
At the end of 2013, the author reported palladium-catalyzed asymmetric [3 + 2] annulation reactions of 5-vinyloxazolidinones **51** with activated trisubstituted alkenes **52** (Scheme 14). The reaction smoothly proceeded and gave **53** with excellent diastereo- and enantioselectivities. The chiral palladium complex bearing phosphine ligand with a chiral ammonium salt enabled individual

yet simultaneous absolute stereocontrol for the construction of three contiguous stereocenters. The detail of this report was described in Chapter 2.



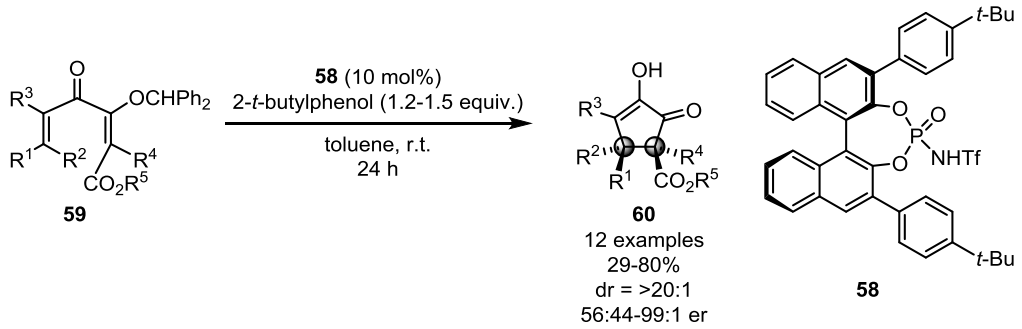
Scheme 14. Palladium-catalyzed asymmetric [3 + 2] cycloaddition of 5-vinyloxazolidinone with activated trisubstituted alkenes

After the author's report, Zhang *et al.* reported palladium-catalyzed decarboxylative [3 + 2] cycloaddition using a chiral phosphoramidite ligand **54** (Scheme 15).[16] They employed a similar reaction system as that of his reaction and obtained highly functionalized tetrahydrofrans **57** bearing contiguous all-carbon quaternary stereocenters albeit moderate diastereoselectivity.



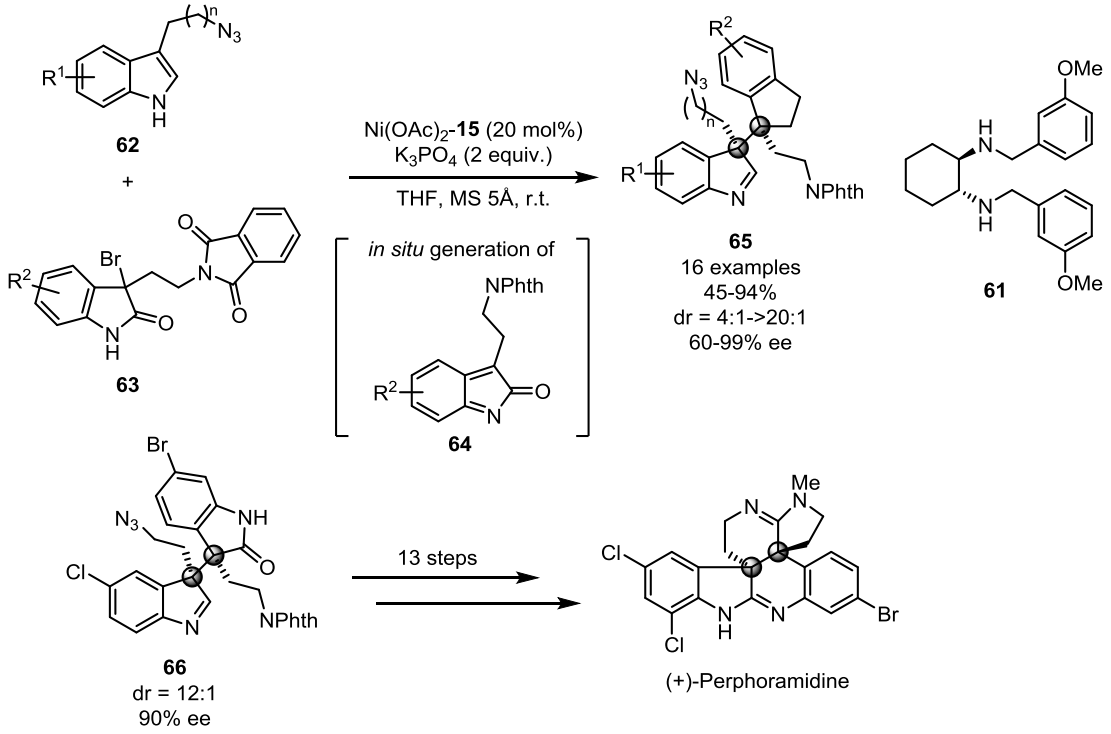
Scheme 15. Asymmetric decarboxylative cycloaddition of vinylethylene carbonates with trisubstitued alkenes

In 2014, Tius reported asymmetric Nazarov cyclization catalyzed by chiral *N*-triflyl phosphoramide **58** (Scheme 16).[17] This result was a remarkable example accomplished by catalytic asymmetric Nazarov cyclization for the first time.



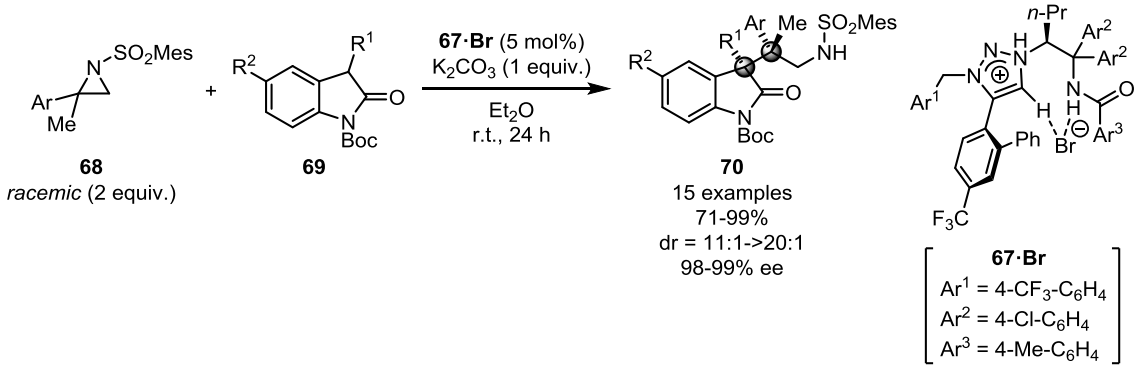
Scheme 16. Asymmetric Nazarov cyclization catalyzed by chiral *N*-triflyl phosphoramide

Around the same time as the author's report, Wang developed catalytic asymmetric alkylation of 3-bromooxindoles **63** with indoles **62** (Scheme 17).[18] Unlike the other reports, this example was achieved by the *intermolecular* reaction. They used chiral nickel-diamine complex as a chiral Lewis acid for the activation of *in situ* generated electrophilic indol-2-one **64**. They also succeeded its application for the enantioselective total synthesis of (+)-Perphoramidine.



Scheme 17. Asymmetric alkylation of 3-bromooxindoles with 3-substitued indoles and total synthesis of (+)-Perphoramidine

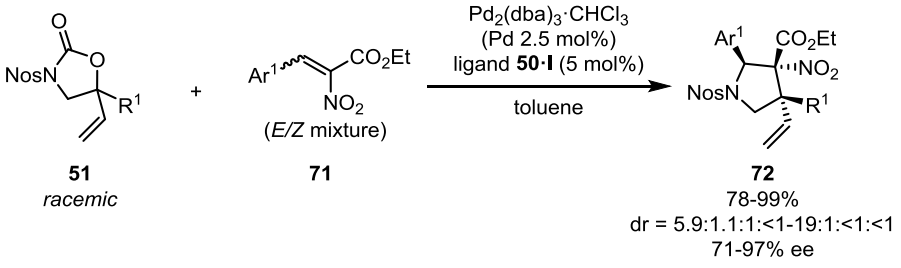
In 2013, Ooi *et al.* disclosed catalytic asymmetric ring-opening alkylation of racemic 2,2-disubstituted aziridines **68** with 3-substituted oxindoles **69** under phase-transfer catalysis (Scheme 18).[19] This reaction represents direct catalytic asymmetric substitution at the tetrasubstituted stereocenter.



Scheme 18. Asymmetric ring-opening alkylation of racemic 2,2-disubstituted aziridines

1.5 Multiple Absolute Stereocontrol in Pd-Catalyzed [3 + 2] Cycloaddition of Oxazolidinones with Trisubstituted Alkenes Using Chiral Ammonium-Phosphine Hybrid Ligands: Chapter 3

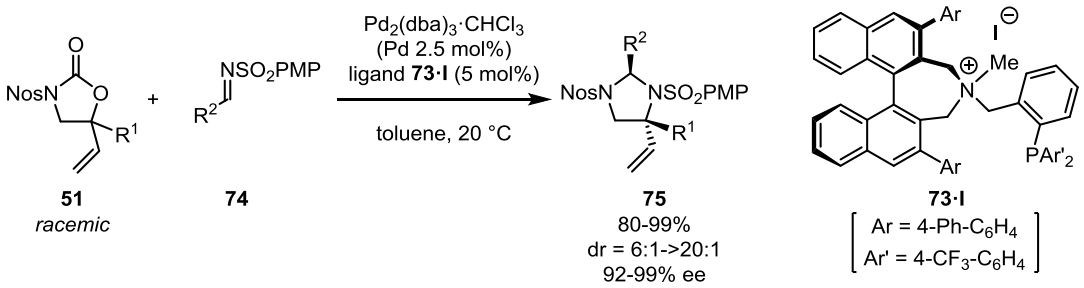
As described in Section 1.4, the author reported palladium-catalyzed asymmetric [3 + 2] cycloaddition of 5-vinyloxazolidinones with imines using chiral ammonium-phosphine hybrid ligand (see Scheme 14). In that study, the author accomplished highly stereoselective [3 + 2] annulation reactions by using geometrically pure alkenes. The author next took interest in the reactions of oxazolidinones with geometrical mixture of trisubstituted alkenes. As a result of the further experiments, the author found that the chiral ammonium-phosphine **50·I** enabled the individual stereocontrol of the C-3 stereocenter and the reactions of oxazolidinones **51** with geometrical mixture of β-aryl α-nitroacrylates **71** resulted in the production of pyrrolidines **72** with high diastereo- and excellent enantioselectivity in high yield. In addition, the author discussed the reaction mechanism especially about stereodetermining step of each stereocenter. The extended treatment of particulars in this study was presented in Chapter 3.



Scheme 19. Reaction with geometrical mixture of β-aryl α-nitroacrylates

1.6 Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand: Chapter 4

Since the stereochemistry of the C-4 chiral carbon of the pyrrolidine was not influenced by the structure of the alkene and was controlled by the chiral ammonium-phosphine hybrid ligand, I conceived that the different dipolarophiles other than trisubstituted alkenes such as imines could be also applicable. Therefore, the author focused on the stereoselective synthesis of chiral imidazolidines **75** containing α-amino quaternary stereocenters as a next synthetic target by utilizing imines as substrates. As a result, in the presence of catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ and chiral ammonium-phosphine hybrid ligand **73·I**, the reaction was smoothly proceeded to give the cycloadduct **75** with high diastereo- and enantioselectivity (Scheme 20). Chapter 4 described the details of this project.



Scheme 20. Asymmetric [3 + 2] cycloaddition of 5-vinyloxazolidinones with imines

1.7 Conclusion

In these studies, the author developed palladium-catalyzed asymmetric [3 + 2] cycloaddition reactions for construction of contiguous all-carbon quaternary stereocenters. The author designed novel phosphine ligand with a pendant chiral ammonium salt. The chiral palladium catalyst enabled multiple absolute stereocontrol for three contiguous stereocenters in the cycloaddition. The author also disclosed the application for the stereoselective synthesis of chiral imidazolidines bearing α-amino quaternary stereocenter by utilizing this unique catalytic system.

References

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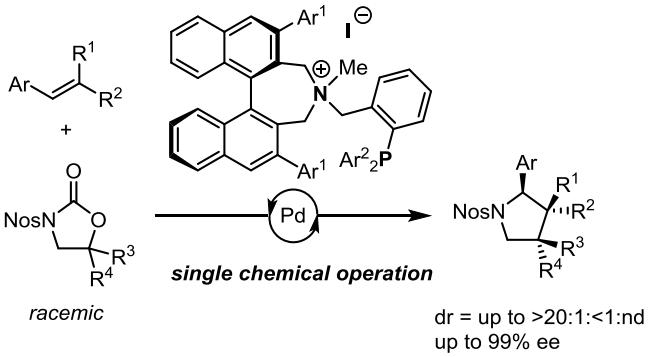
Chapter 2

Ligand-Enabled Multiple Absolute Stereocontrol in Metal-Catalyzed Cycloaddition for Construction of Contiguous All-Carbon Quaternary Stereocenters



Abstract: The development of a general catalytic method for the direct and stereoselective construction of contiguous all-carbon quaternary stereocenters remains a formidable challenge in chemical synthesis. Here, the author reports a highly enantio- and diastereoselective [3 + 2] annulation reaction of 5-vinyloxazolidinones and activated trisubstituted alkenes catalyzed by a palladium complex bearing a newly devised phosphine ligand with a chiral ammonium salt component, which enables the single-step construction of three contiguous stereocenters, including vicinal all-carbon quaternary stereocenters, in a five-membered heterocyclic framework. This stereoselective cycloaddition protocol relies on the remarkable ability of the chiral ligand to rigorously control the absolute stereochemistry of each chiral center associated with the multiple bond-forming events, and provides a reliable catalytic process for the asymmetric synthesis of densely functionalized pyrrolidines.

1. Introduction

A contiguous array of all-carbon quaternary stereocenters is found in many complex natural products and is often crucial for the expression of their biological activities. Accordingly, the establishment of reliable methodologies for the efficient stereoselective construction of this structural motif represents a significant task of high demand, but belongs to the most challenging objectives in organic synthesis.[1] In principle, transformations for the synthesis of contiguous chiral quaternary carbons are categorized into two general schemes. One is the asymmetric addition reaction to tetrasubstituted alkenes (Figure 1a), in which the relative stereochemistries of the two resulting chiral centers highly depend on the geometries of starting alkenes. As such, this scheme requires the geometrically pure alkenes, and impracticability of selective preparation of tetrasubstituted alkenes hinders the development of these asymmetric transformations.[2] The other scheme is the asymmetric reaction of trisubstituted carbon nucleophiles and electrophiles (Figure 1b). Although the complicated stereochemical presetting of substrates is not essential for this type of transformations, there is formidable problem for the realization of high enantio- and diastereoselectivity. The simultaneous recognition and control of complex stereochemistries of two reactants in single bond-forming events are inherently difficult. Furthermore, the bond formation between sterically congested carbon atoms cannot readily proceed. To overcome this reactivity problem, intramolecular processes are generally considered to be advantageous in view of appreciating the enforced proximity of the two reactive sites. In fact, as previously reported, a limited number of approaches for addressing this object rely on the intramolecular reactions such as polyene cyclization,[3,4] sigmatropic rearrangement,[5-9] and intramolecular cycloadditions.[10] However, while diastereoselective methods using chiral substrates have been well explored, the development of catalytic asymmetric transformations for the direct and selective generation of vicinal all-carbon quaternary stereocenters remains at the forefront of research.[9,11-16]

Transition-metal-catalyzed intermolecular cycloaddition have been extensively studied for the rapid assembly of cyclic molecular frameworks.[17,18] Among a wide range of useful variations, the catalytic annulation mediated by a zwitterionic π-allylpalladium intermediate is one of the most powerful tools for the stereoselective synthesis of highly functionalized cyclic compounds from relatively simple materials.[16,19-24] The overall bond connection in this reaction system is believed to take place in a stepwise manner. When readily preparative trisubstituted alkene is used as a coupling partner for cycloaddition, the initial intermolecular addition of the allylpalladium species to alkene should afford the zwitterionic intermediate possessing a trisubstituted carbanion site (Figure 1c). If the rate of subsequent intramolecular ring-closing process is enough fast, the stereochemical information of this carbanion would depend on the geometry of starting alkene. Therefore, the attainment of enantiofacial discrimination of alkene in the initial intermolecular addition step would enable the selective construction not only of trisubstituted chiral center but also of neighboring

quaternary chiral carbon. At the same time, the utilization of allyl compound having tetrasubstituted chiral carbon as a precursor for the generation of 1,1-disubstituted allylpalladium intermediate can also form the quaternary stereosenter in the ring-closing bond formation. Stereoselctive construction of this chiral center necessitates the control of isomerization of planar chiral π-allylpalladium through a π-σ-π interconversion.[24-26] To achieve such double absolute stereocontrol, that is the discrimination of prochiral trisubstituted alkene and the control of chirality of π-allylpalladium, in asymmetric cycloaddition, the author designed a new type of phosphine ligand bearing a chiral ammonium salt (Figure 1d).[27,28] Using this chiral onium-phosphine hybrid ligand, the remote anionic site of zwitterionic intermediate is expected to be precisely recognized by the chiral ammonium ion. Here, the author presents the successful realization of highly enantio- and diastereoselective construction of contiguous all-carbon quaternary stereocenters through the palladium-catalyzed asymmetric [3 + 2] annulation reaction. In particular, the author developed the cyclization of 5-vinyloxazolizinones and activated trisubstituted alkenes, thereby offering a reliable catalytic process for the asymmetric synthesis of densely substituted pyrrolidines.[29-31]

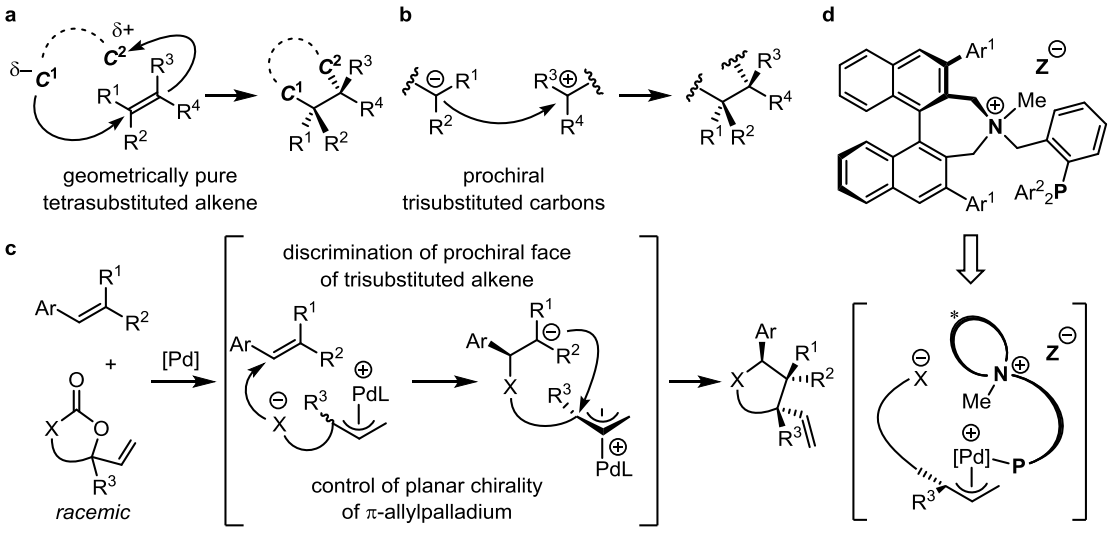


Figure 1. Overview of preparation of contiguous all-carbon quaternary stereocenters

a, Reaction of tetrasubstituted alkenes. **b**, Reaction between prochiral trisubstituted carbon reagents. **c**, Concept of multiple absolute stereocontrol in palladium-catalyzed cycloaddition for asymmetric construction of contiguous stereocenters. **d**, Structure of chiral onium-phosphine hybrid ligand and proposed zwitterionic intermediate.

2. Result and Discussion

The studies were initiated by the identification of a suitable ligand for promoting the palladium-catalyzed asymmetric [3 + 2] cycloaddition. The author selected *N*-(4-nitrobenzenesulfonyl)-5,5-divinyloxazolidin-2-one **3** and 2-benzylidenemalononitrile **4** as model substrates for the following reasons: (i) these compounds can be readily prepared from a commercially available glycine derivative and malononitrile, respectively; (ii) the

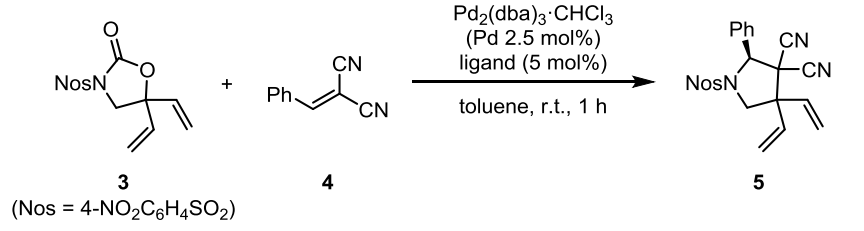
enantioselectivity of the cycloadduct would be a suitable parameter for evaluating the ability of the chiral ammonium-phosphine hybrid ligand to discriminate prochiral **4** in the aza-Michael addition of the anionic site of the allylpalladium species generated from **3**; (iii) this type of transformation could straightly afford highly functionalized chiral pyrrolidines, which are the ubiquitous core structures in natural products and pharmaceuticals.[32-34]

The reaction of **3** with **4** under the influence of the catalyst prepared *in situ* from tris(dibenzylideneacetone)dipalladium–chloroform complex $[Pd_2(dba)_3 \cdot CHCl_3]$ and triphenylphosphine (PPh_3) was first carried out in toluene at room temperature. After 1 h of stirring, the desired pyrrolidine **5** was obtained in moderate yield (Table 1, entry 1). The addition of catalytic amount of tetrabutylammonium bromide to this catalytic system led to the increase of reaction efficiency, resulting in the formation of **5** in 79% yield (entry 2). This result was consistent with the independent observations by Knight and Aggarwal that halide ions accelerated the reactions.[30,31] Halide ions are well known to have strong coordinating ability toward palladium, thus affecting the outcome of catalytic processes.[35] In the reaction of **3** with **4**, the conjugated addition of anionic site of allylpalladium complex to **4** would be retarded by the interaction between amide ion and cationic palladium, which was reduced by the addition and preferential binding of bromide ion. The author then performed the reaction using achiral onium-phosphine ligands for elucidating their performance with respect to activity. In the presence of *ortho*-diphenylphosphinobenzyl-ammonium bromide **1a·Br**,[27] the reaction was smoothly completed within 1 h, affording **5** quantitatively (entry 3).

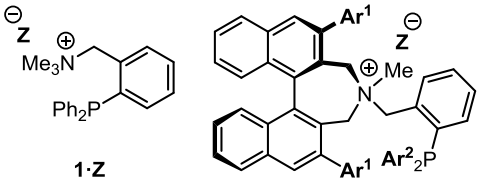
Notably, replacement of the bromide ion of the ligand by the acetate ion resulted in a substantial decrease reaction efficiency, giving credence to the postulate that the coordinating ability of the anion is crucial to the catalytic performance (entry 4). Based on these observations, *ortho*-diphenylphosphinobenzyl-ammonium halide seemed to be appropriate core structure of efficient ligand for zwitterionic allylpalladium-mediated cycloaddition. Therefore, the author next focused on the design and evaluation of chiral ammonium phosphines having such key structures, and introducing 1,1´-binaphthyl-derived azepinium skelton[36] into the ammonium ion component was found to successfully contribute to the stereocontrol. Indeed, the reactions under the influence of chiral ligands of type **2a·Br** furnished the pyrrolidine **5** in excellent yields with moderate to good enantioselectivities (entries 5–8), and the chiral ammonium phosphine **2d·Br** was revealed to be a promising candidate for promoting the reaction with high stereoselectivity. The author then examined the effect of halide ion by taking into account of the importance of counterion of ammonium function. Interestingly, while switching the counterion of **2d** from bromide to chloride affected the stereoselectivity only subtly (entry 9), a dramatic enhancement in enantioselectivity was observed when the counterion was exchanged to iodide (entry 10). Thus, chiral ammonium

phosphine **2d·I** is the most appropriate for this reaction. Finally, lowering the reaction temperature to 0 °C further increased the enantioselectivity to 92% ee (entry 11).

Table 1. Optimization of catalytic system for cycloaddition of 5-vinyloxazolidinone **3** with benzylidenemalononitrile **4**[a]



3 (Nos = 4-$NO_2C_6H_4SO_2$) **4** **5**



1·Z

2a·Z (Ar^1 = Ar^2 = Ph)
2b·Z (Ar^1 = β-Naph, Ar^2 = Ph)
2c·Z (Ar^1 = Ph, Ar^2 = 4-$CF_3C_6H_4$)
2d·Z (Ar^1 = β-Naph, Ar^2 = 4-$CF_3C_6H_4$)

Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	PPh_3	43	-
2[d]	PPh_3	79	-
3	**1·Br**	99	-
4	**1·OAc**	49	-
5	**2a·Br**	94	63
6	**2b·Br**	99	63
7	**2c·Br**	99	57
8	**2d·Br**	99	75
9	**2d·Cl**	99	72
10	**2d·I**	99	90
11[e]	**2d·I**	99	92

[a]Unless otherwise noted, reactions were carried out with 0.10 mmol of **3** and 0.12 mmol of **4** in the presence of $Pd_2(dba)_3·CHCl_3$ (Pd 2.5 mol%) and ligand (5 mol%) in 1.0 mL of toluene at room temperature for 1 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Performed with 5 mol% of tetrabutylammonium bromide (TBAB). [e]Carried out at 0 °C for 3 h.

Having the optimal ligand structure and reaction conditions that enabled precise discrimination of prochiral alkene **4** in the cycloaddition, the author attempted the stereoselective construction of all-carbon quaternary stereocenters using a differently geminal-substituted alkene as a substrate. The reaction of oxazolidinone **3** with (*E*)-ethyl 2-cyano-3-phenylacrylate **6a** was conducted under the influence of the optimized catalytic system, affording the diastereomerically pure pyrrolidine **7** in

excellent yield with high enantioselectivity (Figure 2a). Next, in order to interrogate the possibility of the absolute stereocontrol of planar chiral π-allylpalladium, the author examined the reaction of racemic 5-methyl-5-vinyloxazolidinone **8a** with symmetric terminal alkene **9**. To our delight, under the influence of the identical catalytic system, the reaction of **8a** with **9** also smoothly proceeded, resulting in the quantitative production of pyrrolidine **10** with high enantioselectivity (Figure 2b). These date manifested that chiral ammonium phosphine **2d·I** paved the way for the realization of individual yet simultaneous stereocontrol of plural bond-forming events, termed multiple absolute stereocontrol, in asymmetric cycloaddition reaction.

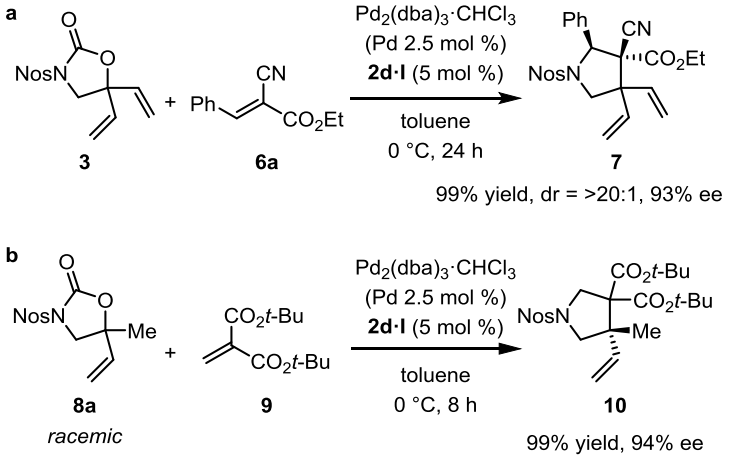


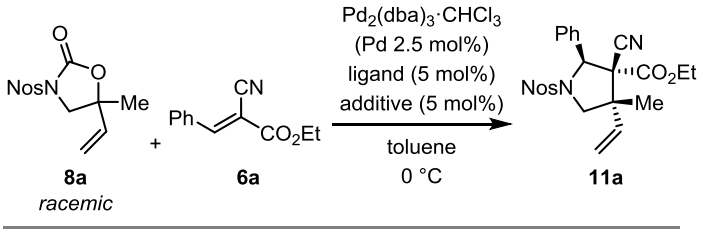
Figure 2. Examinations for individual absolute stereocontrol

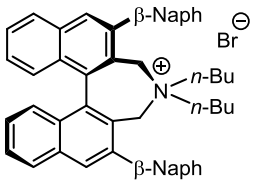
a, The reaction to generate an all-carbon quaternary stereocenter at C-3 position of the pyrrolidine.
b, The reaction to generate an all-carbon quaternary stereocenter at C-4 position of the pyrrolidine.

With this information in hand, the viability of the asymmetric construction of contiguous all-carbon quaternary stereocenters via the [3 + 2] annulations of racemic oxazolidinone **8a** with 2-cyano-3-phenylacrylate **6a** was examined (Table 2). As expected, treatment of **8a** and **6a** to catalysis by $Pd_2(dba)_3{\cdot}CHCl_3$ and **2d·I** in toluene at 0 °C furnished the desired densely substituted pyrrolidine **11a** in an almost stereochemically pure form (entry 1). We then examined the control reactions under the influence of conventional asymmetric catalysis using the combination of phosphine ligand and ammonium salt. For instance, while the reaction using tris(4-trifluoromethyl)phenylphosphine and chiral ammonium bromide **12**[37] proceeded at room temperature to afford **11a** quantitatively, negligible diastereo- and low enantioselectivities were observed (entry 2). The use of chiral phosphine ligands, such as MOP[38] (**13**) or BINAP[39] (**14**), with tetrabutylammonium bromide was ineffective for promoting the cycloaddition reaction (entry 3) or inducing stereoselectivies (entry 4). BINOL-derived phosphoramidite[40] **15** was found to smoothly promote this annulation reaction albeit with very low enantio- and diastereoselectivities (entry 5),[16] and further screening of chiral phosphoramidites failed to improve the stereoselectivities. These results emphasized the effectiveness of ammonium–phosphine hybrid ligand of type **2·I** for enantio-

and diastereoselective construction of contiguous quaternary stereocenters through palladium-catalyzed [3 + 2] cycloaddition.

Table 2. Attempt for asymmetric construction of contiguous all-Carbon quaternary stereocenters[a]





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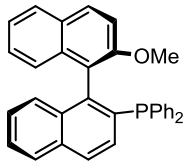

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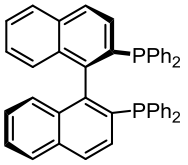

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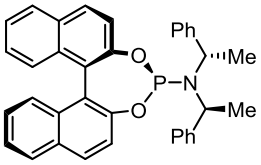


15

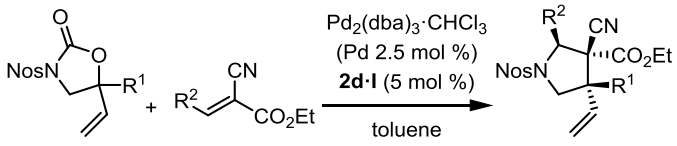
Entry	Ligand	Additive	Yield (%)[b]	dr[c]	ee (%)[d]
1	**2d·I**	–	98	>20:1:<1:nd	98/nd
2[e]	$P(4\text{-}CF_3C_6H_4)_3$	**12**	99	1:1:<1:nd	14/–33
3[e]	**13**	TBAB	trace	–	–
4[e,f]	**14**	TBAB	13	1:1.9:<1:nd	<1/<1
5[e]	**15**	TBAB	95	1:1.2:<1:nd	–15/–23

[a]Unless otherwise noted, reactions were carried out with 0.10 mmol of **8a** and 0.30 mmol of **6a** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%), ligand (5 mol%), and additive (5 mol%) in 1.0 mL of toluene at 0 °C for 24 h. [b]Isolated yield. [c]Determined based on ^{1}H NMR analysis of crude reaction mixture. nd = not detected. [d]Determined by HPLC analysis. [e]Carried out at r.t. for 24 h. [f]With 2.5 mol% of **14**.

The author next explored the scope of this asymmetric [3 + 2] cycloaddition of racemic oxazolidinones **8** with trisubstituted alkenes **6** (Table 3). Cyanoacrylates **6** possessing various aromatic or heteroaromatic substituents at their 3-positions all underwent the cycloaddition reaction with high level of stereoselectivities (entries 2-5). 5-Vinyloxazolidinones **8** with alkyl substituents, including branched one, were also tolerated, resulting in uniformly excellent diaseteo- and enantioselectivities of the corresponding cycloadducts (entries 6-9). Although the reactions of 5-vinyl-5-aryloxazolidinones required higher reaction temperature owing to the considerable rate

retardation, *N*-protected pyrrolidines were isolated almost quantitatively with good diatereo- and high enantioselectivities (entries 10-12).

Table 3. Asymmetric construction of contiguous all-Carbon stereocenters through palladium-catalyzed cycloaddition[a]



8 *racemic* **6** **11**

entry	R^1	8	R^2	6	Temp.	11	Yield (%)[b]	dr[c]	ee (%)[d]
1	Me	**8a**	Ph	**6a**	0 °C	**11a**	98	>20:1:<1:nd	98
2	Me	**8a**	4-Br-C_6H_4	**6b**	0 °C	**11b**	99	17:1:<1:nd	97
3	Me	**8a**	4-MeO-C_6H_4	**6c**	0 °C	**11c**	99	>20:1:<1:nd	99
4	Me	**8a**	2-naphthyl	**6d**	0 °C	**11d**	94	>20:1:<1:nd	99
5	Me	**8a**	2-furyl	**6e**	0 °C	**11e**	99	>20:1:<1:nd	97
6	Et	**8b**	Ph	**6a**	0 °C	**11f**	99	>20:1:<1:nd	98
7	*i*-Bu	**8c**	Ph	**6a**	0 °C	**11g**	99	>20:1:<1:nd	99
8	$PhCH_2$	**8d**	Ph	**6a**	0 °C	**11h**	99	>20:1:<1:nd	95
9[e]	*i*-Pr	**8e**	Ph	**6a**	r.t.	**11i**	70	>20:1:<1:nd	94
10	Ph	**8f**	Ph	**6a**	r.t.	**11j**	99	9.8:1:<1:nd	93
11	4-Cl-C_6H_4	**8g**	Ph	**6a**	r.t.	**11k**	94	8.6:1:<1:nd	94
12	4-MeO-C_6H_4	**8h**	Ph	**6a**	r.t.	**11l**	97	9.3:1:<1:nd	95

[a]Unless otherwise noted, reactions were carried out with 0.10 mmol of **8** and 0.3 mmol of **6** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol %) and **2d·I** (5 mol %) in 1.0 mL of toluene. For reaction temperature and time, see the Experimental Section. [b]Isolated yield. [c]Determined based on ^{1}H NMR analysis of crude reaction mixture. nd = not detected. [d]Enantiomeric excesses of the major diastereomer were indicated, which were analyzed by chiral stationary phase HPLC. The absolute configurations of **3b** and **3i** were confirmed by X-ray diffraction analysis, and the stereochemistries of other examples were assumed by analogy. [e]The reaction was performed with $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 5 mol %) and **2d·I** (10 mol %). r.t. = room temperature.

The synthetic versatility of the present catalytic system was next demonstrated through a large-scale reaction and the product derivatizations (Figure 4). The reaction of **8a** with **6a** on a 10 mmol scale was found to be completed in 48 h even with a reduced amount of catalyst, yielding 4.7 g of cycloadduct **11a** without notable decrease in stereoselectivity (Figure 4a). Cycloadduct **11** can be readily transformed into *N*-unprotected pyrrolidines. For instance, the selective reduction of the

ethyl ester moiety of **11a** by treatment with diisobutylaluminum hydride (DIBAL-H) and subsequent deprotection of the 4-nitrobenzenesulfonyl (Nos) group[41] under well-established conditions afforded the corresponding pyrrolidine **17** (Figure 4b). In addition, **11a** was successfully converted into the densely substituted bicyclic lactam **21**, which is the core structure of the analogue of thrombin inhibitors.[42-44] Thrombin is a key serine protease in the blood-coagulation cascade and a series of lactams with a tricyclic core have been developed as non-peptidic, high affinity inhibitors (Figure 4c). The synthetic sequence from **11a** depicted in Figure 4b could offer an access to the previously elusive analogues bearing carbogenic substituents at the core. Thus, ozonolysis of the vinyl function in **11a** led to the corresponding aldehyde **18**. The formyl group of **18** could be selectively reduced to the primary alcohol by treating with DIBAL-H in THF, and subsequent exposure to TFA gave the bicyclic lactone **19**. Eventually, the transformation of lactone to lactam was executed by the transient opening of **19** with 4-methoxybenzylamine followed by the intramolecular Mitsunobu reaction, furnishing **21** as an essentially single stereoisomer.

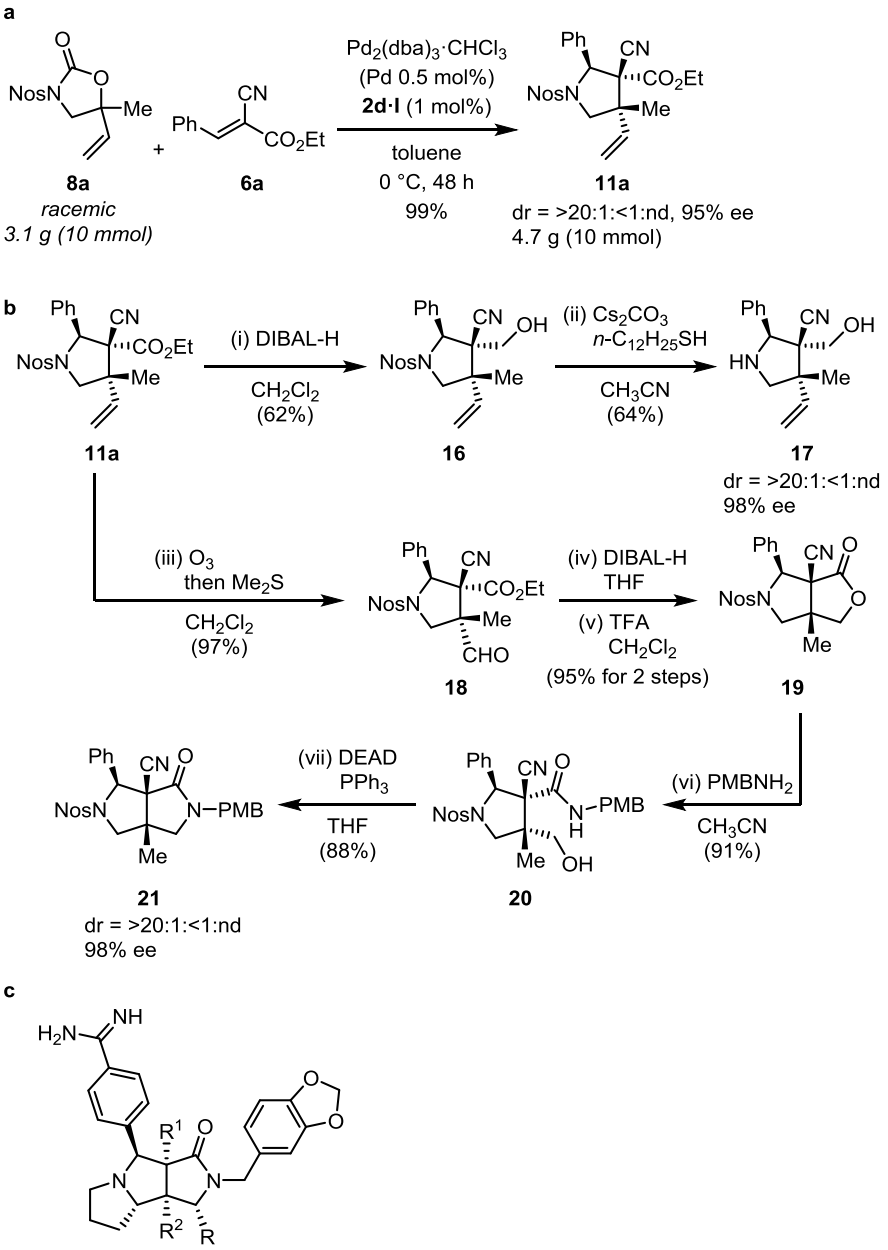


Figure 4. Synthetic versatility of the present catalytic system

a, Scale-up of the cycloaddition process. **b**, Derivatization of cycloaddition product **11a** to unprotected pyrrolidine **17** and multi-substituted bicyclic lactam **21**. Reagents and conditions: (i) diisobutylaluminum hydride (DIBAL-H) (2 equiv.), CH_2Cl_2, –78 °C, 30 min then 0 °C, 1 h; (ii) Cs_2CO_3 (2 equiv.), *n*-$C_{12}H_{25}SH$ (2 equiv.), CH_3CN, r.t., 4 h; (iii) O_3, CH_2Cl_2, –78 °C, 10 min, then Me_2S (10 equiv.), –78 °C to r.t. 2 h; (iv) DIBAL-H (2 equiv.), THF, –78 °C, 2 h; (v) trifluoroacetic acid (TFA)/CH_2Cl_2 = 1:1, r.t., 7 h; (vi) 4-methoxybenzylamine ($PMBNH_2$) (2 equiv.), CH_3CN, reflux, 6 h; (vii) diethyl azodicarboxylate (DEAD) (1.1 equiv.), Ph_3P (1.1 equiv.), THF, r.t., 10 h. **c**, R^1 = R^2 = H; known thrombin inhibitor. R^1, R^2 = alkyl; previously inaccessible analogues.

3. Conclusion

In conclusion, a highly enantio- and diastereoselective [3 + 2] annulation reaction of

5-vinyloxazolidinones and activated trisubstituted alkenes catalyzed by a palladium complex bearing a newly devised phosphine ligand with a chiral ammonium salt component was developed, which allows for the single-step construction of three contiguous stereocenters, including vicinal all-carbon quaternary stereocenters, on the pyrrolidine core. This system relies heavily on the remarkable ability of the chiral onium-phosphine hybrid ligand to facilitate the intermolecular cycloaddition with precise control of the individual absolute stereochemistry across multiple bond formation, and represents a reliable catalytic process for the asymmetric synthesis of densely functionalized pyrrolidines and their derivatives.

4. Experimental Section

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, br = broad) 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. ^{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 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-H (ODH) and CHIRALPAK AD-H (ADH), CHIRALPAK AD-3 (AD3), CHIRALCEL OZ-3 (OZ3), CHIRALPAK IA (IA), CHIRALPAK IC (IC)) with hexane (H), 2-propanol (IPA), and ethanol (EtOH) as eluent.

All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. The manipulations for palladium-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. Oxazolidinones were synthesized as described below.[30] Alkenes were synthesized by following the literature procedure.[45,46] Other simple chemicals were purchased and used as such.

The data reported herein are basically the results of the single runs. The reactions of **8a** and **8f** with **6a**, and the reaction of **8a** with **12** were conducted several times, and the results obtained have proven highly reproducible.

Additional Experimental Data and Discussion:

(A) Kinetic Resolution

In order to elucidate the stereo-determining process in the construction of C-4 chiral carbon, the author examined the possibility of the kinetic resolution in the reaction of racemic oxazolidinone **8a** with trisubstituted alkene **6a** because chiral Pd(0) complex might preferentially undergo oxidative addition to one enantiomer of **8a** (Figure S1). When the reaction was conducted with 2 equiv. of **8a** and 1 equiv. of **6a** under the optimized conditions, the pyrrolidine **11a** was obtained in 99% yield (based on the amount of **6a**) with near-complete stereoselectivities, and the starting material **8a** was recovered in 95% (based on the amount of **6a**) with 17% ee. This result indicated that the rigorous stereocontrol in the construction of C-4 chiral carbon stemmed not from the kinetic resolution of **8a** but from the control of planar chirality of the π-allyl Pd(II) through the π-σ-π interconversion.

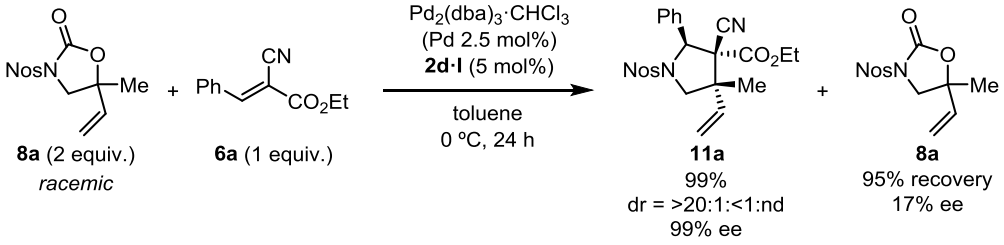
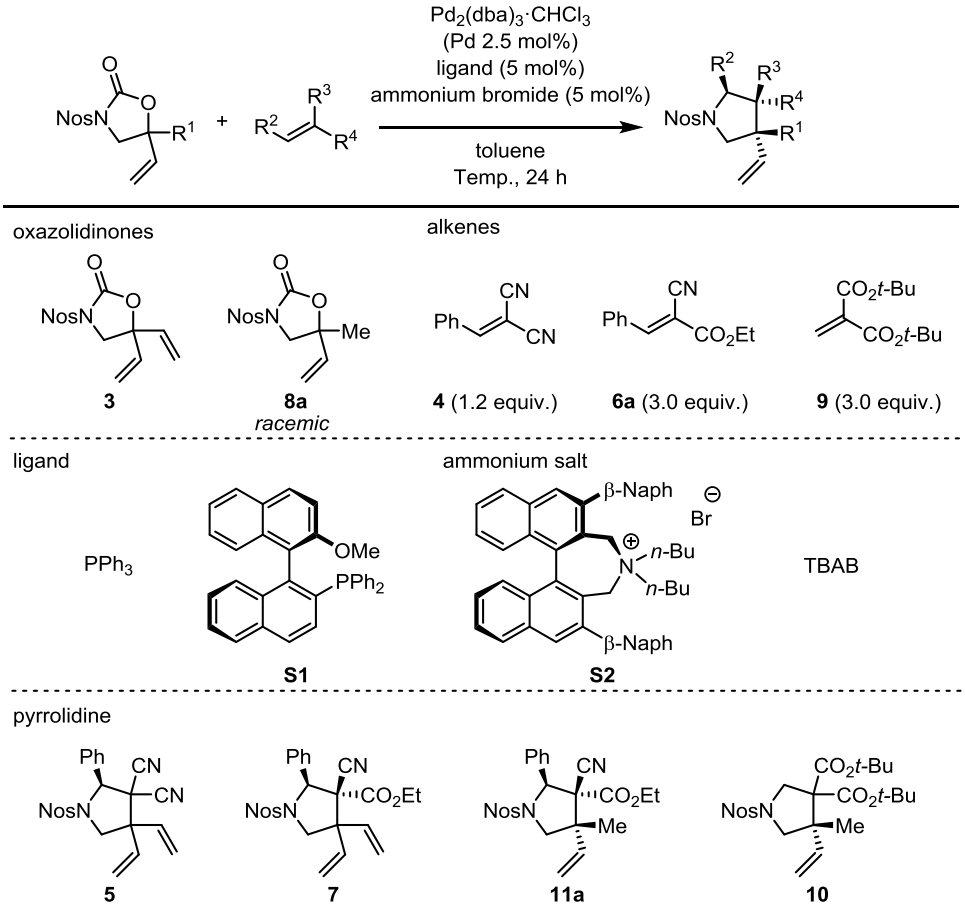


Figure S1.

(B) Control Expeariments

The author attempted a series of reactions of oxazolidinones with activated alkenes using PPh_3 as a ligand in the presence of chiral ammonium salt **S2** or using chiral monophosphine ligand **S1** in the presence of tetrabutylammonium bromide (TBAB). As summarized in Table S1, these reactions afforded the desired pyrrolidines in an almost racemic form or gave only a trace amount of the products, which clearly demonstrated that chiral onium-phosphine ligand **2d·I** played a pivotal role in achieving the present Pd-catalyzed asymmetric [3 + 2] cycloaddition with high efficiency and absolute stereocontrols.

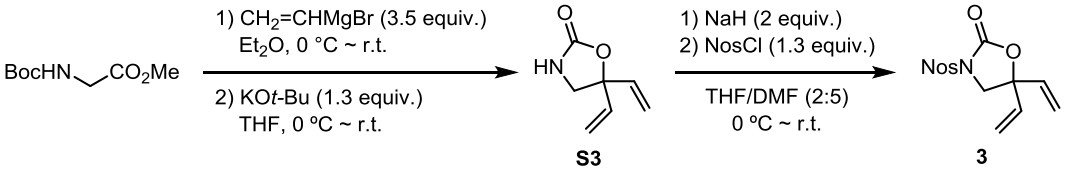
Table S1.



Entry	Oxazolidinone	Alkene	Ligand	Ammonium salt	Temp.	Pyrrolidine	Yield (%)	ee (%)
1	**3**	**4**	PPh_3	**S2**	r.t.	**5**	99	–3
2	**3**	**4**	**S1**	TBAB	r.t.	**5**	trace	–
3	**3**	**6a**	PPh_3	**S2**	r.t.	**7**	trace	–
4	**3**	**6a**	**S1**	TBAB	r.t.	**7**	trace	–
5	**3**	**6a**	PPh_3	**S2**	50 ºC	**7**	17	6
6	**3**	**6a**	**S1**	TBAB	50 ºC	**7**	trace	–
7	**8a**	**6a**	PPh_3	**S2**	r.t.	**11a**	trace	–
8	**8a**	**6a**	**S1**	TBAB	r.t.	**11a**	trace	–
9	**8a**	**9**	PPh_3	**S2**	r.t.	**10**	30	–2
10	**8a**	**9**	**S1**	TBAB	r.t.	**10**	99	–7

Representative Procedure for Synthesis of Oxazolidinones, and Their Characterization:

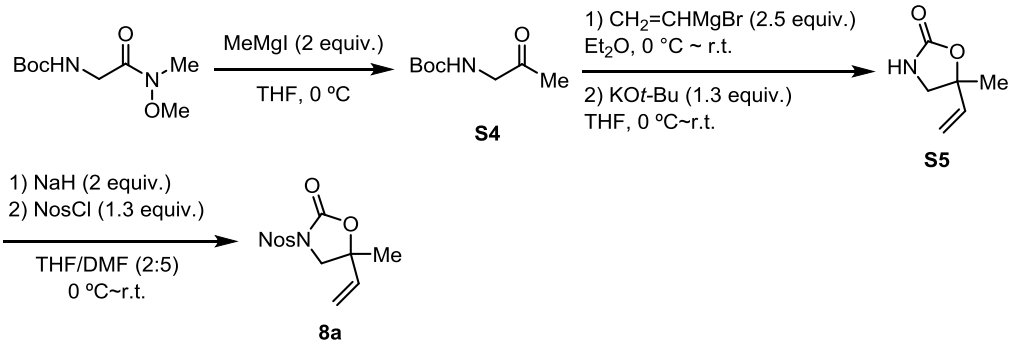
Oxazolidinones **3** was synthesized from *N*-Boc glycine methyl ester as described below.



To a solution of *N*-Boc glycine methyl ester (2.35 g, 12.4 mmol) in Et_2O (40 mL) was added vinylmagnesium bromide (1.0 M THF solution, 43.4 mL) at 0 ºC under Ar and this mixture was stirred at room temperature for 6 h. The reaction mixture was then poured into a saturated aqueous solution of NH_4Cl at 0 ºC and extracted with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. This concentrate was passed through a short silica gel pad with H/EtOAc = 4:1 as eluent to remove the polar compounds. The crude material including *N*-Boc amino alcohol was used for the next step without further purification. To a solution of this crude material (1.42 g) in THF (11 mL) was added KO*t*-Bu (895 mg, 7.97 mmol) in THF (11 mL) at 0 ºC under Ar and this mixture was stirred at room temperature. After the stirring was kept for 10 h, the reaction was quenched by the slow addition of a saturated aqueous solution of NH_4Cl at 0 ºC and extractive work-up was conducted with EtOAc three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica gel (H/EtOAc = 4:1 to 1:1 as eluent) to afford **S3** (470 mg, 3.38 mmol, 27% yield for 2 steps) as a brown oil. **S3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (2H, dd, J = 17.6, 10.7 Hz), 5.85 (1H, brs), 5.44 (2H, d, J = 17.6 Hz), 5.32 (2H, d, J = 10.7 Hz), 3.56 (2H, s).

To a solution of **S3** (470 mg, 3.38 mmol) in THF (9.70 mL) and DMF (24.1 mL) was slowly added NaH (60%, 270 g, 6.76 mmol) at 0 ºC under Ar and the resulting mixture was stirred for 15 min. Then, 4-nitrobenzenesulfonyl chloride (973 mg, 4.39 mmol) was introduced into the flask, and the whole reaction mixture was warmed up to room temperature. After stirring for 4 h, a saturated aqueous solution of NH_4Cl was slowly added to the mixture at 0 ºC and the aqueous phase was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/Acetone = 9:1 to 6:1 as eluent) gave the oxazolidinone **3** (857 mg, 2.64 mmol, 78% yield) as a white solid. **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (2H, d, J = 9.2 Hz), 8.26 (2H, d, J = 9.2 Hz), 5.89 (2H, dd, J = 17.2, 11.0 Hz), 5.42 (2H, d, J = 17.2 Hz), 5.39 (2H, d, J = 11.0 Hz), 4.01 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 150.7, 142.4, 134.7, 129.9, 124.6, 118.6, 82.3, 54.0; IR (film): 3107, 3071, 3030, 1778, 1531, 1348, 1175, 1155, 1090, 854, 735, 681, 611 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{12}N_2O_6SNa^+$ ($[M+Na]^+$) 347.0308. Found 347.0308.

Oxazolidinones **8** were synthesized from *N*-Boc glycine *N'*-methoxy-*N'*-methylamide through the following representative procedure.



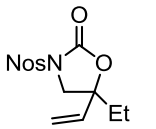
To a solution of *N*-Boc-glycine *N'*-methoxy-*N'*-methylamide (5.46 g, 25.0 mmol) in THF (83.0 mL) was added MeMgI (1.0 M Et_2O solution, 50.0 mL) at 0 ºC under Ar. After stirring for 10 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl at 0 ºC and extracted with EtOAc three times. The combined organics were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica gel (H/EtOAc = 10:1 to 4:1 as eluent) to afford **S4** (3.48 g, 20.1 mmol, 80% yield) as a colorless oil. **S4:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, brs), 4.04 (2H, brd, *J* = 4.6 Hz), 2.18 (3H, s), 1.45 (9H, s).

To a solution of **S4** (3.48 g, 20.1 mmol) in Et_2O (60.0 mL) was added vinylmagnesium bromide (1.0 M THF solution, 50.3 mL) at 0 ºC under Ar. The mixture was warmed up to room temperature and the stirring was maintained for 5 h. The reaction mixture was then poured into a saturated aqueous solution of NH_4Cl at 0 ºC and extractive work-up was conducted with EtOAc three times. The organic phases were washed with brine, dried over Na_2SO_4, and concentrated. This concentrate was passed through a short silica gel pad with H/EtOAc = 4:1 as eluent to remove the polar compounds. The crude material including the corresponding *N*-Boc amino alcohol was used for the next step without further purification. To a solution of this crude material (2.52 g) in THF (33.0 mL) was added KO*t*-Bu (1.83 g, 16.3 mmol) in THF (30.0 mL) at 0 ºC under Ar and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was then quenched by the slow addition of a saturated aqueous solution of NH_4Cl at 0 ºC, and the mixture was extracted with EtOAc three times, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica gel (H/EtOAc = 4:1 to 1:1 as eluent) to afford **S5** (959 mg, 7.55 mmol, 37% yield for 2 steps) as a brown oil. **S5:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (1H, dd, *J* = 17.4, 11.0 Hz), 5.87 (1H, brs), 5.39 (1H, d, *J* = 17.4 Hz), 5.22 (1H, d, *J* = 11.0 Hz), 3.49 (1H, d, *J* = 8.7 Hz), 3.40 (1H, d, *J* = 8.7 Hz), 1.56 (3H, s).

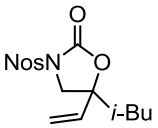
To a solution of **S5** (959 mg, 7.55 mmol) in THF (7.2 mL) and DMF (18.0 mL) was slowly added

NaH (60%, 603 mg, 15.1 mmol) at 0 ºC under Ar and the mixture was stirred for 15 min. Then, 4-nitrobenzenesulfonyl chloride (2.2 g, 9.8 mmol) was introduced into the flask, and the reaction mixture was warmed up to room temperature. After 5 h with stirring, a saturated aqueous solution of NH_4Cl was slowly added at 0 ºC and extractive work-up was performed with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/Acetone = 9:1 to 6:1 as eluent) gave the adduct **8a** (1.49 g, 4.77 mmol, 63% yield) as a white solid. **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (2H, d, J = 9.2 Hz), 8.26 (2H, d, J = 9.2 Hz), 5.87 (1H, dd, J = 17.4, 11.0 Hz), 5.37 (1H, d, J = 17.4 Hz), 5.29 (1H, d, J = 11.0 Hz), 3.95 (1H, d, J = 9.4 Hz), 3.85 (1H, d, J = 9.4 Hz), 1.57 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 150.9, 142.4, 136.9, 129.9, 124.6, 116.8, 81.0, 55.2, 24.9; IR (film): 3107, 3073, 3036, 1175, 1530, 1348, 1177, 1130, 1111, 1090, 854, 754, 735, 681 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{12}O_6N_2NaS^+$ ([M+Na]$^+$) 335.0308. Found 335.0307.

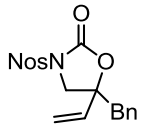
Characterization of Oxazolidinones:



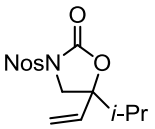
8b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (2H, d, J = 9.2 Hz), 8.26 (2H, d, J = 9.2 Hz), 5.78 (1H, dd, J = 17.4, 11.0 Hz), 5.34 (1H, d, J = 17.4 Hz), 5.31 (1H, d, J = 11.0 Hz), 3.94 (1H, d, J = 9.2 Hz), 3.86 (1H, d, J = 9.2 Hz), 1.75-1.89 (2H, m), 0.93 (3H, t, J = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 151.0, 142.5, 135.8, 129.9, 124.6, 117.1, 83.6, 53.7, 31.6, 7.5; IR (film): 3107, 3071, 3038, 1773, 1530, 1348, 1175, 1144, 1117, 1090, 854, 754, 735, 681, 610 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{14}N_2O_6SNa^+$ ([M+Na]$^+$) 349.0465. Found 349.0468.



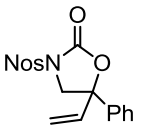
8c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (2H, d, J = 8.7 Hz), 8.25 (2H, d, J = 8.7 Hz), 5.79 (1H, dd, J = 17.3, 11.0 Hz), 5.35 (1H, d, J = 17.3 Hz), 5.29 (1H, d, J = 11.0 Hz), 3.95 (1H, d, J = 9.1 Hz), 3.78 (1H, d, J = 9.1 Hz), 1.76 (1H, dsept, J = 5.9, 6.4 Hz), 1.69 (2H, d, J = 5.9 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.91 (3H, d, J = 6.4 Hz); ^{13}C NMR (101 MHz, CDCl3) δ 151.2, 151.0, 142.5, 136.2, 129.9, 124.6, 116.6, 83.7, 55.2, 47.1, 24.4, 24.0, 23.4; IR (film): 3109, 1778, 1533, 1369, 1350, 1207, 1180, 1144, 1134, 1092, 856, 772, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{18}O_6N_2NaS^+$ ([M+Na]$^+$) 377.0778. Found 377.0777.



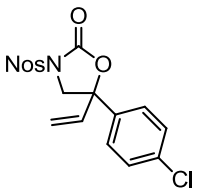
8d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (2H, d, J = 8.9 Hz), 7.93 (2H, d, J = 8.9 Hz), 7.18-7.21 (3H, m), 7.13-7.15 (2H, m), 5.94 (1H, dd, J = 17.4, 11.0 Hz), 5.43 (1H, d, J = 17.4 Hz), 5.34 (1H, d, J = 11.0 Hz), 3.92 (2H, s), 3.14 (1H, d, J = 14.6 Hz), 2.88 (1H, d, J = 14.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 150.7, 142.2, 136.9, 133.0, 130.6, 129.5, 128.8, 127.8, 124.4, 116.9, 82.0, 51.8, 44.3; IR (film): 3107, 3067, 3030, 1780, 1531, 1369, 1350, 1179, 1159, 1092, 856, 754, 735, 706, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{16}O_6N_2NaS^+$ ([M+Na]$^+$) 411.0621. Found 411.0620.



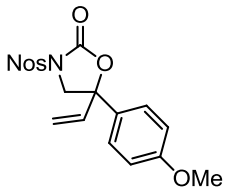
8e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (2H, d, J = 8.9 Hz), 8.25 (2H, d, J = 8.9 Hz), 5.79 (1H, dd, J = 17.4, 11.2 Hz), 5.35 (1H, d, J = 17.4 Hz), 5.34 (1H, d, J = 11.2 Hz), 3.95 (1H, d, J = 9.4 Hz), 3.88 (1H, d, J = 9.4 Hz), 1.98 (1H, sept, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 150.9, 142.6, 134.0, 129.8, 124.6, 117.8, 85.9, 52.7, 36.1, 16.6, 16.3; IR (film): 3109, 3073, 3032, 1775, 1531, 1373, 1350, 1217, 1177, 1134, 1090, 856, 756, 737, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{16}O_6N_2NaS^+$ ([M+Na]$^+$) 363.0621. Found 363.0620.



8f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (2H, d, J = 8.9 Hz), 8.20 (2H, d, J = 8.9 Hz), 7.35-7.42 (3H, m), 7.27-7.30 (2H, m), 6.08 (1H, dd, J = 17.2, 11.0 Hz), 5.37 (1H, d, J = 11.0 Hz), 5.35 (1H, d, J = 17.2 Hz), 4.39 (1H, d, J = 9.6 Hz), 4.22 (1H, d, J = 9.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 150.7, 142.3, 138.4, 136.6, 129.8, 129.2, 124.8, 124.6, 117.8, 83.8, 55.6, one peak for aromatic carbon was not found probably due to overlapping; IR (film): 3107, 3069, 3032, 1782, 1531, 1379, 1364, 1348, 1217, 1177, 1157, 1094, 754, 735, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{14}O_6N_2NaS^+$ ([M+Na]$^+$) 397.0465. Found 397.0461.



8g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (2H, d, J = 8.9 Hz), 8.22 (2H, d, J = 8.9 Hz), 7.38 (2H, d, J = 8.9 Hz), 7.24 (2H, d, J = 8.9 Hz), 6.05 (1H, dd, J = 17.4, 10.7 Hz), 5.39 (1H, d, J = 10.7 Hz), 5.35 (1H, d, J = 17.4 Hz), 4.37 (1H, d, J = 9.4 Hz), 4.17 (1H, d, J = 9.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 150.5, 142.2, 136.9, 136.3, 135.4, 129.9, 129.4, 126.4, 124.6, 118.2, 83.3, 55.4; IR (film): 3107, 3069, 3032, 1782, 1738, 1533, 1375, 1364, 1350, 1217, 1179, 1092, 754, 737, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{13}O_6N_2ClNaS^+$ ([M+Na]$^+$) 431.0075. Found 431.0072.

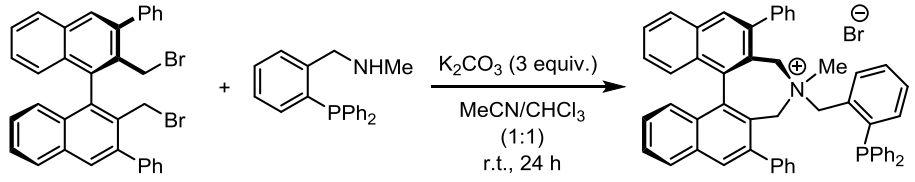


8h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (2H, d, J = 9.2 Hz), 8.20 (2H, d, J = 9.2 Hz), 7.21 (2H, d, J = 9.2 Hz), 6.89 (2H, d, J = 9.2 Hz), 6.06 (1H, dd, J = 17.4, 10.5 Hz), 5.36 (1H, d, J = 10.5 Hz), 5.32 (1H, d, J = 17.4 Hz), 4.33 (1H, d, J = 9.6 Hz), 4.22 (1H, d, J = 9.6 Hz), 3.81 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 151.2, 150.8, 142.4, 136.8, 130.1, 129.8, 126.5, 124.6, 117.7, 114.4, 83.9, 55.6, 55.5; IR (film): 3107, 1775, 1736, 1533, 1364, 1350, 1217, 1177, 772, 756, 737, 683 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{16}O_7N_2NaS^+$ ([M+Na]$^+$) 427.0570. Found 427.0571.

Representative Procedure for Synthesis of Chiral Onium-Phosphine Hybrid Ligands 2·X, and Their Characterization:

Chiral onium-phosphine hybrid ligand **2a·Br** was synthesized from (*R*)-3,3´-diphenyl-2,2´-bis-(bromomethyl)-1,1´-binaphthyl (**S6**)[36] and *N*-methyl 2-diphenylphosphinobenzylamine as described

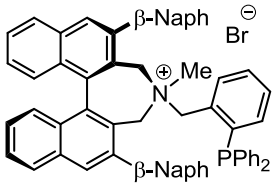
below.



S6 **2a·Br**

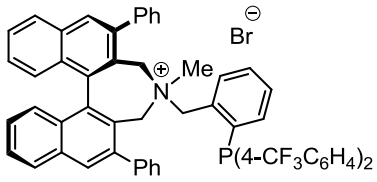
To a mixture of *N*-methyl 2-diphenylphosphinobenzylamine (264.8 mg, 0.60 mmol) and K_2CO_3 (248.8 mg, 1.8 mmol) in MeCN (3 mL) and $CHCl_3$ (3 mL) was added **S6** (355.4 mg, 0.6 mmol) at room temperature under Ar. After stirring for 24 h, water was introduced into the reaction flask and extractive work-up was conducted with $CHCl_3$ three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The resulting concentrate was purified by column chromatography on silica gel ($CHCl_3$ only to $CHCl_3$/MeOH = 20:1 as eluent) to afford **2a·Br** (337.1 mg, 0.35 mmol, 59% yield) as a white solid. **2a·Br:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s), 8.12 (1H, d, J = 8.2 Hz), 8.00 (1H, d, J = 8.7 Hz), 7.95 (1H, s), 7.70 (1H, t, J = 7.8 Hz), 7.65 (1H, t, J = 7.6 Hz), 7.23-7.52 (20H, m), 7.19 (1H, t, J = 7.6 Hz), 7.00-7.06 (3H, m), 6.74 (2H, t, J = 7.3 Hz), 6.62 (2H, t, J = 8.0 Hz), 5.45 (1H, d, J = 13.3 Hz), 5.14 (1H, dd, J = 13.3, 7.3 Hz), 4.31 (1H, brd, J = 10.0 Hz), 3.93 (1H, dd, J = 13.3, 5.5 Hz), 3.83 (1H, d, J = 13.3 Hz), 3.40 (1H, d, J = 13.3 Hz), 2.92 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.8, 138.9 (d, $J_{P\text{-}C}$ = 15.5 Hz), 138.4, 138.4, 138.1, 138.0, 136.7 (d, $J_{P\text{-}C}$ = 7.7 Hz), 136.3, 134.7, 134.7, 134.0 (d, $J_{P\text{-}C}$ = 24.2 Hz), 133.8 (d, $J_{P\text{-}C}$ = 22.3 Hz), 133.0 (d, $J_{P\text{-}C}$ = 8.7 Hz), 132.6, 132.5 (d, $J_{P\text{-}C}$ = 18.4 Hz), 132.3, 131.4, 130.9 (d, $J_{P\text{-}C}$ = 11.6 Hz), 130.5, 130.3, 130.1, 130.1, 129.7, 129.7, 129.0, 128.9, 128.8, 128.8, 128.7, 128.7, 128.3, 128.1, 128.1, 127.7, 127.6, 127.6, 127.2, 125.4, 123.7, 61.9 (d, $J_{P\text{-}C}$ = 19.4 Hz), 61.8, 57.1 (d, $J_{P\text{-}C}$ = 14.5 Hz), 48.0, two peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.1; IR (film): 3377, 3053, 3011, 2907, 1466, 1449, 1435, 897, 866, 741, 698, 658 cm^{-1}; HRMS (ESI) Calcd for $C_{54}H_{43}NP^+$ ([M-Br]$^+$) 736.3128. Found 736.3125. ; $[\alpha]_D^{23}$ = −25.2 (c = 1.0, $CHCl_3$).

Characterization Data for Chiral Onium-Phosphine Hybrid Ligands 2·X:

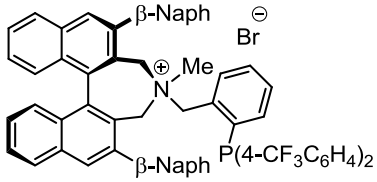


2b·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s), 8.16 (1H, d, J = 8.2 Hz), 8.07 (1H, s), 8.01-8.05 (3H, m), 7.90 (1H, dd, J = 6.4, 3.2 Hz), 7.77 (1H, dd, J = 6.0, 3.2 Hz), 7.72 (2H, t, J = 7.6 Hz), 7.67 (2H, t, J = 7.6 Hz), 7.61 (1H, d, J = 8.7 Hz), 7.44-7.78 (9H, m), 7.31-7.41 (5H, m), 7.21 (1H, t, J = 7.3 Hz), 7.03-7.07 (4H, m), 6.97 (1H, dd, J = 7.2, 3.4 Hz), 6.75-6.82 (3H, m), 6.64 (2H, t, J = 8.0 Hz), 5.60 (1H, d, J = 14.2 Hz), 5.24 (1H, d, J = 13.3, 7.5 Hz), 4.00 (1H, d, J = 14.2 Hz), 3.96 (1H, d, J = 13.3 Hz), 3.96 (1H, d, J = 12.4 Hz), 3.50 (1H, d, J = 12.4 Hz), 2.86 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 139.7, 138.9 (d, $J_{P\text{-}C}$ = 15.5 Hz), 138.3, 138.1, 136.8 (d, $J_{P\text{-}C}$ = 7.7 Hz), 136.3,

136.1, 135.8, 134.1 (d, $J_{P\text{-}C}$ = 22.3 Hz), 133.8 (d, $J_{P\text{-}C}$ = 21.3 Hz), 133.0 (d, $J_{P\text{-}C}$ = 8.1 Hz), 133.0, 132.9, 132.6 (d, $J_{P\text{-}C}$ = 19.4 Hz), 132.4, 132.3, 132.1, 132.0, 131.0 (d, $J_{P\text{-}C}$ = 13.5 Hz), 130.7, 130.5, 129.9, 129.7, 129.7, 129.5, 129.1, 129.0, 128.9, 128.9, 128.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 126.9, 126.9, 126.8, 125.6, 123.8, 62.4, 62.1, 57.2 (d, $J_{P\text{-}C}$ = 10.6 Hz), 48.4, eight peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.7; IR (film): 3377, 3053, 3011, 2176, 1464, 1435, 922, 907, 860, 824, 723, 698, 638 cm^{-1}; HRMS (ESI) Calcd for $C_{62}H_{47}NP^+$ ([M-Br]$^+$) 836.3441. Found 836.3434.; $[\alpha]_D^{23}$ = −43.0 (*c* = 1.0, $CHCl_3$).



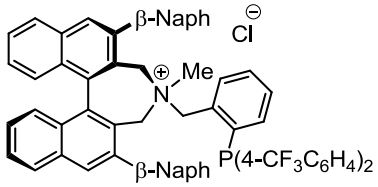
2c·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s), 8.13 (1H, d, *J* = 8.2 Hz), 8.02 (1H, d, *J* = 8.2 Hz), 7.99 (1H, s), 7.65-7.74 (3H, m), 7.58 (2H, d, *J* = 7.8 Hz), 7.42-7.53 (7H, m), 7.26-7.34 (11H, m), 6.92-6.95 (1H, m), 6.85 (2H, t, *J* = 7.8 Hz), 6.76 (2H, t, *J* = 7.8 Hz), 5.51 (1H, d, *J* = 13.8 Hz), 5.04 (1H, dd, *J* = 13.3, 7.3 Hz), 4.67 (1H, d, *J* = 13.3 Hz), 3.81 (1H, d, *J* = 13.8 Hz), 3.81 (1H, *J* = 12.4, 7.3 Hz), 3.46 (1H, d, *J* = 12.4 Hz), 3.00 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.7 (d, $J_{P\text{-}C}$ = 10.6 Hz), 139.6, 138.4, 138.2, 138.1, 137.9, 137.4 (d, $J_{P\text{-}C}$ = 10.6 Hz), 136.4 (d, $J_{P\text{-}C}$ = 13.5 Hz), 136.1, 135.1, 135.1, 134.0 (d, $J_{P\text{-}C}$ = 14.5 Hz), 133.9 (d, $J_{P\text{-}C}$ = 21.3 Hz), 133.0 (d, $J_{P\text{-}C}$ = 28.1 Hz), 132.7 (d, $J_{P\text{-}C}$ = 19.4 Hz), 131.8 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.4 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.4, 131.1, 131.1, 130.8, 130.8, 130.5, 130.0, 129.8, 129.6, 128.9, 128.8, 128.5, 128.3, 128.2, 127.8, 127.5, 127.5, 127.4, 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.2, 123.8 (q, $J_{F\text{-}C}$ = 276.9 Hz), 123.4 (q, $J_{F\text{-}C}$ = 275.8 Hz), 123.3, 61.8, 61.3 (d, $J_{P\text{-}C}$ = 23.2 Hz), 57.3 (d, $J_{P\text{-}C}$ = 19.9 Hz), 48.1, two peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −17.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8, −63.0; IR (film): 3377, 3057, 3026, 2181, 1321, 1167, 1125, 1107, 1059, 1015, 920, 907, 831, 723, 700, 638 cm^{-1}; HRMS (ESI) Calcd for $C_{56}H_{41}NF_6P^+$ ([M-Br]$^+$) 872.2875. Found 872.2866.; $[\alpha]_D^{23}$ = −34.8 (*c* = 1.0, $CHCl_3$).



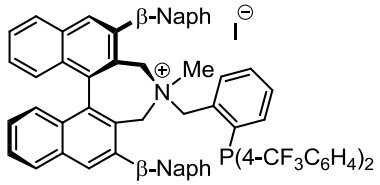
2d·Br: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s), 8.16 (1H, d, *J* = 8.2 Hz), 8.12 (1H, s), 8.07 (1H, d, *J* = 8.7 Hz), 8.01-8.05 (1H, m), 7.98 (1H, s), 7.89-7.92 (1H, m), 7.67-7.80 (5H, m), 7.56-7.59 (3H, m), 7.44-7.53 (9H, m), 7.27-7.33 (4H, m), 7.12-7.17 (2H, m), 6.90-6.91 (1H, m), 6.87 (3H, t, *J* = 7.8 Hz), 6.74 (2H, t, *J* = 8.0 Hz), 5.66 (1H, d, *J* = 13.9 Hz), 5.09 (1H, dd, *J* = 13.3, 7.3 Hz), 4.29 (1H, d, *J* = 13.3 Hz), 3.99 (1H, dd, *J* = 13.9 Hz), 3.82 (1H, brd), 3.62 (1H, d, *J* = 12.4 Hz), 2.91 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.8 (d, $J_{P\text{-}C}$ = 10.6 Hz), 139.6, 138.4, 137.9, 137.5 (d, $J_{P\text{-}C}$ = 10.6 Hz), 136.4 (d, $J_{P\text{-}C}$ 13.5 Hz), 136.1, 135.9, 135.7, 134.3, 134.2 (d, $J_{P\text{-}C}$ = 14.5 Hz), 133.8 (d, $J_{P\text{-}C}$

= 21.3 Hz), 133.5, 133.0, 133.0 (d, $J_{P\text{-}C}$= 29.0 Hz), 132.7 (d, $J_{P\text{-}C}$ = 19.4 Hz), 132.4, 132.0, 132.0, 131.8 (q, $J_{F\text{-}C}$ = 33.9 Hz), 131.4 (q, $J_{F\text{-}C}$ = 33.9 Hz), 131.0, 131.0, 130.9, 130.9, 129.9, 129.5, 129.1, 128.9, 128.8, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.6, 127.3, 127.1, 127.0, 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.5, 123.8 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.5 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.4, 62.3, 61.7 (d, $J_{P\text{-}C}$ = 26.1 Hz), 57.6 (d, $J_{P\text{-}C}$ = 10.8 Hz), 48.6, eight peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7, −62.9; IR (film): 3377, 3055, 3017, 1321, 1167, 1126, 1109, 1061, 1015, 831, 748, 729 cm^{-1}; HRMS (ESI) Calcd for $C_{64}H_{45}NF_6P^+$ ([M-X]$^+$) 972.3188. Found 972.3188.; $[\alpha]_D^{23}$ = −49.6 (*c* = 1.0, $CHCl_3$).

Ion-exchange of ammonium phosphine **2·X** was conducted by following the established procedure.[28]

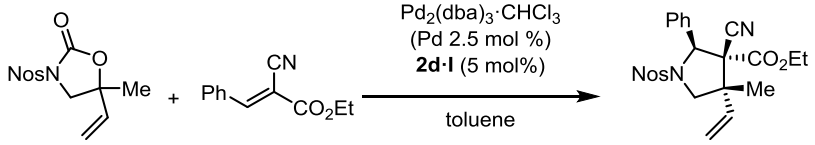


2d·Cl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s), 8.16 (1H, d, *J* = 8.2 Hz), 8.12 (1H, s), 8.07 (1H, d, *J* = 8.2 Hz), 8.02 (1H, d, *J* = 7.8 Hz), 7.97 (1H, s), 7.89-7.91 (1H, m), 7.78-7.80 (1H, m), 7.74 (2H, t, *J* = 8.0 Hz), 7.70 (2H, t, *J* = 8.2 Hz), 7.45-7.60 (12H, m), 7.32 (1H, d, *J* = 8.7 Hz), 7.22-7.30 (4H, m), 7.08-7.13 (1H, m), 6.90-6.91 (1H, m), 6.87 (3H, t, *J* = 7.8 Hz), 6.75 (2H, t, *J* = 8.0 Hz), 5.65 (1H, d, *J* = 13.9 Hz), 5.11 (1H, dd, *J* = 13.3, 7.3 Hz), 4.32 (1H, d, *J* = 13.3 Hz), 3.98 (1H, d, *J* = 13.9 Hz), 3.82 (1H, brd), 3.58 (1H, d, *J* = 12.8 Hz), 2.91 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 141.0 (d, $J_{P\text{-}C}$ = 14.5 Hz), 139.6, 138.4, 137.9, 137.6 (d, $J_{P\text{-}C}$ = 11.6 Hz), 136.3 (d, $J_{P\text{-}C}$ = 13.5 Hz), 136.0, 135.9, 135.7, 134.4, 134.4, 134.2 (d, $J_{P\text{-}C}$ = 14.5 Hz), 133.9 (d, $J_{P\text{-}C}$ = 21.3 Hz), 133.5, 133.2 (d, $J_{P\text{-}C}$ = 30.4 Hz), 133.0, 132.6 (d, $J_{P\text{-}C}$ = 19.4 Hz), 132.4, 132.0, 131.9, 131.8 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.4 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.0, 130.9, 130.8, 129.8, 129.6, 129.1, 128.9, 128.8, 128.6, 128.4, 128.1, 127.9, 127.8, 127.6, 127.6, 127.5, 127.5, 127.3, 127.1, 127.1, 127.0, 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.6, 123.9 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.5 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.5, 62.3, 61.4 (d, $J_{P\text{-}C}$ = 25.2 Hz), 57.3 (d, $J_{P\text{-}C}$ = 8.7 Hz), 48.6, six peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7, −62.9; IR (film): 3375, 3055, 3017, 1323, 1169, 1128, 1061, 1015, 831, 748, 731 cm^{-1}; HRMS (ESI) Calcd for $C_{64}H_{45}NF_6P^+$ ([M-Cl]$^+$) 972.3188. Found 972.3180.; $[\alpha]_D^{23}$ = −61.2 (*c* = 1.0, $CHCl_3$).



2d·I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, *s*), 8.16 (1H, d, *J* = 8.2 Hz), 8.14 (1H, s), 8.06-8.08 (2H, m), 8.02 (1H, s), 7.91-7.93 (2H, m), 7.68-7.80 (5H, m), 7.62 (1H, d, *J* = 8.7 Hz), 7.57 (2H, d, *J* = 7.8 Hz), 7.45-7.54 (9H, m), 7.34 (1H, d, *J* = 8.7 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.09-7.13 (1H, m), 6.80-6.89 (5H, m), 6.71 (2H, t, *J* = 7.8 Hz), 5.58 (1H, d, *J* = 13.8 Hz), 5.05 (1H, dd, *J* = 13.0, 6.9 Hz), 4.13 (1H, d, *J* = 13.0 Hz), 4.03 (1H, d, *J* = 13.8 Hz), 3.84 (1H, brd), 3.77 (1H, d, *J* = 12.4 Hz), 2.83 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 140.5 (d, $J_{P\text{-}C}$ = 10.6 Hz), 139.5, 138.4, 137.9, 137.3 (d, $J_{P\text{-}C}$ = 10.6 Hz), 136.6 (d, $J_{P\text{-}C}$ = 13.5 Hz), 136.2, 135.9, 135.7, 134.2 (d, $J_{P\text{-}C}$ = 9.7 Hz), 133.8, 133.7 (d, $J_{P\text{-}C}$ = 21.3 Hz), 133.5, 132.9, 132.8 (d, $J_{P\text{-}C}$ = 23.2 Hz), 132.7 (d, $J_{P\text{-}C}$ = 19.4 Hz), 132.4, 131.9, 131.4 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.2, 131.0 (q, $J_{F\text{-}C}$ = 32.9 Hz), 131.0, 130.9, 130.2, 129.5, 129.1, 128.9, 128.8, 128.7, 128.7, 128.5, 128.5, 128.1, 128.1, 127.9, 127.8, 127.8, 127.6, 127.6, 127.5, 127.3, 127.2, 127.0, 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.9 Hz), 125.1, 123.8 (q, $J_{F\text{-}C}$ = 276.7 Hz), 123.5 (q, $J_{F\text{-}C}$ = 275.8 Hz), 123.2, 62.3, 61.8 (d, $J_{P\text{-}C}$ = 25.2 Hz), 58.2, 48.8, six peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8, −62.9; IR (film): 3055, 3019, 2187, 1321, 1167, 1126, 1107, 1059, 1015, 907, 826, 723, 700 cm^{-1}; HRMS (ESI) Calcd for $C_{64}H_{45}NF_6P^+$ ([M-I]$^+$) 972.3188. Found 972.3188.; $[\alpha]_D^{23}$ = −33.7 (*c* = 1.0, $CHCl_3$).

Representative Procedure for Palladium-Catalyzed Asymmetric Cycloaddition of 5-Vinyloxazolidinones with Activated Alkenes:

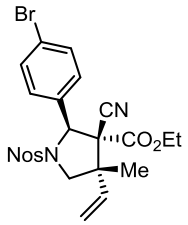


8a *racemic* **6a** (3 equiv.) **11a**

To a Schlenk flask was added $Pd_2(dba)_3{\cdot}CHCl_3$ (1.29 mg, 1.25 μmol), **2d·I** (5.50 mg, 5 μmol), and ethyl 2-cyano 3-phenylacrylate **6a** (60.4 mg, 0.3 mmol) and the flask was degassed by alternating vacuum evacuation/Ar backfill. Then, toluene (1 mL) was introduced, and the resulting catalyst mixture was evacuated and refilled with Ar three times. The mixture was cooled to 0 °C and 5-vinyloxazolidinone **8a** (31.2 mg, 0.1 mmol) was successively added into the reaction flask. After stirring for 10 h, the reaction mixture was filtered through a pad of short silica gel and washed with acetone. The resulting filtrates were concentrated and purified by column chromatography on silica gel (H/Et_2O = 9:1 to 3:1 as eluent) to afford **11a** (46.1 mg, 0.0981 mmol, 98% yield) as a white solid. **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8.9 Hz), 7.59 (2H, d, *J* = 8.9 Hz), 7.22-7.26 (1H, m), 7.11-7.19 (4H, m), 5.86 (1H, dd, *J* = 17.4, 11.0 Hz), 5.68 (1H, s), 5.45 (1H, d, *J* = 17.4 Hz), 5.37 (1H, d, *J* = 11.0 Hz), 4.33 (1H, d, *J* = 11.5 Hz), 4.28 (1H, dq, *J* = 11.0, 7.3 Hz), 4.15 (1H, dq, *J* =

11.0, 7.3 Hz), 3.76 (1H, d, *J* = 11.5 Hz), 1.57 (3H, s), 1.28 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ163.4, 149.9, 145.4, 135.2, 134.1, 129.3, 128.8, 128.5, 128.2, 123.9, 118.4, 115.1, 66.9, 65.0, 63.8, 58.3, 50.6, 19.4, 14.2; IR (film) 3105, 3069, 3036, 2984, 2936, 1744, 1531, 1350, 1240, 1165, 1090, 1042, 741, 698, 563 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{23}N_3O_6SNa^+$ ([M+Na]$^+$) 492.1200. Found 492.1200.; HPLC OZ3, H/IPA = 4:1, flow rate = 1.0 mL/min, λ = 254 nm, 29.3 min (major), 38.9 min (minor).

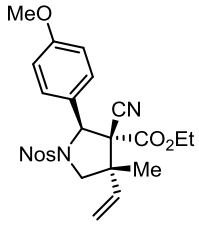
Characterization Data for the Pyrrolidines:



11b

The reaction was stirred for 10 h at 0 °C.

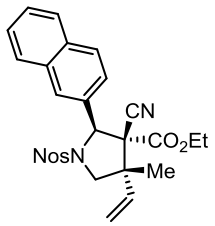
11b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (2H, d, *J* = 8.9 Hz), 7.67 (2H, d, *J* = 8.9 Hz), 7.31 (2H, d, *J* = 8.2 Hz), 7.11 (2H, d, *J* = 8.2 Hz), 5.75 (1H, dd, *J* = 17.4, 11.0 Hz), 5.61 (1H, s), 5.42 (1H, d, *J* = 17.4 Hz), 5.34 (1H, d, *J* = 11.0 Hz), 4.27 (1H, dq, *J* = 11.0, 7.3 Hz), 4.24 (1H, d, *J* = 11.4 Hz), 4.16 (1H, dq, *J* = 11.0, 7.3 Hz), 3.74 (1H, d, *J* = 11.4 Hz), 1.56 (3H, s), 1.28 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 150.1, 145.0, 134.9, 133.5, 131.5, 130.3, 128.5, 124.2, 123.7, 118.6, 114.9, 66.5, 64.7, 64.0, 58.3, 50.6, 19.5, 14.2; IR (film): 3103, 3071, 2986, 2970, 2920, 1744, 1531, 1350, 1240, 1167, 1042, 1011, 754, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{22}N_3O_6BrSNa^+$ ([M+Na]$^+$) 570.0305. Found 570.0306.; HPLC AD3, H/IPA/EtOH = 18:1:1, flow rate = 1.0 mL/min, λ = 210 nm, 22.5 min (minor), 26.5 min (major).



11c

The reaction was stirred for 10 h at 0 °C.

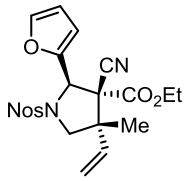
11c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 9.1 Hz), 7.60 (2H, d, *J* = 9.1 Hz), 7.09 (2H, d, *J* = 8.7 Hz), 6.63 (2H, d, *J* = 8.7 Hz), 5.83 (1H, dd, *J* = 17.4, 10.8 Hz), 5.61 (1H, s), 5.44 (1H, d, *J* = 17.4 Hz), 5.36 (1H, d, *J* = 10.8 Hz), 4.30 (1H, d, *J* = 11.0 Hz), 4.27 (1H, dq, *J* = 11.0, 7.3 Hz), 4.15 (1H, dq, *J* = 11.0, 7.3 Hz), 3.75 (1H, d, *J* = 11.0 Hz), 3.73 (3H, s), 1.56 (3H, s), 1.27 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 160.3, 149.9, 145.5, 135.3, 130.2, 128.5, 125.7, 123.9, 118.3, 115.3, 113.5, 66.5, 65.0, 63.7, 58.1, 55.4, 50.4, 19.5, 14.2; IR (film): 3103, 3071, 2984, 2970, 2938, 1744, 1530, 1514, 1348, 1242, 1163, 1032, 752, 737 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{25}N_3O_7SNa^+$ ([M+Na]$^+$) 522.1305. Found 522.1305.; HPLC IA, H/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 24.8 min (minor), 33.0 min (major).



11d

The reaction was stirred for 10 h at 0 °C.

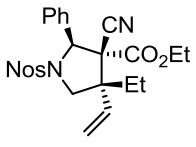
11d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.7 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.59 (2H, d, J = 7.8 Hz), 7.51 (2H, d, J = 8.7 Hz), 7.41-7.55 (3H, m), 7.25-7.28 (1H, m), 5.91 (1H, dd, J = 17.4, 11.0 Hz), 5.83 (1H, s), 5.49 (1H, d, J = 17.4 Hz), 5.41 (1H, d, J = 11.0 Hz), 4.38 (1H, d, J = 11.4 Hz), 4.29 (1H, dq, J = 11.0, 7.3 Hz), 4.16 (1H, dq, J = 11.0, 7.3 Hz), 3.84 (1H, d, J = 11.4 Hz), 1.60 (3H, s), 1.27 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 149.7, 145.4, 135.3, 133.4, 132.5, 131.2, 128.8, 128.4, 128.0, 127.9, 127.8, 127.1, 126.6, 125.8, 123.8, 118.5, 115.2, 67.0, 64.9, 63.8, 58.2, 50.6, 19.4, 14.2; IR (film): 3107, 3061, 3017, 2988, 2926, 1742, 1530, 1348, 1238, 1163, 1040, 854, 741 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{25}N_3O_6SNa^+$ ([M+Na]$^+$) 542.1356. Found 542.1356.; HPLC AD3, H/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 20.0 min (minor), 33.8 min (major).



11e

The reaction was stirred for 10 h at 0 °C.

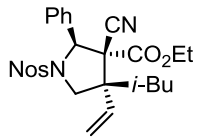
11e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (2H, d, J = 8.9 Hz), 7.72 (1H, d, J = 8.9 Hz), 7.14 (1H, d, J = 1.8 Hz), 6.41 (1H, d, J = 3.2 Hz), 6.28 (1H, dd, J = 3.2, 1.8 Hz), 5.81 (1H, dd, J = 17.6, 11.0 Hz), 5.63 (1H, s), 5.40 (1H, d, J = 17.6 Hz), 5.35 (1H, d, J = 11.0 Hz), 4.26 (1H, dq, J = 11.0, 7.3 Hz), 4.18 (1H, dq, J = 11.0, 7.3 Hz), 4.11 (1H, d, J = 11.0 Hz), 3.70 (1H, d, J = 11.0 Hz), 1.61 (3H, s), 1.29 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.0, 147.1, 144.8, 143.6, 135.4, 128.4, 124.1, 118.3, 114.6, 112.1, 110.9, 63.9, 62.3, 61.1, 57.3, 50.5, 20.4, 14.1; IR (film): 3103, 3022, 2986, 2970, 2928, 1744, 1531, 1350, 1238, 1215, 1167, 743, 613 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{21}N_3O_7SNa^+$ ([M+Na]$^+$) 482.0992. Found 482.0991.; HPLC IA, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 42.9 min (major), 49.1 min (minor).



11f

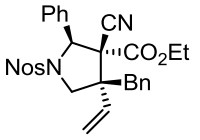
The reaction was stirred for 10 h at 0 °C.

11f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.9 Hz), 7.53 (2H, d, J = 8.9 Hz), 7.23 (1H, t, J = 7.3 Hz), 7.14 (2H, d, J = 7.3 Hz), 7.08 (2H, t, J = 7.3 Hz), 5.53 (1H, s), 5.49-5.63 (3H, m), 4.55 (1H, d, J = 11.4 Hz), 4.28 (1H, dq, J = 11.0, 7.3 Hz), 4.18 (1H, dq, J = 11.0, 7.3 Hz), 3.70 (1H, d, J = 11.4 Hz), 2.11 (1H, dq, J = 15.1, 7.3 Hz), 1.98 (1H, dq, J = 15.1, 7.3 Hz), 1.29 (3H, t, J = 7.3 Hz), 0.91 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 149.8, 145.9, 133.3, 133.2, 129.3, 128.4, 128.1, 123.9, 120.3, 115.3, 67.0, 65.2, 63.7, 54.6, 54.4, 27.2, 14.1, 9.4, one peak for aromatic carbon was not found probably due to overlapping; IR (film): 3105, 3067, 3034, 2938, 1744, 1530, 1348, 1231, 1163, 999, 741, 617, 610, 565 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{25}N_3O_6SNa^+$ ([M+Na]$^+$) 506.1356. Found 506.1359.; HPLC AD3, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, 23.7 min (minor), 25.2 min (major).



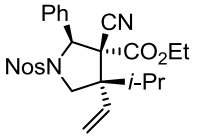
The reaction was stirred for 10 h at 0 °C.

11g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 7.22 (1H, t, J = 7.3 Hz), 7.12 (2H, d, J = 7.3 Hz), 7.06 (2H, t, J = 7.3 Hz), 5.46 (1H, s), 5.51-5.70 (3H, m), 4.72 (1H, d, J = 11.9 Hz), 4.30 (1H, dq, J = 11.0, 7.3 Hz), 4.19 (1H, dq, J = 11.0, 7.3 Hz), 3.76 (1H, d, J = 11.9 Hz), 2.03 (1H, dd, J = 14.4, 4.4 Hz), 1.84 (1H, dd, J = 14.4, 6.4 Hz), 1.63-1.70 (1H, m), 1.29 (3H, t, J = 7.3 Hz), 0.96 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 149.8, 146.1, 134.0, 133.0, 129.4, 129.3, 128.3, 128.1, 123.8, 119.7, 115.4, 66.1, 65.7, 63.7, 54.9, 54.1, 43.3, 25.2, 25.1, 23.5, 14.2; IR (film): 3105, 3067, 3034, 2959, 2938, 1744, 1531, 1350, 1231, 1163, 1094, 745, 619, 559 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{29}N_3O_6SNa^+$ ($[M+Na]^+$) 534.1669. Found 534.1670.; HPLC AD3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 9.5 min (minor), 12.7 min (major).



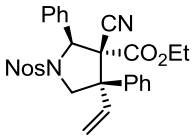
The reaction was stirred for 24 h at 0 °C.

11h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 8.9 Hz), 7.50 (2H, d, J = 8.9 Hz), 7.09-7.32 (10H, m), 5.65 (1H, dd, J = 17.4, 11.4 Hz), 5.50 (1H, d, J = 11.4 Hz), 5.47 (1H, s), 5.35 (1H, d, J = 17.4 Hz), 4.33 (1H, dq, J = 10.5, 7.3 Hz), 4.23 (1H, dq, J = 10.5, 7.3 Hz), 4.18 (1H, d, J = 11.4 Hz), 3.90 (1H, d, J = 11.4 Hz), 3.37 (1H, d, J = 14.2 Hz), 3.20 (1H, d, J = 14.2 Hz), 1.55 (3H, s), 1.33 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 149.8, 145.6, 135.2, 133.2, 133.0, 130.3, 129.4, 128.5, 128.4, 128.1, 127.5, 123.8, 120.8, 115.4, 67.1, 64.8, 63.9, 54.5, 54.0, 41.0, 14.2, one peak for aromatic carbon was not found probably due to overlapping; IR (film): 3105, 3065, 3032, 2986, 2938, 1744, 1531, 1350, 1234, 1217, 1165, 1005, 741, 704 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{27}N_3O_6SNa^+$ ($[M+Na]^+$) 568.1513. Found 568.1514.; HPLC AD3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 19.6 min (major), 23.9 min (minor).



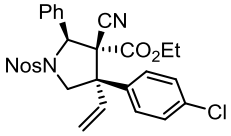
The reaction was stirred for 96 h at room temperature.

11i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 9.2 Hz), 7.52 (2H, d, J = 9.2 Hz), 7.24 (1H, t, J = 7.3 Hz), 7.01-7.09 (4H, m), 5.93 (1H, ddd, J = 17.4, 11.4, 0.9 Hz), 5.69 (1H, d, J = 17.4 Hz), 5.66 (1H, d, J = 11.4 Hz), 5.37 (1H, s), 4.74 (1H, d, J = 11.9 Hz), 4.11-4.20 (2H, m), 3.67 (1H, dd, J = 11.9 Hz), 2.43 (1H, sept, J = 6.8 Hz), 1.17 (3H, t, J = 7.3 Hz), 0.95 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 149.8, 146.2, 132.2, 129.8, 129.6, 128.8, 128.4, 128.2, 123.8, 120.3, 115.6, 69.9, 65.3, 63.7, 57.6, 55.5, 34.1, 19.0, 17.6, 13.8; IR (film): 3105, 3069, 3036, 2970, 2938, 1740, 1531, 1350, 1234, 1165, 1109, 1094, 1003, 743 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{27}N_3O_6SNa^+$ ($[M+Na]^+$) 520.1513. Found 520.1515.; HPLC IA, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 13.7 min (major), 18.4 min (minor).



The reaction was stirred for 40 h at room temperature.

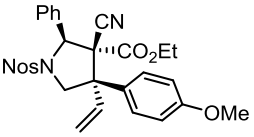
11j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (2H, d, J = 8.9 Hz), 7.63 (2H, d, J = 8.9 Hz), 7.33-7.41 (3H, m), 7.25-7.29 (3H, m), 7.11-7.15 (4H, m), 6.35 (1H, dd, J = 17.2, 11.0 Hz), 5.75 (1H, s), 5.39 (1H, d, J = 11.0 Hz), 5.15 (1H, d, J = 17.2 Hz), 4.88 (1H, d, J = 11.4 Hz), 4.47 (1H, d, J = 11.4 Hz), 4.33 (1H, dq, J = 11.0, 7.3 Hz), 4.25 (1H, dq, J = 11.0, 7.3 Hz), 1.24 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.0, 145.7, 137.4, 136.1, 132.9, 129.7, 128.9, 128.6, 128.5, 128.4, 127.5, 124.0, 119.2, 115.3, 69.4, 65.6, 64.1, 59.0, 57.0, 14.0, one peak for aromatic carbon was not found probably due to overlapping; IR (film): 3105, 3065, 3038, 2986, 2926, 1740, 1531, 1350, 1236, 1167, 1009, 739, 698, 608 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{25}N_3O_6SNa^+$ ([M+Na]$^+$) 554.1356. Found 554.1357.; HPLC AD3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 210 nm, 37.8 min (major), 55.2 min (minor).



11k

The reaction was stirred for 40 h at room temperature.

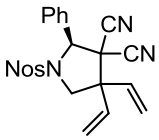
11k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, d, J = 9.2 Hz), 7.61 (2H, d, J = 9.2 Hz), 7.37 (2H, d, J = 8.7 Hz), 7.23-7.27 (3H, m), 7.09-7.15 (4H, m), 6.32 (1H, dd, J = 17.2, 11.0 Hz), 5.76 (1H, s), 5.42 (1H, d, J = 11.0 Hz), 5.14 (1H, d, J = 17.2 Hz), 4.84 (1H, d, J = 11.4 Hz), 4.42 (1H, d, J = 11.4 Hz), 4.33 (1H, dq, J = 10.5, 7.3 Hz), 4.26 (1H, dq, J = 10.5, 7.3 Hz), 1.24 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 150.0, 145.5, 135.8, 135.7, 134.7, 132.7, 129.7, 129.1, 129.0, 128.6, 128.5, 128.4, 124.0, 119.7, 115.1, 69.2, 65.5, 64.2, 58.6, 57.0, 14.0; IR (film): 3105, 3069, 3038, 2984, 2924, 1740, 1531, 1350, 1234, 1167, 1098, 1011, 731, 608 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{24}N_3O_6ClSNa^+$ ([M+Na]$^+$) 588.0967. Found 588.0967.; HPLC IA, H/EtOH = 19:1, flow rate = 1.0 mL/min, λ = 254 nm, 31.4 min (minor), 55.4 min (major).



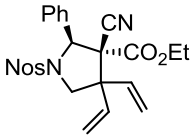
11l

The reaction was stirred for 40 h at room temperature.

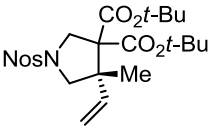
11l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (2H, d, J = 8.9 Hz), 7.63 (2H, d, J = 8.9 Hz), 7.24-7.27 (1H, m), 7.20 (2H, d, J = 8.9 Hz), 7.09-7.15 (4H, m), 6.90 (2H, d, J = 8.9 Hz), 6.32 (1H, dd, J = 16.9, 11.0 Hz), 5.74 (1H, s), 5.37 (1H, d, J = 11.0 Hz), 5.15 (1H, d, J = 16.9 Hz), 4.80 (1H, d, J = 11.4 Hz), 4.46 (1H, d, J = 11.4 Hz), 4.32 (1H, dq, J = 11.0, 7.3 Hz), 4.24 (1H, dq, J = 11.0, 7.3 Hz), 3.82 (3H, s), 1.24 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 159.4, 150.0, 145.6, 136.2, 133.0, 129.6, 129.1, 128.8, 128.6, 128.5, 128.4, 124.0, 119.1, 115.3, 114.1, 69.3, 65.9, 64.0, 58.5, 57.2, 55.4, 14.0; IR (film): 3105, 3067, 3038, 2984, 2936, 1740, 1531, 1518, 1350, 1256, 1236, 1167, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{27}N_3O_7SNa^+$ ([M+Na]$^+$) 584.1462. Found 584.1462.; HPLC ADH, H/EtOH = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 45.0 min (minor), 65.3 min (major).



5: $[\alpha]_D^{23} = -41.8$ (c = 1.0, $CHCl_3$) for 92% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (2H, d, J = 9.2 Hz), 7.57 (2H, d, J = 9.2 Hz), 7.36 (1H, t, J = 7.3 Hz), 7.20 (2H, t, J = 7.8 Hz), 7.13 (2H, d, J = 7.3 Hz), 6.14 (1H, ddd, J = 17.4, 11.0, 0.9 Hz), 6.08 (1H, dd, J = 17.4, 11.0 Hz), 5.83 (1H, d, J = 17.4 Hz), 5.79 (1H, d, J = 11.0 Hz), 5.60 (1H, d, J = 11.0 Hz), 5.46 (1H, d, J = 17.4 Hz), 5.20 (1H, s), 4.67 (1H, d, J = 11.9 Hz), 3.93 (1H, dd, J = 11.9, 0.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ150.2, 145.2, 132.4, 131.4, 130.8, 130.6, 128.8, 128.6, 128.5, 124.1, 122.5, 122.3, 111.4, 110.9, 69.3, 56.2, 53.9, 53.4; IR (film) 3105, 3069, 3036, 2922, 1531, 1350, 1312, 1167, 1107, 991, 856, 756, 743, 613, 565 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{18}N_4O_4SNa^+$ ($[M+Na]^+$) 457.0941 Found 457.0942.; HPLC ODH, H/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 254 nm, 28.0 min (minor), 30.6 min (major).

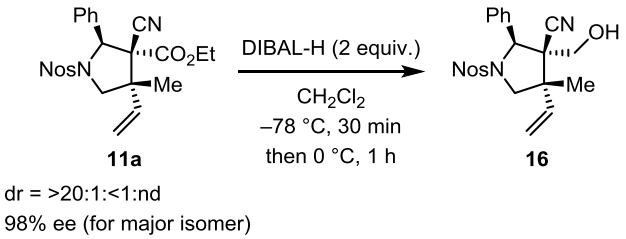


7: ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 8.7 Hz), 7.58 (2H, d, J = 8.7 Hz), 7.24 (1H, t, J = 7.3 Hz), 7.16 (2H, d, J = 7.3 Hz), 7.12 (2H, d, J = 7.3 Hz), 6.29 (1H, dd, J = 17.8, 11.0 Hz), 5.80 (1H, dd, J = 17.4, 11.0 Hz), 5.66 (1H, s), 5.57 (1H, d, J = 17.4 Hz), 5.50 (1H, d, J = 11.0 Hz), 5.49 (1H, d, J = 11.0 Hz), 5.27 (1H, d, J = 17.8 Hz), 4.47 (1H, d, J = 11.5 Hz), 4.30 (1H, dq, J = 11.0, 7.1 Hz), 4.17 (1H, dq, J = 11.0, 7.1 Hz), 4.03 (1H, d, J = 11.5 Hz), 1.27 (3H, t, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ163.1, 149.9, 145.5, 134.4, 133.5, 132.8, 129.3, 128.9, 128.4, 128.2, 123.9, 120.4, 120.1, 115.0, 66.6, 64.5, 63.9, 56.2, 55.2, 14.1; IR (film) 3105, 3067, 3036, 2986, 2926, 1746, 1531, 1350, 1312, 1238, 1167, 1096, 1001, 743, 613, 565 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{23}N_3O_6SNa^+$ ($[M+Na]^+$) 504.1200. Found 504.1200.; HPLC IA, H/IPA = 10:1, flow rate = 0.5 mL/min, λ = 254 nm, 32.1 min (minor), 34.6 min (major).



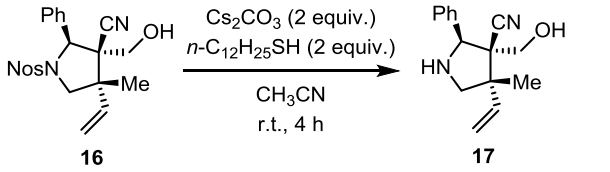
10: $[\alpha]_D^{23} = -10.0$ (c = 1.0, $CHCl_3$) for 94% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (2H, d, J = 8.9 Hz), 8.03 (2H, d, J = 8.9 Hz), 6.01 (1H, dd, J = 17.8, 11.0 Hz), 5.12 (1H, d, J = 11.0 Hz), 5.09 (1H, d, J = 17.8 Hz), 3.78 (1H, d, J = 11.9 Hz), 3.74 (1H, d, J = 11.9 Hz), 3.64 (1H, d, J = 8.9 Hz), 3.45 (1H, d, J = 8.9 Hz), 1.38 (9H, s), 1.34 (9H, s), 1.23 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ167.4, 167.3, 150.2, 143.5, 139.1, 128.7, 124.3, 115.3, 83.1, 82.9, 65.2, 57.8, 52.6, 48.8, 27.9, 27.9, 20.8; IR (film) 3107, 2978, 2934, 1724, 1368, 1350, 1290, 1250, 1159, 1092, 1063, 737, 619 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{32}N_2O_8SNa^+$ ($[M+Na]^+$) 519.1772. Found 519.1774.; HPLC IC, H/IPA = 19:1, flow rate = 1.0 mL/min, λ = 254 nm, 63.8 min (major), 69.1 min (minor).

Derivatization of Cycloaddition Product 11a:



dr = >20:1:<1:nd
98% ee (for major isomer)

To a solution of **11a** (46.5 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was dropwised diisobutylaluminium hydride (1.0 M toluene solution, 0.2 mL) at –78 °C under Ar, and the stirring was kept for 30 min. Then, the reaction mixture was warmed up to 0 °C. After stirring for 1 h at the same temperature, 1N HCl was carefully added to the reaction mixture and extractive work-up was performed with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/Acetone = 8:1 to 4:1 as eluent) gave the corresponding alcohol **16** (26.1 mg, 0.0611 mmol, 62% yield) as a white solid. **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 8.9 Hz), 7.55 (2H, d, J = 8.9 Hz), 7.25 (1H, t, J = 7.8 Hz), 7.14 (2H, t, J = 7.8 Hz), 7.08 (2H, d, J = 7.8 Hz), 6.02 (1H, dd, J = 17.4, 11.2 Hz), 5.54 (1H, d, J = 17.4 Hz), 5.47 (1H, d, J = 11.2 Hz), 4.88 (1H, s), 4.22 (1H, d, J = 11.0 Hz), 3.85 (1H, d, J = 11.4 Hz), 3.67 (1H, d, J = 11.0 Hz), 3.66 (1H, d, J = 11.4 Hz), 1.82 (1H, brs), 1.53 (3H, s).

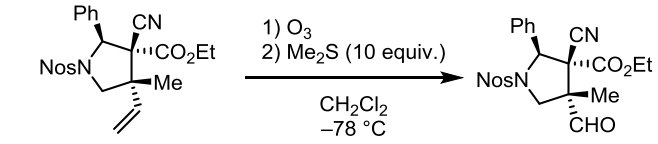


dr = >20:1:<1:nd
98% ee (for major isomer)

To a mixture of **16** (26.1 mg, 0.0611 mmol) and Cs_2CO_3 (39.8 mg, 0.122 mmol) in CH_3CN (1 mL) was slowly added n-$C_{12}H_{25}SH$ (29.2 μL, 0.122 mmol) at room temperature and the whole mixture was stirred for 4 h. After the completion of the reaction was confirmed by TLC analysis, the reaction mixture was directly subjected to the purification by column chromatography on silica gel (H/EtOAc = 8:1 to 2:1 as eluent) to afford pyrrolidine **17** in 64% yield (9.4 mg, 0.0388 mmol) as a white solid.

17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 7.3 Hz), 7.31-7.39 (3H, m), 6.08 (1H, dd, J = 17.4, 11.4 Hz), 5.32 (1H, d, J = 17.4 Hz), 5.32 (1H, d, J = 11.4 Hz), 4.33 (1H, s), 3.81 (1H, d, J = 11.7 Hz), 3.70 (1H, d, J = 11.7 Hz), 3.24 (2H, s), 2.01 (1H, brs), 1.51 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 138.9, 128.7, 128.6, 127.9, 119.6, 116.2, 67.2, 63.7, 59.4, 56.5, 50.5, 23.4; IR (film): 3019, 2930, 1215, 1088, 1078, 754, 700, 667 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{19}N_2O^+$

([M+H]$^+$) 243.1492. Found 243.1491.; HPLC OZ3, H/IPA = 10:1, flow rate = 1.0 mL/min, λ = 254 nm, 11.3 min (major), 15.3 min (minor).

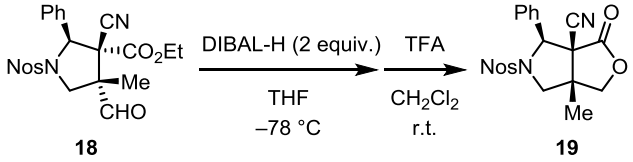


11a **18**

dr = >20:1:<1:nd

98% ee (for major isomer)

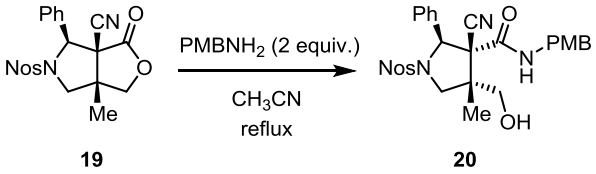
To a solution of **11a** (468 mg, 0.996 mmol) in CH_2Cl_2 (1 mL) was bubbled ozone at –78 °C for 10 min. Then, the mixture was purged by Ar gas to exclude ozone, and dimethyl sulfide (734 μL, 9.99 mmol) was added to the reaction solution at the same temperature. After warming up to room temperature, the stirring was maintained for 2 h. The reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica gel (H/EtOAc = 7:1 to 3:1 as eluent) to afford **18** in 97% yield (455 mg, 0.965 mmol) as a white solid. **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (1H, s), 8.18 (2H, d, J = 8.7 Hz), 7.64 (2H, d, J = 8.7 Hz), 7.20-7.33 (5H, m), 5.54 (1H, s), 4.50 (1H, d, J = 12.4 Hz), 4.30 (1H, dq, J = 11.0, 7.3 Hz), 4.25 (1H, dq, J = 11.0, 7.3 Hz), 3.70 (1H, d, J = 12.4 Hz), 1.63 (3H, s), 1.28 (3H, t, J = 7.3 Hz).



18 **19**

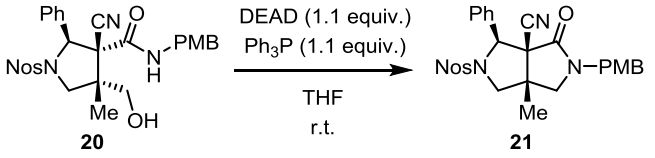
To a solution of **18** (455 mg, 0.965 mmol) in THF (10 mL) was dropwised diisobutylaluminium hydride (1.0 M toluene solution, 1.93 mL) at –78 °C under Ar, and the whole mixture was kept for 2 h with stirring. The reaction was then quenched by the slow addition of 1 N HCl, and the mixture was extracted with EtOAc three times. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. The crude material including the corresponding alcohol was used for the next step without further purification. To a solution of this crude material in CH_2Cl_2 (10.0 mL) was added trifluoroacetic acid (10.0 ml) at room temperature. After stirring for 7 h, a saturated aqueous solution of $NaHCO_3$ was carefully added to the reaction mixture at 0 °C and extractive work-up was performed with $CHCl_3$ three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/EtOAc = 6:1 to 2:1 as eluent) gave the corresponding lactone **19** in 95% yield for 2 steps (392 mg, 0.917 mmol) as a white solid. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (2H, d, J = 8.7 Hz), 7.78 (2H, d, J = 8.7 Hz), 7.33-7.38 (3H, m), 7.24-7.26 (2H, m), 5.44 (1H, s), 4.34 (1H, d, J = 10.1 Hz), 4.19 (1H, d, J = 10.1 Hz), 3.88 (1H, d, J = 11.0 Hz), 3.77 (1H, d, J = 11.0 Hz), 1.52 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 150.5,

142.8, 134.7, 129.9, 129.1, 128.8, 127.4, 124.5, 111.5, 75.0, 69.1, 59.7, 58.0, 51.3, 20.2; IR (film): 3107, 2251, 1784, 1531, 1350, 1169, 737, 613 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{17}N_3O_6NaS^+$ ($[M+Na]^+$) 450.0736. Found 450.0730.



19 **20**

To a solution of **19** (392 mg, 0.917 mmol) in CH_3CN (10 mL) was added 4-methoxybenzylamine (237 μL, 1.83 mmol) at room temperature. After 6 h of stirring, the reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica gel (H/EtOAc = 6:1 to 3:1 as eluent) to afford **20** in 91% yield (471 mg, 0.835 mmol) as a white solid. **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, J = 8.7 Hz), 7.77 (2H, d, J = 8.7 Hz), 7.32 (1H, t, J = 7.1 Hz), 7.19-7.26 (4H, m), 7.07 (2H, d, J = 8.7 Hz), 6.83 (2H, d, J = 8.7 Hz), 6.52 (1H, brt), 5.80 (1H, s), 4.41 (1H, dd, J = 14.6, 6.0 Hz), 4.29 (1H, dd, J = 14.6, 5.5 Hz), 4.12 (1H, d, J = 11.9 Hz), 3.79 (3H, s), 3.58 (2H, d, J = 11.9 Hz), 3.53 (1H, dd, J = 12.4, 6.0 Hz), 3.44 (1H, dd, J = 12.4, 6.4 Hz), 2.33 (1H, brt), 1.34 (3H, s).



20 **21**

dr = >20:1:<1:nd

98% ee (for major isomer)

To a mixture of **20** (56.5 mg, 0.100 mmol) and triphenylphosphine (28.9 mg, 0.110 mmol) in THF (1 mL) was slowly added diethyl azodicarboxylate (40% toluene solution, 50.0 μL, 0.110 mmol) at room temperature, and the whole mixture was stirred for 10 h. The reaction mixture was diluted with water and extractive work-up was performed with EtOAc three times. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/EtOAc = 5:1 to 3:1 as eluent) afforded lactam **21** in 88% yield (47.9 mg, 0.0876 mmol) as a white solid. **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (2H, d, J = 8.9 Hz), 7.79 (2H, d, J = 8.9 Hz), 7.27-7.34 (5H, m), 6.99 (2H, d, J = 8.9 Hz), 6.86 (2H, d, J = 8.9 Hz), 5.44 (1H, s), 4.37 (1H, d, J = 14.6 Hz), 4.23 (1H, d, J = 14.6 Hz), 3.82 (3H, s), 3.73 (1H, d, J = 10.5 Hz), 3.35 (1H, d, J = 10.5 Hz), 3.15 (1H, d, J = 11.0 Hz), 3.11 (1H, d, J = 11.0 Hz), 1.40 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 159.8, 150.3, 143.0, 135.9, 129.7, 129.3, 129.0, 128.9, 127.5, 126.2, 124.3, 114.6, 113.5, 68.3, 61.7, 59.2, 55.5, 54.5, 47.2, 47.1, 21.7; IR (film): 2936, 2253, 1709, 1530, 1514, 1348, 1248, 1169, 737, 613 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{26}N_4O_6NaS^+$ ($[M+Na]^+$) 569.1471. Found 569.1465.; HPLC AD3, H/EtOH = 7:3, flow rate = 1.0 mL/min, λ = 254

nm, 43.2 min (minor), 51.4 min (major).

Crystallographic Structure Determination:

Recrystallization of 11a (CCDC 954515) and 11j (CCDC 954516): A single crystal of **11a and 11j** were obtained from CH_2Cl_2/acetone/CH_3CN solvent system at room temperature. The single crystals thus obtained were mounted on CryoLoop. Data of X-ray diffraction were collected at 133 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.[47] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to oxygen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions. The crystallographic data were summarized in Tables S2-S3 and ORTEP diagrams were shown in Figure S2. A checkcif file for compound **11a** contains a 'B' level alert, which would be generated due to contamination of the anisotropic displacement parameters with disorder of the C(36–37) ethyl substitutents.

Table S2. Crystal data and structure refinement for **11a**.

Empirical formula	C23 H23 N3 O6 S	
Formula weight	469.50	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.0525(17) Å	α= 90°.
	b = 27.518(4) Å	β= 94.477(3)°.
	c = 11.4121(17) Å	γ = 90°.
Volume	3460.3(9) $Å^3$	
Z	6	
Density (calculated)	1.352 Mg/m^3	
Absorption coefficient	0.185 mm^{-1}	
F(000)	1476	
Crystal size	0.60 x 0.50 x 0.30 mm^3	
Theta range for data collection	1.94 to 28.37°.	
Index ranges	-11<=h<=14, -35<=k<=36, -14<=l<=15	
Reflections collected	25674	

Independent reflections	16703 [R(int) = 0.0227]
Completeness to theta = 28.37°	99.5 %
Absorption correction	Empirical
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	16703 / 1 / 898
Goodness-of-fit on F^2	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0993
R indices (all data)	R1 = 0.0390, wR2 = 0.1009
Absolute structure parameter	0.00(3)
Largest diff. peak and hole	0.693 and -0.473 e.$Å^{-3}$

Table S3. Crystal data and structure refinement for **11j**.

Empirical formula	C28 H25 N3 O6 S	
Formula weight	531.57	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.704(2) Å	α= 90°.
	b = 12.588(3) Å	β= 90°.
	c = 26.614(7) Å	γ = 90°.
Volume	2580.9(12) $Å^3$	
Z	4	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.174 mm^{-1}	
F(000)	1112	
Crystal size	0.50 x 0.50 x 0.30 mm^3	
Theta range for data collection	1.53 to 28.42°.	
Index ranges	-9<=h<=10, -11<=k<=16, -32<=l<=35	
Reflections collected	18546	
Independent reflections	6437 [R(int) = 0.0396]	
Completeness to theta = 28.42°	99.4 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9496 and 0.9180	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6437 / 0 / 344	

Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR2 = 0.1223
R indices (all data)	R1 = 0.0463, wR2 = 0.1235
Absolute structure parameter	-0.03(6)
Largest diff. peak and hole	0.805 and -0.320 e.$Å^{-3}$

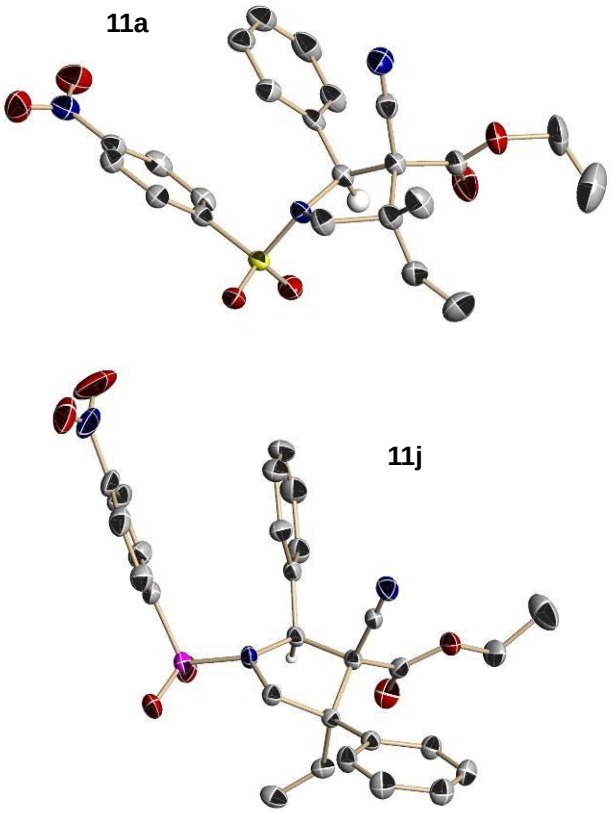


Figure S2. Molecular structure of **11a** and **11j**. All calculated hydrogen atoms are omitted for clarity. Yellow and pink = sulfur, blue = nitrogen, red = oxygen, black = carbon.

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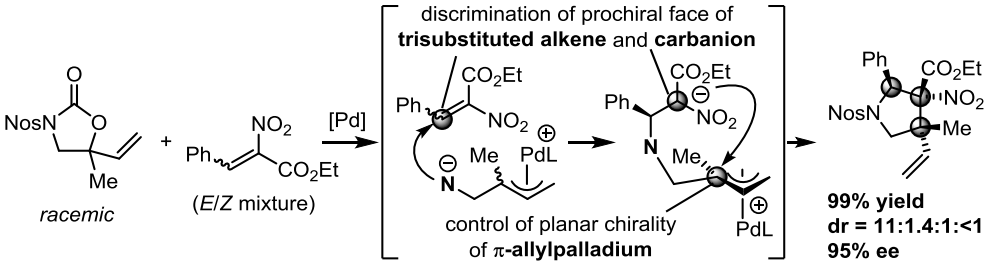
Chapter 3

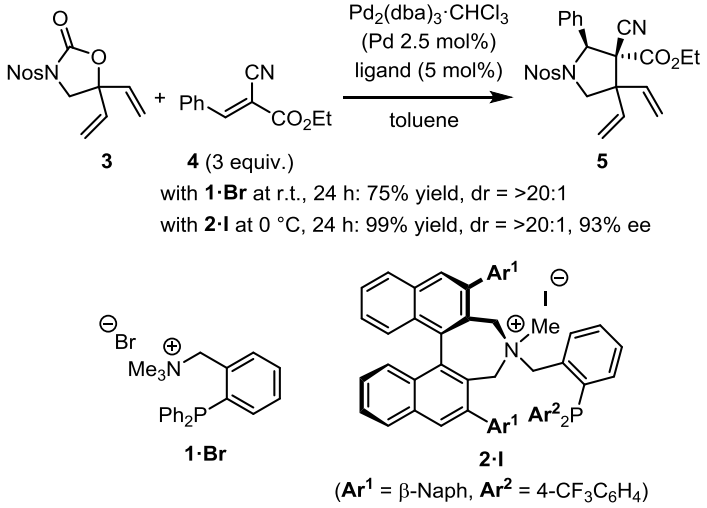
Multiple Absolute Stereocontrol in Pd-Catalyzed [3 + 2] Cycloaddition of Oxazolidinones with Trisubstituted Alkenes Using Chiral Ammonium-Phosphine Hybrid Ligands



Abstract: The development of a Pd-catalyzed highly enantio- and diastereoselective [3 + 2] cycloaddition of 5-vinyloxazolidinones and activated trisubstituted alkenes, enabling the single-step construction of densely functionalized pyrrolidines with three contiguous stereocenters, including vicinal quaternary stereocenters, is described in detail. This protocol relies heavily on the remarkable ability of the newly devised phosphine ligand having chiral ammonium ion moiety to facilitate the intermolecular cycloaddition with precise control of the absolute stereochemistries. A series of control experiments showed that the chiral ammonium-phosphine hybrid ligand enabled the individual yet simultaneous stereocontrol of each chiral center, termed multiple absolute stereocontrol, in the course of asymmetric cycloaddition reaction. The reaction mechanism, especially the stereo-determining events of each stereocenter, is also discussed.

1. Introduction

During the couese of the study of palladium-catalyzed [3 + 2] cycloadditions of 5-vinyloxazolidinones with trisubstituted alkenes in Chapter 2, the author found that the stereoselective construction of all-carbon quaternary stereocenters utilizing 5,5-divinyloxazolidinone **3** and (*E*)-ethyl- 2-cyano-3-phenyl acrylate **4** under the influence of achiral ligand **1·Br** afforded the diastereomerically pure pyrrolidine **5** (Scheme 1). This fact indicated that relative stereochemistry of C-2 and C-3 stereocenters of **5** was come from the geometry of starting alkene **4** in this case. Indeed, similar complete diastereoselectivity was observed in the reaction using **2·I** as a chiral ligand, resulting in the quantitative production of pyrrolidine **5** with high enantioselectivity (Scheme 1). However, all trisubstitued alkenes are not always obtained as geometrically pure form. Therefore, the author next thought to conduct the annulation reaction of 5-vinyloxazolidinones with geometrical mixture of trisubstituted alkenes.



Scheme 1. Asymmetric construction of all-carbon quaternary stereocenter in the C-3 chiral carbon

2. Result and Discussion

The author initially confirmed whether the chiral ammonium-phosphine ligand **2·I** could achieve the individual stereocontrol in the consturuction of C-3 chiral carbon of the pyrrolidine (Figure 1).

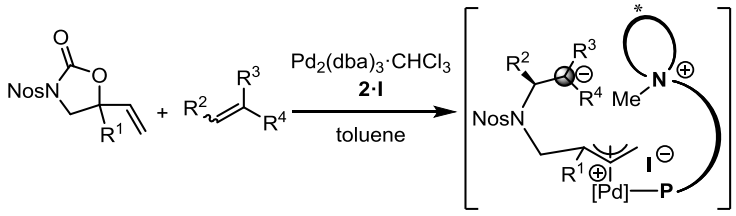
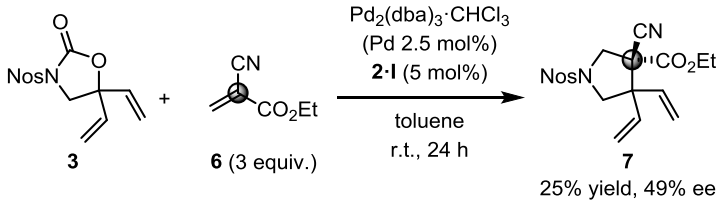


Figure 1. Individual stereocontrol in the consturcution of C-3 chiral carbon

In order to verify this hypothesis, the author performed the reaction of oxazolidinone **3** with ethyl

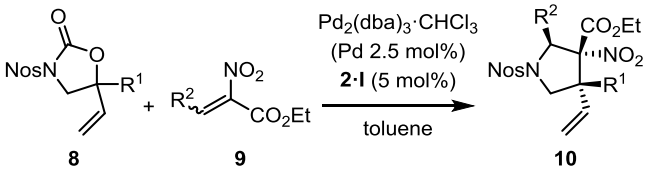
2-cyanoacrylate **6**. Although the reaction gave a complex mixture due to the strong tendency of **6** toward polymerization, the corresponding pyrrolidine **7** was isolated in 25% yield with moderate enantioselecitivity (Scheme 2). The observed asymmetric induction could be accounted for by assuming the doubly ion-pairng intermediate, where conformation of the C-3 carbanion would be controlled by the ligand, particularly the chiral ammonium ion component.



Scheme 2. Examination of the construction of C-3 chiral carbon

On the basis of this prospect, the present catalytic system was applied for the reactions of oxazolidinones **8** wiith 2-nitro-3-arylacrylates **9** (Table 1). It is difficult to prepare these 2-nitroacrylates in geometrically pure form because of their facile *E*/*Z* isomerization. As a control experiment, the author initially conducted the reaction of **8a** with ethyl 2-nitro-3-phenylacrylate (**9a**; *E*/*Z* = 1:2) using achiral ammonium-phosphine **1·Br** at room temperature, resulting in the production of corresponding cycloadduct **10a** in low yield as a complex mixture of the four diastereomers (entry 1). This result highlighted the difficulty to control the asymmetric reactions of these two types of substrates. The potential of chiral ammonium-phosphine **2·I** toward this challenging cycloaddition was validated through the exposure of **8a** and **9a** to the optimized conditions, resulting in the quantitative production of **10a** with high diatereo- (11:1.4:1:<1) and excellent enantioselectivity (95% ee) (entry 2). Further experiments to examine the scope of this [3 + 2] cycloaddition protocol were conducted. With respect to 2-nitroacrylates **9**, a range of 3-aryl substituents, including fused arene and heteroarene, were feasible, and the corresponding pyrrolidines were obtained nearly quantitatively with good diastereo- and high enantioselectivity (entry 3-6). Similar high reaction efficiency and high-to-excellent stereoselectivities were observed in the reactions of oxazolidinones bearing various 5-alkyl substituents (entry 7-11). The reactions of 5-aryl oxazolidinones also proceeded to afford the corresponding products in high yield with excellent diastereoselectivities, albeit certain decrease in the enantioselectivities were detected (entry 12-14).

Table 1. Asymmetric [3 + 2] cycloaddition of oxazolidinone **8** with 2-nitro-3-arylacrylates **9**[a]



8 *racemic* **9** **10**

Entry	R^1	8	R^2	9	Conditions	10	Yield (%)[b]	dr[c]	ee (%)[d]
1[e]	Me	**8a**	Ph	**9a**	r.t., 24 h	**10a**	27	5:8:3:1	–
2	Me	**8a**	Ph	**9a**	0 °C, 8 h	**10a**	99	11:1.4:1<1	95
3	Me	**8a**	4-Me-C_6H_4	**9b**	0 °C, 10 h	**10b**	99	12:1.1:1<1	92
4	Me	**8a**	4-CF_3-C_6H_4	**9c**	0 °C, 10 h	**10c**	99	5.9:1.1:1:<1	89
5	Me	**8a**	2-naphthyl	**9d**	0 °C, 10 h	**10d**	99	11:1.2:1:<1	96
6	Me	**8a**	2-furyl	**9e**	r.t., 24 h	**10e**	97	11:1.1:1:<1	94
7	Et	**8b**	Ph	**9a**	0 °C, 24 h	**10f**	99	15:2.8:1:<1	96
8	*n*-Bu	**8c**	Ph	**9a**	0 °C, 24 h	**10g**	80	17:3.8:1:<1	92
9	*i*-Bu	**8d**	Ph	**9a**	r.t., 24 h	**10h**	83	11:1:<1:<1	97
10	$PhCH_2CH_2$	**8e**	Ph	**9a**	r.t., 36 h	**10i**	99	14:1.3:1:<1	95
11	*i*-Pr	**8f**	Ph	**9a**	r.t., 48 h	**10j**	78	>20:2.6:1:<1	96
12	Ph	**8g**	Ph	**9a**	r.t., 48 h	**10k**	92	16:1:<1:<1	71
13	4-Cl-C_6H_4	**8h**	Ph	**9a**	r.t., 36 h	**10l**	81	19:1:<1:<1	83
14	4-MeO-C_6H_4	**8i**	Ph	**9a**	r.t., 36 h	**10m**	79	17:1:<1:<1	77

[a]Unless otherwise noted, reactions were carried out with 0.10 mmol of **8** and 0.3 mmol of **9** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%) and **2·I** (5 mol%) in 1.0 mL of toluene. [b]Isolated yield. [c]Determined based on ^1H NMR analysis of crude reaction mixture. [d]Enantiomeric excesses of the major diastereomer were indicated, which were analyzed by chiral stationary phase HPLC. The absolute configuration of **10a** was confirmed by X-ray diffraction analysis, and the stereochemistries of other examples were assumed by analogy. [e]The reaction was performed with **1·Br** (5 mol%) instead of **2·I**.

The author then turned his attention to the reaction mechanism of the present cycloaddition of oxazolidinones with trisubstituted alkenes, especially stereo-determining events of each stereocenter. The C-2 and C-3 stereocenters of reaction products would be determined through the enantiofacial discriminations of trisubstituted alkene in aza-Micahel addition and of the subsequently generated carbanion in ring-closing step, respectively (Figure 2).

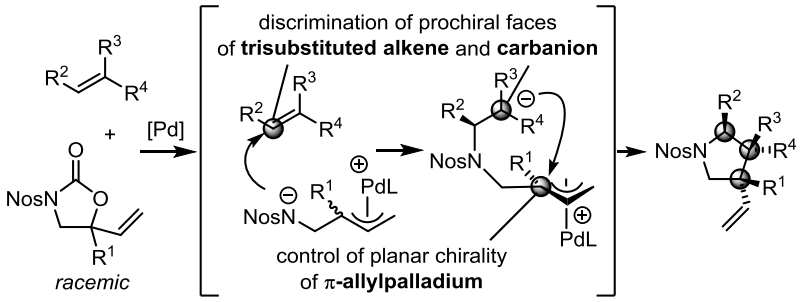


Figure 2. Stereoselective construction of three contiguous stereocenters

In terms of the C-4 stereocenter, which was derived from the C-5 chiral carbon of the racemic oxazolidinone, there were two possible scenarios for the conversion into enantiomerically enriched form (Figure 3): (i) this stereocenter was determined through the isomerization of planar chiral π-allylpalladium via π-σ-π interconversion; (ii) racemic oxazolidinone directly transformed into single stereocenter of π-allylpalladium through direct enantio-convergent mechanism, where one enantiomer of oxazolidinone undergoes an *anti*-S_N2'-type pathway and the other reacts via *syn*-S_N2' pathway.[1]

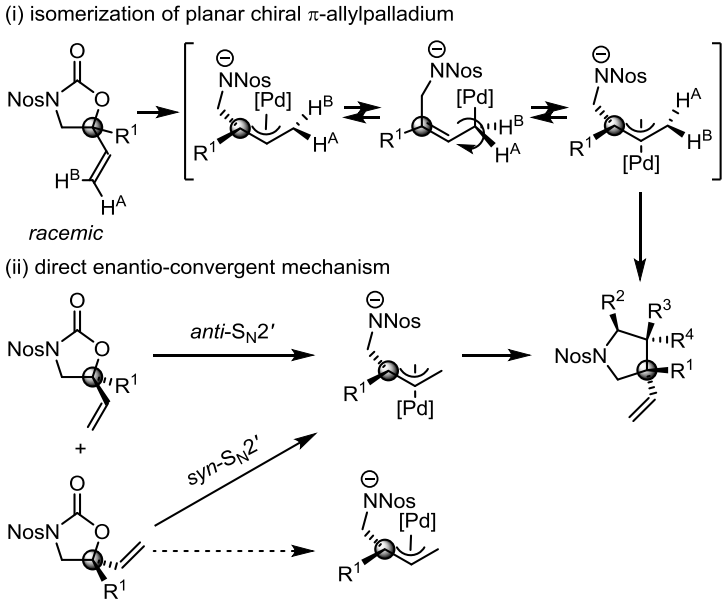
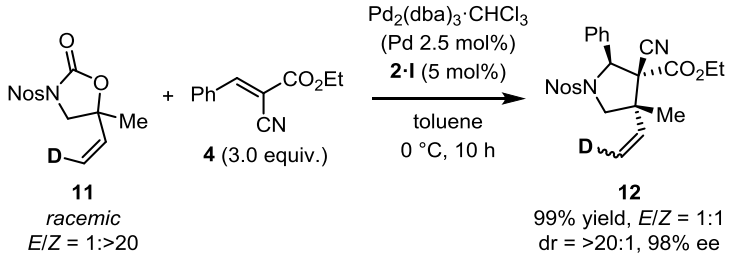


Figure 3. Two possible scenarios for the determination of C-4 stereocenter

To gain the insight into the course of the determination of C-4 stereochemistry, the author performed the asymmetric cycloaddition reaction using racemic oxazolidinone **11** having geometrically pure deuterated vinyl substituent. Treatment of **11** and 2-cyano-3-phenyl acrylate **4** under the influence of **2·I** resulted in smooth conversion to furnish 1:1 ratio of geometrical isomers of chiral pyrrolidine **12** (Scheme 3). This result clearly indicated that absolute stereochemistry of

C-4 carbon converted through the isomerization of planar chiral π-allylpalladium.



11
racemic
E/*Z* = 1:>20

12
99% yield, *E*/*Z* = 1:1
dr = >20:1, 98% ee

Scheme 3. Asymmetric cycloaddition using deuterated oxalozodinone **11**

3. Conclusion

In conclusion, the author have successfully developed a highly enantio- and diastereoselective [3 + 2] annulation reaction between 5-vinyloxazolidinones with geometrical mixture of trisubstituted alkenes based on the use of a palladium complex bearing a chiral ammonium-phosphine hybrid ligand. This study not only provides the efficient synthetic protocols but also offers unprecendented opportunities for the molecular design of chiral phosphine ligands as well as for the development of related applications.

4. Experimental Section

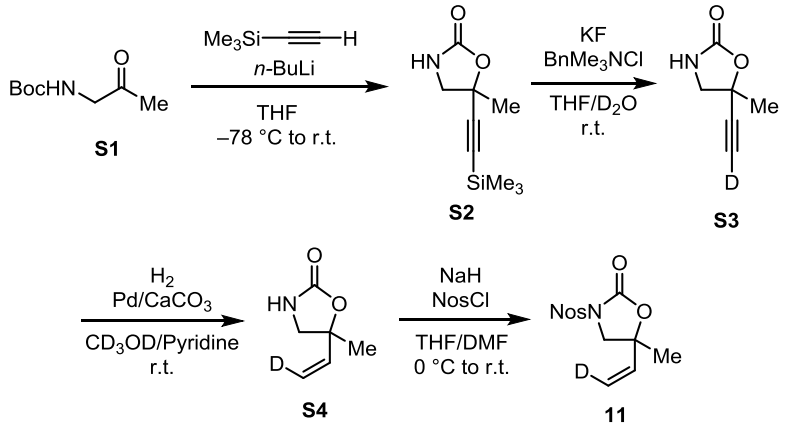
General Information: Infrared spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) or JNM-ECA 600II (600 MHz) spectrometer. Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard ($CDCl_3$). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz) or 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). ^{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.), silica gel 60 N (spherical, neutral, 40-50 μm; Kanto Chemical Co., Inc.), Silica gel 60 (Merck 1.09385.9929, 230-400 mesh), PSQ60AB (spherical, 40-50 μm; Fuji

Silysia Chemical ltd.) and Chromatorex® NH DM2035 (spherical, 45-75 μm; Fuji Silysia Chemical ltd.). Preparative gel permination chromatography (GPC) was performed with a JAI LC-9260 II NEXT instrument equipped with JAIGEL-1HH/JAIGEL-2HH columns or JAI LC-908 instrument equipped with JAIGEL-1HH/JAIGEL-2HH columns using chloroform as an eluent. Enantiomeric excesses were determined by HPLC analysis using chiral columns (φ 4.6 mm x 250 mm, DAICEL CHIRALCEL OZ-3 (OZ3), CHIRALCEL OX-3 (OX3), CHIRALPAK AD-3 (AD3), CHIRALPAK IA (IA), and CHIRALPAK IA-3 (IA3) with hexane (H), 2-propanol (IPA), and ethanol (EtOH) 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. $Pd_2(dba)_3{\cdot}CHCl_3$ was purchased from Sigma-Aldrich Co. and purified by following the procedure in the literature.[2] Ammonium phosphines **2·X**,[3] Oxazolidinones,[3] and Alkenes[4] were synthesized by following the procedures described in the literature. Deuterated oxazolidinone **11** was synthesized as described below. Other simple chemicals were purchased and used as such.

Representative Procedure for Synthesis of Deuterated Oxazolidinone 11, and Their Characterization:

Deuterated oxazolidinone **11** was synthesized from *N*-Boc glycine methyl ketone **S1**[2] as described below.



To a solution of trimethylsilylacetylene (3.67 mL, 26 mmol) in THF (75.0 mL) was dropwised a 2.66 M *n*-hexane solution of *n*-BuLi (9.40 mL, 25 mmol) at –78 °C. After stirring at the same temperature for 30 min, a solution of **S1** (1.73 g, 10 mmol) in THF (10.0 mL) was slowly introduced into the flask and the resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched by saturated aqueous NH_4Cl at 0 °C and extracted with EtOAc three times.

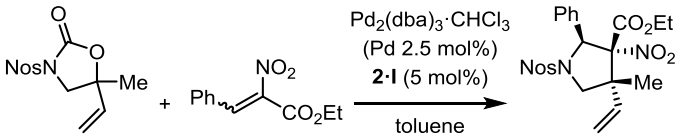
The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (Hex/EtOAc = 4:1 to 2:1 as eluent) gave **S2** in 63% yield (1.24 g, 6.3 mmol) as a yellow solid. **S2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30-5.90 (1H, brm), 3.78 (1H, d, J = 8.8 Hz), 3.48 (1H, d, J = 8.8 Hz), 1.71 (3H, s), 0.18 (9H, s).

To a solution of **S2** (592 mg, 3.0 mmol) and $BnMe_3NCl$ (29.4 mg, 0.16 mmol) in THF (10.0 mL) was added KF (523 mg, 9.0 mmol) in D_2O (2.0 mL) at room temperature, and the whole mixture was stirred at the same temperature for 22 h. The reaction mixture was diluted by the addition of EtOAc (10.0 mL) and the extractive work-up was conducted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (Hex/EtOAc = 3:1 to 1:1 as eluent) to give **S3** (364 mg, 2.9 mmol, 96% yield, >95% D) as a yellow solid. **S3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, brs), 3.80 (1H, d, J = 8.8 Hz), 3.51 (1H, d, J = 8.8 Hz), 1.75 (3H, s).

To a solution of **S3** (75.9 mg, 0.60 mmol) in CD_3OD (2.7 mL) and pyridine (300 μL) was added 5% $Pd/CaCO_3$ (poisoned with lead, 7.7 mg) at 0 °C under Ar, and the reaction flask was then evacuated and refilled with H_2 three times. The resulting suspension was stirred for 35 min at room temperature. After flushing the remaining H_2 out with Ar, the mixture was filtered to remove $Pd/CaCO_3$ and the filtercake was rinsed with EtOAc. The filtrate was washed with 1 N HCl three times and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (Hex/EtOAc = 2:1 to 1:1.2 as eluent) afforded **S4** in 42% yield (32.2 mg, 0.26 mmol, E/Z = 1:>20, >95% D) as a colorless oil. **S4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, app dt, J = 10.8, 2.7 Hz), 5.72 (1H, brs), 5.20 (1H, d, J = 10.8 Hz), 3.49 (1H, d, J = 8.6 Hz), 3.39 (1H, d, J = 8.6 Hz), 1.56 (3H, s).

To a solution of **S4** (32.2 mg, 0.255 mmol) in THF (0.700 mL) and DMF (1.80 mL) was slowly added NaH (60%, 20.4 mg, 0.510 mmol) at 0 °C under Ar, and the mixture was stirred for 15 min. Then, 4-nitrobenzenesulfonyl chloride (73.5 mg, 0.332 mmol) was introduced into the flask, and the reaction mixture was warmed up to room temperature. After stirring for 10 h, a saturated aqueous solution of NH_4Cl was slowly added at 0 °C and extractive work-up was performed with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (Hex/EtOAc = 6:1 to 4:1 as eluent) furnished the adduct **11** (39.2 mg, 0.125 mmol, 49% yield, >95% D) as a white solid. **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (1H, d, J = 9.0 Hz), 8.26 (1H, d, J = 9.0 Hz), 5.86 (1H, app dt, J = 11.0, 2.5 Hz), 5.27 (1H, d, J = 11.0 Hz), 3.94 (1H, d, J = 9.6 Hz), 3.85 (1H, d, J = 9.6 Hz), 1.57 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.3, 150.9, 142.5, 136.9, 129.9, 124.6, 116.5 (t, $J_{C\text{-}D}$ = 24.5 Hz), 80.9, 55.2, 25.0; IR (film) 3119, 3103, 2936, 2922, 2853, 1780, 1533, 1373, 1362, 1350, 1236, 1219, 1180, 1123, 1113, 772 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{12}DN_2O_6S^+$ ($[M+H]^+$) 314.0552. Found 314.0542.

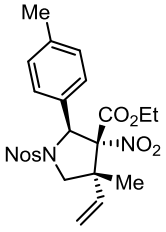
Representative Procedure for Pd-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Geometrical Mixture of Nitroacrylate:



8a *racemic* **9a** (3 equiv.) (*E*/*Z* mixture) **10a**

To a Schlenk flask was added $Pd_2(dba)_3{\cdot}CHCl_3$ (1.29 mg, 1.25 μmol) and **2d·I** (5.50 mg, 5 μmol) and the flask was evacuated and refilled with Ar three times. Then, toluene (1 mL) was introduced, and the resulting catalyst mixture was degassed by alternating vacuum evacuation/Ar backfill. The mixture was cooled to 0 °C and 2-nitro-3-phenylacrylate **9a** (66.4 mg, 0.3 mmol) and 5-vinyloxazolidinone **8a** (31.2 mg, 0.1 mmol) were successively added into the reaction flask. After stirring for 8 h, the reaction mixture was filtered through a pad of short silica gel and rinsed with acetone and the filtrates were concentrated. Purification of the residue by column chromatography on silica gel (H/Et_2O = 11:1 to 3:1 as eluent) gave **10a** (48.4 mg, 0.0989 mmol, 99% yield) as a white solid. **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 8.7 Hz), 7.59 (2H, d, J = 8.7 Hz), 7.17-7.22 (1H, m), 7.05-7.07 (4H, m), 6.08 (1H, s), 5.91 (1H, dd, J = 17.2, 11.0 Hz), 5.50 (1H, d, J = 17.2 Hz), 5.38 (1H, d, J = 11.0 Hz), 4.30 (1H, d, J = 10.5 Hz), 4.21 (1H, d, J = 10.5 Hz), 3.76 (1H, dq, J = 10.5, 7.3 Hz), 3.45 (1H, dq, J = 10.5, 7.3 Hz), 1.56 (3H, s), 0.68 (3H, t, J = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 149.9, 145.7, 136.0, 133.7, 129.1, 128.8, 128.4, 128.0, 123.9, 119.2, 105.0, 66.4, 63.1, 58.2, 50.9, 16.5, 13.2; IR (film) 3105, 3069, 3038, 2984, 2922, 1744, 1557, 1530, 1348, 1236, 1161, 1042, 853, 735, 702, 617, 565 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{23}N_3O_8SNa^+$ ([M+Na]$^+$) 512.1098 Found 512.1101.; HPLC IA, H/EtOH = 83.3:16.7, flow rate = 0.5 mL/min, λ = 254 nm, 15.8 min (minor), 20.1 min (major).

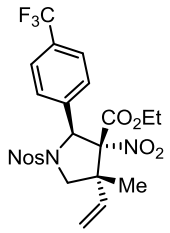
Characterization Data for the Pyrrolidines:



10b

The reaction was stirred for 10 h at 0 °C.

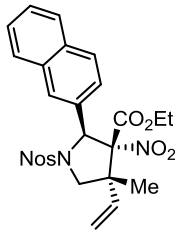
10b: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 9.0 Hz), 7.59 (2H, d, J = 9.0 Hz), 6.95 (2H, brs), 6.85 (2H, d, J = 7.2 Hz), 6.01 (1H, s), 5.89 (1H, dd, J = 17.2, 11.2 Hz), 5.48 (1H, d, J = 17.2 Hz), 5.36 (1H, d, J = 11.2 Hz), 4.27 (1H, d, J = 10.5 Hz), 4.19 (1H, d, J = 10.5 Hz), 3.78 (1H, dq, J = 11.0, 7.2 Hz), 3.51 (1H, dq, J = 11.0, 7.2 Hz), 2.25 (3H, s), 1.55 (3H, s), 0.71 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 149.9, 145.7, 139.2, 136.1, 130.6, 128.7, 128.6, 128.5, 123.8, 119.1, 105.0, 66.3, 63.1, 58.2, 50.9, 21.1, 16.7, 13.2; IR (film) 3105, 2984, 2924, 1746, 1557, 1531, 1350, 1310, 1236, 1167, 1043, 854, 737 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{25}N_3O_8SNa^+$ ([M+Na]$^+$) 526.1255. Found 526.1245.; HPLC OX3, Hex/EtOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 24.6 min (minor), 36.6 min (major).



10c

The reaction was stirred for 10 h at 0 °C.

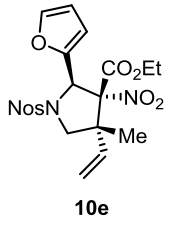
10c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.39 (2H, brd, J = 7.0 Hz), 7.33 (2H, brd, J = 7.0 Hz), 6.09 (1H, s), 5.77 (1H, dd, J = 17.3, 10.9 Hz), 5.47 (1H, d, J = 17.3 Hz), 5.33 (1H, d, J = 10.9 Hz), 4.23 (2H, s), 3.79 (1H, dq, J = 10.7, 7.2 Hz), 3.51 (1H, dq, J = 10.7, 7.2 Hz), 1.55 (3H, s), 0.70 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1, 150.3, 145.1, 138.5, 135.6, 131.5 (q, $J_{C\text{-}F}$ = 32.8 Hz), 128.5, 125.3 (q, $J_{C\text{-}F}$ = 4.2 Hz), 124.9, 124.2, 123.7 (q, $J_{C\text{-}F}$ = 272.3 Hz), 119.5, 104.8, 66.1, 63.4, 58.4, 51.2, 16.6, 13.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ −62.8; IR (film) 3109, 2988, 2920, 1748, 1558, 1533, 1350, 1325, 1167, 1128, 1069, 854, 741 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{22}F_3N_3O_8SNa^+$ ([M+Na]$^+$) 580.0972. Found 580.0967.; HPLC AD3, Hex/IPA = 90.9:9.1, flow rate = 0.5 mL/min, λ = 254 nm, 15.2 min (minor), 18.3 min (major).



10d

The reaction was stirred for 10 h at 0 °C.

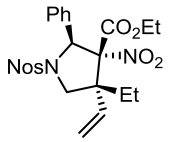
10d: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 8.4 Hz), 7.73 (1H, d, J = 7.6 Hz), 7.61-7.51 (2H, brm), 7.50 (2H, d, J = 8.4 Hz), 7.47 (2H, t, J = 7.6 Hz), 7.43-7.31 (2H, brm), 6.21 (1H, s), 5.97 (1H, dd, J = 17.0, 10.8 Hz), 5.55 (1H, d, J = 17.0 Hz), 5.42 (1H, d, J = 10.8 Hz), 4.38 (1H, d, J = 10.2 Hz), 4.29 (1H, d, J = 10.2 Hz), 3.68 (1H, dq, J = 10.5, 7.2 Hz), 3.33 (1H, dq, J = 10.5, 7.2 Hz), 1.59 (3H, s), 0.45 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.9, 150.2, 146.3, 136.6, 133.7, 132.8, 131.2, 128.8, 128.2, 128.1, 127.7, 127.2, 124.2, 119.7, 105.5, 67.0, 63.5, 58.6, 51.4, 17.2, 13.4, three peaks for aromatic carbons were not found probably due to overlapping; IR (film) 3105, 2984, 2920, 1746, 1557, 1531, 1348, 1233, 1163, 1043, 910, 854, 824, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{25}N_3O_8SNa^+$ ([M+Na]$^+$) 562.1255. Found 562.1255.; HPLC AD3, Hex/IPA/EtOH = 82.5:5:12.5, flow rate = 0.5 mL/min, λ = 254 nm, 25.1 min (major), 30.0 min (minor).



10e

The reaction was stirred for 24 h at room temperature.

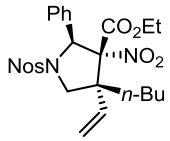
10e: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (2H, d, J = 9.0 Hz), 7.70 (2H, d, J = 9.0 Hz), 6.99 (1H, d, J = 1.8 Hz), 6.45 (1H, d, J = 3.0 Hz), 6.26 (1H, dd, J = 3.0, 1.8 Hz), 5.87 (1H, dd, J = 17.2, 11.0 Hz), 5.86 (1H, s), 5.46 (1H, d, J = 17.2 Hz), 5.38 (1H, d, J = 11.0 Hz), 4.16 (1H, d, J = 10.2 Hz), 4.05 (1H, d, J = 10.2 Hz), 4.04 (1H, dq, J = 11.1, 7.1 Hz), 3.86 (1H, dq, J = 11.1, 7.1 Hz), 1.61 (3H, s), 1.00 (3H, t, J = 7.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 149.9, 146.4, 145.3, 143.1, 136.3, 128.3, 124.0, 118.8, 113.4, 111.2, 102.2, 63.5, 60.7, 57.0, 50.1, 18.3, 13.5; IR (film) 3105, 2984, 2924, 1749, 1558, 1531, 1350, 1236, 1173, 1155, 1090, 1047, 1013, 856, 737 cm^{-1}; HRMS (ESI) Calcd for $C_{20}H_{21}N_3O_9SNa^+$ ([M+Na]$^+$) 502.0891. Found 502.0889.; HPLC OX3, Hex/IPA/EtOH = 75:20:5, flow rate = 0.5 mL/min, λ = 254 nm, 31.8 min (minor), 62.9 min (major).



10f

The reaction was stirred for 24 h at 0 °C.

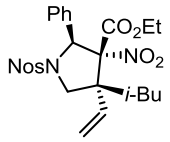
10f: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.17 (1H, t, J = 6.9 Hz), 7.15-6.80 (4H, brm), 5.92 (1H, s), 5.69 (1H, app dt, J = 16.2, 6.0 Hz), 5.60 (1H, dd, J = 16.2, 11.0 Hz), 5.59 (1H, d, J = 11.0 Hz), 4.54 (1H, d, J = 10.5 Hz), 4.19 (1H, d, J = 10.5 Hz), 3.80 (1H, dq, J = 10.7, 7.2 Hz), 3.48 (1H, dq, J = 10.7, 7.2 Hz), 2.10 (1H, dq, J = 10.7, 7.3 Hz), 2.09 (1H, dq, J = 10.7, 7.3 Hz), 0.88 (3H, t, J = 7.3 Hz), 0.69 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 149.8, 146.3, 134.0, 133.1, 129.2, 129.1, 128.3, 127.9, 123.8, 120.9, 105.2, 66.6, 63.1, 54.7, 54.5, 24.0, 13.2, 9.4; IR (film) 3105, 2978, 2926, 1746, 1558, 1531, 1350, 1312, 1234, 1165, 1088, 853, 748, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{25}N_3O_8SNa^+$ ([M+Na]$^+$) 526.1255. Found 526.1253.; HPLC IA3, Hex/IPA = 95:5, flow rate = 0.5 mL/min, λ = 254 nm, 18.1 min (minor), 20.4 min (major).



10g

The reaction was stirred for 24 h at 0 °C. After column chromatography, further purification by GPC was conducted to give the pure **10g**.

10g: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 9.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 7.19-7.15 (1H, brm), 7.12-6.80 (4H, brm), 5.90 (1H, s), 5.68 (1H, d, J = 16.2 Hz), 5.61 (1H, dd, J = 16.2, 10.6 Hz), 5.56 (1H, d, J = 10.6 Hz), 4.53 (1H, d, J = 10.5 Hz), 4.20 (1H, d, J = 10.5 Hz), 3.81 (1H, dq, J = 10.7, 7.2 Hz), 3.49 (1H, dq, J = 10.7, 7.2 Hz), 2.04-2.01 (2H, m), 1.36-1.28 (4H, m), 0.92 (3H, t, J = 7.2 Hz), 0.69 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 149.8, 146.3, 134.5, 133.2, 129.1, 128.3, 127.9, 123.8, 120.6, 105.3, 66.4, 63.1, 54.9, 54.0, 30.9, 27.3, 23.3, 14.1, 13.2, one peak for aromatic carbon was not found probably due to overlapping; IR (film) 3105, 2959, 2934, 1746, 1558, 1531, 1350, 1312, 1234, 1165, 1088, 1011, 853, 772, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{29}N_3O_8SNa^+$ ([M+Na]$^+$) 554.1568. Found 554.1566.; HPLC IA3, Hex/IPA/EtOH = 90:5:5, flow rate = 0.5 mL/min, λ = 254 nm, 12.1 min (minor), 13.8 min (major).

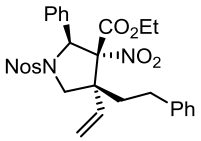


10h

The reaction was stirred for 24 h at room temperature. After column chromatography, further purification by GPC was conducted to give the pure **19h**.

10h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, d, J = 9.0 Hz), 7.51 (2H, d, J = 9.0 Hz), 7.19-7.14 (1H, brm), 7.00 (4H, brs), 5.85 (1H, s), 5.76 (1H, dd, J = 16.7, 0.9 Hz), 5.63 (1H, dd, J = 16.7, 11.2 Hz), 5.57 (1H, d, J = 11.2 Hz), 4.70 (1H, d, J = 10.5 Hz), 4.26 (1H, dd, J = 10.5, 0.9 Hz), 3.81 (1H, dq, J = 10.8, 7.2 Hz), 3.49 (1H, dq, J = 10.8, 7.2 Hz), 2.17 (1H, dd, J = 14.3, 4.6 Hz), 1.85 (1H, dd, J = 14.3, 8.0 Hz), 1.71-1.61 (1H, m), 0.95 (3H, d, J = 6.4 Hz), 0.94 (3H, d, J = 6.4 Hz), 0.69 (3H, t, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3, 149.8, 146.4, 134.8, 133.0, 129.3, 129.1, 128.3, 127.9, 123.8, 120.3, 105.8, 65.7, 63.1, 55.0, 54.2, 40.3, 25.2, 25.2, 23.8, 13.2; IR (film) 3107, 2961, 2940, 1746, 1558, 1531, 1350, 1312, 1236, 1165, 1088, 1013, 853,

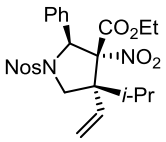
772, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{29}N_3O_8SNa^+$ ($[M+Na]^+$) 554.1568. Found 554.1565.; HPLC AD3, Hex/IPA/EtOH = 75:22.5:2.5, flow rate = 0.25 mL/min, λ = 254 nm, 17.1 min (minor), 18.7 min (major).



10i

The reaction was stirred for 36 h at room temperature.

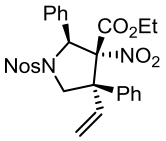
10i: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.7 Hz), 7.51 (2H, d, J = 8.7 Hz), 7.31 (2H, t, J = 7.4 Hz), 7.23 (1H, t, J = 7.4 Hz), 7.22-7.16 (1H, brm), 7.18 (2H, d, J = 7.4 Hz), 7.14-6.84 (4H, brm), 5.93 (1H, s), 5.80 (1H, d, J = 16.6 Hz), 5.72 (1H, dd, J = 16.6, 10.4 Hz), 5.67 (1H, d, J = 10.4 Hz), 4.59 (1H, d, J = 10.8 Hz), 4.26 (1H, d, J = 10.8 Hz), 3.76 (1H, dq, J = 11.0, 7.1 Hz), 3.45 (1H, dq, J = 11.0, 7.1 Hz), 2.72-2.67 (1H, m), 2.44-2.36 (3H, m), 0.65 (3H, t, J = 7.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3, 149.9, 146.2, 141.2, 134.2, 133.1, 129.1, 128.7, 128.5, 128.3, 127.9, 126.5, 123.9, 121.2, 105.1, 66.3, 63.2, 54.8, 53.9, 33.2, 31.5, 13.2, one peak for aromatic carbon was not found probably due to overlapping; IR (film) 3107, 2980, 2924, 1744, 1558, 1531, 1350, 1312, 1236, 1165, 1032, 1011, 853, 750, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{29}N_3O_8SNa^+$ ($[M+Na]^+$) 602.1568. Found 602.1567.; HPLC AD3, Hex/EtOH = 90.9:9.1, flow rate = 1.0 mL/min, λ = 254 nm, 8.8 min (minor), 14.2 min (major).



10j

The reaction was stirred for 48 h at room temperature. After column chromatography, further purification by GPC was conducted to give the pure **10j**.

10j: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.15 (1H, t, J = 7.5 Hz), 6.97 (4H, brs), 6.01 (1H, s), 5.84 (1H, d, J = 17.1 Hz), 5.69 (1H, dd, J = 17.1, 10.8 Hz), 5.62 (1H, d, J = 10.8 Hz), 4.73 (1H, d, J = 11.1 Hz), 4.14 (1H, d, J = 11.1 Hz), 3.82 (1H, dq, J = 11.0, 7.1 Hz), 3.52 (1H, dq, J = 11.0, 7.1 Hz), 2.56 (1H, sept, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 0.73 (3H, t, J = 7.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 149.7, 146.5, 133.0, 132.3, 129.6, 129.0, 128.3, 127.8, 123.8, 120.5, 105.4, 67.8, 63.1, 56.7, 55.9, 32.1, 20.0, 19.6, 13.2; IR (film) 3105, 2972, 2941, 1744, 1558, 1531, 1350, 1312, 1236, 1165, 1111, 1013, 851, 746, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{28}N_3O_8S^+$ ($[M+H]^+$) 518.1592. Found 518.1582.; HPLC OX3, Hex/IPA/EtOH = 94:1:5, flow rate = 0.5 mL/min, λ = 254 nm, 30.8 min (minor), 37.0 min (major).

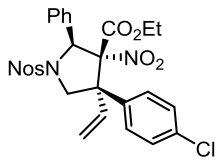


10k

The reaction was stirred for 48 h at room temperature.

10k: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 9.0 Hz), 7.63 (2H, d, J = 9.0 Hz), 7.46 (2H, d, J = 7.4 Hz), 7.34 (2H, t, J = 7.4 Hz), 7.29 (1H, t, J = 7.4 Hz), 7.24-6.80 (4H, brm), 7.19 (1H, t, J = 7.2 Hz), 6.45 (1H, s), 6.12 (1H, dd, J = 16.6, 10.8 Hz), 5.38 (1H, d, J = 10.8 Hz), 5.07 (1H, d, J = 16.6 Hz), 4.94 (1H, d, J = 10.8 Hz), 4.60 (1H, d, J = 10.8 Hz), 3.61 (1H, dq, J = 10.7, 7.2 Hz), 3.49 (1H, dq, J = 10.7, 7.2 Hz), 0.66 (3H, t, J = 7.2

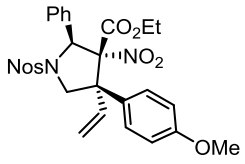
Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2, 150.0, 145.8, 137.8, 136.7, 133.6, 129.1, 129.0, 128.5, 128.0, 127.7, 124.0, 121.2, 107.2, 67.6, 63.2, 60.0, 59.5, 13.2, two peaks for aromatic carbons were not found probably due to overlapping; IR (film) 3105, 3065, 3036, 2982, 2924, 1749, 1560, 1531, 1350, 1236, 1167, 1013, 851, 760, 748, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{25}N_3O_8SNa^+$ ([M+Na]$^+$) 574.1255. Found 574.1255.; HPLC AD3, Hex/IPA/EtOH = 70:20:10, flow rate = 0.5 mL/min, λ = 254 nm, 17.1 min (minor), 19.2 min (major).



10l

The reaction was stirred for 36 h at room temperature. After column chromatography, further purification by GPC was conducted to give the pure **10l**.

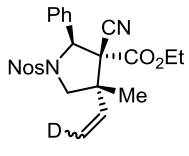
10l: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 8.7 Hz), 7.62 (2H, d, *J* = 8.7 Hz), 7.42 (2H, d, *J* = 8.7 Hz), 7.32 (2H, d, *J* = 8.7 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 7.05 (4H, brs), 6.44 (1H, s), 6.13 (1H, dd, *J* = 17.3, 10.7 Hz), 5.41 (1H, dd, *J* = 10.7, 1.8 Hz), 5.07 (1H, dd, *J* = 17.3, 1.8 Hz), 4.90 (1H, d, *J* = 10.5 Hz), 4.59 (1H, d, *J* = 10.5 Hz), 3.63 (1H, dq, *J* = 10.7, 7.2 Hz), 3.47 (1H, dq, *J* = 10.7, 7.2 Hz), 0.67 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 149.9, 145.6, 136.3, 136.2, 133.8, 133.3, 129.9, 129.2, 128.9, 128.5, 128.4, 128.0, 123.9, 121.5, 106.8, 67.5, 63.4, 59.4, 59.2, 13.1; IR (film) 3105, 2986, 2926, 1748, 1560, 1531, 1495, 1350, 1236, 1167, 1101, 1013, 851, 748, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{27}H_{24}N_3O_8ClSNa^+$ ([M+Na]$^+$) 608.0865. Found 608.0863.; HPLC IA3, Hex/IPA = 70:30, flow rate = 0.25 mL/min, λ = 254 nm, 28.1 min (minor), 35.1 min (major).



10m

The reaction was stirred for 36 h at room temperature. After column chromatography, further purification by GPC was conducted to give the pure **10m**.

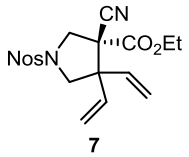
10m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 9.2 Hz), 7.63 (2H, d, *J* = 9.2 Hz), 7.38 (2H, d, *J* = 9.2 Hz), 7.20-7.00 (4H, brm), 7.18 (1H, t, *J* = 7.4 Hz), 6.86 (2H, d, *J* = 9.2 Hz), 6.43 (1H, s), 6.11 (1H, dd, *J* = 17.3, 10.7 Hz), 5.37 (1H, d, *J* = 10.7 Hz), 5.09 (1H, d, *J* = 17.3 Hz), 4.87 (1H, d, *J* = 11.0 Hz), 4.61 (1H, d, *J* = 11.0 Hz), 3.81 (3H, s), 3.61 (1H, dq, *J* = 10.8, 7.2 Hz), 3.48 (1H, dq, *J* = 10.8, 7.2 Hz), 0.67 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2, 158.9, 150.0, 145.8, 136.9, 133.7, 129.8, 129.5, 129.1, 128.5, 128.0, 124.0, 121.0, 113.7, 107.2, 67.6, 63.2, 59.5, 59.4, 55.4, 13.2, one peak for aromatic carbon was not found probably due to broadening; IR (film) 3105, 2982, 2961, 2934, 1748, 1558, 1531, 1516, 1350, 1256, 1236, 1167, 1034, 770 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{27}N_3O_9SNa^+$ ([M+Na]$^+$) 604.1360. Found 604.1358.; HPLC AD3, Hex/IPA/EtOH = 76.5:5:18.5, flow rate = 0.5 mL/min, λ = 254 nm, 28.1 min (minor), 38.5 min (major).



11
(*E*/*Z* = 1:1)

The reaction was stirred for 10 h at room temperature.

11: ^{1}H NMR (600 MHz, $CDCl_3$) (*E*)-isomer δ 8.13 (2H, d, *J* = 8.7 Hz), 7.59 (2H, d, *J* = 8.7 Hz), 7.24 (1H, t, *J* = 7.7 Hz), 7.18 (2H, d, *J* = 7.7 Hz), 7.13 (2H, t, *J* = 7.7 Hz), 5.86 (1H, d, *J* = 17.4 Hz), 5.68 (1H, s), 5.43 (1H, d, *J* = 17.4 Hz), 4.31 (1H, d, *J* = 11.4 Hz), 4.28 (1H, dq, *J* = 10.5, 7.1 Hz), 4.16 (1H, dq, *J* = 10.5, 7.1 Hz), 3.76 (1H, d, *J* = 11.4 Hz), 1.57 (3H, s), 1.28 (3H, t, *J* = 7.1 Hz); (*Z*)-isomer δ 8.13 (2H, d, *J* = 8.7 Hz), 7.59 (2H, d, *J* = 8.7 Hz), 7.24 (1H, t, *J* = 7.7 Hz), 7.18 (2H, d, *J* = 7.7 Hz), 7.13 (2H, t, *J* = 7.7 Hz), 5.85 (1H, d, *J* = 9.9 Hz), 5.68 (1H, s), 5.36 (1H, d, *J* = 9.9 Hz), 4.31 (1H, d, *J* = 11.4 Hz), 4.28 (1H, dq, *J* = 10.5, 7.1 Hz), 4.16 (1H, dq, *J* = 10.5, 7.1 Hz), 3.76 (1H, d, *J* = 11.4 Hz), 1.57 (3H, s), 1.28 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) (*E*/*Z* mixture) δ 163.4, 150.0, 145.5, 135.2, 134.1, 129.3, 128.8, 128.5, 128.3, 123.9, 118.1 (t, $J_{C\text{-}D}$ = 23.9 Hz), 115.1, 67.0, 65.1, 63.8, 58.3, 50.6, 19.4, 14.2; IR (film) 3105, 2986, 2922, 1746, 1531, 1350, 1234, 1165, 1040, 775, 741 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{23}DN_3O_6S^+$ ($[M+H]^+$) 471.1443. Found 471.1442.; HPLC OZ3, Hex/IPA = 80:20, flow rate = 1.0 mL/min, λ = 254 nm, 31.4 min (major), 41.3 min (minor).



7

7: $[\alpha]_D^{23}$ = +50.1 (*c* = 1.0, $CHCl_3$) for 49% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (2H, d, *J* = 9.2 Hz), 8.06 (2H, d, *J* = 9.2 Hz), 6.14 (1H, dd, *J* = 17.4, 10.8 Hz), 5.71 (1H, dd, *J* = 17.4, 10.8 Hz), 5.45 (1H, d, *J* = 10.8 Hz), 5.36 (1H, d, *J* = 10.8 Hz), 5.31 (1H, d, *J* = 17.4 Hz), 5.26 (1H, d, *J* = 17.4 Hz), 4.23-4.11 (1H, m), 4.01 (1H, d, *J* = 11.2 Hz), 3.86 (1H, d, *J* = 11.2 Hz), 3.69 (1H, d, *J* = 9.8 Hz), 3.64 (1H, d, *J* = 9.8 Hz), 1.25 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2, 150.6, 142.7, 134.8, 132.9, 128.8, 124.7, 119.7, 119.7, 115.6, 63.8, 56.2, 54.5, 53.0, 53.0, 14.1; IR (film) 3102, 2988, 2928, 1742, 1530, 1350, 1244, 1171, 1088, 1009, 856, 737 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{19}N_3O_6SNa^+$ ($[M+Na]^+$) 428.0887. Found 428.0888.; HPLC IA, Hex/IPA = 90.9:9.1, flow rate = 1.0 mL/min, λ = 254 nm, 33.2 min (major), 40.1 min (minor).

Crystallographic Structure Determination:

Recrystallization of 10a (CCDC 954517): A single crystal of **10a** was obtained from CH_2Cl_2/acetone/CH_3CN solvent system at room temperature. The single crystals thus obtained were mounted on CryoLoop. Data of X-ray diffraction were collected at 133 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.[5] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded to oxygen atoms were located from a difference synthesis and their coordinates and isotropic thermal parameters refined. The other hydrogen atoms were placed in calculated positions. The crystallographic data were summarized in Tables S1 and ORTEP diagrams were shown in Figure S1.

Table S1. Crystal data and structure refinement for **10a**.

Empirical formula	C22 H23 N3 O8 S	
Formula weight	489.49	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.901(2) Å	α= 90°.
	b = 11.150(2) Å	β= 90°.
	c = 18.652(4) Å	γ = 90°.
Volume	2267.1(8) $Å^3$	
Z	4	
Density (calculated)	1.434 Mg/m^3	
Absorption coefficient	0.197 mm^{-1}	
F(000)	1024	
Crystal size	0.60 x 0.50 x 0.20 mm^3	
Theta range for data collection	2.13 to 28.25°.	
Index ranges	-13<=h<=14, -14<=k<=14, -17<=l<=24	
Reflections collected	16924	
Independent reflections	5596 [R(int) = 0.0281]	
Completeness to theta = 28.25°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9616 and 0.8908	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	5596 / 0 / 309
Goodness-of-fit on F^2	1.118
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0873
R indices (all data)	R1 = 0.0357, wR2 = 0.0884
Absolute structure parameter	0.11(5)
Largest diff. peak and hole	0.357 and -0.210 e.$Å^{-3}$

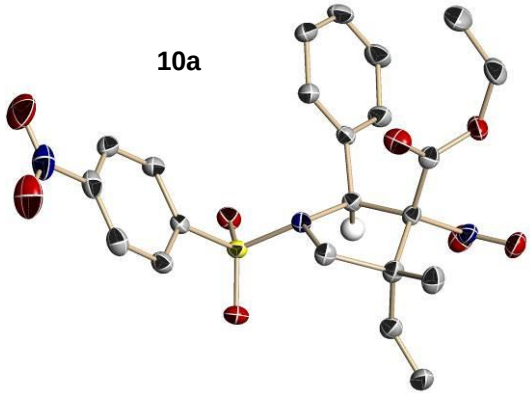


Figure S1. Molecular structure of **10a**. All calculated hydrogen atoms are omitted for clarity. Yellow = sulfur, blue = nitrogen, red = oxygen, black = carbon.

References:

1. Ito, H.; Kunii, S.; Sawamura, M. *Nature Chem.* **2010**, *2*, 972.

2. Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.

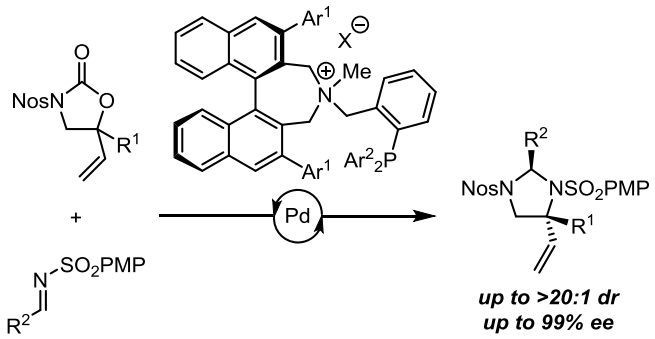
3. Ohmatsu, K. Imagawa, N.; Ooi, T. *Nature Chem*. **2014**, *6*, 47-51.

4. (a) Dong, Z.; Liu, X.; Feng, J.; Wang, M.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2011**, 137. (b) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.

5. Sheldrick, G. M. SHELXTL 5.1, Bruker AXS Inc., Madison, Wisconsin, 1997.

Chapter 4

Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand

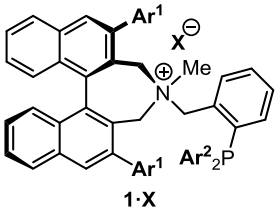


Abstract: A palladium-catalyzed asymmetric [3 + 2] annulation reaction of racemic 5-vinyloxazolidinones with *N*-sulfonyl imines has been established. Under the influence of the chiral ammonium-phosphine hybrid ligand, the cycloadditions proceed to give the chiral imidazolidines bearing α-amino quaternary stereocenter in high yields with excellent diastereo- and enantioselectivities.

1. Introduction

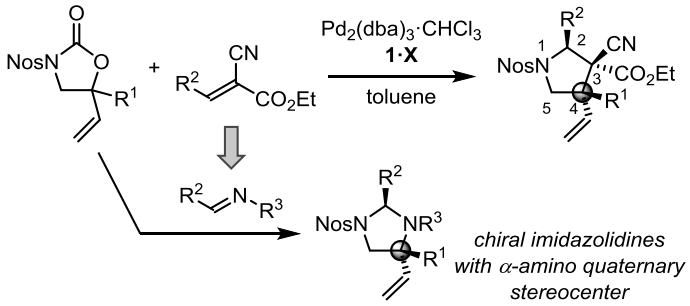
Chiral imidazolidines are frequently found in natural products, biologically active compounds, catalysts and ligands. Therefore, imidazolidine derivatives act as versatile synthetic intermediates with wide applications for organic chemistry and biochemistry.[1] A representative method to construct this structural motif is 1,3-dipolar cycloaddition[2] of azomethine ylides with imines.[3] To date, a few enantioselective cycloadditions have been successfully developed through the use of either the metal or organic catalysts, enabling the efficient access to the multi-substituted chiral imidazolidines.[4] However, reported methodologies showed limited scope and were applicable only for the production of imidazolidines having tertiary stereocenters. Thus, further investigations into the development of new methods, especially to directly and selectively generate these heterocycles with quaternary stereocenters, should prove valuable.

In line with our recent research on the design and application of ion-paired chiral ligands for asymmetric palladium catalysis,[5] we have demonstrated that the phosphine ligand with a pendant chiral ammonium salt of type **1·X** is extremely powerful for asymmetric [3 + 2] annulation reaction of 5-vinyloxazolidinones and activated trisubstituted alkenes (Scheme 1).[6,7] A remarkable feature of this catalytic system is the precise asymmetric construction of contiguous three stereocenters including two quaternary ones, each of which is individually controlled by chiral ammonium-phosphine ligand. For instance, the stereoselectivity for the construction of C(4) stereocenter, which is derived from oxazolidinone, is not influenced by the structure of alkene. Accordingly, chiral ligand **1·X** should be also effective for palladium-catalyzed asymmetric [3 + 2] cycloaddition of vinyloxazolidinones and other dipolarophiles. Herein we report the realization of this approach in the context of asymmetric annulation of oxazolidinones and imines that provide densely substituted chiral imidazolidines bearing α-amino quaternary stereocenter.



1a: Ar^1 = **Ph**, Ar^2 = **Ph**
1b: Ar^1 = **Ph**, Ar^2 = **4-$CF_3C_6H_4$**
1c: Ar^1 = **β-Naph**, Ar^2 = **4-$CF_3C_6H_4$**
1d: Ar^1 = **4-PhC_6H_4**, Ar^2 = **4-$CF_3C_6H_4$**

Figure 1. Chiral ammonium-phosphine hybrid ligands in this study

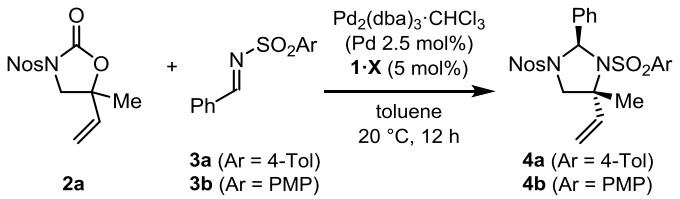


Scheme 1. Previous work on palladium-catalyzed asymmetric [3 + 2] cycloaddition of 5-vinyloxazolidinones

2. Result and Discussion

As an initial investigation, the reaction of vinyloxazolidinone **2a** and *N*-Ts imine **3a** under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ and ligand **1a·Br** was conducted, furnishing the corresponding cycloadduct **4a** in 80% yield with negligible diastereo- and moderate enantioselectivity (Table 1, entry 1). The examination concerning on the effect of protecting group of imines revealed that *N*-(4-methoxy)benzenesulfonyl imine **3b** exhibited excellent reaction efficiency, albeit stereoselectivities were not improved (entry 2). In our previous study, we recognized that halide ion was an important factor for the stereocontrolling ability of ligand **1·X**. While similar stereoselectivities were observed with chloride variant (**1a·Cl**), onium phosphine ligand having iodide ion (**1a·I**) delivered increased diastereoselectivity (entries 3 and 4). The structural modification of aromatic substituent of **1·I** was subsequently tested. Installing the strongly electron-withdrawing trifluoromethyl group into phosphorous benzene (Ar^2) induced a significantly higher level of diastereo- and enantiocontrol (entry 5). Further structural modification on phenyl appendages at the 3,3´-positions of the binaphthyl unit (Ar^1) led to the identification of **1d·I** as an optimal ligand, promoting the cycloaddition to give **4b** quantitatively with excellent diastereo- and enantioselectivity (entry 7).

Table 1. Optimization of reaction conditions[a]



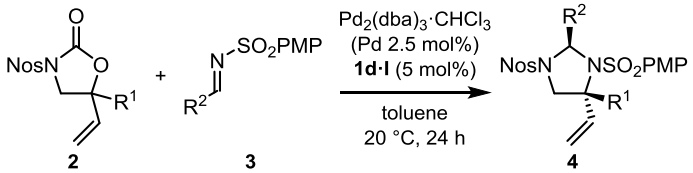
entry	1·X	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a·Br**	**3a**	80	1:1	72/30
2	**1a·Br**	**3b**	92	1.1:1	74/35

3	**1a·Cl**	**3b**	91	1:1.3	72/37
4	**1a·I**	**3b**	92	3.2:1	76/27
5	**1b·I**	**3b**	99	15:1	92/26
6	**1c·I**	**3b**	99	19:1	90/nd
7	**1d·I**	**3b**	99	>20:1	96/nd

[a]Reactions were conducted with vinyloxazolidinones **2a** (0.1 mmol) and imine **3** (0.2 mmol) under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%). ligand **1·X** (5 mol%) in toluene (1 mL) at 20 °C for 12 h. [b]Isolated yield of the mixture of diastereomers. [c]Determined basedon ^{1}H NMR analysis of crude reaction mixture. [d]Determined by chiral HPLC. nd = not determined.

Under the optimized reaction conditions, asymmetric [3 + 2] cycloaddition of a variety of vinyloxazolidinones **2** and imines **3** was investigated. The results are summarized in Table 2. Vinyloxazolidinones bearing 5-alkyl substituents uniformly gave the corresponding products (**4c**-**4f**) excellent yields with high to excellent diastereo- and enantioselectivities (entries 1-4). An array of aromatic imines **3**, which have electron-donating or electron-withdrawing groups at *ortho* position of benzene ring, reacted with oxazolidinones **2b** to afford the cycloadducts **4g**-**4j** in high yields with almost complete stereocontrols (entries 5-7). Although imine with 4-methoxyphenyl group led to diminished reaction efficiency and diastereoselectivity, an excellent enantiomeric purity was retained (entry 8). Hetero- and fused aromatic imines were also well tolerated (entries 9 and 10). The present catalytic system was found to be applicable to the reaction of secondary alkyl-substituted imines, resulting in the quantitative production of **4m** and **4n** with excellent diastereo- and enantioselectivities (entries 11 and 12). The reaction of primary alkyl-substituted imine also smoothly proceeded to give the corresponding product **4o** quantitatively, albeit with diminished diastereoselectivity (entry 13). The absolute configuration of **4g** was confirmed by X-ray crystal structure analysis,[8] and the stereochemistry of the remaining examples were assumed by analogy.

Table 2. Substrate scope[a]

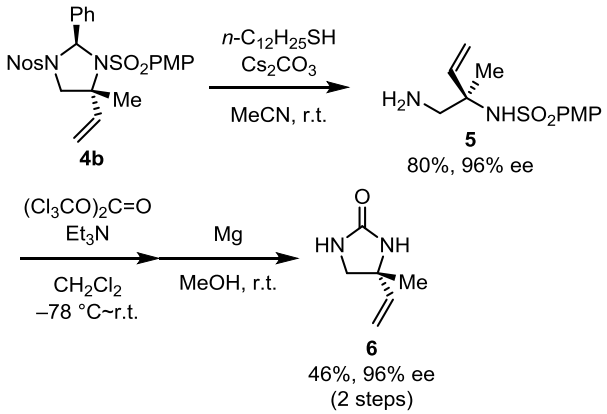


entry	R^1	R^2	4	yield (%)[b]	dr[c]	ee (%)[d]
1	Et	Ph	**4c**	90	>20:1	96
2	*n*-Bu	Ph	**4d**	99	>20:1	96
3[e]	*i*-Bu	Ph	**4e**	99	>20:1	94
4	$(CH_2)_2Ph$	Ph	**4f**	92	11:1	92

5	Me	2-MeC_6H_4	**4g**	93	>20:1	99
6	Me	2-$MeOC_6H_4$	**4h**	92	>20:1	97
7	Me	2-ClC_6H_4	**4i**	92	19:1	95
8	Me	4-$MeOC_6H_4$	**4j**	80	7:1	96
9	Me	2-furyl	**4k**	99	14:1	95
10	Me	1-naphthyl	**4l**	94	>20:1	98
11	Me	*c*-Hex	**4m**	99	>20:1	98
12	Me	*i*-Pr	**4n**	99	>20:1	98
13	Me	*i*-Bu	**4o**	99	6:1	92

[a]Unless otherwise noted, reactions were conducted with vinyloxazolidinone **2** (0.1 mmol) and imine **3** (0.2 mmol) under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol%), ligand **1d·I** (5 mol%) in toluene (1 mL) at 20 °C for 24 h. [b]Isolated yield of the mixture of diastereomers. [c]Determined based on ^1H NMR analysis of crude reaction mixture. [d]Determined by chiral HPLC, and % ee of major diastereomer is indicated. [e]Performed with $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 5 mol%), ligand **1d·I** (10 mol%) for 48 h.

Finally, the synthetic potential of this method was demonstrated via the synthesis of a 1,2-diamine and biologically interesting imidazolidin-2-one[9,10] bearing quaternary stereocenter, from cycloadduct **4b**, as exemplified in Scheme 2. Deprotection of the 4-nitrobenzenesulfonyl (Nos) group[11] under well-established conditions afforded the corresponding monoprotected 1,2-diamine **5** in 80% yield. The formation of cyclic urea framework was executed by treating with triphosgen under basic conditions, and subsequent deprotection of the PMP sulfonyl group in the presence of magnesium afforded the chiral imidazolidinone **6** without loss of enantiomeric excess.



Scheme 2. Synthetic transformation of cycloadduct **4b**

3. Conclusion

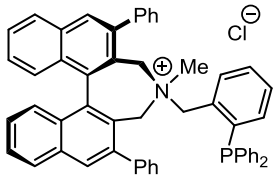
In conclusion, a highly enantio- and diastereoselective [3 + 2] annulation reaction of 5-vinyloxazolidinones and *N*-sulfonyl imines catalyzed by a palladium complex bearing a chiral ammonium-phosphine hybrid ligand has been developed, which allows for the efficient construction

of a variety of chiral imidazolidines with α-amino quaternary stereocenter. The investigation on the reaction mechanism and the further applications of the present methodology in organic synthesis are currently underway.

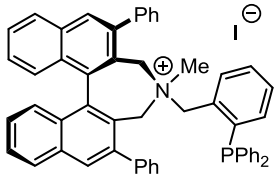
4. Experimental Section

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-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. ^{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 PSQ60AB (spherical, 40-50 μm; FUJI SILYSIA CHEMICAL Co., Inc.) and Chromatorex® NH DM2035 (spherical, 45-75 μm; Fuji Silysia Chemical ltd.). Preparative gel permination chromatography (GPC) was performed with a JAI LC-9210 II NEXT instrument equipped with JAIGEL-2H/JAIGEL-2H columns using chloroform as an eluent. Enantiomeric excesses were determined by HPLC analysis using chiral columns (φ 4.6 mm x 250 mm, DAICEL CHIRALPAK IA (IA), CHIRALPAK IA-3 (IA3), CHIRALPAK IB-3 (IB3), CHIRALPAK IC (IC), CHIRALPAK IE-3 (IE3), and CHIRALPAK AD-3 (AD3) with hexane (H), isopropyl alcohol (IPA) and ethanol (EtOH) 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. Ammonium phosphines **1**·**X**[6] were synthesized by following the literature methods. Other simple chemicals were purchased and used as such.

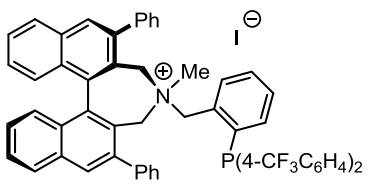
Characterization Data for Chiral Ammonium-Phosphine Hybrid Ligands:



1a·Cl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, s), 8.12 (1H, d, J = 8.0 Hz), 8.00 (1H, d, J = 8.0 Hz), 7.94 (1H, s), 7.69 (1H, ddd, J = 8.0, 7.0, 1.2 Hz), 7.64 (1H, ddd, J = 8.0, 7.0, 1.2 Hz), 7.59-7.61 (1H, m), 7.22-7.51 (18H, m), 7.18 (2H, td, J = 7.6, 1.2 Hz), 7.04 (2H, td, J = 7.6, 1.2 Hz), 6.98-7.01 (1H, m), 6.73 (2H, td, J = 8.0, 1.2 Hz), 6.62 (2H, td, J = 8.0, 1.2 Hz), 5.46 (1H, d, J = 13.6 Hz), 5.11 (1H, dd, J = 13.2, 7.4 Hz), 4.42 (1H, d, J = 13.2 Hz), 3.98 (1H, dd, J = 13.0, 5.8 Hz), 3.82 (1H, d, J = 13.6 Hz), 3.40 (1H, d, J = 13.0 Hz), 2.93 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 139.9, 138.9 (d, $J_{P\text{-}C}$ = 15.5 Hz), 138.5, 138.1, 138.1, 136.8 (d, $J_{P\text{-}C}$ = 7.8 Hz), 136.2, 135.0, 135.0, 134.0 (d, $J_{P\text{-}C}$ = 24.2 Hz), 133.9 (d, $J_{P\text{-}C}$ = 21.3 Hz), 133.3 (d, $J_{P\text{-}C}$ = 8.7 Hz), 132.8, 132.6 (d, $J_{P\text{-}C}$ = 18.4 Hz), 131.4, 131.0, 130.9, 130.5, 130.2 (d, $J_{P\text{-}C}$ = 8.7 Hz), 129.8, 129.7, 129.0, 128.9, 128.9, 128.8, 128.7, 128.7, 128.3, 128.1, 127.8, 127.7, 127.6, 127.1, 125.6, 123.9, 62.0 (d, $J_{P\text{-}C}$ = 19.4 Hz), 61.9, 57.1 (d, $J_{P\text{-}C}$ = 14.5 Hz), 47.9, six peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −17.8; IR (film): 1470, 1433, 1344, 1337, 1261, 1186, 1152, 1026, 897, 723 cm^{-1}; HRMS (ESI) Calcd for $C_{54}H_{43}NP^+$ ([M-Cl]$^+$) 736.3128. Found 736.3123.; $[\alpha]_D^{23}$ = −31.5 (c = 1.0, $CHCl_3$).

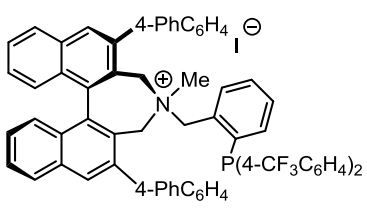


1a·I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, s), 8.12 (1H, d, J = 8.4 Hz), 8.00 (1H, d, J = 8.4 Hz), 7.96 (1H, s), 7.70 (1H, ddd, J = 8.4, 7.2, 1.2 Hz), 7.65 (1H, ddd, J = 8.4, 6.8, 1.2 Hz), 7.22-7.54 (19H, m), 7.19 (2H, td, J = 7.6, 1.0 Hz), 7.00-7.06 (3H, m), 6.75 (2H, td, J = 8.2, 1.2 Hz), 6.62 (2H, td, J = 8.2, 1.2 Hz), 5.44 (1H, d, J = 14.0 Hz), 5.14 (1H, dd, J = 13.2, 7.2 Hz), 4.23 (1H, d, 13.2 Hz), 3.92 (1H, dd, J = 12.8, 5.2 Hz), 3.85 (1H, d, J = 14.0 Hz), 3.42 (1H, d, J = 12.8 Hz), 2.92 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.8, 139.1 (d, $J_{P\text{-}C}$ = 16.5 Hz), 138.5, 138.4, 138.2, 138.0, 136.6 (d, $J_{P\text{-}C}$ = 7.8 Hz), 136.4, 134.7, 134.6, 134.1 (d, $J_{P\text{-}C}$ = 23.2 Hz), 133.9 (d, $J_{P\text{-}C}$ = 21.2 Hz), 133.1 (d, $J_{P\text{-}C}$ = 7.7 Hz), 132.6 (d, $J_{P\text{-}C}$ = 19.4 Hz), 132.5, 132.2, 131.5, 131.0, 130.9, 130.6, 130.4, 130.2 (d, $J_{P\text{-}C}$ = 6.7 Hz), 130.0, 129.9, 129.7, 129.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.7, 128.4, 128.2, 128.2, 127.8, 127.7, 127.2, 125.3, 123.7, 62.0 (d, $J_{P\text{-}C}$ = 24.0 Hz), 61.9, 57.5 (d, $J_{P\text{-}C}$ = 14.5 Hz), 48.3, one peak for aromatic carbon was not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −18.1; IR (film): 1450, 1433, 1157, 1026, 918, 868, 746, 723 cm^{-1}; HRMS (ESI) Calcd for $C_{54}H_{43}NP^+$ ([M–I]$^+$) 736.3128. Found 736.3122.; $[\alpha]_D^{23}$ = −16.7 (c = 1.0, $CHCl_3$).



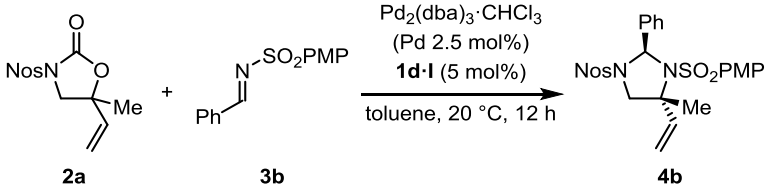
1b·I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, s), 8.13 (1H, d, J = 8.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.00 (1H, s), 7.65-7.74 (3H, m), 7.43-7.59 (9H, m), 7.22-7.37 (11H, m), 6.94-6.97 (1H, m), 6.87 (2H, t, J = 8.0 Hz), 6.77 (2H, t, J = 8.0 Hz), 5.49 (1H, d, J = 14.0

Hz), 5.01 (1H, dd, J = 13.6, 7.2 Hz), 4.53 (1H, d, J = 13.6 Hz), 3.85 (1H, d, J = 14.0 Hz), 3.78 (1H, dd, J = 12.6, 4.4 Hz), 3.49 (1H, d, J = 12.6 Hz), 2.97 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 140.5 (d, $J_{P\text{-}C}$ = 10.6 Hz), 139.6, 138.4, 138.2, 138.1, 137.9, 137.4 (d, $J_{P\text{-}C}$ = 11.6 Hz), 136.6 (d, $J_{P\text{-}C}$ = 13.5 Hz), 136.2, 134.8, 134.8, 134.1 (d, $J_{P\text{-}C}$ = 15.4 Hz), 133.9 (d, $J_{P\text{-}C}$ = 22.2 Hz), 132.9, 132.7 (d, $J_{P\text{-}C}$ = 19.3 Hz), 132.6, 131.9 (q, $J_{F\text{-}C}$ = 33.7 Hz), 131.4 (d, $J_{F\text{-}C}$ = 33.7 Hz), 131.4, 131.2, 131.1, 130.8, 130.8, 130.6, 130.0, 129.7, 128.9, 128.8, 128.6, 128.4, 128.3, 127.8, 127.5, 127.5, 125.8 (q, $J_{F\text{-}C}$ = 3.8 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.8 Hz), 125.0, 123.8 (q, $J_{F\text{-}C}$ = 279.4 Hz), 123.4 (q, $J_{F\text{-}C}$ = 279.4 Hz), 123.1, 61.9, 61.4 (d, $J_{P\text{-}C}$ = 24.0 Hz), 57.6 (d, $J_{P\text{-}C}$ = 11.5 Hz), 48.3, three peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −17.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8, −63.0; IR (film): 1433, 1395, 1321, 1163, 1125, 1098, 1059, 1015, 905, 866, 831, 750, 704 cm^{-1}; HRMS (ESI) Calcd for $C_{56}H_{41}NF_6P^+$ ([M–I]$^+$) 872.2875. Found 872.2864.; $[\alpha]_D^{23}$ = −21.1 (c = 1.0, $CHCl_3$).



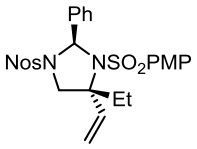
1d·I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s), 8.15 (1H, d, J = 8.4 Hz), 8.06 (1H, s), 8.05 (1H, d, J = 7.6 Hz), 7.73-7.77 (5H, m), 7.70 (2H, ddd, J = 8.6, 6.8, 1.6 Hz), 7.55 (2H, d, J = 7.6 Hz), 7.43-7.52 (14H, m), 7.32-7.41 (4H, m), 7.19-7.28 (4H, m), 6.93 (1H, ddd, J = 7.6, 4.0, 1.2 Hz), 6.88 (2H, t, J = 7.8 Hz), 6.79 (2H, t, J = 8.2 Hz), 5.68 (1H, d, J = 14.0 Hz), 4.96 (1H, dd, J = 13.6, 7.0 Hz), 4.56 (1H, d, J = 13.6 Hz), 3.93 (1H, d, J = 14.0 Hz), 3.82 (1H, dd, J = 13.2, 4.0 Hz), 3.69 (1H, d, J = 13.2 Hz), 3.02 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 141.4, 140.6, 140.5 (d, $J_{P\text{-}C}$ = 10.6 Hz), 140.3, 139.8, 139.3, 138.4, 138.0, 137.5 (d, $J_{P\text{-}C}$ = 11.6 Hz), 137.3, 136.9, 136.8 (d, $J_{P\text{-}C}$ = 14.5 Hz), 136.1, 134.8, 134.7, 134.2 (d, $J_{P\text{-}C}$ = 12.5 Hz), 134.0 (d, $J_{P\text{-}C}$ = 21.3 Hz), 132.9 (d, $J_{P\text{-}C}$ = 18.4 Hz), 132.8 (d, $J_{P\text{-}C}$ = 28.1 Hz), 132.0 (q, $J_{F\text{-}C}$ = 33.8 Hz), 131.9 (q, $J_{F\text{-}C}$ = 33.8 Hz), 131.4, 131.3, 131.2, 131.0, 131.0, 130.6, 130.3, 129.1, 129.0, 128.9, 128.7, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.5, 127.1, 125.9 (q, $J_{F\text{-}C}$ = 3.8 Hz), 125.8 (q, $J_{F\text{-}C}$ = 3.8 Hz), 125.3, 124.2 (q, $J_{F\text{-}C}$ = 277.6 Hz), 123.5 (q, $J_{F\text{-}C}$ = 275.7 Hz), 123.3, 61.9, 61.5 (d, $J_{P\text{-}C}$ = 24.1 Hz), 58.1 (d, $J_{P\text{-}C}$ = 10.7 Hz), 48.4, five peaks for aromatic carbons were not found probably due to overlapping; ^{31}P NMR (162 MHz, $CDCl_3$) δ −17.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8, −63.0; IR (film): 1321, 1167, 1125, 1109, 1059, 920, 907, 897, 831, 766, 733 cm^{-1}; HRMS (ESI) Calcd for $C_{68}H_{49}NF_6P^+$ ([M−I]$^+$) 1024.3501. Found 1024.3489.; $[\alpha]_D^{23}$= −26.1 (c = 1.0, $CHCl_3$).

Representative Procedure for Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines:



To a Schlenk flask was added $Pd_2(dba)_3{\cdot}CHCl_3$ (1.29 mg, 1.25 μmol), **1d·I** (5.76 mg, 5 μmol), and imine **3b** (55.1 mg, 0.2 mmol) and the flask was degassed by alternating vacuum evacuation/Ar backfill. Then, toluene (1 mL) was introduced, and the resulting catalyst mixture was evacuated and refilled with Ar three times. 5-Vinyloxazolidinone **2a** (31.2 mg, 0.1 mmol) was added into the reaction flask. After stirring for 12 h at 20 °C, the reaction mixture was filtered through a short pad of silica gel with the aid of acetone. The filtrates were concentrated and purified by column chromatography on silica gel (H/EtOAc = 5:1 to 2:1 as eluent) to afford **4b** (53.8 mg, 0.099 mmol, 99% yield) as a white solid. **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, d, J = 9.2 Hz), 7.36 (2H, d, J = 9.2 Hz), 7.23 (2H, d, J = 9.2 Hz), 7.15-7.19 (1H, m), 6.99-7.16 (4H, m), 6.62 (2H, d, J = 9.2 Hz), 6.25 (1H, s), 6.10 (1H, dd, J = 17.4, 10.8 Hz), 5.50 (1H, d, J = 17.4 Hz), 5.28 (1H, d, J = 10.8 Hz), 3.97 (1H, d, J = 10.4 Hz), 3.77 (3H, s), 3.41 (1H, d, J = 10.4 Hz), 1.83 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.7, 149.5, 145.0, 138.6, 136.7, 132.5, 129.7, 129.2, 128.4, 128.3, 127.8, 123.8, 115.8, 113.5, 77.5, 67.6, 58.6, 55.7, 23.1; IR (film) 1595, 1531, 1497, 1346, 1337, 1306, 1261, 1217, 1152, 1088, 1072, 1061, 1013, 993, 984, 772, 739, 696 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{25}N_3O_7S_2Na^+$ ([M+Na]$^+$) 566.1026. Found 566.1027.; HPLC IE3, H/IPA = 60:40, flow rate = 1.0 mL/min, λ = 210 nm, 26.7 min (major), 38.3 min (minor).

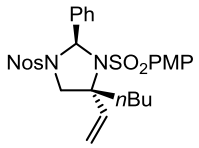
Characterization Data for the Imidozolidines 4:



The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4c**.

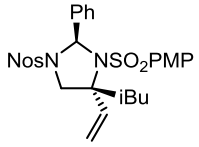
4c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, J = 9.0 Hz), 7.26 (2H, d, J = 9.0 Hz), 7.13 (2H, d, J = 9.0 Hz), 7.11-7.15 (1H, m), 6.93-6.99 (4H, m), 6.56 (2H, d, J = 9.0 Hz), 6.23 (1H, dd, J = 17.8, 11.2 Hz), 6.16 (1H, s), 5.58 (1H, d, J = 17.8 Hz), 5.41 (1H, d, J = 11.2 Hz), 4.12 (1H, d, J = 10.0 Hz), 3.73 (3H, s), 3.39 (1H, d, J = 10.0 Hz), 2.64 (1H, dq, J = 14.5, 7.4 Hz), 1.98 (1H, dq, J = 14.5, 7.4 Hz), 0.97 (3H, t, J = 7.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 149.4, 145.1, 136.5, 132.6, 129.6, 129.2, 128.8, 128.2, 127.6, 123.7, 117.0, 113.4, 71.5, 55.6, 55.0, 29.8, 9.6, one peak for aromatic carbon and one peak for aliphatic carbon were not found probably due to overlapping; IR (film): 1597, 1531, 1501, 1346, 1335, 1306, 1261, 1215, 1152, 1121, 1088, 1026, 1011, 831, 739, 692 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{27}N_3O_7S_2Na^+$ ([M+Na]$^+$)

580.1183. Found 580.1180.; HPLC AD3, H/IPA/EtOH = 82:9:9, flow rate = 1.0 mL/min, λ = 210 nm, 35.5 min (minor), 57.6 min (major).



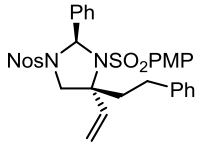
The reaction was stirred for 24 h.

4d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 9.2 Hz), 7.26 (2H, d, J = 9.2 Hz), 7.14 (2H, d, J = 9.2 Hz), 7.12-7.17 (1H, m), 6.93-7.00 (4H, m), 6.57 (2H, d, J = 9.2 Hz), 6.25 (1H, dd, J = 17.8, 11.0 Hz), 6.15 (1H, s), 5.59 (1H, d, J = 17.8 Hz), 5.41 (1H, d, J = 11.0 Hz), 4.14 (1H, d, J = 10.1 Hz), 3.75 (3H, s), 3.40 (1H, d, J = 10.1 Hz), 2.59-2.67 (1H, m), 1.86-1.94 (1H, m), 1.36-1.41 (3H, m), 1.16-1.22 (1H, m), 0.95 (3H, t, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 149.4, 145.1, 136.7, 136.4, 132.7, 129.6, 129.2, 128.9, 128.2, 127.6, 123.7, 116.8, 113.4, 71.0, 55.6, 55.2, 36.9, 27.3, 23.3, 14.1, one peak for aliphatic carbon was not found probably due to overlapping; IR (film): 1595, 1530, 1499, 1346, 1337, 1310, 1260, 1233, 1217, 1152, 1109, 1090, 1067, 1026, 1001, 831, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{31}N_3O_7S_2Na^+$ ([M+Na]$^+$) 608.1496. Found 608.1493.; HPLC AD3, H/IPA/EtOH = 86:9:5, flow rate = 1.0 mL/min, λ = 210 nm, 32.6 min (minor), 54.9 min (major).



The reaction was stirred for 48 h.

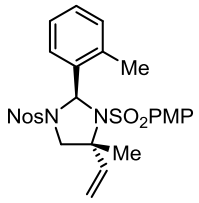
4e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 9.2 Hz), 7.23 (2H, d, J = 9.2 Hz), 7.10-7.14 (1H, m), 7.10 (2H, d, J = 9.2 Hz), 6.92-6.95 (4H, m), 6.54 (2H, d, J = 9.2 Hz), 6.39 (1H, dd, J = 18.2, 11.2 Hz), 6.09 (1H, s), 5.67 (1H, d, J = 18.2 Hz), 5.44 (1H, d, J = 11.2 Hz), 4.37 (1H, d, J = 10.2 Hz), 3.74 (3H, s), 3.39 (1H, d, J = 10.2 Hz), 2.81-2.87 (1H, m), 1.67-1.74 (2H, m), 1.04 (3H, d, J = 6.4 Hz), 1.00 (3H, d, J = 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 149.3, 145.1, 137.2, 135.9, 132.9, 129.4, 129.1, 129.0, 128.1, 127.5, 123.7, 116.5, 113.4, 76.6, 71.4, 55.6, 55.1, 46.7, 25.5, 24.7, 24.5; IR (film): 1530, 1348, 1337, 1310, 1258, 1152, 1111, 1082, 1016, 984, 837, 741, 692 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{31}N_3O_7S_2Na^+$ ([M+Na]$^+$) 608.1496. Found 608.1496.; HPLC IA3, H/EtOH = 95:5, flow rate = 0.5 mL/min, λ = 210 nm, 58.4 min (minor), 77.3 min (major).



The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4f**.

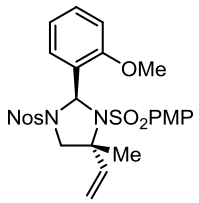
4f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.8 Hz), 7.32-7.36 (3H, m), 7.22-7.27 (4H, m), 7.17 (2H, d, J = 8.8 Hz), 7.14 (1H, dt, J = 7.2, 1.6 Hz), 6.94-7.01 (4H, m), 6.56 (2H, d, J = 9.2 Hz), 6.34 (1H, dd, J = 18.0, 11.2 Hz), 6.16 (1H, s), 5.66 (1H, d, J = 18.0 Hz), 5.48 (1H, d, J = 11.2 Hz), 4.18 (1H, d, J = 10.2 Hz), 3.74 (3H, s), 3.44 (1H, d, J = 10.2 Hz), 2.97 (1H, ddd, J = 13.5, 12.5, 4.7 Hz), 2.79 (1H, ddd, J = 13.4, 13.1, 4.1 Hz), 2.58 (1H, ddd, J = 13.5, 13.1, 5.5 Hz), 2.26 (1H, ddd, J = 13.4, 12.5, 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ

162.7, 149.4, 144.9, 140.9, 136.3, 132.2, 129.7, 129.2, 128.8, 128.7, 128.4, 128.2, 127.6, 126.5, 123.7, 117.4, 113.5, 70.8, 55.6, 55.1, 38.6, 31.4, one peak for aromatic carbon and one peak for aliphatic carbon were not found probably due to overlapping; IR (film): 1530, 1346, 1337, 1308, 1302, 1258, 1217, 1148, 1088, 1072, 1024, 1013, 982, 976, 831, 752, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{31}N_3O_7S_2Na^+$ ($[M+Na]^+$) 656.1496. Found 656.1496.; HPLC IA, H/EtOH = 85:15, flow rate = 1.0 mL/min, λ = 254 nm, 36.2 min (minor), 40.6 min (major).



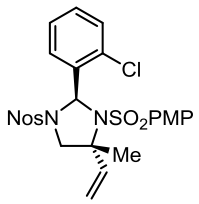
The reaction was stirred for 24 h.

4g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 9.2 Hz), 7.23 (2H, d, J = 9.2 Hz), 7.03 (2H, d, J = 9.2 Hz), 6.97-7.01 (2H, m), 6.51 (2H, d, J = 9.2 Hz), 6.44-6.48 (2H, m), 6.31 (1H, dd, J = 17.7, 11.1 Hz), 5.59 (1H, d, J = 17.7 Hz), 5.38 (1H, d, J = 11.1 Hz), 4.11 (1H, d, J = 10.0 Hz), 3.72 (3H, s), 3.46 (1H, d, J = 10.0 Hz), 2.48 (3H, s), 1.84 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 149.4, 145.1, 138.8, 138.6, 133.7, 133.0, 130.7, 129.1, 129.0, 127.5, 125.8, 123.7, 115.7, 113.4, 73.7, 67.6, 58.7, 55.6, 23.0, 19.0, one peak for aromatic carbon was not found probably due to overlapping; IR (film): 1530, 1346, 1312, 1260, 1152, 1088, 1072, 1024, 1015, 991, 750, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{27}N_3O_7S_2Na^+$ ($[M+Na]^+$) 580.1183. Found 580.1183.; HPLC IA3, H/EtOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 12.9 min (minor), 16.8 min (major).



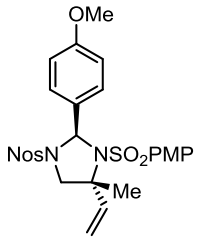
The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4h**.

4h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 9.0 Hz), 7.31-7.33 (1H, m), 7.31 (2H, d, J = 9.0 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.08-7.14 (1H, m), 6.87 (1H, ddd, J = 7.6, 7.2, 0.9 Hz), 6.54 (2H, d, J = 9.0 Hz), 6.30 (1H, s), 6.19 (1H, dd, J = 17.6, 10.8 Hz), 6.03 (1H, d, J = 8.4 Hz), 5.55 (1H, d, J = 17.6 Hz), 5.31 (1H, d, J = 10.8 Hz), 4.00 (1H, d, J = 9.2 Hz), 3.74 (3H, s), 3.60 (1H, d, J = 9.2 Hz), 3.07 (3H, s), 1.82 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 156.8, 149.3, 145.1, 139.6, 133.0, 132.9, 131.2, 129.2, 127.8, 123.3, 122.2, 120.4, 115.0, 113.0, 110.0, 76.2, 68.1, 59.3, 55.6, 54.2, 22.5; IR (film): 1337, 1252, 1150, 1067, 1049, 1026, 754, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{27}N_3O_8S_2Na^+$ ($[M+Na]^+$) 596.1132. Found 596.1132.; HPLC IC, H/EtOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 37.9 min (minor), 50.0 min (major).



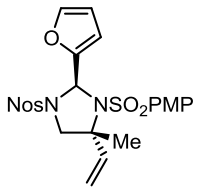
The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4i**.

4i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 9.0 Hz), 7.45 (2H, d, J = 9.0 Hz), 7.25 (2H, d, J = 9.2 Hz), 7.20-7.22 (1H, m), 7.08 (1H, td, J = 8.0, 1.8 Hz), 7.00-7.04 (1H, m), 6.87 (1H, d, J = 8.0 Hz), 6.60 (2H, d, J = 9.2 Hz), 6.46 (1H, s), 6.14 (1H, dd, J = 17.5, 10.9 Hz), 5.52 (1H, d, J = 17.5 Hz), 5.29 (1H, d, J = 10.9 Hz), 4.11 (1H, d, J = 10.0 Hz), 3.76 (3H, s), 3.69 (1H, d, J = 10.0 Hz), 1.88 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 149.7, 145.0, 138.4, 134.0, 133.0, 132.3, 132.0, 130.6, 130.2, 129.6, 127.9, 126.9, 123.8, 115.8, 113.4, 75.3, 68.1, 59.0, 55.7, 22.8; IR (film): 1595, 1530, 1497, 1346, 1312, 1260, 1219, 1152, 1107, 1088, 1063, 1013, 993, 910, 854, 816, 804, 762, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{24}N_3O_7S_2Na^+$ ([M+Na]$^+$) 600.0636. Found 600.0635.; HPLC ID3, H/EtOH = 75:25, flow rate = 1.0 mL/min, λ = 210 nm, 21.7 min (minor), 26.5 min (major).



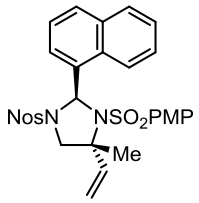
The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4j**.

4j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.8 Hz), 7.39 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 9.2 Hz), 6.91 (2H, d, J = 8.8 Hz), 6.63 (2H, d, J = 9.2 Hz), 6.49 (2H, d, J = 8.8 Hz), 6.18 (1H, s), 6.09 (1H, dd, J = 17.6, 11.0 Hz), 5.50 (1H, d, J = 17.6 Hz), 5.28 (1H, d, J = 11.0 Hz), 3.95 (1H, d, J = 10.2 Hz), 3.77 (3H, s), 3.73 (3H, s), 3.40 (1H, d, J = 10.2 Hz), 1.82 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 160.4, 149.5, 145.1, 138.6, 132.6, 129.8, 129.7, 128.6, 127.9, 123.8, 115.8, 113.5, 67.5, 58.6, 55.6, 55.5, 23.2, one peak for aromatic carbon and one peak for aliphatic carbon were not found probably due to overlapping; IR (film): 1337, 1252, 1165, 1150, 1088, 829, 754, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{26}H_{27}N_3O_8S_2Na^+$ ([M+Na]$^+$) 596.1132. Found 596.1130.; HPLC IB3, H/EtOH = 95:5, flow rate = 0.5 mL/min, λ = 210 nm, 130.5 min (minor), 143.9 min (major).



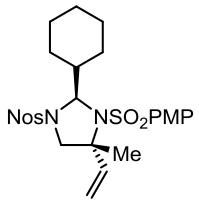
The reaction was stirred for 24 h.

4k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (2H, d, J = 9.0 Hz), 7.59 (2H, d, J = 9.0 Hz), 7.40 (2H, d, J = 9.2 Hz), 6.80 (1H, d, J = 1.8 Hz), 6.76 (2H, d, J = 9.2 Hz), 6.44 (1H, d, J = 3.2 Hz), 6.33 (1H, s), 6.15 (1H, dd, J = 3.2, 1.8 Hz), 6.06 (1H, dd, J = 17.6, 10.6 Hz), 5.43 (1H, d, J = 17.6 Hz), 5.25 (1H, d, J = 10.6 Hz), 3.88 (1H, d, J = 9.6 Hz), 3.81 (3H, s), 3.49 (1H, d, J = 9.6 Hz), 1.71 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 149.8, 149.6, 144.2, 143.0, 139.2, 132.6, 129.7, 128.2, 124.1, 115.6, 113.8, 112.2, 110.4, 70.1, 67.4, 58.9, 55.7, 22.8; IR (film): 1152, 1084, 1072, 750, 735 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{23}N_3O_8S_2Na^+$ ([M+Na]$^+$) 556.0819. Found 556.0819.; HPLC IA, H/EtOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 30.4 min (minor), 42.5 min (major).



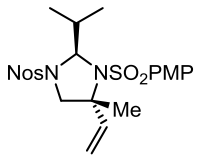
The reaction was stirred for 24 h. After column chromatography, further purification by GPC was conducted to give the pure **4l**.

4l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, br), 7.56 (1H, d, J = 8.4 Hz), 7.48 (2H, d, J = 9.0 Hz), 7.15-7.37 (4H, m), 6.93 (2H, d, J = 9.0 Hz), 6.89 (2H, d, J = 9.0 Hz), 6.61-6.63 (1H, m), 6.46 (1H, dd, J = 17.8, 11.2 Hz), 6.13 (2H, d, J = 9.0 Hz), 5.68 (1H, d, J = 17.8 Hz), 5.49 (1H, d, J = 11.2 Hz), 4.38 (1H, d, J = 10.4 Hz), 3.71 (1H, d, J = 10.4 Hz), 3.55 (3H, s), 2.00 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 148.9, 144.6, 138.0, 133.4, 131.3, 130.8, 130.5, 129.3, 128.2, 127.1, 126.2, 125.7, 124.7, 122.9, 122.8, 116.1, 112.7, 67.8, 58.2, 55.4, 23.5, two peaks for aromatic carbons and one peak for aliphatic carbon were not found probably due to overlapping; IR (film): 1530, 1344, 1335, 1258, 1152, 1070, 779, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{29}H_{27}N_3O_7S_2Na^+$ ([M+Na]$^+$) 616.1183. Found 616.1183.; HPLC IE3, H/EtOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 28.5 min (major), 35.8 min (minor).



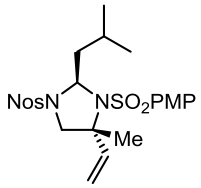
The reaction was stirred for 24 h.

4m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, J = 8.8 Hz), 7.86 (2H, d, J = 8.8 Hz), 7.74 (2H, d, J = 9.0 Hz), 6.98 (2H, d, J = 9.0 Hz), 5.43 (1H, d, J = 4.2 Hz), 5.13 (1H, d, J = 17.6 Hz), 4.96 (1H, dd, J = 17.6, 11.0 Hz), 4.80 (1H, d, J = 11.0 Hz), 3.93 (3H, s), 3.74 (1H, d, J = 12.8 Hz), 3.43 (1H, d, J = 12.8 Hz), 1.92-1.99 (1H, m), 1.72-1.76 (4H, m), 1.65 (3H, s), 0.88-1.25 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.1, 145.5, 139.2, 132.5, 130.8, 128.8, 124.4, 115.1, 113.8, 81.4, 66.8, 60.5, 55.8, 44.8, 30.2, 27.4, 26.3, 26.2, 26.1, 23.7; IR (film): 1530, 1346, 1335, 1306, 1258, 1157, 1088, 1013, 993, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{25}H_{31}N_3O_7S_2Na^+$ ([M+Na]$^+$) 572.1496. Found 572.1495.; HPLC IA, H/IPA = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 19.0 min (minor), 20.4 min (major).



The reaction was stirred for 24 h.

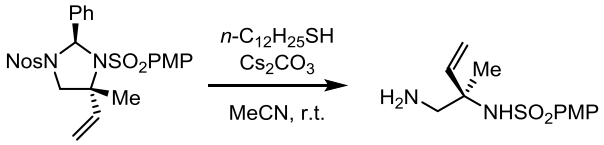
4n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, J = 9.2 Hz), 7.86 (2H, d, J = 9.2 Hz), 7.75 (2H, d, J = 9.2 Hz), 6.98 (2H, d, J = 9.2 Hz), 5.46 (1H, d, J = 4.1 Hz), 5.16 (1H, d, J = 17.4 Hz), 5.03 (1H, dd, J = 17.4, 10.5 Hz), 4.85 (1H, d, J = 10.5 Hz), 3.93 (3H, s), 3.79 (1H, d, J = 12.8 Hz), 3.45 (1H, d, J = 12.8 Hz), 2.40 (1H, dsept J = 6.9, 4.1 Hz), 1.67 (3H, s), 0.95 (3H, d, J = 6.9 Hz), 0.91 (3H, d, 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.1, 145.6, 138.9, 132.3, 130.9, 128.7, 124.4, 115.3, 113.9, 81.8, 66.9, 60.6, 55.8, 35.2, 23.6, 19.7, 17.0; IR (film): 1595, 1530, 1346, 1306, 1261, 1152, 1090, 1070, 1015, 997, 934, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{27}N_3O_7S_2Na^+$ ([M+Na]$^+$) 532.1183. Found 532.1184.; HPLC IA, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 24.9 min (minor), 27.1 min (major).



The reaction was stirred for 24 h.

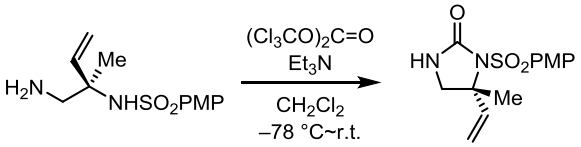
4o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (2H, d, J = 9.2 Hz), 7.85 (2H, d, J = 9.2 Hz), 7.72 (2H, d, J = 9.2 Hz), 6.97 (2H, d, J = 9.2 Hz), 5.58 (1H, dd, J = 11.0, 2.6 Hz), 5.13 (1H, d, J = 17.4 Hz), 5.00 (1H, dd, J = 17.4, 10.8 Hz), 4.86 (1H, d, J = 10.8 Hz), 3.93 (3H, s), 3.81 (1H, d, J = 13.0 Hz), 3.52 (1H, d, J = 13.0 Hz), 1.85 (1H, ddd, J = 14.0, 10.5, 2.6 Hz), 1.74 (1H, ddd, J = 14.0, 11.0, 3.2 Hz), 1.66 (3H, s), 1.49 (1H, dseptd, J = 10.5, 6.6, 3.2 Hz), 0.99 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.1, 145.3, 138.9, 132.7, 130.4, 128.7, 124.4, 115.2, 113.9, 75.8, 66.3, 59.2, 55.8, 46.3, 25.4, 24.6, 23.8, 21.0; IR (film): 1595, 1530, 1497, 1346, 1335, 1310, 1260, 1155, 1111, 1088, 1074, 997, 756, 739 cm^{-1}; HRMS (ESI) Calcd for $C_{23}H_{29}N_3O_7S_2Na^+$ ($[M+Na]^+$) 546.1339. Found 546.1340.; HPLC IA, H/IPA = 85:15, flow rate = 1.0 mL/min, λ = 210 nm, 17.3 min (minor), 18.8 min (major).

Derivatization of Cycloaddition Product 4b:



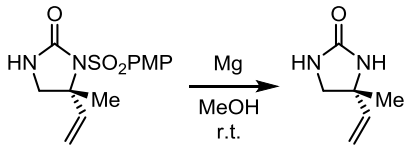
4b **5**

To a mixture of **4b** (52.1 mg, 0.096 mmol) and Cs_2CO_3 (312.8 mg, 0.96 mmol) in MeCN (1 mL) was slowly added *n*-$C_{12}H_{25}SH$ (46.3 μL, 0.192 mmol) at room temperature. After stirring for 8 h, the reaction was quenched by the addition of water and extractive work-up was performed with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (H/EtOAc = 2:1 to $CHCl_3$/MeOH = 5:1 as eluent) afforded **5** (18.9 mg, 0.07 mmol, 78% yield) as a white solid. **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.8 Hz), 6.94 (2H, d, *J* = 8.8 Hz), 5.68 (1H, dd, *J* = 17.6, 11.2 Hz), 5.16 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 11.2 Hz), 3.86 (3H, s), 2.68 (1H, d, *J* = 12.8 Hz), 2.60 (1H, d, *J* = 12.8 Hz), 1.24 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 141.2, 135.1, 129.4, 115.2, 114.0, 60.1, 55.7, 51.5, 22.2; IR (film): 1597, 1580, 1497, 1462, 1441, 1414, 1317, 1300, 1258, 1177, 1148, 1094, 1024, 995, 976, 920, 835, 800 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{19}N_2O_3S^+$ ([M+H]$^+$) 271.1111. Found 271.1112.



5 **S1**

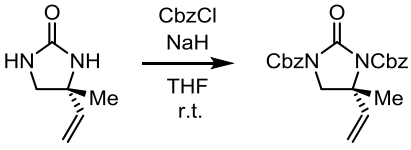
To a mixture of **5** (18.9 mg, 0.070 mmol) and Et_3N (28 μL, 0.21 mmol) in CH_2Cl_2 (800 μL) was slowly added a 47 mM CH_2Cl_2 solution of triphosgene (1.5 mL, 0.070 mmol) at –78 °C, and the mixture was warmed up to room temperature. After stirring for 45 min, H_2O was added to the reaction mixture and extractive work-up was performed with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$ only to $CHCl_3$/MeOH = 40:1 as eluent) gave the cyclic urea **S1** in 99% yield (20.5 mg, 0.069 mmol) as a white solid. **S1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* = 9.2 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 6.15 (1H, dd, *J* = 17.6, 11.0 Hz), 5.37 (1H, d, *J* = 17.6 Hz), 5.30 (1H, d, *J* = 11.0 Hz), 5.14 (1H, s), 3.86 (3H, s), 3.33 (1H, d, *J* = 9.2 Hz), 3.22 (1H, d, *J* = 9.2 Hz), 1.82 (3H, s).



S1 **6**

A mixture of **S1** (18.9 mg, 0.070 mmol) and magnesium powder (51 mg, 0.21 mmol) in MeOH (1.5 mL) was stirred at room temperature for 9 h. Then, the mixture was treated with a saturated aqueous solution of NH_4Cl at 0 °C to quench the reaction, and the aqueous phase was neutralized by 1N NaOH. Extractive work-up was performed with EtOAc three times, and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 40:1 to 20:1 as eluent) to give the chiral imidazolidinone **6** in 46% yield (4.04 mg, 0.032 mmol) as a white solid. **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, dd, J = 17.4, 10.8 Hz), 5.26 (1H, d, J = 17.4 Hz), 5.14 (1H, d, J = 10.8 Hz), 4.53 (1H, br), 4.48 (1H, br), 3.35 (1H, d, J = 8.8 Hz), 3.29 (1H, d, J = 8.8 Hz), 1.43 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 141.9, 113.6, 58.7, 53.3, 25.8; IR (film): 1697, 1643, 1487, 1445, 1290, 1260, 1152, 1092, 772, 752, 731 cm^{-1};HRMS (ESI) Calcd for $C_6H_{10}N_2ONa^+$ ([M+Na]$^+$) 149.0685. Found 149.0686.; $[\alpha]_D^{23} = -29.0$ (c = 0.3, $CHCl_3$).

The enantiomeric excess (ee) of **6** was determined after the following *N*-protection.



6 **S2**

To a mixture of **6** (4.04 mg, 0.032 mmol) in THF (1.0 mL) was slowly added NaH (60% dispersion in mineral oil, 7.0 mg, 0.16 mmol) at 0 °C. After stirring for 15 min at room temperature, a 1.0 M solution of CbzCl in THF (160 μL, 0.16 mmol) was introduced, and the stirring was kept for 3 h. The reaction was quenched by a saturated aqueous solution of NH_4Cl at 0 °C, and extractive work-up was conducted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (Hex/EtOAc = 20:1 to 8:1 as eluent) gave the protected cyclic urea **S2** in 60% yield (7.49 mg, 0.019 mmol) as a white solid. **S2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.44 (4H, m), 7.31-7.39 (6H, m), 5.96 (1H, dd, J = 17.5, 10.7 Hz), 5.30 (2H, s), 5.28 (2H, s), 5.22 (1H, d, J = 10.7 Hz), 5.20 (1H, d, J = 17.5 Hz), 3.69 (1H, d, J = 10.8 Hz), 3.56 (1H, d, J = 10.8 Hz), 1.64 (3H, s); HPLC IA3, H/EtOH = 80:20, flow rate = 1.0 mL/min, λ = 210 nm, 11.5 min (minor), 12.3 min (major).

Crystallographic Structure Determination:

Recrystallization of 4g: A single crystal of **4g** was obtained from CH_2Cl_2/EtOH system at room temperature. The single crystals thus obtained were mounted on CryoLoop. Data of X-ray was taken on a Rigaku CCD diffractometer (Saturn 724 with MicroMax-007) with Varimax Mo optics using graphite monochromated Mo-Kα radiation (λ = 0.71075 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.[12] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions. The crystallographic data were summarized in Tables S1.

Table S1. Crystal data and structure refinement for **4g**.

Identification code	shelxl	
Empirical formula	$C_{26}H_{26}N_3O_7S_2$	
Formula weight	556.62	
Temperature	103(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.080(2) Å	a= 90°.
	b = 20.648(4) Å	b= 107.503(3)°.
	c = 13.183(3) Å	g = 90°.
Volume	2616.8(10) $Å^3$	
Z	4	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	0.255 mm^{-1}	
F(000)	1164	
Crystal size	0.300 x 0.300 x 0.030 mm^3	
Theta range for data collection	3.030 to 27.480°.	
Index ranges	-13<=h<=11, -26<=k<=26, -13<=l<=17	
Reflections collected	21973	
Independent reflections	11711 [R(int) = 0.0413]	
Completeness to theta = 25.242°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11711 / 1 / 691	
Goodness-of-fit on F^2	0.963	
Final R indices [I>2sigma(I)]	R1 = 0.0475, wR2 = 0.1050	
R indices (all data)	R1 = 0.0807, wR2 = 0.1308	

Absolute structure parameter	0.04(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.549 and -0.590 e.Å^{-3}

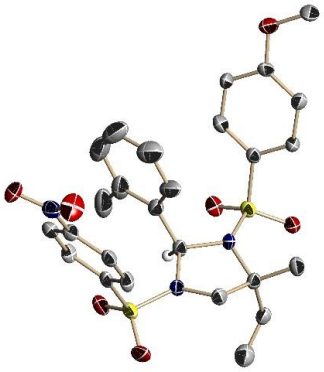


Figure S1. Molecular structure of **4g**. Calculated hydrogen atoms are omitted for clarity. Yellow = sulfur, blue = nitrogen, red = oxygen, black = carbon.

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List of Publications

(1) Ligand-enabled multiple absolute stereocontrol in metal-catalysed cycloaddition for construction of contiguous all-carbon quaternary stereocentres
Ohmatsu, K.; Imagawa, N.; Ooi, T. *Nature Chem.* **2014**, *6*, 47-51.

(2) Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand
Ohmatsu, K.; Kawai, S.; Imagawa, N.; Ooi, T. *ACS Catal.* **2014**, *4*, 4304-4306.

(3) Multiple Absolute Stereocontrol in Pd-Catalyzed [3 + 2] Cycloaddition of Oxazolidinones with Trisubstituted Alkenes Using Chiral Ammonium-Phosphine Hybrid Ligands
Imagawa, N.; Nagato, Y.; Ohmatsu, K.; Ooi, T. *Bull. Chem. Soc. Jpn.* **2016**, *accepted.*

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