Helical Poly(quinoxaline-2,3-diyl)s Bearing Boronyl Pendants as a Platform of New Chiral Catalysts and Ligands

Ryo Murakami

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Michinori Suginome at Kyoto University during 2013–2018. The studies are concerned with Helical Poly(quinoxaline-2,3-diyl)s Bearing Boronyl Pendants as a Platform of New Chiral Catalysts and Ligands.

First of all, the author wishes to express his great gratitude to Professor Michinori Suginome for his kind guidance, continuous support, and encouragement throughout this work. The author learned a lot of things from him including chemistry and way of life.

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Contents

General Introduction

Asymmetric molecular environments formed by chiral biomacromolecules play an extremely important role in various chemical processes including asymmetric reactions, molecular recognition, and biomolecular interactions. In living organisms and even in in vivo reactions, polypeptides precisely arrange various functional groups in three-dimensional ways to form an asymmetric environment, which enables highly stereoselective and substrate specific asymmetric reactions.[1] However, the use of biomacromolecules as an asymmetric catalyst is very limited in terms of the diversity of chemical transformations, because of their poor reaction and substrate generality.[2] In addition, since nature supplies only one enantiomer of each building block, it is virtually impossible to construct a mirror-image asymmetric environment, which provides enantiomeric products in asymmetric reactions.

On the other hand, small-molecule-based chiral catalysts have been rapidly developed in these decades and widely used in laboratory synthesis and industrial production. In the small molecular catalysts, essential structural components, e.g. catalytically active sites, coordination sites, sterically demanding groups, and functional groups for secondary interaction, are installed on the small chiral molecular frameworks. This design principle along with the availability of both enantiomeric forms allows development of various chiral ligands and catalysts that exhibit wide reaction/substrate scope.[3] On the other hand, the compactness of the molecular scaffolds often limits their ability of enantiodiscrimination. More importantly, structural modification of those small-molecular catalysts often encounters significant change of the conformation of core chiral scaffolds, which makes the optimization process laborious and less rationale. It would be highly desirable if structurally robust, easily modifiable molecular scaffolds for general catalyst design are established on the basis of synthetic macromolecular scaffolds by taking advantages of both small molecular and biomacromolecular scaffolds.

Although polymer-based chiral catalysts have attracted much attention, their molecular design mostly relies on the attachment of well-established small-molecule-based chiral catalysts on the common polymeric scaffolds such as polystyrene and polymethacrylates.[4] In these polymer catalysts, the macromolecular scaffolds were just utilized as an insoluble support to make them insoluble to the reaction media without any positive contribution to catalytic activity and enantioselectivity. On the other hand, challenges to utilize chiral macromolecular scaffolds as exclusive source of chirality in asymmetric reactions have been commenced in these decades.[5] Helical macromolecules have an extremely large chiral steric hindrance and are expected not only

to enable excellent stereocontrol in asymmetric reactions, but also to improve the catalytic activity and stability. The helically chiral polymer could be synthesized by their enantioselective synthesis, and helical chirality was affected by external stimuli such as solvent, temperature, and pressure.[6] These features make helical macromolecules highly attractive as the chiral molecular scaffolds utilized as a chiral source in asymmetric reactions. However, the helically chiral polymer-based catalyst has yet been developed, mainly because of the difficulties in perfect induction of single-handed helical structure as well as in incorporation of catalytically active sites in their synthesis. It is essential to develop a new helical polymer skeleton that enables complete control of helical chirality with easy introduction of catalytically active groups while maintaining the rigid helical structure.

Poly(quinoxaline-2,3-diyl)s (hereafter PQX) synthesized by living polymerization of *o*-diisocyanobenzenes has a robust but dynamic helical structure. This polymer takes pure single-handed helical structure by introducing chiral side chains, and the helical chirality was completely inverted by changing the solvents.[7] Recently, it has been reported that helically chiral **PQXphos** bearing coordinating phosphine groups served as a highly enantioselective ligand for palladium catalysts (Figure 1).[8] Taking advantage of the polymeric scaffolds, the PQX-based catalysts allowed their reuse without noticeable decrease in catalyst activity and enantioselectivity.[8b] Remarkably, improvement of enantioselectivity[8c] and rate acceleration[8d] in comparison to the

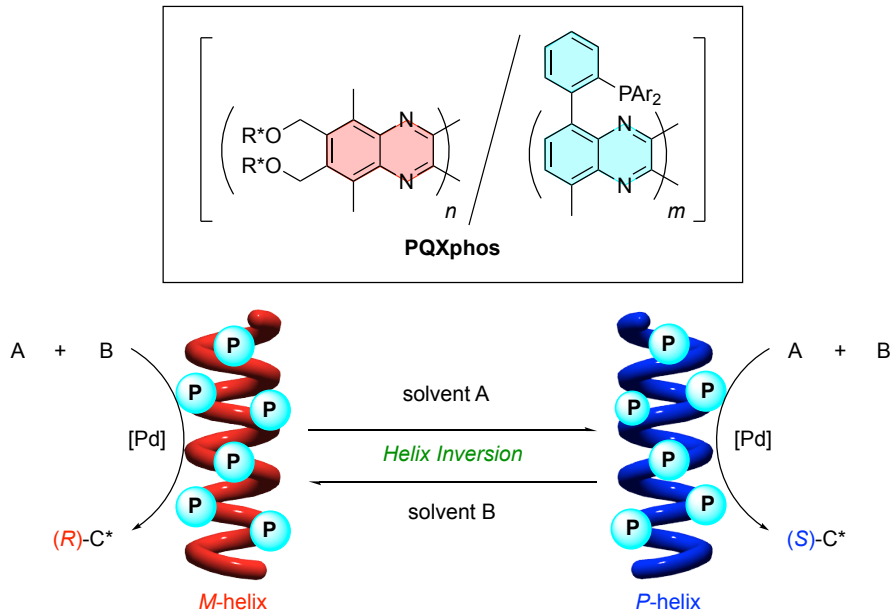

Figure 1. Pd-catalyzed asymmetric reactions using chirality-switchable PQX-based phosphine ligand (**PQXphos**).

corresponding small-molecular catalysts was also observed. The solvent-dependent helix inversion enabled the development of chirality-switchable ligands for transition-metal catalysis.[8b–d,f,g,h] However, the use of helically chiral scaffold of PQX was so far limited to the monodentate phosphine (**PQXphos**) and bidentate bypyridyl (**PQXbpy**) ligands.[9] It is highly desirable to develop various asymmetric catalysts by introducing other catalytically active groups on the PQX scaffolds. In addition, helical chirality induction by host-guest interaction, instead of covalently bound chiral side chains, would open up a new possibility of PQX as a chiral-guest-responsive chiral catalyst.

The author became interested in installation of boronic acid functionality[10] to the PQX skeleton, which enables various chemical modifications. A boronyl group can be easily converted to other functional groups by coupling reactions such as Suzuki–Miyaura cross coupling reaction. Boronic acids also allow reversible introduction of functionalities on their boron atom in their reactions with chiral molecules such as sugars and amino acids by Lewis acid-base interaction as well as through condensation reactions.[11] PQX bearing boronyl pendants is therefore expected to serve as a platform of new helically chiral catalysts by converting the boronic acid moiety to catalytically active site or by utilizing chiral guests to control the helical chirality through host-guest interaction.

4-Dimethylaminopyridine (DMAP) is widely used as a nucleophilic catalyst,[12] which exhibits high nucleophilicity and a large stabilizing effect of an acylpyridinium intermediate. In 1997, Fu[13] and Kawabata[14] independently reported kinetic resolution of secondary alcohols catalyzed by the chiral DMAP derivatives. Several chiral DMAP derivatives have been developed and applied for kinetic resolution of secondary alcohols and asymmetric acyl migration reactions such as Steglich rearrangement.[15] It is expected that highly sterically demanding helical PQX would serve as a chiral scaffold for highly enantioselective nucleophilic organocatalyst by attaching nucleophilic 4-aminopyridine pendants.

On the other hand, Yashima and Okamoto have reported that helical chirality of polyacetylene bearing acceptor sites such as carboxylic acid,[16] crown ether[17] and boronic acid[18] can be induced by chiral guests. However, the perfect helical chirality induction was not achieved, and this concept has never been applied to asymmetric catalysis.[19] The author envisioned that complete helical chirality would be induced to PQX having catalytically active sites by incorporating boronyl pendants, which serve as receptor sites for chiral guests.

In this thesis, the author describes the development of helically chiral nucleophilic organocatalysts bearing 4-aminopyrid-3-yl pendants and chiral-guest-responsive helical polymer

catalyst by modification of poly(quinoxaline-2,3-diyl)s bearing boronyl pendants.

In chapter 1, the author describes the synthesis of a helical polymer-based nucleophilic catalyst bearing 4-amino-pyrid-3-yl pendants and its application to asymmetric Steglich rearrangement (Figure 2). (*P*)-(*R*)-**PQXboh** bearing a boronic acid moiety at the 5-position of the quinoxaline ring was newly synthesized. Subsequently, (*P*)-(*R*)-**PQXmdpp** was synthesized by Suzuki–Miyaura cross coupling of (*P*)-(*R*)-**PQXboh** with 3-bromo-4-aminopyridine derivatives. (*P*)-(*R*)-**PQXmdpp** takes right-handed helical structure, which is induced by a covalently attached chiral side chains. The Steglich rearrangement of *O*-acylated azlactone was carried out using (*P*)-(*R*)-**PQXmdpp**, giving *C*-acylated isomer with up to 97% ee. This polymer catalyst showed high catalytic activity and remarkably low catalyst loading down to 0.1 mol%. Furthermore, both the reaction yield and enantioselectivity did not drop at all during at least 11 times reuse. The highly sterically demanding polymer catalyst mediated intramolecular acyl transfer selectively over intermolecular acyl transfer, in contrast to the reported asymmetric Steglich reactions using small-molecular chiral catalysts.

In chapter 2, the author describes the kinetic resolution of secondary alcohols using chirality-switchable helically chiral nucleophilic organocatalyst (Figure 3). In the presence of (*P*)-(*R*)-**PQXdpap** bearing 4-(dipropylamino)pyrid-3-yl pendants, kinetic resolution of racemic 1-(1-naphthyl)ethanol (**1**) with acetic anhydride proceeded in toluene at –60 °C, giving (*R*)-**1** with >99% ee at 54% conversion (selectivity factor $s > 56$). Inversion of the helical chirality of (*P*)-(*R*)-**PQXdpap** in 1,1,2-trichloroethane-based solvent afforded (*M*)-(*R*)-**PQXdpap**, which gave

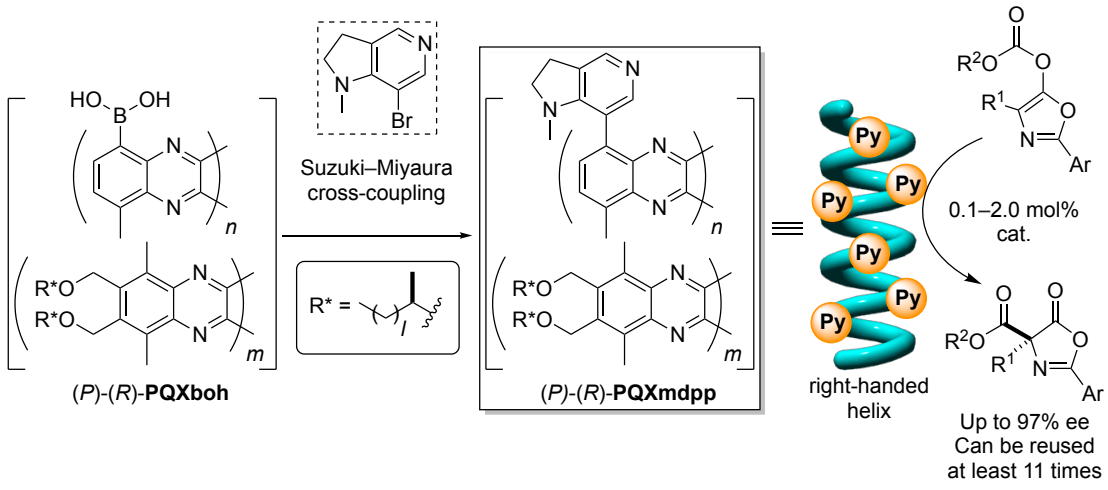

Figure 2. The synthesis of helically chiral PQX bearing 4-amino-pyrid-3-yl pendants (**PQXdmap**) and its application to asymmetric Steglich rearrangement.

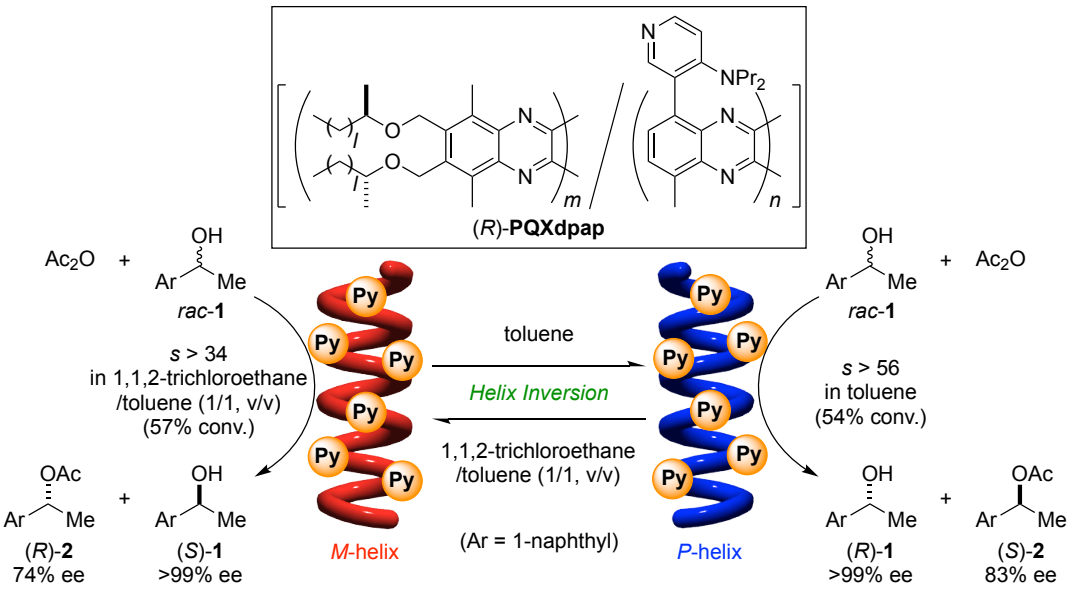

Figure 3. Kinetic resolution of secondary alcohols using chirality-switchable helically chiral nucleophilic organocatalyst (**PQXdpap**).

the opposite enantiomer (*S*)-**1** with >99% ee at 57% conversion (*s* > 34). These results demonstrate utility of the PQX-based chirality-switchable catalyst in asymmetric kinetic resolution. To the best of the author's knowledge, there was no report on switching of enantiodiscrimination by inverting the catalyst chirality in kinetic resolution processes.

In chapter 3, the author describes chirality-amplifying induction of single-handed helix by chiral guests to macromolecular chiral catalysts bearing boronyl pendants as receptor sites (Figure 4). Enantioenriched chiral guests (x% ee) induced screw-sense excess (se, y%) to PQX bearing boronyl groups with higher se than ee of the chiral guests (x < y) based on the majority-rule-effect.[20] Thus induced chiral polymer catalyst **PQXphos** exhibited high enantioselectivity in asymmetric palladium-catalyzed silaboration of *meso*-methylenecyclopropane[21] with up to 92% ee.

In summary, the author describes the synthesis and utilization of new PQX derivatives **PQXboh** bearing boronyl pendants in creation of helically chiral PQX-based nucleophilic organocatalysts **PQXmdpp** and **PQXdpap**, and chiral-guest-responsive helical polymer catalysts **PQXphos**, whose chirality induction relies on the chiral guests. Helically chiral PQX bearing 4-amino-pyrid-3-yl pendants showed not only high catalytic activity and enantioselectivity, but also high reusability and switching of enantioselectivity. The chiral-guest-responsive **PQXphos** showed high enantioselectivities in palladium-catalyzed silaboration through induction of single-

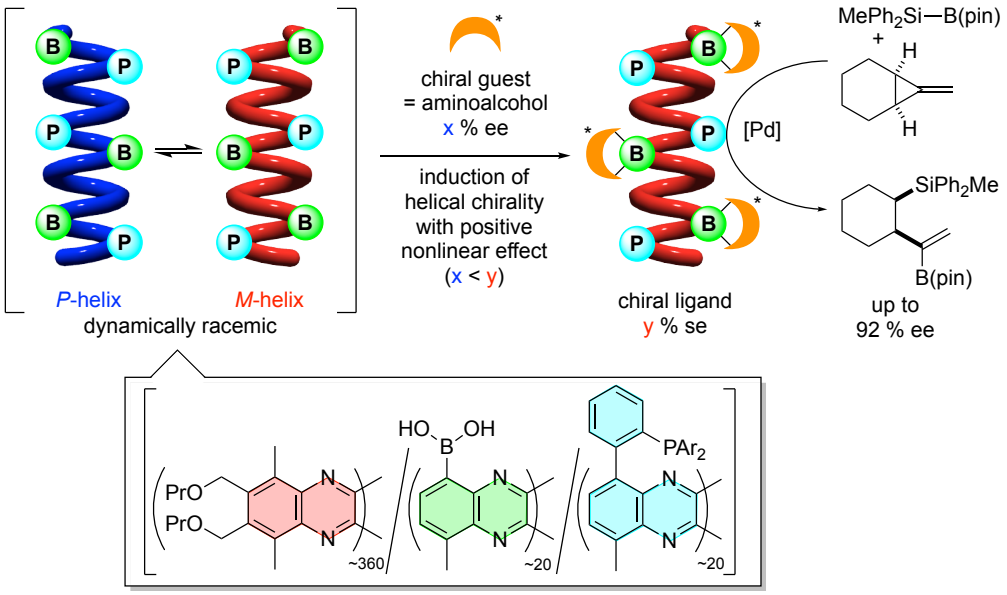

Figure 4. Chirality-amplifying induction of single-handed helix by chiral guests and its application for Pd-catalyzed silaboration of *meso*-methylenecyclopropane.

handed screw-sense by using chiral aminoalcohols as chiral guests. The chiral induction occurred through efficient amplification of chirality on the basis of the majority-rule-effect. It is expected that PQX bearing boronyl pendants will serve as a versatile platform for creation of PQX-based polymer catalysts, leading to the establishment of asymmetric amplification reaction system where even chiral sources of low enantiopurity provide high enantioselectivities in asymmetric catalysis.

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Chapter 1

Single-Handed Helical Poly(quinoxaline-2,3-diyl)s Bearing Achiral 4-Aminopyrid-3-yl Pendants as Highly Enantioselective, Reusable Chiral Nucleophilic Organocatalysts in the Steglich Reaction

ABSTRUCT

Helically chiral poly(quinoxaline-2,3-diyl)s bearing 4-aminopyrid-3-yl pendants were synthesized as new helical-polymer-based chiral nucleophilic organocatalysts. The obtained chiral nucleophilic polymer catalysts exhibited high catalytic activity, enantioselectivity, and reusability in asymmetric Steglich rearrangement of oxazolyl carbonate to *C*-carboxyazlactone. The polyquinoxaline-based, helically chiral DMAP catalyst mediated intramolecular acyl transfer selectively, by contrast with known small-molecule-based chiral organocatalysts, which also mediate intermolecular acyl transfers.

Introduction

Polymer-based immobilized chiral catalysts, in which conventional small-molecule-based chiral catalysts are embedded in common polymers, attract much interest from the viewpoint of practical asymmetric synthesis because they are easily separable from the reaction mixtures and reusable by virtue of the insoluble nature of the polymer backbones.[1] By contrast, increasing attention is being focused on utilization of the helical macromolecular scaffold[2] as a source of chirality in catalytic asymmetric reactions.[3] In addition to the separability/reusability issues, the macromolecular chiral scaffold is highly expected to serve as huge chiral steric shielding, which could be superior to small-molecule-based chiral structures. However, there has been only limited success in the use of helical macromolecules as the scaffolds of chiral catalysts. There are some successes in the use of helically chiral poly(arylacetylene)s bearing chiral organocatalytic pendants such as cinchona alkaloids,[4] proline-based groups,[5] and oligopeptides.[6] In these cases, the enantioselectivities mainly arise from the chiral pendants with relatively minor contribution of macromolecular chirality. There is another class of polymer-based chiral catalysts whose enantiodiscrimination relies solely on the main-chain chirality of helical macromolecules with attachment of achiral ligand/organocatalytic pendants.[7] This approach is extremely attractive because it only requires the introduction of simple, achiral ligand/organocatalytic pendants, although there has been no highly enantioselective macromolecular catalyst within this class.

In 2009, Suginome and coworkers established poly(quinoixaline-2,3-diyl)s (hereafter PQX) as the first chiral macromolecular scaffolds that achieve high enantioselectivities (up to 98% ee) without the assistance of additional chiralities in the pendants.[8] In this system, attachment of achiral *o*-(diarylphosphino)phenyl pendants allows high enantioselectivity in palladium-catalyzed hydrosilylation of styrenes. Subsequently, they could successfully apply the catalysts to several palladium-catalyzed reactions with high enantioselectivity.[9] Moreover, they have shown that the induction of helical chirality largely depends upon the nature of solvents:[10] the helicity can be inverted between two solvents such as chloroform/1,1,2-trichloroethane,[10a,b] cyclopentyl methyl ether/*t*-butyl methyl ether,[10c] and even *n*-octane/cyclooctane.[10d] The author's current interest is to verify the extensibility of PQX as a general chiral platform onto which various achiral pendants are attached to gain high enantioselectivities in various asymmetric reactions.

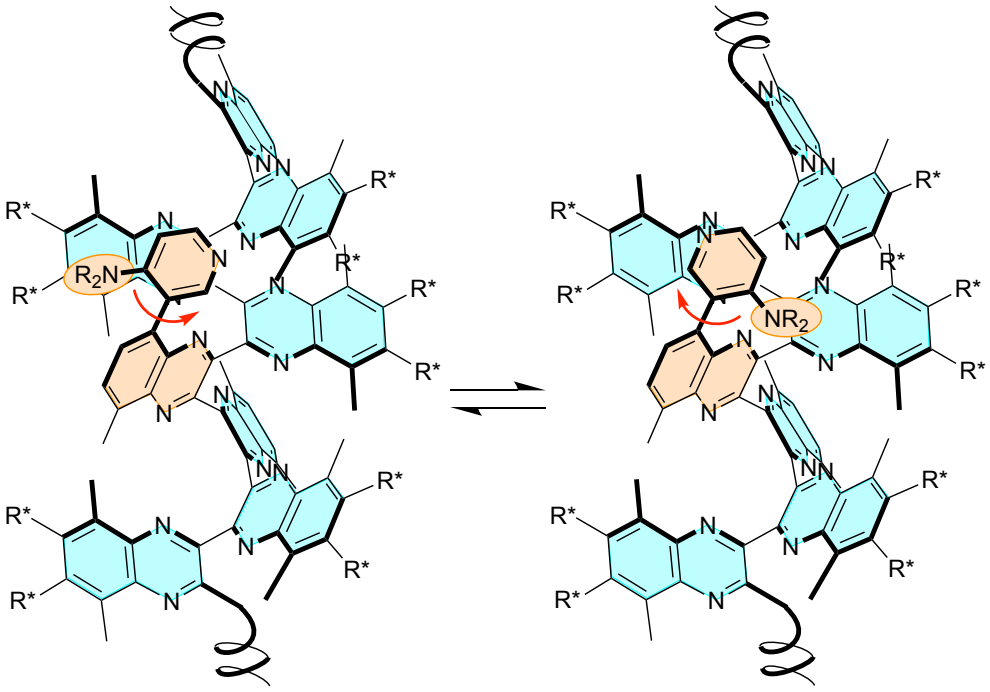
Incorporation of pyridyl pendants is highly attractive, because they serve not only as a ligand in transition-metal catalysts[11] but also as chiral bases or nucleophilic organocatalysts.[12,13] In this

paper, the author reports the synthesis of a series of PQXs bearing 4-aminopyrid-3-yl pendants and their use in asymmetric Steglich rearrangement.[13–15] High catalytic activity of one of the derivatives was found, which allows to attain high enantioselectivity with remarkably low catalyst loading and to reuse the catalyst at least 11 times without any drop of selectivity or catalytic activity.

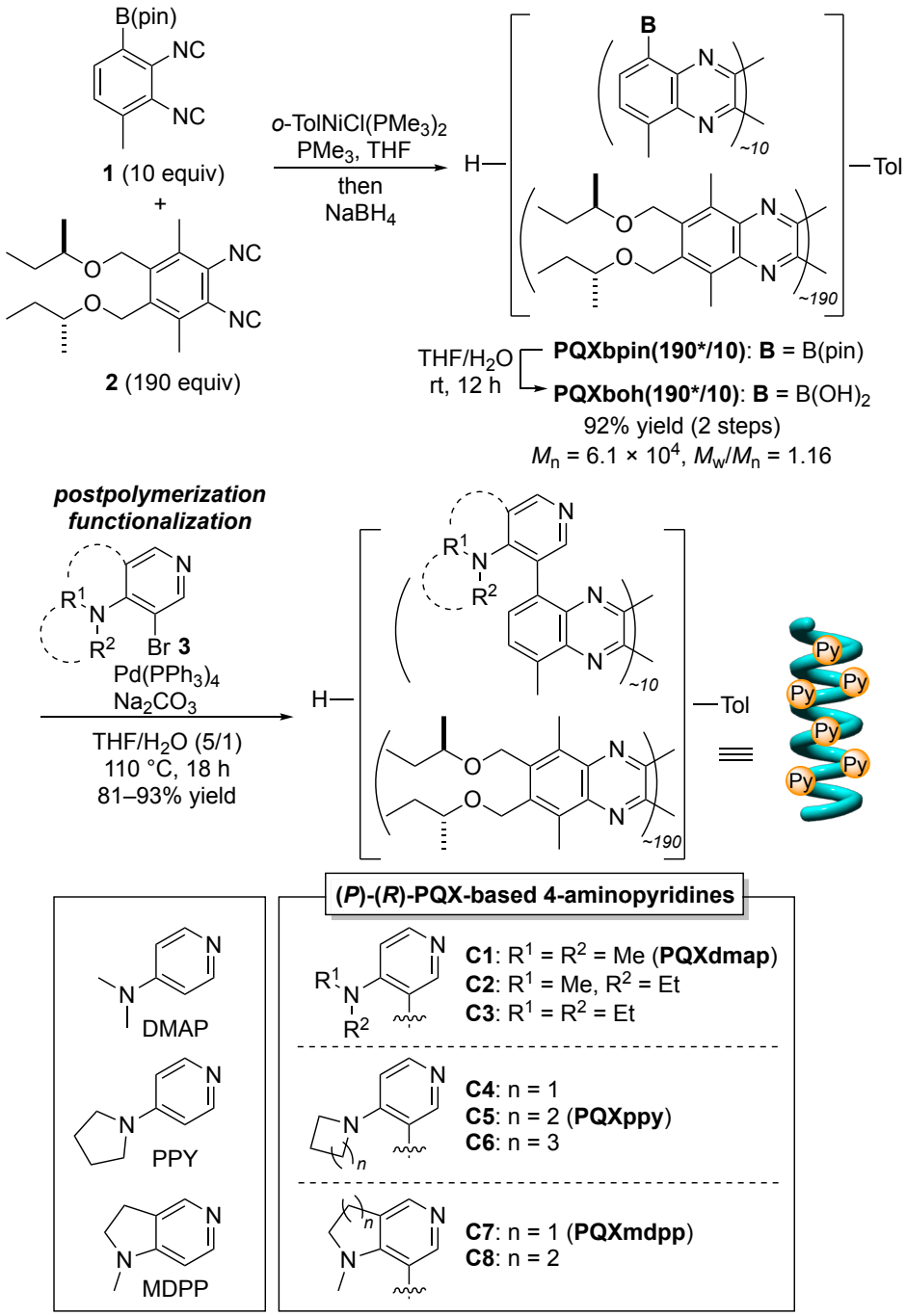
Results and Discussion

Molecular design is shown in Scheme 1. 4-Amino-substituted pyrid-3-yl groups are introduced at the 5-position of the quinoxaline rings in the helical backbone of PQX, of which right-handed (*P*-) helicity is induced by the (*R*)-chiral side chains. The axial chirality between the pyridyl and the quinoxaline rings is not fixed and induced thermodynamically by the *P*-helical structure of PQX. Their synthesis was performed by postpolymerization functionalization of **PQXboh** bearing a boronyl pendant at the 5-position of the quinoxaline ring (Scheme 2). Synthesis of the corresponding *ortho*-diisocyanobenzene monomer **1** bearing a B(pin) pendant is shown in the Supporting Information (SI). In the presence of an organonickel initiator, living random copolymerization of **1** and chiral monomer **2**, which has (*R*)-2-butoxymethyl side chains, gave

Scheme 1. (*P*)-PQX-based Nucleophilic Organocatalyst



Scheme 2. Synthesis of Polyquinoxaline-based Helically Chiral Nucleophilic Catalysts



(*P*)-(*R*)-**PQXbpin** bearing 10 boronyl units along with 190 chiral units on average. Hydrolysis of the B(pin) group on the quinoxaline ring proceeded smoothly in a mixture of THF/H_2O, giving (*P*)-(*R*)-**PQXboh**. (*P*)-(*R*)-**PQXdmap** (**C1**) bearing the DMAP pendant was obtained in high yield through Suzuki–Miyaura cross-coupling of (*P*)-(*R*)-**PQXboh** with 3-bromo-4-dimethylaminopyridine, which is readily available by bromination of the corresponding 4-

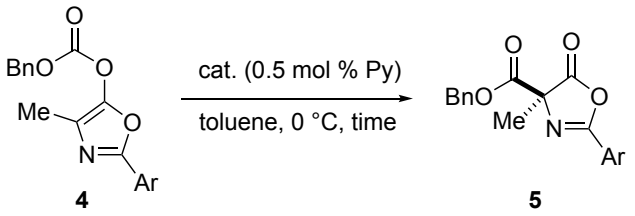
(dimethylamino)pyridine. Conversion of the boronyl group on **PQXboh** was confirmed by ^{1}H NMR spectroscopy. PQX derivatives bearing a 4-dialkyl amino group (**C2** and **C3**), cyclic amino group (**C4**, **PQXppy** (**C5**), and **C6**), and fused cyclic amino group (**PQXmdpp** (**C7**) and **C8**)) were also prepared under similar reaction conditions.

The obtained (*P*)-(*R*)-PQX derivatives were used in asymmetric Steglich rearrangement,[13,15] in which oxazolyl carbonates isomerize to *C*-carboxyazlactones forming a quaternary stereocenter (Table 1). In the presence of (*P*)-(*R*)-**PQXdmap** (**C1**) (0.5 mol % pyridyl pendants), rearrangement of oxazolyl carbonate **4Aa** proceeded at 0 °C. In the screening of reaction solvent, toluene showed the higher enantioselectivity than chloroform and THF, giving **5Aa** in 92% yield with 62% ee (entry 1, see SI). Replacement of the methyl group(s) on the amino group of catalyst **C1** with ethyl group(s) (**C2** and **C3**) decreased both catalytic activity and enantioselectivity (entries 2 and 3). PQXs bearing azetidino (**C4**) or pyrrolidino group **PQXppy** (**C5**) showed high catalytic activities with moderate enantioselectivities (entries 4 and 5), whereas **C6** bearing piperidino group exhibited low catalytic activity and enantioselectivity (entry 6). PQXs bearing a fused cyclic amino group also served as efficient catalysts (entries 7 and 8). In these series, **PQXmdpp** (**C7**) bearing *N*-methyldihydropyrrolopyridine (MDPP) pendants afforded the highest catalytic activity and enantioselectivity. These results clearly suggest that higher coplanarity of the dialkylamino moiety and the pyridine ring enhances both the catalytic activity and enantioselectivity. The effect of the substituents in 2-methyloxazolyl carbonates **4** on the reactivity and enantioselectivity was also evaluated using (*P*)-(*R*)-**C7**. The presence of an electron-withdrawing group on the benzene ring significantly enhanced the reactivity of the substrate (entries 9 and 10). The ee of the product at 0 °C was improved to 75% ee by using **4Ca** bearing a 4-trifluoromethyl group.

According to the previous works,[9,10] solvent-dependent helix inversion of **C7** to reverse the enantioselectivity was also conducted.[13i] It was found that the helical chirality of (*P*)-(*R*)-**C7** could be completely changed to (*M*)-helix in a 1:1 mixture of toluene and 1,1,2-trichloroethane (see SI). Thus obtained (*M*)-(*R*)-**C7** afforded enantiomeric product **5Ca** in 78% yield but with lower enantiomeric excess (45% ee), probably because of negative solvent effect of 1,1,2-trichloroethane used as a cosolvent in the reaction (entry 11).

The catalytic activities of **PQXdmap** (**C1**) and **PQXmdpp** (**C7**) were compared by NMR experiments at 24 °C in benzene-d_6 (see SI). In terms of the half-life of **4Aa** ($t_{1/2}$), **C7** showed 9-fold higher catalyst activity ($t_{1/2}$ = 27 min) than **C1** ($t_{1/2}$ = 247 min). It should be noted that $t_{1/2}$ of **C7** was identical to that of MDPP in spite of the presence of the highly sterically demanding

Table 1. Asymmetric Steglich Rearrangement Using (*P*)-(*R*)-PQXdmap Derivatives[a]



4 **5**

entry	cat.	Ar	time (h)	% yield[b]	% ee[c]
1	**C1**	4-$MeOC_6H_4$ (**4Aa**)	35	92 (**5Aa**)	62
2	**C2**	**4Aa**	96	84 (**5Aa**)	60
3	**C3**	**4Aa**	120	90 (**5Aa**)	52
4	**C4**	**4Aa**	12	89 (**5Aa**)	62
5	**C5**	**4Aa**	12	96 (**5Aa**)	60
6	**C6**	**4Aa**	300	77[d] (**5Aa**)	42
7	**C7**	**4Aa**	3	99 (**5Aa**)	69
8	**C8**	**4Aa**	11	83 (**5Aa**)	50
9	**C7**	4-ClC_6H_4 (**4Ba**)	1	91 (**5Ba**)	72
10	**C7**	4-$CF_3C_6H_4$ (**4Ca**)	1	88 (**5Ca**)	75
11[e]	**C7**	4-$CF_3C_6H_4$ (**4Ca**)	1	78 (**5Ca**)	−45

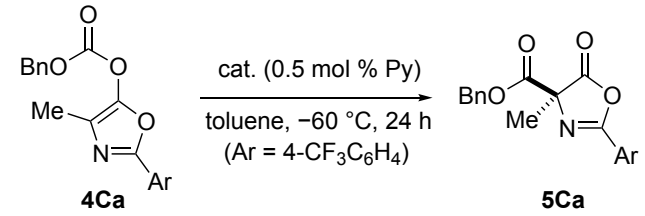
[a]**4Aa** (0.3 mmol), and (*P*)-(*R*)-**PQXdmap** derivatives (0.5 mol % pyridyl pendants) were stirred in solvent (6.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral SFC analysis. [d]88% conversion. NMR yield. [e]The reaction was carried out using (*M*)-(*R*)-**C7** in a 1:1 mixture of toluene and 1,1,2-trichloroethane.

helical polymer backbone.

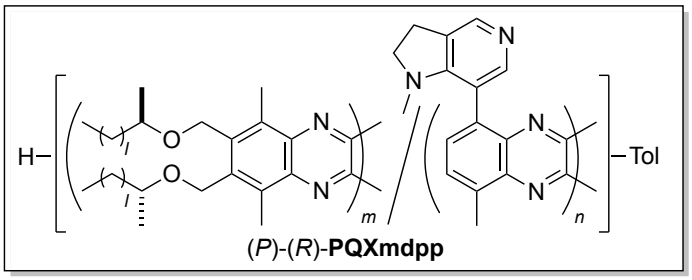
Based on these results, further optimization of catalyst structure was performed at −60 °C, keeping the polymerization degree of the catalysts ($m + n = 200$, Scheme 3). With (*P*)-(*R*)-**C7**, ee of the product was improved to 88% by lowering the reaction temperature to −60 °C. Under the same reaction conditions, (*P*)-(*R*)-**C9** ($n = 10$) bearing (*R*)-2-octyloxymethyl side chains, which induces the right-handed structure more efficiently,[10b] showed higher enantioselectivity, giving **5Ca** with 90% ee. Increase of the ratio of the pyridyl units ((*P*)-(*R*)-**C10**, $n = 20$) resulted in a little decrease in enantioselectivity (88% ee). Finally, 91% ee was obtained by using (*P*)-(*R*)-**C11**, in which less pyridyl units ($n = 5$) are contained.

Under the optimized conditions using (*P*)-(*R*)-**C11**, substrate structure was varied at −60 °C by

Scheme 3. Optimization of the Polymer Structure



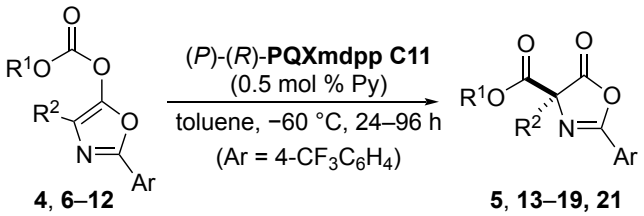
(*P*)-(*R*)-**C7** (*l* = 1, *m* = 190, *n* = 10): 83% yield, 88% ee
(*P*)-(*R*)-**C9** (*l* = 5, *m* = 190, *n* = 10): 88% yield, 90% ee
(*P*)-(*R*)-**C10** (*l* = 5, *m* = 180, *n* = 20): 91% yield, 88% ee
(*P*)-(*R*)-**C11** (*l* = 5, *m* = 195, *n* = 5): 95% yield, 91% ee



using oxazolyl carbonates bearing a 4-trifluoromethylphenyl group (Table 2). As for the effect of the acyl groups, benzyl, *p*-substituted benzyl, and 1-naphthyl groups afforded high enantioselectivities (entries 1–4). Although methylcarbonate **4Ce** showed lower ee (entry 5), 2-methoxyethyl carbonate **4Cf** gave high ee (entry 6). Substituents on the oxazole core were varied using benzyl carbonates. Oxazolyl carbonates bearing alkyl groups such as ethyl, propyl, and isobutyl groups afforded the corresponding products with 94%, 92%, and 86% ee, respectively (entries 7–9). Benzyl, methylthioethyl, and allyl substituted carbonates also afforded the corresponding products in high yields with high enantioselectivities (entries 10–12). It is noteworthy that gram-scale synthesis of allyl substituted **18Ca** needed catalyst loading of 0.1 mol % of (*P*)-(*R*)-**C11**, giving 1.07 g of **18Ca** in 88% yield with 92% ee (entry 13). To the author's knowledge, there has been no single example of the use of less than 0.5 mol % of chiral nucleophilic catalyst in the asymmetric Steglich rearrangement.[13h] Phenyl substituted **12Ca**, which resulted in low conversion at −60 °C, was converted to **19Ca** in 79% yield at 0 °C with low enantioselectivity (entry 14). On the other hand, ethyl substituted oxazole bearing 1-naphthyl methyl carbonate **6Cd** showed highest enantioselectivity, giving product **21Cd** in 99% yield with 97% ee (entry 15). The synthesized *C*-carboxyazlactone **18Ca** was easily converted to dipeptide and α-allylserine derivatives (Figure 1).

Taking advantage of using a polymer scaffold, reuse of **PQXmdpp C11** was demonstrated (Scheme 4). After the initial reaction of **11Ca** with 1.0 mol % (*P*)-(*R*)-**C11**, acetonitrile was added

Table 2. Scope of the Substrate[a]



entry	substrate	R^1	R^2	% yield[b]	% ee[c]
1	**4Ca**	Bn	Me	91 (**5Ca**)	92
2	**4Cb**	4-$MeC_6H_4CH_2$	Me	88 (**5Cb**)[d]	90
3	**4Cc**	4-$CF_3C_6H_4CH_2$	Me	72 (**5Cc**)	92
4	**4Cd**	1-naphthylmethyl	Me	98 (**5Cd**)	94
5	**4Ce**	Me	Me	57 (**5Ce**)[d]	71
6	**4Cf**	$MeOCH_2CH_2$	Me	71 (**5Cf**)[g]	90
7	**6Ca**	Bn	Et	96 (**13Ca**)	94
8	**7Ca**	Bn	Pr	86 (**14Ca**)	92
9	**8Ca**	Bn	^{i}PrCH_2	79 (**15Ca**)	86
10	**9Ca**	Bn	Bn	93 (**16Ca**)	91
11	**10Ca**	Bn	$MeSCH_2CH_2$	85 (**17Ca**)	87
12	**11Ca**	Bn	allyl	82 (**18Ca**)	93
13[e]	**11Ca**	Bn	allyl	88 (**18Ca**)	92
14[f]	**12Ca**	Bn	Ph	79 (**19Ca**)	18
15	**6Cd**	1-naphthylmethyl	Et	99 (**21Cd**)	97

[a]Oxazolyl carbonate (0.1 mmol), and **PQXmdpp** (0.5 mol % pyridyl pendants) were stirred in solvent (2.0 mL) at −60 °C. [b]Isolated yield. [c]Determined by chiral SFC analysis. [d]>95% conversion. NMR yield. [e]**11Ca** (3.0 mmol), and **PQXmdpp** (0.1 mol % pyridyl pendants) were stirred in solvent (3.0 mL) at −60 °C. [f]Reaction at 0 °C for 48 h. [g]0.1 M, 2.0 mol % of catalyst.

to the reaction mixture to precipitate (*P*)-(*R*)-**C11**. Centrifugation of the resulting suspension under air allowed recovery of (*P*)-(*R*)-**C11** along with separation of the product in the solution. After drying under vacuum, the recovered (*P*)-(*R*)-**C11** could be reused 11 times without any fall in the catalytic activity and enantioselectivity. On average, 95% (*P*)-(*R*)-**C11** was recovered in each cycle.

To elucidate the reaction mechanism of the Steglich rearrangement in the presence of

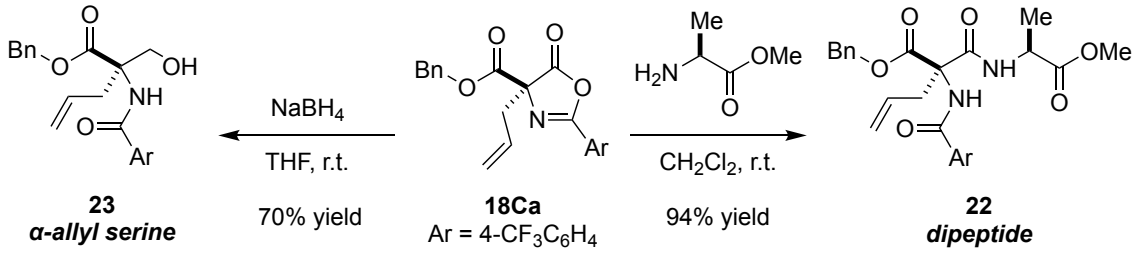
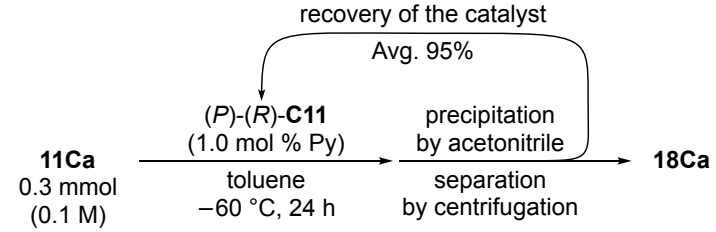


Figure 1. Derivatization of *C*-carboxyazlactone

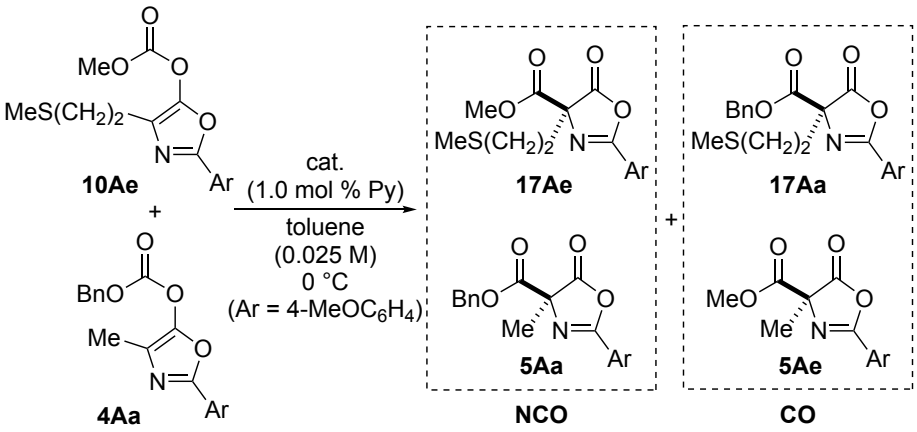
PQXmdpp, crossover experiments were conducted using an equimolar amount of **4Aa** and **10Ae** in the presence of several nucleophilic catalysts at 0 °C (Table 3).[13a] The use of DMAP or MDPP resulted in the formation of crossover products (**CO**) along with noncrossover products (**NCO**) in ratios of 2.4:1 and 1:1, respectively (entries 1 and 2). Similar formation of crossover products was generally observed in asymmetric Steglich reactions in which crossover experiments were conducted.[13a,h,15a,f,g] This scrambling has been well explained by the involvement of intermolecular acyl transfer from acylpyridinium intermediate to the enolate generated from the substrate. A DMAP-type catalyst **20** bearing a quinoxalinyl group at 3-position also afforded a significant amount of the crossover products (entry 3). Moreover, PS-DMAP, i.e. DMAP immobilized on polystyrene, afforded crossover products with the same ratio as DMAP (entry 4). By contrast, no crossover products were observed when **PQXdmap C1** and **PQXmdpp C7** and **C9** were employed as catalysts (entries 5–7). These results strongly suggest that the highly sterically demanding polymer scaffold of PQX protects the acylpyridinium intermediate from attack by the enolates generated on the other **PQXmdpp** molecules or promotes the intramolecular acyl transfer significantly.

Scheme 4. Reuse of the Polymer Catalyst



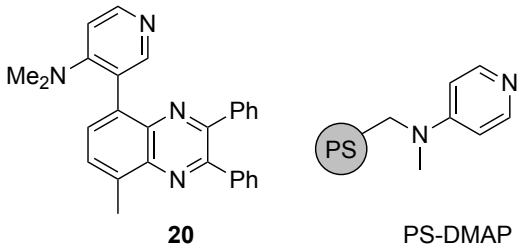
run	% yield	% ee	run	% yield	% ee	run	% yield	% ee
initial	99	91	4	98	92	8	99	92
1	99	92	5	97	93	9	97	93
2	99	92	6	99	92	10	96	93
3	99	92	7	99	93	11	99	93

Table 3. Crossover Experiment[a]



entry	catalyst	NCO : CO[b]
1	DMAP	2.4:1
2	MDPP	1:1
3	**20**	1.7:1
4[c]	PS-DMAP	2.4:1
5	(*P*)-(*R*)-**C1**	>50:1
6	(*P*)-(*R*)-**C7**	>50:1
7	(*P*)-(*R*)-**C9**	>50:1

[a]**10Ae** (0.15 mmol), **4Aa** (0.15 mmol), and catalyst (1.0 mol % pyridyl pendants) were stirred in toluene (6.0 mL) at 0 °C. [b]Determined by ^{1}H NMR analysis. [c]8.8 mol % pyridyl pendants.



Conclusion

The author established the synthesis of helically chiral polyquinoxaline-based DMAP-type nucleophilic catalysts via postpolymerization functionalization of polyquinoxalines bearing boronyl pendants. The obtained (*P*)-(*R*)-**PQXmdpp** showed high catalyst activity and enantioselectivity in an asymmetric Steglich rearrangement, giving *C*-carboxyazlactones in high

yields up to 97% ee. The observed macromolecular effect on the selective intramolecular reaction pathway opens up a new synthetic strategy using the polymer catalyst.

Experimental Section

1. General

All reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Materials were weighted by an electric balance, Sartorius CPA225D (readability: 0.01 mg). Column chromatography was performed with Ultra Pure Silica Gel (SILICYCLE, pH 7.0, 40–63 μm, 60 Å). ^{1}H NMR spectra were recorded on a Varian 400-MR (400 MHz) spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a Varian 400-MR (100 MHz) spectrometer at ambient temperature. ^{11}B NMR spectra were recorded on a Varian 400-MR (128 MHz) spectrometer at ambient temperature. ^{19}F NMR spectra were recorded on a Varian 400-MR (376 MHz) spectrometer at ambient temperature. ^{1}H NMR data are reported as follows: chemical shift in ppm downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet and br = broad), coupling constant (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). ^{11}B and ^{19}F NMR chemical shifts are reported in ppm downfield from BF_3•Et_2O (δ scale). The GPC analysis was carried out with TSKgel GMH_{XL} ($CHCl_3$, polystyrene standards). Circular dichroism (CD) spectra were recorded on a JASCO J-1500 spectrometer. UV-vis absorption spectra were recorded on a JASCO V-770 spectrometer. The chiral SFC analysis was carried out on JASCO SF-2000 analytical SFC system equipped with Daicel CHIRALCEL OD-H or OJ-H (CO_2 and 2-propanol).

2. Materials

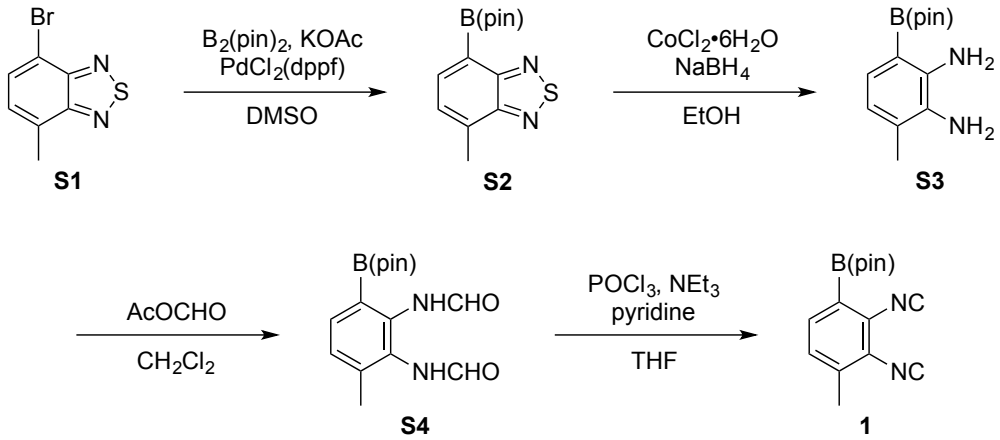
Toluene, chloroform, *m*-xylene, pyridine, dimethyl sulfoxide, phosphoryl chloride, triethylamine, 4-methylbenzyl alcohol, 4-trifluoromethylbenzyl alcohol, 1-naphthalenemethanol and 2-naphthalenemethanol were distilled over before use. Tetrahydrofuran (Wako), acetonitrile (Wako), benzene (Wako), 2-propanol (Wako), dichloromethane (Nacalai), ethanol (Nacalai), ethyl acetate (Nacalai), hexane (Nacalai), diethyl ether (Nacalai), distillated water (Nacalai), sodium hydroxide (Nacalai), hydrochloric acid (Nacalai), magnesium sulfate (Nacalai), sodium sulfate

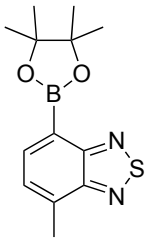
(Wako), sodium borohydride (TCI), potassium acetate (Aldrich), trimethyl phosphine (Strem), sodium carbonate (Nacalai), cesium carbonate (Nacalai), sodium hydrogen carbonate (Nacalai), sodium chloride (Nacalai), *N*-bromosuccinimide (Wako), benzil (Wako), *N*,*N*-dimethyl-4-aminopyridine (Wako), 4-pyrrolidinopyridine (TCI), 4-piperidinylpyridine (TCI), 3-bromo-4-chloropyridine (Wako), PS-DMAP (1.49 mmol/g) (Biotage), acetic acid (Wako), dicyclohexylcarbodiimide (Wako), cobalt dichloride hexahydrate (Wako), bis(pinacolato)diboron (Boron Molecular), benzyl chloroformate (Wako), methyl chloroformate (Nacalai), ethyl chloroformate (TCI), isopropyl chloroformate (TCI), 2-methoxyethyl chloroformate (TCI), phenyl chloroformate (TCI), 4-cyanobenzoyl chloride (Aldrich), 4-(trifluoromethyl)benzoyl chloride (TCI), L-alanine methyl ester hydrochloride (TCI), DL-2-aminobutanoic acid (Aldrich), DL-2-aminopentanoic acid (TCI), L-leucine (Nacalai), DL-phenylalanine methyl ester hydrochloride (Nacalai), L-methionine methyl ester hydrochloride (TCI), DL-2-allylglycine (TCI), L-2-phenylglycine (Wako) were used as received from commercial sources. Acetic formic anhydride,[16] *o*-TolNiCl(PMe_3)$_2$,[17] *N*-ethyl-*N*-methyl-4-aminopyridine,[18] *N,N*-diethyl-4-aminopyridine,[18] 1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine,[19] 1-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine,[20] 2-(4-methoxyphenyl)-4-methyloxazolone,[13a] 2-(4-chlorophenyl)-4-methyloxazolone,[21] 2-(4-trifluoromethylphenyl)-4-methyloxazolone,[22] **2**,[10a] **S1**,[23] **S5**,[10b] **S14**,[24] $PdCl_2$(dppf), and $Pd(PPh_3)_4$ were prepared according to the reported procedure.

3. Experimental Procedure and Spectral Data for New Compounds

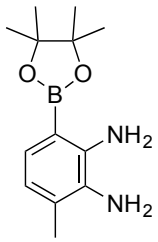
3.1. Synthesis of Monomer 1

Scheme S1. Synthesis of Monomer 1

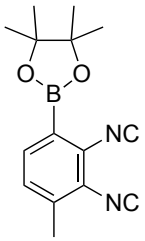




Synthesis of **S2**: A mixture of **S1** (5.73 g, 25.0 mmol), bis(pinacolato)diboron $B_2(pin)_2$ (6.98 g, 27.5 mmol), potassium acetate (7.24 g, 73.7 mmol), and $PdCl_2(dppf)$ (0.55 g, 0.75 mmol) in DMSO (75 mL) was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was concentrated under vacuum and utilized to bulb-to-bulb distillation to give the title compound **S2** (7.45 g, 85% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.06 (d, J = 6.8 Hz, 1H), 7.35 (dd, J = 6.4, 0.8 Hz, 1H), 2.75 (d, J = 0.4 Hz, 3H), 1.42 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.5, 155.4, 139.4, 135.2, 127.8, 84.3, 25.0, 18.4. ^{11}B NMR (128 MHz, $CDCl_3$, δ): 30.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{17}BN_2O_2S$, 277.1177; found, 277.1171.



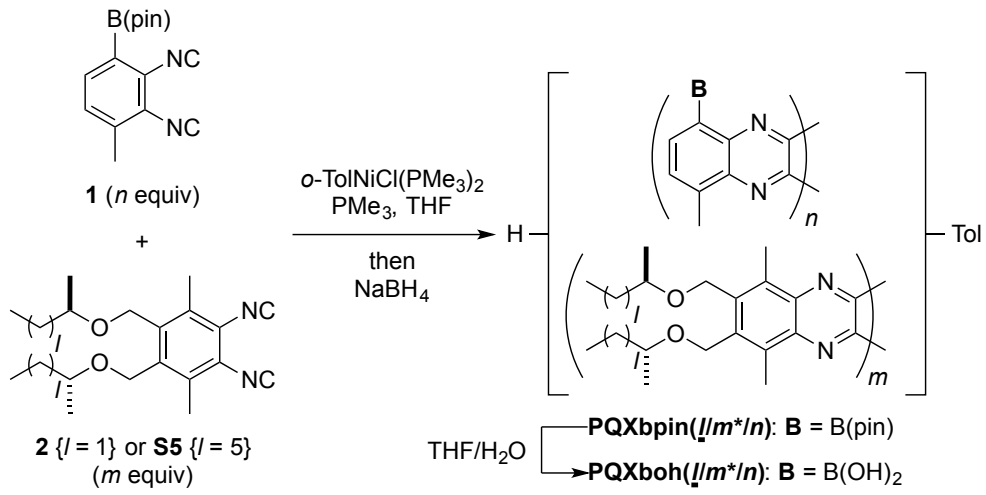
Synthesis of **S3**: To a solution of **S2** (8.68 g, 31.4 mmol) and $CoCl_2$•$6H_2O$ (2.59 g, 9.5 mmol) in EtOH (300 mL) was added $NaBH_4$ (4.75 g, 126.0 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, and then passed through a pad of Celite. The filtrate was evaporated *in vacuo*, and then the residual material was dissolved in AcOEt. The organic phase was washed with water and brine, and dried over Na_2SO_4. The mixture was passed through a pad of Celite, and the resultant solution was evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (hexane:AcOEt = 3:2) to give the title compound **S3** (3.35 g, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.13 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 4.44 (brs, 2H), 3.35 (brs, 2H), 2.21 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.3, 132.3, 127.0, 126.9, 120.6, 83.5, 25.0, 18.0. ^{11}B NMR (128 MHz, $CDCl_3$, δ): 30.9. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{21}BN_2O_2$, 249.1769; found, 249.1765.



Synthesis of **1**: To a solution of **S3** (2.95 g, 11.9 mmol) in CH_2Cl_2 (240 mL) was added acetic formic anhydride (AcOCHO) (4.21 g, 47.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 h, and then volatiles were removed *in vacuo*. The resultant solid was recrystallized from CH_2Cl_2, giving **S4** (3.56 g, 98% yield) as a colorless sold. A part of **S3** (0.61 g, 2.0 mmol) was dissolved in THF (40 mL), and then NEt_3 (2.02 g, 19.9 mmol), pyridine (1.56 g, 19.7 mmol), and $POCl_3$ (0.95 g, 6.2 mmol) were added to the solution at 0 °C. After stirring for 1 h, the mixture was diluted with water and extracted with AcOEt. The organic phase was washed with water and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to DIOL-silica gel column chromatography (hexane:Et_2O = 3:1) to give the title compound **1** (0.14 g, 26% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.71 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 2.49 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.3, 173.2, 139.4, 136.0, 130.4, 128.0, 124.5, 85.0, 25.0, 19.3. ^{11}B NMR (128 MHz, $CDCl_3$, δ): 29.4. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{15}H_{17}BN_2O_2$, 291.1275; found, 291.1267.

3.2. Synthesis of (*P*)-(*R*)-PQXboh(*l*/*m**/*n*)

Scheme S2. Synthesis of (*P*)-(*R*)-PQXboh(*l*/*m/*n*)**



Typical Procedure for the Preparation of (*P*)-(*R*)-PQXboh(*l*/*m/*n*)**

Synthesis of (*P*)-(*R*)-**PQXboh(1/190*/10)**: To a solution of organonickel initiator *o*-TolNiCl(PMe$_3$)$_2$ (6.78 mg, 20.1 μmol) and PMe$_3$ (1.0 M in THF, 100 μL, 100 μmol) in THF (180 mL) was added a mixture of monomer **1** (53.6 mg, 0.200 mmol) and **2** (1.248 g, 3.80 mmol) in THF (20 mL) at room temperature. The mixture was stirred for 4 h at room temperature. To the reaction mixture was added NaBH$_4$ (75.5 mg, 2.00 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water, extracted with CHCl$_3$ (400 mL), washed with water and brine, dried over Na$_2$SO$_4$, filtrated through a pad of Celite, and evaporated under vacuum. The residue was dissolved in CHCl$_3$ (10 mL), and the mixture was poured into vigorously stirred acetonitrile (200 mL). The precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, the obtained (*P*)-(*R*)-**PQXbpin(1/190*/10)** was dissolved in THF (8 mL), and then distillated water (400 μL) was added and stirred at room temperature for 5 h. The mixture was poured into vigorously stirred acetonitrile, and the precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, (*P*)-(*R*)-**PQXboh(1/190*/10)** (1.240 g, 96%) was obtained as a beige solid. CD and UV spectra of this polymer indicate that this polymer takes a pure *P*-helical structure in toluene at 20 °C. ^{1}H NMR (400 MHz, C$_6$D$_6$, 70 °C, δ): 8.50–6.60 (brm, peak top; 8.17, 7.32, 7.02 (4n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.84 (28m+3n+3)H). ^{11}B NMR (160 MHz, C$_6$D$_6$, δ): 22.8. M_n = 6.6 × 10^4, M_w/M_n = 1.17. g_{abs} ($\Delta\varepsilon/\varepsilon$ (dissymmetry ratio), 371.5 nm) = 2.35 × 10^{-3}.

(*P*)-(*R*)-**PQXboh(5/190*/10)**: The reaction was carried out according to the typical procedure using *o*-TolNiCl(PMe$_3$)$_2$ (2.04 mg, 6.05 μmol), PMe$_3$ (1.0 M in THF, 30 μL, 30 μmol), **1** (16.1 mg, 60 μmol), **S5** (502.1 mg, 1.14 mmol), and THF (75 mL). (*P*)-(*R*)-**PQXboh(5/190*/10)** (472 mg, 91%) was obtained as a beige solid. ^{1}H NMR (400 MHz, C$_6$D$_6$, 70 °C, δ): 8.70–6.70 (brm, peak top; 8.23, 7.36, 7.03 (4n+4)H), 6.00–0.00 (brm, peak top; 4.66, 3.44, 2.78, 1.66, 1.45, 1.35, 1.18, 0.93 (44m+3n+3)H). M_n = 9.7 × 10^4, M_w/M_n = 1.73. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.07 × 10^{-3}.

(*P*)-(*R*)-**PQXboh(5/180*/20)**: The reaction was carried out according to the typical procedure using *o*-TolNiCl(PMe$_3$)$_2$ (0.01 M in THF, 41 μL, 0.41 μmol), PMe$_3$ (0.1 M in THF, 21 μL, 2.1 μmol), **1** (2.22 mg, 8.28 μmol), **S5** (32.8 mg, 74.4 μmol), and THF (10 mL). (*P*)-(*R*)-**PQXboh(5/180*/20)** (20.3 mg, 60%) was obtained as a beige solid. ^{1}H NMR (500 MHz, C$_6$D$_6$, 70 °C, δ): 8.80–6.00 (brm, peak top; 8.22, 7.36, 7.07, 6.46 (4n+4)H), 6.00–0.00 (brm, peak top;

4.66, 3.43, 2.78, 1.65, 1.45, 1.35, 1.17, 0.92 (44m+3n+3)H). M_n = 5.1 × 10^4, M_w/M_n = 4.13. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.02 × 10^{-3}.

(*P*)-(*R*)-**PQXboh(5/195*/5)**: The reaction was carried out according to the typical procedure using *o*-TolNiCl(PMe_3)$_2$ (0.01 M in THF, 450 μL, 4.5 μmol), PMe_3 (1.0 M in THF, 23 μL, 23 μmol), **1** (6.03 mg, 22.5 μmol), **S5** (386.1 mg, 876 μmol), and THF (45 mL). (*P*)-(*R*)-**PQXboh(5/195*/5)** (385 mg, 98%) was obtained as a beige solid. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 8.50–6.80 (brm, peak top; 8.22, 7.36, 7.05 (4n+4)H), 6.00–0.00 (brm, peak top; 4.60, 3.44, 2.78, 1.66, 1.45, 1.35, 1.17, 0.93 (44m+3n+3)H). M_n = 6.5 × 10^4, M_w/M_n = 1.15. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.03 × 10^{-3}.

3.3. Synthesis of (*P*)-(*R*)-PQX-based 4-Aminopyridines

Typical Procedure for Suzuki–Miyaura Cross Coupling of (*P*)-(*R*)-PQXboh(*l*/*m/*n*) with DMAP Derivatives**

Synthesis of (*P*)-(*R*)-**C1** (**PQXdmap**): A mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (192.2 mg, 29.9 μmol B), **S6** (8.60 mg, 41.3 μmol), sodium carbonate (9.84 mg, 92.8 μmol) and Pd(PPh_3)$_4$ (3.49 mg, 3.02 μmol) in THF (10 mL) and water (2 mL) was stirred at 110 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtrated through a pad of Celite, and evaporated under vacuum. The residue was dissolved in toluene and poured into vigorously stirred acetonitrile, and precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, (*P*)-(*R*)-**C1** (178 mg, 93 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. CD and UV spectra of this polymer indicate that this polymer takes a pure *P*-helical structure in toluene at 20 °C. GPC analysis with TSKgel GMH_{XL} (eluent: $CHCl_3$) showed weak broad tailing peaks, which could not be analyzed by molecular weight calibration curve using polystyrene standards (peak start: 8.5 × 10^6, peak end: out of measuring range). GPC analysis with TSKgel α-4000, α-3000, and α-2500 in series (eluent: THF) showed a broad tailing peak, which could not be analyzed by molecular weight calibration curve using polystyrene standards (peak start: 3.2 × 10^4, peak top: 6.5 × 10^2, peak end: out of measuring range). ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.20–6.00 (brm, peak top; 8.31, 7.26, 7.00, 6.44 (5n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86

(28m+9n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.34×10^{-3}.

(*P*)-(*R*)-**C2**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.5 mg, 14.8 μmol B), **S7** (33.8 mg, 157 μmol), sodium carbonate (16.1 mg, 152 μmol) and $Pd(PPh_3)_4$ (19.8 mg, 17.1 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C2** (82.0 mg, 86 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.20–6.00 (brm, peak top; 8.32, 7.32, 7.02, 6.54 (5n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+11n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.35×10^{-3}.

(*P*)-(*R*)-**C3**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.0 mg, 14.8 μmol B), **S8** (35.0 mg, 153 μmol), sodium carbonate (14.7 mg, 139 μmol), and $Pd(PPh_3)_4$ (20.3 mg, 17.6 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C3** (84.6 mg, 89 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.00–6.00 (brm, peak top; 8.29, 7.38, 7.05, 6.64 (5n+4)H), 6.0–0.0 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+13n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.37×10^{-3}.

(*P*)-(*R*)-**C4**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.3 mg, 14.8 μmol B), **S9** (30.0 mg, 141 μmol), sodium carbonate (16.0 mg, 151 μmol), and $Pd(PPh_3)_4$ (18.5 mg, 16.0 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C4** (87.5 mg, 92 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.10–5.80 (brm, peak top; 8.58, 8.25, 7.28, 6.99, 6.00 (5n+4)H), 5.80–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+9n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.32×10^{-3}.

(*P*)-(*R*)-**C5** (**PQXppy**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (185.1 mg, 28.8 μmol B), **S10** (8.78 mg, 38.7 μmol), sodium carbonate (9.47 mg, 89.3 μmol), and $Pd(PPh_3)_4$ (3.96 mg, 3.43 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C5** (173 mg, 93 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.30–6.00 (brm, peak top; 8.62, 8.39, 7.25, 6.99, 6.40 (5n+4)H), 6.00–0.00 (brm, peak top; 4.56, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+11n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.28×10^{-3}.

(*P*)-(*R*)-**C6**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.6 mg, 14.9 μmol B), **S11** (39.4 mg, 163 μmol), sodium carbonate (15.8 mg, 149 μmol), and $Pd(PPh_3)_4$ (20.5 mg, 17.7 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C6** (87.7 mg, 92 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.20–6.00 (brm, peak top; 8.35, 7.53, 7.09, 6.66 (5n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+13n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.22×10^{-3}.

(*P*)-(*R*)-**C7** (**PQXmdpp**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (195.2 mg, 30.3 μmol B), **S12** (8.12 mg, 38.1 μmol), sodium carbonate (9.95 mg, 93.9 μmol), and $Pd(PPh_3)_4$ (3.43 mg, 2.97 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C7** (175 mg, 90 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 8.70–6.00 (brm, peak top; 8.39, 8.07, 7.24, 6.99 (4n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+10n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.26×10^{-3}. CD and UV spectra of this polymer indicate that this polymer takes a pure *M*-helical structure in toluene/1,1,2-trichloroethane (1/1, v/v) at 20 °C. g_{abs} (toluene/1,1,2-trichloroethane (1/1, v/v), $\Delta\varepsilon/\varepsilon$, 371.5 nm) = -3.04×10^{-3}.

(*P*)-(*R*)-**C8**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (94.0 mg, 14.6 μmol B), **S13** (34.1 mg, 150 μmol), sodium carbonate (21.3 mg, 201 μmol), and $Pd(PPh_3)_4$ (19.9 mg, 17.2 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C8** (77.7 mg, 83 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.00–6.00 (brm, peak top; 8.55, 8.11, 7.24, 6.99 (4n+4)H), 6.00–0.00 (brm, peak top; 4.56, 3.28, 2.75, 1.51, 1.41, 1.09, 0.86 (28m+12n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.34×10^{-3}.

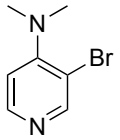
(*P*)-(*R*)-**C9** (**PQXmdpp**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(5/190*/10)** (172.8 mg, 20.2 μmol B), **S12** (8.82 mg, 41.4 μmol), sodium carbonate (6.35 mg, 59.9 μmol), and $Pd(PPh_3)_4$ (9.30 mg, 9.05 μmol) in THF (9 mL) and water (1.8 mL). (*P*)-(*R*)-**C9** (154 mg, 89 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 9.00–6.00 (brm, peak top; 8.37, 8.10, 7.29, 7.07 (4n+4)H), 6.00–0.00 (brm, peak top;

4.67, 3.44, 2.78, 1.67, 1.45, 1.35, 1.18, 0.93 (44m+10n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 2.02×10^{-3}.

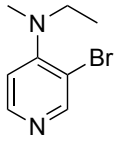
(*P*)-(*R*)-**C10** (**PQXmdpp**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(5/180*/20)** (12.0 mg, 2.89 μmol B), **S12** (3.71 mg, 17.4 μmol), sodium carbonate (4.71 mg, 44.4 μmol), and $Pd(PPh_3)_4$ (3.91 mg, 3.38 μmol) in THF (600 μL) and water (120 μL). (*P*)-(*R*)-**C10** (12.8 mg, >99 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>70%) was determined by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, C_6D_6, 70 °C, δ): 8.80–6.00 (brm, peak top; 8.37, 8.28, 8.11, 7.75, 7.28, 7.07 (4n+4)H), 6.00–0.00 (brm, peak top; 4.67, 3.44, 2.78, 1.66, 1.45, 1.35, 1.17, 0.93 (44m+10n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 1.92×10^{-3}.

(*P*)-(*R*)-**C11** (**PQXmdpp**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(5/195*/5)** (173.3 mg, 9.99 μmol B), **S12** (4.04 mg, 19.0 μmol), sodium carbonate (3.48 mg, 32.8 μmol), and $Pd(PPh_3)_4$ (2.84 mg, 2.46 μmol) in THF (9 mL) and water (1.8 mL). (*P*)-(*R*)-**C11** (151 mg, 87 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, 70 °C, δ): 8.70–6.00 (brm, peak top; 8.38, 8.10, 7.30, 7.06 (4n+4)H), 6.00–0.00 (brm, peak top; 4.59, 3.44, 2.78, 1.67, 1.45, 1.35, 1.18, 0.93 (44m+10n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm) = 1.97×10^{-3}.

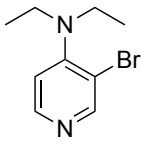
3.4. Synthesis of DMAP Derivatives 3



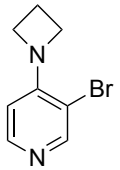
Synthesis of **S6**: To a solution of *N,N*-dimethyl-4-aminopyridine (6.11 g, 50.0 mmol) in acetonitrile (400 mL) was added *N*-bromosuccinimide (9.34 g, 52.5 mmol). The reaction mixture was stirred at room temperature for 8 h and then diluted with water. The resulted mixture was extracted with Et_2O, washed with water and brine, and then dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (hexane:AcOEt = 1:2), giving the title compound **S6** (2.54 g, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.48 (s, 1H), 8.25 (d, J = 5.6 Hz, 1H), 6.76 (d, J = 5.2 Hz, 1H), 2.94 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.1, 153.5, 148.9, 113.9, 112.6, 42.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_7H_9BrN_2$, 201.0022; found, 201.0019.



Synthesis of **S7**: To a solution of *N*-ethyl-*N*-methyl-4-aminopyridine (0.86 g, 6.3 mmol) in acetonitrile (50 mL) was added *N*-bromosuccinimide (1.18 g, 6.6 mmol). The reaction mixture was stirred at room temperature for 10 h, and then diluted with water. The resulted mixture was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (hexane:AcOEt = 1:1) to give the title compound **S7** (0.27 g, 20% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.49 (s, 1H), 8.24 (d, J = 6.0 Hz, 1H), 6.78 (d, J = 5.6 Hz, 1H), 3.28 (q, J = 7.2 Hz, 2H), 2.86 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.8, 153.5, 148.7, 114.5, 113.0, 49.0, 38.7, 12.7. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_8H_{11}BrN_2$, 215.0178; found, 215.0176.

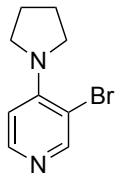


Synthesis of **S8**: To a solution of *N,N*-diethyl-4-aminopyridine (0.66 g, 4.4 mmol) in acetonitrile (35 mL) was added *N*-bromosuccinimide (0.82 g, 4.6 mmol). The reaction mixture was stirred at room temperature for 12 h and then diluted with water. The resulted mixture was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (hexane:AcOEt = 2:1), giving the title compound **S8** (0.13 g, 13% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.52 (s, 1H), 8.24 (d, J = 5.6 Hz, 1H), 6.79 (d, J = 6.0 Hz, 1H), 3.32 (q, J = 7.2 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.4, 153.8, 148.4, 115.7, 114.1, 45.3, 12.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_9H_{13}BrN_2$, 229.0335; found, 229.0332.

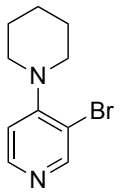


Synthesis of **S9**: To a solution of 3-bromo-4-chloropyridine (53.7 mg, 0.28 mmol) in DME (0.6 mL) was added azetidine (22.2 mg, 0.39 mmol) and Cs_2CO_3 (0.11 g, 0.34 mmol). The reaction

mixture was stirred at 90 °C for 18 h, cooled to room temperature, and then diluted with water. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried over with Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt) to giving the title compound **S9** (39 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.29 (s, 1H), 8.10 (d, J = 5.6 Hz, 1H), 6.23 (d, J = 5.6 Hz, 1H), 4.27 (t, J = 3.6 Hz, 4H), 2.36 (quint, J = 3.6 Hz, H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.8, 152.2, 147.6, 108.1, 103.8, 53.8, 16.8. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_8H_9BrN_2$, 213.0022; found, 213.0018.



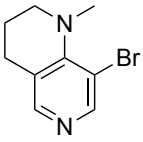
Synthesis of **S10**: To a solution of 4-pyrrolidinopyridine (2.04 g, 13.7 mmol) in acetonitrile (100 mL) was added *N*-bromosuccinimide (2.57 g, 14.4 mmol). The reaction mixture was stirred at room temperature for 4 h and then diluted with water. The mixture was extracted with Et_2O, washed with water and brine, dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (CH_2Cl_2:AcOEt = 1:4), giving the title compound **S10** (1.14 g, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.37 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 6.48 (d, J = 6.0 Hz, 1H), 3.62–3.56 (m, 4H), 2.00–1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.7, 151.7, 147.8, 110.6, 105.1, 50.7, 25.8. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_9H_{11}BrN_2$, 227.0178: found, 227.0174.



Synthesis of **S11**: To a solution of 4-piperidinylpyridine (4.66 g, 28.7 mmol) in acetonitrile (230 mL) was added *N*-bromosuccinimide (5.37 g, 30.1 mmol). The reaction mixture was stirred at room temperature for 14 h and then diluted with water. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to NH-silica gel column chromatography (hexane:AcOEt = 4:1) to give the title compound **S11** (1.71 g, 25% yield). ^{1}H NMR (400 MHz,

$CDCl_3$, δ): 8.52 (s, 1H), 8.29 (d, *J* = 5.6 Hz, 1H), 6.81 (d, *J* = 5.6 Hz, 1H), 3.16–3.06 (m, 4H), 1.78–1.68 (m, 4H), 1.65–1.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.7, 153.2, 149.3, 115.5, 115.2, 51.8, 25.9, 24.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_{13}BrN_2$, 241.0335; found, 241.0031.

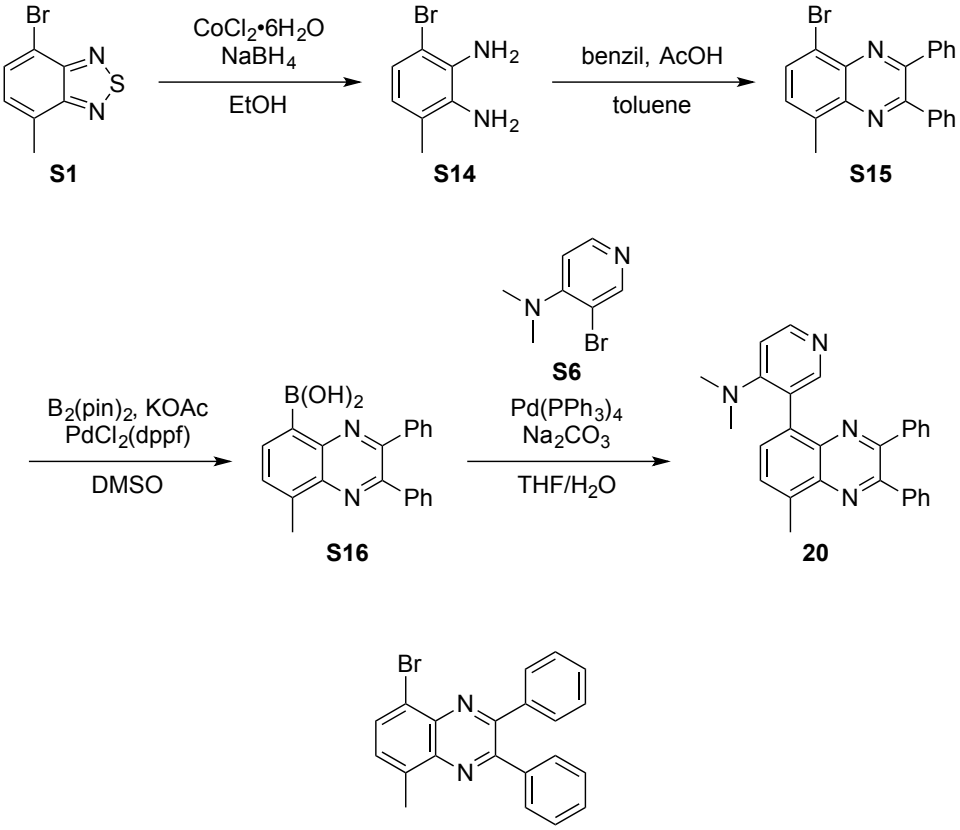
Synthesis of **S12**: To a solution of 1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (0.28 g, 2.1 mmol) in DMF (7 mL) was added *N*-bromosuccinimide (0.41 g, 2.3 mmol) at 0 °C. The reaction mixture was stirred for 9 h at 0 °C and then diluted with water. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt) to give the title compound **S12** (0.31 g, 69% yield). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.16 (s, 1H), 7.90 (s, 1H), 3.58 (t, *J* = 8.8 Hz, 2H), 3.26 (s, 3H), 3.01 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 154.2, 152.4, 142.5, 128.1, 98.3, 56.2, 36.3, 25.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_8H_9BrN_2$, 213.0022; found, 213.0018.



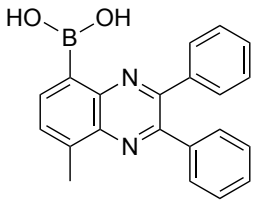
Synthesis of **S13**: To a solution of 1-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.38 g, 2.6 mmol) in DMF (9 mL) was added *N*-bromosuccinimide (0.51 g, 2.9 mmol). The reaction mixture was stirred at 0 °C for 2 h, and then diluted with water. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt) to give the title compound **S13** (0.13 g, 23% yield). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.28 (s, 1H), 7.93 (s, 1H), 3.22–3.17 (m, 2H), 3.15 (s, 3H), 2.69 (t, *J* = 6.4 Hz, 2H), 1.92–1.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.2, 152.0, 147.7, 124.5, 109.1, 52.8, 42.8, 25.7, 20.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_9H_{11}BrN_2$, 227.0178; found, 227.0175.

3.5. Synthesis of Model Compound 20

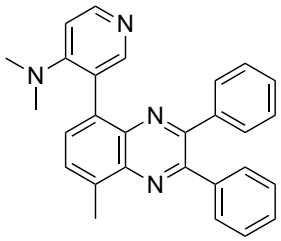
Scheme S3. Synthesis of Model Compound 20



Synthesis of **S15**: To a solution of **S1** (4.59 g, 20.0 mmol) and $CoCl_2$•$6H_2O$ (0.48 g, 2.0 mmol) in EtOH (160 mL) was added $NaBH_4$ (2.98 g, 80.0 mmol). The mixture was stirred at room temperature for 3 h, and then passed through a pad of Celite. The resultant solution was evaporated *in vacuo*. The residual material was dissolved in AcOEt, washed with water and brine, dried over $MgSO_4$, filtrated through a pad of Celite. The filtrate was concentrated under vacuum to give **S14**. A solution of **S14**, benzil (4.41 g, 21.0 mmol) and acetic acid (0.21 g, 3.2 mmol) in toluene (70 mL) was stirred at 120 °C for 2 h. After cooling to room temperature, the mixture was concentrated *in vacuo*, and then subjected to silica gel column chromatography (hexane:CH_2Cl_2 = 2:1) to give the title compound **S15** (5.82 g, 78% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.95 (d, J = 8.0 Hz, 1H), 7.67–7.62 (m, 2H), 7.62–7.58 (m, 2H), 7.48–7.43 (m, 1H), 7.42–7.31 (m, 6H), 2.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.1, 152.4, 141.1, 139.1, 138.8, 137.7, 133.0, 130.4, 130.2, 130.1, 129.2, 129.2, 128.4, 121.3, 17.1. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{21}H_{15}BrN_2$, 375.0491; found, 375.0500.



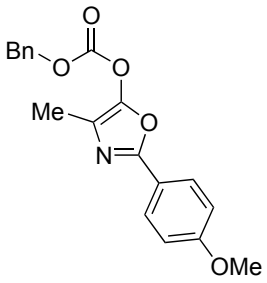
Synthesis of **S16**: A mixture of **S15** (113.6 mg, 0.302 mmol), bis(pinacolato)diboron (90.6 mg, 0.357 mmol), potassium acetate (80.6 mg, 0.821 mmol) and $PdCl_2$(dppf) (12.1 mg, 16.5 μmol) in DMSO (1.5 mL) was stirred at 110 °C for 3 h under nitrogen atmosphere. After cooling to room temperature, the mixture was diluted with and extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (CH_2Cl_2 to CH_2Cl_2:AcOEt = 10:1 to AcOEt) to giving the title compound **S16** (63.5 mg, 62% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.30 (d, *J* = 7.2 Hz, 1H), 7.69 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.60–7.55 (m, 2H), 7.55–7.50 (m, 2H), 7.44–7.20 (m, 8H), 2.89 (d, *J* = 0.8 Hz, 3H). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.48 (d, *J* = 6.8 Hz, 1H), 7.54–7.48 (m, 2H), 7.45–7.32 (m, 4H), 7.27 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.09–7.02 (m, 3H), 7.02–6.96 (m, 3H), 2.73 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 151.9, 151.3, 144.7, 141.4, 140.6, 139.1, 138.8, 138.5, 130.4, 130.3, 129.8, 129.3, 129.1, 128.7, 128.4, 17.7. ^{11}B NMR (128 MHz, $CDCl_3$, 70 °C, δ): 29.8. ^{11}B NMR (160 MHz, C_6D_6, δ): 30.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{21}H_{17}BN_2O_2$, 341.1456; found, 341.1449.



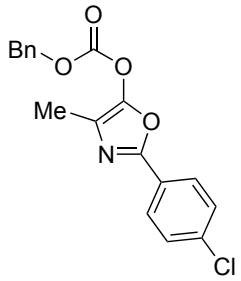
Synthesis of **20**: A mixture of **S16** (0.34 g, 1.0 mmol), **S6** (0.31 g, 1.5 mmol), sodium carbonate (0.32 g, 3.0 mmol) and $Pd(PPh_3)_4$ (63.0 mg, 55.0 μmol) in THF (3.5 mL) and water (0.23 mL) was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to NH-silica gel column chromatography (hexane:AcOEt = 1:1) to give the title compound **20** (0.10 g, 24% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.32–8.24 (m, 2H), 7.70–7.59 (m, 4H), 7.48–7.42 (m, 2H), 7.42–7.31 (m, 3H), 7.31–7.21 (m, 3H), 6.80 (d,

J = 6.4 Hz, 1H), 2.89 (s, 3H), 2.63 (s, 6H). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.67 (s, 1H), 8.47 (d, *J* = 4.4 Hz, 1H), 7.68–7.62 (m, 2H), 7.62–7.55 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.27–7.22 (m, 1H), 7.10–7.04 (m, 3H), 7.00–6.94 (m, 3H), 6.42 (d, *J* = 4.4 Hz, 1H), 2.86 (d, *J* = 0.8 Hz, 3H), 2.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.9, 152.3, 151.9, 151.6, 147.5, 140.2, 139.5, 139.2, 139.0, 137.5, 136.2, 130.2, 130.2, 129.7, 129.0, 128.8, 128.3, 128.1, 122.0, 110.0, 41.8, 17.3. ^{13}C NMR (100 MHz, C_6D_6, δ): 156.6, 154.5, 152.1, 151.7, 149.7, 140.7, 140.2, 139.7, 139.6, 137.3, 137.0, 130.5, 130.5, 130.5, 129.8, 128.9, 128.4, 122.9, 110.6, 41.4, 17.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{28}H_{24}N_4$, 417.2074; found, 417.2071.

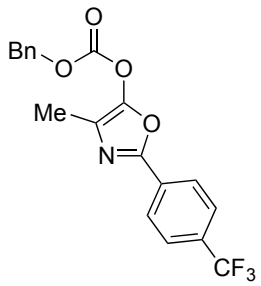
3.6. Synthesis of Oxazolyl Carbonates



Synthesis of **4Aa**: To a solution of 2-(4-methoxyphenyl)-4-methyloxazolone (2.054 g, 10.0 mmol) in THF (200 mL) was added Et_3N (1.136 g, 11.2 mmol) and benzyl chloroformate (1.875 g, 11.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 36 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 3:2) to give **4Aa** as a colorless solid (2.223 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.91–7.84 (m, 2H), 7.47–7.39 (m, 5H), 6.96–6.90 (m, 2H), 5.32 (s, 2H), 3.84 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.4, 155.1, 151.8, 145.7, 134.0, 129.3, 128.9, 128.8, 127.7, 120.1, 120.0, 114.3, 71.8, 55.5, 10.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{19}H_{17}NO_5$, 340.1179; found, 340.1175.

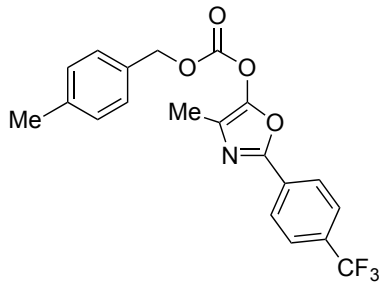


Synthesis of **4Ba**: To a solution of 2-(4-chlorophenyl)-4-methyloxazolone (1.049 g, 5.00 mmol) in THF (100 mL) was added Et_3N (0.573 g, 5.66 mmol) and benzyl chloroformate (1.007g, 5.90 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into H_2O, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 4:1) to give **4Ba** as a colorless solid (1.353 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.90–7.84 (m, 2H), 7.47–7.37 (m, 7H), 5.33 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 154.0, 151.6, 146.2, 136.5, 133.9, 129.3, 129.2, 129.0, 128.8, 127.2, 125.7, 120.8, 72.0, 10.4. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{14}ClNO_4$, 344.0684; found, 344.0682.

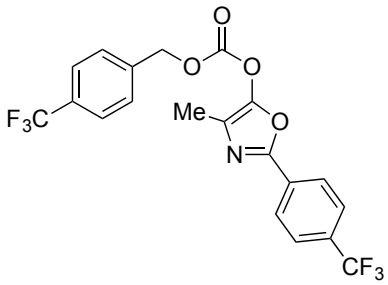


Synthesis of **4Ca**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (2.439 g, 10.0 mmol) in THF (200 mL) was added Et_3N (1.132 g, 11.2 mmol) and benzyl chloroformate (1.734 g, 10.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 11 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **4Ca** as a colorless solid (3.465 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.48–7.40 (m, 5H), 5.34 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.5, 151.5, 146.7, 133.9, 132.0 (q, J = 32.5 Hz), 130.4, 129.4, 129.0, 128.9, 126.2, 125.9 (q, J = 3.9 Hz), 124.0 (q, J = 270 Hz), 121.3, 72.1, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.3. HRMS-ESI (m/z): [M +

H]$^+$ calcd for $C_{19}H_{14}F_3NO_4$, 378.0948; found, 378.0945.

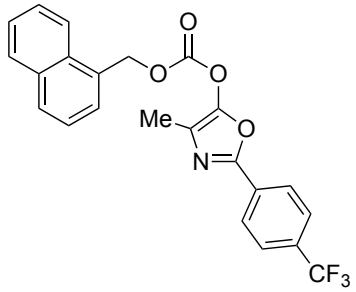


Synthesis of **4Cb**: To a solution of 4-methylbenzyl alcohol (1.223 g, 10.0 mmol) in CH_2Cl_2 (50 mL) was added pyridine (0.901 g, 11.4 mmol) and triphosgene (1.203 g, 4.05 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight, partially evaporated under reduced pressure, and then diluted with hexane. The precipitate was removed by filtration, and the filtrate was concentrated to afford 4-methylbenzyl chloroformate (1.49 g, impure) as a colorless liquid, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (2.34 g, 9.62 mmol) in THF (100 mL) was added Et_3N (1.024 g, 10.1 mmol) and 4-methylbenzyl chloroformate (1.49 g, impure) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into H_2O, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **4Cb** as a colorless solid (0.341 g, 9%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 5.30 (s, 2H), 2.39 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.4, 151.5, 146.7, 139.4, 131.9 (q, *J* = 31.7 Hz), 130.9, 130.4, 129.6, 129.1, 126.2, 125.9 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 271 Hz), 121.3, 72.1, 21.4, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{20}H_{16}F_3NO_4$, 392.1104; found, 392.1094.



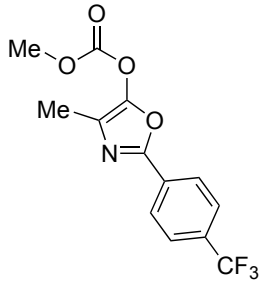
Synthesis of **4Cc**: A flask containing Na_2CO_3 (3.81 g, 36.0 mmol) was dried with a heat gun under

reduced pressure. To the flask was added a solution of triphosgene (2.355 g, 7.93 mmol) in toluene (15 mL) at 0 °C. After stirring for 0.5 h at 0 °C, a solution of 4-trifuloromethylbenzyl alcohol (0.701 g, 3.98 mmol) in toluene (5 mL) was added to the mixture, and then stirred for 28 h at room temperature. The precipitate was removed by filtration and the filtrate was concentrated under vacuum. The residue was subjected to bulb-to-bulb distillation to give 4-trifluoromethylbenzyl chloroformate (0.899 g, impure) as a colorless liquid, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.788 g, 4.02 mmol) in THF (40 mL) was added Et_3N (0.455 g, 4.49 mmol) and 4-trifluoromethylbenzyl chloroformate (0.899 g, impure) at 0 °C. The mixture was stirred at 0 °C for 10 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **4Cc** as a colorless solid (0.330 g, 18%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, J = 8.4 Hz, 2H), 7.72–7.66 (m, 4H), 7.57 (d, J = 8.0 Hz, 2H), 5.38 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.6, 151.5, 146.5, 137.7, 132.1 (q, J = 32.5 Hz), 131.5 (q, J = 32.5 Hz), 130.3, 128.7, 126.2, 126.0 (q, J = 3.9 Hz), 125.9 (q, J = 3.9 Hz), 124.0 (q, J = 271 Hz), 123.9 (q, J = 271 Hz), 121.4, 70.8, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.1, −63.3. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{20}H_{13}F_6NO_4$, 446.0822; found, 446.0812.

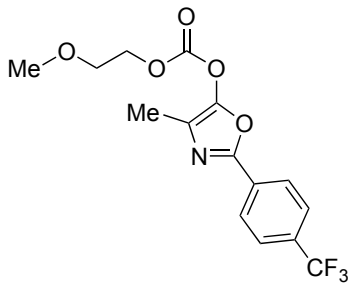


Synthesis of **4Cd**: A flask containing Na_2CO_3 (3.04 g, 28.7 mmol) was dried with a heat gun under reduced pressure. To the flask was added a solution of triphosgene (3.064 g, 10.3 mmol) in toluene (20 mL) was added at 0 °C. After stirring for 0.5 h at 0 °C, a solution of 1-naphthylmethanol (0.790 g, 5.00 mmol) in toluene (5 mL) was added to the mixture, and then stirred for 21 h at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under vacuum. The residue was purified by silica gel column chromatography (hexane to hexane:Et_2O = 5:1) to give 1-naphthylmethyl chloroformate (1.01 g, impure) as a colorless solid, which was used for the next step without further purification. To a solution of 2-

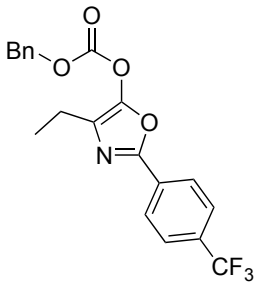
(4-trifluoromethylphenyl)-4-methyloxazolone (0.732 g, 3.01 mmol) in THF (30 mL) was added Et_3N (0.321 g, 3.17 mmol) and 1-naphthylmethyl chloroformate (1.01 g, impure) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then poured into H_2O, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **4Cd** as a colorless solid (0.722 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.70–7.53 (m, 5H), 7.52–7.47 (m, 1H), 5.82 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.4, 151.5, 146.7, 133.9, 131.9 (q, *J* = 32.5 Hz), 131.7, 130.5, 130.3, 129.4, 129.0, 128.6, 127.2, 126.4, 126.2, 125.9 (q, *J* = 3.1 Hz), 125.3, 124.0 (q, *J* = 271 Hz), 123.3, 121.3, 70.4, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{23}H_{16}F_3NO_4$, 428.1104, found, 428.1094.



Synthesis of **4Ce**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (1.216 g, 5.00 mmol) in THF (50 mL) was added Et_3N (0.612 g, 6.05 mmol) and methyl chloroformate (0.566 g, 5.99 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 4:1) to give **4Ce** as a colorless solid (0.815 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 3.99 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.5, 152.2, 146.7, 132.0 (q, *J* = 32.5 Hz), 130.4, 126.2, 125.9 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 271 Hz), 121.3, 56.8, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.3. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{10}F_3NO_4$, 302.0635; found, 302.0631.

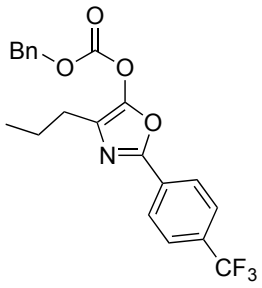


Synthesis of **4Cf**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.9725 g, 4.00 mmol) in THF (80 mL) was added Et_3N (0.6166 g, 4.45 mmol) and 2-methoxyethyl chloroformate (0.4898 g, 4.84 mmol) at 0 °C. The mixture was stirred at 0 °C for 11 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **4Cf** as a colorless liquid (1.02 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08–8.00 (m, 2H), 7.72–7.64 (m, 2H), 4.52–4.42 (m, 2H), 3.76–3.64 (m, 2H), 3.43 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.4, 151.6, 146.6, 132.4 (q, J = 32.5 Hz), 130.4, 126.2, 125.9 (q, J = 3.8 Hz), 123.9 (q, J = 270 Hz), 121.3, 69.8, 69.2, 59.2, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.3. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}F_3NO_5$, 346.0897; found, 346.0889.



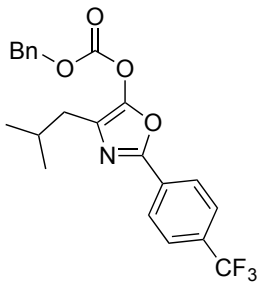
Synthesis of **6Ca**: 1N aqueous NaOH (75 mL) was added to a flask containing DL-2-aminobutanoic acid (3.078 g, 30.0 mmol) at room temperature. To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (6.307 g, 30.2 mmol) in portions over 30 minutes at 0 °C. After the additions were complete, the mixture was allowed to room temperature and then stirred overnight. Concentrated hydrochloric acid (6 mL) was added to the mixture, and the resulting precipitate was collected by filtration and dried under vacuum to afford *N*-2-(4-trifluoromethylbenzoyl)-aminobutanoic acid (4.98 g, 60%, impure) as a colorless solid. A solution of DCC (1.401 g, 6.79 mmol) in CH_2Cl_2 (34 mL) was added to a suspension of the *N*-2-(4-trifluoromethylbenzoyl)-aminobutanoic acid (1.88 g, 6.83 mmol) in CH_2Cl_2 (34 mL) at 0 °C.

After stirring for 1 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-ethyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-ethyloxazolone (1.76 g, 6.8 mmol) in THF (68 mL) was added Et_3N (0.804 g, 7.95 mmol) and benzyl chloroformate (1.228 g, 7.20 mmol) at 0 °C. The mixture was stirred at 0 °C for 13 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **6Ca** as a colorless solid (1.658 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08–8.04 (m, 2H), 7.71–7.66 (m, 2H), 7.48–7.40 (m, 5H), 5.34 (s, 2H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.6, 151.7, 146.0, 133.9, 131.9 (q, *J* = 32.5 Hz), 130.5, 129.4, 129.0, 128.8, 126.6, 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 270 Hz), 72.0, 18.5, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): δ −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{20}H_{16}F_3NO_4$, 392.1094; found, 392.1094.



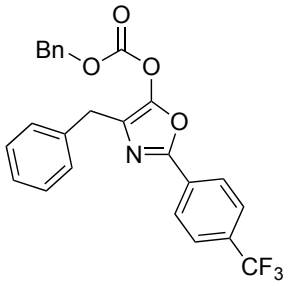
Synthesis of **7Ca**: 1N aqueous NaOH (90 mL) was added to a flask containing DL-2-aminopentanoic acid (3.506 g, 29.9 mmol) at room temperature. To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (6.174 g, 29.6 mmol) in portions over 30 minutes at 0 °C. After the additions were complete, the mixture was allowed to room temperature and then stirred overnight. Concentrated hydrochloric acid (7 mL) was added to the mixture, and the resulting precipitate was collected by filtration and dried under vacuum to afford *N*-2-(4-trifluoromethylbenzoyl)-aminopentanoic acid (6.87 g, 79%, impure) as a colorless solid. DCC (2.071 g, 10.0 mmol) was added to a suspension of *N*-2-(4-trifluoromethylbenzoyl)-aminopentanoic acid (2.90 g, 10.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After stirring for 3 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was

concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-propyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-propyloxazolone (2.71 g, 10.0 mmol) in THF (100 mL) was added Et_3N (1.0 g, 9.9 mmol) and benzyl chloroformate (1.7 g, 9.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 15:1) to give **7Ca** as a colorless solid (2.181 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08–8.03 (m, 2H), 7.71–7.66 (m, 2H), 7.48–7.40 (m, 5H), 5.34 (s, 2H), 2.46 (t, *J* = 7.6 Hz, 2H), 1.69 (tq, *J* = 7.6, 7.6 Hz, 2H), 0.96 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.6, 151.7, 146.6, 133.9, 131.9 (q, *J* = 32.5 Hz), 130.5, 129.4, 129.0, 128.8, 126.2, 125.9 (q, *J* = 3.8 Hz), 125.4, 124.0 (q, *J* = 271 Hz), 72.0, 26.9, 21.3, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{18}F_3NO_4$, 406.1252; found, 406.1261.



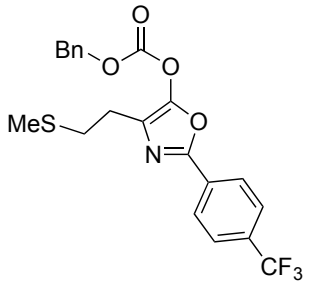
Synthesis of **8Ca**: 1N aqueous NaOH (75 mL) was added to a flask containing L-leucine (3.929 g, 30.0 mmol) at room temperature. To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (6.145 g, 29.5 mmol) in portions over 30 minutes at 0 °C. After the additions were complete, the mixture was allowed to room temperature and then stirred overnight. Concentrated hydrochloric acid (6 mL) was added to the mixture, and the resulting precipitate was collected by filtration and dried under vacuum to afford *N*-4-trifluoromethylbenzoyl-leucine (8.08 g, 89%, impure) as a colorless solid. A solution of DCC (1.49 g, 7.22 mmol) in CH_2Cl_2 (30 mL) was added to a 0 °C slurry of the *N*-4-trifluoromethylbenzoyl-leucine (2.09 g, 6.89 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of

acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-isobutyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-isobutyloxazolone (1.97 g, 6.9 mmol) in THF (100 mL) was added Et_3N (0.839 g, 8.29 mmol) and benzyl chloroformate (1.325 g, 7.77 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **8Ca** as a colorless solid (2.058 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.48–7.40 (m, 5H), 5.34 (s, 2H), 2.35 (d, *J* = 7.2 Hz, 2H), 2.05–1.98 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.6, 151.7, 147.1, 133.9, 131.9 (q, *J* = 32.5 Hz), 130.5, 129.4, 129.0, 128.9, 126.3, 125.9 (q, *J* = 3.8 Hz), 124.7, 124.0 (q, *J* = 270 Hz), 72.0, 33.9, 27.7, 22.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{22}H_{20}F_3NO_4$, 420.1417; found, 420.1404.



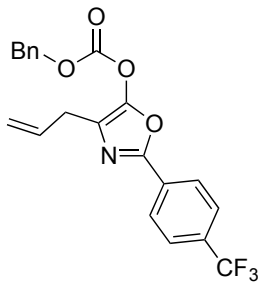
Synthesis of **9Ca**: CH_2Cl_2 (200 mL) and NEt_3 (4.180 g, 41.5 mmol) were added to a flask containing DL-phenylalanine methyl ester hydrochloride (4.020 g, 18.6 mmol). To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (4.127 g, 19.8 mmol) at 0 °C. After stirring for 1 h, the mixture was allowed to room temperature and stirred for 12 h. The mixture was washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and filtrated. The filtrate was concentrated under vacuum to give *N*-4-trifluoromethylbenzoyl-phenylalanine methyl ester as a white solid. The solid was dissolved in methanol (43 mL), 1 M aqueous NaOH (23 mL) and water (20 mL). The resulting mixture was stirred for 1 h, and then acidified with 1 M hydrochloric acid (23 mL). The resulting precipitate was collected by filtration and then dried over under vacuum to afford *N*-4-trifluoromethylbenzoyl-phenylalanine (6.163 g, 98%) as a colorless solid. DCC (1.313 g, 6.36

mmol) was added to a suspension of *N*-4-trifluoromethylbenzoyl-phenylalanine (2.023 g, 6.00 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After stirring for 2 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-benzyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-benzyloxazolone (1.9 g, 6.0 mmol) in THF (60 mL) was added Et_3N (0.747 g, 7.38 mmol) and benzyl chloroformate (1.142 g, 6.69 mmol) at 0 °C. The mixture was stirred at 0 °C for 36 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **9Ca** as a colorless solid (2.363 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.04 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.43–7.37 (m, 5H), 7.28–7.17 (m, 5H), 5.22 (s, 2H), 3.87 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.8, 151.4, 146.9, 137.3, 133.8, 132.0 (q, *J* = 32.6 Hz), 130.3, 129.4, 129.0, 128.9, 128.9, 128.6, 126.8, 126.3, 125.8 (q, *J* = 3.9 Hz), 124.3, 123.9 (q, *J* = 271 Hz), 72.0, 31.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.1. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{25}H_{18}F_3NO_4$, 454.1261, found, 454.1249.



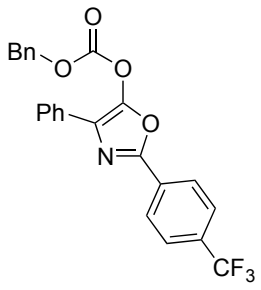
Synthesis of **10Ca**: CH_2Cl_2 (100 mL) and NEt_3 (2.029 g, 20.1 mmol) were added to a flask containing L-methionine methyl ester hydrochloride (1.886 g, 9.45 mmol). To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (1.863 g, 8.93 mmol) at 0 °C. After stirring for 1 h, the mixture was allowed to room temperature and stirred for 12 h. The mixture was washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and filtrated. The filtrate was concentrated under vacuum to give *N*-4-trifluoromethylbenzoyl-methionine methyl ester as a white solid. The solid was dissolved in methanol (17 mL), and 2 M aqueous NaOH (6 mL). The resulting mixture was stirred for 1 h, and

then methanol was removed by rotary evaporation. The residue was dissolved in water, and the aqueous solution was washed with CH_2Cl_2, and then acidified with 1 M hydrochloric acid (12 mL). The resulting precipitate was collected by filtration and then dried over under vacuum to afford *N*-4-trifluoromethylbenzoyl-methionine (2.659 g, 88%) as a colorless solid. A solution of DCC (0.840 g, 4.07 mmol) in CH_2Cl_2 (40 mL) was added to a suspension of *N*-4-trifluoromethylbenzoyl-methionine (1.280 g, 3.98 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 1 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-(2-methylthio)ethyloxazolone as a colorless solid in quantitative yield, which was for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-(2-methylthio)ethyloxazolone (1.2 g, 4.0 mmol) in THF (40 mL) was added Et_3N (0.462 g, 4.57 mmol) and benzyl chloroformate (0.768 g, 4.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **10Ca** as a colorless solid (0.879 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.48–7.40 (m, 5H), 5.34 (s, 2H), 2.85–2.74 (m, 4H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.8, 151.5, 146.9, 133.8, 132.0 (q, *J* = 32.6 Hz), 130.3, 129.4, 129.0, 128.9, 126.3, 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 270 Hz), 123.7, 72.1, 32.3, 25.3, 15.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ): δ −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{18}F_3NO_4S$, 438.0981; found, 438.0975.



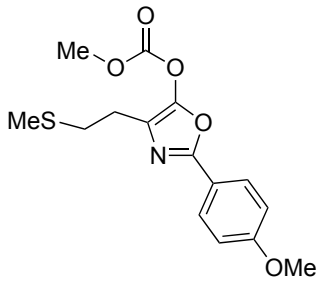
Synthesis of **11Ca**: 1N aqueous NaOH (45 mL) was added to a flask containing DL-2-allylglycine (2.0 g, 17 mmol) at room temperature. To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (3.516 g, 16.9 mmol) in portions over 30 minutes at 0 °C. After

the additions were complete, the mixture was allowed to room temperature and then stirred overnight. Concentrated hydrochloric acid (6 mL) was added to the mixture, and the resulting precipitate was collected by filtration and dried under vacuum to afford *N*-2-(4-trifluoromethylbenzoyl)-allylglycine (3.63 g, 74%) as a colorless solid. A solution of DCC (1.52 g, 6.37 mmol) in CH_2Cl_2 (30 mL) was added to a suspension of *N*-2-(4-trifluoromethylbenzoyl)-allylglycine (1.99 g, 6.93 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring for 1 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-allyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-allyloxazolone (1.9 g, 6.9 mmol) in THF (70 mL) was added Et_3N (0.859 g, 8.48 mmol) and benzyl chloroformate (1.342 g, 7.87 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **11Ca** as a colorless solid (2.042 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.06 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.47–7.40 (m, 5H), 6.00–5.88 (m, 1H), 5.33 (s, 2H), 5.20–5.06 (m, 2H), 3.32–3.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.7, 151.5, 146.8, 133.8, 133.3, 132.0 (q, *J* = 32.5 Hz), 130.3, 129.4, 128.9, 128.9, 126.3, 125.9 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 270 Hz), 123.4, 117.4, 72.1, 29.7. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{16}F_3NO_4$, 404.1104; found, 404.1093.



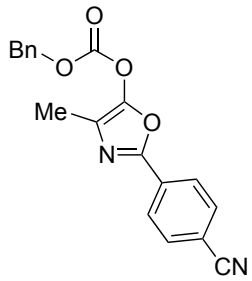
Synthesis of **12Ca**: 1N aqueous NaOH (75 mL) was added to a flask containing L-2-phenylglycine (4.5222 g, 29.9 mmol) at room temperature. To the resulting suspension was added 4-trifluoromethylbenzoyl chloride (6.0591 g, 29.1 mmol) in portions over 30 minutes at 0 °C. After the additions were complete, the mixture was allowed to room temperature and then stirred

overnight. Concentrated hydrochloric acid (6 mL) was added to the mixture, and the resulting precipitate was collected by filtration and dried under vacuum to afford *N*-2-(4-trifluoromethylbenzoyl)-phenylglycine (8.36 g, 86%, impure) as a colorless solid. A solution of DCC (2.0878 g, 10.1 mmol) in CH_2Cl_2 (100 mL) was added to a suspension of the *N*-2-(4-trifluoromethylbenzoyl)-phenylglycine (3.180 g, 9.84 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After stirring for 10 h at room temperature, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-trifluoromethylphenyl)-4-phenyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-phenyloxazolone (3.05 g, 10.0 mmol) in THF (100 mL) was added Et_3N (1.01 g, 10.0 mmol) and benzyl chloroformate (1.70 g, 10.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 14 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 20:1) to give **12Ca** as a colorless solid (0.2258 g, 5%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.17 (d, *J* = 8.0 Hz, 2H), 7.82–7.79 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.47–7.41 (m, 7H), 7.37–7.32 (m, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.8, 151.2, 145.9, 133.8, 132.2 (q, *J* = 32.5 Hz), 130.2, 129.5, 129.4, 129.0, 128.9, 128.9, 128.3, 126.5, 126.1, 125.9 (q, *J* = 3.9 Hz), 124.4, 124.0 (q, *J* = 271 Hz), 72.3. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{24}H_{16}F_3NO_4$, 440.1104; found, 440.1093.



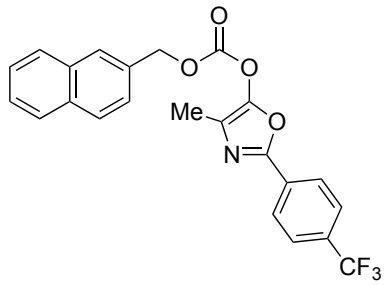
Synthesis of **10Ae**: To a solution of 2-(4-methoxyphenyl)-4-(2-methylthio)ethyloxazolone (1.063 g, 4.0 mmol) in THF (80 mL) was added Et_3N (0.459 g, 4.53 mmol) and methyl chloroformate (0.425 g, 4.49 mmol) at 0 °C. The mixture was stirred at 0 °C for 11 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was

purified by silica gel column chromatography (hexane:Et_2O = 1:1) to give **10Ae** as a colorless solid (1.242 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.89–7.83 (m, 2H), 6.96–6.89 (m, 2H), 3.96 (s, 3H), 3.83 (s, 3H), 2.84–2.73 (m, 4H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.5, 155.4, 152.3, 145.9, 127.7, 122.6, 120.0, 114.2, 56.7, 55.5, 32.4, 25.4, 15.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{15}H_{17}NO_5S$, 324.0900; found, 324.0892.

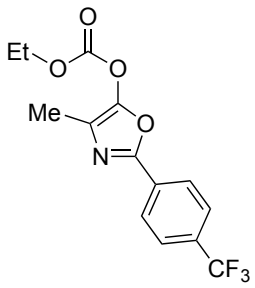


Synthesis of **S17**: CH_2Cl_2 (80 mL) and NEt_3 (4.155 g, 41.1 mmol) were added to a flask containing L-alanine methyl ester hydrochloride (2.812 g, 20.1 mmol). To the resulting suspension was added 4-cyanobenzoyl chloride (3.346 g, 20.2 mmol) at 0 °C. After stirring for 1 h, the mixture was allowed to room temperature and stirred for 12 h. The mixture was washed with 1 M hydrochloric acid, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and filtrated. The filtrate was concentrated under vacuum to give *N*-4-cyanobenzoyl-alanine methyl ester as a colorless solid. The solid was dissolved in methanol (30 mL) and 1 M aqueous NaOH (25 mL). The resulting mixture was stirred for 1 h, and then methanol was removed by rotary evaporation. The residue was dissolved in water, and then the aqueous solution was washed with CH_2Cl_2. The aqueous layer was acidified with 1 M hydrochloric acid (25 mL), extracted with CH_2Cl_2, and dried over $MgSO_4$. After filtration, the filtrate was concentrated under vacuum to give *N*-4-cyanobenzoyl-alanine (1.218 g, 28%) as a colorless solid. A solution of DCC (1.145 g, 5.55 mmol) in CH_2Cl_2 (50 mL) was added to a suspension of the *N*-4-cyanobenzoyl-alanine (1.218 g, 5.58 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After stirring for 1 h at 0 °C, the precipitate (dicyclohexylurea) was removed by filtration, and the filtrate was concentrated under vacuum. The resulting colorless solid was dissolved in a minimum amount of acetone, and the solution was passed through a syringe filter. The filtrate was concentrated under vacuum to afford 2-(4-cyanophenyl)-4-methyloxazolone as a colorless solid in quantitative yield, which was used for the next step without further purification. To a solution of 2-(4-cyanophenyl)-4-methyloxazolone (1.1 g, 5.6 mmol) in THF (50 mL) was added Et_3N (0.562 g, 5.56 mmol) and benzyl chloroformate (0.946 g, 5.55 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water,

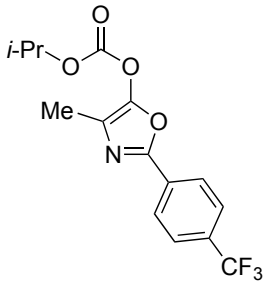
and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 2:1) to give **S17** as a colorless solid (1.46 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.04–7.99 (m, 2H), 7.73–7.68 (m, 2H), 7.47–7.39 (m, 5H), 5.33 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.9, 151.4, 146.9, 133.8, 132.7, 130.9, 129.4, 129.0, 128.8, 126.3, 121.8, 118.4, 113.6, 72.1, 10.4. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{19}H_{14}N_2O_4$, 335.1026; found, 335.1017.



Synthesis of **S18**: A flask containing Na_2CO_3 (4.734 g, 44.7 mmol) was dried with a heat gun under reduced pressure. The flask was added a solution of triphosgene (2.971 g, 10.0 mmol) in toluene (20 mL) at 0 °C. After stirring for 0.5 h at 0 °C, a solution of 2-naphthylmethanol (0.790 g, 5.00 mmol) in toluene (5 mL) was added to the mixture, and then stirred for overnight at room temperature. The precipitate was removed by filtration and the filtrate was concentrated under vacuum to afford 2-naphthylmethyl chloroformate (1.14 g, impure) as a colorless solid, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.474 g, 1.95 mmol) in THF (20 mL) was added Et_3N (0.216 g, 2.13 mmol) and 2-naphthylmethyl chloroformate (1.14 g, impure) at 0 °C. The mixture was stirred at 0 °C for 4 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **S18** as a colorless solid (0.362 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.04 (d, J = 8.0 Hz, 2H), 7.94–7.84 (m, 4H), 7.68 (d, J = 8.4 Hz, 2H), 7.58–7.50 (m, 3H), 5.50 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.5, 151.6, 146.7, 133.6, 133.2, 131.9 (q, J = 32.5 Hz), 131.2, 130.3, 128.9, 128.5, 128.3, 127.9, 127.0, 126.8, 126.2, 125.9, 125.9 (q, J = 3.8 Hz), 124.0 (q, J = 271 Hz), 121.3, 72.2, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{23}H_{16}F_3NO_4$, 428.1104; found, 428.1096.

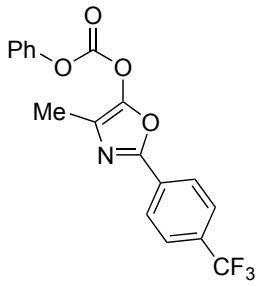


Synthesis of **S19**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.63 g, 2.6 mmol) in THF (50 mL) was added Et_3N (0.288 g, 2.85 mmol) and ethyl chloroformate (0.420 g, 3.87 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **S19** as a colorless solid (0.48 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 4.40 (q, J = 6.8 Hz, 2H), 2.16 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.4, 151.5, 146.7, 131.9 (q, J = 32.5 Hz), 130.4, 126.2, 125.9 (q, J = 3.9 Hz), 124.0 (q, J = 271 Hz), 121.3, 66.7, 14.2, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{14}H_{12}F_3NO_4$, 316.0791; found, 316.0790.

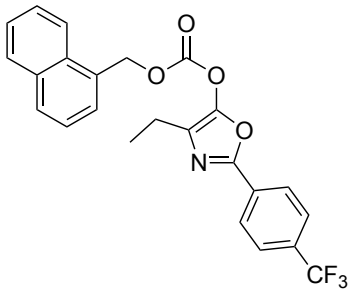


Synthesis of **S20**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.75 g, 3.0 mmol) in THF (60 mL) was added Et_3N (0.338 g, 3.34 mmol) and isopropyl chloroformate (0.460 g, 3.75 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **S20** as a colorless solid (0.59 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.06 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 5.03 (sept, J = 6.4 Hz, 1H), 2.16 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.4, 150.9, 146.8, 131.9 (q, J = 32.5 Hz), 130.4, 126.2, 125.9 (q, J = 3.9 Hz), 124.0 (q, J =

271 Hz), 121.2, 75.6, 21.7, 10.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{15}H_{14}F_3NO_4$, 330.0948; found, 330.0943.



Synthesis of **S21**: To a solution of 2-(4-trifluoromethylphenyl)-4-methyloxazolone (0.74 g, 3.0 mmol) in THF (60 mL) was added Et_3N (0.338 g, 3.34 mmol) and phenyl chloroformate (0.549 g, 3.51 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, then poured into water, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **S21** as a colorless solid (0.68 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.49–7.42 (m, 2H), 7.36–7.28 (m, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.7, 150.8, 150.1, 146.4, 132.1 (q, *J* = 32.5 Hz), 130.3, 129.9, 127.1, 126.2, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 271 Hz), 121.6, 120.6, 10.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): δ −63.2. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{18}H_{12}F_3NO_4$, 364.0791; found, 364.0786.



Synthesis of **6Cd**: A flask containing Na_2CO_3 (9.432 g, 89.0 mmol) was dried with a heat gun under reduced pressure. To the flask was added a solution of triphosgene (5.940 g, 20.0 mmol) in toluene (40 mL) was added at 0 °C. After stirring for 0.5 h at 0 °C, a solution of 1-naphthylmethanol (1.573 g, 9.94 mmol) in toluene (10 mL) was added to the mixture, and then stirred for 12 h at room temperature. The precipitate was removed by filtration, and the filtrate was evaporated under vacuum. The residue was purified by silica gel column chromatography

(hexane to hexane:Et_2O = 4:1) to give 1-naphthylmethyl chloroformate (2.583 g, impure) as a colorless solid, which was used for the next step without further purification. To a solution of 2-(4-trifluoromethylphenyl)-4-ethyloxazolone (0.254 g, 0.986 mmol) in THF (10 mL) was added Et_3N (0.127 g, 1.25 mmol) and 1-naphthylmethyl chloroformate (2.583 g, impure) at 0 °C. The mixture was stirred at 0 °C for 11 h, then poured into H_2O, and extracted with Et_2O. The combined organic layer was washed with 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:Et_2O = 5:1) to give **6Cd** as a colorless solid (0.094 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.15–7.99 (m, 3H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.71–7.47 (m, 6H), 5.81 (s, 2H), 2.51 (q, *J* = 8.0 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.6, 151.7, 146.0, 133.9, 131.9 (q, *J* = 32.5 Hz), 131.7, 130.5, 129.5, 129.1, 128.7, 127.2, 126.6, 126.4, 126.3, 125.9 (q, *J* = 3.9 Hz), 125.4, 124.0 (q, *J* = 271 Hz), 123.4, 70.4, 18.5, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.9. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{24}H_{18}F_3NO_4$, 442.1261; found, 442.1250.

3.7. Steglich Rearrangement using Nucleophilic Organocatalyst

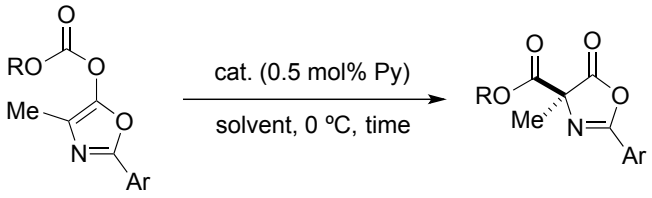
3.7.1 General Procedure for Table 1, entry 1–10

To a solution of oxazolyl carbonate **4** (0.30 mmol) in solvent (3.0 mL) was added a solution of catalyst (9.0–10 mg, 1.5 μmol pyridyl pendants) in solvent (3.0 mL) by cannula at 0 °C. After the reaction was complete (checked by ^{1}H NMR analysis), the solvent was removed by rotary evaporation, and acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silica gel column chromatography to afford *C*-carboxyazlactone **5**. The enantiomeric excesses of the products were determined by chiral SFC analysis.

3.7.2. Procedure for Table 1, entry 11

(*P*)-(*R*)-**PQXmdpp C7** (10.0 mg, 1.5 μmol pyridyl pendants) in toluene (1.5 mL) and 1,1,2-trichloroethane (1.5 mL) was stirred at room temperature for 48 h. The obtained solution of (*M*)-(*R*)-**PQXmdpp C7** was added to a solution of **4Ca** (114.4 mg, 0.30 mmol) in toluene (1.5 mL) and 1,1,2-trichloroethane (1.5 mL) by cannula at 0 °C. The mixture was stirred for 1 h. After the reaction was complete (checked by ^{1}H NMR analysis), the solvent was removed by rotary evaporation, and acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was

Table S1. Optimization of Steglich Rearrangement using Nucleophilic Organocatalyst[a]



entry	substrate	Ar	R	cat.	solvent	time (h)	% yield[b]	% ee[c]
1	**4Aa**	4-$MeOC_6H_4$	Bn	**C1**	$CHCl_3$	14	79 (**5Aa**)	51
2	**4Aa**	4-$MeOC_6H_4$	Bn	**C1**	THF	60	87 (**5Aa**)	50
3	**4Aa**	4-$MeOC_6H_4$	Bn	**C1**	*m*-xylene	48	86 (**5Aa**)	60
4	**4Aa**	4-$MeOC_6H_4$	Bn	**C1**	toluene	35	92 (**5Aa**)	62
5	**4Aa**	4-$MeOC_6H_4$	Bn	**C7**	toluene	3	99 (**5Aa**)	69
6	**4Ba**	4-ClC_6H_4	Bn	**C7**	toluene	1	91 (**5Ba**)	71
7	**S17**	4-CNC_6H_4	Bn	**C7**	toluene	1	59 (**S22**)[d]	74
8	**4Ca**	4-$CF_3C_6H_4$	Bn	**C7**	toluene	1	88 (**5Ca**)	75
9	**4Cb**	4-$CF_3C_6H_4$	4-$MeC_6H_4CH_2$	**C7**	toluene	1	86 (**5Cb**)	73
10	**4Cc**	4-$CF_3C_6H_4$	4-$CF_3C_6H_4CH_2$	**C7**	toluene	1	74 (**5Cc**)	71
11	**4Cd**	4-$CF_3C_6H_4$	1-naphthylmethyl	**C7**	toluene	1	83 (**5Cd**)	70
12	**S18**	4-$CF_3C_6H_4$	2-naphthylmethyl	**C7**	toluene	1	81 (**S23**)	62
13	**4Ce**	4-$CF_3C_6H_4$	Me	**C7**	toluene	1	75 (**5Ce**)	72
14	**S19**	4-$CF_3C_6H_4$	Et	**C7**	toluene	2	79 (**S24**)	63
15	**S20**	4-$CF_3C_6H_4$	^{i}Pr	**C7**	toluene	236	61 (**S25**)[d,e]	50
16	**S21**	4-$CF_3C_6H_4$	Ph	**C7**	toluene	1	73 (**S26**)	<1

[a]Substrate (0.3 mmol), and (*P*)-(*R*)-**PQXdmap** derivatives (0.5 mol% pyridyl pendants) were stirred in solvent (6.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by chiral SFC analysis. [d]NMR yield. [e]78% conversion.

removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silica gel column chromatography (hexane:Et_2O = 5:1) to afford **5Ca** (89.7 mg, 78% with −45% ee). The enantiomeric excess of the product was determined by chiral SFC analysis.

3.7.3. General Procedure for Scheme 3

To a solution of **4Ca** (113 mg, 0.30 mmol) in toluene (3.0 mL) was slowly added a solution of

(*P*)-(*R*)-**PQXmdpp** (**C7**: 9.90 mg, **C9**: 13 mg, **C10**: 6.44 mg, or **C11**: 26 mg, 1.5 μmol pyridyl pendants) in toluene (3.0 mL) over 5 minutes at −60 °C under nitrogen atmosphere. The reaction mixture was stirred at −60 °C for 24 h. After yellow color of the reaction mixture disappeared, the solvent was then removed by rotary evaporation, and acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silica gel column chromatography (hexane:Et_2O = 5:1) to afford **5Ca** as a colorless liquid. The enantiomeric excesses of the products were determined by chiral SFC analysis.

3.7.4. General Procedure for Table 2

To a solution of oxazolyl carbonate (0.10 mmol) in toluene (1.0 mL) was slowly added a solution of (*P*)-(*R*)-**PQXmdpp C11** (8.6–9.0 mg, 0.5 μmol pyridyl pendants) in toluene (1.0 mL) over 5 minutes at −60 °C under nitrogen atmosphere. The mixture was stirred for 24–96 h at −60 °C. After yellow color of the reaction mixture disappeared, the solvent was removed by rotary evaporation, and then acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silica gel column chromatography to afford *C*-carboxyazlactone. The enantiomeric excesses of the products were determined by chiral SFC analysis.

3.7.5. Gram Scale Synthesis of 18Ca (Table 2, entry 13)

To a suspension of **11Ca** (1.278 g, 3.02 mmol) in toluene (1.5 mL) was slowly added a solution of (*P*)-(*R*)-**PQXmdpp C11** (52.6 mg, 3.01 μmol pyridyl pendants) in toluene (1.5 mL) over 15 minutes at −60 °C under nitrogen atmosphere. The mixture was stirred for 48 h. After the reaction was complete (^{1}H NMR analysis), the solvent was then removed by rotary evaporation, and then acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was separated by centrifugation followed by washing with acetonitrile for two times (52.6 mg, 99% of polymer catalyst was recovered). The supernatant solution was evaporated under vacuum and was subjected to silica gel column chromatography (hexane:Et_2O = 5:1) to afford **18Ca** (1.076 g, 88% with 92% ee). The enantiomeric excess of the product was determined by chiral SFC analysis.

3.7.6. Reuse of the Polymer Catalyst (Scheme 4)

To a solution of **11Ca** (121 mg, 0.30 mmol) in toluene (1.5 mL) was slowly added a solution of (*P*)-(*R*)-**PQXmdpp C11** (52.3 mg, 2.99 μmol pyridyl pendants) in toluene (1.5 mL) over 5

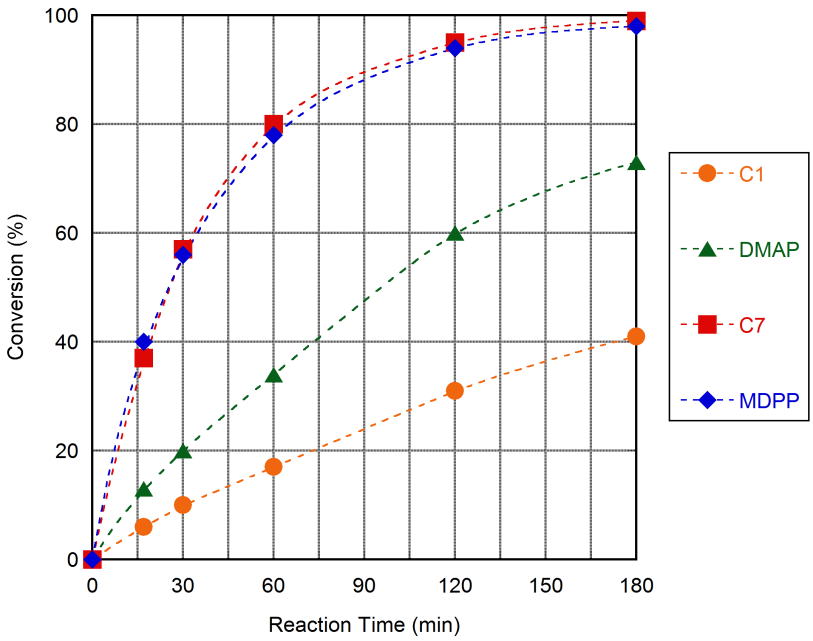


Figure S1. Time course for Steglich rearrangement of **4Aa**

minutes at −60 °C under nitrogen atmosphere. The resulting yellow reaction mixture was stirred at −60 °C for 24 h. After yellow color of the reaction mixture disappeared, the solvent was removed by rotary evaporation, and acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was separated by centrifugation followed by washing with acetonitrile for two times. The supernatant solution was evaporated under vacuum, and the residue was subjected to silica gel column chromatography (hexane:Et_2O = 5:1) to **18Ca** (120 mg, 99% with 91% ee). The recovered polymer catalyst was freeze-dried from benzene, and used for the next run. After 11th reuse run, 24.6 mg of (*P*)-(*R*)-**PQXmdpp C11** was recovered (on average, 95% recovery in each cycle). The enantiomeric excesses of the products were determined by chiral SFC analysis.

3.7.7. Time Course for Steglich Rearrangement of 4Aa

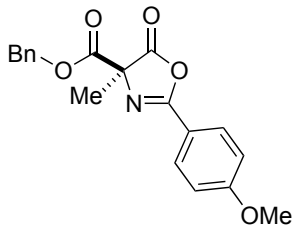
To a solution of **4Aa** (0.10 M in benzene-d_6, 350 μL, 35 μmol) was added a solution of catalyst (0.25 mM in benzene-d_6, 350 μL, 0.088 μmol) in a NMR tube under nitrogen atmosphere. The conversion of **4Aa** at 24 °C was checked by ^{1}H NMR analysis.

3.7.8. Crossover Experiment (Table 3)

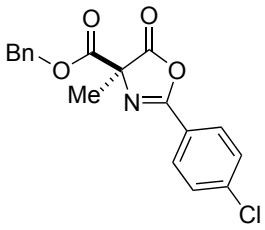
To a mixture of **10Ae** (48 mg, 0.15 mmol) and **4Aa** (51 mg, 0.15 mmol) in toluene (3.0 mL) was added a solution of catalyst (1.5 μmol pyridyl pendants) in toluene (3.0 mL) at 0 °C. The solution

was stirred at 0 °C until the reaction was complete (checked by ^{1}H NMR analysis). The mixture was concentrated under vacuum, and acetonitrile was added to precipitate polymer catalyst. The polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The ratios of noncrossover and crossover products were determined by ^{1}H NMR analysis.

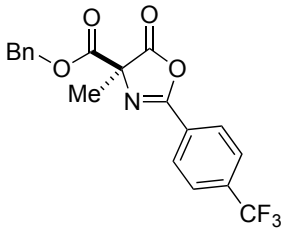
3.8. Spectral Data for *C*-Carboxyazlactone



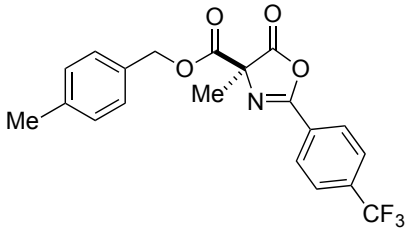
5Aa: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.99–7.94 (m, 2H), 7.36–7.24 (m, 5H), 7.01–6.95 (m, 2H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.20 (d, *J* = 12.4 Hz, 1H), 3.87 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 175.3, 166.2, 163.8, 163.0, 134.9, 130.3, 128.7, 128.5, 127.9, 117.5, 114.4, 72.9, 68.2, 55.6, 20.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{19}H_{17}NO_5$, 340.1179; found, 340.1177. $[\alpha]^{20}_D$ −45° (*c* 0.99, $CHCl_3$; for product with 77% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/5, v/v, flow late = 3.15 mL/min, UV = 220 nm), t_R = 5.7 min (minor), t_R = 6.2 min (major), 69% ee.



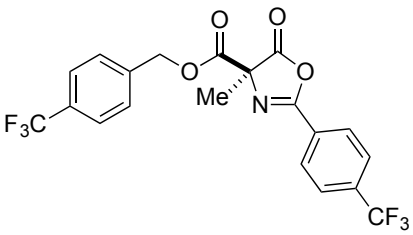
5Ba: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.98–7.93 (m, 2H), 7.50–7.45 (m, 2H), 7.34–7.28 (m, 5H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.7, 165.7, 162.6, 139.9, 134.7, 129.7, 129.4, 128.7, 128.6, 128.0, 123.8, 73.1, 68.4, 20.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{14}ClNO_4$, 344.0684; found, 344.0682. $[\alpha]^{20}_D$ −43° (*c* 0.48, $CHCl_3$; for product with 71% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/5, v/v, flow late = 3.15 mL/min, UV = 220 nm), t_R = 4.1 min (minor), t_R = 4.7 min (major), 71% ee.



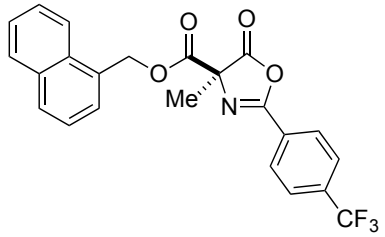
5Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18–8.12 (m, 2H), 7.80–7.74 (m, 2H), 7.37–7.27 (m, 5H), 5.27 (d, *J* = 12.8 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 165.5, 162.4, 134.9 (q, *J* = 32.5 Hz), 134.7, 128.8, 128.8, 128.7, 128.7, 128.0, 126.0 (q, *J* = 3.6 Hz), 123.6 (q, *J* = 272 Hz), 73.2, 68.6, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{19}H_{14}F_3NO_4$, 378.0948; found, 378.0941. $[\alpha]^{20}_D$ −57° (*c* 0.53, $CHCl_3$; for product with 92% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.8 min (minor), t_R = 7.5 min (major), 92% ee.



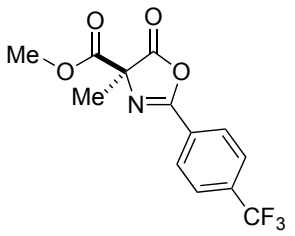
5Cb: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.17–8.11 (m, 2H), 7.80–7.74 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 2.33 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 165.6, 162.3, 138.6, 134.9 (q, *J* = 32.5 Hz), 131.7, 129.4, 128.8, 128.7, 128.2, 126.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 271 Hz), 73.2, 68.6, 21.3, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.5. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{20}H_{16}F_3NO_4$, 392.1104; found, 392.1094. $[\alpha]^{20}_D$ −42° (*c* 0.67, $CHCl_3$; for product with 73% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.8 min (minor), t_R = 7.5 min (major), 90% ee.



5Cc: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18–8.13 (m, 2H), 7.82–7.75 (m, 2H), 7.63–7.58 (m, 2H), 7.41–7.38 (m, 2H), 5.31 (d, J = 12.8 Hz, 1H), 5.25 (d, J = 12.8 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.4, 165.4, 162.5, 138.6, 135.1 (q, J = 32.5 Hz), 130.9 (q, J = 32.5 Hz), 128.8, 128.6, 128.0, 126.1 (q, J = 3.6 Hz), 125.8 (q, J = 3.6 Hz), 124.0 (q, J = 271 Hz), 123.5 (q, J = 271 Hz), 73.1, 67.5, 20.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.1, −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{20}H_{13}F_6NO_4$, 446.0822; found, 446.0813. $[\alpha]^{20}_D$ −38° (*c* 0.86, $CHCl_3$; for product with 71% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 4.4 min (minor), t_R = 8.7 min (major), 92% ee.

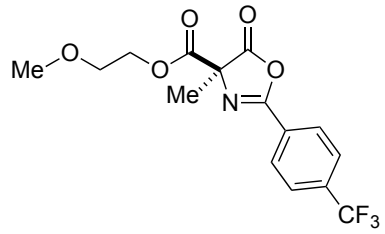


5Cd: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05–8.00 (m, 2H), 7.88–7.80 (m, 3H), 7.74–7.69 (m, 2H), 7.51–7.47 (m, 1H), 7.46–7.33 (m, 3H), 5.70 (d, J = 12.8 Hz, 1H), 5.66 (d, J = 12.8 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 165.5, 162.4, 134.8 (q, J = 33.3 Hz), 133.8, 131.5, 130.0, 129.9, 128.8, 128.8, 128.6, 127.8, 126.7, 126.1, 125.9 (q, J = 3.9 Hz), 125.3, 123.6 (q, J = 272 Hz), 123.3, 73.3, 67.3, 20.2. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.5. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{23}H_{16}F_3NO_4$, 428.1104; found, 428.1096. $[\alpha]^{20}_D$ −42° (*c* 0.88, $CHCl_3$; for product with 70% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/3, v/v, flow late = 3.09 mL/min, UV = 220 nm), t_R = 8.3 min (minor), t_R = 9.1 min (major), 94% ee.

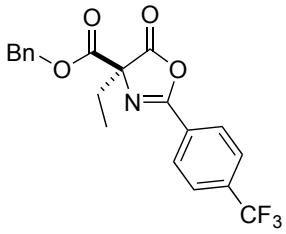


5Ce: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.75 (m, 2H), 3.81 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 166.2, 162.3, 135.0 (q, J = 32.5 Hz), 128.9, 128.7, 126.0 (q, J = 3.6 Hz), 123.6 (q, J = 272 Hz), 73.0, 54.0, 20.7. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{10}F_3NO_4$, 302.0635; found, 302.0632. $[\alpha]^{20}_D$ −56° (*c* 0.99, $CHCl_3$; for product with 72% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-

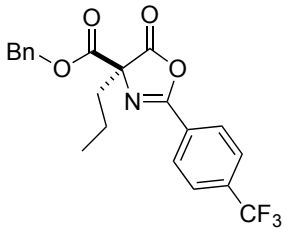
PrOH = 100/0.5, v/v, flow late = 3.02 mL/min, UV = 220 nm), t_R = 3.0 min (minor), t_R = 4.3 min (major), 72% ee.



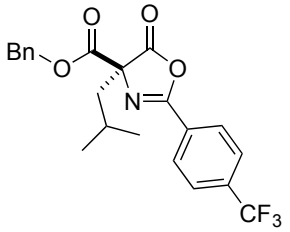
5Cf: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.12 (m, 2H), 7.79–7.74 (m, 2H), 4.40–4.29 (m, 2H), 3.58 (t, *J* = 4.4 Hz, 2H), 3.32 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.4, 165.7, 162.3, 134.9 (q, *J* = 32.5 Hz), 128.8, 128.7, 126.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 271 Hz), 73.1, 69.9, 66.1, 59.2, 20.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}F_3NO_5$, 346.0897; found, 346.0889. $[\alpha]^{20}_D$ −56° (*c* 0.50, $CHCl_3$; for product with 73% ee). SFC analysis: Daicel CHIRALCEL OZ-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.9 min (minor), t_R = 7.3 min (major), 90% ee.



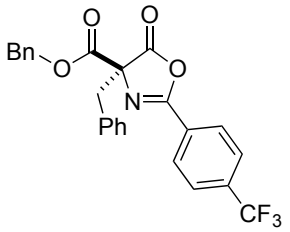
13Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.75 (m, 2H), 7.36–7.29 (m, 5H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 2.43–2.23 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.7, 165.3, 162.3, 134.9 (q, *J* = 32.5 Hz), 134.8, 128.8, 128.8, 128.7, 128.6, 128.1, 126.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 272 Hz), 77.6, 68.4, 28.1, 7.83. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{20}H_{16}F_3NO_4$, 392.1104; found, 392.1097. $[\alpha]^{20}_D$ −49° (*c* 0.80, $CHCl_3$; for product with 94% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.5 min (minor), t_R = 8.5 min (major), 94% ee.



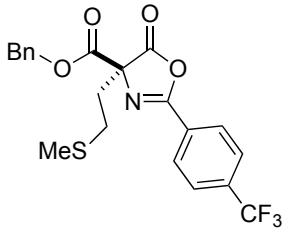
14Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18–8.13 (m, 2H), 7.80–7.74 (m, 2H), 7.36–7.28 (m, 5H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 2.37–2.14 (m, 2H), 1.41–1.17 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.8, 165.4, 162.1, 134.9 (q, *J* = 32.6 Hz), 134.7, 128.8, 128.8, 128.7, 128.6, 128.1, 126.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 271 Hz), 68.5, 36.5, 17.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{18}F_3NO_4$, 406.1261; found, 406.1254. $[\alpha]^{20}_D$ −47° (*c* 0.85, $CHCl_3$; for product with 92% ee). SFC analysis: Daicel CHIRALCEL OJ-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 3.5 min (major), t_R = 7.1 min (minor), 92% ee.



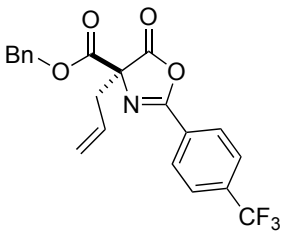
15Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.75 (m, 2H), 7.36–7.29 (m, 5H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 2.43 (dd, *J*= 14.4, 6.0 Hz, 1H), 2.08 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.76–1.65 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.3, 165.5, 161.9, 134.9 (q, *J* = 33.3 Hz), 134.7, 128.8, 128.8, 128.7, 128.1, 126.1 (q, *J* = 3.6 Hz), 123.6 (q, *J* = 271 Hz), 76.8, 68.5, 42.9, 24.8, 23.8, 23.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{22}H_{20}F_3NO_4$, 420.1417; found, 420.1409. $[\alpha]^{20}_D$ −62° (*c* 0.82, $CHCl_3$; for product with 86% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.2 min (minor), t_R = 7.1 min (major), 86% ee.



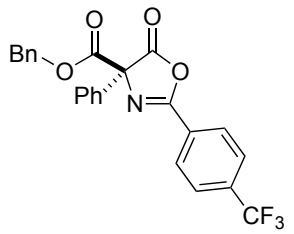
16Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.01–7.98 (m, 2H), 7.72–7.67 (m, 2H), 7.37–7.30 (m, 5H), 7.18–7.15 (m, 5H), 5.30 (d, *J* = 12.4 Hz, 1H), 5.26 (d, *J* = 12.0 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 3.54 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.1, 165.2, 162.1, 134.8 (q, *J* = 32.5 Hz), 134.7, 132.6, 130.4, 128.8, 128.8, 128.7, 128.5, 128.4, 128.2, 127.9, 125.9 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 271 Hz), 77.9, 68.7, 40.3. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{25}H_{18}F_3NO_4$, 454.1261; found, 454.1252. $[\alpha]^{20}_D$ −130° (*c* 0.90, $CHCl_3$; for product with 91% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/3, v/v, flow late = 3.09 mL/min, UV = 220 nm), t_R = 5.0 min (minor), t_R = 6.9 min (major), 91% ee.



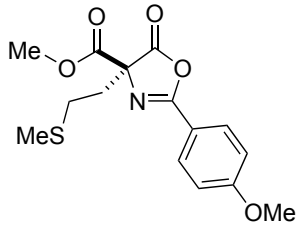
17Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.75 (m, 2H), 7.35–7.27 (m, 5H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 2.76–2.44 (m, 4H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.9, 165.1, 163.0, 135.0 (q, *J* = 32.5 Hz), 134.6, 128.9, 128.8, 128.6, 128.2, 126.1 (q, *J* = 3.1 Hz), 123.6 (q, *J* = 271 Hz), 75.9, 68.7, 33.1, 28.4, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{18}F_3NO_4S$, 438.0981; found, 438.0974. $[\alpha]^{20}_D$ −91° (*c* 0.79, $CHCl_3$; for product with 87% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/3, v/v, flow late = 3.09 mL/min, UV = 220 nm), t_R = 4.5 min (minor), t_R = 6.9 min (major), 87% ee.



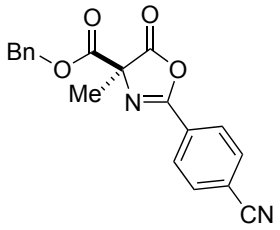
18Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): δ 8.18–8.13 (m, 2H), 7.80–7.74 (m, 2H), 7.37–7.29 (m, 5H), 5.67–5.55 (m, 1H), 5.30–5.14 (m, 4H), 3.14–3.07 (m, 1H), 3.01–2.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.1, 165.0, 162.3, 134.9 (q, J = 32.5 Hz), 134.6, 129.0, 128.9, 128.8, 128.8, 128.5, 128.2, 126.0 (q, J = 3.8 Hz), 123.6 (q, J = 267 Hz), 122.2, 77.0, 68.6, 38.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{21}H_{16}F_3NO_4$, 404.1104; found, 404.1098. $[\alpha]^{20}_D$ −75° (*c* 0.81, $CHCl_3$; for product with 93% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 5.7 min (minor), t_R = 8.3 min (major), 93% ee.



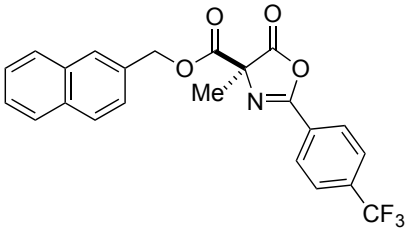
19Ca: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.28–8.22 (m, 2H), 7.82–7.77 (m, 2H), 7.75–7.70 (m, 2H), 7.44–7.40 (m, 3H), 7.32–7.29 (m, 3H), 7.26–7.24 (m, 2H), 5.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.0, 165.1, 162.5, 135.1 (q, J = 33.3 Hz), 134.7, 133.3, 129.5, 129.0, 129.0, 128.7, 128.7, 128.0, 126.6, 126.1 (q, J = 3.8 Hz), 123.6 (q, J = 272 Hz), 77.9, 68.8. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{24}H_{16}F_3NO_4$, 440.1104; found, 440.1097. $[\alpha]^{20}_D$ −27° (*c* 0.69, $CHCl_3$; for product with 15% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/3, v/v, flow late = 3.09 mL/min, UV = 220 nm), t_R = 7.2 min (minor), t_R = 9.7 min (major), 18% ee.



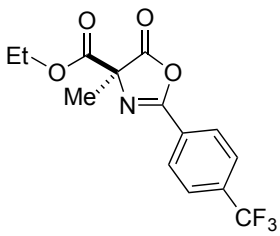
17Ae: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.00–7.94 (m, 2H), 7.00–6.96 (m, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 2.67–2.41 (m, 4H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.6, 166.3, 163.9, 163.5, 130.4, 117.4, 114.4, 75.5, 55.7, 53.8, 33.4, 28.3, 15.1. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{15}H_{17}NO_5S$, 324.0900; found, 324.0893.



S22: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.16–8.09 (m, 2H), 7.84–7.76 (m, 2H), 7.38–7.23 (m, 5H), 5.26 (d, *J* = 12.8 Hz, 1H), 5.20 (d, *J* = 12.4 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.2, 165.4, 162.0, 134.6, 132.7, 129.3, 128.9, 128.8, 128.8, 128.1, 117.8, 116.9, 73.3, 68.6, 20.5. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{19}H_{14}N_2O_4$, 335.1026; found, 335.1020. $[\alpha]^{20}_D$ −43° (*c* 0.61, $CHCl_3$; for product with 74% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/5, v/v, flow late = 3.15 mL/min, UV = 220 nm), t_R = 5.8 min (minor), t_R = 7.9 min (major), 74% ee.

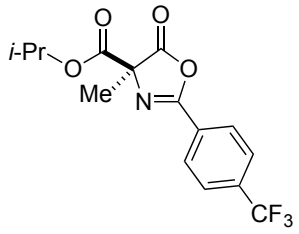


S23: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.14 (d, *J* = 8.0 Hz, 2H), 7.84–7.72 (m, 6H), 7.52–7.45 (m, 2H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.40 (s, 2H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 165.6, 162.4, 134.9 (q, *J* = 32.5 Hz), 133.3, 133.2, 132.0, 128.8, 128.7, 128.7, 128.1, 127.8, 127.5, 126.6, 126.6, 126.0 (q, *J* = 3.8 Hz), 125.5, 123.6 (q, *J* = 272 Hz), 73.3, 68.7, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{23}H_{16}F_3NO_4$, 428.1104; found, 428.1098. $[\alpha]^{20}_D$ −36° (*c* 0.97, $CHCl_3$; for product with 62% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/5, v/v, flow late = 3.15 mL/min, UV = 220 nm), t_R = 6.0 min (minor), t_R = 8.2 min (major), 62% ee.

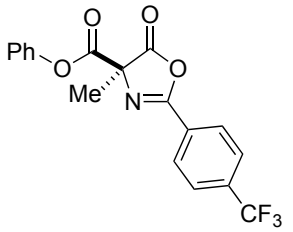


S24: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.73 (m, 2H), 4.34–4.19 (m, 2H),

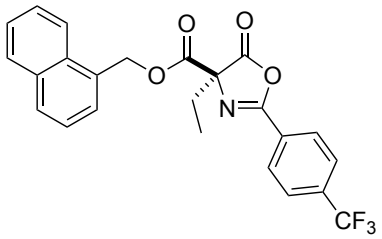
1.79 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.7, 165.7, 162.2, 134.9 (q, J = 32.6 Hz), 128.8, 128.8, 126.0 (q, J = 3.9 Hz), 123.6 (q, J = 272 Hz), 73.2, 63.4, 20.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{12}F_3NO_4$, 338.0611; found, 338.0608. $[\alpha]^{20}_D$ −60° (*c* 0.53, $CHCl_3$; for product with 63% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/0.2, v/v, flow late = 3.01 mL/min, UV = 220 nm), t_R = 3.3 min (minor), t_R = 4.1 min (major), 63% ee.



S25: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19–8.14 (m, 2H), 7.80–7.74 (m, 2H), 5.13–5.00 (m, 1H), 1.26 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.8, 165.2, 162.1, 134.9 (q, J = 33.3 Hz), 128.8, 126.0 (q, J = 3.6 Hz), 123.6 (q, J = 270.9 Hz), 73.4, 71.5, 21.5, 20.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}F_3NO_4$, 330.0948; found, 330.0945. $[\alpha]^{20}_D$ −36° (*c* 0.50, $CHCl_3$; for product with 50% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/1, v/v, flow late = 3.03 mL/min, UV = 220 nm), t_R = 2.0 min (minor), t_R = 2.2 min (major), 50% ee.

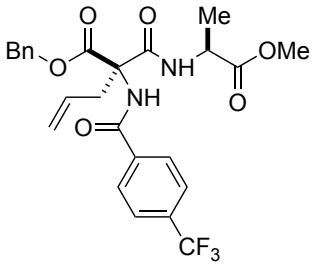


S26: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.24–8.19 (m, 2H), 7.83–7.77 (m, 2H), 7.41–7.35 (m, 2H), 7.28–7.23 (m, 1H), 7.12–7.08 (m, 2H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.3, 164.3, 162.8, 150.3, 135.1 (q, J = 33.3 Hz), 129.7, 128.9, 128.6, 126.8, 126.1 (q, J = 3.9 Hz), 123.6 (q, J = 271 Hz), 121.1, 73.3, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{12}F_3NO_4$, 364.0791; found, 364.0791. SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/0.2, v/v, flow late = 3.01 mL/min, UV = 220 nm), t_R = 11.4 min (minor), t_R = 12.9 min (major), 0.7% ee.



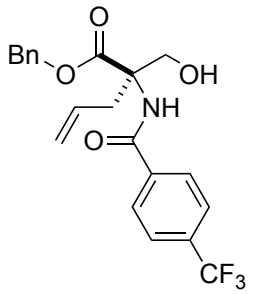
21Cd: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.07 (d, *J* = 8.0 Hz, 2H), 7.92–7.86 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.48–7.36 (m, 3H), 5.71 (d, *J* = 12.4 Hz, 1H), 5.67 (d, *J* = 12.4 Hz, 1H), 2.42–2.21 (m, 2H), 0.89 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.7, 165.3, 162.4, 134.8 (q, *J* = 32.5 Hz), 133.8, 131.5, 130.1, 129.9, 128.8, 128.8, 128.6, 127.8, 126.7, 126.1, 125.9 (q, *J* = 3.9 Hz), 125.3, 123.6 (q, *J* = 272 Hz), 123.4, 77.7, 67.1, 27.8, 7.79. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.4. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{24}H_{18}F_3NO_4$, 442.1261; found, 442.1250. $[\alpha]^{20}_D$ −38° (*c* 1.12, $CHCl_3$; for product with 97% ee). SFC analysis: Daicel CHIRALCEL OD-H (CO_2/*i*-PrOH = 100/10, v/v, flow late = 3.30 mL/min, UV = 220 nm), t_R = 3.1 min (minor), t_R = 3.6 min (major), 97% ee.

3.9. Derivatization of *C*-carboxyazlactone (Figure 1)



Synthesis of **22**: The azlactone **18Ca** (120 mg, 0.30 mmol; 92% ee of the (–)-enantiomer, from a rearrangement conducted with (*P*)-(*R*)-**PQXmdpp C11** at −60 °C) was dissolved in CH_2Cl_2 (5 mL) and added to a mixture of L-alanine methyl ester hydrochloride (66 mg, 0.48 mmol), NEt_3 (58 mg, 0.58 mmol), and DMAP (18 mg, 0.15 mmol) in CH_2Cl_2 (3 mL). The resulting clear, colorless solution was stirred at room temperature for 23 h. The mixture was directly subjected to flash column chromatography (hexane:Et_2O = 1:2) as the eluent, giving **22** as a colorless, viscous oil (141 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.92–7.86 (m, 2H), 7.73–7.67 (m, 3H), 7.38–7.27 (m, 5H), 6.91 (d, *J* = 6.8 Hz, 1H), 5.66–5.51 (m, 1H), 5.27 (d, *J* = 12.0 Hz, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.16–5.08 (m, 2H), 4.57–4.47 (m, 1H), 3.73 (S, 3H), 3.48–3.39 (m, 1H), 3.12–3.03 (m, 1H), 1.40 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.4, 169.3, 165.7, 165.2, 137.1, 134.9, 133.7 (q, *J* = 32.5 Hz), 130.7, 128.6, 128.5, 127.7, 125.8, 123.7 (q, *J* = 271 Hz),

120.7, 68.6, 66.4, 52.8, 49.0, 38.1, 18.2. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.9. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{25}F_3N_2O_6$, 529.1557; found, 529.1543.



Synthesis of **23**: The azlactone **18Ca** (119 mg, 0.29 mmol; 92% ee of the (–)-enantiomer, from a rearrangement conducted with (*P*)-(*R*)-**PQXmdpp C11** at −60 °C) was dissolved in THF (3 mL) in a round-bottom flask with a stir bar at room temperature. Solid $NaBH_4$ (7 mg. 0.18 mmol) was added in one portion to the solution. After 12 h, TLC analysis (hexane:EtOAc = 1:1) revealed that substrates were slightly remaining, so another $NaBH_4$ (5 mg. 0.18 mmol) was added. The solution was stirred for 10 h, after which saturated aqueous $NaHCO_3$ was added. The THF was removed by rotary evaporation, and the products was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash column chromatography (hexane: EtOAc = 1:1) as the eluent. The product **23** was bright yellow, viscous oil (84 mg, 70%). At the same time, over reduced diol was also obtained (28mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.92–7.82 (m, 2H), 7.73–7.66 (m, 2H), 7.43–7.31 (m, 5H), 7.20 (brs, 1H), 5.64–5.50 (m, 1H), 5.29 (d, J = 12.0 Hz, 1H), 5.25 (d, J = 12.4 Hz, 1H), 5.16–5.00 (m, 2H), 4.43–4.30 (m, 1H), 4.02–3.91 (m, 1H), 3.57 (brs, 1H), 3.12–2.99 (m, 1H), 2.70–2.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.1, 166.4, 137.6, 135.0, 133.8 (q, J = 32.6 Hz), 131.2, 128.9, 128.6, 127.7, 125.9, 123.7 (q, J = 270 Hz), 120.7, 68.4, 66.6, 65.8, 36.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −62.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{20}F_3NO_4$, 430.1237; found, 430.1227.

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Chapter 2

Kinetic Resolution of Secondary Alcohols Using Helical Poly(quinoxaline-2,3-diyl)s Bearing 4-Dialkylaminopyrid-3-yl Pendants as Chirality-Switchable Nucleophilic Catalysts

ABSTRUCT

Helically chiral poly(quinoxaline-2,3-diyl)s bearing 4-(dipropylamino)pyrid-3-yl pendants at 5 position of the quinoxaline ring (**PQXdpap**) exhibited high catalytic activity and moderate to high selectivity (up to $s = 71$) in acylative kinetic resolution of secondary alcohols. Kinetic studies indicated that sterically demanding single-handed macromolecular scaffold disturbs the reaction of one enantiomer of alcohol with acylpyridinium intermediate. Solvent-dependent helical chirality switching of **PQXdpap** between pure toluene and a 1/1 mixture of toluene and 1,1,2-trichloroethane achieved preparation of either of a pair of enantiomerically pure alcohols (>99% ee) from a single catalyst.

Introduction

Preparation of optically pure chiral compound is highly desirable in organic synthesis, especially for pharmacological investigations. Kinetic resolution is one of the most reliable methods to obtain highly enantioenriched chiral alcohol from readily available racemic alcohol.[1] In kinetic resolution, chiral catalysts are evaluated by selectivity factor (*s*), which is corresponds to the rate constants of enantiomeric substrates (k_{fast}/k_{slow}).[2] In general, moderate selectivity (s = 10) is sufficient to obtain the unreacted enantioenriched alcohol with >99.5% ee at 75% conversion allowing recovery of almost a half of one enantiomer containing in the starting racemic alcohol. Although the opposite enantiomeric alcohol can be obtained by hydrolysis of the ester, significantly high selectivity (s > 600) is needed to obtain the chiral ester with >99.5% ee even at 25% conversion. Therefore, in a practical synthesis, a pair of enantiomeric catalyst should be used to obtain both of enantiomers with high ee.

Recently, increasing attention is being focused on non-enzymatic kinetic resolution of alcohols using chiral organocatalysts.[3] Among them, from the view point of high catalytic activity, 4-(dimethylamino)pyridine (DMAP)-based chiral catalysts are highly attractive.[4,5] However, major drawbacks of these DMAP-based chiral catalysts are the necessity of troublesome resolution of racemic catalyst or tedious preparation of a pair of chiral catalysts. In this context, use of chirality-switchable catalyst is highly desirable because it requires single catalyst to prepare either of enantiomeric alcohols. There are some successes in the use of chirality-switchable catalysts.[6] However, to the best of the author's knowledge, none of them have used in kinetic resolution of racemic alcohols.

Suginome and coworkers have established chiral macromolecular catalysts on the basis of single-handed helical poly(quinoxaline-2,3-diyl)s (hereafter PQX) bearing chiral side chains, whose screw-sense is switchable either to *P*- or *M*-helix by using different solvents.[7] Introduction of achiral ligand/organocatalytic sites onto the helically chiral PQX scaffold allowed to find highly enantioselective catalysts in asymmetric reactions, in which enantioselection is switchable by changing reaction solvents.[8] For instance, introduction of achiral (diarylphosphino)phenyl (**PQXphos**)[8a–e] and 2,2′-bipyridyl pendants (**PQXbpy**)[8g] resulted in the development of highly enantioselective helical polymer ligands in palladium- and copper-catalyzed asymmetric reactions. Furthermore, PQX-based nucleophilic catalysts bearing 4-dialkylaminopyrid-3-yl pendants (Figure 1) served as an efficient helically chiral macromolecular nucleophilic catalyst in asymmetric Steglich rearrangement of oxazolyl carbonate to *C*-carboxyazlactone.[8f] In these

systems, switch of helical chirality by solvent effect allowed synthesis of either of enantiomeric products from a single PQX-based catalyst. These results demonstrate versatility and unique advantages of helical PQX-based catalysts over other helically chiral polymer catalysts.[9] Herein, the author demonstrates kinetic resolution of secondary alcohols using PQX-based nucleophilic catalyst as a highly selective, chirality-switchable catalyst. Helical chirality switching of PQX scaffold depending on solvent effect enabled preparation highly enantioenriched either of enantiomeric alcohols from a single catalyst.

Results and Discussion

According to the reported procedure,[8f] (*R*)-2-butoxymethyl group-modified (*R*)-PQXs bearing 10 pyridyl units along with 190 chiral units on average were prepared by Suzuki–Miyaura cross-coupling of 3-bromo-4-dialkylaminopyridines with (*R*)-PQXs bearing boronyl pendants (Figure 1). In this molecular design, 4-dialkylamino pyrid-3-yl groups are attached at the 5-position of the quinoxaline rings in the PQX scaffold, whose single-handed helicity is induced by the (*R*)-2-butoxymethyl side chains. The dynamic axial chirality between the pyridyl and the quinoxaline rings is induced by the *P*- or *M*-helical structure of PQX.

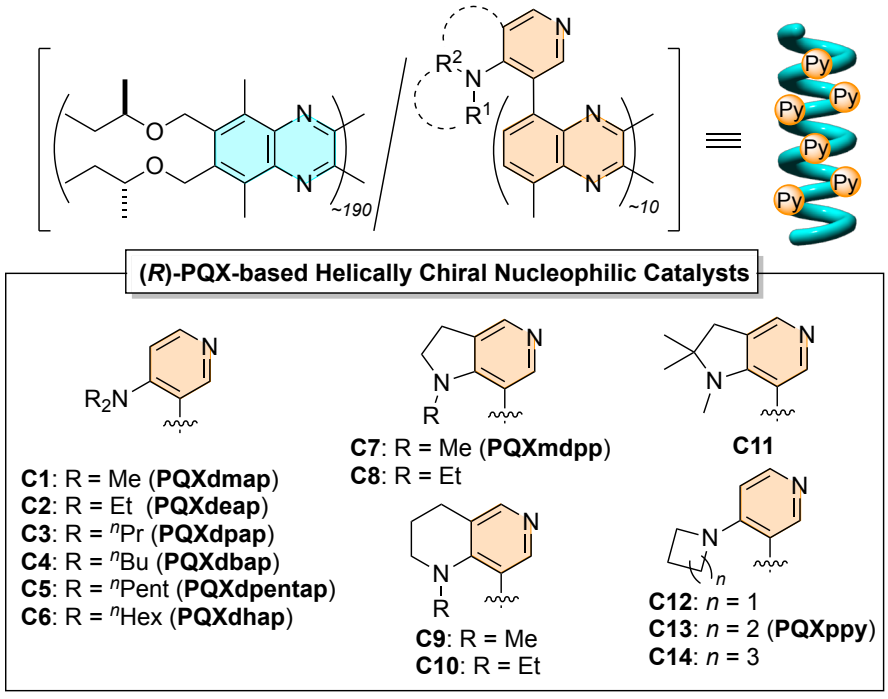
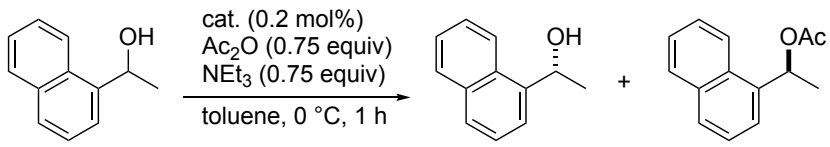


Figure 1. PQX-based helically chiral nucleophilic catalysts.

In the presence of (*P*)-(*R*)-PQX-based nucleophilic catalysts (0.2 mol% pyridy pendant) in toluene, kinetic resolution of 1-(naphthalen-1-yl)ethan-1-ol (**1a**) with acetic anhydride was carried out at 0 °C for 1 h (Table 1). (*P*)-(*R*)-**PQXdmap** (**C1**) bearing DMAP pendant showed high catalytic activity albeit with low selectivity (entry 1, $s = 4.4$). (*P*)-(*R*)-**PQXdeap** (**C2**) bearing a diethylamino group showed higher selectivity (entry 2). Further improvement of the selectivity was observed in use of (*P*)-(*R*)-**PQXdpap** (**C3**) and (*P*)-(*R*)-**PQXdbap** (**C4**), which have a dipropylamino and dibutylamino group, respectively (entries 3 and 4). However, further extension of alkyl chain length resulted in drop of the selectivity (entries 5 and 6). These results clearly

Table 1. Kinetic Resolution of 1a Using (*P*)-(*R*)-PQXdmap Derivatives[a]



rac-**1a** (*R*)-**1a** (*S*)-**2a**

entry	Catalyst	% conv[b]	% ee[c]		*s*[d]
			1a	**2a**	
1	**C1**	52	50	46	4.4
2	**C2**	49	55	57	6.2
3	**C3**	54	78	67	12
4	**C4**	53	77	67	12
5	**C5**	53	72	65	9.8
6	**C6**	53	69	61	8.4
7	**C7**	69	56	26	2.8
8	**C8**	71	64	26	3.0
9	**C9**	68	85	39	5.7
10	**C10**	67	79	39	5.1
11	**C11**	66	75	39	4.8
12	**C12**	57	50	37	3.4
13	**C13**	60	52	33	3.3
14	**C14**	17	12	60	4.5

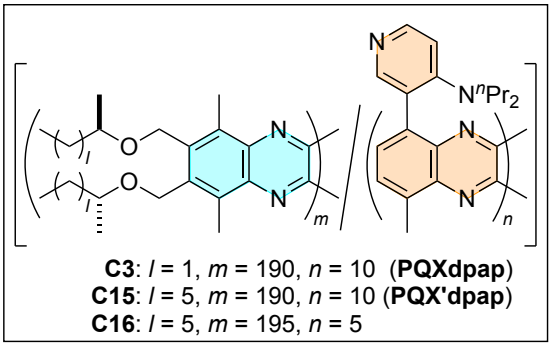
[a]**1a** (0.30 mmol), Ac_2O (0.225 mmol), catalyst (0.2 mol% pyridyl pendants), and NEt_3 (0.225 mmol) in toluene (600 μL) was stirred at 0 °C. [b]Conversion was calculated according to $C = ee_{1a}/(ee_{1a}+ee_{2a})$. [c]Determined by chiral SFC analysis. [d]Determined by Kagan's equation.

exhibit the significant effect of the dialkylamino moiety on the selectivity.[10] Additionally, PQXs bearing a fused cyclic amino group (**C7**–**11**) showed high catalytic activities (entries 7–11). In these series, (*P*)-(*R*)-**PQXmdpp** (**C7**) bearing *N*-methyldihydropyrrolopyridine (MDPP) pendants, which showed the highest enantioselectivity in asymmetric Steglich rearrangement, exhibited the lowest selectivity (entry 7). Replacement of the methyl group on the amino group with ethyl group (**C8**) resulted in similar selectivity (entry 8). (*P*)-(*R*)-PQXs bearing a fused six-membered cyclic amino group (**C9** and **C10**) showed higher selectivity compared to the corresponding catalysts **C7** and **C8** bearing a fused five-membered cyclic amino group (entries 9 and 10). (*P*)-(*R*)-**C11** bearing a sterically demanding fused cyclic amino group also showed higher selectivity than that of **C7** (entry 11). In a series of the catalyst bearing non-fused cyclic amino group (**C12**–**14**), PQXs bearing azetidino (**C12**) or pyrrolidino group (**C13**, **PQXppy**) showed high catalytic activities with low selectivities (entries 12 and 13), while **C14** bearing piperidino group exhibited low catalytic activity with higher selectivity (entry 14).

Based on these results, further optimization of catalyst structure and reaction conditions was carried out (Table 2). (*P*)-(*R*)- **PQX′dpap** (**C15**) bearing (*R*)-2-octyloxymethyl groups, which induces right-handed helical structure more efficiently, showed higher selectivity (s = 17, entry 2). Keeping the polymerization degree of the catalysts ($m + n$ = 200), decrease of the ratio of the pyridyl units (**C16**, n = 5) showed almost no effect on the selectivity (entry 3). Further optimization of reaction conditions such as acylation reagent, base, and solvent was performed with using (*P*)-(*R*)-**PQXdpap** (see Supporting Information (SI)). Significant improvement of reaction rate and selectivity was observed by using chloroform as a solvent (entries 4 and 5). However, significant drop of the selectivity was observed when reaction temperature was decreased to −60 °C, provably due to the low solubility of the polymer catalyst in chloroform at low temperature (entry 6). The selectivity was improved in toluene by decreasing reaction temperature to −60 °C (entry 7). Use of (*P*)-(*R*)-**PQX′dpap** in toluene at −60 °C resulted in high selectivity (s = 71), giving (*R*)-**1a** with 98% ee at 53% conversion (entry 8).

To gain insights into the enantiodiscrimination of (*P*)-(*R*)-**PQXdpap** and **PQX′dpap**, time-course of acylation of enantiomeric (*R*)-**1a** and (*S*)-**1a** under pseudo-first-order reaction condition was investigated by NMR experiments at 23 °C in benzene-d_6 (Figure 2). In the presence of 10 equiv of acetic anhydride and 0.2 mol% 4-dipropylaminopyridine (DPAP), which showed higher catalytic activity than DMAP, the reaction was completed within 1 h. In spite of the presence of the sterically demanding PQX scaffold, (*P*)-(*R*)-**PQXdpap** showed high catalytic activity for (*S*)-**1a** more than half of that of DPAP. By contrast, significant decrease of reaction rate of (*R*)-**1a** was

Table 2. Optimization of the Polymer Structure and Reaction Conditions[a]



entry	Cat.	solvent	Temp (°C)	time (h)	% conv[b]	% ee[c]		s[d]
						1a	**2a**	
1	**C3**	toluene	0	1	54	78	67	12
2	**C15**	toluene	0	1	50	77	76	17
3	**C16**	toluene	0	1	52	79	75	17
4	**C3**	$CHCl_3$	0	1	58	93	67	17
5	**C15**	$CHCl_3$	0	1	55	93	77	26
6	**C3**	$CHCl_3$	−60	12	51	71	68	11
7	**C3**	toluene	−60	12	54	99.1	83	57
8	**C15**	toluene	−60	12	53	98	88	71

[a]See footnote a in Table 1. [b]Conversion was calculated according to $C = ee_{1a}/(ee_{1a}+ee_{2a})$. [c]Determined by chiral SFC analysis. [d]Determined by Kagan's equation.

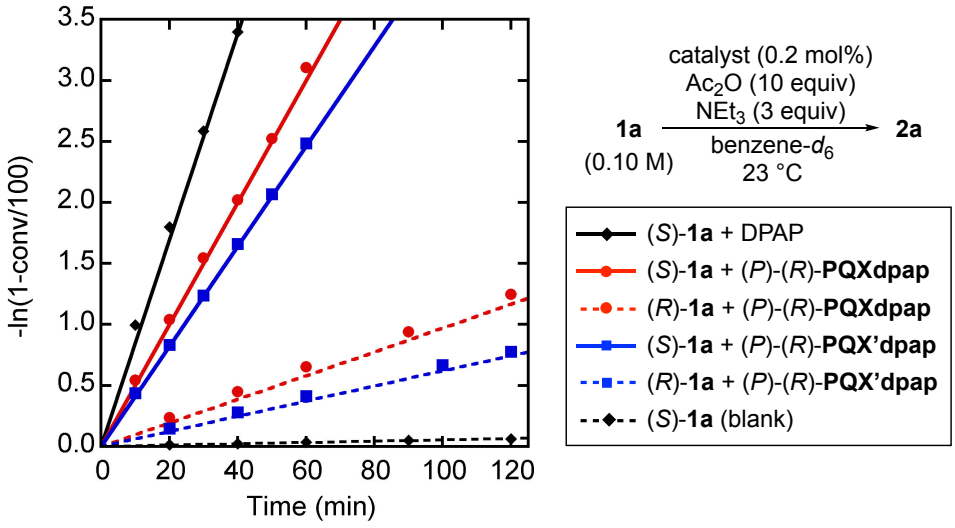
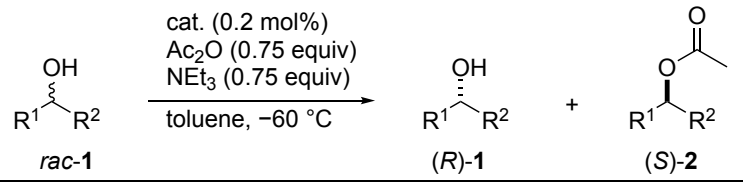


Figure 2. Kinetic profiles of acylation of (*S*)- or (*R*)-**1a** with DPAP, (*P*)-(*R*)-**PQXdpap**, and (*P*)-(*R*)-**PQX'dpap** under pseudo-first-order reaction conditions.

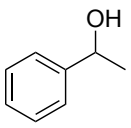
observed. In terms of the rate constants, (*S*)-**1a** showed 4.6-fold higher activity than (*R*)-**1a**. The activities of (*R*)-**1a** and (*S*)-**1a** with (*P*)-(*R*)-**PQX′dpap** were lower than those with (*P*)-(*R*)-**PQXdpap**, and (*S*)-**1a** showed 6.0-fold higher activity than (*R*)-**1a**. These results suggest that the highly sterically demanding *P*-helical macromolecular scaffold of PQX including chiral ether side chains disturbs the reaction of acylpyridinium intermediate with (*R*)-**1a** significantly.

Substrate scope of secondary alcohol was investigated under the optimized reaction conditions with (*P*)-(*R*)-**PQX′dpap** (**C15**) (Scheme 1). The selectivity for 1-phenylethan-1-ol (**1b**) was moderate (*s* = 8.9), which is sufficient to obtain (*R*)-**1b** with >95% ee at >68% conversion. The

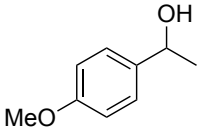
Scheme 1. Substrate Scope



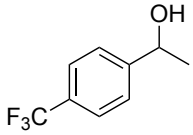
rac-**1** (*R*)-**1** (*S*)-**2**



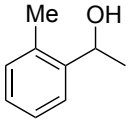
1b
10 h, 45% conv
alcohol: 55% ee
ester: 68% ee
s = 8.9



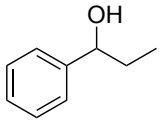
1c
10 h, 37% conv
alcohol: 42% ee
ester: 73% ee
s = 9.6



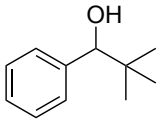
1d
10 h, 52% conv
alcohol: 74% ee
ester: 69% ee
s = 12



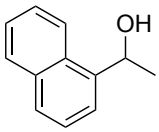
1e
10 h, 46% conv
alcohol: 59% ee
ester: 68% ee
s = 9.4



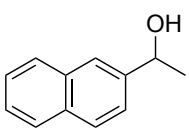
1f
10 h, 43% conv
alcohol: 51% ee
ester: 66% ee
s = 8.0



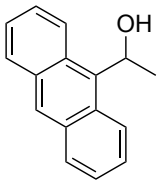
1g
21 h, 49% conv
alcohol: 69% ee
ester: 73% ee
s = 13



1a
10 h, 49% conv
alcohol: 87% ee
ester: 91% ee
s = 61



1h
10 h, 47% conv
alcohol: 69% ee
ester: 80% ee
s = 18

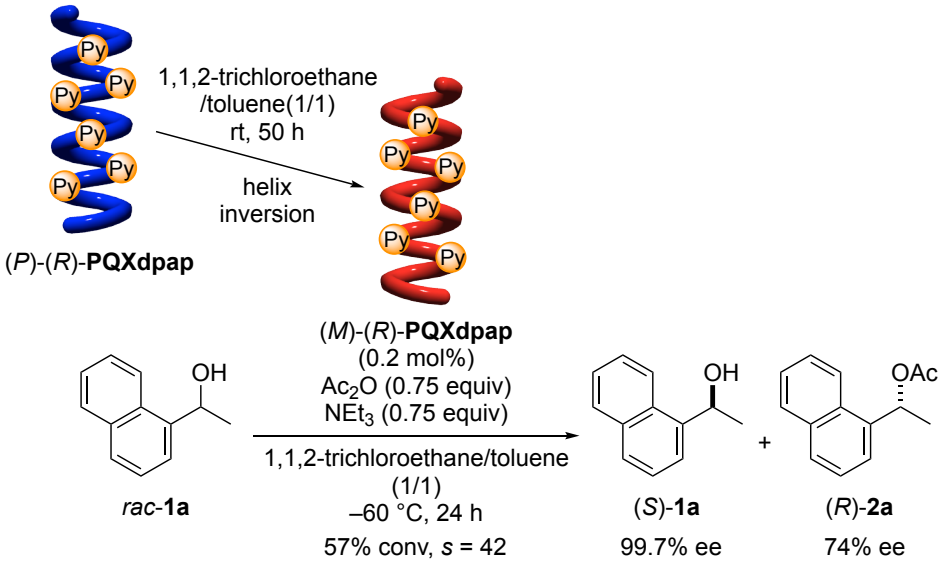


1i
10 h, 42% conv
alcohol: 59% ee
ester: 80% ee
s = 16

presence of substituents on the benzene ring enhanced the selectivity of the substrates (**1c**–**e**). While ethyl substituted carbinol **1f** showed lower selectivity, *t*-butyl substituted carbinol **1g** gave higher selectivity. Furthermore, 1-Arylethan-1-ol derivatives bearing 2-naphthyl (**1h**) and 9-anthracenyl (**1i**) groups afforded high selectivities (s = 18 and 16, respectively).

The use of (*R*)-**PQXdpap** as a chirality-switchable catalyst allowed to obtain highly enantioenriched (*S*)-**2a** (Scheme 2). Inversion of the helical chirality of (*P*)-(*R*)-**PQXdpap** proceeded at room temperature in a 1:1 mixture of toluene and 1,1,2-trichloroethane (1,1,2-TCE), which induces *M*-helical structure on PQX scaffold. The obtained (*M*)-(*R*)-**PQXdpap** afforded the opposite enantiomer (*S*)-**1a** with >99% ee at 57% conversion (s = 42). This result demonstrates high utility of the PQX-based chirality-switchable catalyst in asymmetric kinetic resolution. It should be noted that use of (*M*)-(*R*)-**PQX′dpap** under the same procedure resulted in lower selectivity (s = 10), probably because of the negative effect of longer chiral ether side chains on the selectivity.

Scheme 2. Use of (*M*)-(*R*)-PQXdpap in Kinetic Resolution



Conclusion

The author demonstrated efficient kinetic resolution of secondary alcohols with PQX-based helically chiral nucleophilic catalysts. Single-handed (*R*)-**PQXdpap** bearing 4-(dipropylamino)pyrid-3-yl group showed high catalyst activity and selectivity in kinetic resolution of secondary alcohols. Solvent-driven helical chirality switching of (*R*)-**PQXdpap**

between toluene and 1,1,2-TCE-based solvent enabled preparation of either of chiral enantiomeric alcohols with >99% ee from a single catalyst.

Experimental Section

1. General

All reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Materials were weighted by an electric balance, Sartorius CPA225D (readability: 0.01 mg). Column chromatography was performed with Ultra Pure Silica Gel (SILICYCLE, pH 7.0, 40–63 μm, 60 Å) or Chromatorex NH-Silica Gel (Fuji Silysia Chemical Ltd. NH DM2035, pH 9.5, 45-75 μm, 100 Å, for purification of **S7**). ^{1}H NMR spectra were recorded on a Varian 400-MR (400 MHz) spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a Varian 400-MR (100 MHz) spectrometer at ambient temperature. ^{1}H NMR data are reported as follows: chemical shift in ppm downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet and br = broad), coupling constant (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). The GPC analysis was carried out with TSKgel GMH_{XL} ($CHCl_3$, polystyrene standards). Circular dichroism (CD) spectra were recorded on a JASCO J-1500 spectrometer ($\Delta\varepsilon/\varepsilon$, dissymmetry ratio). UV-vis absorption spectra were recorded on a JASCO V-770 spectrometer. The chiral SFC analysis was carried out on JASCO SF-2000 analytical SFC system equipped with Daicel CHIRALCEL OD-H, OZ-H, OJ-H or AD-H (CO_2 and 2-propanol). The chiral GC analysis was carried out on Shimadzu GC-2014 equipped with Agilent J&W CP-Chirasil-DEX CB.

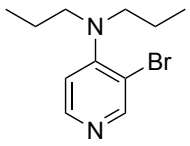
2. Materials

Toluene, chloroform, 1,1,2-trichloroethane, *t*-amyl alcohol, methanol, *N*,*N*-dimethylformamide, triethylamine, *N*,*N*-diisopropylethylamine, 2,6-lutidine, acetic anhydride, isovaleric anhydride, pivalic anhydride, benzoic anhydride and vinyl acetate were distilled over before use. Tetrahydrofuran (Wako), dichloromethane (Nacalai), ethanol (Nacalai), acetonitrile (Wako), ethyl acetate (Nacalai), hexane (Nacalai), diethyl ether (Nacalai), distillated water (Nacalai), magnesium sulfate (Nacalai), sodium sulfate (Wako), sodium borohydride (TCI), trimethyl

phosphine (Strem), sodium carbonate (Nacalai), potassium carbonate (Nacalai), sodium hydride (Nacalai), sodium chloride (Nacalai), *N*-bromosuccinimide (Wako), ethyl bromide (TCI), dimethyl sulfate (Nacalai), 3-bromo-4-chloropyridine (Wako), dipropylamine (TCI), Celite (Wako), were used as received from commercial sources. *N,N*-Dipropyl-4-aminopyridine,[10b] *N,N*-dibutyl-4-aminopyridine,[10b] *N,N*-dipentyl-4-aminopyridine,[10b] *N,N*-dihexyl-4-aminopyridine,[10b] 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine, 1,2,3,4-tetrahydro-1,6-naphthyridine,[11] 2,2-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine,[12] 3-bromo-*N,N*-dimethyl-4-aminopyridine,[8f] 3-bromo-*N,N*-diethyl-4-aminopyridine,[8f] 7-bromo-1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine,[8f] 8-bromo-1-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine,[8f] 3-bromo-4-azetidinopyridine,[8f] 3-bromo-4-pyrrolidinopyridine,[8f] 3-bromo-4-pyperidinolpyridine,[8f] $Pd(PPh_3)_4$, *o*-TolNiCl$(PMe_3)_2$,[13] **S11**,[8f] **S12**,[7a] **S13**,[7b] **S14**[8f] were prepared according to the reported procedure. Substrate alcohols were purchased from commercial suppliers: Alfa Aesar, Nacalai, Sigma Aldrich, TCI, Wako. Some of them were prepared according to the reported procedure.

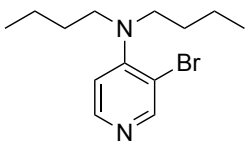
3. Synthesis of Catalysts, Substrates and Products

3.1. Synthesis of DMAP Derivatives

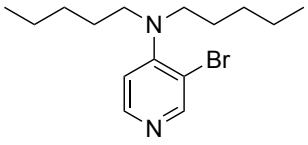


Synthesis of **S1**: (Method A) To a solution of *N,N*-dipropyl-4-aminopyridine (355 mg, 2.0 mmol) in acetonitrile (20 mL) was added *N*-bromosuccinimide (428 mg, 2.4 mmol). The reaction mixture was stirred at 0 °C to room temperature for 10 h and then concentrated under vacuum. The residue was directly subjected to silica gel column chromatography (hexane:Et_2O = 1:1), giving the title compound **S1** (43 mg, 8% yield). (Method B) The mixture of 3-bromo-4-chloropyridine (599.5 mg, 3.12 mmol), dipropylamine (3.0 mL, 22 mmol) and Cs_2CO_3 (1.1787 g, 3.62 mmol) was stirred at 170 °C for 7 days, cooled to room temperature, and then diluted with water. The mixture was extracted with AcOEt, washed with water and brine, dried over with $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (hexane:Et_2O = 2:1) to giving the title compound **S1** (183 mg, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.50 (s, 1H), 8.22 (d, J = 5.2 Hz, 1H), 6.78 (d, J = 5.6 Hz, 1H), 3.28–3.15 (m, 4H), 1.63–1.48 (m, 4H), 0.87 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.6,

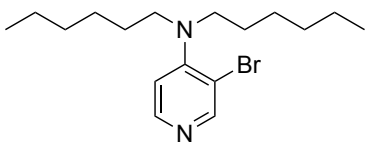
154.0, 148.5, 115.9, 114.0, 53.4, 20.7, 11.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}BrN_2$, 257.0648; found, 257.0644.



Synthesis of **S2**: To a solution of *N,N*-dibutyl-4-aminopyridine (804 mg, 3.9 mmol) in acetonitrile (39 mL) was added *N*-bromosuccinimide (836 mg, 4.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated under vacuum. The residue was directly subjected to silica gel column chromatography (hexane:Et_2O = 4:1 to 1:1), giving the title compound **S2** (127 mg, 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.51 (s, 1H), 8.23 (d, J = 5.2 Hz, 1H), 6.79 (d, J = 5.6 Hz, 1H), 3.32–3.18 (m, 4H), 1.57–1.46 (m, 4H), 1.35–1.23 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.7, 154.0, 148.5, 116.0, 114.2, 51.4, 29.5, 20.3, 14.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{21}BrN_2$, 285.0961; found, 285.0957.

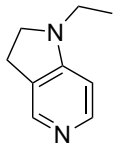


Synthesis of **S3**: To a solution of *N,N*-dipentyl-4-aminopyridine (569 mg, 2.4 mmol) in acetonitrile (24 mL) was added *N*-bromosuccinimide (519 mg, 2.9 mmol). The reaction mixture was stirred at room temperature for 21 h and then diluted with water. The resulting mixture was extracted with Et_2O, washed with water and brine, and then dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (hexane: Et_2O = 1:1), giving the title compound **S3** (82 mg, 11% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.50 (s, 1H), 8.23 (d, J = 6.0 Hz, 1H), 6.78 (d, J = 5.6 Hz, 1H), 3.24 (t, J = 7.2 Hz, 4H), 1.72–1.41 (m, 4H), 1.40–1.18 (m, 8H), 0.88 (t, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.6, 153.9, 148.5, 116.0, 114.1, 51.6, 29.3, 27.1, 22.6, 14.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{15}H_{25}BrN_2$, 313.1274; found, 313.1268.

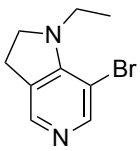


Synthesis of **S4**: To a solution of *N,N*-dihexyl-4-aminopyridine (596 mg, 2.3 mmol) in acetonitrile

(24 mL) was added *N*-bromosuccinimide (488 mg, 2.7 mmol). The reaction mixture was stirred at room temperature for 21 h and then concentrated under vacuum. The residue was directly subjected to silica gel column chromatography (hexane: Et_2O = 1:1), giving the title compound **S4** (78 mg, 10% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.50 (s, 1H), 8.23 (d, *J* = 5.2 Hz, 1H), 6.78 (d, *J* = 5.2 Hz, 1H), 3.24 (t, *J* = 7.2 Hz, 4H), 1.61–1.42 (m, 4H), 1.36–1.17 (m, 12H), 0.87 (t, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.6, 153.9, 148.4, 115.9, 114.0, 51.7, 31.7, 27.3, 26.8, 22.8, 14.2. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{17}H_{29}BrN_2$, 341.1587; found, 341.1583.

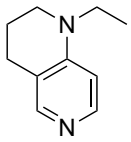


Synthesis of **S5**: To a solution of 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (0.378 g, 3.2 mmol) in DMF (3 mL) under nitrogen was added NaH (0.153 g, ca. 3.2 mmol). The reaction mixture was stirred at 80 °C for 20 min and then cooled to 0 °C. After EtBr (0.388 g, 3.6 mmol) was added slowly, the resulting mixture was stirred at room temperature for 17 h. Then diluted with EtOH (2 mL) and excess amount of CH_2Cl_2 and filtrated through a pad of Celite. The filtrate was evaporated *in vacuo*, and then residual material was dissolved in CH_2Cl_2. The organic phase was washed with water, and then dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and used to next reaction without further purification (0.229 g, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (d, *J* = 5.2 Hz, 1H), 6.24 (d, *J* = 5.6 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 2H), 3.18 (q *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 8.4 Hz, 2H), 1.15 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 157.4, 149.2, 144.0, 125.5, 101.3, 51.1, 41.1, 25.9, 11.8. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_9H_{12}N_2$, 149.1073; found, 149.1070.

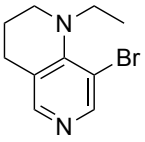


Synthesis of **S6**: To a solution of **S5** (206 mg, 1.4 mmol) in DMF (5 mL) was added *N*-bromosuccinimide (279 mg, 1.6 mmol). The reaction mixture was stirred at 0 °C to room temperature for 12 h and then diluted with water. The resulting mixture was extracted with CH_2Cl_2, washed with water, and then dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt),

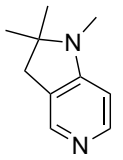
giving the title compound **S6** (193 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.14 (s, 1H), 7.88 (s, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.62 (t, *J* = 8.8 Hz, 2H), 3.01 (t, *J* = 9.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 153.2, 152.4, 142.5, 128.4, 97.9, 52.5, 42.3, 25.4, 13.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_9H_{11}BrN_2$, 227.0178; found, 227.0172.



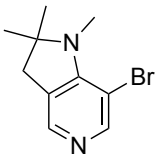
Synthesis of **S7**: To a solution of 1,2,3,4-tetrahydro-1,6-naphthyridine (93 mg 0.70 mmol) in DMF (0.7 mL) was added NaH (32 mg, ca. 0.79 mmol). The reaction mixture was stirred at 80 °C for 1 h and then cooled to 0 °C. After EtBr (82 mg, 0.75 mmol) was added slowly, the resulting mixture was stirred at 80 °C for 4 h. Then diluted with EtOH (2 mL) and excess amount of CH_2Cl_2 and filtrated through a pad of Celite. The filtrate was evaporated *in vacuo*, and then residual material was dissolved in CH_2Cl_2. The organic phase was washed with water, and then dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to NH-silica gel column chromatography (hexane:AcOEt = 1:4), giving the title compound **S7** (35 mg, 31% yield).^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.04 (d, *J* = 5.6 Hz, 1H), 7.92 (s, 1H), 6.37 (d, *J* = 6.0 Hz, 1H), 3.38–3.28 (m, 4H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.01–1.89 (m, 2H), 1.15 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 149.9, 148.6, 148.4, 117.0, 104.6, 48.1, 44.7, 24.9, 21.4, 11.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_{14}N_2$, 163.1230; found, 163.1225.



Synthesis of **S8**: To a solution of **S7** (35 mg, 0.22 mmol) in acetonitrile (1.4 mL) was added *N*-bromosuccinimide (43 mg, 0.24 mmol). The reaction mixture was stirred at 0 °C to room temperature for 12 h and then concentrated under vacuum. The residue was directly subjected to silica gel column chromatography (hexane:AcOEt = 1:1), giving the title compound **S8** (10 mg, 19% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.32 (s, 1H), 7.97 (s, 1H), 3.39 (q, *J* = 6.8 Hz, 2H), 3.22–3.16 (m, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 1.91–1.81 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.5, 151.6, 148.1, 124.8, 110.5, 48.8, 48.7, 25.8. 20.0, 13.8. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_{13}BrN_2$, 241.0335; found, 241.0328.



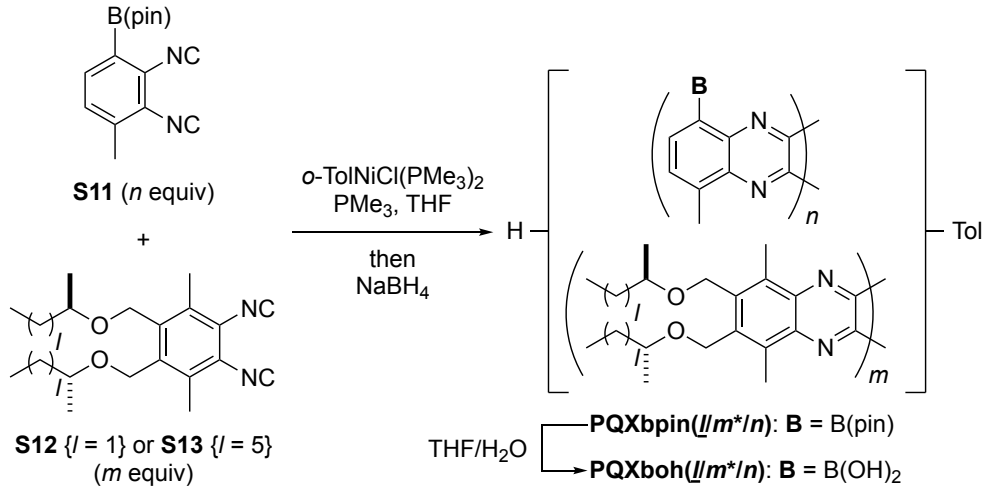
Synthesis of **S9**: To a solution of 2,2-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (1.103 g, 7.44 mmol) in DMF (7.5 mL) under nitrogen was added NaH (1.063 g, ca. 22 mmol). The reaction mixture was stirred at 80 °C for 1 h and then cooled to 0 °C. After Me_2SO_4 (0.994 g, 7.9 mmol) was added slowly, the resulting mixture was stirred at 80 °C for 12 h. Then diluted with EtOH (2 mL) and excess amount of CH_2Cl_2 and filtrated through a pad of Celite. The filtrate was evaporated *in vacuo*, and then residual material was dissolved in AcOEt. The organic phase was washed with water and brine, and then dried over $MgSO_4$, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt:NEt_3 = 20:1), giving the title compound **S9** (0.679 g, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.11 (d, *J* = 5.2 Hz, 1H), 8.02–7.97 (m, 1H), 6.16 (d, *J* = 5.2 Hz, 1H), 2.85 (s, 2H), 2.69 (s, 3H), 1.24 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.8, 149.6, 143.8, 123.3, 101.1, 65.4, 41.5, 27.1, 24.9. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_{14}N_2$, 163.1230; found, 163.1225.



Synthesis of **S10**: To a solution of **S9** (552 mg, 3.4 mmol) in DMF (11 mL) was added *N*-bromosuccinimide (727 mg, 4.1 mmol). The reaction mixture was stirred at 0 °C for 2 h and then diluted with water. The resulted mixture was extracted with CH_2Cl_2, washed with water and brine, and then dried over Na_2SO_4, and filtrated through a pad of Celite. The filtrate was evaporated under vacuum and subjected to silica gel column chromatography (AcOEt), giving the title compound **S10** (627 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.14 (s, 1H), 7.87–7.83 (m, 1H), 3.14 (s, 3H), 2.82 (s, 2H), 1.26 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.8, 152.4, 142.4, 125.7, 97.6, 66.2, 41.1, 29.4, 25.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{10}H_{13}BrN_2$, 241.0335; found, 241.0329.

3.2. Synthesis of (*P*)-(*R*)-PQXboh(*l*/*m**/*n*)

Scheme S1. Synthesis of (*P*)-(*R*)-PQXboh(*l*/*m/*n*)**



Typical Procedure for the Preparation of (*P*)-(*R*)-PQXboh(*l*/*m/*n*)**

Synthesis of (*P*)-(*R*)-**PQXboh(1/190*/10)**: To a solution of organonickel initiator *o*-TolNiCl(PMe_3)$_2$ (15.2 mg, 45.0 μmol) and PMe_3 (1.0 M in THF, 225 μL, 225 μmol) in THF (350 mL) was added a mixture of monomer **S11** (120.5 mg, 0.449 mmol) and **S12** (2.8082 g, 8.550 mmol) in THF (50 mL) at room temperature. The mixture was stirred for 16 h at room temperature. To the reaction mixture was added $NaBH_4$ (170.8 mg, 4.52 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water, extracted with $CHCl_3$ (1 L), washed with water and brine, dried over Na_2SO_4, filtrated through a pad of Celite, and evaporated under vacuum. The residue was dissolved in $CHCl_3$ (10 mL), and the mixture was poured into vigorously stirred acetonitrile (400 mL). The precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, the obtained (*P*)-(*R*)-**PQXbpin(1/190*/10)** was dissolved in THF (14 mL), and then distillated water (700 μL) was added and stirred at room temperature for 12 h. The mixture was poured into vigorously stirred acetonitrile (400 mL), and the precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, (*P*)-(*R*)-**PQXboh(1/190*/10)** (2.787 g, 96%) was obtained as a beige solid. CD and UV spectra of this polymer indicate that this polymer takes a pure *P*-helical structure in toluene at 20 °C. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 8.80–6.20 (brm, peak top; 8.34, 8.25, 7.85, 6.94 (4n+4)H), 6.00–0.00 (brm, peak top; 4.48, 3.25, 2.81, 1.52, 1.40, 1.09, 0.87 (28m+3n+3)H). M_n = 4.8 × 10^4, M_w/M_n = 1.21. g_{abs}

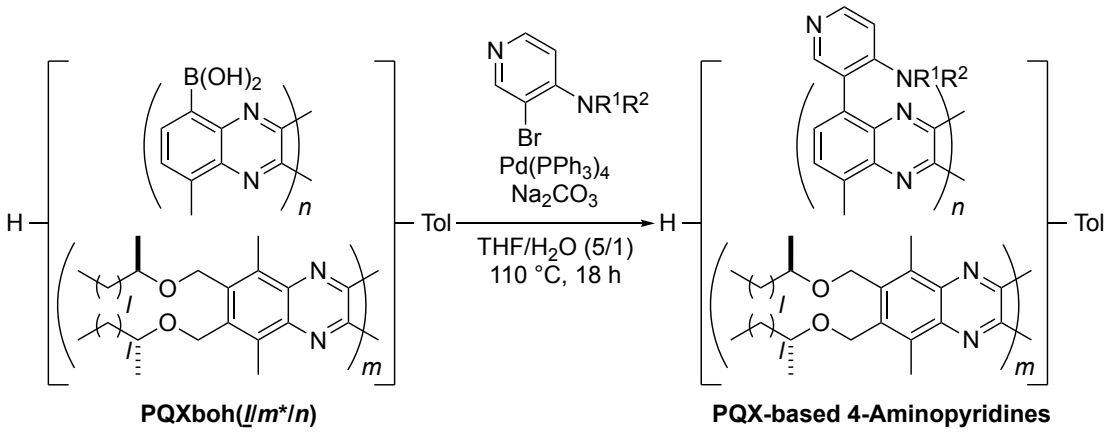
($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = +2.39 × 10^{-3}.

(*P*)-(*R*)-**PQXboh(5/190*/10)**: The reaction was carried out according to the typical procedure using *o*-TolNiCl(PMe_3)$_2$ (3.43 mg, 10.2 μmol), PMe_3 (1.0 M in THF, 50 μL, 50 μmol), **S11** (26.9 mg, 100 μmol), **S13** (838.0 mg, 1.90 mmol), and THF (120 mL). (*P*)-(*R*)-**PQXboh(5/190*/10)** (798 mg, 91%) was obtained as a beige solid. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.48 (s, 1H), 8.70–6.40 (brm, peak top; 8.36, 8.30, 7.90, 7.08 (4n+4)H), 6.00–0.00 (brm, peak top; 4.61, 3.40, 2.84, 1.65, 1.35, 1.18, 0.94 (44m+3n+3)H). M_n = 8.9 × 10^4, M_w/M_n = 1.34. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = +2.00 × 10^{-3}.

(*P*)-(*R*)-**PQXboh(5/195*/5)**: The reaction was carried out according to the typical procedure using *o*-TolNiCl(PMe_3)$_2$ (0.01 M in THF, 450 μL, 4.5 μmol), PMe_3 (1.0 M in THF, 23 μL, 23 μmol), **S11** (6.03 mg, 22.5 μmol), **S13** (386.1 mg, 876 μmol), and THF (45 mL). (*P*)-(*R*)-**PQXboh(5/195*/5)** (385 mg, 98%) was obtained as a beige solid. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.47 (s, 1H), 8.70–6.80 (brm, peak top; 8.36, 8.29, 7.90, 7.08 (4n+4)H), 6.00–0.00 (brm, peak top; 4.54, 3.40, 2.84, 1.65, 1.45, 1.34, 1.18, 0.94 (44m+3n+3)H). M_n = 6.5 × 10^4, M_w/M_n = 1.15. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = +2.03 × 10^{-3}.

3.3. Synthesis of (*P*)-(*R*)-PQX-based 4-Aminopyridines

Scheme S2. Synthesis of (*P*)-(*R*)-PQX-based 4-Aminopyridines



PQXboh(*l*/*m/*n*)** **PQX-based 4-Aminopyridines**

Typical Procedure for Suzuki–Miyaura Cross Coupling of (*P*)-(*R*)-PQXboh(*l*/*m/*n*) with 3-bromo-4-alkylaminopyridine Derivatives**

Synthesis of (*P*)-(*R*)-**C1** (**PQXdmap**): A mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (45.0 mg, 6.99 μmol B), 3-bromo-*N,N*-dimethyl-4-aminopyridine (9.10 mg, 45.3 μmol), sodium carbonate (8.16 mg, 77.0 μmol) and $Pd(PPh_3)_4$ (8.60 mg, 7.44 μmol) in THF (2.5 mL) and distillated water (0.5 mL) was stirred at 110 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted with toluene. The organic phase was washed with brine, dried over Na_2SO_4, filtrated through a pad of Celite, and evaporated under vacuum. The residue was dissolved in toluene and poured into vigorously stirred acetonitrile, and precipitated polymer was collected by centrifugation followed by washing with acetonitrile for two times. After drying *in vacuo*, (*P*)-(*R*)-**C1** (33.1 mg, 74 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. CD and UV spectra of this polymer indicate that this polymer takes a pure *P*-helical structure in toluene at 20 °C. GPC analysis with TSKgel GMH_{XL} (eluent: $CHCl_3$) showed weak broad tailing peaks, which could not be analyzed by molecular weight calibration curve using polystyrene standards (peak start: 8.5×10^6, peak end: out of measuring range). GPC analysis with TSKgel α-4000, α-3000, and α-2500 in series (eluent: THF) showed a broad tailing peak, which could not be analyzed by molecular weight calibration curve using polystyrene standards (peak start: 3.2×10^4, peak top: 6.5×10^2, peak end: out of measuring range). ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 9.10–6.00 (brm, peak top; 8.69, 8.48, 8.34, 7.24, 6.93, 6.43 (5n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.25, 2.81, 1.95, 1.52, 1.40, 1.09, 0.88 (28m+9n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.40 \times 10^{-3}$.

(*P*)-(*R*)-**C2** (**PQXdeap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (51.9 mg, 8.06 μmol B), 3-bromo-*N,N*-diethyl-4-aminopyridine (6.92 mg, 30.2 μmol), sodium carbonate (8.36 mg, 78.9 μmol), and $Pd(PPh_3)_4$ (8.44 mg, 7.30 μmol) in THF (2.5 mL) and water (0.5 mL). (*P*)-(*R*)-**C2** (41.6 mg, 80 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.20–6.30 (brm, peak top; 8.81, 8.47, 8.35, 7.37, 6.99, 6.66 (5n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.25, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+13n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.28 \times 10^{-3}$.

(*P*)-(*R*)-**C3** (**PQXdpap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (196.8 mg, 30.6 μmol B), **S1** (11.2 mg, 43.6 μmol),

sodium carbonate (32.1 mg, 303 μmol), and $Pd(PPh_3)_4$ (44.5 mg, 38.5 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C3** (178 mg, 90 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.10–6.20 (brm, peak top; 8.74, 8.38, 8.35, 7.70, 7.34, 6.58 (5n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.24, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+17n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.37 \times 10^{-3}$. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, $CHCl_3$) = $+2.50 \times 10^{-3}$. CD and UV spectra of this polymer indicate that this polymer takes a pure *M*-helical structure in toluene/1,1,2-trichloroethane (1/1, v/v) at 20 °C. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene/1,1,2-trichloroethane) = -3.13×10^{-3}.

(*P*)-(*R*)-**C4** (**PQXdbap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (48.8 mg, 7.58 μmol B), **S2** (5.45 mg, 19.1 μmol), sodium carbonate (8.12 mg, 76.6 μmol), and $Pd(PPh_3)_4$ (8.52 mg, 7.37 μmol) in THF (2.5 mL) and water (0.5 mL). (*P*)-(*R*)-**C4** (38.6 mg, 79 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.00–6.30 (brm, peak top; 8.74, 8.35, 7.69, 7.32, 6.59 (5n+4)H), 6.00–0.00 (brm, peak top; 4.50, 3.25, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+21n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.27 \times 10^{-3}$.

(*P*)-(*R*)-**C5** (**PQXdpentap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (48.8 mg, 7.58 μmol B), **S3** (4.51 mg, 14.4 μmol), sodium carbonate (7.47 mg, 70.4 μmol), and $Pd(PPh_3)_4$ (9.50 mg, 8.22 μmol) in THF (2.5 mL) and water (0.5 mL). (*P*)-(*R*)-**C5** (33.8 mg, 69 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.10–6.20 (brm, peak top; 8.72, 8.35, 7.94, 7.70, 7.32, 6.59 (5n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.24, 2.81, 1.52, 1.40, 1.09, 0.87 (28m+25n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.41 \times 10^{-3}$.

(*P*)-(*R*)-**C6** (**PQXdhap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (46.8 mg, 7.27 μmol B), **S4** (7.33 mg, 21.5 μmol), sodium carbonate (8.29 mg, 78.2 μmol), and $Pd(PPh_3)_4$ (9.07 mg, 7.85 μmol) in THF (2.5 mL) and water (0.5 mL). (*P*)-(*R*)-**C6** (37.2 mg, 79 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52

(s, 1H), 9.00–6.30 (brm, peak top; 8.69, 8.39, 8.35, 7.96, 7.70, 7.33, 6.60 (5n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.25, 2.81, 1.53, 1.40, 1.09, 0.87 (28m+29n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.35 \times 10^{-3}$.

(*P*)-(*R*)-**C7** (**PQXmdpp**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (189.1 mg, 29.4 μmol B), 7-bromo-1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (7.77 mg, 36.5 μmol), sodium carbonate (9.76 mg, 92.1 μmol), and $Pd(PPh_3)_4$ (3.42 mg, 2.96 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C7** (132 mg, 70 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 8.90–6.40 (brm, peak top; 8.49, 8.35, 8.19, 6.90 (4n+4)H), 6.00–0.00 (brm, peak top; 4.50, 3.25, 2.81, 1.51, 1.40, 1.09, 0.88 (28m+10n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.26 \times 10^{-3}$.

(*P*)-(*R*)-**C8**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (198.3 mg, 30.4 μmol B), **S6** (8.98 mg, 39.5 μmol), sodium carbonate (10.5 mg, 99.4 μmol), and $Pd(PPh_3)_4$ (3.20 mg, 2.77 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C8** (174 mg, 88 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 8.90–6.30 (brm, peak top; 8.46, 8.35, 8.20, 6.90 (4n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.24, 2.80, 1.52, 1.40, 1.09, 0.87 (28m+12n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.41 \times 10^{-3}$.

(*P*)-(*R*)-**C9**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (94.0 mg, 14.6 μmol B), 8-bromo-1-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (34.1 mg, 150 μmol), sodium carbonate (21.3 mg, 201 μmol), and $Pd(PPh_3)_4$ (19.9 mg, 17.2 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C9** (77.7 mg, 83 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 9.00–6.50 (brm, peak top; 8.66, 8.35, 8.25, 7.69, 7.26, 6.94 (4n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.24, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+12n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.34 \times 10^{-3}$.

(*P*)-(*R*)-**C10**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.1 mg, 14.8 μmol B), **S8** (10.2 mg, 42.3 μmol), sodium carbonate

(16.2 mg, 153 μmol), and $Pd(PPh_3)_4$ (17.4 mg, 15.1 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C10** (70.3 mg, 74 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.00–6.00 (brm, peak top; 8.61, 8.34, 8.09, 7.68 (4n+4)H), 6.00–0.00 (brm, peak top; 4.50, 3.25, 2.81, 1.53, 1.40, 1.09, 0.87 (28m+14n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.26 \times 10^{-3}$.

(*P*)-(*R*)-**C11**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (194.5 mg, 30.2 μmol B), **S10** (11.6 mg, 48.1 μmol), sodium carbonate (10.4 mg, 98.1 μmol), and $Pd(PPh_3)_4$ (4.14 mg, 3.58 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C11** (163 mg, 84 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.51 (s, 1H), 9.10–6.40 (brm, peak top; 8.76, 8.35, 6.93 (4n+4)H), 6.00–0.00 (brm, peak top; 4.49, 3.24, 2.80, 1.51, 1.40, 1.09, 0.87 (28m+14n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.18 \times 10^{-3}$.

(*P*)-(*R*)-**C12**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (95.3 mg, 14.8 μmol B), 3-bromo-4-azetidinopyridine (30.0 mg, 141 μmol), sodium carbonate (16.0 mg, 151 μmol), and $Pd(PPh_3)_4$ (18.5 mg, 16.0 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C12** (87.5 mg, 92 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 9.00–5.70 (brm, peak top; 8.66, 8.37, 7.26, 6.92, 5.98 (5n+4)H), 5.70–0.00 (brm, peak top; 4.49, 3.24, 2.81, 1.53, 1.40, 1.10, 0.88 (28m+9n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.32 \times 10^{-3}$.

(*P*)-(*R*)-**C13** (**PQXppy**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(1/190*/10)** (97.5 mg, 15.1 μmol B), 3-bromo-4-pyrrolidinopyridine (34.4 mg, 151 μmol), sodium carbonate (17.5 mg, 165 μmol), and $Pd(PPh_3)_4$ (21.6 mg, 18.7 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C13** (92.1 mg, 94 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 9.00–6.00 (brm, peak top; 8.70, 8.53, 8.35, 7.26, 6.91, 6.42 (5n+4)H), 6.00–0.00 (brm, peak top; 4.48, 3.24, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+11n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.28 \times 10^{-3}$.

(*P*)-(*R*)-**C14**: The reaction was carried out according to the typical procedure using a mixture of

(*P*)-(*R*)-**PQXboh(1/190*/10)** (95.6 mg, 14.9 μmol B), 3-bromo-4-pyperidinolpyridine (39.4 mg, 163 μmol), sodium carbonate (15.8 mg, 149 μmol), and $Pd(PPh_3)_4$ (20.5 mg, 17.7 μmol) in THF (5 mL) and water (1 mL). (*P*)-(*R*)-**C14** (87.7 mg, 92 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.52 (s, 1H), 9.30–6.30 (brm, peak top; 8.99, 8.53, 8.35, 7.55, 7.05, 6.70 (5n+4)H), 6.00–0.00 (brm, peak top; 4.48, 3.24, 2.81, 1.53, 1.40, 1.09, 0.88 (28m+13n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.22 \times 10^{-3}$.

(*P*)-(*R*)-**C15** (**PQX'dpap**): The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(5/190*/10)** (202.0 mg, 23.6 μmol B), **S1** (7.51 mg, 29.2 μmol), sodium carbonate (8.55 mg, 80.7 μmol), and $Pd(PPh_3)_4$ (33.6 mg, 29.0 μmol) in THF (10 mL) and water (2 mL). (*P*)-(*R*)-**C15** (193 mg, 96 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.47 (s, 1H), 9.10–6.20 (brm, peak top; 8.73, 8.37, 7.77, 6.62 (5n+4)H), 6.00–0.00 (brm, peak top; 4.52, 3.40, 2.84, 1.65, 1.34, 1.18, 0.94 (44m+17n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+1.97 \times 10^{-3}$. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, $CHCl_3$) = $+2.46 \times 10^{-3}$. CD and UV spectra of this polymer indicate that this polymer takes a pure *M*-helical structure in toluene/1,1,2-trichloroethane (1/1, v/v) at 20 °C. g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene/1,1,2-trichloroethane) = -3.20×10^{-3}.

(*P*)-(*R*)-**C16**: The reaction was carried out according to the typical procedure using a mixture of (*P*)-(*R*)-**PQXboh(5/195*/5)** (47.5 mg, 2.73 μmol B), **S1** (1.96 mg, 7.62 μmol), sodium carbonate (4.75 mg, 44.8 μmol), and $Pd(PPh_3)_4$ (6.56 mg, 5.68 μmol) in THF (2 mL) and water (0.4 mL). (*P*)-(*R*)-**C16** (42.6 mg, 90 wt%) was obtained as a beige solid. The introduction ratio of pyridyl group (>90%) was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, C_6D_6, δ): 10.48 (s, 1H), 9.00–6.30 (brm, peak top; 8.73, 8.36, 7.78, 6.61 (5n+4)H), 6.00–0.00 (brm, peak top; 4.55, 3.41, 2.84, 1.66, 1.45, 1.34, 1.18, 0.94 (44m+17n+3)H). g_{abs} ($\Delta\varepsilon/\varepsilon$, 371.5 nm, toluene) = $+2.00 \times 10^{-3}$.

4. Experimental Procedure of Kinetic Resolutions

4.1. Determination of Enantiomeric Excesses, Conversions and Selectivities

Enantiomeric excesses of recovered alcohols and ester products were determined by chiral SFC or chiral GC analysis (see Table S1). Absolute configurations of compounds obtained by kinetic resolution using *P*-helical catalysts were assigned by optical rotation analysis.

Conversion C_{calc} was calculated according to:

$C_{calc} = ee_A / (ee_A + ee_E)$

Selectivity factor s was calculated according to Kagan's equation:

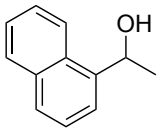
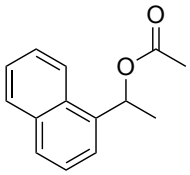
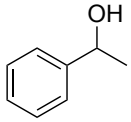
$s = \ln ((1 - C_{calc}) (1 - ee_A)) / \ln ((1 - C_{calc}) (1 + ee_A))$

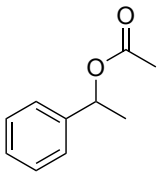
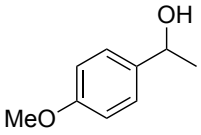
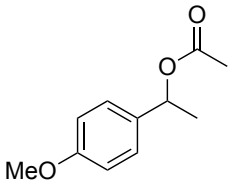
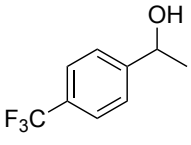
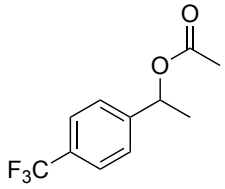
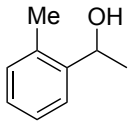
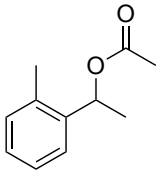
ee_A: enantiomeric excess of the recovered alcohol

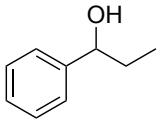
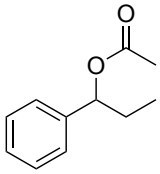
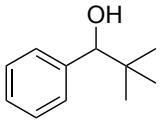
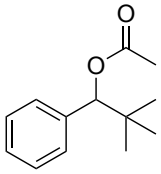
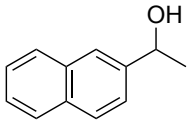
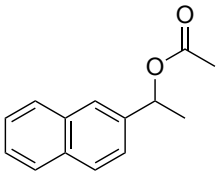
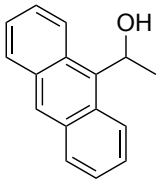
ee_E: enantiomeric excess of the ester

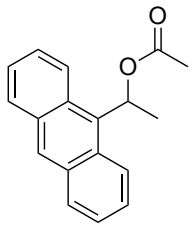
The calculated conversion values were found to be generally within 1-2% of the values obtained by ^{1}H NMR integration of the crude reaction mixtures.

Table S1. SFC/GC Conditions and Sign of Optical Rotation

Compound	Tool Column	Eluent Ratio Flow rate	Retention Time of (*R*) Isomer (min)	Retention Time of (*S*) Isomer (min)	Optical Rotation
 **1a**	SFC OD-H	*i*-PrOH/CO_2 15% 3.45 ml/min	6.79	4.79	+
 **2a**	SFC OD-H	*i*-PrOH/CO_2 3% 3.09 ml/min	4.65	7.59	−
 **1b**	SFC OD-H	*i*-PrOH/CO_2 5% 3.15 ml/min	3.52	4.04	+

 **2b**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	2.15	2.43	−
 **1c**	GC DEX CB	N_2 carrier gas 100 ℃ 1.82 ml/min	62.51	71.57	+
 **2c**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	3.11	3.50	−
 **1d**	SFC OZ-H	*i*-PrOH/CO_2 0.1% 3.00 ml/min	11.89	9.76	+
 **2d**	SFC AD-H	*i*-PrOH/CO_2 0.1% 3.00 ml/min	1.62	1.78	−
 **1e**	SFC AD-H	*i*-PrOH/CO_2 5% 3.15 ml/min	4.12	5.03	+
 **2e**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	2.23	2.78	−

 **1f**	SFC OD-H	*i*-PrOH/CO_2 5% 3.15 ml/min	3.63	4.04	+
 **2f**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	2.44	2.66	−
 **1g**	SFC AD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	7.72	8.97	+
 **2g**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	2.11	2.55	−
 **1h**	SFC OJ-H	*i*-PrOH/CO_2 10% 3.30 ml/min	10.24	7.41	+
 **2h**	SFC OD-H	*i*-PrOH/CO_2 1% 3.03 ml/min	5.97	9.87	−
 **1i**	SFC AD-H	*i*-PrOH/CO_2 20% 3.60 ml/min	9.41	11.49	+

 **2i**	SFC AD-H	*i*-PrOH/CO_2 10% 3.30 ml/min	3.34	4.67	–

4.2. General Procedure for Table 1

To a mixture of *rac*-**1a** (51.7 mg, 0.300 mmol) and catalyst (3.9 mg, 0.6 μmol pyridyl pendants) and NEt_3 (22.8 mg, 0.225 mmol) in toluene (600 μL) was added Ac_2O (23.0 mg, 0.225 mmol) at 0 °C. After stirring for 1 h, MeOH (300 μL) was added to quench the reaction, then crude solution was analyzed by ^{1}H NMR to check the conversion of alcohol. The residue was directly subjected to preparative thin layer chromatography (hexane:AcOEt = 4:1) to afford alcohol **1a** and ester **2a**. The enantiomeric excesses were determined by chiral SFC analysis. Detailed experiments for optimization of reaction condition were shown in Table S2.

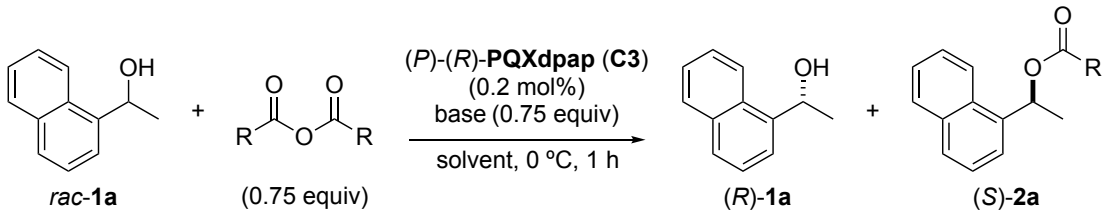
4.4. General Procedure for Table 2 (entry 1–5)

To a mixture of *rac*-**1a** (51.7 mg, 0.300 mmol) and catalyst (**C3**: 3.9 mg, **C15**: 5.2 mg, or **C16**: 10.2 mg, 0.6 μmol pyridyl pendants) and NEt_3 (22.8 mg, 0.225 mmol) in solvent (600 μL) was added Ac_2O (23.0 mg, 0.225 mmol) at 0 °C. After stirring for 1 h, MeOH (300 μL) was added to quench the reaction, then crude solution was analyzed by ^{1}H NMR to check the conversion of alcohol. The residue was directly subjected to preparative thin layer chromatography (hexane:AcOEt = 4:1) to afford alcohol **1a** and ester **2a**. The enantiomeric excesses were determined by chiral SFC analysis.

4.5. General Procedure for Table 2 (entry 6–8)

To a mixture of *rac*-**1a** (51.7 mg, 0.300 mmol) and catalyst (**C3**: 3.9 mg or **C15**: 5.2 mg, 0.6 μmol pyridyl pendants) and NEt_3 (22.8 mg, 0.225 mmol) in solvent (600 μL) was added Ac_2O (23.0 mg, 0.225 mmol) at −60 °C. After stirring for 12 h, MeOH (300 μL) was added to quench the reaction, then crude solution was analyzed by ^{1}H NMR to check the conversion of alcohol. The residue was directly subjected to preparative thin layer chromatography (hexane:AcOEt = 4:1) to afford alcohol **1a** and ester **2a**. The enantiomeric excesses were determined by chiral SFC analysis.

Table S2. Optimization of Kinetic Resolution by Using *Rac*-1a[a]



rac-**1a** (0.75 equiv) (*R*)-**1a** (*S*)-**2a**

entry	solvent	R	base	C_{calc} (%)[b]	ee_A (%)[c]	ee_E (%)[d]	*s*[e]
1	toluene	Me	NEt_3	54	78	67	12
2[f]	toluene	Me	NEt_3	<1	n.d.	n.d.	n.d.
3	$CHCl_3$	Me	NEt_3	58	93	67	17
4	THF	Me	NEt_3	31	30	66	6.6
5[g]	*t*-AmOH	Me	NEt_3	61	−73	−47	5.9
6[h]	neat	Me	NEt_3	68	79	37	4.8
7	toluene	*i*-Pr	NEt_3	13	9.2	60	4.4
8	toluene	Ph	NEt_3	4.4	2.2	48	2.9
9	toluene	Me	$N(i\text{-}Pr)_2Et$	51	73	69	12
10	toluene	Me	2,6-lutidine	34	36	69	7.9
11	toluene	Me	K_2CO_3	24	21	67	6.2
12	toluene	Me	none	21	18	68	6.3

[a]**1a** (0.300 mmol), anhydride (0.225 mmol), catalyst (0.2 mol% pyridyl pendants), and base (0.225 mmol) in solvent (600 μL) was stirred at 0 °C for 1 h. [b]Conversion C_{calc} was calculated according to $C_{calc} = ee_A/(ee_A+ee_E)$. [c]The ee of recovered alcohol determined by SFC analysis. [d]The ee of product ester determined by SFC analysis. [e]Selectivity factor *s* was calculated according to $s = \ln((1-C_{calc})(1-ee_A))/\ln((1-C_{calc})(1+ee_A))$. [f]Without catalyst. [g]The reaction was carried out using (*M*)-(*R*)-**C3**. [h]0.6 mmol scale, 0.05 mol% of catalyst, room temperature.

4.6. General Procedure for Figure 2

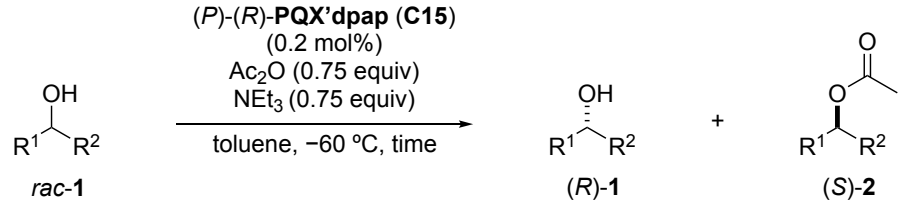
To a mixture of **1a** (12.0 mg, 70 μmol) and NEt_3 (21.2 mg, 210 μmol) in benzene-d_6 (500 μL) was added a solution of catalyst (0.70 mM in benzene-d_6, 200 μL, 0.14 μmol) in a NMR tube under nitrogen atmosphere. Then, Ac_2O (71.5 mg, 700 μmol) was added and reacted at 23 °C. The conversion of **1a** was checked by ^1H NMR analysis. Then, acetonitrile was added, and precipitated polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silicagel column chromatography (Et_2O). The

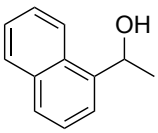
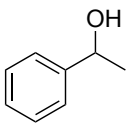
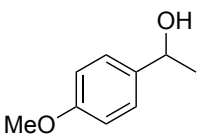
enantiomeric excesses were determined by chiral SFC analysis of a mixture of the substrate and product.

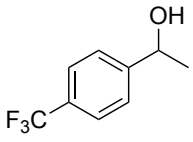
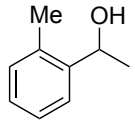
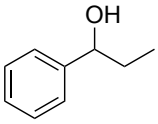
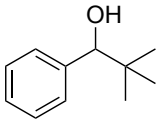
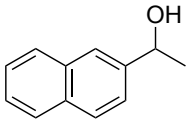
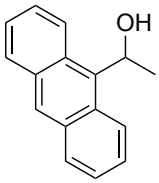
4.7. General Procedure for Scheme 1

To a mixture of *rac*-**1** (0.300 mmol) and (*P*)-(*R*)-**PQX'dpap C15** (5.2 mg, 0.6 μmol pyridyl pendants) and NEt_3 (22.8 mg, 0.225 mmol) in toluene (600 μL) was added Ac_2O (23.0 mg, 0.225 mmol) at 0 °C. After stirring for corresponding time, MeOH (300 μL) was added to quench the reaction, then crude solution was analyzed by ^1H NMR to check the conversion of alcohol. Then, acetonitrile was added, and precipitated polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to preparative thin layer chromatography to afford alcohol **1** and ester **2**. The enantiomeric excesses were determined by chiral SFC or chiral GC analysis. The results were summarized in Table S3.

Table S3. Kinetic Resolution of Alcohols 1a-i[a]



entry	Substrate	t (h)	C_{NMR} (%)[b]	C_{calc} (%)[c]	ee_A (%)[d]	ee_E (%)[e]	S[f]
1	 **1a**	10	49.88	48.98	87.406	91.046	61.21
2	 **1b**	10	45.13	44.72	54.780	67.730	8.90
3	 **1c**	10	35.48	36.51	42.004	73.040	9.64

4	 **1d**	10	49.91	51.82	74.108	68.902	11.85
5	 **1e**	10	47.02	46.48	58.900	67.818	9.35
6	 **1f**	10	44.48	43.41	50.690	66.078	8.01
7	 **1g**	21	46.92	48.71	69.254	72.938	13.07
8	 **1h**	10	46.96	46.60	69.476	79.618	18.18
9	 **1i**	10	41.97	42.23	58.508	80.052	16.23

[a]**1** (0.300 mmol), Ac_2O (0.225 mmol), catalyst (0.2 mol% pyridyl pendants), and NEt_3 (0.225 mmol) in toluene (600 μL) was stirred at −60 °C. [b]Conversion C_{NMR} was determined by ^1H NMR analysis. [c]Conversion C_{calc} was calculated according to $C_{calc} = ee_A/(ee_A+ee_E)$. [d]The ee of recovered alcohol determined by SFC analysis. [e]The ee of product ester determined by SFC analysis. [f]Selectivity factor s was calculated according to $s = \ln((1-C_{calc})(1-ee_A))/\ln((1-C_{calc})(1+ee_A))$.

4.8. General Procedure for Scheme 2

The catalyst (**C3**: 3.9 mg, or **C15**: 5.2 mg, 0.6 μmol pyridyl pendants) were dissolved in toluene (300 μL) and 1,1,2-trichloroethane (300 μL), and stirred at room temperature for two days. To a solution of catalyst were added *rac*-**1a** (0.300 mmol) and NEt_3 (22.8 mg, 0.225 mmol), and the mixture was cooled to −60 °C. Then, Ac_2O (23.0 mg, 0.225 mmol) was added and reacted at −60 °C for 24 h. The reaction was quenched by additional MeOH (300 μL), then crude solution was analyzed by ^1H NMR to check the conversion of alcohol. Then, acetonitrile was added, and precipitated polymer catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated under vacuum. The residue was subjected to silicagel column chromatography (Et_2O). The enantiomeric excesses were determined by chiral SFC analysis of a mixture of the substrate and product.

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Chapter 3

Chirality-Amplifying, Dynamic Induction of Single-Handed Helix by Chiral Guests to Macromolecular Chiral Catalysts Bearing Boronyl Pendants as Receptor Sites

ABSTRUCT

Helical chirality of poly(quinoxaline-2,3-diyl)s bearing a boronyl pendant at the 5-position of the quinoxaline ring was induced by condensation with chiral guests such as a diol, diamine, and amino alcohol. Reversible induction of a single-handed helical structure was achieved by using less than an equimolar amount of chiral amino alcohols to the boronyl pendants. Majority-rule-effect-based chiral amplification on the polyquinoxaline main chain was demonstrated with chiral amino alcohols with low enantiomeric excess (ee). The helical macromolecular scaffold whose helicity was thus induced was utilized in palladium-catalyzed asymmetric silaboration of *meso*-methylenecyclopropane (up to 92% ee) by introducing (diarylphosphino)phenyl pendants at their side chains.

Introduction

Because of their unique chiral structures, helical synthetic macromolecules that contain either *P*- or *M*-helical conformation in excess are finding various applications, including chiral separation, chirality sensing, circularly polarized light (CPL) emission, and CPL reflection.[1] Particular interest is being focused on the use of purely single-handed helical macromolecules as chiral catalysts in asymmetric catalysis,[2] although the requirement for the induction of the "pure" helical sense still hampers this development. In all these applications, the dynamic nature of helical structures along with their rod-like molecular shape makes them highly characteristic, in comparison with chiral small molecules, thus enabling switchable chiral functions, where the change of external conditions alters the enantiodiscrimination or CPL handedness.[3] One major strategy for induction of the nonracemic helical sense involves introduction of chiral side chains through inconvertible, strong covalent bonds into all planar or quasiplanar repeating units.[4] Such inconvertible chiral groups in the macromolecular scaffolds make the whole structure robust, but it does make their synthesis laborious.

In contrast, there is another class of induction where chiral guests serve as a source of helical chirality.[5] This strategy allows the use of macromolecules devoid of chiral groups on their backbones, to which chirality is induced by the addition of chiral guests. Most typically, Yashima and co-workers reported that achiral polyacetylenes bearing carboxyl or boronyl groups at the pendant groups adopt nonracemic helical structures upon addition of chiral guests to their solutions.[5b–d] This type of helix induction by a chiral guest has the advantages of less-laborious synthesis and wider variation of the choice of chiral sources. However, despite these advantages, helix induction by chiral guests has never yet been combined with application to asymmetric catalysis.

In this paper, the author demonstrates the induction of a single-handed helical structure to helical poly(quinoxaline-2,3-diyl)s[4q,r] (PQX hereafter) bearing boronyl pendants (PQXboh) using several chiral guest molecules.[6,7] The single-handed PQX was used as a chiral catalyst in asymmetric catalytic reactions with high enantioselectivity. The use of a chiral guest with low enantiopurity to obtain high enantioselectivities through chiral amplification is also demonstrated.

Results and Discussion

A binary, "achiral" random copolymer PQXboh bearing boronyl pendants along with

propoxymethyl side chains was chosen as a scaffold and synthesized by living polymerization. PQXboh is reported to be a versatile synthetic intermediate, to which various pyridine-based pendants such as 4-aminopyrid-3-yl and 2,2′-bipyrid-6-yl are easily introduced by postpolymerization cross-coupling.[2p,q] **PQXboh(190/10*)** containing 10 boronyl pendants (on average) was dissolved in toluene in the presence of molecular sieves 4A with various chiral diol, diamine, and amino alcohols (0.01 M, 200 equiv to boronyl group), separately (Figure 1a). After stirring for 15–24 h at room temperature, circular dichroism (CD) spectra were measured to determine the degree of helix induction without removing the chiral guest. The screw-sense excess (se) of each sample was determined by comparison of the *g* value (Kuhn dissymmetry factors, $\Delta\varepsilon/\varepsilon$) at 371.5 nm with the expected *g* value (g_{max}) for purely single-handed PQX (*vide infra*) (Figure 1b).[8] The chiral diol (*S*,*S*)-**1** induced *M*-helical structure ($g = -1.87 \times 10^{-3}$), which was assumed to be ca. 90% se, while the diamine derivative (*S*,*S*)-**2** induced *M*-helical structure with moderate se. It was found that the corresponding amino alcohol (*S*,*S*)-**3** induced almost pure *M*-helical conformation efficiently ($g = -2.10 \times 10^{-3}$). Similarly, its diastereomer, (*S*,*R*)-**4**, afforded single-handed *P*-helical conformation efficiently ($g = +2.03 \times 10^{-3}$). The two diastereomers (*S*,*S*)-**3** and (*S*,*R*)-**4** gave a pair of mirror-image CD spectra of *P*- and *M*-helices (Figure 1c). Aminoindanol (*S*,*R*)-**5** also induced the *M*-helix efficiently. Amino alcohols derived from amino acids were further tested. Phenylglycinol (*R*)-**6** showed efficient induction of the *P*-helical structure ($g = +2.16 \times 10^{-3}$), while valinol (*R*)-**7** showed moderate but clear induction of the *P*-helix. Use of alaninol (*S*)-**8** with opposite absolute configuration resulted in formation of the *M*-helical structure with much less screw-sense induction. These results clearly indicate that the stereochemistry of a *N*-bound stereogenic carbon center serves as a determinant of the helical chirality of PQXboh. Amino alcohol (*R*)-**9**, which lacks a *N*-bound stereogenic carbon center, resulted in the formation of a *M*-helix with moderate se. *N*-Methylated amino alcohol (*S*,*S*)-**10** exhibited the induction of screw-sense opposite to that of nonmethylated (*S*,*S*)-**3** with much lower se.

To determine the effect of chiral guests in detail, the helix stabilization energy (ΔG_h) per chiral guest was estimated by changing the degree of polymerization (DP) of **PQXboh(*n*/*m**)** ($[n + m] = 60–400$), while the ratio of boronyl units ($n/m = 19/1$) was maintained. The *g* values were plotted against the DP of **PQXboh(*n*/*m**)** (Figure 2a). Hyperbolic tangent curves fit into the obtained positive nonlinear plots.[4e] The ΔG_h of (*S*,*S*)-**3** in toluene was found to be highest; it was estimated to be -1.54 kJ mol^{-1}. It should be remarked here that this value is 1.5 times higher than the highest ΔG_h for PQX bearing covalently attached 2-alkoxymethyl groups at the 6- and 7-positions of the

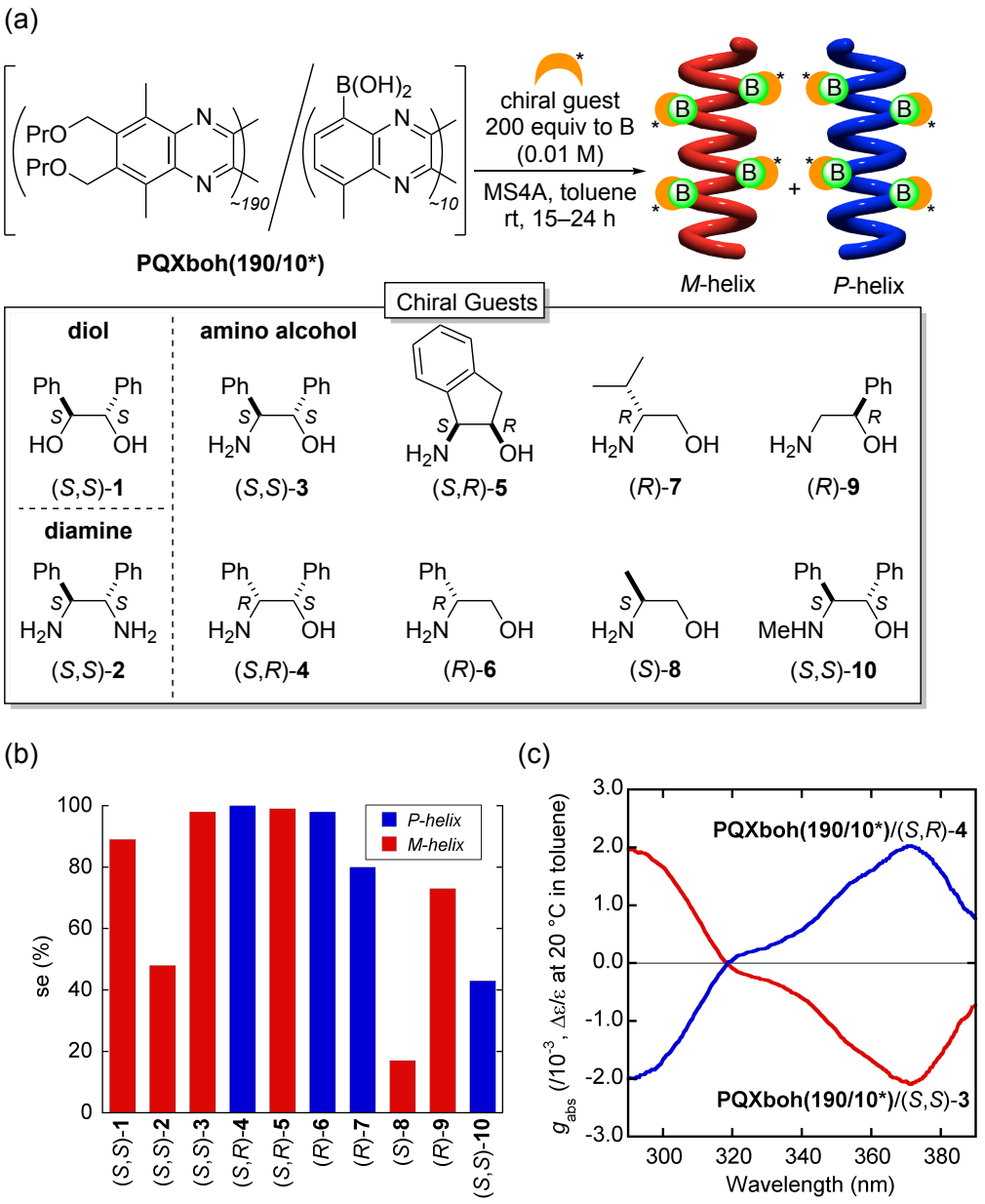


Figure 1. (a) Helical chirality induction of **PQXboh(190/10*)** with chiral guests. (b) Induced se of **PQXboh(190/10*)** with chiral guests in toluene at 20 °C. (c) CD spectra of **PQXboh(190/10*)** with chiral guests (*S*,*S*)-**3** and (*S*,*R*)-**4** in toluene at 20 °C.

quinoxaline rings (–1.01 kJ mol^{-1} for 2-octyloxymethyl).[4r] It was found that the amount of chiral guest could be reduced to 1.0 equiv to boronyl groups for the induction of pure helical sense of **PQXboh(380/20*)** (Figure 2b). Remarkably, even the use of 0.5 equiv of chiral guest (*S*,*S*)-**3** afforded 92% se.

By reprecipitation from acetonitrile, **PQXboh(190/10*)**/(*S*,*S*)-**3**, in which the boronyl group

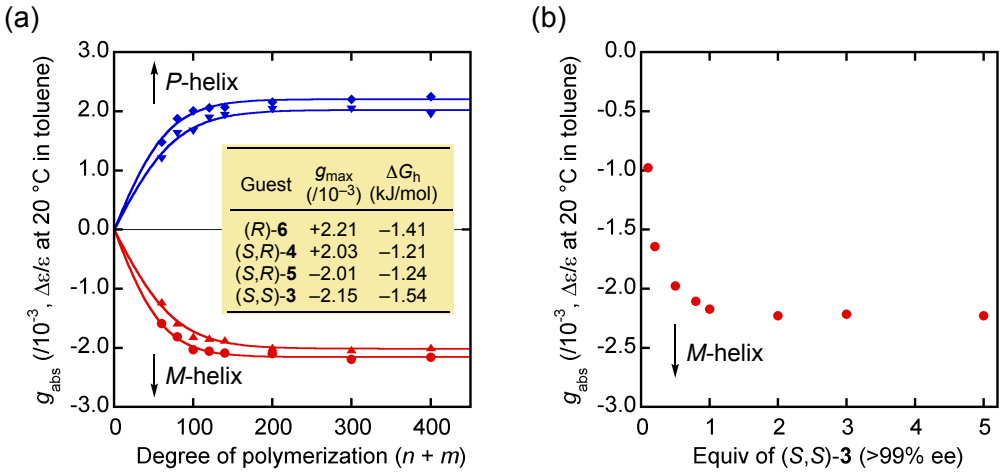
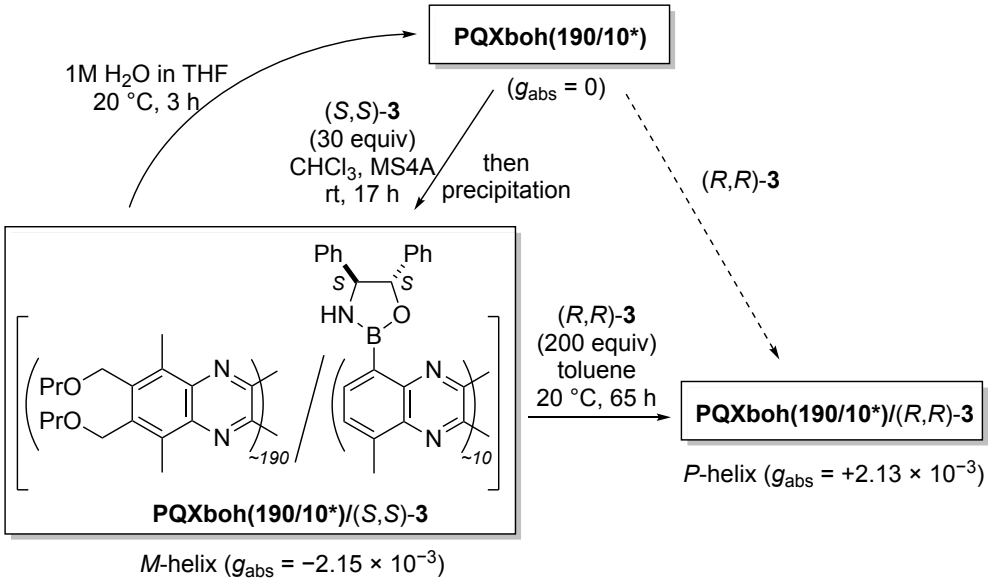


Figure 2. (a) Relationships between DP ($n + m$) and dissymmetry factor g of **PQXboh(*n*/*m**)** (n/m = 19/1) at 371.5 nm in toluene at 20 °C: (*S*,*S*)-**3** (red ●), (*S*,*R*)-**4** (blue ▼), (*S*,*R*)-**5** (red ▲), and (*R*)-**6** (blue ♦). In the table insert, g_{max} (g values for pure helix) and ΔG_h (helix stabilization energy per unit) calculated from curve fittings are shown. (b) Helical chirality induction of **PQXboh(380/20*)** with different equivalents (equiv) of (*S*,*S*)-**3**.

was converted to an oxazaborolidine group, was isolated (Scheme 1). The isolated PQX showed pure left-handed helical structure on measurement of its CD spectrum in the absence of the excess chiral guest (toluene, 20 °C). **PQXboh(190/10*)**/(*S*,*S*)-**3** was made CD silent within 3 h upon hydrolysis (1 M H_2O in tetrahydrofuran at 20 °C). Direct replacement of the chiral amino alcohol on **PQXboh** was achieved by mixing **PQXboh(190/10*)**/(*S*,*S*)-**3** with 200 equiv of (*R*,*R*)-**3**, resulting in complete reversal of the screw-sense (Scheme 1).

Based on these results, a chiral-guest-responsive helical polymer ligand was synthesized by incorporating coordinating groups as the third component.[2i–m,o] The ternary **PQXphos(360/20*/<u>20</u>)** bearing both boronyl and 2-[bis(3,5-dimethylphenyl)phosphino]phenyl pendants was employed in the palladium-catalyzed asymmetric silaborative C–C bond cleavage of *meso*-methylenecyclopropane **11** (Table 1).[21,9] A control experiment without **PQXphos(360/20*/<u>20</u>)** but with (*S*,*S*)-**3** gave only a trace amount of product **13** (<1%, entry 1). In the absence of chiral guest, **PQXphos(360/20*/<u>20</u>)** afforded racemic product **13** (entry 2). However, upon pretreatment of achiral **PQXphos(360/20*/<u>20</u>)** (2.4 mol% P and 2.4 mol% B) with (*S*,*S*)-**3** (1.2 mol%, 0.5 equiv to the boronyl pendants) at 50 °C for 24 h in toluene, the silaboration afforded (*R*,*R*)-**13** in 85% yield with 87% ee (entry 3). Use of larger amounts of chiral guest in the pretreatment afforded the product with slightly higher enantioselectivity (92% ee with 2.0 equiv chiral guest, entries 4 and 5). Use of the enantiomeric chiral guest (*R*,*R*)-**3** resulted in the

Scheme 1. Reversible Helical Chirality Induction of PQXboh with Chiral Amino Alcohol



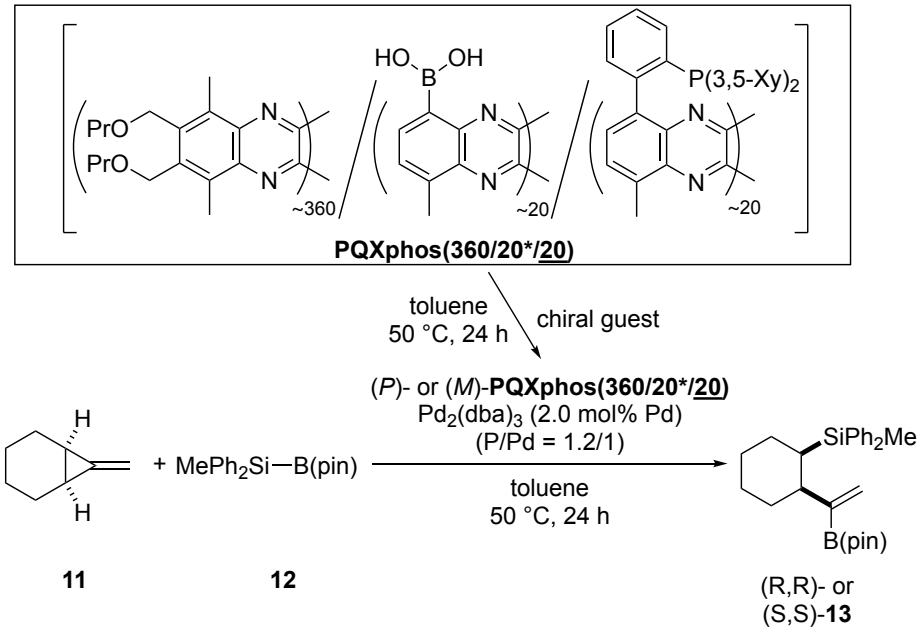
formation of an enantiomeric product with the same ee (entry 6).

These results suggest that the chirality of the chiral guest was successfully transferred to the helical main chain of PQX and in turn to the reaction center, as found in PQXphos bearing covalently bonded chiral side chains. Note that ligand exchange on the silylboron reagents was not observed during the reaction. It may also be interesting to note that **PQXphos(380/20)** bearing no boronyl pendant unexpectedly resulted in the formation of (*S*,*S*)-**13** in 5% ee in the presence of (*S*,*S*)-**3**, which, however had preference to form the opposite enantiomer (entry 7). As suggested by the mechanism of chirality transfer, some other chiral guests (*S*,*R*)-**4**, (*S*,*R*)-**5**, and (*R*)-**6** (1.0 equiv) shown in Figure 2 can also be used as the source of chirality in the silaboration reactions (entries 8–10).

We then looked at the possibility and the degree of chiral amplification[10,11] using binary **PQXboh(380/20*)** (Figure 3a). In the presence of 200 equiv of (*S*,*S*)-**3** with varying optical purity, helical chirality induction was carried out at 80 °C. A positive nonlinear relationship between the enantiopurity of the chiral guest and screw-sense induction was observed in a CD spectrum, measured in toluene at 20 °C. The plot indicated that even a chiral guest with 20% ee can induce >90% se. A similar chiral amplification was observed for phosphorus-containing, ternary **PQXphos(360/20*/20)** (Figure 3b).

Chirality-amplifying catalytic asymmetric synthesis was demonstrated with the use of **PQXphos(360/20*/20)** and (*S*,*S*)-**3** (Scheme 2). **PQXphos(360/20*/20)** was treated with 10 equiv

Table 1. Palladium-Catalyzed Asymmetric Silaborative C–C Bond Cleavage of *meso*-Methylenecyclopropane[a]



entry	**PQXphos**	chiral guest (equiv to B atom)	% yield[b]	% ee[c]
1	–	(*S*,*S*)-**3**[d]	<1	N.D.[e]
2	**(360/20*/20)**	no addition	88	0
3	**(360/20*/20)**	(*S*,*S*)-**3** (0.5 equiv)	85	87 (*R*,*R*)
4	**(360/20*/20)**	(*S*,*S*)-**3** (1.0 equiv)	86	91 (*R*,*R*)
5	**(360/20*/20)**	(*S*,*S*)-**3** (2.0 equiv)	86	92 (*R*,*R*)
6	**(360/20*/20)**	(*R*,*R*)-**3** (1.0 equiv)	81	92 (*S*,*S*)
7	**(380/20)**	(*S*,*S*)-**3** (1.0 equiv)	84	5 (*S*,*S*)
8	**(360/20*/20)**	(*S*,*R*)-**4** (1.0 equiv)	88	72 (*S*,*S*)
9	**(360/20*/20)**	(*S*,*R*)-**5** (1.0 equiv)	93	86 (*R*,*R*)
10	**(360/20*/20)**	(*R*)-**6** (1.0 equiv)	94	82 (*S*,*S*)

[a]**11** (0.15 mmol), **12** (0.10 mmol), $Pd_2(dba)_3$ (1.0 μmol), and ligand (2.4 μmol) were heated with toluene (0.20 mL) at 50 °C. [b]Isolated yield. [c]Determined by chiral SFC analysis after oxidation to the corresponding β-silyl ketones. [d]2.4 mol % to **12**. [e]Not determined.

of (*S*,*S*)-**3** with 33% ee at 80 °C for 96 h, and then excess (*S*,*S*)-**3** was removed by precipitation with acetonitrile. The recovered (*M*)-**PQXphos(360/20*/20)**/(*S*,*S*)-**3** afforded (*R*,*R*)-**13** with 87%

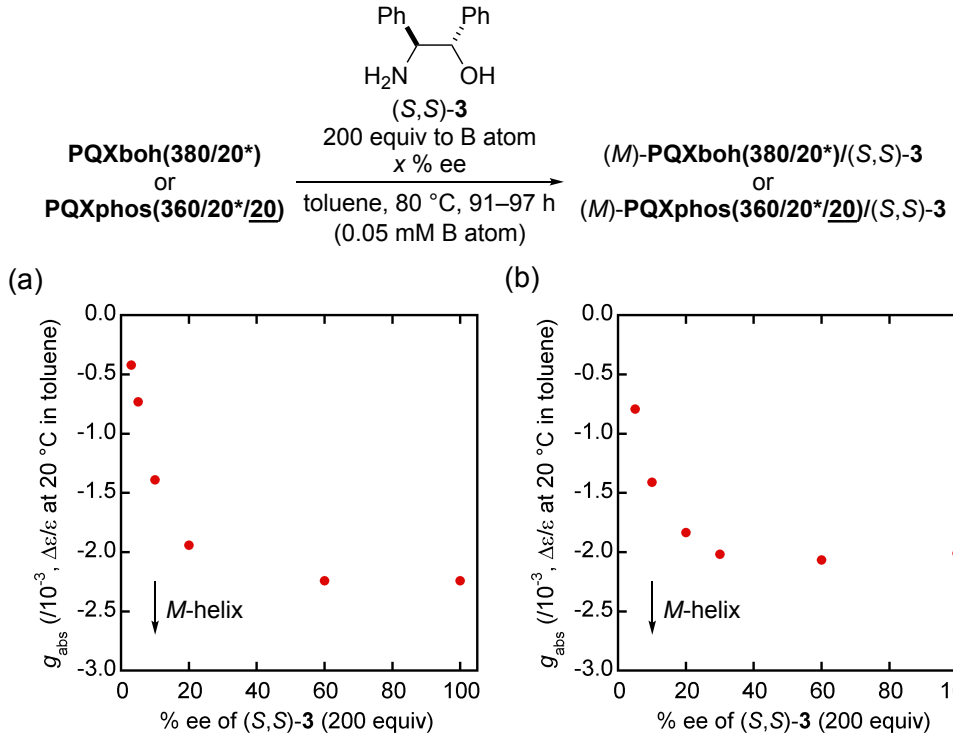
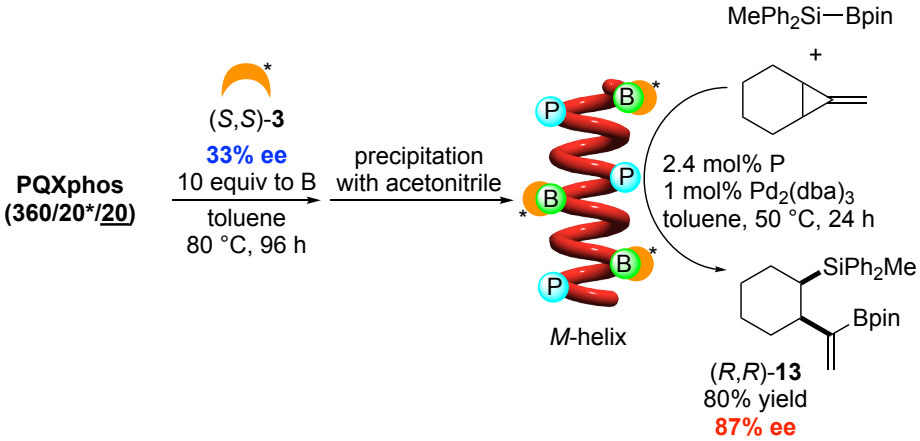


Figure 3. Helical chirality induction of (a) **PQXboh(380/20*)** and (b) **PQXphos(360/20*/20)** with 200 equiv of (*S*,*S*)-**3** with varying optical purity.

Scheme 2. Chiral Amplification on Polyquinoxaline Scaffold toward Pd-Catalyzed Asymmetric Silaboration.



ee. This result demonstrates that PQX serves as an efficient chiral amplifier in catalytic asymmetric synthesis.[2o]

Conclusion

The author demonstrated the efficient helical chirality induction of PQXs by introducing boronyl pendants as chiral guest receptor sites. Taking advantage of the long persistence length of the helical PQX scaffold, a pure single-handed structure was induced by condensation with a small amount of chiral amino alcohol. Chiral amplification on the PQX scaffold was achieved by using a chiral guest with low ee, forming a pure single-handed helical structure. The induced helically chiral macromolecular scaffold provided an efficient asymmetric reaction environment in a palladium-catalyzed reaction. Separation of chirality induction sites and catalytically active sites in the macromolecular scaffold enables the rational design of chiral amplification systems.

Experimental Section

1. General

All reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Materials were weighted by an electric balance, Sartorius CPA225D (readability: 0.01 mg). Column chromatography was performed with Ultra Pure Silica Gel (SILICYCLE, pH 7.0, 40–63 μm, 60 Å). ^{1}H NMR spectra were recorded on a Varian 400-MR (400 MHz) spectrometer at ambient temperature. ^{1}H NMR data are reported as follows: chemical shift in ppm downfield from tetramethylsilane (δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet and br = broad), coupling constant (Hz), and integration. The GPC analysis was carried out with TSKgel GMH_{XL} ($CHCl_3$, polystyrene standards). Circular dichroism (CD) spectra were recorded on a JASCO J-1500 spectrometer. UV-vis absorption spectra were recorded on a JASCO V-770 spectrometer. The chiral SFC analysis was carried out on JASCO SF-2000 analytical SFC system equipped with Daicel CHIRALCEL OX-H (CO_2 and 2-propanol).

2. Materials

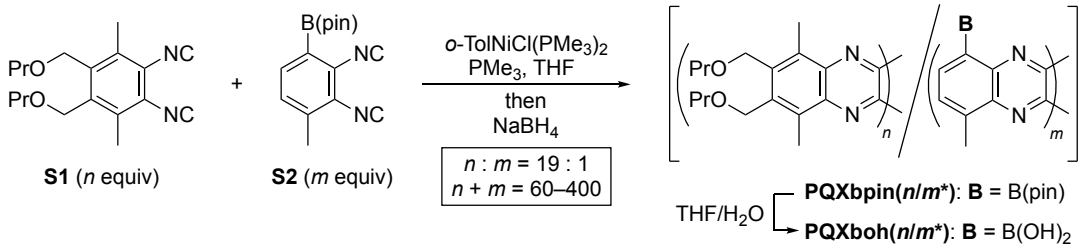
Toluene and chloroform were distilled over before use. Tetrahydrofuran (Wako), acetonitrile (Wako), 2-propanol (Wako), dichloromethane (Nacalai), hexane (Nacalai), diethyl ether (Nacalai), distillated water (Nacalai), magnesium sulfate (Nacalai), sodium sulfate (Wako), sodium

borohydride (TCI), trimethyl phosphine (Strem), (*S*,*S*)-**1** (TCI), (*S*,*S*)-**2** (TCI), (*S*,*S*)-**3** (Aldrich), (*R*,*R*)-**3** (Aldrich), (*S*,*R*)-**4** (TCI), (*S*,*R*)-**5** (Wako), (*R*)-**6** (TCI), (*R*)-**7** (TCI), (*S*)-**8** (TCI), and (*R*)-**9** (Ark Pharm) were used as received from commercial sources. (*S*,*S*)-**10**,[12] **11**,[21] **12**,[21] *o*-TolNiCl(PMe_3)$_2$,[13] **S1**,[14] **S2**,[2p] and **S3**[2k] were prepared according to the reported procedure.

3. Experimental Procedure and Spectral Data for New Compounds

3.1. Synthesis of PQXboh(*n*/*m**)

Scheme S1.



Synthesis of PQXboh(57/3*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 700 μL, 7.0 μmol) and PMe_3 (1.0 M in THF, 35 μL, 35 μmol) in THF (10 mL) was added a solution of **S1** (120 mg, 0.40 mmol) and **S2** (5.6 mg, 21 μmol) in THF (11 mL) at room temperature. The mixture was stirred at room temperature for 14 h. To the mixture was added $NaBH_4$ (20 mg, 0.53 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(57/3*)** was obtained as a beige solid. The obtained **PQXbpin(57/3*)** was dissolved in a mixture of THF (0.5 mL) and water (330 μL). After stirring at room temperature overnight, the solution was precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXboh(57/3*)** was obtained as a beige solid (95.9 mg, 77%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–6.20 (brm, peak top; 8.26, 7.67, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.53, 4.36, 3.22, 2.84, 1.48, 0.84 (24n+3m+3)H). M_n = 1.19 × 10^4, M_w/M_n = 1.18.

Synthesis of PQXboh(76/4*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 300 μL, 3.0 μmol) and PMe_3 (0.1 M in THF, 200 μL, 20 μmol) in THF (5 mL) was added a solution of **S1** (68.5 mg, 0.23 mmol) and **S2** (3.2

mg, 12 μmol) in THF (5 mL) at room temperature. The mixture was stirred at room temperature for 112 h. To the mixture was added $NaBH_4$ (27.4 mg, 0.72 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to preparative GPC to give **PQXbpin(76/4*)** as a beige solid. The obtained **PQXbpin(76/4*)** was dissolved in a mixture of THF (1 mL) and water (100 μL). After stirring at room temperature overnight, the mixture was diluted with brine, extracted with $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to preparative GPC to give **PQXboh(76/4*)** as a beige solid (57.2 mg, 81%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.60–6.30 (brm, peak top; 8.26, 7.65, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 1.48, 0.85 (24n+3m+3)H). $M_n = 1.84 \times 10^4$, $M_w/M_n = 1.40$.

Synthesis of PQXboh(95/5*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 420 μL, 4.2 μmol) and PMe_3 (1.0 M in THF, 21 μL, 21 μmol) in THF (10 mL) was added a solution of **S1** (120 mg, 0.40 mmol) and **S2** (5.6 mg, 21 μmol) in THF (5 mL) at room temperature. The mixture was stirred at room temperature for 36 h. To the mixture was added $NaBH_4$ (12.9 mg, 0.34 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(95/5*)** was obtained as a beige solid. The obtained **PQXbpin(95/5*)** was dissolved in a mixture of THF (0.5 mL) and water (330 μL). After stirring at room temperature overnight, the solution was precipitated with acetonitrile. After drying in vacuo, **PQXboh(95/5*)** was obtained as a beige solid (80.0 mg, 64%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–6.20 (brm, peak top; 8.27, 7.67, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 1.48, 0.85 (24n+3m+3)H). $M_n = 2.25 \times 10^4$, $M_w/M_n = 1.24$.

Synthesis of PQXboh(114/6*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 350 μL, 3.5 μmol) and PMe_3 (1.0 M in THF, 17.5 μL, 17.5 μmol) in THF (10 mL) was added a solution of **S1** (120 mg, 0.40 mmol) and **S2** (5.6 mg, 21.0 μmol) in THF (11 mL) at room temperature. The mixture was stirred at room temperature for 36 h. To the mixture was added $NaBH_4$ (12.7 mg, 0.345 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic

layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(114/6*)** was obtained as a beige solid. The obtained **PQXbpin(114/6*)** was dissolved in THF (0.5 mL) and water (330 μL). After stirring at room temperature for 5.5 h, the solution was precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXboh(114/6*)** was obtained as a beige solid (101 mg, 81%, 2 steps).^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–6.20 (brm, peak top; 8.27, 7.67, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 1.48, 0.85 (24n+3m+3)H). $M_n = 2.87 \times 10^4$, $M_w/M_n = 1.15$.

Synthesis of PQXboh(133/7*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 200 μL, 2.0 μmol) and PMe_3 (0.1 M in THF, 100 μL, 10 μmol) in THF (5 mL) was added a solution of **S1** (79.9 mg, 0.27 mmol) and **S2** (3.7 mg, 14 μmol) in THF (5 mL) at room temperature. The mixture was stirred at room temperature for 22 h. To the mixture was added $NaBH_4$ (9.9 mg, 0.26 mmol), and the mixture was stirred for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed two times with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(133/7*)** was obtained as a beige solid. The obtained **PQXbpin(133/7*)** was dissolved in a mixture of THF (500 μL) and water (50 μL). After stirring at room temperature for 16 h, the solution was precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXboh(133/7*)** was obtained as a beige solid (40.6 mg, 49%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.60–6.40 (brm, peak top; 8.26, 7.64, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 1.48, 0.85 (24n+3m+3)H). $M_n = 3.74 \times 10^4$, $M_w/M_n = 1.25$.

Synthesis of PQXboh(190/10*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 700 μL, 7.0 μmol) and PMe_3 (1.0 M in THF, 35 μL, 35 μmol) in THF (56 mL) was added a solution of **S1** (400 mg, 1.33 mmol) and **S2** (18.8 mg, 70 μmol) in THF (14 mL) at room temperature. The mixture was stirred at room temperature for 20 h. To the mixture was added $NaBH_4$ (23.1 mg, 0.61 mmol), and the mixture and stirred for 1 h. The mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL) and separated by centrifugation. After drying in vacuo, **PQXbpin(190/10*)** was obtained as a beige solid. The obtained

PQXbpin(190/10*) was dissolved in a mixture of THF (5 mL) and water (330 μL). After stirring at room temperature for 17 h, the solution was precipitated with acetonitrile. After drying in vacuo, **PQXboh(190/10*)** was obtained as a beige solid (275 mg, 67%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–6.60 (brm, peak top; 8.26, 7.68, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.38, 3.22, 2.84, 1.49, 0.85 (24n+3m+3)H). $M_n = 7.19 \times 10^4$, $M_w/M_n = 1.29$.

Synthesis of PQXboh(285/15*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 100 μL, 1.0 μmol) and PMe_3 (0.10 M in THF, 50 μL, 5.0 μmol) in THF (10 mL) was added a solution of **S1** (85.7 mg, 285 μmol) and **S2** (3.9 mg, 15 μmol) in THF (10 mL) at room temperature. The mixture was stirred at room temperature for 20 h. To the mixture was added $NaBH_4$ (128 mg, 0.34 mmol), and the mixture and stirred for 1 h. The mixture was diluted with brine and extracted with $CHCl_3$. The organic layer was washed two times with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(285/15*)** was obtained as a beige solid. The obtained **PQXbpin(285/15*)** was dissolved in a mixture of THF (1.0 mL) and water (100 μL). After stirring at room temperature for 8.5 h, the solution was precipitated with acetonitrile. After drying in vacuo, **PQXboh(285/15*)** was obtained as a beige solid (44.3 mg, 50%, 2 steps). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–6.40 (brm, peak top; 8.26, 7.67, 6.94 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 1.49, 0.85 (24n+3m+3)H). $M_n = 1.08 \times 10^5$, $M_w/M_n = 1.22$.

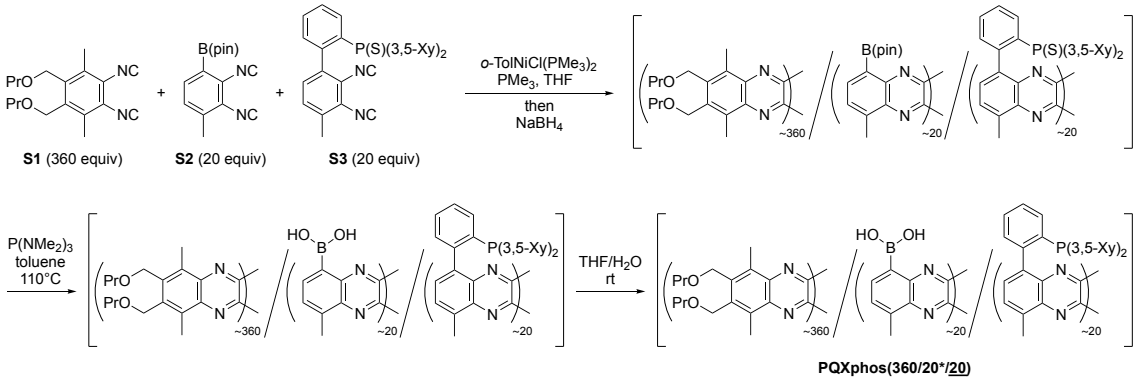
Synthesis of PQXboh(380/20*):

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 200 μL, 2.0 μmol) and PMe_3 (0.1 M, 100 μL, 10 μmol) in THF (20 mL) was added a solution of **S1** (228.4 mg, 760 μmol) and **S2** (10.7 mg, 40 μmol) in THF (20 mL) at room temperature. The mixture was stirred at room temperature for 20 h. To the mixture was added $NaBH_4$ (9.4 mg, 0.25 mmol), and the mixture and stirred for 1 h. The mixture was diluted with brine and extracted with $CHCl_3$. The organic layer was washed two times with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in toluene (0.5 mL) and precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXbpin(380/20*)** was obtained as a beige solid. The obtained **PQXbpin(380/20*)** was dissolved in a mixture of THF (1.0 mL) and water (100 μL). After stirring at room temperature for 9 h, the solution was precipitated with acetonitrile (10 mL). After drying in vacuo, **PQXboh(380/20*)** was obtained as a beige solid (149 mg, 63%, 2 steps). ^{1}H NMR (400 MHz,

C_6D_6, δ): 8.70–6.30 (brm, peak top; 8.27, 7.67, 6.93 (4m+4)H), 6.00–0.00 (brm, peak top; 4.54, 4.36, 3.22, 2.84, 1.49, 0.85 (24n+3m+3)H). $M_n = 1.39 \times 10^5$, $M_w/M_n = 1.32$.

3.2. Synthesis of PQXphos(*n*/*m**/*l*)

Scheme S2.



Synthesis of PQXphos(360/20*/<u>20</u>):

[Polymerization]

To a solution of *o*-TolNiCl(PMe_3)$_2$ (10.0 mM in THF, 200 μL, 2.0 μmol) and PMe_3 (0.1 M in THF, 100 μL, 10 μmol) in THF (40 mL) was added a solution of **S1** (216 mg, 0.72 mmol) and **S2** (10.8 mg, 40 μmol) and **S3** (18.9 mg, 39 μmol) in THF (40 mL) at room temperature. The mixture was stirred at room temperature for 25 h. To the mixture was added $NaBH_4$ (25.2 mg, 0.67 mmol), and the mixture and stirred for 1 h. The mixture was concentrated and passed through a pad of Celite using $CHCl_3$ as an eluent. The filtrate was concentrated, dried in vacuo, and dissolved in toluene (1 mL). The solution was precipitated with acetonitrile (50 mL). The precipitated polymer was collected by centrifugation and washed two times with acetonitrile. After drying in vacuo, **P1** was obtained as a beige solid (205 mg, 85%). $M_n = 1.29 \times 10^5$, $M_w/M_n = 1.38$.

[Reduction of P=S]

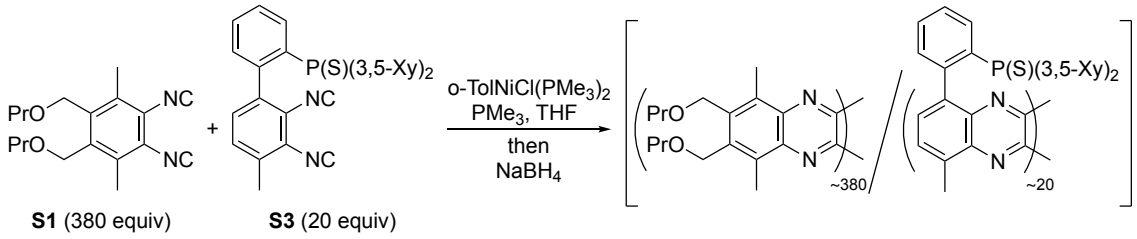
A mixture of **P1** and P(NMe_2)$_3$ (259 mg, 1.59 mmol) in toluene (3 mL) was stirred at 110 °C for 24 h. The solution was precipitated with acetonitrile (50 mL). The precipitated polymer was collected by centrifugation and washed two times with acetonitrile. After drying in vacuo, **P2** was obtained as a beige solid (160 mg, 85%).

[Hydrolysis of Boronic Acid Pinacol Ester]

A solution of **P2** in THF (2.0 mL) and degassed water (200 μL) was stirred at room temperature overnight. The mixture was precipitated with acetonitrile (50 mL). The precipitated polymer was

collected by centrifugation and washed with acetonitrile for two times. After drying in vacuo, **PQXphos(360/20*/<u>20</u>)** was obtained as a beige solid (141 mg, 91%). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–5.70 (brm, peak top; 7.99, 7.58, 7.04, 6.74, 6.20 (4m+12l+4)H), 5.70–0.00 (brm, peak top; 4.54, 4.37, 3.22, 2.84, 2.04, 1.49, 1.09, 0.85 (24n+3m+15l+3)H). M_n = 1.69 × 10^5, M_w/M_n = 1.14.

Scheme S3.



S1 (380 equiv) **S3** (20 equiv)

Synthesis of PQXphos(380/<u>20</u>):

[Polymerization]

To a solution of *o*-TolNiCl(PMe$_3$)$_2$ (10.0 mM, 100 μL, 1.0 μmol) and PMe$_3$ (0.1 M, 50 μL, 5.0 μmol) in THF (5 mL) was added a solution of **S1** (114 mg, 0.38 mmol) and **S3** (9.8 mg, 20 μmol) in THF (15 mL) at room temperature. The mixture was stirred at room temperature for 71 h. To the mixture was added $NaBH_4$ (17.4 mg, 0.460 mmol), and the mixture was stirred for 1 h. The mixture was concentrated and passed through a pad of Celite using $CHCl_3$ as an eluent. The filtrate was concentrated, dried in vacuo, and dissolved in toluene (1 mL). The solution precipitated with acetonitrile (50 mL). The precipitated polymer was collected by centrifugation and washed two times with acetonitrile. After drying in vacuo, **P3** was obtained as a beige solid (122 mg, 98%). M_n = 1.28 × 10^5, M_w/M_n = 1.09.

[Reduction of P=S]

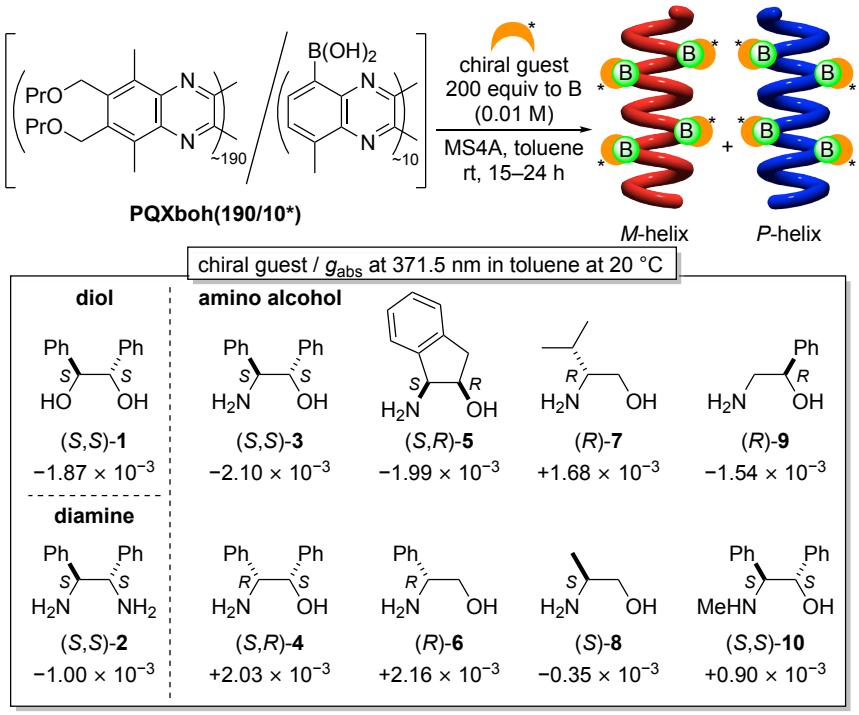
A mixture of **P3** and P(NMe$_2$)$_3$ (131 mg, 0.80 mmol) in toluene (1 mL) was stirred at 110 °C for 24 h. After cooling to room temperature, the mixture was precipitated with acetonitrile (50 mL). The precipitated polymer was collected by centrifugation and washed two times with acetonitrile. After drying in vacuo, **PQXphos(380/<u>20</u>)** was obtained as a beige solid (61.9 mg, 58%). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.50–6.10 (brm, peak top; 7.49, 7.29, 7.24, 7.06, 6.81, 6.36 (12l+4)H), 6.00–0.00 (brm, peak top; 4.55, 4.37, 3.22, 2.84, 2.09, 1.49, 0.85 (24n+15l+3)H). M_n = 1.19 × 10^5, M_w/M_n = 1.61.

3.3. Helical Chirality Induction of PQXboh(190/10*) with Chiral Guests (Figure 1)

General Procedure:

In the presence of a grain of MS4A (10–20 mg), a solution of **PQXboh(190/10*)** (3 mg/10 mL, 1.0 mL, 0.05 μmol of boron atom) and a chiral guest (0.01 mmol) was stirred at room temperature for 15–24 h. After filtration through syringe filter, the filtrate was diluted to 10 mL with toluene. The solution was subjected to UV and CD measurement (light path length = 1 cm, 20 °C). The observed dissymmetry factors ($g_{abs} = \Delta\varepsilon/\varepsilon$) were shown in Scheme S4.

Scheme S4.



3.4. Determination of the Helical Induction Energy ΔG_h (Figure 2a)

Measurement:

In the presence of a grain of MS4A (10–20 mg), a solution of **PQXboh(*n*/*m**)** (3 mg/10 mL, 1 mL, 0.05 μmol of boron atom) and chiral amino alcohol (0.01 mmol) was stirred at room temperature for 15–24 h. After filtration through syringe filter, the filtrate was diluted to 10 mL with toluene. The solution was subjected to UV and CD measurement (light path length = 1 cm, 20 °C).

Analysis:

According to the previous reports by Green's group[4e] and Suginome's group,[4q,r] the observed dissymmetry factor ($g_{abs} = \Delta\varepsilon/\varepsilon$) of poly(quinixaline-2,3-diyl) can be expressed as follows.

$$g_{abs} = \tanh(-\Delta G_h N/2RT) \times g_{max}$$

g_{max}: g value for the purely single-handed poly(quinoxaline-2,3-diyl)s

ΔG_h: helix stabilization energy per a chiral monomer unit

N: number of chiral units

R: gas constant (8.314 J K^{-1} mol^{-1})

T: operating temperature (293.15 K)

Non-linear least-squares fitting of g_{abs} versus N was performed by using the Solver Function in Microsoft Office Excel. Sums of the squares of the deviation were minimized by varying two parameters g_{max} and ΔG_h. These parameters were successfully converged and the values were shown in Table S1.

Table S1. Dissymmetry Factor g_{abs} of PQXboh(n/m^*)/Chiral Guest

PQXboh(n/m^*)	g_{abs} (/10^{-3}, 371.5 nm)			
	(*S*,*S*)-**3**	(*S*,*R*)-**4**	(*S*,*R*)-**5**	(*R*)-**6**
PQXboh(57/3*)	−1.59	+1.20	−1.22	+1.48
PQXboh(76/4*)	−1.81	+1.62	−1.57	+1.88
PQXboh(95/5*)	−2.03	+1.67	−1.80	+2.01
PQXboh(114/6*)	−2.06	+1.89	−1.83	+2.06
PQXboh(133/7*)	−2.09	+1.93	−1.86	+2.07
PQXboh(190/10*)	−2.10	+2.03	−1.99	+2.16
PQXboh(285/15*)	−2.19	+2.04	−2.03	+2.20
PQXboh(380/20*)	−2.16	+1.94	−1.99	+2.25

3.5. Helical Chirality Induction to PQXboh(380/20*) with Varied Equiv of (*S*,*S*)-3 (Figure 2b)

A solution of **PQXboh(380/20*)** (3.0 mg) and (*S*,*S*)-**3** (0.1–5.0 equiv to B) in toluene (1 mL) was

stirred at room temperature for 20 h. After dilution to 10 mL with toluene, the solution was subjected to UV and CD measurements (light path length = 1 mm, 20 °C).

Table S2. **Helical Chirality Induction to PQXboh(380/20*) with Varied Equiv of (*S*,*S*)-3**

Equiv of (*S*,*S*)-**3**	g_{abs} (/10^{-3}, 371.5 nm)
0.1	−0.97
0.2	−1.64
0.5	−1.98
0.8	−2.11
1.0	−2.17
2.0	−2.23
3.0	−2.21
5.0	−2.23

3.6. Reversible Helical Chirality Induction of PQXboh (Scheme 1)

[Isolation of PQXboh(190/10*)/(*S*,*S*)-3]

A mixture of **PQXboh(190/10*)** (31.1 mg), (*S*,*S*)-**3** (38.3 mg), and MS4A in $CHCl_3$ (300 μL) was stirred at room temperature for 17 h. After filtration through syringe filter, the filtrate was precipitated with acetonitrile **PQXboh(190/10*)**/(*S*,*S*)-**3** (21.6 mg) was obtained as a beige solid. The obtained **PQXboh(190/10*)**/(*S*,*S*)-**3** was subjected to UV and CD measurement (light path length = 1 mm, 20 °C). ^{1}H NMR (400 MHz, C_6D_6, δ): 8.70–5.70 (brm, peak top; 8.28, 7.52, 7.03, 6.84, 6.48, 6.18, (14m+4)H), 5.70–0.00 (brm, peak top; 5.23, 4.55, 4.38, 3.22, 2.84, 1.48, 0.85 (24n+6m+3)H).

[Hydrolysis of PQXboh(190/10*)/(*S*,*S*)-3]

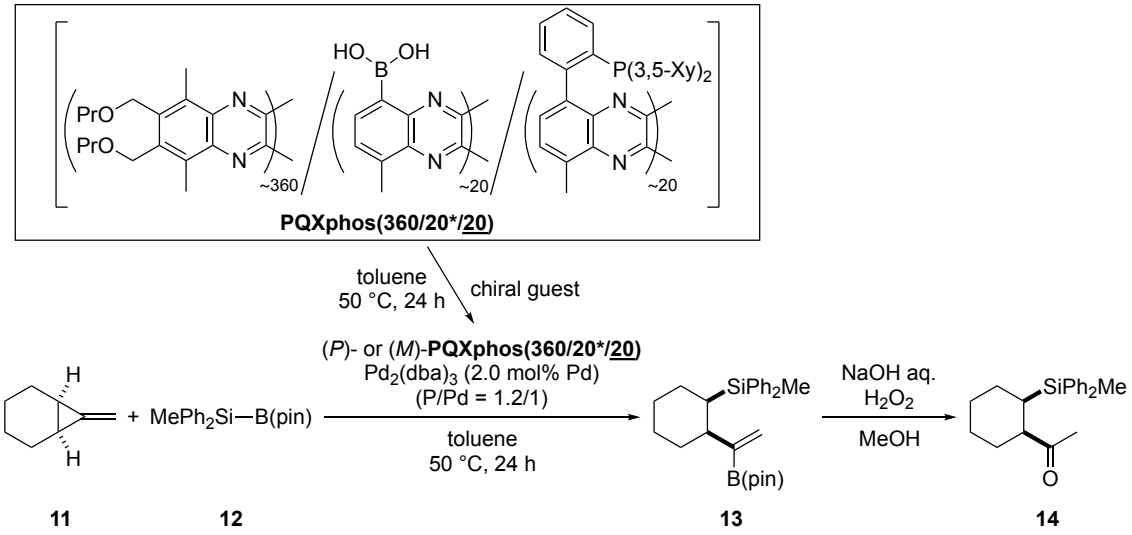
A mixture of **PQXboh(190/10*)**/(*S*,*S*)-**3** (3 mg/100 mL, 3 mL) and water (55 μL) was stirred at 20 °C. The reaction was monitored by CD measurement (light path length = 1 cm, 20 °C).

[Direct Replacement of the Chiral Amino Alcohol on PQXboh (190/10*)/(*S*,*S*)-3]

A solution of **PQXboh(190/10*)**/(*S*,*S*)-**3** (2.9 mg/10 mL in toluene, 1 mL) and (*R*,*R*)-**3** (2 mg, 200 equiv to boron atom) was stirred at room temperature. The solution was subjected to UV and CD measurements (light path length = 1 mm, 20 °C)

3.7. Palladium-Catalyzed Asymmetric Silaborative C–C Bond Cleavage of *meso*-Methylenecyclopropane (Table 1)

Scheme S5.



A solution of chiral amino alcohol (24 mM in toluene, 100 μL 2.4 μmol) and **PQXboh(360/20*/20)** (14.5 mg, 2.4 μmol phosphorous atom) in toluene (100 μL) was stirred at 50 °C for 24 h. To the solution was added Pd_2dba_3 (0.01 M in toluene, 100 μL, 1.0 μmol). The mixture was stirred at room temperature for 5 min. To the mixture was added **11** (0.15 mmol) and **12** (0.1 mmol) in this order, and the resulting mixture was heated at 50 °C with stirring. The mixture was analyzed by GC. After 24 h, the crude product was subjected to silica gel column chromatography. To determine the enantiomeric excess, obtained **13** was converted to β-silyl ketone **S4**.[9] To a methanol solution (2 mL) of **13** was added aqueous NaOH solution (3N, 2.5 mL) and the mixture was cooled to 0 °C. Aqueous H_2O_2 solution (30%, 1.5 mL) was slowly added to the mixture. The resulting solution was stirred at room temperature for 12 h. The resulting mixture was extracted with Et_2O and the extracts were washed with water. After drying with anhydrous $MgSO_4$, the concentrated mixture was purified by silica gel column chromatography to give a β-silyl ketone **S4**. Enantiomeric excess of this compound was determined by chiral SFC analysis (Daicel CHIRALCEL OX-H, CO_2/*i*-PrOH = 100/2, v/v, flow rate = 3.06 mL/min, UV = 220 nm). **13**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.55–7.58 (m, 2H), 7.51–7.53 (m, 2H), 7.28–7.36 (m, 6H), 5.79 (d, *J* = 2.8 Hz, 1H), 5.59 (dd, *J* = 2.8, 1.2 Hz, 1H), 2.76–2.79 (m, 1H), 1.87–2.01 (m, 2H), 1.71–1.78 (m, 1H), 1.53–1.63 (m, 3H), 1.28–1.46 (m, 3H), 1.23 (s, 12 H), 0.64 (s, 3H). **S4**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.56–7.58 (m, 2H), 7.46–7.48 (m, 2H), 7.31–7.37 (m, 6H), 2.64–

2.67 (m, 1H), 1.98–2.10 (m, 2H), 1.77–1.81 (m, 1H), 1.73 (s, 3H), 1.57–1.73 (m, 3H), 1.53 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.18–1.39 (m, 2H), 0.71 (s, 3H).

3.8. Helical Chirality Induction of PQXboh(380/20*) and PQXphos(360/20*/20) with 200 Equiv of (*S*,*S*)-3 with Varying Optical Purity (Figure 3)

A solution of **PQXboh(360/20*/20)** (9 mg/10 mL, 500 μL, 0.075 μmol of boron atom) and (*S*,*S*)-**3** and (*R*,*R*)-**3** (200 equiv to boron atom, total 1 mL) was stirred at 80 °C for 91–97 h. After cooling to room temperature, the solution was subjected to CD measurement (light path length = 1 mm, 20 °C).

Table S3. **Helical Chirality Induction to PQXboh(380/20*) with 200 Equiv of (*S*,*S*)-3 with Varying Optical Purity**

% ee of (*S*,*S*)-**3**	g_{abs} ($/10^{-3}$, 371.5 nm)
3	−0.43
5	−0.73
10	−1.39
20	−1.94
60	−2.24
100	−2.24

Table S4. **Helical Chirality Induction to PQXphos(360/20*/20) with 200 Equiv of (*S*,*S*)-3 with Varying Optical Purity**

% ee of (*S*,*S*)-**3**	g_{abs} ($/10^{-3}$, 371.5 nm)
5	−0.79
10	−1.41
20	−1.83
30	−2.02
60	−2.07
100	−2.01

3.9. Chiral Amplification on Polyquinoxaline Scaffold toward Pd-Catalyzed Asymmetric Silaboration (Scheme 2)

[Helical Chirality Induction of PQXboh(360/20*/20)]

A solution of (*S*,*S*)-**3** (9.8 mg, 46 μmol), (*R*,*R*)-**3** (5.0 mg, 23 μmol) and **PQXboh(360/20*/20)** (47.8 mg, 7.9 μmol phosphorous atom) in toluene (500 μL) was stirred at 80 °C for 96 h. The mixture was precipitated with acetonitrile. After drying in vacuo, **PQXboh(360/20*/20)**/(*S*,*S*)-**3** was obtained as a beige solid (49.6 mg, >99 %). The obtained **PQXboh(360/20*/20)**/(*S*,*S*)-**3** was subjected to UV and CD measurement (light path length = 1 mm, 20 °C).

[Pd-Catalyzed Asymmetric Silaboration]

To a solution of **PQXboh(360/20*/20)**/(*S*,*S*)-**3** (15.1 mg) in toluene (100 μL) was added a solution of Pd_2dba_3 (0.01 M in toluene, 100 μL, 1.0 μmol). The mixture was stirred at room temperature for 5 min. To the mixture was added **11** (16.8 mg, 0.15 mmol) and **12** (30.3 mg, 0.1 mmol) in this order, and the resulting mixture was heated at 50 °C with stirring. After 24 h, the crude product was subjected to silica gel column chromatography. To determine the enantiomeric excess, obtained **13** (32.4 mg, 80 %) was converted to β-silyl ketone **S4**. To a methanol solution (2 mL) of **13** was added aqueous NaOH solution (3N, 2.5 mL) and the mixture was cooled to 0 °C. Aqueous H_2O_2 solution (30%, 1.5 mL) was slowly added to the mixture. The resulting solution was stirred at room temperature for 12 h. The resulting mixture was extracted with Et_2O and the extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography to give a β-silyl ketone **S4** (20.2 mg). Enantiomeric excess of this compound was determined by chiral SFC analysis (Daicel CHIRALCEL OX-H, CO_2/*i*-PrOH = 100/2, v/v, flow rate = 3.06 mL/min, UV = 220 nm).

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List of Publications

Chapter 1

Single-Handed Helical Poly(quinoxaline-2,3-diyl)s Bearing Achiral 4-Aminopyrid-3-yl Pendants as Highly Enantioselective, Reusable Chiral Nucleophilic Organocatalysts

Takeshi Yamamoto, Ryo Murakami, Michinori Suginome

J. Am. Chem. Soc. **2017**, *139*, 2557–2560.

Chapter 2

Kinetic Resolution of Secondary Alcohols Using Helical Poly(quinoxaline-2,3-diyl)s Bearing 4-Dialkylaminopyrid-3-yl Pendants as Chirality-Switchable Nucleophilic Catalysts

Takeshi Yamamoto, Ryo Murakami, Michinori Suginome

Manuscript in Preparation.

Chapter 3

Chirality-Amplifying, Dynamic Induction of Single-Handed Helix by Chiral Guests to Macromolecular Chiral Catalysts Bearing Boronyl Pendants as Receptor Sites

Takeshi Yamamoto, Ryo Murakami, Satoko Komatsu, Michinori Suginome

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