学位論文

Development of Novel Carbon-Carbon Bond Forming Reactions Utilizing Fluorene Structure

（フルオレン構造を用いた分子活性化法に基づく革新的炭素—炭素結合形成反応の開発）

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Abstract

Fluorene, which can be extracted from coal tar, is a molecule possessing fused 6,5,6-ring system. Due to its intriguing features, which include optical and electronic properties, it is expected that a fluorene is one of the simplest motifs that can be used as a π-conjugated functional material in industrial and academic researches. Fluorene and its derivatives have been employed as important building blocks in a broad range of materials including light-emitting devices, organic field-effect transistors (OFET), organic photovoltaic cells (OPV), biosensors, etc. On the other hand, the fluorene moiety has been focused as a protecting group in organic synthesis. There are limited reports of a synthetic utility, with most literature using the fluorene moiety - 9-fluorenylmethyl carbamate (Fmoc-NR_2) - as a protecting group of amino acids in peptide synthesis. It was expected that this highly conjugated system would show further interesting reactivity, thereby achieving novel organic reactions.

During Ph.D. studies, new synthetic methods for the functionalization of nitrogen containing compounds were developed. By employing remarkable ability of the fluorene moiety, several interesting carbon-carbon bond forming reactions were demonstrated.

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INDEX

I. General Introduction

In organic chemistry, carbon-carbon bond forming reactions are among the most important for the construction of basic skeletons of target molecules. As a key component of carbon-carbon bond forming reactions, carbanion species, prepared from appropriate precursors, are well-investigated intermediates for various transformations due to their high reactivity (Figure 1-1).

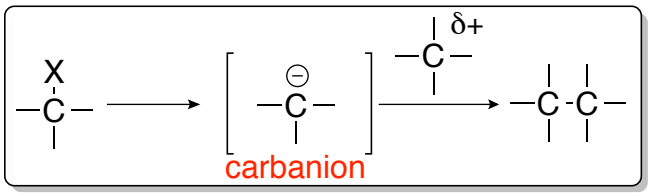
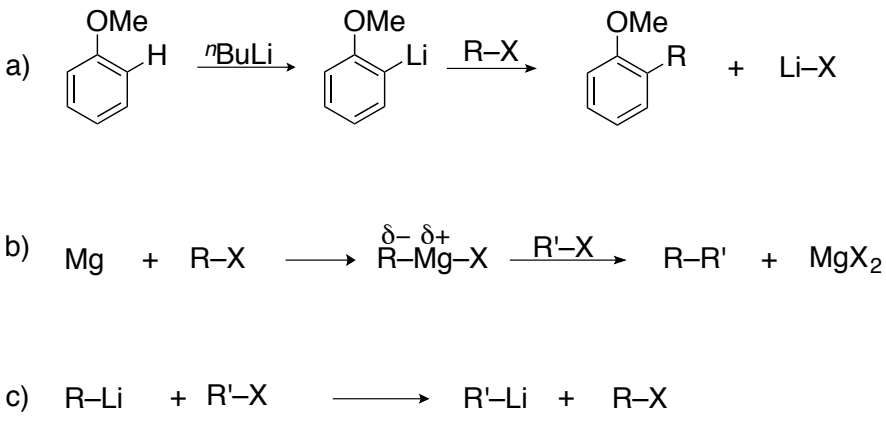


Figure 1-1. Generation of a carbanion

There are numerous moieties that can react with carbanions, *e.g.* carbonyl derivatives, carbon-carbon multiple bonds and activated alkanes with leaving groups *etc*. Historically, the generation of carbanion species is well investigated. There are mainly three categories (Scheme 1-1). The first method to generate carbanion species is *via* deprotonation using a stoichiometric amount of a strong base, an example is shown in the scheme below (Scheme 1-1a). When anisole was treated with a stoichiometric amount of ^{n}BuLi, the *ortho* hydrogen was deprotonated to give a lithiated aryl species. It is regarded as a carbanion species which can react with different types of electrophiles to give various products. Another way is by oxidative addition, in which Mg metal reacts with alkyl halides to generate Grignard reagents (Scheme 1-1b). It is also recognized as a carbanion species. The third method is the application of the metal-halogen exchange reaction, where alkyl Li reacts with alkyl halide to exchange their respective alkyl moieties (Scheme 1-1c).

Scheme 1-1. The ways of carbanion generation.



Because of the high utility of carbanions, various alternative methods have been developed. These methods, however, produce a stoichiometric amount of metal salt waste. From an atom economical point of view, these methods have room for improvement. Additionally, all classical methods require strong basic conditions. In the synthesis of complex molecules, *e.g.* natural products, bioactive compounds and chiral ligands etc., such strong basic conditions can cause decomposition or expose functionality tolerance problems. In contrast, reduction of the amount of a base required is one of the main goals currently in organic synthesis, as shown by the development of many catalytic synthetic reactions. These new methods, which work with a catalytic amount of carbanion species, are highly demanded and well investigated. Generation of carbanion species with only a catalytic amount of base, especially a mild base, is still a very hot topic in organic chemistry field. This is different from conventional carbanion chemistry, in which stoichiometric amounts of bases have been used. Theoretically, deprotonation of the substrate, which is a carbanion precursor, by the base species produces the protonated base (**Base–H**). For the recovery of the base species, it is necessary for the reacted substrate complex to deprotonate protonated base (**Base-H**) *via* proton transfer. However, the use of a strong base leads to retarded catalyst turnover. The recovery of strong base species seems thermodynamically unfavorable. Therefore, only mild bases can be considered as recyclable base species (Figure 1-2).

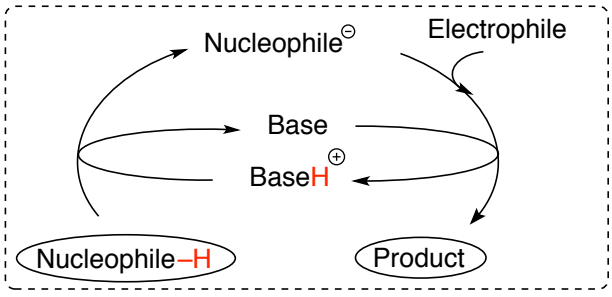


Figure 1-2. The reaction model.

If chemists wish to utilize a substrate with an inert hydrogen at the desired position for a carbon-carbon bond forming reaction under basic conditions, it is obvious a mild base system cannot be employed. However, if a proper functional group with the ability to activate inert hydrogen can be introduced in the molecule, deprotonation of the desired hydrogen even with a mild base is plausible. Once the substrate-derived carbanion species is present in solution, it will react with various types of substrates to form a new carbon-carbon bond (Figure 1-3).

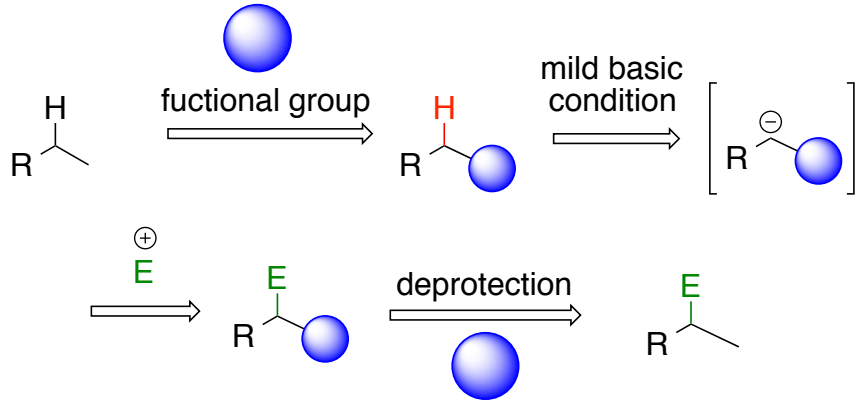


Figure 1-3. The model of a desired reaction system.

The activation methods of inert substrates are well investigated. There are several examples. Esters and primary amines are known as synthetically vital units. In spite of their wide utility, it is difficult to employ those substrates directly by the generation of their corresponding carbanion under basic conditions due to the high pK_a barrier of α-hydrogen of both substrates. The synthetic equivalents of both substrates are known as the malonate and nitro alkane (Figure 1-4).

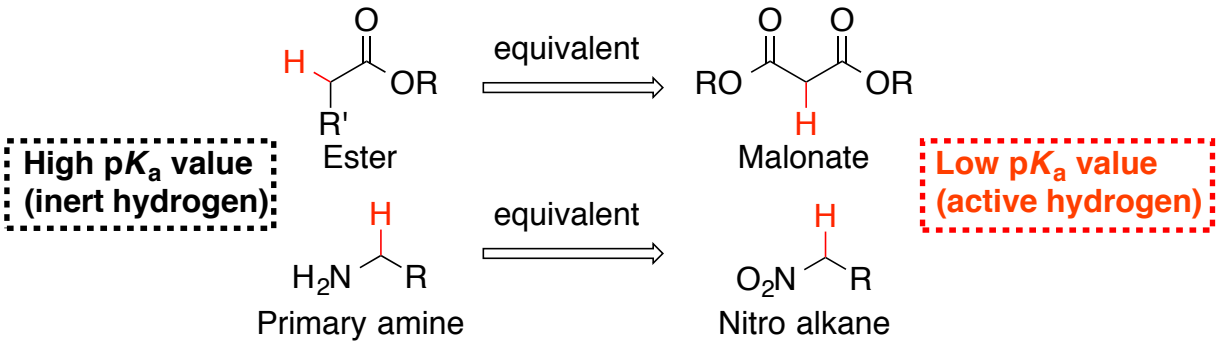


Figure 1-4. The examples of using synthetic equivalents

By employing those synthetic equivalents, chemists have succeeded in carbon-carbon bond forming reactions *via* the corresponding carbanion species that can be generated even in mild basic conditions.[1] After the desired reaction, those functionalities are then converted to original unit with the proper transformation methods (malonate: decarboxylation, nitro alkane: reduction). Typical examples of the activation strategy of these inert substrates are mentioned bellow. Kobayashi group has developed two different strategies of functionalization of ester equivalents.[2] The essence of concept for the first example is explained in Figure 1-5.[2a]

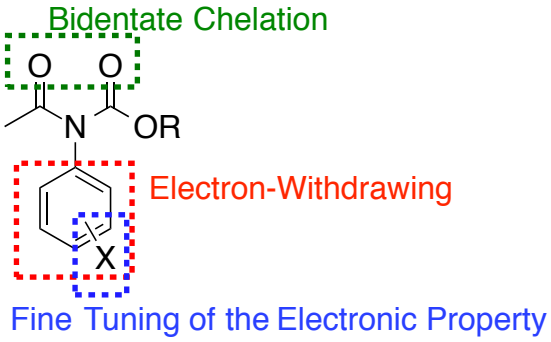
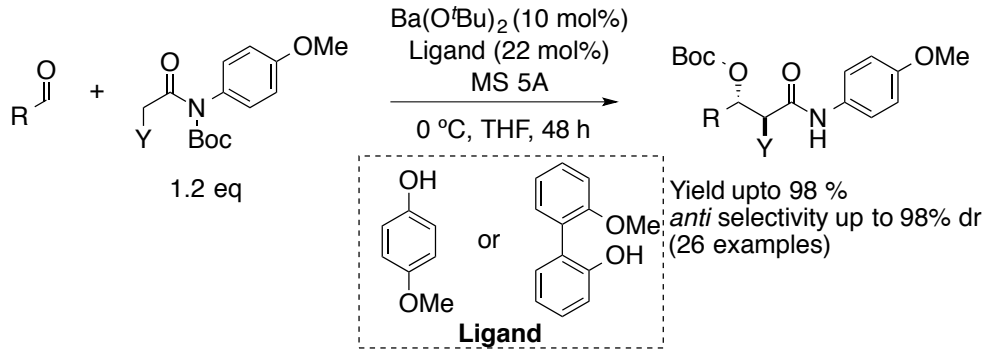


Figure 1-5. The well designed amide substrate.

Introducing a carbonyl group on the amide nitrogen allows it to function as a tether for bidentate chelation and enable further α-proton activation by a Lewis acidic metal counter cation. An aryl group is chosen as the second substituent on the nitrogen atom, which should be sufficiently versatile to fine-tune the overall steric and electronic property of the nucleophile. Employing that well-tuned molecule as nucleophile, Kobayashi *et. al.* achieved the catalytic aldol reaction with an excellent *anti*-selectivity (Scheme 1-2)[2a].

Scheme 1-2. The example of aldol reaction using well designed amides.



Due to the bidentate coordination of the metal to the substrate and the introduction of an electron withdrawing group on the nitrogen atom, the reaction proceeded as planned, even with a catalytic amount of base species - phenoxide anion showed relatively mild basicity. Additionally, the Boc group has another key role in the reaction system. After the nucleophilic attack of the amide to the aldehyde, intermolecular Boc transfer occurred. This phenomenon suppressed the retro aldol reaction pathway which caused a low chemical yield and diastereoselectivity in general. Another smart idea for making the synthetic equivalent of esters is shown in Figure 1-6[2g].

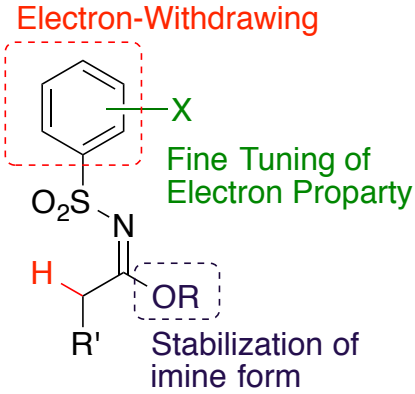
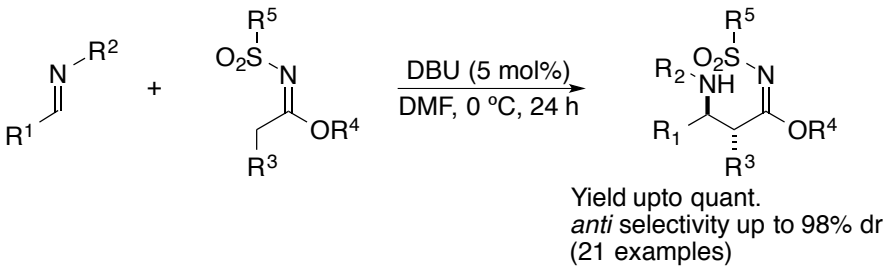


Figure 1-6. The well designed sulfonylimidate.

The sulfonylimidates were synthesized as a tunable ester equivalent. They anticipated that by introducing a heteroatom, such as oxygen, adjacent to the π(C=N) bond, stabilization of the corresponding enamine geometry might be achieved. In addition, the functionality on nitrogen atom was expected to control the acidity of α-hydrogen. They demonstrated the catalytic Mannich-type reaction of sulfonylimidate catalyzed by organobase species such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) which exhibits the pK_a value of 12 in DMSO (Scheme 1-3)[2g].

Scheme 1-3. The example of Mannich reaction using well designed sulfonylimidates.



In this thesis, a new activation method of inert substrates for novel carbon-carbon forming reaction like those mentioned above is documented. For the introduction of the new activation strategy of inert substrates, a very interesting paper reported by O'Donnell in 1988[3] must be highlighted. In their paper, the pK_a value of the α-hydrogen of ester equivalents was mentioned. As a part of their report, one substrate ''*N*-fluorene protected imine'' was reported to possess very interesting intrinsic features (Figure 1-7).

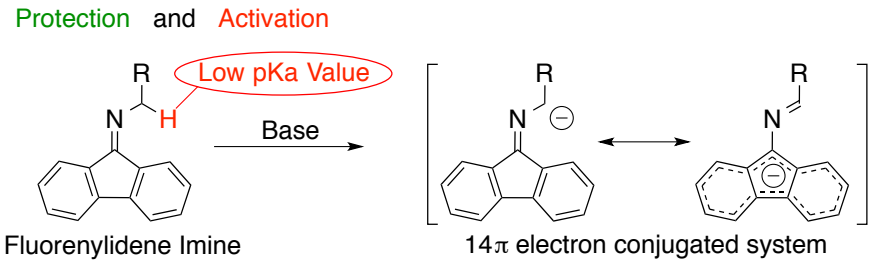
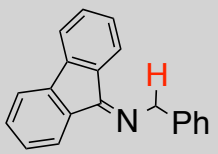


Figure 1-7. The activation system using fluorene moiety.

The *N*-fluorene protected imine (named fluorenylidene imine) exhibits high acidity at α-hydrogen due to the 14π-electron conjugated system of the fluorene molecule. It strongly stabilizes the corresponding anion through the delocalization of negative charge in the molecule. The exact pK_a value in DMSO of the fluorenylidene imine and other equivalents are shown below (Table 1-1).

Table 1-1. The pK_a value of α-hydrogen of different Schiff bases in DMSO.

Structure	pK_a (in DMSO at 25 ºC)[a]
$Ph_2C{=}NCH_2CO_2Et$	18.7
$Ph_2C{=}NCH_2CN$	17.8
$Ph_2C{=}NCH_2Ph$	24.3 (24.1[b])
	14.5
$Ph(EtO)C{=}NCH_2CO_2Et$	22.1
$PhCH{=}NCH_2CO_2Et$	19.5
$4\text{-}ClC_6H_4CH{=}NCH_2CO_2Et$	18.8
$Ph_2C{=}NCH(CH_3)CO_2Et$	22.8
$4\text{-}ClC_6H_4C{=}NCH(CH_3)CO_2Et$	19.2[c]
$Ph_2C{=}NCH(CH_2Ph)CO_2Et$	23.2[c]
$4\text{-}ClC_6H_4C{=}NCH(CH_2Ph)CO_2Et$	19.0
$Ph_2C{=}NCH(Ph)CO_2Et$	21.2[c]
$4\text{-}ClC_6H_4C{=}NCH(Ph)CO_2Et$	17.2

[a] Determined by the method described in reference.[4] The pK, measurements were generally made against two standard acids with the Schiff basesas indicators. The values are reproducible to ±0.05 pK, unit. [b] Corrected for tautomerism; see reference.[5] [c] Equilibrations in these titrations were slow (due to steric hindrance in these systems), but the values are reproducible.

The fluorenylidene imine possessed the lowest pK_a value at α-hydrogen value. It is even lower than that of the corresponding nitroalkane (Figure 1-8).

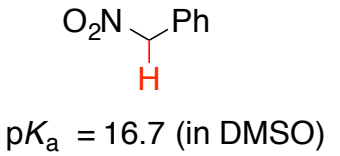


Figure 1-8. The pK_a value of nitro alkane in DMSO.

Considering the pK_a value of the α-hydrogen among these substrates, the fluorene moiety can effectively activate the α-hydrogen. It appears that carbon-carbon bond forming reaction utilizing the fluorene moiety as a protecting and activating group of nitrogen atom with the mild

base such as organobase species (the basicity of general base reagents are summarized in Figure 1-9) might be possible.

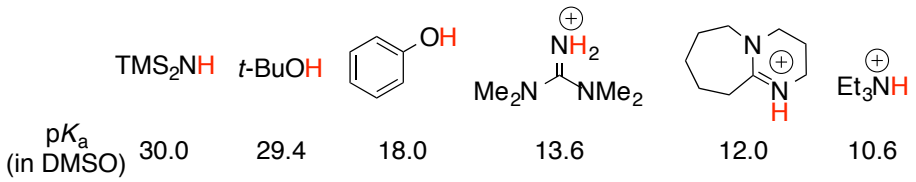
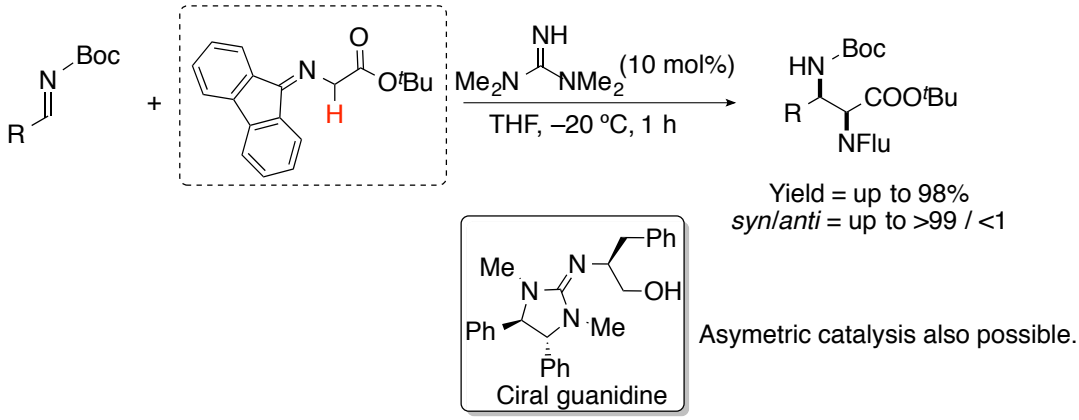


Figure 1-9. The pKa value of typical base species.

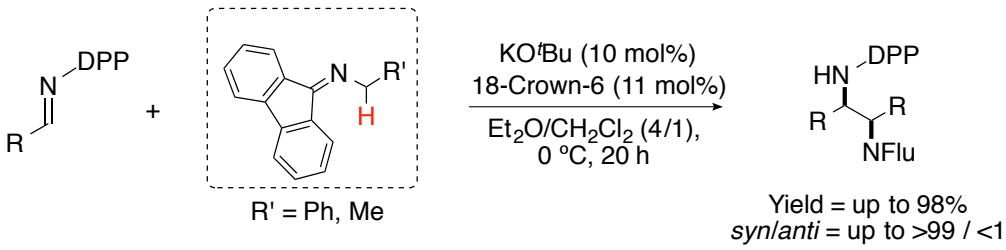
Another report from G. A. Pagani also supported this interesting activation system by the fluorene moiety.[6] Previously, the Kobayashi group has already demonstrated the carbon-carbon bond forming reaction utilizing the protection and activation concept with the fluorene moiety (Scheme 1-4a,b).[7,8] They achieved Mannich-type reaction of glycine esters protected by the fluorene, by using only a catalytic amount of a guanidine base, in an excellent yield and diastereoselectivity. They managed to accomplish the asymmetric reaction as well.

Scheme 1-4a. The reaction using fluorene moiety reported by Kobayashi *et. al*. (2008)



More recently, the Mannich-type reaction of a primary amine protected by the fluorene moiety also has been demonstrated by same group.

Scheme 1-4b. The reaction using fluorene moiety reported by Kobayashi *et. al*. (2010)



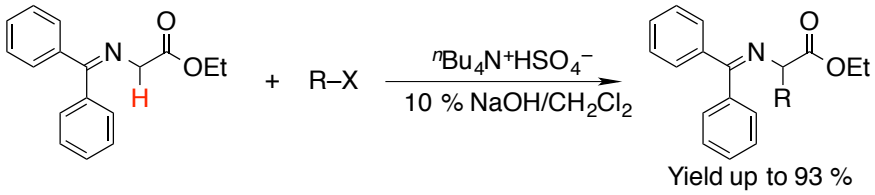
In this thesis, further investigation of a carbon-carbon bond forming reaction utilizing a protecting and activation ability of the fluorene moiety are documented. This thesis is composed of mainly three chapters. Firstly, the Mannich-type reaction of α-aminoacetonitrile protected and activated by the fluorene moiety is described. Secondly, the aldol reaction of fluorenylidene imines is demonstrated. Thirdly, the imine-imine cross coupling reaction achieved by utilizing a novel feature of the fluorene moiety is detailed.

II. Catalytic Mannich-type reactions of α-aminoacetonitrile using fluorenylidene as a protecting and activating group

Section 2-1. Introduction

In the syntheses of aminoalkane derivatives, a protection and (an activation) of the amino group is consequently needed. In 1978, Martin. J. O'Donnell reported the first successful examples of using glycine Schiff bases derived from the benzophenone for carbon–carbon bond forming reactions.[9] By utilizing the benzophenone moiety as a nitrogen protecting group, they demonstrated that a glycine Schiff base reacted with an alkyl halide under basic conditions in the presence of a phase transfer catalyst (PTC) to afford the monoalkylated product (Scheme 2-1-1).

Scheme 2-1-1. O'Donnell *et. al.* (1978)



Since their first report, many applications for various carbon–carbon bond forming reactions using glycine Schiff bases introduced the benzophenone moiety as nucleophiles; such as aldol reaction, Mannich reaction, Michael reaction, have been developed. However, the limitation exists in this strategy, in some substrates, acidities of α-hydrogen are not enough high. The carbon-carbon bond forming reactions using the fluorene moiety as a protecting and activating group of a nitrogen atom have previously been reported by Kobayashi group. They demonstrated Mannich-type reaction employing glycine esters,[7] primary amines[8] and an α-aminoacetonitrile[10] as nucleophiles mentioned in a general introduction. As a basic principle of these works, the fluorene moiety behaves key roles. The fluorene moiety contributes to inhibit deprotonation from undesired hydrogen on a nitrogen atom as a protecting group and to activate the α-hydrogen on a carbon adjacent to a nitrogen atom by using its 14π-electron conjugated system as mentioned in a former section. As the result of Mannich type reaction of α-aminoacetnitrile to imines, a synthetically very useful diaminoacetonitrile can be constructed in one step. There are various types of bioactive compounds containing diaminoacetonitrile unit (Figure 2-1-1).[11]

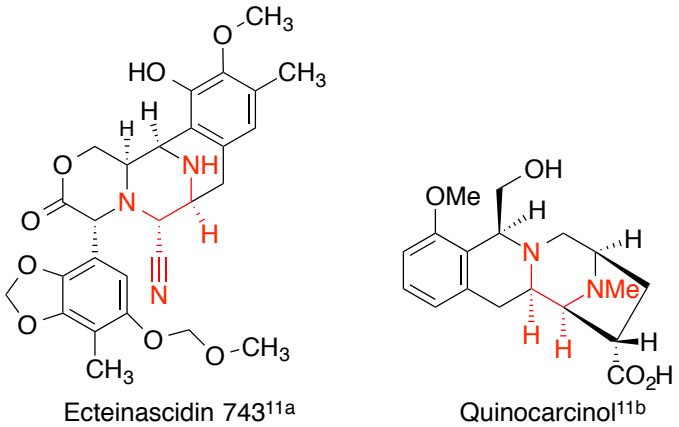
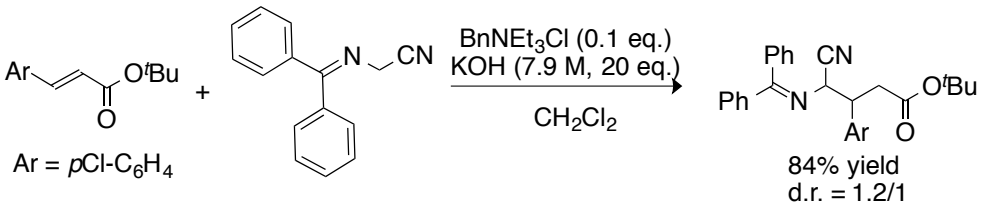


Figure 2-1-1. Bioactive compounds with diamine structure.

Only a few reports of the functionalized method of an α-aminoacetonitrile derivative exists. T. Opatz reported functionalization method of *N*-benzophenone protected α-aminoacetonitrile under the basic condition. However, due to the high pK_a value of a α-hydrogen of *N*-benzophenone protected α-aminoacetonitrile, more than stoichiometric amount of a strong base was required to form product (Scheme 2-1-2).[12]

Scheme 2-1-2. Opatz *et. al*. (2007)



The importance of a cyano functional group is easy transformation to several other synthetically variable function groups such as acid, amine, amide, and ketone (Figure 2-1-2).

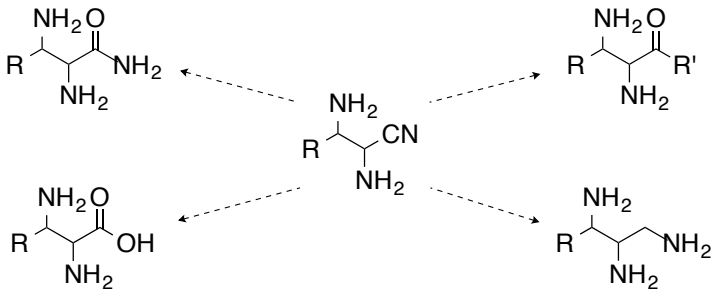
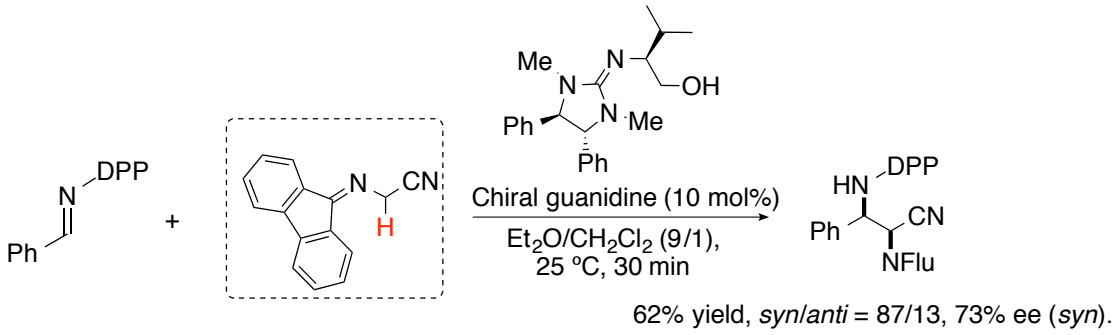


Figure 2-1-2. Utility of cyano functional group.

Hence, in this chapter, further investigation of asymmetric Mannich type reaction especially focusing on α-aminoacetonitrile as a nucleophile is disclosed. Preliminary work has been done by using a chiral guanidine (Scheme 2-1-3).

Scheme 2-1-3. Mannich-type reaction of α-aminoacetonitrile activating by a fluorene.



62% yield, *syn*/*anti* = 87/13, 73% ee (*syn*).

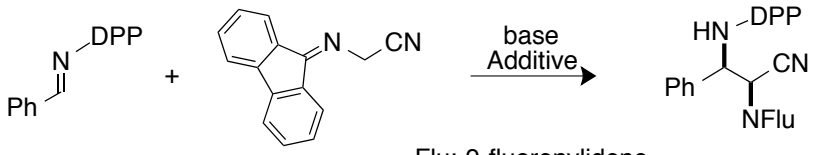
However, enantioselectivity is achieved to only moderate level. The purpose of this work is development of more efficient chiral catalyst by tuning of the structure of a chiral guanidine.

Section 2-2. Screening of catalyst structures

The screening of reaction conditions

The conditions of desired catalytic base mediated Mannich-type reaction of α-aminoacetonitrile were examined (Table 2-2-1). Firstly catalysts were screened. When KO^{t}Bu was employed as a base species, the desired adduct was synthesized with a moderate yield and diastereoselectivity (entry 1). To enhance catalyst basicity further, 18-crown-6 was employed as an additive. The result improved to a high yield but did not improve a diastereoselectivity (entry 2). Another additive, 2,6-dimethylphenol, also was attempted to Mannich-type reaction. Only a disappointed result was observed (entry 3). Potassium bicarbonate, much weaker base than KO^{t}Bu, was utilized in spite of using strong base species. Surprisingly even such a weak base catalyst, desired reaction system worked, and gave a desired product with a moderate yield and *syn*-selectivity. These results supposed that the use of weaker bases was a key for a high *syn*-selectivity. Hence, organobase species were considered as a catalyst candidate. Whereas triethylamine did not work at all, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,1,3,3-tetramethylguanidine (TMG) promoted the reaction successfully (entry 5-7). Especially the reaction provided by TMG gave the best yield and *syn*-selectivity. The reason why TMG showed the highest yield and diastereoselectivity is that TMG exhibited more suitable basicity for the reaction than other bases, and TMG possessed some steric hindrance larger than TEA, smaller than DBU. That suitable steric effect might work well. In order to compare the activation ability of the fluorene moiety, diphenylmethylene protected α-aminoacetonitrile (**1b**) was examined in current system. The reaction did not work at all (entry 8). The current fluorene activated substrate (**1a**) exhibited higher reactivity than the corresponding substrate (**1b**) under the basic conditions. Then, solvent screening among CH_3CN, CH_2Cl_2, toluene, Et_2O was conducted (entries 9-12). In the case of using Et_2O as the reaction solvent, the highest *syn*-selectivity was emerged. Curiously the reaction showed the highest *syn*-selectivity at around room temperature compared with decreased temperature (entries 13,14). The reactions using lower catalyst loadings also proceeded well, and a good yield was obtained even employing 2.5 mol% of TMG (entry 16). Finally the result described in entry 15 was decided as an optimum reaction condition.

Table 2-2-1: Screening of base.[a]



2a **1a** **3aa**

Entry	Base	Additive	Solvent	Yield[b]	*syn*/*anti*[b]
1	KO^{t}Bu	–	THF	68	60:40
2	KO^{t}Bu	18-crown-6	THF	91	64:36
3	KO^{t}Bu	2,6-Me_2-phenol	THF	62	59:41
4	K_2CO_3	–	THF	33	72:28
5	Et_3N	–	THF	Trace	–
6	DBU	–	THF	90	63:37
7	TMG	–	THF	94	78:22
8[c]	TMG	–	THF	12	76:24
9	TMG	–	CH_3CN	91	95:5
10	TMG	–	CH_2Cl_2	95	60:40
11	TMG	–	Toluene	96	86:14
12	TMG	–	Et_2O	89	97:3
13[d]	TMG	–	Et_2O	91	91:9
14[e]	TMG	–	Et_2O	76	77:23
15[f]	TMG	–	Et_2O	90	97:3
16[g]	TMG	–	Et_2O	77	97:3

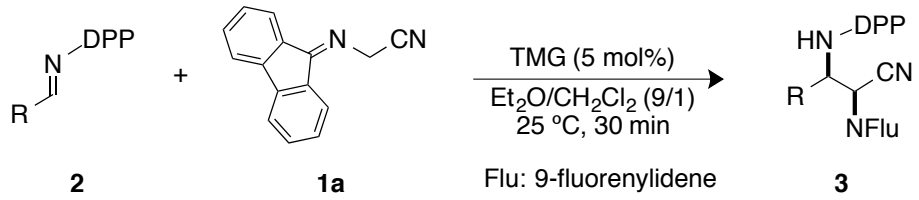
[a] The reaction of **1a** (0.24 mmol) with **2a** (0.20 mmol) was performed in the presence of base (10 mol %) at 25 ºC for 30 min in 0.05 M unless otherwise noted. TMG:1,1,3,3-tetramethylguanidine. [b] Yield and selectivity were determined by ^{1}H NMR spectroscopic analysis of the crude product using an internal standard (benzyl). [c] Diphenylmethylene-protected α-aminoacetonitrile (**1b**) was used instead of **1a**. [d] At 0 ºC. [e] At –20 ºC. [f] Catalyst of 5 mol % was used. [g] Catalyst of 2.5 mol % was used.

Substrate generality

The optimized condition in hand, the scope of desired Mannich-type reaction was then examined (Table 2-2-2). An Et_2O/CH_2Cl_2 (9/1) mixed solvent was used to improve the solubility of DPP imine **2** in the solvent. The aminoacetonitrile **1a** successfully reacted with aromatic or aliphatic DPP imines, and the desired products were obtained in high yields with good to high

syn-selectivities. The reactions of aromatic imines with the electron-withdrawing (entry 2) or electron-donating groups (entries 3, 4) did not affect the *syn*-selectivity significantly. The large steric hindrance on aromatic part was found to affect the selectivity. Whereas the reaction of *ortho*-tolyl or 1-naphthyl DPP imine gave similar good results (entries 5,6), a somewhat lower *syn*-selectivity was obtained in the case of 1-naphthyl DPP-imine (entry 7). Heteroaromatic DPP imines also reacted with imine **1** a very well, and moderate to good yields and *syn*-selectivities were obtained (entries 8-10). The desired Mannich reactions also conducted using aliphatic imines, which were sometimes less stable and less reactive compounds compared with aromatic imines. The reaction of DPP imines with secondary aliphatic groups, cyclohexyl or isopropyl, proceeded smoothly to afford the desired products in high yields with high selectivities (entries 11 and 12). On the other hand, a primary aliphatic imine also reacted, although, the selectivity decreased (entry 13). It should be noted that the current reaction system using TMG has a wide substrate scope for the synthesis of α,β-diaminonitriles **3**.

Table 2-2-2: Substrate scope.[a]



2 **1a** Flu: 9-fluorenylidene **3**

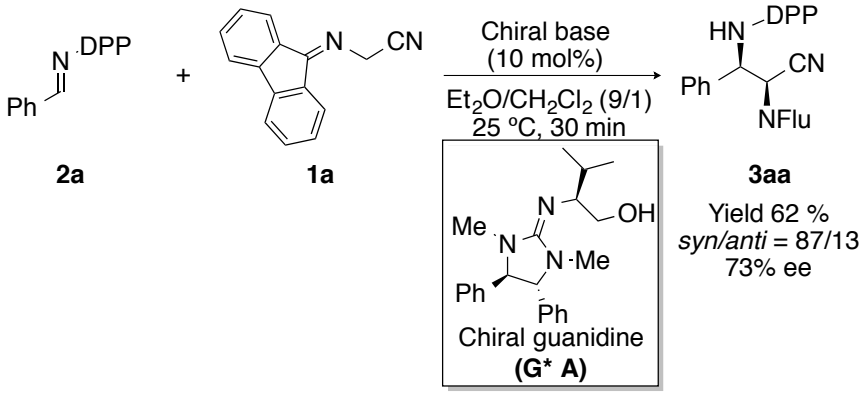
Entry	R	Isolated yield (%)	*syn*/*anti*[b]
1	Ph (**2a**)	90	97:3
2	4-BrC_6H_4 (**2b**)	99	92:8
3	4-$MeOC_6H_4$ (**2c**)	85	95:5
4	4-MeC_6H_4 (**2d**)	95	96:4
5	2-MeC_6H_4 (**2e**)	84	96:4
6[c]	2-Naphthyl (**2f**)	92	93:7
7	1-Naphthyl (**2g**)	99	86:14
8	3-pyridyl (**2h**)	70	94:6
9	2-Furyl (**2i**)	93	94:6
10	2-Thienyl (**2j**)	92	73:27
11[d]	Cyclohexyl (**2k**)	99	93:7
12[d]	isopropyl (**2l**)	97	89:11
13[d]	*n*-Hexyl (**2m**)	85	74:26

[a] The reaction of **1a** (0.24 mmol) with **2** (0.20 mmol) was performed in the presence of TMG (5 mol %) in a Et_2O/CH_2Cl_2 (9:1) mixed solvent system at 25 ºC for 30 min in 0.05 M unless otherwise noted. The crude product was purified by using preparative TLC (CH_2Cl_2/MeOH.100:3). [b] *syn*/*anti* selectivity was determined by ^1H NMR spectroscopic analysis of the crude product. [c] The crude product was purified by using silica gel column chromatography (CH_2Cl_2/MeOH.100:3). [d] Compounds **1a** (0.20 mmol) and **2** (0.30 mmol) were employed for the reaction.

Section 2-3. Asymmetric catalysis

Previously, the Kobayashi group investigated the asymmetric catalytic Mannich-type reaction of fluorenylidene-α-aminoacetonitrile with imines. The chiral catalyst reported by Ishikawa[13] was chosen for optimization and it exhibited a good enantioselectivity (Scheme 2-3-1).

Scheme 2-3-1. Previous best result.



However, the desired Mannich product was only synthesized in maximum 73% enantiomeric excess (ee). There is still room for improvement, especially in ee, in the desired asymmetric reaction. Assumed transition state (TS) of desired reaction is illustrated in Figure 2-3-1. The TS model was inspired by Ishikawa's report.[13e] Their group utilized a chiral guanidine for the Michael reactions of ethyl acrylate.

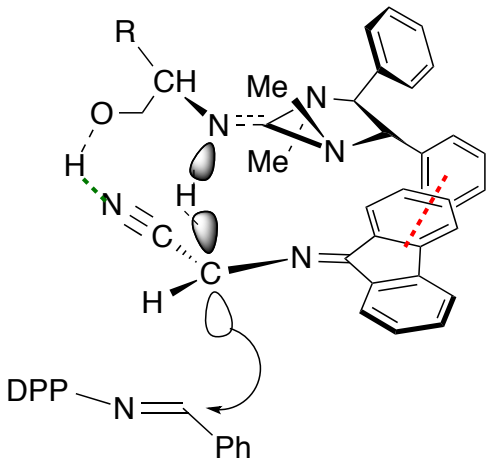


Figure 2-3-1. Assumed transition state of the reaction.

Analyzing the assumed TS suggests the chiral environment consists of mainly two interactions; hydrogen bonding network (illustrated with green line) and π–π interaction (red line) between a fluorenylidene imine and the chiral guanidine. In order to construct a mare competent chiral environment in TS, both chemical interactions were candidates of modification. Previous results of structural modification of a chiral guanidine are summarized in Figure 2-3-2.

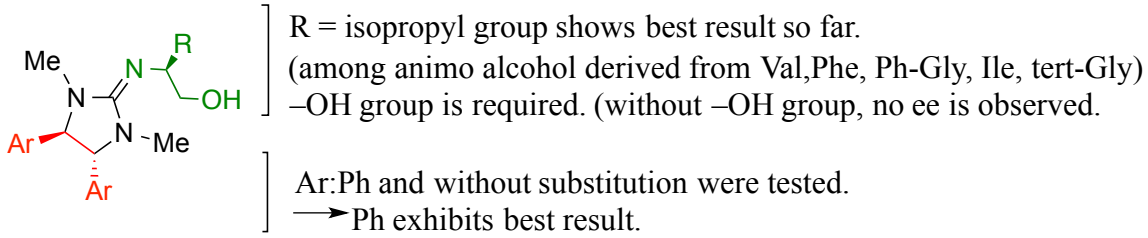


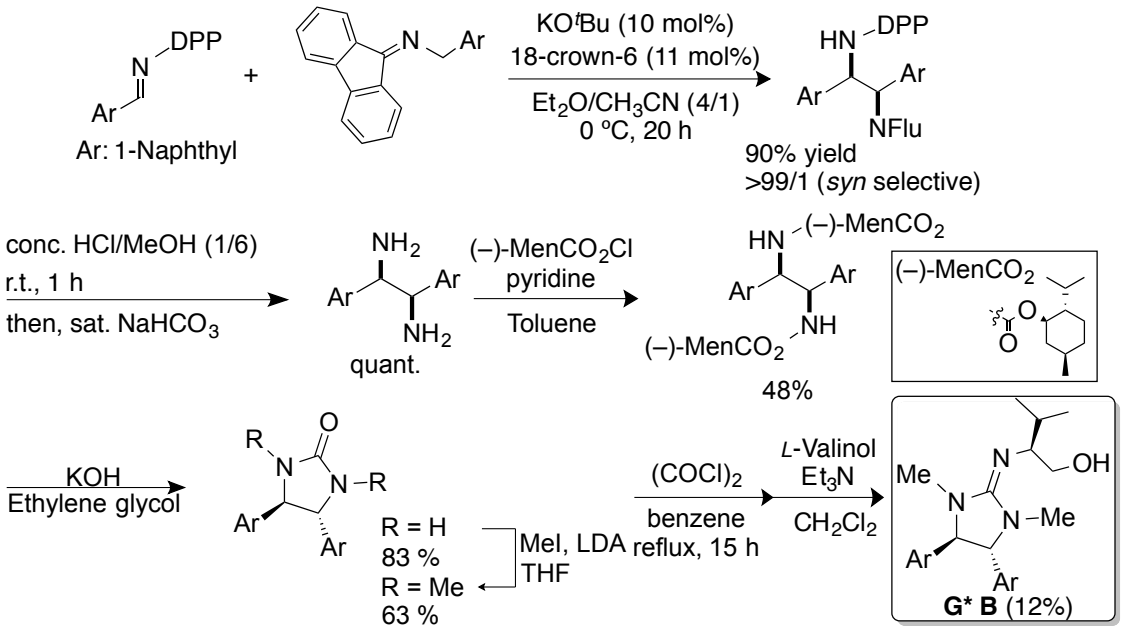
Figure 2-3-2. The plan for further modification

Indeed, there are mainly three essential components in the catalyst. Firstly, screening of the steric effect of the R group by varying the types of amino alcohols revealed that an isopropyl substituent introduced the highest ee in the product. Secondly, the OH functionality of an amino alcohol has a very important role for the chiral induction. Without this OH functionality, no chiral induction was observed. Finally, the chirality of the vicinal diaryl moiety also contributes as essential units. (*R*,*R*) isomer and opposite (*S*,*S*) isomer shows reversed enantioselectivity. In addition, chirality is diminished when the vicinal diaryl is removed. These structural insights led to the development of a more efficient chiral catalyst.

Modification of vicinal diaryl moiety of catalyst structure.

Firstly, to induce stronger π–π interaction, naphthyl ring is introduced into the vicinal aryl part of catalyst. From a synthetic view points, the desired unit is derived from a chiral diamine. The synthetic route of the chiral dinaphthyl diamine had been established by Kobayashi group. Following the reported method shown below, further modification of a diamine unit to urea, then to 2-chloro-1,3-dimethylimidazolinium chloride was conducted. The 2-chloro-1,3-dimethylimidazolinium chloride was then reacted with *L*-Valinol to afford the target chiral guanidine with 12% yield (Scheme 2-3-2).

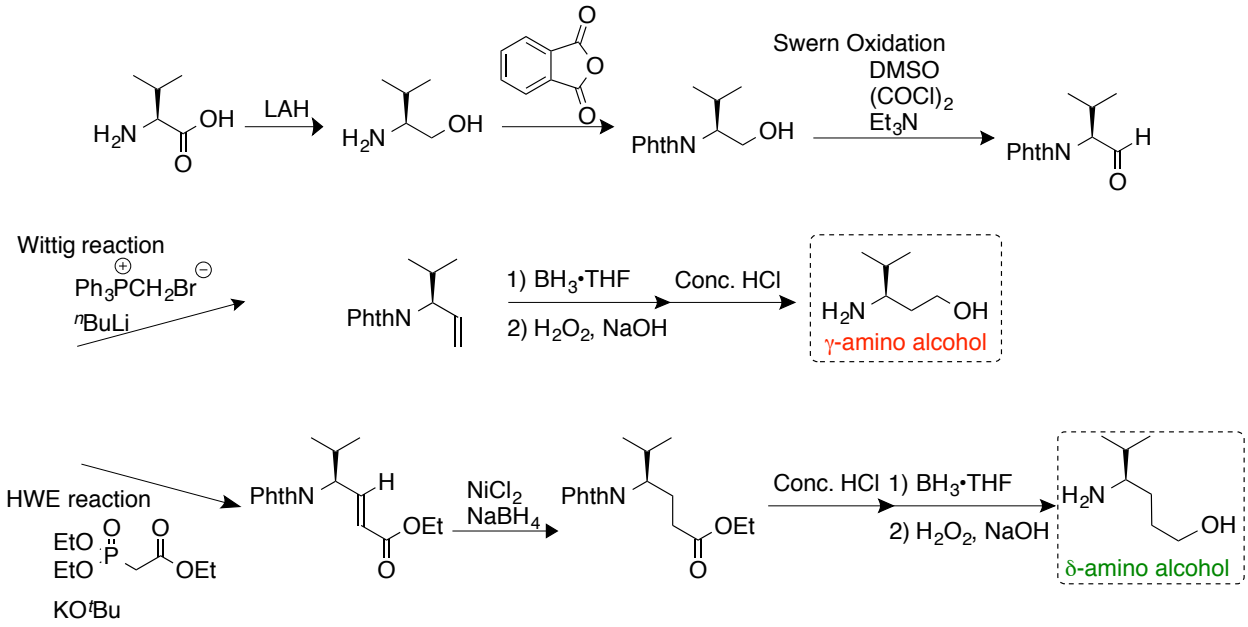
Scheme 2-3-2. Synthesis of a new guanidine.



Modification of amino alcohol units

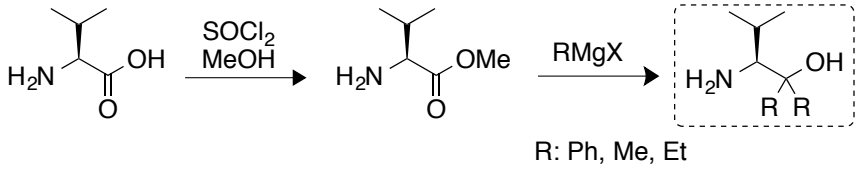
Concurrently, the modification of an amino alcohol was also conducted to improve an enantioselectivity. Focusing on the effect of the OH functionality, γ or δ-amino alcohol with a suitable substituent such as a isopropyl, which showed the best enantioselectivity in the previous screening, and β-amino alcohol with an alkyl substituent germinal to the OH group were planned to be synthesized. The synthesis of desired amino alcohols were started from easily available corresponding α-amino acids. The desired carbon extension was achieved by the following reaction conditions shown in Scheme 2-3-3.

Scheme 2-3-3. The synthetic route of carbon chain extension.



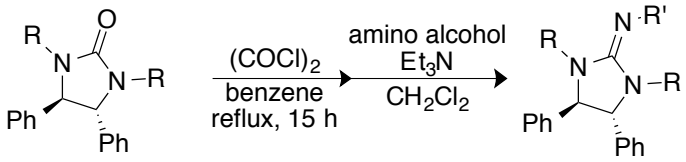
The desired *β*-amino alcohol was prepared by modification of the method[14] in Scheme 2-3-4.

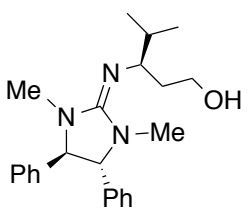
Scheme 2-3-4. Functionalization of a *β*-amino alcohol.



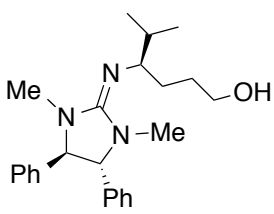
With several types of synthesized amino acids in hand, the chiral guanidines were prepared by Ishikawa's method (Scheme 2-3-5).[13]

Scheme 2-3-5. The list of synthesized guanidines.

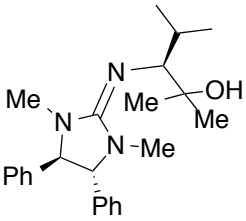




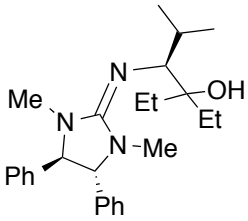
G*C



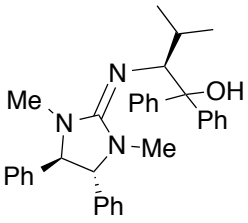
G*D



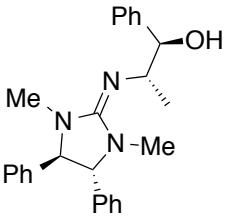
G*E



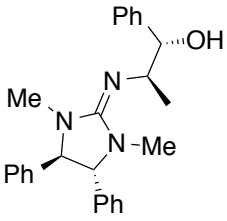
G*F



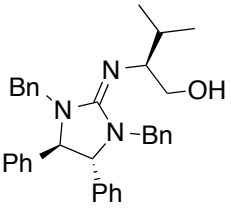
G*G



G*H



G*I



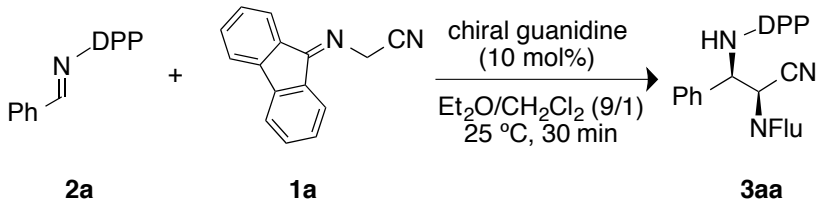
G*J

Finally eight different types of chiral guanidines were synthesized. By using these chiral guanidines, the asymmetric catalytic Mannich-type reaction was tested for a higher enantioselectivity.

Section 2-4. Optimization of reaction condition

By utilizing the previous optimized conditions (in Et_2O/CH_2Cl_2 (9/1) at 25 ºC for 30 min), efficiency of the newly synthesized chiral guanidines were confirmed (Table 2-4-1). The best result was obtained by employing chiral guanidine A (**G*A**) (entry 1). Expecting stronger π–π interaction, **G*B** possessing vicinal 1-naphthyl moieties was employed. Disappointedly, a very poor ee was observed (entry 2). Due to the steric hindrance of the vicinal naphthyl unit, the fluorenylidene imine (**1a**) could not get strong interaction with the chiral guanidine. The effect of guanidines having a longer alkyl chain on the amino alcohol unit was also tested (entry 3,4). The moderate yield, d.r. and poor ee were obtained both cases. Clearly the α-amino alcohol exhibited the highest enantioselectivity. In order to construct a more efficient chiral environment, guanidines with an alkyl chains were employed (entry 5,6,7). But probably due to the steric hindrance of the dialkyl chain, low reactivity and low ee were observed. The catalysts derived from ephedrine were also employed but only induced moderate enantioselectivity (entry 8,9). Substituents on nitrogen of a guanidine was changed from Me to Bn (**G*J**. entry 10). However ee was severely diminished.

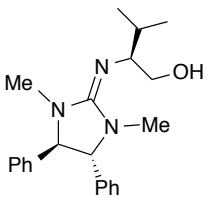
Table 2-4-1. Optimization of the chiral guanidine structure.



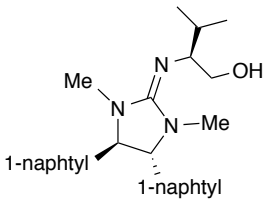
2a **1a** **3aa**

Entry	G*	Yield (%)[a]	d.r.[b]	ee (%)[b]
1[c]	**A**	62	87/13	73
2	**B**	70	87/13	6
3	**C**	78	90/10	<5
4	**D**	74	91/9	12
5	**E**	32	75/25	<5
6	**F**	36	62/38	<5
7	**G**	10	64/36	<5
8	**H**	78	89/11	40
9	**I**	89	89/11	–20
10	**J**	84	82/18	27

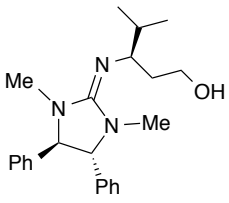
[a] Isolated yield. [b] Determined by chiral HPLC. [c] Previous best result.



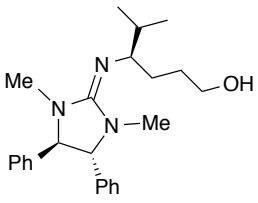
G*A



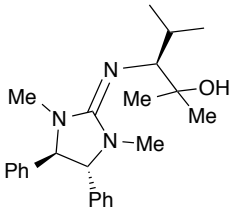
G*B



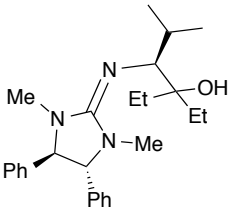
G*C



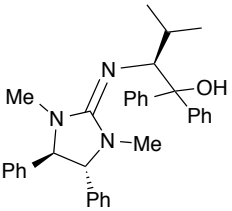
G*D



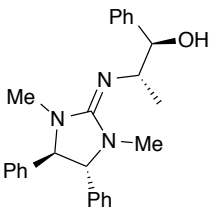
G*E



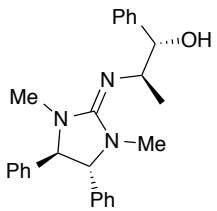
G*F



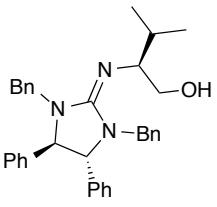
G*G



G*H



G*I



G*J

Hence, even after the modification of several different parts of the catalyst structure, G*A still exhibited the highest enantioselectivity.

Section 2-5. Summary

The Mannich type reaction of a 9-fluorenylidene protected α-aminoacetonitrile with DPP protected imines, mediated by a chiral base catalyst, have been demonstrated. The α-hydrogen of the fluorenylidene imine substrates were highly activated by a 14π-electron conjugated system of the fluorene molecule. The desired reaction proceeded with a catalytic amount of the chiral guanidine which has relatively mild basicity. In order to construct a suitable chiral environment, the catalyst structure was modified carefully. Finally the reaction provides synthetically useful 1,2-diaminonitrile with a good yield, diastereo- and enantioselectivity. There are only a few reports of using an α-aminoacetonitrile as nucleophile in basic condition due to the high pK_a value of α-hydrogen, much less its asymmetric reactions.

III. Direct-Type Aldol Reactions of Fluorenylidene-Protected/Activated Glycine Esters with Aldehydes for the Synthesis of β-Hydroxy-α-amino Acid Derivatives

Section 3-1. Introduction

The derivatives of α-amino acids are extremely important for synthetic organic chemistry, as well as in peptide and medicinal chemistry. Especially in the human body, α-amino acids are utilized as chiral resources for various enzymes, proteins and chemical messengers.[15] Due to huge utility of α-amino acid derivatives, the development of synthetic methods of these derivatives is highly demanded from both academia and industry. Over the years, many classes of synthetic methods have been developed for not only natural α-amino acids, but also artificial α–amino acids.[16] In this chapter, the development of a synthetic method for β-hydroxy-α-amino acid is discussed. It is an extremely important class of amino acids that makes up the structural framework[17] of many complex biologically active compounds such as vancomycine[18] and lactacystin.[19]

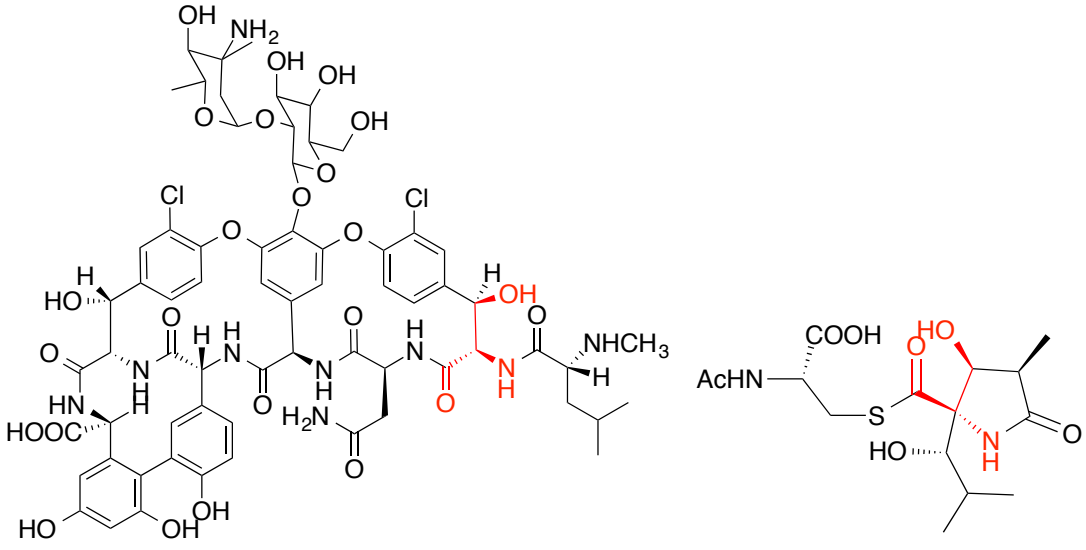
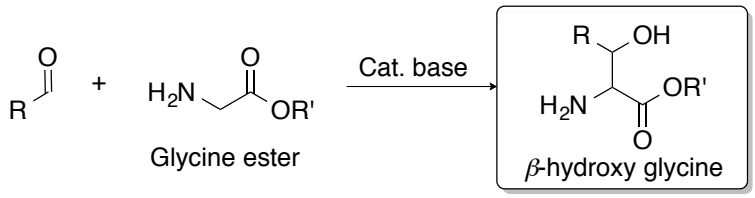


Figure 3-1-1. Structures of the natural products.

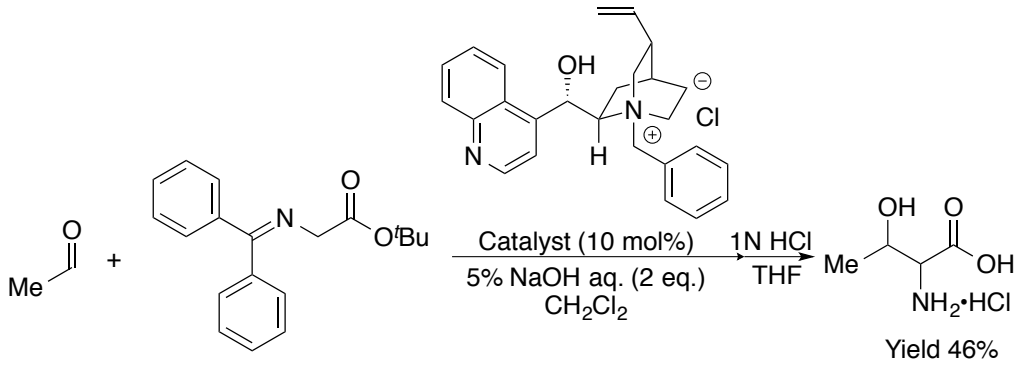
To access synthetically important β-hydroxy-α-amino acid derivatives, aldol reactions of glycine equivalents with aldehydes are considered to be one of the most efficient and powerful methods[20] (Scheme 3-1-1).

Scheme 3-1-1. Aldol reaction of a glycine ester.



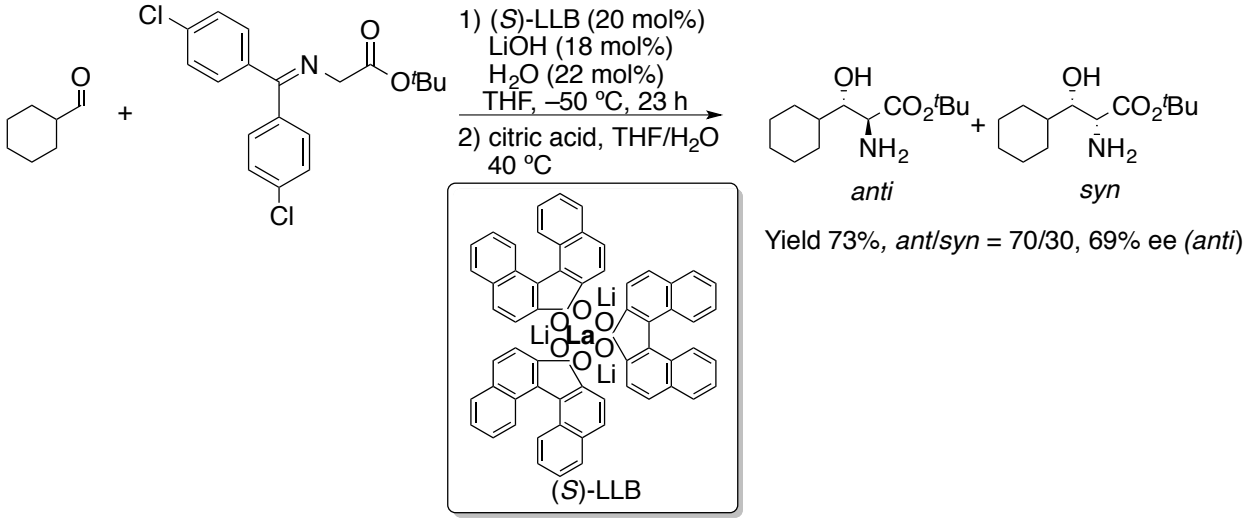
The first catalytic asymmetric synthesis of β-hydroxy-α-amino acids by the direct-type aldol condensation was achieved by Miller and co-workers under phase-transfer conditions.[21] The reactions of a glycine Schiff base with aldehydes, in the presence of *N*-benzyl-cinchoninium chloride as a catalyst, afforded β-hydroxy-α-amino esters in moderate yields. Unfortunately, the diastereo- and enantioselectivities were not satisfactory (Scheme 3-1-2).

Scheme 3-1-2. Aldol reaction reported by Miller and co-worker (1991).



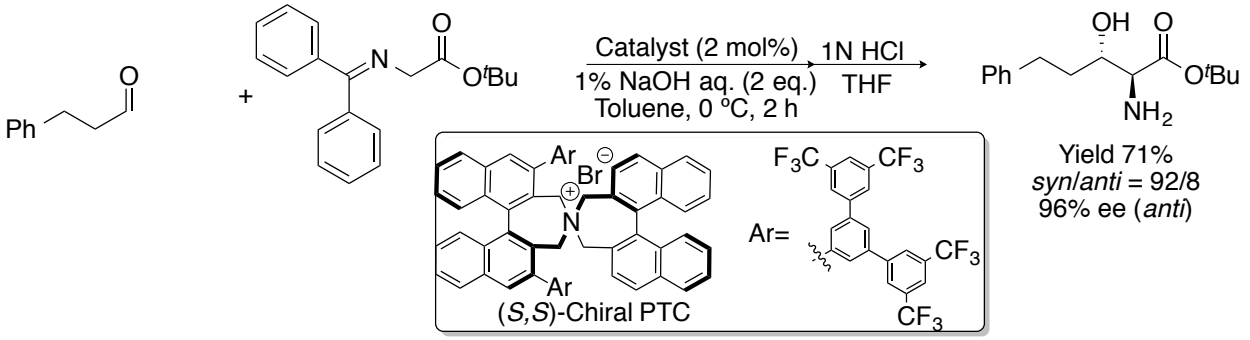
More recently, Shibasaki and co-worker reported successful direct-type asymmetric aldol reactions between a glycine Schiff base and several aliphatic aldehydes, achieving a moderate diastereo- and enantioselectivities by utilizing a bimetallic catalyst system (Scheme 3-1-3).[22]

Scheme 3-1-3. Aldol reaction demonstrated by Shibasaki and co-worker (2002).



In the same year, Ooi and Maruoka reported the synthesis of optically active β-hydroxy-α-amino acid derivatives.[23] They utilized glycine derivatives and aldehydes in the presence of a chiral phase transfer catalyst (PTC), that was developed by their own group, under basic conditions. The reactions gave good yields and selectivities with aliphatic aldehydes, although aromatic aldehydes showed poor results. They did not mention the substrate limitation of the reaction. In general, the corresponding aldol products of aromatic aldehydes have labile protons, which can be deprotonated under basic conditions and thereby cause breakdown of the products back to starting materials. This is the retro-aldol reaction pathway and its reaction rate is known to be difficult to control (Scheme 3-1-4).

Scheme 3-1-4. Aldol reaction reported by Maruoka and co-worker (2004).



Other groups have also reported similar aldol condensations using glycine Schiff bases.[24] As alternative nucleophilic species, 5-alkoxyoxazole, [25] α-isocyano acetates, [26] and α-isothiocyanatoimides[27] were also used for these types of reactions. Moreover, enzymatic

examples have been reported but showed substrate limitations.[28] For the synthesis of the *β*-hydroxy-*α*-amino acid framework, glycine ester equivalents were chosen as the reaction substrates. The exact pK_a value of the benzophenone protected glycine ester in DMSO is shown in Figure 3-1-2. The *α*-hydrogen of its ethyl ester exhibits a pK_a value of 18.7. Judging from the pK_a value of this substrate, the choice of base catalysts is limited only to strong base species. However, if the fluorene moiety can be introduced as a *N*-protecting and an activating group, it is expected that the pK_a value of the observed *α*-hydrogen would be higher due to the activation by the 14π-electron conjugated system of the fluorene moiety.

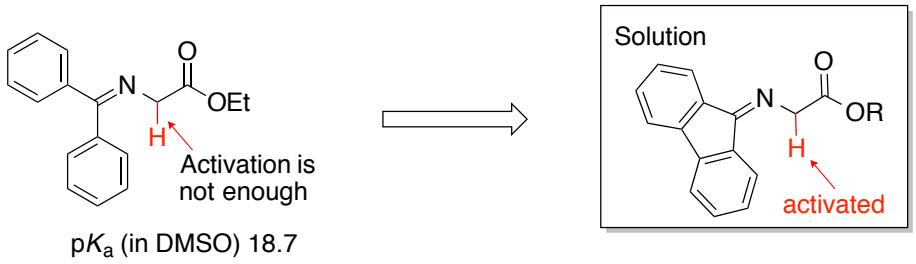


Figure 3-1-2. The activation of the glycine Schiff base.

Weak bases such as guanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), even Et_3N can be considered as catalyst candidates (pK_a table of base species are shown in Figure 3-1-3).

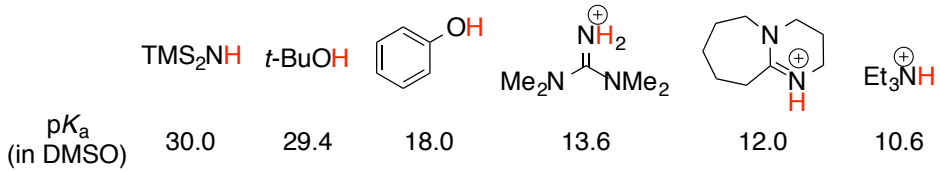


Figure 3-1-3. The pK_a value of typical base species.[29]

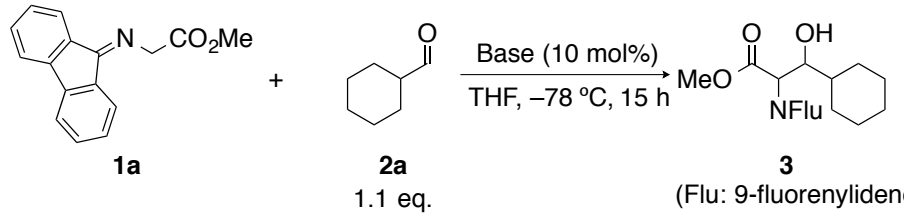
Additionally, the Kobayashi group has showed that aminoalkanes could be protected and activated at the same time by using the 9-fluorenylidene group.[30] This activating group allows for a strong activation of the *α*-position of the nitrogen atom *via* stabilization by the 14π electron system.[31] Based on that idea, Kobayashi has developed an efficient synthetic method for diamine compounds by Mannich-type reactions of *N*-protected imines, such as *N*-*tert*-butoxycarbonyl (Boc) or *N*-diphenylphosphinoyl (DPP) imines. These results inspired the investigation of the direct-aldol reactions of a fluorenylidene-protected glycine Schiff bases. In this chapter, the development of an efficient aldol reaction mediated by a catalytic amount of a mild base is described.

Section 3-2. Aldol reaction of glycine ester

Optimization of reaction conditions

The investigation was initiated by using fluorenylidene glycine methyl ester (**1a**) and a typical aliphatic aldehyde, cyclohexanecarboxyaldehyde (**2a**), in THF with 10 mol% base catalyst (Table 3-2-1). When KO^{t}Bu was employed as the base, the desired aldol product was isolated in a poor yield and diastereoselectivity. In the case of using Et_3N as the base, the reaction hardly proceeded. However, these preliminary studies gave different insights to the reaction. The pK_a values of both species have already been reported in the literature.[32] Given fluorenylidene glycine methyl ester (**1a**), KO^{t}Bu should deprotonate the α-hydrogen of substrate **1a**. It is likely that the desired aldol reaction occurs once in the reaction. Due to the strong basicity of KO^{t}Bu (pK_a = 29.4 in DMSO), a second deprotonation from the product OH happens, and hence the retro-aldol reaction leads to low yield and especially low diastereoselectivity. On the other hand, the deprotonation of the desired α-hydrogen of substrate **1a** is difficult or very slow with Et_3N (pK_a = 9.00 in DMSO). Suitable basicity for the desired aldol reaction might lie in the range of that between KO^{t}Bu and Et_3N. A base catalyst screening focused on the phenoxide species (the pK_a value of the simple Ph-OH is reported as 18.0 in DMSO). When phenoxide **4a** was employed as a base catalyst, the desired aldol product was obtained with a moderate yield and *anti*-selectivity (entry 1). In this reaction, the choice of a base appears to be crucial for the reactivity and selectivity. The sodium *N*-aryltosylamide species gave promising results as compared to the other results (entries 2-4). Among them, a sterically hindered amide **4d** showed the highest yield and *ant-i*selectivity (entry 4). Next, metal effects were investigated with *N*-5,6,7,8-tetrahydro-1-naphthyltosylamide. In the case of using zinc amide (**4e**) instead of sodium amide (**4f**), the yield decreased to 5% (entry 5). On the other hand, when magnesium amide (**4f**) was employed as a base catalyst, excellent reactivity and *anti*-selectivity were obtained (entry 6). When Et_2O was employed as a solvent Instead of THF, the diastereoselectivity was slightly lowered. The amide (**4f**) showed great ability at a lower catalyst loading as well. In 5 mol% catalyst loading (entry 8), even at 2 mol% catalyst loading, the reaction smoothly proceeded with an excellent yield and *anti*-selectivity. The condition shown in entry 9 was determined as the optimized reaction condition.

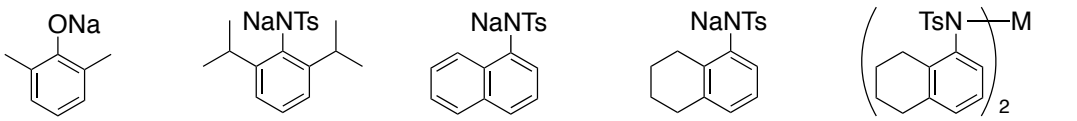
Table 3-2-1. Optimization of reaction conditions.



1a **2a** 1.1 eq. **3** (Flu: 9-fluorenylidene)

KO*t*Bu 32% yield, d.r. ≈ 1/1 (pK_a = 29.4 in DMSO)

Et_3N = <5% yield (pK_a = 9.00 in DMSO)



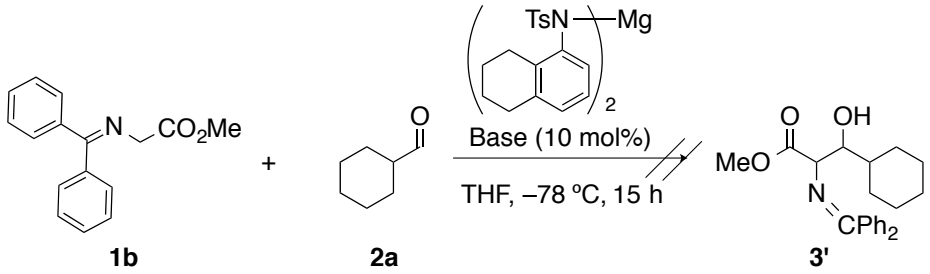
4a **4b** **4c** **4d** M = Zn (**4e**) or Mg (**4f**)

Entry	base **4**	Yield of **3** (%)[b]	*anti*/*syn*[c]
1	**4a**	45	78/22
2	**4b**	69	79/21
3	**4c**	82	87/13
4	**4d**	85	90/10
5	**4e**	5	n.d.
6	**4f**	95	96/4
7[d]	**4f**	72	96/4
8[e]	**4f**	96	96/4
9[f]	**4f**	96	96/4

[a] The reaction was performed using **1a** and cyclohexanecarboxyaldehyde (**2a**, 1.1 equiv) in THF at –78 ºC for 15 h in the presence of base **4** (10 mol%). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude mixture. n.d.=not determined. [d] The reaction was performed in Et_2O. [e] Catalyst loading of 5 mol% was used. [f] Catalyst loading of 2 mol% was used.

In order to compare the activation ability of the fluorene moiety, a typical glycine Schiff base **1b,** which has the nitrogen protected by a diphenylmethylene moiety, was employed in the presence of 10 mol% catalyst loading of the amide **4f**. The reaction hardly proceeded and almost all of Schiff base **1b** was recovered. Clearly, the fluorene moiety played a key role in the reaction. It is noted that the fluorene molecule activated the α-hydrogen of the glycine ester effectively and facilitated the desired deprotonation step under the basic conditions (Scheme 3-2-1).

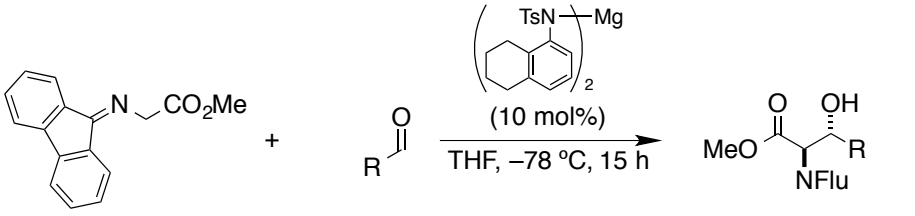
Scheme 3-2-1. The control experiment.



Substrate Generality

With the optimum reaction condition in hand, the substrate generality was examined (Table 3-2-2). Typical aliphatic aldehydes such as *n*-hexanal (**2b**), isobutyl aldehyde (**2c**) and isovaleric aldehyde (**2d**) reacted smoothly with fluorenylidene glycine ester (**1a**) to afford the aldol products in high yields with high *anti*-selectivities (entries 1-3). The reaction was not sensitive for substitutions at the α-position of aldehydes. The aliphatic aldehydes bearing an aromatic moiety, such as 2-phenylacetaldehyde (**2e**), 3-phenylpropionaldehyde (**2f**) and diphenylacetaldehyde (**2g**) were found to be effective, and good to high yields with high *anti*-selectivity were observed (entries 4-6). Interestingly, easily enolizable aldehydes, e.g. aldehyde **2e** and aldehyde **2g**, gave the desired aldol products in good yields without significant side reactions. In spite of the good results obtained for aliphatic aldehydes, aromatic aldehydes (**2h, 2i**) and α,β-unsaturated aldehydes (**2j,2k**) only gave the desired products with moderate to good yields and poor diastereoselectivities (entries 7-10). This is probably because retro-aldol processes from the aldol products was significant when conjugated aldehydes employed.

Table 3-2-2. The substrate generality.[a]



1a **2** 1.1 eq. **3** (Flu: 9-fluorenylidene)

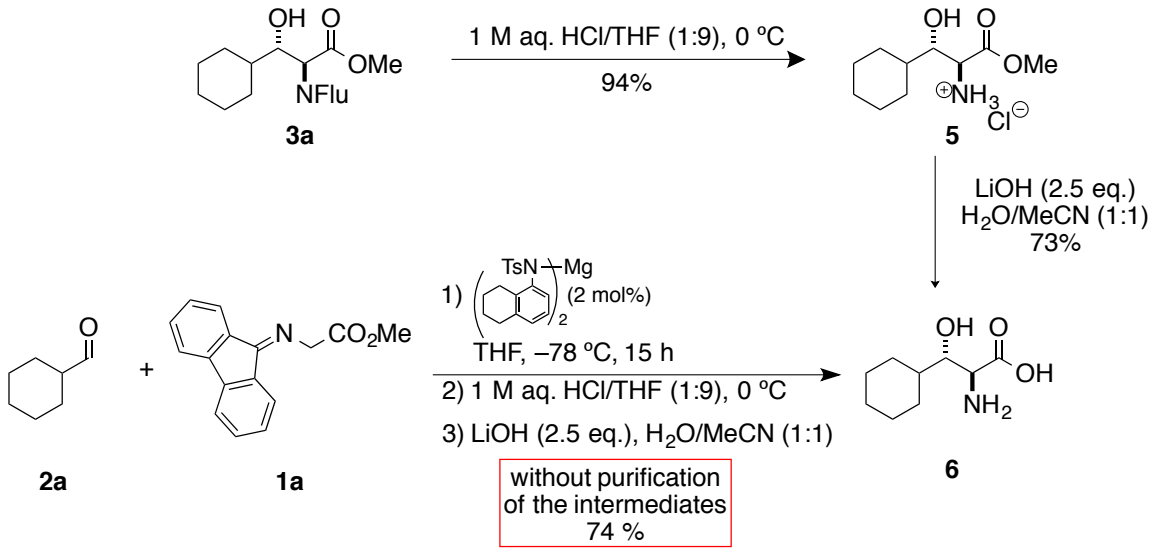
Entry	R	Yield[b]	*anti*/*syn*[c]
1	*n*-C_5H_{11} (**2b**)	91	89/11
2	^{i}Pr (**2c**)	88	94/6
3	$(CH_3)_2CHCH_2$ (**2d**)	90	92/8
4	$PhCH_2$ (**2e**)	85	95/5
5	$PhCH_2CH_2$ (**2f**)	87	95/5
6	Ph_2CH (**2g**)	74	94/6
7	Ph (**2h**)	35	55/45
8	*o*-$O_2NC_6H_4$ (**2i**)	79	54/45
9	(*E*)-PhCH=CH (**2j**)	N.R.	-
10	(*E*)-CH_3CH=CH (**2k**)	53	52/48

[a] The reaction was performed using **1a** and **2** (1.1 equiv.) in THF at –78 ºC for 15 h in the presence of **4f** (2 mol%). [b] Isolated yield. [c] Determined by ^{1}HNMR analysis of the crude mixture.

Diversity of aldol product

The desired aldol product (**3a**) was easily converted to the synthetically important moiety β-hydroxy-α-amino acid[33] (Scheme 3-2-2). The product (**3a**) was treated under mildly acidic conditions, (1N HCl in THF), cleaving the fluorenylidene moiety to afford ammonium salt **5**. Employing the basic treatment (LiOH in H_2O/MeCN) the ester moiety was converted to free acid **6** in a good yield. Direct access to β-hydroxy-α-amino acid **6** from fluorenylidene imine (**1a**) and an aldehyde (**2a**) was also possible. After the described aldol reaction, acid and base treatments gave the desired β-hydroxy-α-amino acid in over all 74% yield.

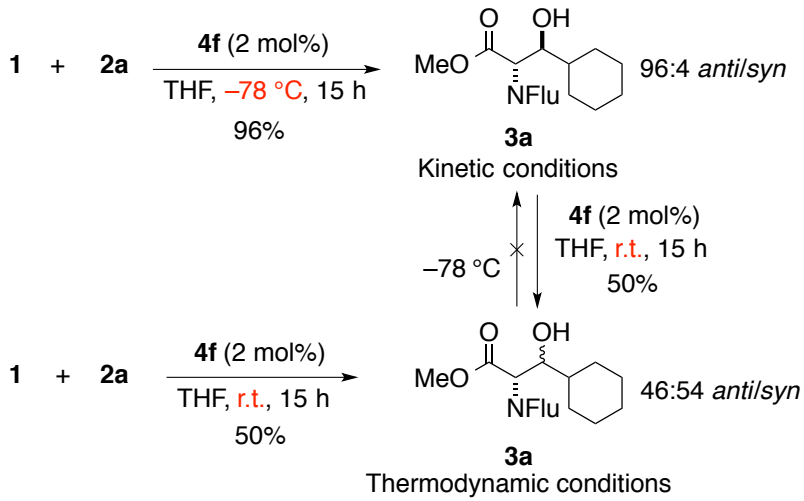
Scheme 3-2-2. The synthesis of β-hydroxy-α-amino acid



Section 3-3. Retro-reaction process

The desired aldol reaction gave poor results, especially with diastereoselectivities, when aromatic or α,β-unsaturated akdehydes were employed. It is presumably because of the contribution of a retro-aldol process of the desired reaction. The reaction was conducted with 2 mol% of optimized base catalyst at –78 ºC. It afforded the aldol product with a kinetically favored *anti*-configuration. If the retro-aldol process existed, the starting substrate would be regenerated even after forming the aldol product. In order to confirm the existence of the retro-reaction pathway, the isolated aldol product **3a** was treated under the optimized reaction condition at room temperature (Scheme 2-3-1). As expected, the diastereoselectivity of the aldol product **3a** was diminished, and small amounts of the starting substrates (both **1a** and **2a**) were regenerated. Additionally, when the desired aldol reaction was carried out under the optimized reaction condition at room temperature, the reaction provided the desired product with a moderate yield and poor diastereoselectivity. The product that possessed poor diastereoselectivity was treated under the optimized reaction condition at –78 ºC again, but no improvement of the diastereoselectivity was observed. Obviously, the retro-reaction pathway existed. The substrates, that was derived from aliphatic aldehydes, exhibited perfect *anti*-selectivity with the kinetic condition. However, due to the lower acidity of the OH functionality in the aldol product, which was obtained from aromatic or α,β-unsaturated aldehydes, the retro-aldol reaction easily occurred even under kinetic conditions. Hence, the desired aldol reaction provided the product with poor diastereoselectivity.

Scheme 3-3-1. Retro-aldol process.



Section 3-4. Catalyst structure

The structure of the catalyst **4f** was confirmed by ^{1}H-NMR analysis. In THF-d_8, the tosyl amide and catalyst **4f** gave different ^{1}H spectra (Figure 3-4-1). The disappearance of the NH peak indicated deprotonation of the tosyl amide NH hydrogen by treatment of *n*-butyl lithium during the preparation of the catalyst **4f**.

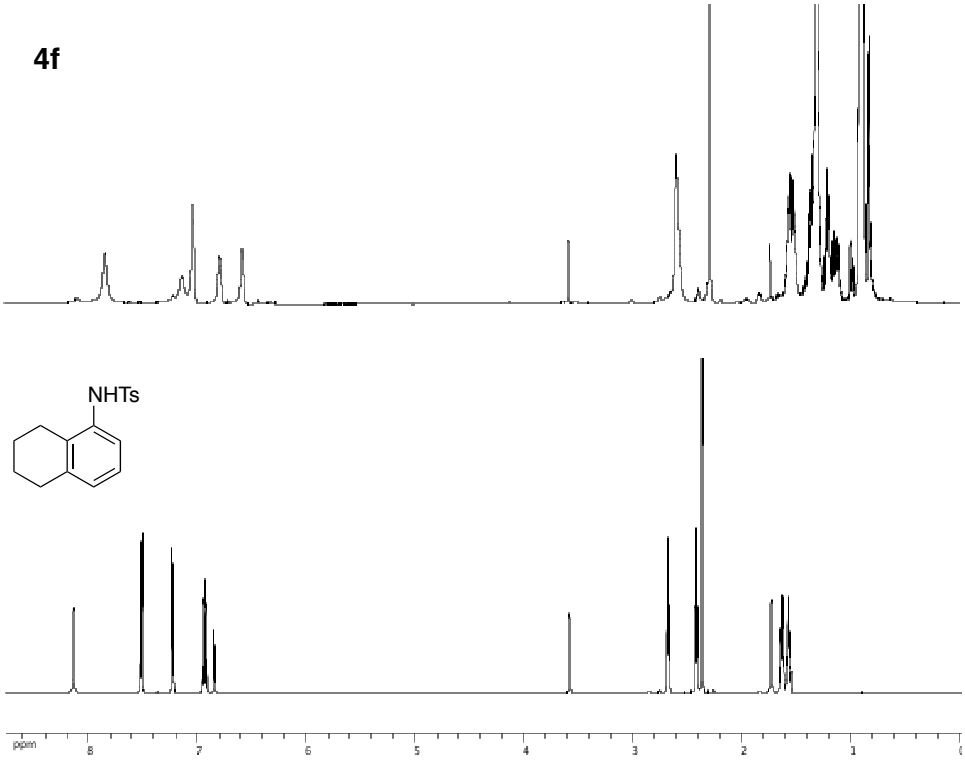


Figure. 3-4-1. ^{1}H-NMR spectrum of a tosyl amide and catalyst **4f**.

Section 3-5. Summary

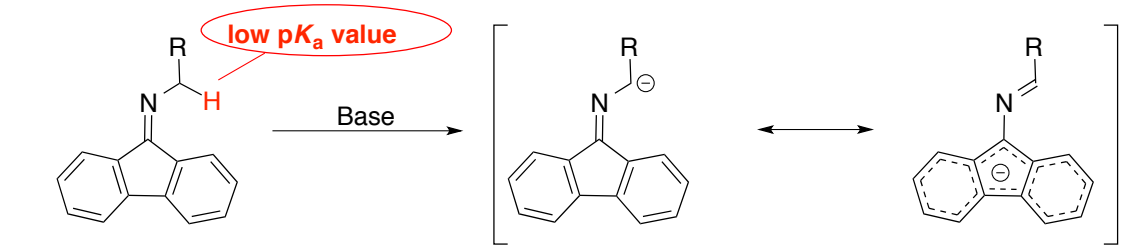
The aldol reaction of fluorenylidene glycine ester (**1a**) with various types of aldehydes was demonstrated. The desired reaction constructed synthetically important β-hydroxy-α-amino acid derivatives in one step. Due to the high activation ability of the fluorene moiety provided by its 14π-electron conjugated system, the fluorenylidene glycine ester (**1a**) exhibited great reactivity even under mildly basic conditions. The reaction employed only 2 mol% of the synthesized sodium *N*-5,6,7,8-tetrahydro-1-naphthyltosylamide as the base catalyst at –78 ºC in THF. This is a rare example of achieving the aldol reactions of the glycine Schiff base at such a low catalyst loading, especially with mild base species. The desired aldol reaction provided the products with the kinetically favored *anti*-configuration, especially when aliphatic aldehydes were employed as electrophiles. But a limitation of the described reaction exists. When aromatic or α,β-unsaturated aldehydes were attempted, only moderate to good yields and poor diastereoselectivities were observed because of the retro aldol process. The retro-aldol process was also accelerated for those aldehydes, because of the high activation ability of the fluorene moiety. The solution of these drawbacks is still under investigation. In order to over come the problems of low chemical yields and diastereoselectivities for the aromatic and α,β-unsaturated aldehydes, these solutions were considerable. One is the modification of the fluorene moiety itself; by introducing an electronwithdrawing group or electrondonating group to change electronic propaties of fluorenylidene substrates. Another is combination of Brønsted base and Lewis acid. If the Lewis acid, which stabilized an aldol product form more than starting substrates, is found, the problem will be solved.

IV. Imine-imine Cross-coupling Reaction Mediated by Base Catalyst Using Fluorene moiety

Section 4-1. Introduction

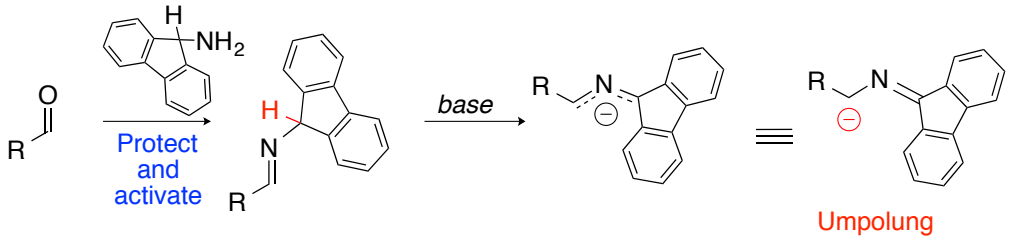
In an attempt to develop a novel new reaction system, the original concept of the fluorene moiety was reevaluated. When the fluorene is introduced as a protecting and activating group of a primary amine, the α-hydrogen of the substrate is activated by the 14π electron conjugated system of the fluorene. The negative charge of carbanion is strongly stabilized and distributed throughout the whole the fluorene moiety (Scheme 4-1-1).[34]

Scheme 4-1-1. Protection and activation mode of a fluorene moiety.



If the fluorene can be introduced on not only the *N*-atom of a primary amine but also on other species, for example aldehydes, what might happen? Theoretically the hydrogen on C9 of the fluorenyl imine, which is synthesized from a fluorene-amine and an aldehyde, can be deprotonated under basic conditions. As the result of this deprotonation, the corresponding anion will be produced. This species might exhibit the same characteristic feature of the fluorenylidene imine anion considering the delocalization of the negative charge. In other words, an umpolung reaction system can be expected, where the inherently electrophilic imine-carbon originating from the aldehyde is of the nucleophilic nature. (Scheme 4-1-2)

Scheme 4-1-2. New assumed feature of fluorenyl imine.



A 1,2-vicinal diamine framework was decided as the target chemical structure with that new concept. 1,2-Vicinal diamines are found as the core framework in numerous chemicals, such as agrochemicals, medicines, and insecticides *etc.*[35] They also serve as chiral auxiliaries or metal ligands in catalytic asymmetric synthesis (Figure 4-1-1). [36]

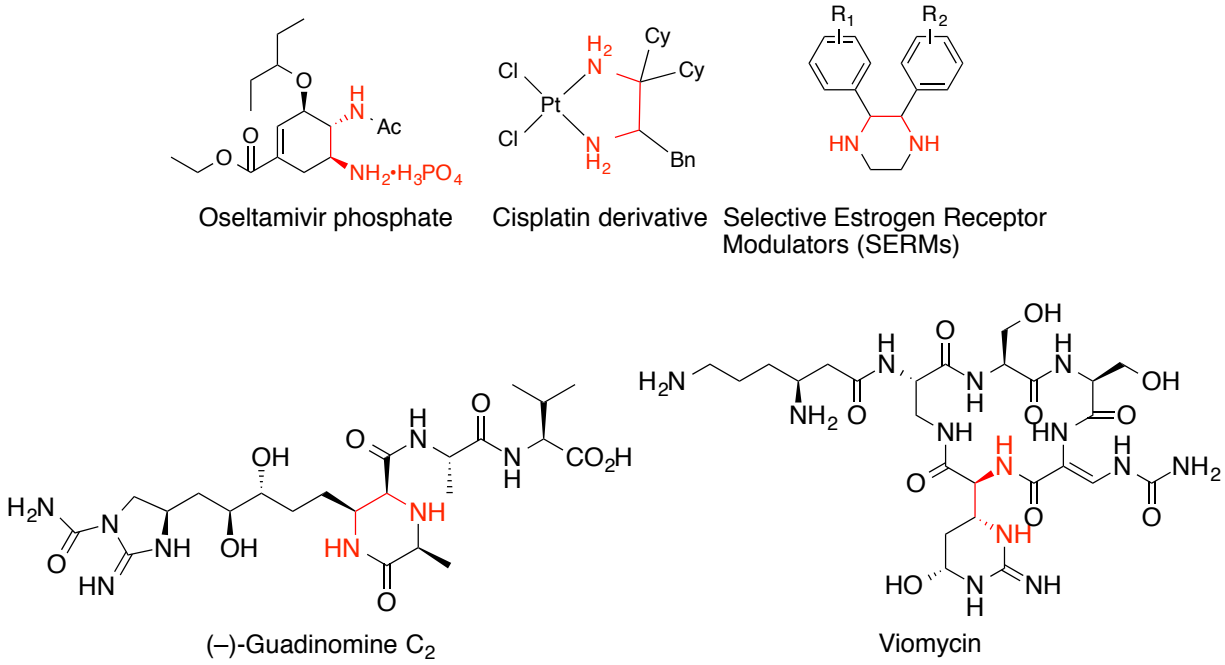
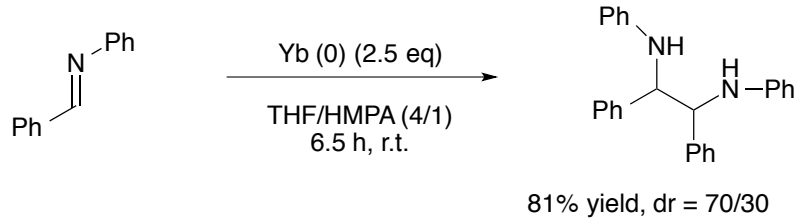


Figure 4-1-1. The structure of bioactive compounds.

Due to their incorporation in a huge variety of chemicals, the development and novel synthesis of this diamine core is important not only for academia but also for industry. Several strategies have been employed to construct such units, *e.g.*, the introduction of diamine functionalities into olefins, diols, or their derivatives and the creation of diamines with the simultaneous construction of the interconnecting carbon-carbon bonds.[37] Among such processes, imine-imine coupling is one of the most powerful methods to access these useful 1,2-vicinal diamines in one step. Historically, the coupling reaction of aldehydes to provide diols has been

known as the pinacol coupling reaction. A pioneer in the application of Yb metal for the pinacol reaction, Fujiwara was the first to report imine-imine homo-coupling reactions mediated by Yb metal as a reductant.[38] They achieved the desired homo-coupling reaction with *N*-Ph benzaldimine as the target imine in presence of Yb metal, obtaining the desired coupling product in good yields (Scheme 4-1-3).

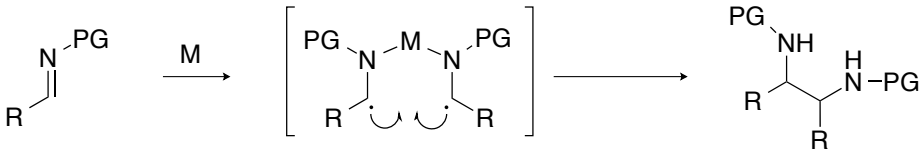
Scheme 4-1-3. First example of imine-imine coupling reaction.



81% yield, dr = 70/30

After their seminal work, many groups turned their focus onto the imine-imine coupling reaction by utilizing various kinds of metal species such as (lanthanides, Al, Ti, Zr, In, Zn-Cu, Mn, Li etc.).[39] The reaction mechanism was considered to proceed *via* a radical pathway (Scheme 4-1-4).

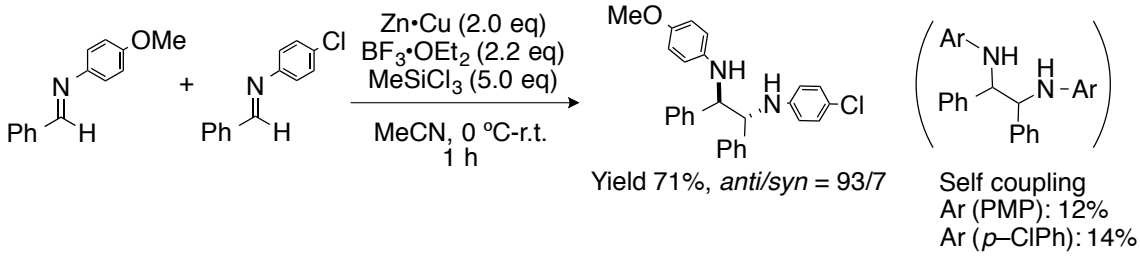
Scheme 4-1-4. Mechanism of imino-pinacol coupling.



M = Lanthanide, Al, Ti, Zr, In, Zn-Cu, Mn, Li etc.,

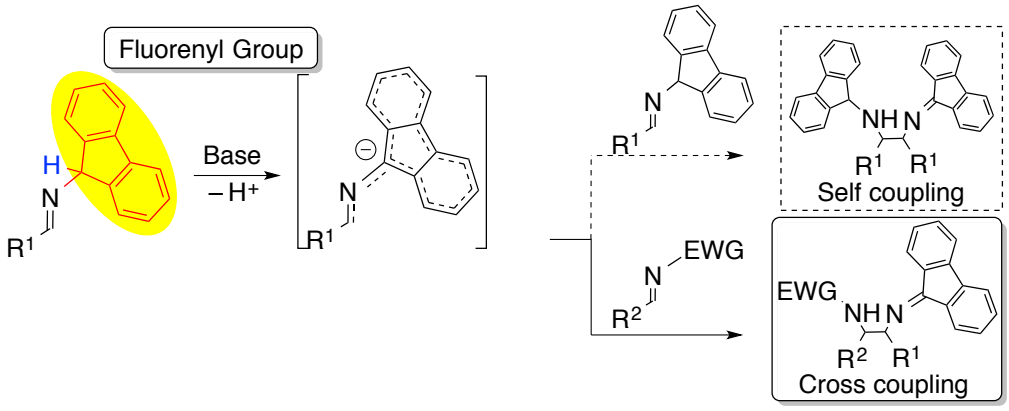
However, the radical-mediated imine-imine coupling is usually difficult to control, with poor coupling selectivity between homo-coupling and cross-coupling. This is especially true for selective cross-coupling reactions, where there are only a few successful reports. Among them, Shimizu and co-workers successfully achieved the first examples of reductive imine-imine cross-coupling reaction by using a Zn-Cu system in 2003 (Scheme 4-1-5).[40]

Scheme 4-1-5. Example of cross coupling reaction.



In their system, an imine possessing an electron-withdrawing protecting group and an imine possessing electron-donating group were adopted as substrates, giving high chemo- and diastereoselectivity. However, some self-coupling product was still observed. Additionally the variation of the imine-imine coupling is very limited. A summary of the major drawbacks of the imino-pinacol coupling are enumerated as follows; firstly, reaction always requires a more than stoichiometric amount of the metal species, which is unsatisfactory from an atom-economical point of view, as large amounts of waste metal are produced. Therefore, a highly efficient coupling system is greatly sought after. Secondly, controlling selectivity between self-coupling and cross-coupling remains a big task for synthetic utility. Indeed, there are only a few reports of cross imino-pinacol coupling reactions, much less any with perfect cross-coupling selectivity. Thirdly, the control of the coupling product stereochemistry remains a difficult problem. In order to solve these remaining problems, the design of a new reaction system is accomplished by utilizing the remarkable umpolung feature of a fluorenyl imine as mentioned above (Scheme 4-1-6).

Scheme 4-1-6. Design of new reaction system.



Firstly, the active hydrogen of a fluorenyl imine is deprotonated under basic conditions to afford the corresponding carbanion species stabilized by 14π electron conjugated system. The

nucleophilic attack from a fluorenyl imine carbanion to its partner imine generates a new carbon-carbon bond under the umpolung reaction system to give the desired cross-coupling product selectively. The homo-coupling product is not formed due to the low electrophilicity of a fluorenyl imine. The advantages of this system as compared with the previous reported methods are analyzed below. Firstly, the reaction stands out as it proceeds with only a catalytic amount of base, with coupling selectivity being extremely high as a result of the reaction mechanism. Secondly, this imine-imine coupling reaction follows a base-mediated mechanism, and hence is completely novel. Thirdly, the reaction system does not require metal reductants. The fluorene moiety of imine acts like a sacrificial reductant in this novel system. In all previous reports of imino-pinacol coupling reaction, it is always necessary to employ a more than stoichiometric amount of a metal reductant. Furthermore, according to the reaction mechanism, perfect coupling selectivity would be expected. Of the few reports demonstrating the cross-coupling imino-pinacol reaction, perfect cross-coupling selectivity over homo coupling has not been achieved thus far. Additionally, the fluorenyl part can be easily removed after the desired coupling reaction. With these advantages in mind, the investigation of the imine-imine coupling reaction commenced.

Section 4-2. Base catalyzed imine-imine cross-coupling reaction

In order to confirm the hypothesis indicated in the background section, the model reaction was conducted with fluorenyl imine (**1a**) and diphenylphosphine (DPP) imine (**2a**) in the presence of a catalytic amount of base species. Considering the pK_a value of the α-hydrogen of the fluorenylidene imine (**1a'**), its benzylic position is highly activated by the 14p-electron conjugated system of the fluorene molecule. As a substrate should pass through the same intermediate *via* deprotonation of the α-hydrogen, both fluorenyl imine (**1a**) and fluorenylidene imine (**1a'**) might exhibit the same pK_a value (Figure 4-2-1).

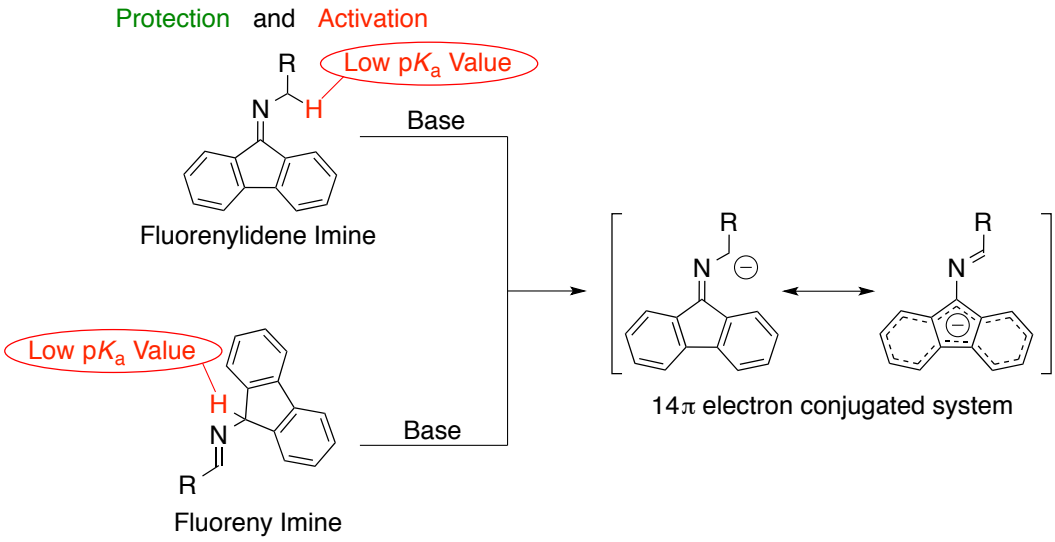


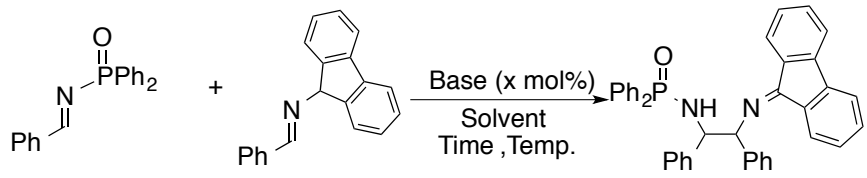
Figure 4-2-1. The common reaction intermediate.

Initial investigation

Firstly, 25 mol% loading of KO^{t}Bu and 18-crown-6 the system, which was well investigated in the previous project done by Dr. Chen[8], were employed in Et_2O/CH_2Cl_2 for 5 h at 0 ºC. Surprisingly, the reaction gave the desired coupling product in 39% yield with 99/1 excellent diastereoselectivity (Table 4-2-1, Entry 1). Obviously the KO^{t}Bu/18-crown-6 system worked and catalyzed the imine-imine coupling reaction without the need for any metal reductants. To obtain higher catalyst efficiency, longer reaction time was tested under the same condition. The yield was improved to 70 % with a excellent diastereoselectivity (Entry 2). Judging from these results,

a base-catalyzed imine-imine cross-coupling reaction seems to be achievable. Further optimization of the reaction conditions, especially with 5 mol% loading of KO^{t}Bu/ 18-crown-6 system, was conducted. Single solvent systems were tested, starting from Et_2O. Because of the low solubility of both fluorenyl imine (**1a**) and the coupling product, the reaction gave a poor yield, and a decrease of diastereoselectivity was observed (entry 3). THF as solvent also provided the same experimental insight, and corresponding a poor result (entry 4). In spite of the good solubility of those species in CH_2Cl_2, the reaction gave a very low yield (entry 5). Only Et_2O/CH_2Cl_2 co-solvent supplied a high catalyst efficiency and diastereoselectivity (entry 6). Cyclopentylmethyl ether (CPME), which has a nonsymmetrical structure, was adopted instead of Et_2O, the coupling product was observed with a lower yield and selectivity (entry 7). Next, other types of milder base species such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), KOPh, $KOCH_2CF_3$ were attempted instead of KO^{t}Bu and 18-crown-6 system. DBU is represented as an organobase whose basicity is easily modified by changing its functionality, but it shows a lower basicity than metal bases. The pK_a of $DBUH^+$ was estimated at 12 units in DMSO.[41] Due to its a mild basicity, not many substrates can be applicable *via* the deprotonation pathway. However, DBU was able to deprotonate the fluorenyl imine, giving the coupling product in a good yield with high diastereoselectivity (entry 8). This result clearly showed how effective the fluorenyl part can activate the whole substrate. Similarly other milder bases could catalyze the desired coupling reaction efficiently. KOPh gave 86% yield and 94/6 d.r. (entry 9). Notably, $KOCH_2CF_3$ displayed the best result so far (entry 10). Interestingly, when toluene was employed as a solvent in the optimized condition, the observed stereochemistry was inversed to an *anti*-selectivity (entry 11). By shortening the reaction time and fixing the reaction temperature, the yield and an *anti*-selectivity were enhanced (entry 12). The reaction gave a lower yield when KO^{t}Bu was utilized as a base without 18-crown-6 (entry 13). The cause of the inversed selectivity is explained in a later section. Finally, both conditions using 5 mol% of KO^{t}Bu with 18-crown-6 in Et_2O/CH_2Cl_2 (entry 6) and 5 mol% of $KOCH_2CF_3$ (entry 10) were decided as the optimized conditions of the base-catalyzed imine-imine cross coupling reaction.

Table 4-2-1. The optimization of the reaction conditions.



2a **1a** **3a**

Entry	Base (x mol%)	Solvent	Time (h)	Temp.(ºC)	Yield (%)	d.r.
1	KO^{t}Bu (25)[a]	Et_2O/CH_2Cl_2 (4/1)	5	0	39	99/1
2	KO^{t}Bu (25) [a]	Et_2O/CH_2Cl_2 (4/1)	24	0	70	99/1
3	KO^{t}Bu (5)[b]	Et_2O	24	20	39	67/33
4	KO^{t}Bu (5) [b]	THF	24	20	60	60/40
5	KO^{t}Bu (5) [b]	CH_2Cl_2	24	20	18	50/50
6	KO^{t}Bu (5) [b]	Et_2O /CH_2Cl_2 (4/1)	24	20	90	99/1
7	KO^{t}Bu (5) [b]	CPME/CH_2Cl_2 (4/1)	24	20	78	86/14
8	DBU (5)	Et_2O/CH_2Cl_2 (4/1)	18	20	67	94/6
9	KOPh (5)	Et_2O/CH_2Cl_2 (4/1)	18	20	86	94/6
10	$KOCH_2CF_3$ (5)	Et_2O/CH_2Cl_2 (4/1)	18	20	97	>99/1
11	KO^{t}Bu (5)[b]	Toluene	24	r.t.	67	7/93
12	KO^{t}Bu (5)[b]	Toluene	6	20	78	5/95
13	KO^{t}Bu (5)	Toluene	24	20	63	5/95

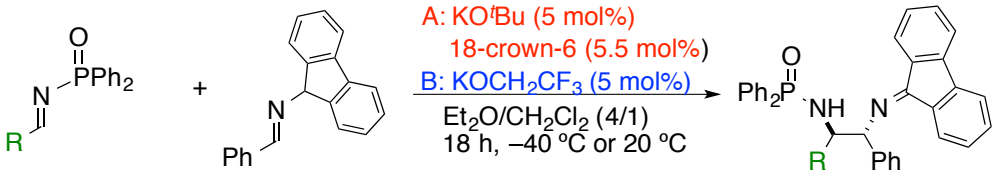
[a] 18-crown-6 (26 mol%) was added. [b] 18-crown-6 (6 mol%) was added.

Substrate generality

With the optimized conditions in hand, the base catalyzed imine-imine cross coupling reactions of fluorenyl imine (**1a**) with several different types of DPP-imines were attempted. Indeed, either one of the two different optimized conditions was utilized (Table 4-2-2). The substrates bearing electron-donating group (EDG) on its molecule such as a methyl or methoxy at a different position demonstrated high yields and *syn*-selectivities (entries 2–5). Except *p*-toluene DPP-imine (**2b**), condition A, which was using KO^{t}Bu and 18-crown-6 as the catalyst, was employed at –40 ºC. On the other hand, the substrate bearing electron-withdrawing group (EWG) such as a bromo reacted with fluorenyl-imine (**1a**) under condition B using $KOCH_2CF_3$,

to give a high yield and diastereoselectivity were observed (entry 6). Heteroaromatic DPP-imines also reacted with fluorenyl-imine (**2a**) nicely under the optimized conditions (entries 8,9) as well as in the case of using aliphatic DPP-imines as electrophiles (entries 9,10). Due to the instability and a low reactivity of a DPP-imine derived from *n*-pentanal, the reaction provided a poor result (entry 11).

Table 4-2-2. Substrate generality of DPP-imines.



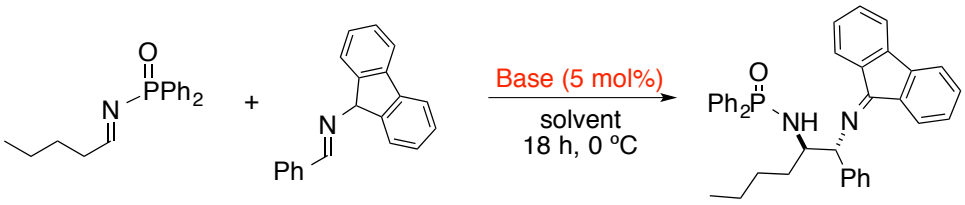
2 **1a** **3**

Entry	DPP-imine (R)	Conditions (A or B)	Product	Yield	*anti*/*syn*
1	Ph (**2a**)	B (20 °C)	**3aa**	97	>99/1
2	*p*-$CH_3C_6H_4$ (**2b**)	B (–40 °C)	**3ab**	99	94/6
3	*m*-$CH_3C_6H_4$ (**2c**)	A (–40 °C)	**3ac**	97	96/4
4	*o*-$CH_3C_6H_4$ (**2d**)	A (–40 °C)	**3ad**	91	97/3
5	*p*-$CH_3OC_6H_4$ (**2e**)	A (–40 °C)	**3ae**	90	84/16
6	*p*-BrC_6H_4 (**2f**)	B (–40 °C)	**3af**	99	96/4
7	2-furyl (**2g**)	B (20 °C)	**3ag**	>99	>99/1
8	3-pyridyl (**2h**)	B (20 °C)	**3ah**	93	99/1
9	Cyclohexyl (**2i**)	B (20 °C)	**3ai**	99	90/10
10	Isobutyl (**2j**)	B (20 °C)	**3aj**	99	90/10
11	*n*-butyl (**2k**)	B (20 °C)	**3ak**	Messy	-

For the linear alkyl DPP-imine, the reaction condition was reoptimized (Table 4-2-2). Condition A employing KO^{t}Bu was attempted, and a moderate yield and good diastereoselectivity was observed (entry 1). In order to overcome the low reactivity of linear aliphatic DPP-imine (**2k**), the reaction was conducted at a higher temperature, but no improvement was observed (entry 2). To enhance the solvation effect on the reaction intermediate, an aprotic solvent was employed as the reaction media. Selecting $KOCH_2CF_3$ as a base in DMF, the desired coupling reaction proceeded in a moderate yield with high diastereoselectivity (entry 3). Higher catalyst loading improved only the diastereoselectivity but

not the yield (entry 4). When a sterically hindered phenoxide was used, the yield was improved dramatically (entry 5). Finally, the simple potassium phenoxide exhibited a high activity and excellent diastereoselectivity (entry 6).

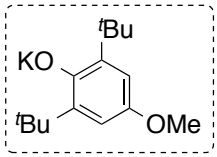
Table 4-2-3. Reoptimization of reaction conditions for aliphatic DPP-imines.



2k **1a** **3ak**

Entry	Base	Solvent	Yield (%)	*anti*/*syn*
1	KOtBu + 18-crown-6[a]	Et_2O/CH_2Cl_2 =4/1	46	92/8
2	$KOCH_2CF_3$	Et_2O/CH_2Cl_2 =4/1	Messy	
3	$KOCH_2CF_3$	DMF	62	97/3
4	$KOCH_2CF_3$	DMF	60	99/1
5	Phenoxide A[b]	DMF	80	99/1
6	KOPh[b]	DMF	91	>99/1

[a] at –20 ºC [b] Prepared from 5.5 mol% of corresponding phenol and 5 mol% of KO^{t}Bu.

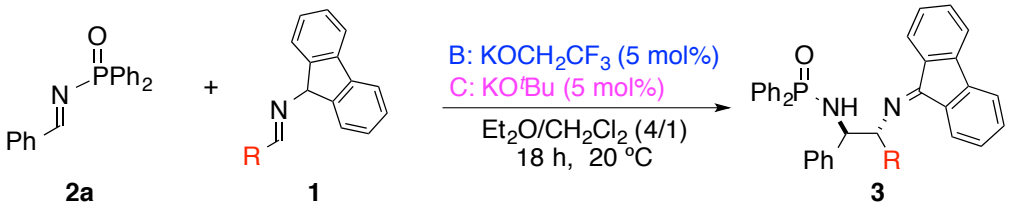


Phenoxide A

On the other hand, the coupling reactions of different fluorenyl imine units were also tested by using 5 mol % of $KOCH_2CF_3$ in Et_2O/CH_2Cl_2 (4/1) co-solvent (Table 4-2-4). The desired reactions proceeded using fluorenyl imines with a methyl substituent (EDG) at different positions to give products with excellent yields and *anti*-selectivity (entry 2–4), The fluorenyl imine with 4-chloro substituent (EWG) gave excellent results as well (entry 5). When the sterically hindered 2-naphthyl or heteroaromatic substituted fluorenyl imines (**1f, 1g, 1h**) were selected, excellent yields and diastereoselectivities were obtained (entry 6–8). Due to the instability of an aliphatic imine, there are very few reports of an aliphatic imino-pinacol coupling. In the case of this catalytic imine-imine coupling reaction, the fluorenyl imines derived from aliphatic aldehydes (**1i, 1j, 1k, 1l**) possessed instability under ambient conditions, but those substrates were tolerated in the reaction conditions to afford the coupling products with high

yields and diastereoselectivities (entries 9–12).

Table. 4-2-4. Substrate generality for fluorenyl imines.

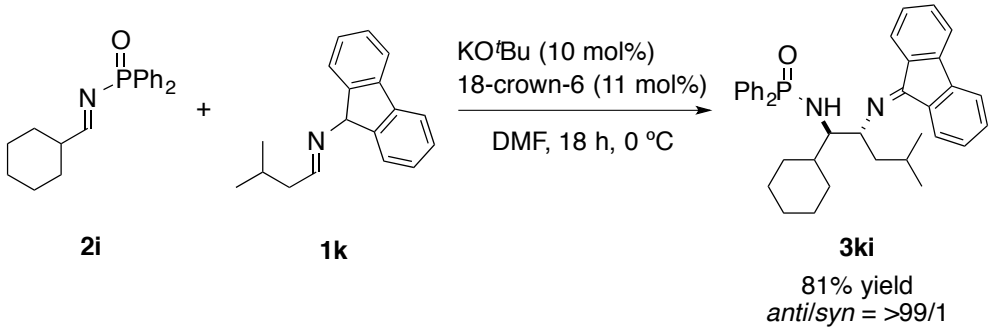


Entry	Fluorenyl imine (R)	Condition	Product	Yield (%)	*anti*/*syn*
1	Ph (**1a**)	**B**	**3aa**	97	>99/1
2	*p*-$CH_3C_6H_4$ (**1b**)	**B**	**3ba**	99	98/2
3	*m*-$CH_3C_6H_4$ (**1c**)	**B**	**3ca**	>99	>99/1
4	*o*-$CH_3C_6H_4$ (**1d**)	**B**	**3da**	>99	98/2
5	*p*-ClC_6H_4 (**1e**)	**B**	**3ea**	>99	95/5
6[a]	2-naphthyl (**1f**)	**B**	**3fa**	92	>99/1
7	2-furyl (**1g**)	**B**	**3ga**	83	96/4
8	2-thienyl (**1h**)	**B**	**3ha**	>99	97/3
9	Cyclohexyl (**1i**)	**C**	**3ia**	82	90/10
10	*tert*-butyl (**1j**)	**C**	**3ja**	78	>99/1
11	Isobutyl (**1k**)	**C**	**3ka**	79	85/15
12	*n*-butyl (**1l**)	**C**	**3la**	81	93/7

[a] at –20 ºC.

As a more challenging subject, the coupling reaction using both an aliphatic fluorenyl imine and a DPP imine was attempted. After extensive screening, the base-catalyzed imine-imine cross-coupling reaction using both aliphatic substrates was achieved with a high yield and diastereoselectivity (Scheme 4-2-1).

Scheme 4-2-1. Cross-coupling reaction of both aliphatic imines.

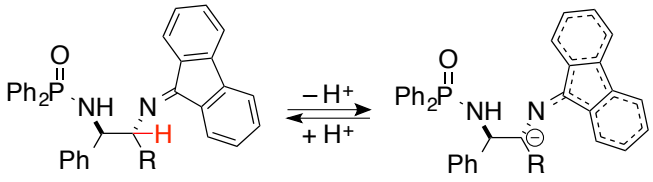


This is an advantage of the newly developed system. In the corresponding aliphatic imino-pinacol cross coupling reaction, the combination of aliphatic-aliphatic substrates is not possible. Additionally, during the whole investigation of the reaction, homo coupling products have been never been observed.

Investigation of inversed reaction condition

When the reaction was conducted in the presence of 10 mol% $KOCH_2CF_3$ in toluene at 20 ºC, reversed stereoselectivity was observed (Table 4-2-1, entry 12). The reason of this interesting phenomenon can be explained by a solvent effect and an epimerization mechanism. Firstly, the DPP imine was attacked by the fluorenyl imine *via* deprotonation by a base catalyst to afford the cross-coupling product in a *syn*-selective manner. However if the DPP imine has an electronwithdrawing substituent on the aryl ring, secondary deprotonation at the α-hydrogen might be possible (Scheme 4-2-2).

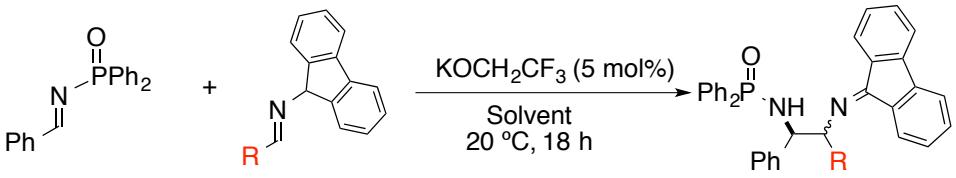
Scheme 4-2-2. Explanation of reversed diastereoselectivities.



Additionally, the pK_a value is normally very sensitive to solvents and a temperature. Indeed, in the case of DPP imine (**2a**) as a coupling partner, stereoselectivity was dramatically changed from mainly *anti* to *syn* when the solvent was changed from Et_2O/CH_2Cl_2 co-solvent system to

toluene. In *p*-chlorophenyl-fluorenyl imine (**1e**) case, selectivity was changed to a *syn*-selectively just at higher reaction temperature. For the fluorenyl imine with stronger electron-withdrawing substituents, such as in *p*-NO_2 phenyl-fluorenyl imine (**1m**) case, even at a low temperature and in the Et_2O/CH_2Cl_2 system, *syn*-selectivity was confirmed. On the other hand, *m*-chlorophenyl-fluorenyl imine (**1n**) gave exclusively an *anti* adduct in Et_2O/CH_2Cl_2 co-solvent system. Due to *m*-position substitution, less electron influence was provided to the aryl part (Table 4-2-5).

Table 4-2-5. Substrate generality of *syn*-selective imine-imine cross-coupling reaction.



2a **1** **3**

Entry	Fluorenyl imine (R)	Conditions	Yield (%)	*anti*/*syn*
1	Ph (**1a**)	Et_2O/CH_2Cl_2 (4/1), 20 °C, 18 h	97	>99/1
2	Ph (**1a**)	Toluene, 20 °C, 18 h	92	3/97
3	*p*-ClC_6H_5 (**1e**)	Et_2O/CH_2Cl_2 (4/1), –20 °C, 18 h	99	95/5
4	*p*-ClC_6H_5 (**1e**)	Et_2O/CH_2Cl_2 (4/1), 20 °C, 18 h	92	13/87
5	*p*-$NO_2C_6H_5$ (**1m**)	Et_2O/CH_2Cl_2 (4/1), 20 °C, 18 h	70	7/93
6	*p*- $NO_2C_6H_5$ (**1m**)	Toluene, –20 °C, 18 h	90	2/98
7	*m*-ClC_6H_5 (**1n**)	Et_2O/CH_2Cl_2 (4/1), 20 °C, 18 h	>99	99/1

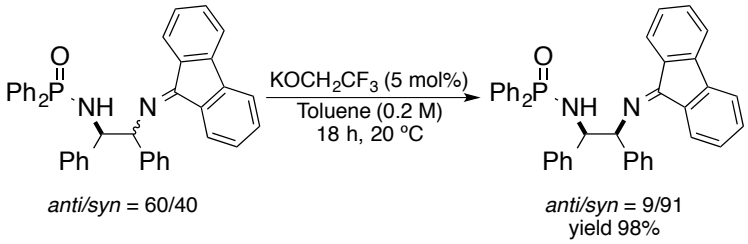
Further investigations were conducted by testing different bases (Table 4-2-6). The reaction utilizing KO^{t}Bu and 18-crown-6 was quenched after a short reaction time (0.5 h). Almost a 1:1 *anti*/*syn* mixture of product was obtained (entry 2). This result supports the epimerization mechanism strongly. The result of other weaker bases also supported the hypothesis. Potassium ethoxide gave a similar result to the case of *tert*-butoxide (entry 3). However, due to the low basicity, potassium phenoxide showed a poor epimerization ability which caused a low *anti*-selectivity (entry 4). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), which has even a lower basicity, showed a high *anti*-selectivity, which implied a no epimerization occurred (entry 5).

Table 4-2-6. The effect of the several bases for a diastereoselectivity.

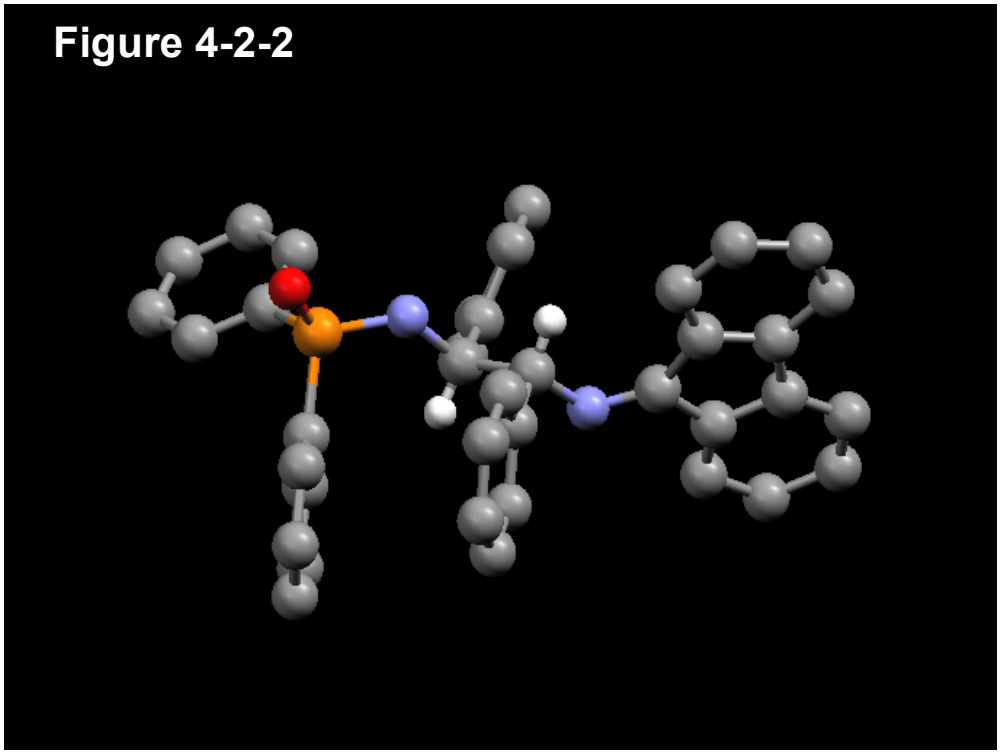
Entry	Base	Time (h)	Yield (%)	*anti*/*syn*
1	KO^{t}Bu, 18-crown-6	18	80	7/93
2	KO^{t}Bu, 18-crown-6	0.5	73	58/42
3	$KOCH_2CH_3$	18	92	3/97
4	KOPh	18	96	75/25
5	DBU	18	53	94/6

Another evidence of the epimerization reaction pathway is shown in Scheme 4-2-3. When the coupling product was treated by the optimized base condition in toluene at 20 ºC for 18 h, a poor selectivity of the product was dramatically improved to a high *syn*-selectivity. The reaction selectivity was determined not only in the first addition step, but also in the epimerization step. These reaction observations strongly support the hypothesis mentioned above.

Scheme 4-2-3. The another proof for epimerization.



The *syn*-configuration of the product **3aa** was confirmed by X-ray analysis (Figure 4-2-2).



Reaction mechanism

The reaction mechanism of the base-mediated catalytic imine-imine cross-coupling was explained as shown in Figure 4-2-3. Firstly, a fluorenyl imine is deprotonated by a base to afford the corresponding carbanion which is stabilized by the 14π-electron conjugated system of the fluorene molecule. It reacts with a DPP imine to afford the desired amide with an *anti*-selectivity. The proton transfer from a protonated base to the amide provides the desired coupling product and a base. Then the second catalytic cycle starts. However, the coupling product still possesses an active hydrogen on α-position of a fluorenyl imine. Under the basic condition, this activated hydrogen is deprotonated again and gave the corresponding carbanion again. Second proton transfer occurs to provide the thermodynamically favored a *syn*-stereoisomer.

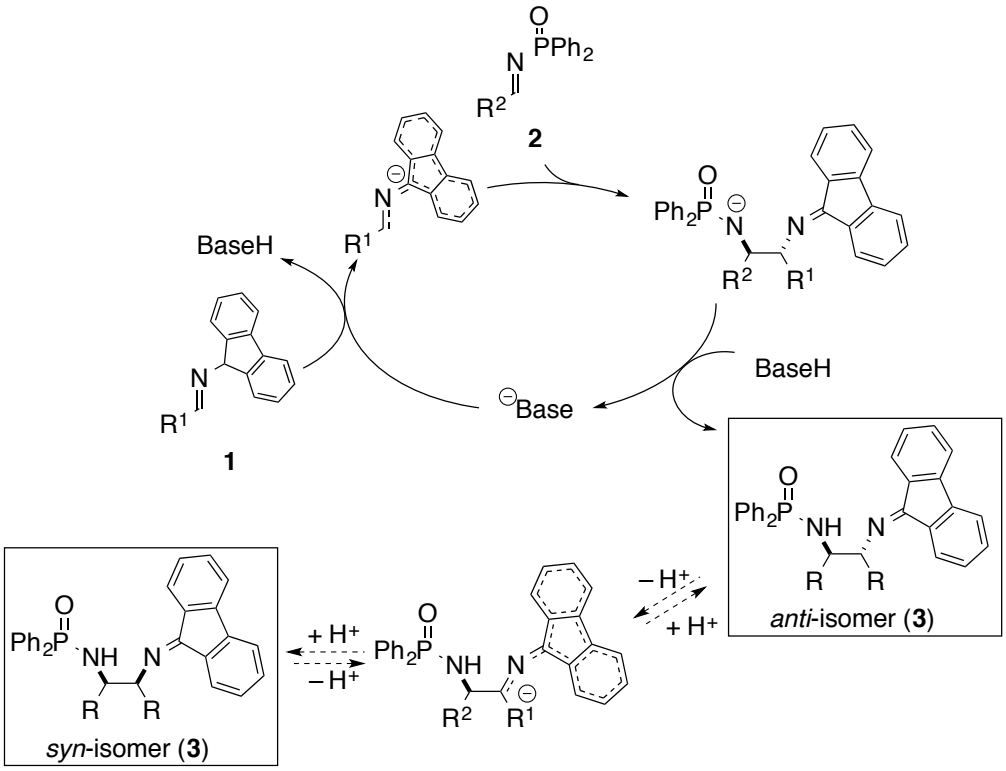


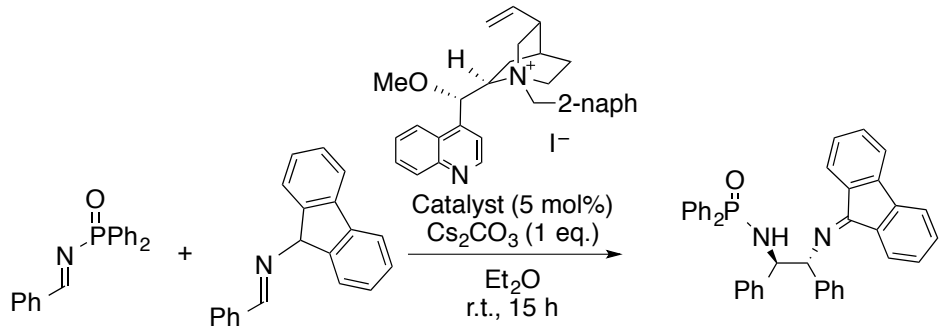
Figure 4-2-3. Assumed reaction mechanism.

Section 4-3. Asymmetric catalytic imine-imine cross-coupling reaction

Preliminary study

As indicated in the previous section, the catalytic imine-imine coupling reaction was achieved. The advantages of the reaction system are that the reaction requires only a catalytic amount of a base with no metal reductants, perfect cross-coupling selectivity, and the activated functionality, the fluorenyl moiety, can be easily removed after the desired reaction. To expand the utility of this discovered, the catalytic imine-imine cross coupling reaction mediated by an asymmetric catalyst is proposed. Inspired from the previous Mannich-type reaction reported by Dr, Chen[8], the chiral phase transfer catalyst was used for the preliminary study (Scheme 4-3-1). The reaction was conducted with *N*-fluorenyl imine (**1a**) and *N*-diphenylphosphinoyl (DPP) imine (**2a**) in the presence of a stoichiometric amount of Cs_2CO_3 and 5 mol% of the phase transfer catalyst in Et_2O. The desired coupling product was observed with 92% yield, 81/19 diastereoselectivity and <30 % enantioselectivity.

Scheme 4-3-1. Preliminary study.



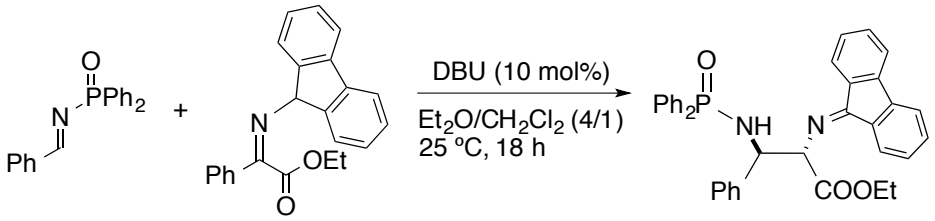
2a **1a** **3aa**

anti/syn = 81/19
92% yield, <30% ee

The result was not satisfactory, but it suggested that the catalytic imine-imine cross-coupling reaction could be expanded to the corresponding an asymmetric variant. Due to the high pK_a value of fluorenyl imine (**1a**), the choice of chiral bases was quite limited. In order to achieve an efficient asymmetric reaction system, the *N*-fluorenyl imine possessing a lower pK_a value at the desired hydrogen was synthesized (*N*-fluorenyl Et glyoxylate imine **4a**). The model reaction employed the synthesized *N*-fluorenyl glyoxylate **4a** to react with DPP-imine (**2a**) in the

presence of 10 mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The pK_a value of DBU is estimated to be 12.0 in DMSO, and it is regarded as a much milder base than KO^{t}Bu. The model reaction provided the desired coupling product with a high yield and a diastereoselectivity (Scheme 4-3-2).

Scheme 4-3-2. Imine-imine cross-coupling reaction of fluorenyl glyoxylate imine **4a.**



2a **4a** **5aa**

83% Yield

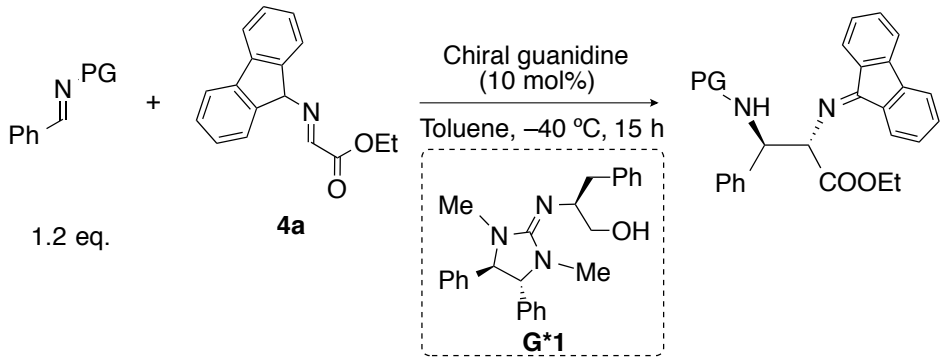
anti/syn = 91/9

This result suggested the use of a chiral organobase as the chiral source for the desired asymmetric catalytic imine-imine cross coupling reaction.

Asymmetric catalytic imine-imine coupling reaction

The first trial was conducted with *N*-fluorenyl ethyl glyoxylate imine (**4a**) and DPP-imine (**2a**) in the presence of 10 mol% of chiral guanidine **1**[42] (entry 1 of Table 4-3-1), which was previously used in the Mannich-type reaction of a *N*-fluorenylidene imine and several types of imines.[7,10] The reaction supplied the coupling product with a good yield but only a moderate *anti*-selectivity and enantioselectivity. Guanidine **1** succeeded in introducing a chirality into the product. In order to check the influence of the protecting group (PG) on the chiral environment, different types of PG on a nitrogen atom, i.e. *N*-*p*-toluenesulfonyl (Ts) group or *N*-*tert*-butoxycarbonyl group (Boc), were examined. When the Ts group was utilized under the standard conditions, *anti*- and enantioselectivity were improved (entry 2). Furthermore, when the Boc group was used, the highest *anti*- and enantioselectivity was achieved (entry 3).

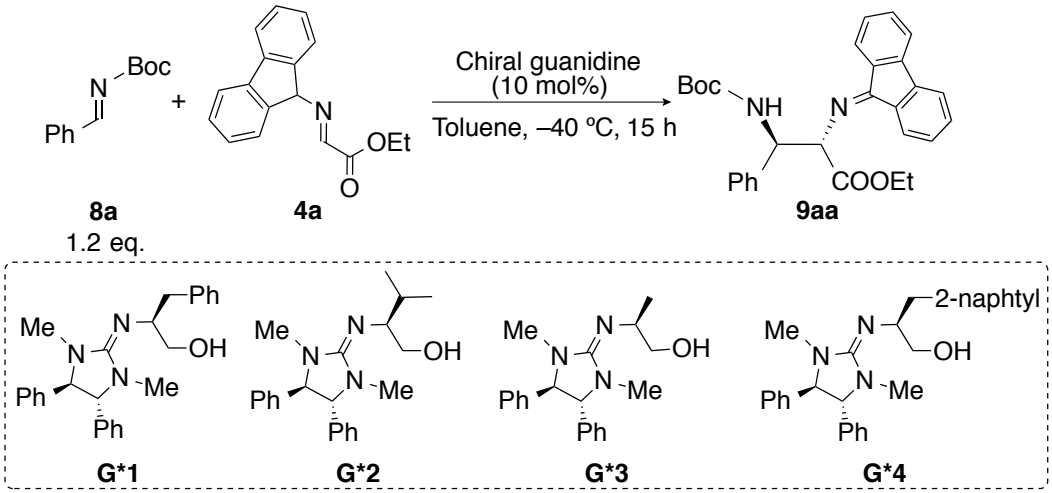
Table 4-3-1. The effect of the protecting groups.



Entry	PG	Products	Yield	*anti/syn*	ee%
1	DPP (**2a**)	**5aa**	81	64/36	65
2	TS (**6a**)	**7aa**	72	85/15	85
3	Boc (**8a**)	**9aa**	82	95/5	91

In order to improve both a diastereo- and enantioselectivity, the structure of the chiral guanidine was modified (Table 4-3-2). When chiral guanidine **2**, which was derived from (*S*)-valinol on the aminoalcohol moiety, was employed, the reaction afforded slightly a lower diastereo- and enantioselectivity than entry 1 (entry 2). Chiral guanidine **3** synthesized from (*S*)-alaninol as the aminoalcohol caused decreased an enantioselectivity. In the case of employing chiral guanidine **4**, which is supplied from (*S*)-2-naphthyl alaninol as the aminoalcohol, the desired coupling product was isolated with a slightly lower diastereo- and enantioselectivity than entry 1. Finally, chiral guanidine **1** was selected as the most suitable structure for desired asymmetric reaction.

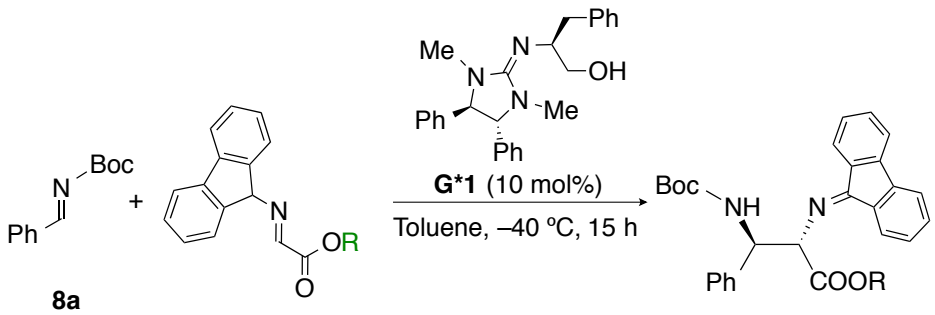
Table 4-3-2. The effect of the chiral guanidines.



Entry	Guanidine	Yield of 9aa	*anti/syn*	ee%
1	**1**	82	95/5	91
2	**2**	43	92/8	85
3	**3**	90	82/18	58
4	**4**	91	93/7	87

Further optimization of the reaction system was conducted. Firstly, the steric effect of a ester was tested. The *N*-fluorenyl glyoxylate imines substituted with alkyl groups of different sizes were synthesized by the reported method.[11] The imine-imine cross-coupling reaction with the sterically unhindered methoxy ester (**10a**) yielded the desired product with 90/10 *anti*-selectivity, and a slightly lower ee was observed (Table 4-3-3. entry 1). On the other hand, when the alkyl substituent was changed to an isopropyl group, a diastereo- and enantioselectivity improved (entry 3). The more hindered *tert*-butyl group provided the highest *anti*-selectivity and excellent enantioselectivity (entry 4). The sterically hindered substituent on the ester position tended to give the desired coupling product with a higher diastereo- and *anti*-selectivity. Further optimization of the desired reaction conditions was conducted with the *N*-fluorenyl *tert*-butyl glyoxylate **4d**. The solvent screening revealed that toluene supplied the best result among commonly used organic solvents (entries 5-7). After a small modification of the reaction conditions, the condition shown in entry 8 gave an excellent yield and *anti*-selectivity, as well as the highest enantioselectivity. Finally, the optimized condition was decided. Notably, during optimization, homo-coupling products have never been observed.

Table 4-3-3. Optimization of reaction condition.



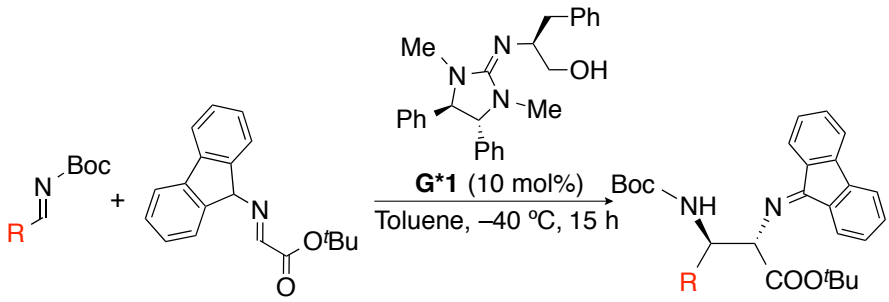
Entry	R	Conditions	Product	Yield (%)	*anti*/*syn*	ee%
1	Me (**10a**)	Toluene, –40 ºC, 15 h	**11aa**	90	90/10	87
2	Et (**4a**)	Toluene, –40 ºC, 15 h	**5aa**	82	95/5	91
3	^{i}Pr (**12a**)	Toluene, –40 ºC, 15 h	**13aa**	85	98/2	92
4	^{t}Bu (**14a**)	Toluene, –40 ºC, 15 h	**15aa**	94	98/2	92
5	^{t}Bu (**14a**)	THF, –40 ºC, 15 h	**15aa**	99	99/1	<5
6	^{t}Bu (**14a**)	Et_2P –40 ºC, 15 h	**15aa**	99	98/2	32
7	^{t}Bu (**14a**)	CH_2Cl_2, –40 ºC, 15 h	**15aa**	50	95/5	94
8	^{t}Bu (**14a**)	Toluene, –60 ºC, 18 h	**15aa**	90	98/2	96

Substrate Generality

The substrate generality was tested with the optimized condition (Table 4-3-4). Firstly, the *N*-Boc imine substituted with a methyl group on the phenyl ring at three different positions was utilized as electrophiles. All substrates reacted with *N*-fluorenyl *tert*-butyl glyoxylate imine **14a** smoothly to afford the desired cross-coupling products with high yields, diastereo- and enantioselectivities (entries 2-4). 4-Methoxyphenyl substituted *N*-Boc imine (**8e**) also provided a high yield, diastereo- and enantioselectivity (entry 5). Hence, the electron-donating substituent showed good results with the optimized condition. The effect of electron-withdrawing substituents on the phenyl ring was also examined. The halogen-substituted phenyl *N*-Boc imines afforded to the desired coupling product with a sufficient yield, *anti*-selectivity and high enantioselectivity (entries 6,7). The *N*-Boc imine with a trifluromethyl (CF_3-) substituent (**8h**), which exhibits a stronger electron-withdrawing effect than a halogen atom, gave a excellent yield, diastereo and enantioselectivity (entry 8). The sterically hindered 1-naphthyl (**8i**) and 2-naphthyl (**8j**) *N*-Boc imines supplied very good results (entries 9,10). The 3-pyridyl *N*-Boc

imine (**8k**) also provided a sufficient yield, *anti*-selectivity and enantioselectivity (entry 11). Remarkably, the desired coupling reaction showed a wide substrate generality for not only the aromatic imine substrates but also for the aliphatic imine substrates. The 3-phenyl propyl *N*-Boc imine (**8l**), cyclohexyl *N*-Boc imine (**8m**), and *n*-propyl *N*-Boc imine (**8n**) were reacted with *N*-fluorenyl *tert*-butyl glyoxylate imine (**14a**) clearly to afford the products with high yields and diastereoselectivities, and excellent enantioselectivities (entries 12-14). In total, the application of 14 different *N*-Boc imines was allowed under the catalytic asymmetric condition to achieve the desired imine-imine cross coupling reaction.

Table 4-3-4. Substrate Scope.



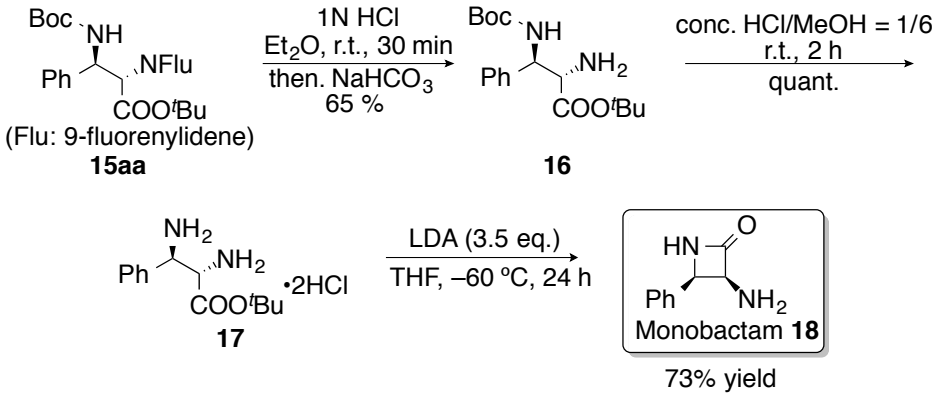
8 **14a** **15**

Entry	R	Products	Yield (%)	*anti*/*syn*	ee%
1	Ph (**8a**)	**15aa**	90	98/2	96
2	2-MeC_6H_4 (**8b**)	**15ab**	95	85/15	87
3	3-MeC_6H_4 (**8c**)	**15ac**	87	99/1	93
4	4-MeC_6H_4 (**8d**)	**15ad**	92	96/4	92
5	4-OMeC_6H_4 (**8e**)	**15ae**	89	95/5	76
6	4-FC_6H_4 (**8f**)	**15af**	93	99/1	95
7	4-ClC_6H_4 (**8g**)	**15ag**	99	99/1	88
8	4-$CF_3C_6H_4$ (**8h**)	**15ah**	93	99/1	95
9	1-Naphthyl (**8i**)	**15ai**	96	98/2	96
10	2-Naphthyl (**8j**)	**15aj**	99	99/1	88
11	3-pyridyl (**8k**)	**15ak**	95	97/3	93
12	3-$PhCH_2CH_2$ (**8l**)	**15al**	91	99/1	95
13	Cy (**8m**)	**15am**	93	99/1	97
14	$CH_3CH_2CH_2$ (**8n**)	**15an**	85	89/11	90

Synthesis of Monobactam

The protecting groups of the coupling product (**15aa**) were selectively cleaved by employing different acidic conditions. The mildly acidic condition (1N HCl in Et_2O) selectively removed the fluorenylidene (Flu) moiety from the coupling product (**15aa**) under ambient temperature in 30 minutes to afford the *N*-Boc diamine *tert*-butyl ester (**16**). This is followed by the harsher acidic condition (conc. HCl/MeOH =1/6), under which the *N*-Boc protecting group was disconnected from compound **16** under ambient temperature in 2 hours to supply diamine *tert*-butyl ester (**17**) in a quantitative yield. From compound **17**, monobactam **18** was synthesized by the reported method[43] with a good yield (Scheme 4-3-2). The reported bioactivity of monobactam **18** was indicated that it exhibited a monoamine oxidase (MAO) inhibiter activity and an antibacterial activity in human cell line.

Scheme 4-3-2. Derivatization of coupling product.



Section 4-4. Summary

A catalytic base-mediated imine-imine cross-coupling reaction has been discovered. The desired coupling reaction was achieved by utilizing an interesting feature of the fluorene moiety, - 14π-electron conjugated system that can strongly stabilize a corresponding carbanion form. A *N*-fluorenyl imine, which is synthesized from a fluorenyl amine and aldehydes, can be deprotonated at the activated hydrogen position under a mild basic condition and exhibited a nucleophilic nature at the imine carbon position instead of a its typical electrophilic nature. Following an umpolung reaction mechanism, a fluorenyl imine reacted with several other types of imines to afford a diamine derivative with excellent reactivity. Unexpectedly, a diastereoselectivity was inverted by changing only the solvent system. The desired coupling reaction could be expanded to an asymmetric catalysis as well. The advantages of the described cross-coupling reaction are mentioned below. Firstly, the desired coupling reaction requires only a catalytic amount of base species, even in the asymmetric reaction. Secondly, the reaction has never produced the homo-coupling product. Perfect an *anti*-selectivity was demonstrated. Thirdly, the reaction does not require any external oxidant. The fluorenyl moiety contributes as a sacrificial oxidant to achieve this novel system. Finally, the protecting groups on both nitrogens in the coupling product can be easily removed under acidic conditions. The reaction described in this chapter is the first example of an achieving base catalyst mediated imine-imine cross coupling reaction.

V. Conclusion

In this thesis, the novel feature of the fluorene moiety was described. The first report of an interesting fluorene feature was introduced by Prof. Martin. J. O'Donnell[3] in 1988 (Figure. 5-1). More than two decades later, the Kobayashi group focused on that α-hydrogen activation ability and demonstrated in a publication the use of the fluorene moiety for organic synthesis.[7,8] In order to expand the utility of this activation and protection strategy with a fluorene moiety, several new reactions employing the fluorene moiety as an activating and protecting group of a nitrogen atom are demonstrated.

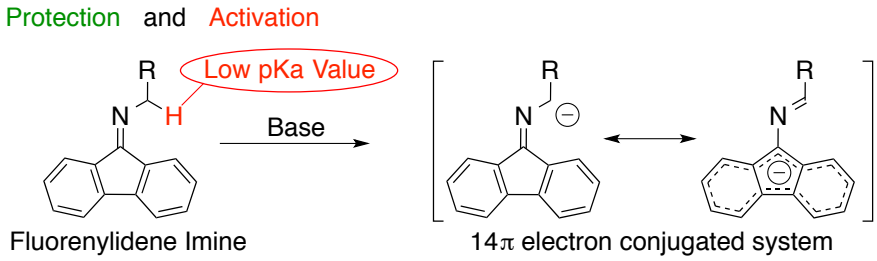
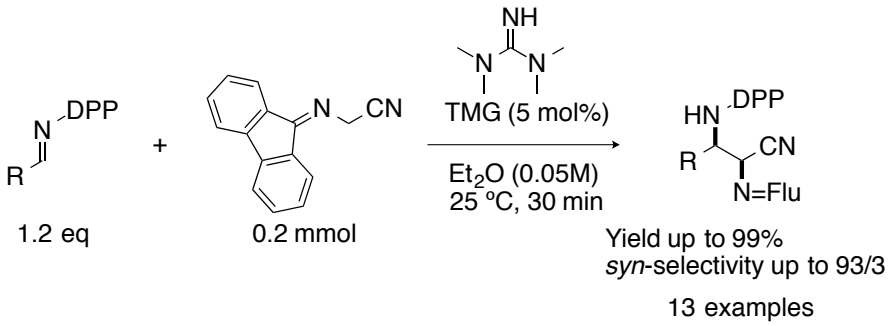


Figure 5-1. The feature of the fluorene moiety.

Firstly, Mannich-type reaction of the *N*-fluorenylidene protected α-aminoacetonitrile with diphenylphosphinyl (DPP) imine was documented. The desired Mannich-type reaction was smoothly promoted by a catalytic amount of a mild base, 1,1,3,3-tetramethylguanidine (TMG), to give the Mannich adduct in good to excellent yields and *syn*-selectivities with thirteen different DPP-imines in total (Scheme 5-1).

Scheme 5-1. Mannich-type reaction of *N*-fluorenylidene protected *α*-aninoacetonitrile.



The desired Mannich-type reaction could be expanded to its asymmetric variant with a chiral guanidine base. After the modification of the chiral guanidine structure, the synthesized guanidine exhibited the highest efficiency (Figure 5-2).

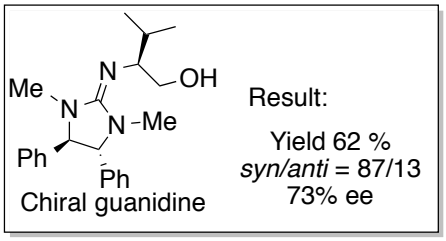
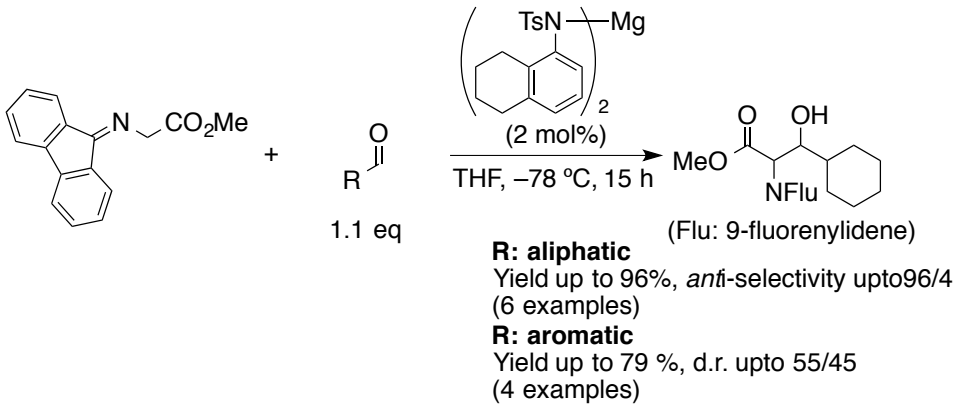


Figure 5-2. Asymetric catalytic Mannich-type reaction.

These examples for the modification of α-aminoacetonitrile derivatives have proved to be difficult due to the low acidity of the substrate at the desired α-hydrogen position. This achievement demonstrated the further applicability of the fluorene activation strategy in the field of Mannich-type reaction.[10]

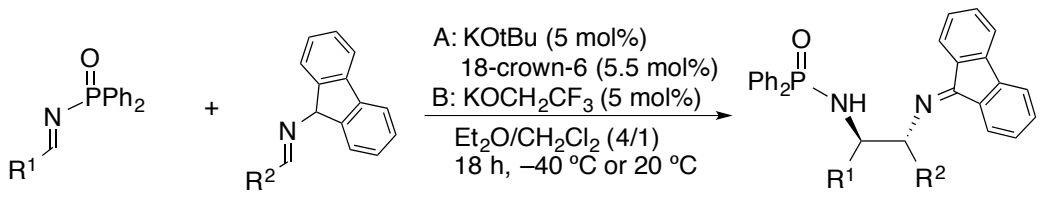
Secondly, the aldol reaction of the *N*-fluonylidene protected glycine ester with various kinds of aldehydes was achieved. Generally speaking, in spite of the huge utility of the resulting, α-hydroxy-β-amino acid derivatives, only a synthetic method employing strong base conditions has been reported, because of the high pK_a barrier. Hence, a fluorene moiety was chosen as an activating and protecting group of the nitrogen atom of the glycine ester. The desired aldol reaction smoothly proceeded in the presence of 2 mol% of *N*-5,6,7,8-tetrahydro-1-naphthyltosyl amide in THF at –78 ºC. Notably, aliphatic aldehydes provided aldol adducts with good to excellent yield and *anti*-selectivity among six typical aliphatic aldehydes. However, aromatic and α,β-unsaturated aldehydes gave only moderate to good yields and poor diastereoselectivities (Scheme 5-2). The fluorene moiety showed a strong activation effect of the glycine ester. However, the strong activation effect also caused the retro-aldol process for aromatic and α,β-unsaturated aldehydes even at low temperature. This is a rare successful example of the aldol reaction mediated by only a catalytic amount of mild base species.[44]

Scheme 5-2. The aldol reaction of glycine Schiff base.



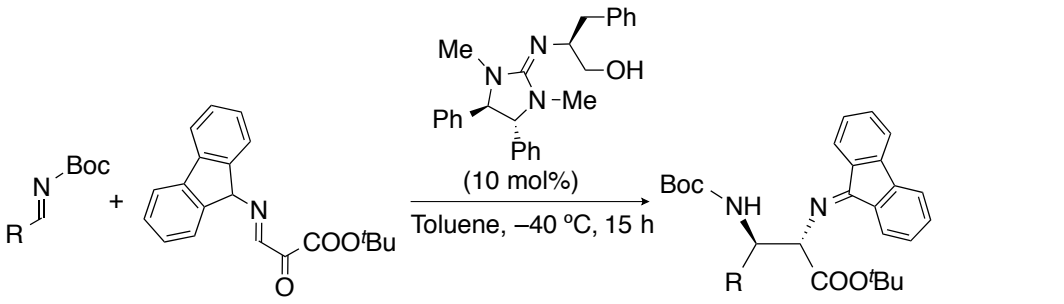
Finally, the imine-imine cross-coupling reaction promoted by a catalytic amount of base was developed (Scheme 5-3). The imine-imine coupling reaction is a direct way to achieve the 1,2-vicinal diamine core structure. Comparing with the previously reported imine-imine coupling methods, the reaction described in this chapter has several advantages. Firstly, the desired coupling reaction requires only a catalytic amount of the base species, even in the asymmetric reaction. Secondly, the reaction has never produced any homo-coupling product. Perfect *anti*-selectivity was also demonstrated. Thirdly, the reaction does not require any external oxidant. The fluorenyl moiety contributes as a sacrificial oxidant to achieve this novel system. Fourthly, the protecting groups on both nitrogen atoms in the coupling product can be easily removed under acidic conditions. Additionally for some substrates, the developed imine-imine coupling reaction provided the products with inversed diastereoselectivities by simply changing the solvent system. This imine-imine coupling reaction is completely novel, and would provide a new choice for the synthesis of complex molecules containing the 1,2-vicinal diamine framework.

Scheme 5-3. The imine-imine cross-coupling reaction mediated by base catalyst.



Yield up to >99%, *anti*-selectivity >99/1
26 examples
Yield up to 92%, *syn*-selectivity 98/2
3 examples

Scheme 5-4. The catalytic asymmetric imine-imine cross-coupling reaction



Yield up to 99%, *anti*-selectivity 99/11, 97 %ee
14 examples

VI. Experimental Data

General:

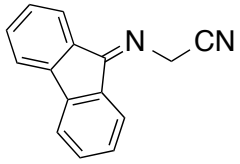
^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on JEOL JNM ECX400, JNM ECX500 and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^{1}H NMR, and $CDCl_3$ ($\delta = 77.0$) were used as internal standard for ^{13}C NMR. In ^{13}C NMR analysis, detectable peaks were written in cases of the DPP imine adducts. IR spectra were measured on a JASCO FT/IR-610 or JASCO FT/IR-4200 spectrometer. Specific rotations were recorded with a JASCO P-1200 polarimeter. High-resolution mass spectrometry was recorded with a JEOL JMS-T100TD (ESI or DART®). Column chromatography was conducted on Silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.), and preparative thin-layer chromatography (PTLC) was carried out using plates with Wakogel B-5F. All reactions were carried out under argon atmosphere in well-dried glassware. All solvents were dried and distilled by following standard procedures. 9-Fluorenylidene-protected α-aminoacetonitrile (**1**) was prepared according to a literature method.[10] *N*-diphenylphosphinyl imines were prepared according to the reported method.[16] The chiral guanidines (**8a** and **8b**) were prepared by a literature method.[15]

Experimental Data of Chapter 2

General procedure of the preparation of 9-fluorenylidene-protected α-aminoacetonitrile (1a)

9*H*-fluoren-9-imine (fluorenone imine, 1.00 g, 5.58 mmol) and α-aminoacetonitrile hydrochloric acid salt (5.58 mmol) were combined in CH_2Cl_2 (30 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered using filter paper to remove ammonium salt and concentrated *in vacuo* to remove all volatile materials, and the residue was dissolved in Et_2O. The ether solution was then washed with H_2O and dried over anhydrous Na_2SO_4. The desired product was obtained in a pure form after filtration and concentration of the ether solution (full conversion). The product was further purified by recrystallization (AcOEt/hexane) before use.

2-(9*H*-Fluoren-9-ylideneamino)acetonitrile (1a)

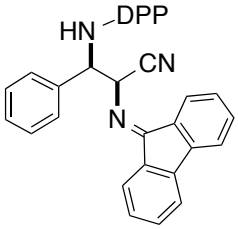


M.p. 170 ºC (dec.); IR (neat): 3154, 3063, 2986, 2924, 2313, 2254, 1648, 1453, 1098; ^{1}H NMR ($CDCl_3$, 399.78 MHz): δ 7.82 (d, *J* = 7.3 Hz, 1H), 7.63 (dd, *J* = 10.3 7.6 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.50-7.40 (m, 2H), 7.31-7.29 (m, 2H), 5.00 (s, 2H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.56, 144.11, 141.16, 137.40, 132.63, 132.00, 130.98, 128.79, 128.05, 127.27, 123.16, 120.91, 119.62, 117.39, 40.91; HRMS (DART®): Exact mass calcd for $C_{15}H_{11}N_2$ $[M+H]^+$ 219.09222, Found 219.09325.

General procedure for the catalytic Mannich-type addition of 1 to DPP imines 2

1 (0.24 mmol) and **2** (0.20 mmol) were placed in a flame-dried 30 mL round-bottom-flask with a sleeve stopper. To the flask was added anhydrous Et_2O (3.6 mL) via a syringe. 1,1,3,3-tetramethylguanidine (0.020 mmol) was then added to the mixture at room temperature, then CH_2Cl_2 (0.4 mL) was added via a syringe. The resulting yellow solution was stirred at 25 ºC for 30 min under Ar and quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2, and the organic layers were combined and dried over Na_2SO_4. After filtration and concentration *in vacuo*, the obtained crude product was purified by PTLC or silica gel column chromatography ($CHCl_3$/MeOH) to afford the desired product.

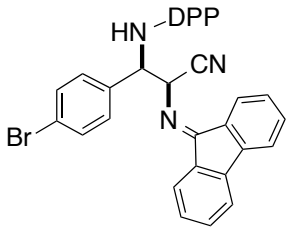
(1*R*,2*S*)-*syn*-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylidene)amino-3-phenylpropane -nitrile (3aa)



M.p. 200 ºC (dec.); IR (neat): 3401, 3165, 3058, 2917, 2361, 2344, 1646, 1597, 1451,1436, 1309, 1178, 1124, 1108,1072; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.01-7.94 (m, 4H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.63-7.38 (m, 13H), 7.32-7.22 (m, 5H), 5.61 (d, *J* = 3.4 Hz, 1H), 4.82-4.77 (m, 1H), 4.65 (dd, *J* = 10.2, 7.4, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.57, 144.25, 141.35, 138.53, 137.49, 132.83, 132.53, 132.46, 132.40, 132.25, 132.19, 132.16, 132.14, 132.01, 131.66, 131.16, 130.72, 128.75, 128.66, 128.61, 128.59, 128.57, 128.45, 128.29, 127.78, 127.46, 123.22, 120.70, 119.58, 117.07, 57.86, 57.72 (J_{PC} = 5.7 Hz); ^{31}P NMR ($CDCl_3$, 161.83 MHz): δ 23.46;

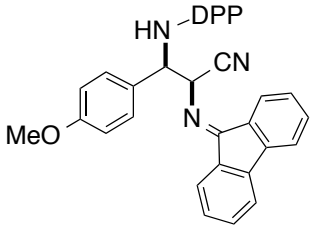
HRMS (DART®): Exact mass calcd for $C_{34}H_{27}N_3OP$ $[M+H]^+$ 524.18917, Found 524.19125; Chiral HPLC: Daicel Chiralcel AD-H: hexane/*i*PrOH =2/1, flow rate = 0.7 mL/min; tR =15.9 min (1*R*,2*S*), 47.7 min (1*S*, 2*R*). $[a]_D^{20}$ +9.6 (c 0.50, CH_2Cl_2, 73% ee).

syn-3-(_p_-Bromophenyl)-3-diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylidene)-aminopropanenitrile (3ab)



M.p. 210 ºC (dec.); IR (neat): 3054, 2986, 2685, 2372, 2348, 2308, 1698, 1636, 1421, 1265; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93-7.88 (m, 4H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.56-7.30 (m, 12H), 7.26-7.17 (m, 5H), 5.47 (d, *J* = 3.4 Hz, 1H), 4.68-4.66 (m, 1H), 4.57 (dd, *J* = 10.3, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.98, 144.33, 141.59, 141.41, 137.63, 137.35, 133.02, 132.44, 132.39, 132.34, 132.32, 132.27, 132.20, 131.64, 131.57, 131.51, 131.50, 129,99, 129.20, 128.84, 128.75, 128.69, 128.67, 128.60, 128.57, 128.55, 128.28, 127.75, 123.19, 122.46, 120.81, 119.68, 116.81, 57.44, 57.40; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.42; HRMS (ESI): Exact mass calcd for $C_{34}H_{26}BrN_3OP$ $[M+H]^+$ 602.09914, Found 602.09948.

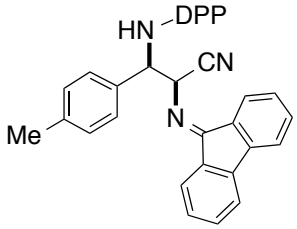
syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(*p*-methoxyphenyl) -propanenitrile (3ac)



M.p. 204 ºC (dec.); IR (neat): 2921, 2851, 2363, 2328, 1698, 1682, 1649, 1456, 1273. ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93-7.92 (m, 4H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.62-7.36 (m, 10H), 7.30-7.21 (m, 5H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.57 (d, *J* = 3.4 Hz 1H), 4.73 (m, 1H), 4.55 (m. 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.50, 159.41, 144.23, 141.35, 137.53, 132.80, 132.60, 132.45, 132.38, 132.24, 132.22, 132.18, 132.12, 131.73, 131.24, 130.75, 130.64, 129.39, 128.73, 128.63, 128.60, 128.58, 127.79, 123.21, 120.68, 119.57, 117.15, 113.80, 113.73, 57.92 (J_{PC} = 5.8 Hz), 57.42, 55.19; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.36; HRMS (ESI): Exact mass calcd for $C_{35}H_{29}N_3O_2P$ $[M+H]^+$ 554.19974, Found 554.19886.

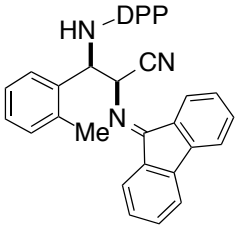
syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(*p*-tolyl)propanenitrile

(3ad)



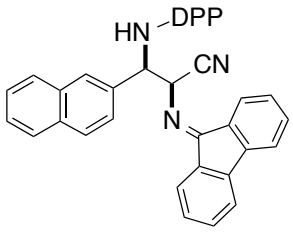
M.p. 200 ºC (dec.); IR (neat): 3161, 2361, 1772, 1646, 1600, 1449, 1435, 1179, 1106; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.94 (m, 4H), 7.77 (d, *J* = 10.0 Hz, 1H), 7.59-7.34 (m, 10H), 7.28-7.17 (m, 5H), 7.07 (d, *J* = 7.6 Hz, 2H), 5.56 (d, *J* = 4.1 Hz, 1H), 4.73-4.70 (m, 1H), 4.57 (dd, *J* = 10.3, 6.9 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.48, 144.21, 141.33, 138.00, 137.52, 135.55, 132.77, 132.46, 132.40, 132.27, 132.20, 132.15, 132.12, 132.10, 130.74, 129.14, 128.72, 128.66, 128.63, 128.58, 128.55, 127.80, 127.32, 123.23, 120.66, 119.55, 57.85 (J_{PC} = 4.2 Hz), 57.67, 21.10; ^{31}P NMR ($CDCl_3$, 242.83 MHz): δ 23.38; HRMS (ESI): Exact mass calcd for $C_{35}H_{29}N_3OP$ $[M+H]^+$ 538.20482, Found 538.20692.

***syn*-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(*o*-tolyl)propanenitrile (3ae)**



M.p.: 195 ºC (dec.); IR (neat): 3168, 3051, 2788, 2373, 2349, 1764, 1694, 1641, 1597, 1436, 1288, 1211, 1180, 1012; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.85 (m, 4H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.50-7.29 (m, 11H), 7.23-7.10 (m, 4H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.53 (d, *J* = 4.1 Hz, 1H), 4.99 (dt, *J* = 9.3, 4.1 Hz, 1H), 4.49 (dd, *J* = 10.3, 7.6 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.67, 144.18, 141.33, 137.49, 137.12, 135.48, 132.77, 132.49, 132.43, 132.35, 132.20, 132.17, 132.10, 132.04, 131.98, 131.27, 130.73, 130.23, 128.73, 128.64, 128.61, 128.57, 128.55, 128.53, 128.08, 127.77, 126.71, 126.42, 123.21, 120.66, 119.55, 116.98, 57.36 (J_{PC} = 6.0 Hz), 53.07, 19.44; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.69; HRMS (ESI): Exact mass calcd for $C_{35}H_{29}N_3OP$ $[M+H]^+$ 538.20482, Found 538.20229.

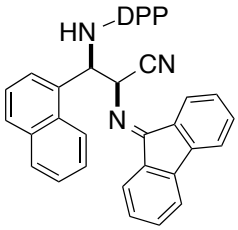
***syn*-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(2-naphthyl) -propanenitrile (3af)**



M.p. 206 ºC (dec.); IR (neat): 3054, 2986, 2373, 2348, 2306, 1698, 1649, 1436, 1421, 1265, 1203, 1174, 1157; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.99-7.94 (m, 4H), 7.82-7.79 (m, 5H), 7.61 (d, *J* = 7.6 Hz 1H), 7.56-7.20 (m, 15H), 5.67 (d, *J* = 3.4 Hz, 1H), 4.94 (m, 1H), 4.75 (dd, *J* =

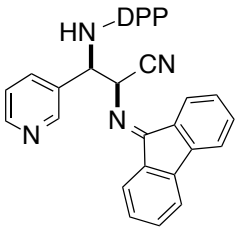
10.7, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 174.29, 144.26, 141.37, 137.47, 136.06, 135.07, 134.33, 133.16, 133.00, 132.86, 132.49, 132.43, 132.27, 132.24, 132.22, 132.18, 132.01, 131.65, 128.78, 128.69, 128.62, 128.57, 128.21, 127.94, 127.80, 127.58, 126.72, 126.69, 126.25, 126.20, 125.18, 123.23, 120.71, 119.59, 117.09, 58.05, 57.90 (J_{PC} = 4.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.63; HRMS (ESI): Exact mass calcd for $C_{38}H_{29}N_3OP$ $[M+H]^+$ 574.20482, Found 574.20844.

syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(1-naphthyl) -propanenitrile (3ag)



M.p. 210 ºC (dec.); IR (neat): 3149, 2373, 2348, 1701, 1646, 1599, 1509, 1436, 1261, 1182, 1111; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.13 (*d*, *J* = 6.7 Hz, 1H) 7.94 (*dd*, *J* = 2.7 12.4 Hz, 1H), 7.90-7.71 (*m*, 8H), 7.65 (*d*, *J* = 18.7 Hz, 1H), 7.58-715 (*m*, 14H), 5.87 (*dt*, *J* = 3.9, 10.2 Hz, 1H), 5.76 (*d*, *J* = 4.4 Hz, 1H), 4.29 (*dd*, *J* = 7.9, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 173.34, 145.21, 139.17, 137.80, 137.03, 134.16, 134.33, 133.20, 132.98, 132.59, 132.44, 132.38, 132.23, 132.21, 132.19, 131.55, 128.79, 128.65, 128.62, 128.54, 128.21, 128.18, 127.80, 127.58, 126.72, 126.69, 126.26, 126.19, 125.29, 123.24, 120.68, 120.01, 117.09, 58.13, 57.01 (J_{PC} = 4.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.65; HRMS (ESI): Exact mass calcd for $C_{38}H_{29}N_3OP$ $[M+H]^+$ 574.20482, Found 574.20459.

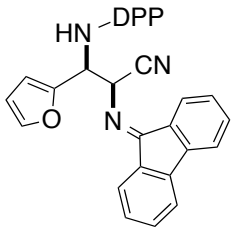
syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(3-pyridyl) -propanenitrile (3ah)



M.p.: 130 ºC (dec.). IR (neat): 3055, 2374, 2349, 2316, 1757, 1693, 1645, 1591, 1435, 1187, 1109; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.48 (d, *J* = 4.8 Hz 1H), 7.86-7.83 (m, 4H), 7.63-7.33 (m, 11H), 7.23-7.13 (m, 6H), 5.84 (*d*, *J* = 5.5 Hz, 1H), 4.96 (dt, *J* = 10.1, 5.7 Hz, 1H), 4.58 (dd, *J* = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.07, 157.01, 149.15, 144.16, 141.36, 136.81, 132.62, 132.50, 132.44, 132.11, 132.07, 132.05, 132.02, 131.93, 131.91, 130.69, 128.62, 128.53, 128.51, 128.48, 128.43, 128.35, 127.92, 123.30, 123.27, 123.19, 120.56, 119.47, 117.17, 58.94, 57.62 (J_{PC} = 7.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 24.91; HRMS (ESI): Exact mass

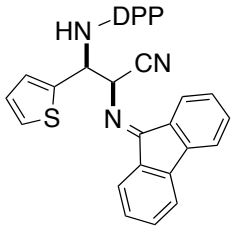
calcd for $C_{33}H_{26}N_4OP$ $[M+H]^+$ 525.18442, Found 525.18497.

syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(2-furyl) -propanenitrile (3ai)



M.p. 115 ºC (dec.): IR (neat): 2360, 2340, 1646, 1598, 1437, 1191, 1107; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.95-7.90 (m, 4H), 7.83 (d, *J* = 7.9 Hz 1H), 7.44-7.30 (m, 15H), 6.51 (s, 1H), 5.70 (d, *J* = 3.4 Hz, 1H), 4.69-4.64 (m, 1H), 4.18 (dd, *J* = 11.1, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 124.51 MHz): δ 168.31, 144.19, 143.23, 141.35, 140.81, 137.48, 132.80, 132.41, 132.33, 132.28, 132.25, 132.20, 132.07, 132.04, 131.98, 131.14, 130.64, 128.82 128.78, 128.71, 128.67 128.65, 128.58, 127.87, 123.81, 123.76, 123.15, 120.67, 119.60, 117.16, 109.61, 57.94 (J_{PC} = 4.7 Hz), 51.03; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.68; HRMS (ESI): Exact mass calcd for $C_{32}H_{25}N_3O_2P$ $[M+H]^+$ 514.16844, Found 514.16835.

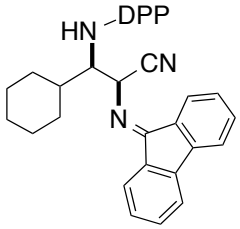
syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-(thiophen-2-yl) -propanenitrile (3aj)



M.p. 120 ºC (dec.); IR (neat): 2360, 2340, 1647, 1541, 1437, 1186, 1107; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.95-7.90 (m, 1H), 7.79 (m, 2H), 7.71-7.66 (m, 2H), 7.50-7.15 (m, 14H), 7.04 (d, *J* = 3.4 Hz, 1H), 6.93 (dd, *J* = 3.6, 4.8 Hz, 1H), 5.67 (d, *J* = 3.4 Hz, 1H), 5.17 (dt, *J* = 3.6, 7.6 Hz 1H), 4.12 (dd, *J* = 11.0, 7.6 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 170.16, 144.26, 144.21, 141.53, 141.41, 132.91, 132.64, 132.57, 132.29, 132.01, 131.47, 130.66, 128.71, 128.68, 128.53, 128.53, 128.50, 128.15, 127.89, 127.33, 126.59, 126.20, 123.54, 120.68, 119.61, 116.61, 115.89, 58.19 (J_{PC} = 4.4 Hz), 54.35; ^{31}P NMR ($CDCl_3$, 242.95 MHz) δ 24.77; HRMS (ESI): Exact mass calcd for $C_{32}H_{25}N_3OPS$ $[M+H]^+$ 530.14425, Found 530.14464.

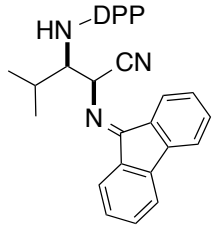
syn-3-Cyclohexyl-3-diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino) -propanenitrile (3ak)

M.p. 187 ºC (dec.); IR (neat): 3054, 2986, 2372, 2348, 2308, 1748, 1733, 1716, 1698, 1540,



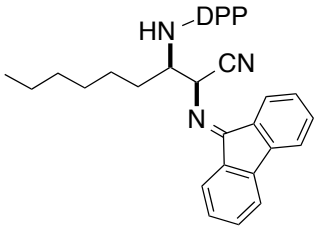
1508, 1455, 1421, 1374; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.03-7.96 (m, 4H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.48-7.32 (m, 9H), 7.23-7.17 (m, 2H), 5.54 (d, *J* = 3.4 Hz, 1H), 3.33 (m, 1H), 2.18 (d, *J* = 12.4 Hz, 1H), 1.79-1.69 (m, 3H), 1.57-1.48 (m, 3H), 1.19-0.97 (m, 5H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 167.81, 144.25, 141.33, 137.60, 133.12, 132.74, 132.61, 132.54, 132.47, 132.24, 132.19, 132.01, 131.86, 131.01, 130.72, 128.65, 128.62, 128.59, 128.54, 128.51, 127.68, 123.18, 120.74, 119.60, 118.14, 58.70, 54.58 (J_{PC} = 5.7 Hz), 41.03 (J_{PC} = 3.0 Hz), 30.30, 28.84, 26.27, 26.08, 26.04; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 22.57; HRMS (ESI): Exact mass calcd for $C_{34}H_{33}N_3OP$ $[M+H]^+$ 530.23612, Found 530.23378.

syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)-3-isopropylpropanenitrile (3al)



M.p. 186 ºC (dec.); IR (neat): 3057, 2962, 2360, 2340, 1645, 1598, 1451, 1308, 1188; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.00 (m, 1H), 7.88 (dd, *J* = 11.7, 7.6 Hz, 2H), 7.73 (m, 3H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.39-7.26 (m, 11H), 5.46 (d, *J* = 4.8 Hz, 1H), 3.58-3.54 (m, 1H), 3.34 (dd, *J* = 10.9, 6.8 Hz, 1H), 2.23 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.76, 144.25, 141.40, 137.81, 132.89, 132.72, 132.53, 132.49, 132.41, 132.35, 132.22, 132.08, 132.02, 131.96, 131.82, 131.66, 130.72, 128.64, 128.62, 128.54, 128.48, 128.45, 128.36, 128.02, 123.19, 120.67, 119.57, 117.22, 58.92, 55.21 (J_{PC} = 4.4 Hz), 31.03 (J_{PC} = 5.9 Hz), 21.23, 17.96; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 24.47; HRMS (ESI): Exact mass calcd for $C_{31}H_{29}N_3OP$ $[M+H]^+$ 490.20482, Found 490.20612.

syn-3-Diphenylphosphiniylamino-2-(9*H*-fluoren-9-ylideneamino)nonanenitrile (3am)



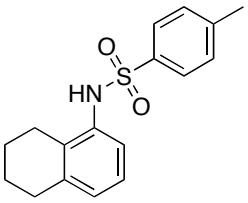
M.p. 179 ºC (dec.); IR (neat): 2926, 2857, 2361, 1644, 1599, 1451, 1438, 1309, 1192, 1123, 1108, 1027; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93 (m, 4H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.47-7.13 (m, 11H), 5.67 (d, *J* = 4.1 Hz, 1H), 3.65 (dd, *J* = 7.6, 11.0 1H), 3.45-3.44 (m, 1H), 1.22-1.13

(m, 10H), 0.81 (t, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 167.70, 144.04, 141.04, 141.26, 137.56, 132.53, 132.36, 132.16, 132.14, 132.05, 132.03, 132.01, 131.99, 131.93, 131.53, 131.51, 130.60, 128.69, 128.61, 128.47, 128.41, 127.81, 123.06, 122.99, 120.51, 119.50, 119.44, 117.68, 56.99 (J_{PC} = 2.9 Hz), 54.62, 32.54 (J_{PC} = 5.7 Hz), 31.50, 28.82, 25.96, 22.45, 13.97; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.25; HRMS (ESI): Exact mass calcd for $C_{34}H_{35}N_3OP$ $[M+H]^+$ 532.25177, Found 532.25399.

Experimental Data of Chapter 3

Di-*n*-butyl magnesium in heptane was purchased from Aldrich Co., Ltd. Tosylamides were prepared by a typical experimental procedure. Commercially available aldehydes were purchased from Tokyo Chemical Industry Co., Ltd. and purified by distillation. THF and Et_2O were purchased from Wako Pure Chemical Industries, Ltd. as dry solvents, and purified in the presence of benzophenone and sodium.

4-Methyl-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)benzenesulfonamide



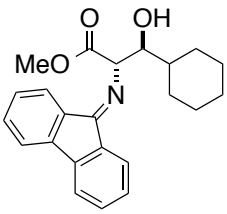
IR (neat): 2361, 2337, 2279, 2252, 1458, 1388, 1328, 1265; ^{1}H NMR (C_6D_6, 500 MHz) δ: 7.79 (dd, J = 1.6, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.05-6.98 (br. s, 1H), 6.90 (t, J = 7.7Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 6.64 (d, J = 8.2 Hz, 2H), 2.36 (t, J = 5.7 Hz, 2H), 2.25-2.19 (m, 3H), 1.77 (s, 3H), 1.36-1.25 (m, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 138.5, 138.1, 135.2, 130.7, 129.6 (2C), 127.6 (2C), 127.1, 126.0, 121.6, 29.8, 24.5, 22.9, 22.5, 20.1; HRMS (DART®): Exact mass calcd for $C_{17}H_{20}NO_2S$ $[M+H]^+$ 302.1209, Found 302.1214.

General procedure of the aldol reaction:

In a well-dried 10 mL reaction tube, the tosyl amide (2.4 mg, 0.0080 mmol, 0.040 equiv.) was dissolved in anhydrous THF (1 mL) and cooled down to -78°C. ^{n}Bu$_2$Mg in heptane (0.0040

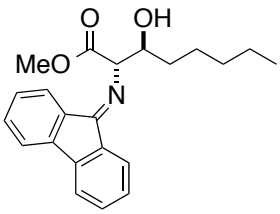
mmol, 0.020 equiv.) was then added dropwise to the mixture, and the mixture was stirred at room temperature. After 30 min stirring, the reaction tube was cooled down again to -78°C, and a solution of *N*-fluorenylideneglycine ester **1** (50 mg, 0.20 mmol, 1.0 equiv.) and aldehyde **2** (0.22 mmol, 1.1 equiv.) in dry THF (1 mL) were introduced. After 15 hr, the reaction was quenched by addition of sat. NH_4Cl (1 mL) and extracted with Et_2O (5 mL x 3). The combined organic layers were then dried over Na_2SO_4 and concentrated under vacuum. Finally the crude material was purified on column chromatography (deactivated silica gel (10% of water)) using a mixture of Et_2O/Hexane to give the corresponding aldol product.

***Anti*- methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-cyclohexyl-3-hydroxypropanoate (3a)**:



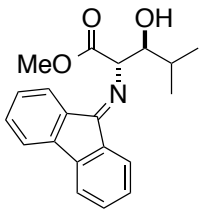
IR (neat): 2361, 2338, 2279, 2252, 1736, 1720, 1649, 1619, 1455, 1378, 1329, 1265; ^{1}H NMR (C_6D_6, 500MHz) δ: 7.97 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.21-6.92 (m, 6H), 5.48 (d, *J* = 6.1 Hz, 1H), 4.24 (tbr, *J* = 5.9 Hz, 1H), 3.24 (s, 3H), 2.18-2.11 (m, 1H), 2.02-1.91 (m, 2H), 1.73-1.63 (m, 2H), 1.51-1.57 (m, 1H), 1.37-1.25 (m, 3H), 1.14-1.06 (m, 2H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 171.0, 165.8, 144.4, 141.5, 138.8, 132.1, 131.9, 131.6, 128.7, 128.4, 127.4, 123.5, 120.7, 119.6, 78.2, 67.3, 51.8, 40.0, 30.0, 27.7, 26.8, 26.6, 26.3; HRMS (DART®): Exact mass calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$ 364.1907, Found 364.1910.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxyoctanoate (3b):**



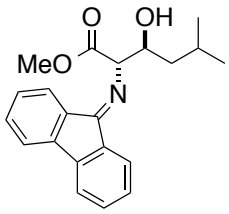
IR (neat): 3234, 2361, 2337, 2277, 1735, 1453, 1329; ^{1}H NMR (C_6D_6, 500MHz) δ: 7.93 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 6.92-6.73 (m, 6H), 5.23 (d, *J* = 6.2 Hz, 1H), 4.48-4.43 (m, 1H), 3.22(s, 3H), 1.80-1.67(m, 3H), 1.55-1.52(m, 1H), 1.29-1.26 (m, 5H) 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 170.7, 165.9, 144.4, 141.4, 138.8, 131.8, 131.5, 128.6, 128.3, 127.8, 127.5, 123.5, 120.6, 119.5, 74.1, 70.0, 51.7, 33.6, 32.1, 25.8, 23.0, 14.2; HRMS (DART®): Exact mass calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$ 352.1907, Found 352.1915.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-4-metylpentanoate (3c):**



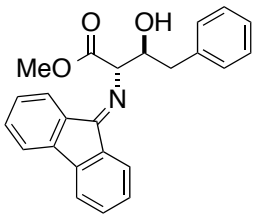
IR (neat): 3090, 3071, 3035, 2361, 2337, 2277, 1960, 1815, 1736, 1617, 1478, 1329, 1035; ^{1}H NMR (C_6D_6, 500MHz) δ: 7.69 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 6.93-6.62 (m, 6H), 5.13 (d, *J* = 6.8 Hz, 1H), 3.99 (dd, *J* = 6.8, *J* = 5.1 Hz, 1H), 2.93 (s, 3H), 1.89-1.82(m, 1H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR C_6D_6, 150 MHz) δ: 171.1 165.6, 144.4, 141.4, 138.8, 131.9, 131.5, 128.6, 128.4, 128.2, 127.5, 123.5, 120.6, 119.5, 78.3, 67.8, 51.7, 30.0, 19.8, 16.5; HRMS (DART®): Exact mass calcd for $C_{20}H_{22}NO_3[M+H]^+$ 324.1594, Found 324.1609.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-5-metylhexanoate (3d):**



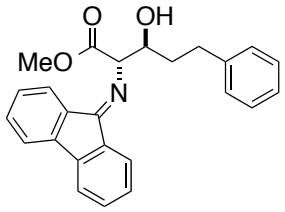
IR (neat): 3234, 2954, 2361, 2337, 2277, 1737, 1617, 1453, 1329; ^{1}H NMR (C_6D_6, 500MHz) δ: 7.81 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 6.94-6.59 (m, 6H), 4.89 (d, *J* = 5.5 Hz, 1H), 4.27-4.25 (m, 1H), 2.84 (s, 3H), 1.85-1.83 (m, 1H), 1.53-1.49(m, 1H), 1.27-1.25 (m, 1H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 172.7, 166.7, 146.6, 144.0, 141.6, 138.9, 132.0, 131.8, 131.5, 128.7,127.5, 123.5, 120.0, 119.4, 70.3, 55.4, 45.3, 31.9, 24.9, 21.9, 14.3; HRMS (DART®): Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ 338.1751, Found 338.1769.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-4-phenylbutanoate (3e)**:



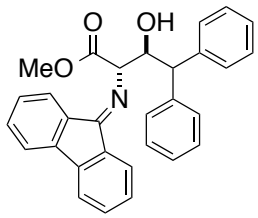
IR (neat): 3235, 3051, 2985, 2362, 2338, 2279, 2253, 1737, 1619, 1454, 1377, 1329, 1265; ^{1}H NMR (C_6D_6, 500MHz) δ: 7.97 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.32-7.27 (m, 2H), 7.22-6.96 (m, 8H), 6.86 (t, *J* = 7.8 Hz, 1H), 5.24 (m, 1H), 4.74-4.68 (m, 1H), 3.22 (s, 3H), 2.95 (dd, *J* = 14.2, *J* = 6.3 Hz, 1H), 2.95 (dd, *J* = 14.2 Hz, *J* = 7.6 Hz, 1H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 170.6, 166.1, 144.3, 141.5, 138.8, 138.7, 132.1, 131.8, 131.6, 130.2, 130.0, 128.7, 128.6, 127.6, 126.5, 123.6, 120.5, 119.5, 75.4, 68.9, 51.8, 40.0; HRMS (DART®): Exact mass calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ 372.1594, Found 372.1591.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-5-phenylpentanoate (3f):**



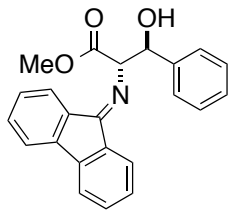
IR (neat): 3089, 3070, 3034, 2362, 2330, 1960, 1815, 1736, 1524, 1478, 1034; ^{1}H NMR (C_6D_6, 500 MHz) δ: 7.87 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.26-6.85 (m, 12H), 5.13 (d, J = 5.8 Hz, 1H), 4.41 (dd, J = 12.3, J = 5.9 Hz, 1H,), 3.25 (s, 3H), 3.05-2.97 (m, 1H), 2.90-2.78 (m, 1H), 2.13-2.03 (m, 2H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 170.6, 166.1, 144.4, 142.4, 141.5, 138.7, 132.1, 131.9, 131.6, 128.9, 128.7, 128.6, 127.4, 126.0, 123.5, 120.6, 119.5, 73.2, 69.8, 51.7, 35.5, 32.4; HRMS (DART®): Exact mass calcd for $C_{25}H_{24}NO_3$ $[M+H]^+$ 386.1751, Found 386.1767.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy -4,4-diphenylbutanoate (3g):**



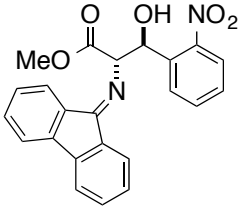
IR (neat): 3090, 3071, 3035, 2362, 2337, 2277, 1815, 1737, 1617, 1478, 1329, 1213, 1162, 1035; ^{1}H NMR (C_6D_6, 600 MHz) δ: 7.99 (d, J = 7.6 Hz, 1H), 7.46-7.43 (m, 3H), 7.30 (d, J = 6.9 Hz, 2H), 7.16-6.88 (m, 11H), 6.74-6.70 (m, 1H), 5.34-5.31 (m, 2H), 4.58 (d, J = 4.1 Hz, 1H), 3.13 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 170.8, 166.1, 144.1, 142.9, 141.5, 140.3, 138.9, 132.0, 131.6, 131.6, 130.4, 129.3, 128.6, 128.6, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 126.6, 126.5, 123.5, 120.3, 119.5, 76.6, 67.9, 53.2, 51.8; HRMS (DART®): Exact mass calcd for $C_{30}H_{26}NO_3$ $[M+H]^+$ 448.1907, Found 448.1891.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-3-phenylpropanoate (3h):**



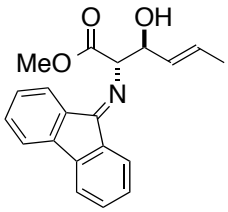
IR (neat): 3234, 2950, 2858, 2361, 2338, 2277, 1738, 1617, 1453, 1329; ^{1}H NMR (C_6D_6, 600 MHz) δ: 7.80 (d, J = 7.4 Hz, 1H), 7.58-7.53 (m, 2H), 7.41-7.20 (m, 4H), 6.93-6.53 (m, 6H), 5.46 (d, J = 4.0 Hz, 1H), 5.14 (d, J = 4.5 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 170.2, 165.9, 144.3, 142.3, 141.4, 141.3, 138.6, 133.8, 132.0, 131.9, 131.5, 131.2, 129.4, 128.7, 128.5, 127.1, 126.8, 123.4, 120.4, 119.4, 67.7, 51.6, 25.7; HRMS (DART®): Exact mass calcd for $C_{23}H_{20}NO_3$ $[M+H]^+$ 358.1438, Found 358.1455.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-3-(2-nitrophenyl) propanoate (3i):** IR (neat): 3089, 3070, 3034, 2361, 2337, 1960, 1815, 1746, 1526, 1478, 1035; ^{1}H NMR



(C_6D_6, 600 MHz) δ: 7.55 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 6.2 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.86-6.39 (m, 8H), 5.54 (d, *J* = 4.5 Hz, 1H), 4.45-4.41 (m, 1H), 3.05 (s, 1H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 171.6, 164.1, 144.1, 142.5, 141.4, 141.2, 138.2, 133.8, 132.0, 131.8, 131.2, 130.2, 129.2, 128.8, 128.2, 126.2, 124.0, 120.2, 119.4, 67.9, 50.1, 26.5; HRMS (DART®): Exact mass calcd for $C_{23}H_{19}N_2O_5$ $[M+H]^+$ 403.1288, Found 403.1282.

***Anti*- Methyl 2-((9*H*-fluoren-9-ylidene)amino)-3-hydroxy-4-hexenoate (3k)**

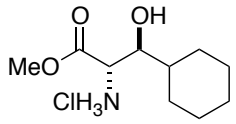


IR (neat): 3234, 2858, 2361, 2338, 2277, 1737, 1617, 1453, 1329; ^{1}H NMR (C_6D_6, 600 MHz) δ: 7.69 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 6.93-6.57 (m, 6H), 6.49-6.47 (m, 1H), 6.37-6.33 (m, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 3.29-3.27 (m, 1H), 2.93 (s, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 150 MHz) δ: 171.1, 165.8, 144.4, 141.4, 138.8, 131.9, 129.2, 128.4, 127.8, 126.0, 124.1, 121.7, 119.3, 74.4, 69.2, 69.0, 66.9, 51.7, 17.6; HRMS (DART®): Exact mass calcd for $C_{20}H_{20}NO_3$$[M+H]^+$ 322.1438, Found 322.1439.

Procedure of removal of the fluorenylidene group:

To a solution of 3a (180 mg, 0.50 mmol) in a mixture of THF (20 mL) and 0.5 M aq. HCl (3.0 mL) was stirred at 0 ^{o}C. After 10min, the solution was diluted with Water (5mL), and extracted with DCM to remove the fluorenone. The aqueous layer was then neutralized with sat. $NaHCO_3$ (pH around 7) and the product extracted with dichloromethane (20mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting oil was then dissolved in 1 M HCl in MeOH and concentrated to afford 5 (95 mg, 0.47 mmol, 94%).

***Anti*- Methyl 2-amino-3-cyclohexyl-3-hydroxypropanoate hydrochloric acid salt (5):** IR(neat) : 3411, 2932, 2578, 2359, 1738, 1538,1209; ^{1}H NMR (D_2O, 600 MHz) δ: 4.23 (d, *J* =

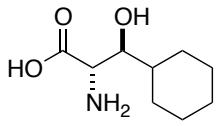


2.7 Hz, 1H), 3.67 (s, 3H), 3.45 (dd, J = 10.0, J = 2.4 Hz, 1H), 1.76-1.74 (m, 1H), 1.63-1.43 (m, 5H), 1.13-0.94 (m, 3H), 0.83-0.76 (m, 2H); ^{13}C NMR (D_2O, 150 MHz, 40 ºC) (standard d: 49.50 MeOH) δ: 169.6, 76.5, 56.4, 54.7, 41.0, 30.4, 29.8, 27.0, 26.5, 26.4; HRMS (DART®): Exact mass calcd for $C_{10}H_{20}NO_3$ [M-Cl]$^+$ 202.1438, Found 202.1434.

Hydrolysis of the ester:[45]

To a solution of 5 (95 mg, 0.47 mmol) in a mixture of acetonitrile (5 mL) and water (5 mL) was added LiOH (2.5 equiv.). The mixture was heated to 60^{o}C overnight. The mixture was then concentrated to dryness. The material was dissolved in MeOH and loaded on a column of DOWEX WX8 conditioned in methanol and then washed with one column volume of methanol. The product was then eluted with one column volume of 7 M ammonia in methanol solution and concentrated under vacuo to afford the desired 6 (64 mg, 0.34 mmol, 73%).

***Anti*- 2-Amino-3-cyclohexyl-3-hydroxypropanoic acid (6)**:[46]



IR (neat): 3430, 2936, 2857, 2600, 2358, 1739, 1700, 1648, 1560, 1452, 1210; ^{1}H NMR (D_2O, 600 MHz) δ: 3.74 (br, 1H), 3.44 (d, J = 8.9 Hz, 1H), 1.75-1.74 (m, 1H), 1.58-1.47 (m, 5H), 1.09-0.79 (m, 5H); ^{13}C NMR (D_2O, 150 MHz) (standard δ: 49.50 MeOH, at 40 ºC) d: 169.3, 76.3, 58.3,40.8, 30.3, 30.2, 27.1, 26.6, 26.5.

For the sequence without purification of the intermediates:

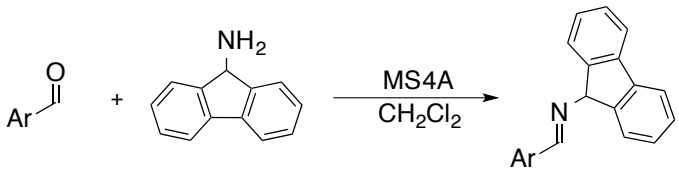
In a well-dried 10 mL reaction tube, the tosyl amide (4.8 mg, 0.016 mmol, 0.040 equiv.) was dissolved in anhydrous THF (2.0 mL) and cooled down to –78 °C. ^{n}Bu$_2$Mg in heptane (0.0080 mmol, 0.020 eq.) was then added dropwise to the mixture, and the mixture was stirred at room temperature. After 30 min stirring, the reaction tube was cooled down again to –78 °C, and a solution of *N*-fluorenylideneglycine methyl ester **1** (100 mg, 0.40 mmol, 1.0 equiv.) and aldehyde **2a** (0.44 mmol, 1.1 equiv.) in anhydrous THF (2.0 mL) were introduced. After 15 hr, the reaction was quenched by addition of sat. NH_4Cl (2.0 mL) and extracted with Et_2O (10 mL x

3). The combined organic layers were then dried over Na_2SO_4 and concentrated under vacuum to afford the crude **3a**. To a solution of the crude **3a** in a mixture of THF (10 mL) and 0.5 M aq. HCl (1.5 mL) was stirred at 0 ^oC. After 10 min, the solution was diluted with water (5.0 mL) and extracted with dichloromethane to remove the 9-fluorenone. The aqueous layer was concentrated under vacuum to afford crude **5**. To a solution of crude **5** in a mixture of acetonitrile (3.0 mL) and water (3.0 mL) was added LiOH (3 equiv.). The mixture was heated to 60 ^oC overnight. The mixture was then concentrated to dryness. The material was dissolved in MeOH and loaded on a column of DOWEX WX8 conditionnedin methanol and then washed with one column volume of methanol. The product was then eluted with one column volume of 7 M ammonia in methanol solution and concentrated under vacuo to afford the desired **6** (28 mg, 0.15 mmol, 74%).

Experimental Data of Chapter 4

KO^{t}Bu and 18-crown-6 were supplied from Wako Pure Chemical Industries, Ltd. 1,1,3,3-Tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Tokyo chemical industry co., Ltd. $KOCH_2CF_3$ was prepared from CF_3CH_2OH and KH (purchased from Kanto chemical co., Inc.). *tert*-Butyl glyoxylate was prepared in the similar way to the literature method.[47] 9*H*-9-Fluorenylamine was prepared based on the reported method.[11]

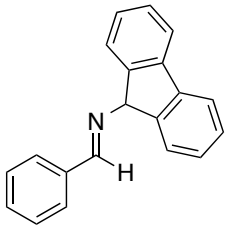
General procedure for preparation of aromatic fluorenyl imines 2:



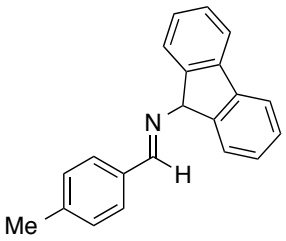
In a 100 mL flask, 9*H*-9-fluorenylamine (1.00 g, 5.52 mmol) and aromatic aldehyde (5.80 mmol) was mixed in anhydrous CH_2Cl_2 (50 mL) in the presence of 5.0 g of well dried MS 4A, and the mixture was stirred overnight at room temperature. The mixture was filtrated through Celite pad, and the remained solid was washed with 20 mL of CH_2Cl_2 further. The filtrate was

concentrated *in vacuo* to remove all volatile materials on a rotary evaporator. The crude mixture obtained was purified by recrystallization (toluene/DCM/hexane). The following compounds were prepared as described above.

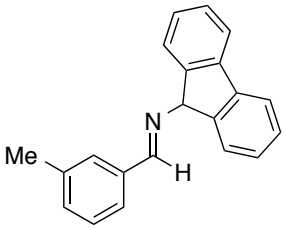
***N*-9-Fluorenylbenzaldehyde imine (1a):** m.p.: 139 ºC (dec.); IR (KBr): 3060, 3030, 2842, 1631, 1578, 1475, 1449, 1386, 1286, 1168, 1043, 845, 761, 742, 729, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.78 (s, 1H), 7.81 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.76 (d, *J* = 7.4Hz, 2H), 7.41–7.28 (m, 9H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 163.4, 144.8, 141.1, 136.1, 131.0, 128.6, 128.5, 128.43, 127.42, 125.3, 120.1, 74.7; HRMS (ESI): Exact mass calcd for $C_{20}H_{16}N$ $[M+H]^+$ 270.12827, Found 270.12712.



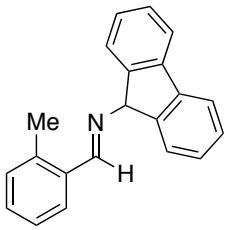
***N*-9-Fluorenyl-*p*-tolaldehyde imine (1b):** m.p.: 123 ºC (dec.); IR (KBr): 3433, 3037, 3019, 2870, 2846, 1610, 1448, 1376, 1271, 1174, 1033, 843, 814, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.75 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.42–7.22 (m, 8H), 5.40 (s, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 163.4, 144.9, 141.3, 141.0, 133.5, 129.3, 128.5, 128.4, 127.4, 125.2, 120.0, 74.7, 21.5; HRMS (ESI): Exact mass calcd for $C_{21}H_{18}N$ $[M+H]^+$ 284.14392, Found 284.14251.



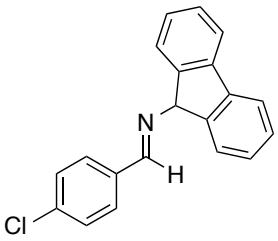
***N*-9-Fluorenyl-*m*-tolaldehyde imine (1c):** m.p.: 133 ºC (dec.); IR (KBr): 3042, 3021, 2915, 2864, 2829, 1634, 1604, 1582, 1450, 1374, 1278, 1166, 1046, 982, 797, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.73 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.66 (s, 1H), 7.54 (d, J =7.5 Hz, 1H), 7.39–7.21 (m, 8H), 5.37 (s, 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 163.8, 144.8, 141.0, 138.4, 135.9, 131.8, 128.6, 128.5, 128.42, 128.41, 126.2, 125.2, 120.1, 74.8, 21.2; HRMS (ESI): Exact mass calcd for $C_{21}H_{18}N$ $[M+H]^+$ 284.14392, Found 284.14466.



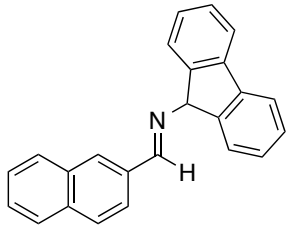
***N*-9-Fluorenyl-*o*-tolaldehyde imine (1d):** m.p.: 126–127 ºC; IR (KBr): 3017, 2963, 2883, 1626, 1598, 1476, 1449, 1395, 1379, 1370, 1285, 1228, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 9.08 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.41–7.17 (m, 9H), 5.40 (s, 1H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 162.0, 144.8, 141.0, 137.6, 134.1, 130.7, 130.5, 128.4, 127.9, 127.4, 126.2, 125.2, 120.1, 75.2, 19.4; HRMS (ESI): Exact mass calcd for $C_{21}H_{18}N$ $[M+H]^+$ 284.14392, Found 284.14366.



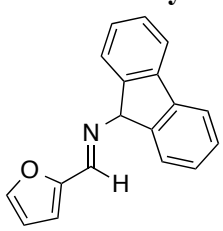
***N*-9-Fluorenyl-*p*-fluorobenzaldehyde imine (1e):** m.p.: 144 ºC (dec.); IR (KBr): 3067, 3023, 2871, 1637, 1594, 1572, 1489, 1449, 1377, 1274, 1082, 1045, 1011, 824, 766, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.72 (s, 1H), 7.76–7.73 (m, 4H), 7.42–7.24 (m, 8H), 5.42 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 161.9, 144.5, 141.1, 137.0, 134.5, 129.7, 128.9, 128.5, 127.5, 125.2, 120.2, 74.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{15}ClN$ $[M+H]^+$ 304.08930, Found 304.08997.



***N*-9-Fluorenyl-2-naphthaldehyde imine (1f):** m.p.: 208 ºC (dec.); IR (KBr): 3046, 3022, 2868, 2832, 1956, 1630, 1596, 1343, 1303, 1274, 1174, 1121, 1042, 975, 958, 828, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.93 (s, 1H), 8.16 (s, 1H), 8.02 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.90–7.82 (m, 3H), 7.77 (d, *J* =7.6 Hz, 2H), 7.53–7.29 (m, 8H), 5.49 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 163.5, 144.8, 141.1, 134.9, 133.7, 133.1, 130.2, 128.7, 128.5, 128.2, 127.9, 127.5, 127.3, 126.5, 125.3, 124.3, 120.1, 74.8; HRMS (ESI): Exact mass calcd for $C_{24}H_{18}N$ $[M+H]^+$ 320.14392, Found 320.14393.

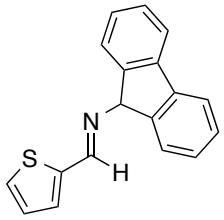


***N*-9-Fluorenyl-2-furaecarbaldehyde imine (1g):** m.p.: 121 ºC (dec.); IR (KBr): 3117, 3078, 3017, 2885, 2853, 1958, 1923, 1639, 1478, 1447, 1393, 1363, 1300, 1272, 1155, 1050, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.51 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.51 (s, 1H), 7.42–7.38 (m, 4H), 7.29 (t, *J* = 7.6 Hz, 2H), 6.83 (d, *J* =3.5 Hz, 1H), 6.48 (m, 1H), 5.42 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.91

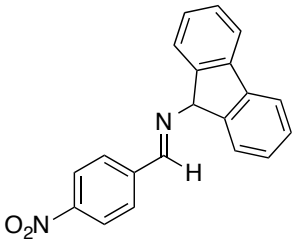


MHz): δ151.4, 151.3, 144.9, 144.4, 141.0, 128.4, 127.3, 125.3, 119.9, 114.5, 111.7, 74.1; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}NO$ $[M+H]^+$ 260.10754, Found 260.10639.

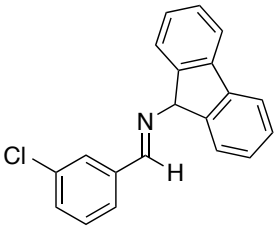
***N*-9-Fluorenyl-2-thiophenecarbaldehyde imine (1h):** m.p.: 139 ºC (dec.); IR (KBr): 3019, 2912, 2848, 1624, 1449, 1430, 1333, 1223, 1045, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.80 (s, 1H), 7.74 (d, J = 7.6Hz, 2H), 7.42–7.26 (m, 8H), 7.09–7.07 (m, 1H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 156.2, 144.6, 142.2, 141.0, 130.9, 129.5, 128.4, 127.4, 127.3, 125.3, 120.1, 74.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}NS$ $[M+H]^+$ 276.08470, Found 276.08497.



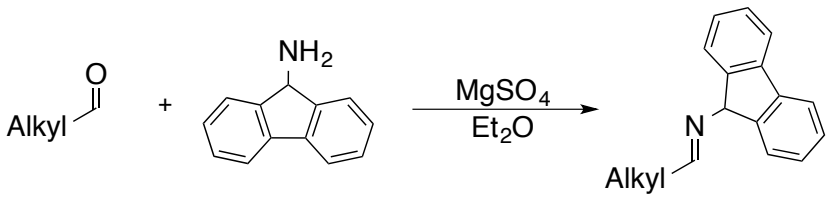
***N*-9-Fluorenyl-4-nitrobenzaldehyde imine (1m):** m.p.: 134 ºC (dec.); IR (KBr): 3437, 3035, 2831, 1639, 1600, 1519, 1449, 1340, 1279, 1048, 860, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.82 (s, 1H), 8.25 (d, J =8.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.77 (d, J =7.6 Hz, 2H), 7.44–7.37 (m, 4H), 7.31 (td, J = 7.4, 0.8 Hz, 2 H), 5.51 (s, 1H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 160.7, 149.2, 144.0, 141.4, 141.1, 129.2, 128.7, 127.6, 125.2, 123.8, 120.3, 74.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{15}N_2O_2$ $[M+H]^+$ 315.11335, Found 315.11186.



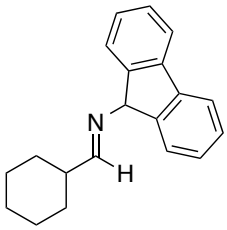
***N*-9-Fluorenyl-*m*-fluorobenzaldehyde imine (2n):** m.p.: 123–124 ºC; IR (KBr): 3069, 3040, 3016, 2865, 1634, 1567, 1475, 1449, 1363, 1272, 1217, 1181, 1098, 1072, 1035, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.71 (s, 1H), 7.85 (s, 1H), 7.76 (d, J = 7.7 Hz, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.43–7.29 (m, 8H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 161.8, 144.4, 141.1, 137.8, 134.9, 130.9, 129.8, 128.6, 128.1, 127.5, 126.8, 125.2, 120.2, 74.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{15}ClN$ $[M+H]^+$ 304.08930, Found 304.08855.



General procedure for preparation of aliphatic fluorenyl imines 2:

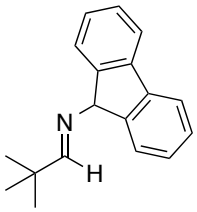


9*H*-9-fluorenylamine (0.700 g, 3.86 mmol) and well-dried anhydrous $MgSO_4$ (1.0 g) were placed in a flame dried 50 mL flask. To the flask was added Et_2O (20 mL) and aliphatic aldehyde (4.63 mmol) via syringe, and the resulting mixture was stirred at room temperature for 30 min. Volatile materials were removed under reduced pressure, and then the residue was dissolved in Et_2O and passed through a short pad of Iatrobeads 6RS-8060 to remove remaining fluoreneamine. The crude mixture was further purified by recrystallization (CH_2Cl_2/hexane). The following compounds were prepared as described above unless otherwise noted. In the case of *N*-9-fluorenylisovaleraldehyde imine (**2j**), after filtration through a short pad of Iatrobeads 6RS-8060, the remaining solid was used for the reaction without further purification after complete removal of volatile solvent and aldehyde. In the case of *N*-9-fluorenylpentanealdehyde imine (**2i**), 0.450 mmol (81.6 mg) of the 9-fluorenylamine and 0.495 mmol (52.7 μL) of pentanal were used. After filtration through a pad of Celite and removal of all volatile materials under reduced pressure, the remaining oily product was used for the reaction immediately without further purification.



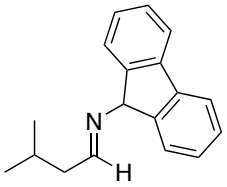
***N*-9-fluorenylcyclohexanecarbaldehyde imine (1i):** m.p.: 72–73 ºC; IR (KBr): 3064, 3040, 3020, 2925, 2852, 1654, 1447, 1374, 1303, 1280, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.04 (d, *J* = 5.3 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.37 (td, *J* = 7.3, 1.1 Hz, 2H), 7.32–7.27 (m, 4H), 5.10 (s, 1H), 2.36–2.32 (m, 1H), 1.91–1.89 (m, 2H), 1.79–1.77 (m, 2H), 1.70–1.67 (m, 1H), 1.41–1.21 (m, 5H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 172.1, 144.9, 141.0, 128.2, 127.3, 124.9, 119.9, 74.4, 43.7, 29.9, 26.0, 25.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}N$ $[M+H]^+$ 276.17522, Found 276.17602.

***N*-9-fluorenylpivalaldehyde imine (1j):** m.p.: 142–143 ºC; IR (KBr): 3064, 3020, 2964, 2928,



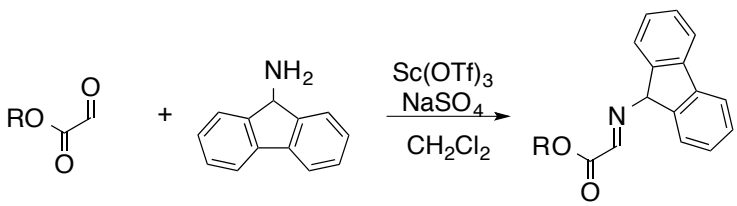
2867, 1957, 1919, 1655, 1475, 1448, 1397, 1373, 1363, 1301, 1102, 1057, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 600.13 MHz): δ 8.07 (s, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.39–7.36 (m, 2H), 7.30–7.28 (m, 4H), 5.11 (s, 1H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 175.5, 145.1, 141.0, 128.2, 127.3, 124.9, 120.0, 74.5, 36.5, 27.2; HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N$ $[M+H]^+$ 250.15957, Found 250.15839.

***N*-9-fluorenylisovaleraldehyde imine (1k):** m.p.: 62–63 ºC; IR (KBr): 3064, 3040, 3018, 2952, 2929, 2865, 1655, 1464, 1448, 1382, 1305, 1154, 1018, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 8.18 (t, J = 5.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.39–7.26 (m, 6H), 5.16 (s, 1H), 2.3 (dd, J = 6.9, 5.3 Hz, 2H), 2.08–1.97 (m, 1H), 1.02 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 167.6, 144.7, 140.9, 128.2, 127.3, 124.9, 119.9, 74.5, 44.9, 26.4, 22.5; HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N$ $[M+H]^+$ 250.15957, Found 250.15856.



***N*-9-fluorenylpentanealdehyde imine (1l):** IR (KBr): 3066, 3041, 3020, 2956, 2928, 2858, 1659, 1450, 1377, 1302, 1100, 1030, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 8.02 (t, J = 5.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.27–7.16 (m, 6H), 5.02 (s, 1H), 2.28 (td, J =7.4 Hz, 2H), 1.49 (tt, J = 15.0, 7.5 Hz, 2H), 1.34–1.28 (m, 2H), 0.84 (t, J =7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 168.2, 144.8, 141.0, 128.3, 127.3, 125.0, 120.0, 74.4, 35.9, 28.3, 22.4, 13.9; HRMS (ESI): Exact mass calcd for $C_{17}H_{18}N$ $[M+H]^+$ 250.15957, Found 250.15925.

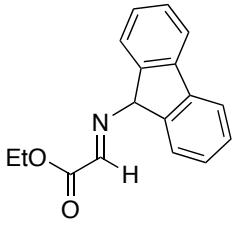
General procedure for preparation of fluorenyl imines 2 derived from glyoxylate:



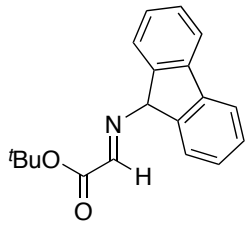
Under Ar atmosphere, 9*H*-9-fluorenylamine (1.00 g, 5.51 mmol), $Sc(OTf)_3$ (203mg 7.5

mol%) and Na_2SO_4 (400 mg) were measured in a well-dried 100 ml 2-neck round bottom flask. To the flask was added CH_2Cl_2 (30 ml) and glyoxylate (5.0 mmol) *via* syringe at room temperature, and the white suspension was immediately generated. The resulting solution was stirred at the same temperature for 1 h. The solution was diluted with another CH_2Cl_2 (30 ml) followed by filtration through filter paper, and the clear filtrate was collected. The solvent was removed under reduced pressure to obtain a crude mixture of the desired product. Recrystallization of the crude material using hexane/Et_2O was conducted to afford the pure desired product.

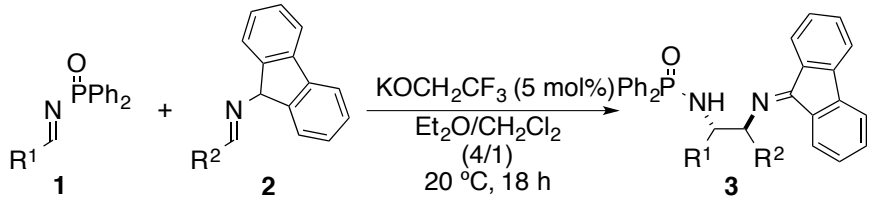
***N*-9-fluorenylethylglyoxylate imine (4a):** m.p.: 65 ºC (dec.). IR (neat) 3464, 2975,1742, 1448,1184,1029: ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.04 (s, 1H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.41–7.37 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 2H), 5.58 (s, 1H), 4.33 (q, *J* = 6.9 Hz, 2H), 1.32 (t, *J* = 6.9 Hz, 3H);^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 163.2, 154.9, 142.71, 141.24, 128.9, 127.6, 125.5, 120.2, 73.4, 62.0, 14.1. HRMS (ESI): Exact mass calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.11756, Found 266.11810.



***N*-9-fluorenyl*tert*-butylglyoxylate imine (14a):** m.p.: 73 ºC (dec.). IR (neat): 3464, 2975, 1742, 1448, 1184, 1029: ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.92 (s, 1H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.42–7.38 (m, 4H), 7.31 (t, *J* = 7.4 Hz, 2H), 5.60 (s, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 162.1, 156.0, 142.9, 141.1, 128.8, 127.5, 125.6, 120.2, 82.8, 73.1, 27.9. HRMS (ESI): Exact mass calcd for $C_{19}H_{19}NO_2$ $[M+H]^+$ 294.14886, Found 294.14940.

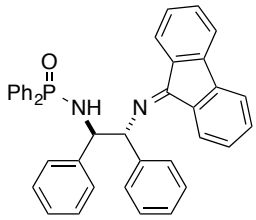


General procedure for catalytic imine–imine coupling reaction:

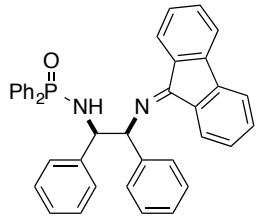


Under Ar atmosphere, fluorenyl substrate **2** (0.30 mmol) and $KOCH_2CF_3$ (0.015 mmol) were placed in a flame-dried test tube with a sleeve stopper. To the test tube was added dry Et_2O (1.2 mL) via syringe, and the resulting mixture was stirred at room temperature for 10 min, and then kept at 20 ºC. DPP–imine **1** (0.36 mmol) in dichloromethane (0.3 mL) was added to the mixture at the same temperature, and the whole was stirred for another 18 hours under Ar. The reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was extracted with dichloromethane (10 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was obtained. The crude product was purified by column chromatography on silica gel (hexane-acetone) to afford the desired adduct **3**. The following compounds were prepared as described above unless otherwise noted. In the cases of using 18-crown-6 or phenol derivatives as additive, additive and base (0.015 mmol) were combined in a flame dried test tube with a sleeve stopper. To the test tube was added dry Et_2O (0.5 mL) via syringe, and the resulting mixture was stirred at room temperature for 10 min. The mixture was transferred to the test tube with suspension of fluorenyl substrate (0.3 mmol) in Et_2O (0.5 mL) via cannula, and the test tube was washed with Et_2O (0.2 mL). After stirring at room temperature for 10 min, DPP–imine (**1**) (0.36 mmol) in dichloromethane (0.3 mL) was added to the mixture at 20 ºC, and the whole was stirred for another 18 hours under Ar. The diastereoselectivity of desired coupling products were determined by ^{1}HNMR spectroscopy by comparing with previously reported ^{1}HNMR spectrum of authentic samples.

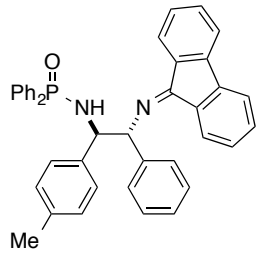
***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1,2-diphenylethyl)-*P*,*P*-diphenylphosphinic -amide (3aa-*anti*):** ^{1}H NMR ($CDCl_3$, 600.17 MHz): 7.87 (d, J = 7.4 Hz, 1H), 7.73–7.70 (m, 2 H), 7.51 (d, J = 7.6 Hz, 2H), 7.44–7.19 (m, 19H), 7.16 (t, J = 7.7 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 5.71 (s, 1H), 5.07 (dd, J = 10.3, 8.0 Hz, 1H), 4.61 (ddd, J = 9.8, 7.5, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ165.2, 144.1 142.9, 141.9, 141.5, 138.4, 134.37, 133.50, 132.55, 132.46, 132.43, 132.36, 131.71, 131.7, 131.6, 131.5, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 127.2, 122.8, 120.4, 119.6, 70.3 (J_{PC} = 7.6 Hz), 62.8; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.7.



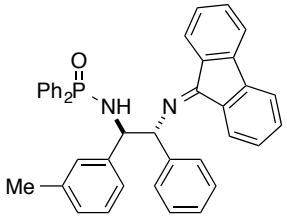
***N*-((1*RS*,2*SR*)-2-((9*H*-fluoren-9-ylidene)amino)-1,2-diphenylethyl)-*P*,*P*-diphenylphosphinic -amide (3aa-*syn*):** m.p.: 160 ºC (dec.); IR (KBr): 3386, 3173, 3059, 3028, 2900, 1645, 1601, 1450, 1438, 1174, 1123, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.97 (d, *J* =7.4 Hz, 1H), 7.75 (dd, *J* =12.1, 7.6 Hz, 4H), 7.54–7.53 (m, 3H), 7.42–7.24 (m, 9H), 7.16–7.05 (m, 9H), 6.97–6.95 (m, 2H), 6.00 (d, *J* =3.8 Hz, 1H), 4.74 (ddd, *J* = 10.5, 10.5, 3.8 Hz, 1H), 4.14 (dd, *J* = 10.9, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.6, 143.8, 141.3, 140.6, 139.9 (J_{PC} =5.6 Hz), 138.7, 133.4, 133.0, 132.5 (J_{PC} = 9.9 Hz), 132.1, 131.8 (J_{PC} = 9.6 Hz), 131.61, 131.56, 131.4, 131.2, 131.1, 128.33, 128.29 (J_{PC} = 88.3 Hz), 128.27, 128.25, 128.19, 128.13, 128.09, 127.3 (J_{PC} = 39.4 Hz), 126.9 (J_{PC} = 21.5 Hz), 122.6, 120.0, 199.3, 70.3 (J_{PC} = 2.8Hz), 61.7; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 24.1; HRMS (ESI): Exact mass calcd for $C_{39}H_{32}N_2OP$ $[M+H]^+$ 575.22523, Found 575.22781.



***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-phenyl-1-(*p*-tolyl)ethyl)-*P*,*P*-diphenyl -phosphinic amide (3ab-*anti*):** m.p.: 145–146 ºC; IR (KBr): 3356, 3058, 2917, 1650, 1600, 1513, 1492, 1449, 1439, 1394, 1304, 1235, 1189, 1121, 1028, 975, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.87 (d, *J* = 7.2 Hz, 1H), 7.75–7.71 (m, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.43–7.19 (m, 17H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 2H), 5.70 (s, 1H), 5.02 (dd, *J* = 10.1, 7.8 Hz, 1H), 4.57 (dd, *J* = 10.2, 7.1 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.8, 143.9, 141.8, 141.3, 139.8, 138.7, 138.5, 138.2, 136.4, 134.3, 133.5, 132.6, 132.3 (J_{PC} = 9.2 Hz), 132.2 (J_{PC} = 9.3 Hz), 131.8, 131.40, 131.36, 131.3, 131.2, 128.4, 128.24, 128.16, 128.07, 128.0, 127.6, 127.5, 127.4, 127.1, 122.6, 120.1, 119.3, 70.2 (J_{PC} = 7.7 Hz), 62.4, 21.0; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ21.5; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2OP$ $[M+H]^+$ 589.24088, Found 589.23939.

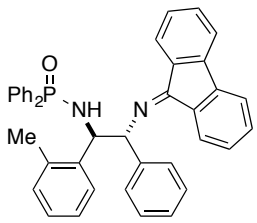


***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-phenyl-1-(*m*-tolyl)ethyl)-*P*,*P*-diphenyl -phosphinic amide (3ac-*anti*):** m.p.: 160 ºC (dec.); IR (KBr): 3346, 3058, 3023, 1656, 1606, 1491, 1449, 1440, 1398, 1306, 1236, 1214, 1157, 1121, 1027, 973 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.81 (d, *J* = 7.4 Hz, 1H), 7.64 (dd, *J* =11.9, 7.6 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.37–7.12 (m, 17H), 7.03–6.93 (m, 4H), 6.82 (d, *J* = 7.4 Hz, 1H), 5.61 (s, 1H), 4.99 (dd, *J* = 10.4,



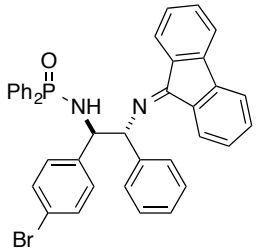
8.1 Hz, 1H), 4.49 (ddd, J = 9.7, 7.7, 2.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.9, 143.9, 142.6, 141.7, 171.2, 138.2, 137.3, 134.1, 133.3, 132.5, 132.3 (J_{PC} = 9.6 Hz), 132.2 (J_{PC} = 9.6 Hz), 131.5, 131.4, 131.3, 131.2, 130.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.94, 127.89, 127.7, 127.6, 127.5, 127.4, 124.3, 122.6, 120.1, 119.4, 70.1 (J_{PC} = 8.0 Hz), 62.6, 21.4; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.9; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2OP$ $[M+H]^+$ 589.24088, Found 589.23885.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-phenyl-1-(*o*-tolyl)ethyl)-*P*,*P*-diphenyl -phosphinic amide (3ad-*anti*):** m.p.: 74–76 ºC; IR (KBr): 3358, 3057, 1648, 1600, 1491, 1449, 1438, 1406, 1303, 1195, 1122, 1073 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.88 (d, J = 7.5 Hz, 1H), 7.73–7.69 (m, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.42–7.19 (m, 17H), 7.09–6.99 (m, 4H), 6.88 (d, J = 7.3 Hz, 1H), 5.70 (s, 1H), 5.02 (dd, J =10.3, 8.0 Hz, 1H), 4.58 (ddd, J =10.1, 7.6, 2.0 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.0, 143.8, 141.7, 141.1, 140.6, 138.0, 133.8, 133.7, 133.0, 132.3, 132.2, 132.2, 132.1, 131.5, 131.4, 131.3, 131.2, 131.1, 129.7, 128.5, 128.3, 128.14, 128.06, 127.8, 127.7, 127.4, 127.3, 127.2, 126.7, 125.8, 122.5, 120.1, 119.3, 68.2 (J_{PC} = 7.1 Hz), 58.2, 19.1; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.9; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2OP$ $[M+H]^+$ 589.24088, Found 589.24321.

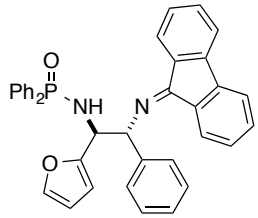


***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-*p*-methoxyphenyl-2-phenylethyl)-*P*,*P* -diphenylphosphinic amide (3ae-*anti*):** m.p.: 98–100 ºC; IR (KBr): 3425, 1648, 1609, 1512, 1449, 1439, 1249, 1179, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.87 (d, J = 7.7 Hz, 1H), 7.75–7.71 (m, 2H), 7.52 (d, J = 7.7 Hz, 2H), 7.44–7.18 (m, 19H), 7.04–7.01 (m, 1H), 6.71–6.69 (m, 2H), 5.68 (s, 1H), 5.05–5.02 (m, 1H), 4.55 (ddd, J = 9.4, 7.0, 2.4 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.9, 158.5, 143.9, 141.7, 141.2, 138.1, 135.0, 134.2, 133.3, 132.3 (J_{PC} = 9.4 Hz), 312.2 (J_{PC} = 9.5 Hz), 131.5, 131.4, 131.3, 131.2, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 122.6, 120.2, 119.4, 113.4, 112.6, 112.2, 70.2 (J_{PC} = 8.6 Hz), 62.0, 55.1; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.5; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2O_2P$ $[M+H]^+$ 605.23579, Found 605.23484.

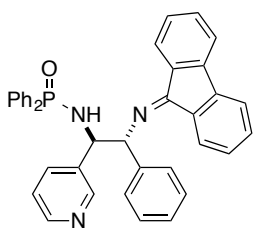
***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-*p*-bromophenyl-2-phenylethyl)-*P*,*P*-diphenylphosphinic amide (3af-*anti*):** ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.84 (d, J = 7.4 Hz, 1H), 7.74–7.71 (m, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.44–7.17 (m, 21H), 7.00 (t, J = 7.5 Hz, 1H), 5.66 (s, 1H), 5.05 (dd, J = 10.2, 8.1 Hz, 1H), 4.57 (ddd, J = 9.8, 7.2, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.3, 143.9, 141.7, 141.2 (J_{PC} = 3.4 Hz), 137.9, 133.9, 133.1, 132.2 (J_{PC} = 9.8 Hz), 132.0 (J_{PC} = 9.4 Hz), 131.6, 131.4, 131.3, 131.0, 128.9, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 122.4, 120.9, 120.2, 119.4, 69.8 (J_{PC} = 7.8 Hz), 62.0; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.7.



***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-(2-furyl)-2-phenylethyl)-*P*,*P*-diphenyl-phosphinic amide (3ag-*anti*):** ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.82–7.76 (m, 3H), 7.53–7.15 (m, 20H), 7.06 (t, J = 7.7 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.16–6.15 (m, 1H), 6.02 (s, 1H), 4.83 (dd, J = 10.4, 7.4 Hz, 1H), 4.65–4.61 (m, 1H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 164.7, 155.0, 143.8, 141.2, 141.1, 141.1, 138.1, 134.0, 133.0, 132.3 (J_{PC} =9.5 Hz), 132.0 (J_{PC} = 8.5Hz), 131.5, 131.4, 131.3, 131.23, 131.17, 130.8, 138.5, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 122.6, 120.1, 119.3, 110.4, 108.2, 66.8 (J_{PC} = 7.0 Hz), 56.9; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.6.

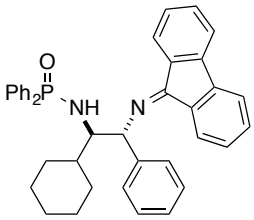


***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-phenyl-1-(3-pyridyl)ethyl)-*P*,*P*-diphenyl-phosphinic amide (3ah-*anti*):** m.p.: 160 ºC (dec.); IR (KBr): 3309, 3056, 1647, 1599, 1450, 1439, 1402, 1308, 1196, 1120, 1028, 974, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$, 399.78 MHz): δ 8.35 (s, 1H), 8.27 (d, J = 4.8 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.66–7.61 (m, 3H), 7.41–7.02 (m, 20H), 6.93 (t, J = 7.7 Hz, 1H), 5.61 (s, 1H), 4.96 (dd, J =10.2, 8.1 Hz, 1H), 4.57 (ddd, J = 9.6, 7.3, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.6, 148.5 (J_{PC} = 26.2 Hz), 143.9, 141.3, 140.8, 138.0, 137.9, 135.1, 133.7, 132.8, 132.1 (J_{PC} = 10.1 Hz), 132.0 (J_{PC} = 10.1 Hz), 131.7, 131.5, 131.0, 128.7, 128.42, 128.37, 128.32, 128.29, 128.24, 128.0, 127.8, 127.5, 127.5, 123.0, 122.5, 120.2, 119.4, 69.7 (J_{PC} = 7.4 Hz), 60.3; ^{31}P NMR ($CDCl_3$, 200.43 Hz): δ 21.9;

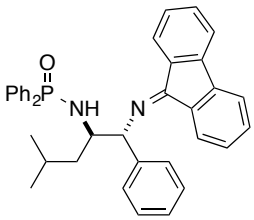


HRMS (ESI): Exact mass calcd for $C_{38}H_{31}N_3OP$ $[M+H]^+$ 576.22047, Found 576.22167.

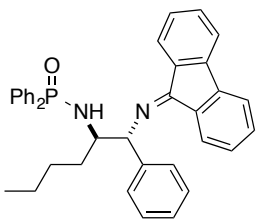
***N*-((1*R*,2*R*)-2-((9*H*-fluoren-9-ylidene)amino)-1-cyclohexyl-2-phenylethyl)-*P*,*P*-diphenyl -phosphinic amide (3ai-*anti*):** ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.94–7.86 (m, 2H), .7.79 (d, *J* = 7.4 Hz, 1H), 7.61–7.57 (m, 2H), 7.46–7.28 (m, 13H), 7.23–7.13 (m, 4H), 7.09 (td, *J* = 7.7, 0.8 Hz, 1H), 5.75 (s, 1H), 4.87 (dd, J = 10.6 Hz, 1H), 3.31–3.28 (m, 1H), 1.93 (m, 1H), 1.77–1.53 (m, 5H), 1.21–1.02 (m, 5H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.0, 144.0, 143.2, 141.3, 138.2, 135.3, 134.4, 132.6 (J_{PC} = 9.4 Hz), 132.1 (J_{PC} = 9.4 Hz), 131.5, 131.4, 131.3, 130.9, 128.5, 128.3, 128.2, 128.0 (J_{PC} = 12.6 Hz), 127.4, 127.3, 127.0, 122.6, 120.3, 119.4, 64.8 (J_{PC} = 8.2 Hz), 64.0, 44.5, 30.3, 29.2, 26.7, 26.4; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 20.4.



***N*-((1*RS*,2*RS*)-1-((9*H*-fluoren-9-ylidene)amino)-4-methyl-1-phenylpentan-2-yl)-*P*,*P* -diphenylphosphinic amide (3aj-*anti*):** ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.87–7.82 (m, 3H), 7.61–7.54 (m, 3H), 7.46–7.19 (m, 16H), 7.12 (t, *J* = 7.6 Hz, 1H), 5.64 (s, 1H), 4.32–4.29 (m, 1H), 3.47–3.41 (m, 1H), 1.81–1.67 (m, 3H), 0.83 (d, *J* = 6.3 Hz, 3H), 0.72 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.7, 143.9, 142.4, 141.2, 138.2, 134.6, 133.7, 132.5 (d, J_{PC} = 9.0 Hz), 132.2 (d, J_{PC} = 9.2 Hz), 131.5, 131.4, 131.3, 131.1, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.7, 127.5, 127.1, 122.6, 120.3, 119.4, 65.9 (d, J_{PC} = 8.1 Hz), 56.9, 45.5, 24.6, 23.1, 22.2; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 23.2.

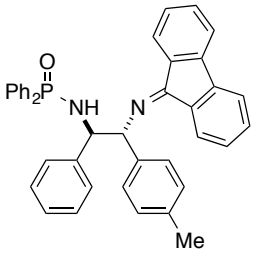


***N*-((1*RS*,2*RS*)-1-((9*H*-fluoren-9-ylidene)amino)-1-phenylhexan-2-yl)-*P*,*P*-diphenyl -phosphinic amide (3ak-*anti*):** m.p.: 79 ºC (dec.); IR (KBr): 3058, 2954, 2927, 2869, 1648, 1601, 1450, 1439, 1401, 1304, 1193, 1122, 1110, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.97–7.91 (m, 3H), 7.68–7.60 (m, 3H), 7.52–7.26 (m, 16H), 7.20–7.18 (m, 1H), 5.80 (s, 1H), 4.42 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.49–3.46 (m, 1H), 2.04–1.88 (m, 2H), 1.51–1.48 (m, 1H), 1.36–1.24 (m, 3H), 0.87 (t, *J* =7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.6, 143.6, 141.1, 138.1, 134.5, 133.7, 132.4 (J_{PC} = 9.2 Hz), 132.2, 131.9 (J_{PC} = 8.9



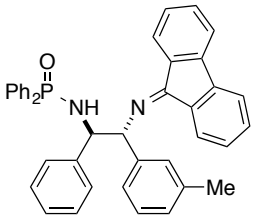
Hz), 131.3 (J_{PC} = 5.2 Hz), 131.14, 131.12, 131.0, 128.3, 128.2, 128.1 (J_{PC} = 5.7 Hz), 128.05, 128.02, 127.6, 127.4, 127.0, 122.5, 120.1, 119.3, 65.6 (J_{PC} = 8.1 Hz), 58.8, 35.8, 28.4, 22.4, 13.9; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 20.4; HRMS (ESI): Exact mass calcd for $C_{37}H_{36}N_2OP$ $[M+H]^+$ 555.25653, Found 555.25620.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-phenyl-2-(*p*-tolyl)ethyl)-*P*,*P*-diphenyl -phosphinic amide (3ba-*anti*):** ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.88 (d, *J* = 7.4 Hz, 1H), 7.74



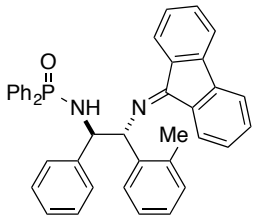
(dd, J = 11.8, 7.6 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.45–7.17 (m, 20 H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 5.65 (s, 1H), 5.16 (t, *J* = 9.5 Hz, 1H), 4.57 (ddd, *J* = 9.9, 7.7, 2.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.9, 143.8, 142.9, 141.0, 138.7, 138.1, 137.0, 134.0, 133.1, 132.3 (J_{PC} = 9.3 Hz), 132.1 (J_{PC} = 9.4 Hz), 131.6, 131.4, 131.3, 131.1, 129.2, 128.3 (J_{PC} = 7.9 Hz), 128.2 (J_{PC} = 6.4 Hz), 128.1, 128.00, 127.95, 127.5, 127.4, 127.2, 127.0, 122.5, 120.1, 119.4, 69.9 (J_{PC} = 8.1 Hz), 62.5, 21.2; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.9.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-phenyl-2-(*m*-tolyl)ethyl)-*P*,*P*-diphenyl -phosphinic amide (3ca-*anti*):** m.p.: 164–166 ºC; IR (KBr): 3345, 3058, 1649, 1606, 1450,



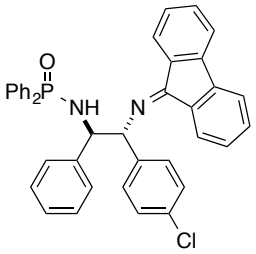
1439, 1401, 1304, 1236, 1200, 1120, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.88–7.86 (m, 1H), 7.77–7.74 (m, 2H), 7.46–7.16 (m, 22H), 7.09–7.06 (m, 1H), 7.01–6.98 (m, 1H), 5.67 (s, 1H), 5.16–5.12 (m, 1H), 4.60–4.56 (m, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 164.8, 143.8, 142.8, 141.7, 141.2, 138.1, 134.2, 133.4, 132.3 (J_{PC} = 9.5 Hz), 132.1 (J_{PC} = 9.5 Hz), 131.4, 131.3, 131.2, 131.1, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.4, 127.1, 126.9, 124.6, 122.5, 120.1, 119.3, 70.1 (J_{PC} = 7.5 Hz), 62.6, 21.5; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.5; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2OP$ $[M+H]^+$ 589.24088, Found 589.24140.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-phenyl-2-(*o*-tolyl)ethyl)-*P*,*P*-diphenylphos -phinic amide (3da-*anti*):** m.p.: 185 ºC (dec.); IR (KBr): 3355, 3058, 1648, 1603, 1450, 1439, 1402, 1304, 1244, 1199, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.89 (d, *J* = 7.4 Hz, 1H), 7.80–7.77 (m, 2H), 7.49–7.08 (m, 23H), 6.97 (t, *J* =7.8 Hz, 1H), 5.68 (s, 1H), 5.37 (dd, *J* = 10.8, 8.5 Hz, 1H), 4.50 (dd, *J* = 10.8, 6.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ



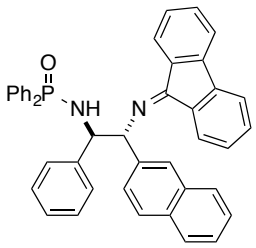
164.9, 143.9, 143.5, 141.2, 140.2, 138.1, 134.6, 132.4 (J_{PC} = 9.8 Hz), 132.1 (J_{PC} = 9.7 Hz), 131.5, 131.4, 131.3, 131.2, 131.0, 128.4, 128.3, 128.22, 128.16, 128.08, 127.9, 127.8, 127.5, 127.0, 126.7, 126.5, 126.0, 122.5, 120.2, 119.4, 67.1 (J_{PC} = 8.3 Hz), 59.1, 19.3; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.2; HRMS (ESI): Exact mass calcd for $C_{40}H_{34}N_2OP$ $[M+H]^+$ 589.24088, Found 589.23918.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(4-chlorophenyl)-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (3ea-*anti*):** ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.99 (d, *J* = 7.4 Hz, 1H), 7.88–7.84 (m, 2H), 7.58–7.22 (m, 23H), 7.11 (t, *J* =7.7 Hz, 1H), 5.88 (s, 1H), 5.10 (dd, *J* = 10.4, 8.2 Hz, 1H), 4.77 (ddd, *J* = 10.0, 7.5, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 165.0, 143.7, 142.0, 131.0, 139.7, 137.8, 133.6, 133.0, 132.5, 131.9, 131.8, 131.4, 131.3, 130.8, 128.8, 128.5, 128.19, 128.17, 128.1, 128.0, 127.9, 127.8, 127.2, 127.03, 126.97, 122.3, 120.1, 119.3, 69.1 (J_{PC} = 7.5 Hz), 62.1; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 24.4.



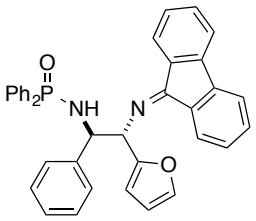
***N*-((1*RS*,2*SR*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(4-chlorophenyl)-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (3ea-*syn*):** m.p.: 185 ºC (dec.); IR (KBr): 3176, 3059, 1644, 1606, 1489, 1449, 1438, 1178, 1124, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.86 (d, *J* = 7.4 Hz, 1h), 7.64 (dd, *J* = 12.1, 7.6 Hz, 4H), 7.45–6.93 (m, 20H), 6.81 (d, *J* = 8.2 Hz, 2H), 5.92 (d, *J* = 3.8 Hz, 1H), 4.61 (td, *J* = 10.7, 3.6 Hz, 1H), 4.06 (dd, *J* = 11.0, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.9, 143.8, 141.3, 139.4 (J_{PC} = 5.6 Hz), 138.5, 133.3, 132.6, 132.4, 132.4, 131.6, 131.6, 131.5, 131.3, 130.9, 128.7, 128.6, 128.32, 128.27, 128.23, 128.20, 128.15, 128.1, 128.0, 127.3, 127.0, 122.6, 120.1, 119.4, 69.4, 61.5; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 24.5; HRMS (ESI): Exact mass calcd for $C_{39}H_{31}ClN_2OP$ $[M+H]^+$ 609.18625, Found 609.18381.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(2-naphthyl)-1-phenylethyl)-*P*,*P*-diphenyl-phosphinic amide (3fa-*anti*):** m.p.: 114 ºC (dec.); IR (KBr): 3366, 3057, 1648, 1602, 1450,



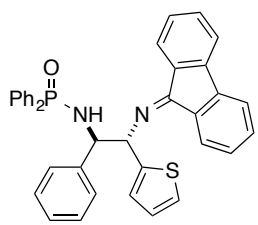
1439, 1400, 1303, 1197, 1122, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.94 (d, *J* = 7.4 Hz, 1H), 7.89–7.60 (m, 4H), 7.68–7.64 (m, 2H), 7.56–7.10 (m, 20H), 6.97–6.92 (m, 3H), 5.86 (s, 1H), 5.15 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.69 (ddd, *J* = 9.6, 7.4, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.3, 143.9, 142.8, 141.3, 139.1, 138.1, 134.0, 133.4, 133.2, 132.9, 132.14, 132.12, 132.07, 131.5, 131.4, 131.1, 128.4 (J_{PC} = 7.2 Hz), 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 127.2, 127.0, 126.3, 126.0, 125.7, 122.7, 120.2, 119.4, 70.2 (J_{PC} = 8.0 Hz), 62.4; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 21.9; HRMS (ESI): Exact mass calcd for $C_{43}H_{34}N_2OP$ $[M+H]^+$ 625.24088, Found 625.24051.

***N*-((1*RS*,2*SR*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(furan-2-yl)-1-phenylethyl)-*P*,*P*-diphenyl , -phosphinic amide (3ga-*anti*):** m.p.: 96 ºC (dec.); IR (KBr): 3365, 3058, 1713, 1647, 1600,



1450, 1439, 1406, 1305, 1194, 1123, 1071, 1007, 917 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ7.71–7.66 (m, 3H), 7.47 (dd, *J* = 12.1, 7.6 Hz, 2H), 7.49–6.96 (m, 18H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.10 (d, *J* = 3.2 Hz, 1H), 5.62 (s, 1H), 5.13 (dd, *J* = 10.2, 8.5 Hz, 1H), 4.79–4.75 (m, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 166.2, 152.5, 143.6, 142.3, 141.7, 141.1, 137.8, 133.8, 132.9, 132.6, 132.2, 132.12, 132.10, 132.06, 131.8, 131.6, 131.4, 131.3, 131.0, 128.22, 128.15, 128.1, 127.94, 127.88, 127.3, 127.0, 126.9, 122.5, 120.1, 199.3, 110.4, 107.9, 65.2 (d, J_{PC} = 6.9 Hz), 59.0; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 22.3; HRMS (ESI): Exact mass calcd for $C_{37}H_{30}N_2O_2P$ $[M+H]^+$ 565.20449, Found 565.20663.

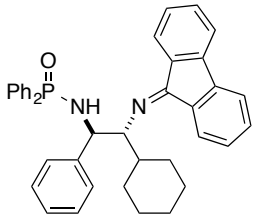
***N*-((1*RS*,2*SR*)-2-((9*H*-fluoren-9-ylidene)amino)-1-phenyl-2-(thiophen-2-yl)ethyl)-*P*,*P* -diphenylphosphinic amide (3ha-*anti*):** m.p.: 117–118 ºC; IR (KBr): 3348, 3059, 1648, 1599,



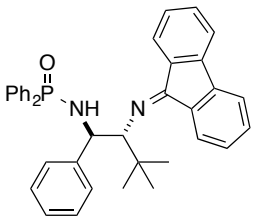
1450, 1439, 1397, 1303, 1193, 1122, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.72–7.68 (m, 2H), 7.46–6.94 (m, 23H), 5.93 (s, 1H), 4.94 (dd, *J* = 10.3, 8.1 Hz, 1H), 4.59 (ddd, *J* = 10.2, 7.4, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 143.9, 143.8, 141.9, 141.2, 138.0, 133.7, 132.9, 132.7, 132.3, 132.2, 132.1, 131.8, 131.6, 131.5, 131.4, 131.4, 131.2, 128.4, 128.3, 128.24, 128.19, 128.15, 128.1, 127.9, 127.5, 127.3, 127.1, 126.6, 124.7, 124.9, 124.3, 122.7, 120.2, 119.4, 66.3 (J_{PC} = 6.9 Hz), 62.7; ^{31}P NMR

($CDCl_3$, 242.95 Hz): δ 22.3; HRMS (ESI): Exact mass calcd for $C_{37}H_{30}N_2OPS$ $[M+H]^+$ 581.18165, Found 581.17962.

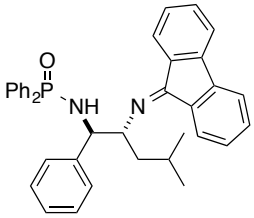
***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-cyclohexyl-1-phenylethyl)-*P*,*P*-diphenyl -phosphinic amide (3ia-*anti*):** m.p.: 82–84 ºC; IR (KBr): 3379, 3058, 2926, 2850, 1648, 1609, 1449, 1439, 1400, 1302, 1205, 1123, 1069 cm^{-1}; ^1H NMR (CDCl3, 600.17 MHz): δ 7.94–7.91 (m, 2H), 7.76–7.72 (m, 3H), 7.51–7.21 (m, 12H), 7.05–6.92 (m, 6H), 5.10 (dd, *J* = 9.1, 8.6 Hz, 1H), 4.75 (dd, *J* = 10.7, 9.4 Hz, 1H), 4.43 (d, *J* = 8.6 Hz, 1H), 2.28–2.19 (m, 2H), 1.84–0.84 (m, 9H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 162.6, 143.8, 143.7, 140.7, 138.2, 134.2, 133.3, 133.1, 132.4 (J_{PC} = 9.6 Hz), 132.2, 132.0 (J_{PC} = 9.3 Hz), 131.6, 131.4, 130.8 (J_{PC} = 13.8 Hz), 128.4 (J_{PC} = 12.6 Hz), 128.1 (J_{PC} = 8.7 Hz), 128.0, 127.8, 127.5, 126.6, 126.5, 126.5, 122.4, 120.0, 119.1, 71.1 (J_{PC} = 3.7 Hz), 56.2, 40.0, 30.5, 29.8, 26.4, 26.2, 26.1; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 23.0; HRMS (ESI): Exact mass calcd for $C_{39}H_{38}N_2OP$ $[M+H]^+$ 581.27218, Found 581.27127.



***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-3,3-dimethyl-1-phenylbutyl)-*P*,*P*-diphenyl -phosphinic amide (3ja-*anti*):** m.p.: 82–84 ºC; IR (KBr): 3367, 3058, 2960, 2866, 1656, 1449, 1439, 1399, 1201, 1122, 1110, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 495.13 MHz): δ 7.71 (dd, *J* = 7.5, 5.4 Hz, 2H), 7.64–7.21 (m, 17H), 7.15 (t, *J* = 7.5 Hz, 2H), 7.07–7.06 (m, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 4.68–4.59 (m, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 170.2, 146.7, 145.2, 140.7, 140.4, 139.6, 133.4, 132.8, 132.3, 132.1 (d, J_{PC} = 9.6 Hz), 131.9 (J_{PC} = 9.6 Hz), 131.8, 131.3 (d, J_{PC} = 14.4 Hz), 129.2, 128.5, 128.1, 128.0, 127.9 (J_{PC} = 13.7 Hz), 127.0, 126.9, 126.8, 126.6, 125.9, 119.7 (J_{PC} = 35.2 Hz), 79.1 (J_{PC} = 8.8 Hz), 63.4, 36.7, 26.5; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 22.6; HRMS (ESI): Exact mass calcd for $C_{37}H_{36}N_2OP$ $[M+H]^+$ 555.25658, Found 555.25746.

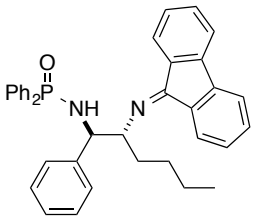


***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-4-methyl-1-phenylpentyl)-*P*,*P*-diphenylphos -phinic amide (3ka-*anti*):** m.p.: 181 ºC (dec.); IR (KBr): 3259, 3060, 2954, 1656, 1606, 1450,



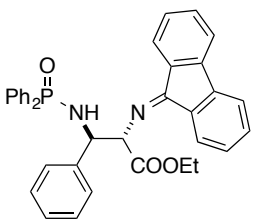
1439, 1403, 1302, 1123, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.95–7.92 (m, 2H), 7.74–7.71 (m, 3H), 7.58–7.24 (m, 12H), 7.15–7.04 (m, 6H), 5.20 (t, *J* =9.3 Hz, 1H), 4.77–4.75 (m, 1H), 4.55 (t, *J* = 10.2 Hz, 1H), 2.18–2.13 (m, 1H), 1.92–1.86 (m, 1H), 1.60–1.55 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.5, 3H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 161.8, 144.1, 143.8, 140.8, 138.3, 134.2, 133.4, 133.1, 132.5 (J_{PC} = 8.2 Hz), 132.2, 131.9 (J_{PC} = 8.2 Hz), 131.61, 131.57, 131.4, 131.1, 130.9, 128.5 (J_{PC} = 11.4 Hz), 128.2, 128.1, 128.0, 127.8, 126.7, 126.6, 122.3, 120.2, 119.2, 64.0 (J_{PC} = 4.4 Hz), 57.1, 41.4, 24.9, 21.9; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 23.2; HRMS (ESI): Exact mass calcd for $C_{37}H_{36}N_2OP$ $[M+H]^+$ 555.25658, Found 555.25661.

***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-phenylhexyl)-*P*,*P*-diphenylphosphinic amide (3la-*anti*):** m.p.: 61–63 ºC (dec.); IR (KBr): 3347, 3058, 2954, 2928, 2858, 1647, 1602,



1449, 1439, 1402, 1304, 1199, 1122, 1110, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 600.17 MHz): δ 7.97–7.93 (m, 2H), 7.79–7.73 (m, 3H), 7.52–7.02 (m, 18H), 5.24 (dd, *J* = 9.5, 8.4 Hz, 1H), 4.59–4.53 (m, 2H), 2.31–2.27 (m, 1H), 1.76–1.71 (m, 1H), 1.56–1.35 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 162.1, 144.0, 143.7, 140.7, 138.2, 134.2, 133.1, 132.5 (J_{PC} = 9.7 Hz), 132.1, 131.9 (J_{PC} = 9.3 Hz), 131.6, 131.5, 131.4, 131.1, 130.9, 128.8, 128.4 (J_{PC} = 12.6 Hz), 128.1 (J_{PC} = 11.5 Hz), 128.0, 127.8, 127.7, 126.7, 126.6 (J_{PC} = 3.7 Hz), 122.3, 120.2, 119.2, 66.5 (J_{PC} = 3.8 Hz), 57.2, 33.0, 28.8, 22.7, 14.1; ^{31}P NMR ($CDCl_3$, 200.43 Hz): δ 23.1; HRMS (ESI): Exact mass calcd for $C_{37}H_{36}N_2OP$ $[M+H]^+$ 555.25658, Found 555.25764.

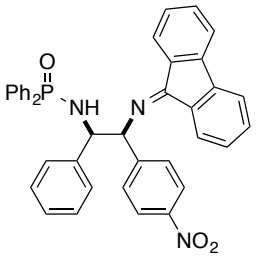
(2*SR*,3*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-3-((diphenylphosphoryl)amino)-3-phenyl -propanic acid ethyl ester (5aa-*anti*): m.p.: 125 ºC; IR (neat.): 3339, 1729, 1660



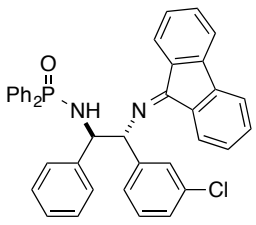
1275,1201,1102, 919; ^1H NMR ($CDCl_3$, 495.13 MHz): δ. 7.84-7.78 (m, 4H), 7.55 (d, *J* = 5.9 Hz, 1H), 7.49-7.45 (m, 2H), 7.42-7.25 (m, 12H), 7.20-7.18 (m, *J* = 5.9 Hz, 2H), 7.15-7.11 (m, 2H), 5.25-5.21 (m, 2H), 5.04-5.00 (m, 1H), 4.33-4.29 (m, 1H), 4.26-4.20 (m, 1H), 1.20 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ.169.6, 166.9, 144.0, 142.0, 141.3, 138.0, 134.7, 133.5, 133.2, 132.6, 132.5, 132.1, 132.0, 131.8, 131.6, 131.5, 129.1, 128.4,

128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.2, 127.2, 126.8, 126.5, 124.3, 123.0, 120.5, 120.3, 119.4, 69.8 (J_{PC} = 4.9), 61.9, 57.8, 14.1; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ. 22.9; HRMS (ESI): Exact mass calcd for $C_{36}H_{32}N_2O_3P$ $[M+H]^+$ 571.21451, Found 571.21436.

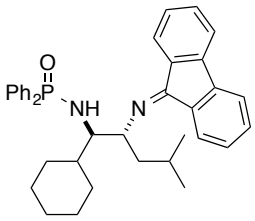
***N*-((1*RS*,2*SR*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(4-nitrophenyl)-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (3ea-*syn*):** m.p.: 125 ºC (dec.); IR (KBr): 3367, 3059, 1648, 1601, 1520, 1450, 1438, 1344, 1190, 1123, 1108, 1069, 1029, 927 cm^{-1}; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.97–7.91 (m, 3H), 7.73 (m, 4H), 7.60–7.07 (m, 20H), 6.20 (s, 1H), 4.78–4.72 (m, 1H), 4.20–4.16 (m, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 166.6, 148.3, 146.6, 143.9, 141.3, 138.7 (J_{PC} = 5.7 Hz), 138.2, 133.1, 132.4 (J_{PC} = 9.6 Hz), 131.80, 131.76, 131.7, 131.5, 131.5, 131.4, 130.7, 128.4, 128.3, 128.2, 128.1, 127.7, 127.4, 127.3, 123.2, 122.6, 120.2, 119.4, 69.3, 61.4; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 28.9; HRMS (ESI): Exact mass calcd for $C_{39}H_{31}N_3O_3P$ $[M+H]^+$ 620.21030, Found 620.20837.



***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-2-(3-chlorophenyl)-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (3na-*anti*):** m.p.: 175 ºC (dec.); IR (KBr): 3342, 3059, 1648, 1595, 1450, 1439, 1400, 1200, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.87 (d, *J* =7.4 Hz, 1H), 7.74 (dd, *J* = 11.3, 7.6 Hz, 2H), 7.52 (t, *J* = 6.8 Hz, 1H), 7.47–7.10 (m, 22H), 7.04 (t, *J* = 7.6 Hz, 1H), 5.69 (s, 1H), 5.02 (dd, *J* = 10.6, 7.7 Hz, 1H), 4.56–4.53 (m, 1H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 165.4, 144.0, 143.7, 142.4, 141.3, 137.9, 134.5, 132.23, 132.17, 132.1, 131.7, 131.5, 131.4, 131.1, 129.8, 128.4 (J_{PC} = 9.1 Hz), 128.3 (J_{PC} = 5.9 Hz), 128.2, 128.1, 128.0, 127.7, 127.1, 125.8, 122.7, 120.3, 119.5, 69.4 (J_{PC} = 7.3 Hz), 62.4; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 22.0; HRMS (ESI): Exact mass calcd for $C_{39}H_{31}ClN_2OP$ $[M+H]^+$ 609.18625, Found 609.18349.



***N*-((1*RS*,2*RS*)-2-((9*H*-fluoren-9-ylidene)amino)-1-cyclohexyl-4-methylpentyl)-*P*,*P*-diphenyl-phosphinic amide (3ki-*anti*):** m.p.: 76–79 ºC; IR (KBr): 3348, 3058, 2926, 2850, 1716, 1647, 1606, 1448, 1404, 1302, 1203 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.00–7.93 (m, 4H),

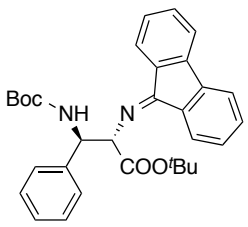


7.90 (d. J = 7.8 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.52–7.25 (m, 10H), 4.99 (t, J = 10.5 Hz, 1H), 4.82 (dd, J = 10.3, 4.5 Hz, 1H), 3.37–3.33 (m, 1H), 2.00 (ddd, J = 14.1, 10.4, 3.8 Hz, 1H), 1.74–1.50 (m, 7H), 1.20–0.81 (m, 12H); ^{13}C NMR ($CDCl_3$ 150.91 MHz): δ 160.2, 143.9, 140.7, 138.5, 134.8, 134.4, 133.9, 133.6, 132.14, 132.08, 132.0, 131.6, 131.4, 131.3, 131.2, 130.8, 128.3, 128.2, 128.1, 126.7, 122.2, 120.4, 119.3, 58.1 (J_{PC} = 4.6 Hz), 56.4, 44.4, 41.3, 30.5, 28.9, 26.5, 26.6, 23.7, 21.2; ^{31}P NMR ($CDCl_3$, 242.95 Hz): δ 22.3; HRMS (ESI): Exact mass calcd for $C_{37}H_{42}N_2OP$ $[M+H]^+$ 561.30348, Found 561.30184.

General procedure for catalytic asymmetric imine-imine coupling reactions of fluorenyl glyoxylate imine with Boc-imines:

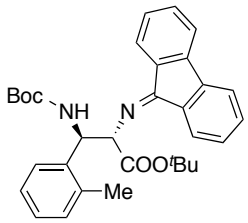
Under Ar atmosphere, the fluorenyl ^{t}Bu-glyoxylate imine **2o** (58.6 mg, 0.200 mmol) was dissolved in anhydrous toluene (2 mL) in a well-dried 10 mL reaction tube, and the reaction tube was cooled at -60°C. A chiral guanidine (8.0 mg, 0.020 mmol, 10 mol%) in toluene (1.0 mL) was then added dropwise, and the mixture was stirred at -60 ºC. To the mixture was added a solution Boc-imine (49.2 mg, 0.240 mmol, 1.2 eq.) in toluene (1.0 mL), and the whole was stirred at –60 ºC for 18 h. The reaction was quenched by sat. NH_4Cl solution (1.0 mL), and extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. Finally the crude material was purified on column chromatography using silica gel using a mixed solvent (hexane/Et_2O) to give the corresponding coupling product **6**.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-phenyl-propionic acid *tert*-butyl ester (15aa): m.p.: 181 -182ºC; IR (neat): 3322, 2974, 2885, 2542, 2256, 1926, 1759, 1660, 1451, 1381, 1328, 1274, 1090, 1050, 881, 803, 686; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.88 (d, J = 7.4 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.50–7.27 (m, 7H), 7.24-7.20 (m, 2H), 7.18-7.11 (m, 2H), 6.36 (d, J = 7.9 Hz, 1H), 5.63 (d, J = 7.9 Hz, 1H), 5.19 (s, 1H), 1.37 (s, 9H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 168.3, 166. 8, 155.2, 144.0, 141.1, 138.0, 131.7, 131.7, 131.4, 128.6, 128.4, 128.2, 127.8, 127.1, 127.0, 126.5, 123.1, 120.4, 119.3, 82.7,

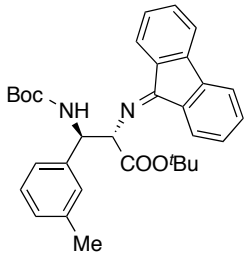


79.3, 68.9, 56.7, 28.37, 27.89; HRMS (ESI): Exact mass calcd for $C_{31}H_{34}N_2O_4$ $[M+H]^+$ 499.25968, Found 499.25780; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 5.5 min. 28.8 min. (major), 7.2 min. 11.0 min. (minor). $[\alpha]_D^{24}$ = –139 (c 0.200, CH_2Cl_2).

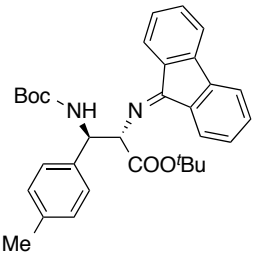
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-*o*-tolylpropionic acid *tert*-butyl ester (15ab): m.p.: 198-199 ºC; IR (neat): 3345, 2974, 2927, 2885, 2360, 2339, 1925, 1381, 1332, 1275, 1090, 1050; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.90 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H),7.55-7.53 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41-7.24 (m, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.07-7.02 (m, 2H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.89 (d, *J* = 8.4 Hz, 1H), 5.00 (s, 1H), 2.54 (s, 3H), 1.50 (s, 9H), 1.42 (s, 1H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.4, 166.7, 155.2, 151.6, 144.0, 141.2, 138.6, 138.1, 136.7, 131.7, 131.3, 128.9, 128.3, 127.8, 126.9, 126.5, 123.1, 120.4, 119.3, 82.7, 79.3, 69.0, 56.5, 28.4, 27.9, 20.9; HRMS (ESI): Exact mass calcd for $C_{32}H_{37}N_2O_4$ $[M+H]^+$ 513.27533, Found 513.27660; HPLC Column OD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 17.1 min. 44.1 min. (major), 20.6 min. 30.4 min. (minor); $[a]_D^{24}$ = –120.2 (c 0.200, CH_2Cl_2).



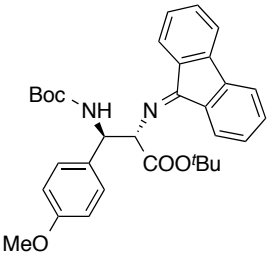
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-*m*-tolylpropionic acid *tert*-butyl ester (15ac): m.p.: 193-194 ºC; IR (neat): 3338, 2974, 2927, 2885, 2361, 2339, 1926, 1453, 1381, 1331, 1275, 1090, 1050, 881, 804, 442; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.49-7.46 (m, 2H), 7.38–7.33 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.21-7.14 (br, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 5.58 (d, *J* = 7.8 Hz, 1H), 5.15 (s, 1H), 2.24 (br, 3H) 1.47 (*s*, 9H), 1.43 (*s*, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.4, 166.7, 155.3, 144.0, 141.2, 141.1, 138.1, 137.7, 131.7, 131.4, 128.3, 128.1, 127.9, 127.8, 126.5, 124.0, 123.1, 120.4, 119.3, 82.7, 79.3, 69.0, 56.8, 28.4, 27.9, 21.4; HRMS (ESI): Exact mass calcd for $C_{32}H_{37}N_2O_4$ $[M+H]^+$ 513.27533, Found 513.27674; HPLC Column OD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 15.0 min. 20.9 min. (major), 8.4 min. 12.7 min. (minor); $[a]_D^{24}$ = –83.4 (c 0.200, CH_2Cl_2).



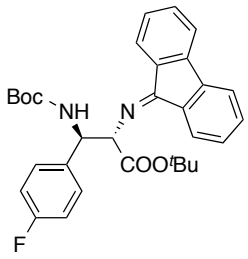
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-*p*-tolylpropionic acid *tert*-butyl ester (15ad): m.p.: 192-193 ºC; IR (neat): 3348, 2974, 2885, 2498, 2360, 2339, 1926, 1453, 1380, 1332, 1275, 1090, 1049, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.50–7.46 (m, 2H), 7.39-7.34 (m, 2H), 7.30-7.23 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.32 (brs, 1H), 5.56 (brs, 1H), 5.16 (s, 1H), 2.21 (s, 3H), 1.46 (s, 9H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.4, 166.8, 155.2, 144.0, 141.2, 138.1, 136.7, 131.7, 131.7, 131.4, 128.9, 128.4, 128.3, 127.8, 126.9, 126.6, 123.1, 120.4, 119.3, 82.7, 79.3, 69.0, 56.5, 28.4, 27.9, 20.9; HRMS (ESI): Exact mass calcd for $C_{32}H_{37}N_2O_4$ $[M+H]^+$ 513.27533, Found 513.27448; HPLC Column AD=H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 5.1 min. 27.8 min. (major), 7.1 min. 8.9 min. (minor) ; $[a]_D^{24}$ = –120 (c 0.200, CH_2Cl_2).



(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-*(*4-methoxy-phenyl) -propionic acid *tert*-butyl ester (15ae): m.p.: 198-199 ºC; IR (neat): 3358, 2974, 2896, 2592, 2360, 2339, 1714, 1382, 1275, 1090, 1049, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50–7.46 (m, 2H), 7.39-7.29 (m, 5H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.75-6.74 (m, 2H), 6.31 (d, *J* = 6.6 Hz, 1H), 5.57 (d, *J* = 7.2 Hz, 1H), 5.15 (s, 1H), 3.69 (s, 3H) 1.47 (*s*, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.3, 166.7, 158.6, 155.2, 144.0, 141.2, 138.1, 131.7, 131.4, 128.3, 128.1, 127.9, 126.5, 123.1, 120.4, 119.3, 113.6, 82.7, 79.2, 69.0, 56.2, 55.1, 28.4, 27.9; HRMS (ESI): Exact mass calcd for $C_{32}H_{37}N_2O_5$ $[M+H]^+$ 529.27025, Found 529.26970; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 5.3min. 48.0 min. (major), 8.9 min. 17.4 min. (minor) ; $[a]_D^{24}$ = –36.5 (c 0.200, CH_2Cl_2).

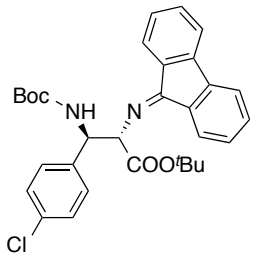


(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(4-fluoro-phenyl) propionic acid *tert*-butyl ester (15af): m.p.: 155-156 ºC; IR (neat): 3346, 2974, 2927, 2885, 2360, 2339, 1926, 1453, 1380, 1331, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz,



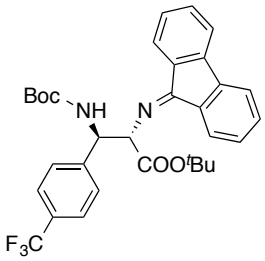
1H), 7.40-7.35 (m, 4H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.90 (t, *J* = 9.0 Hz, 2H), 6.32 (brs, 1H), 5.58 (brs, 1H), 5.14 (s, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.2, 167.0, 155.2, 144.1, 141.2, 138.0, 131.9, 131.7, 131.5, 128.7, 128.6, 128.4, 127.9, 126.5, 123.0, 120.5, 119.4, 115.1, 114.9, 82.9, 79.5, 68.9, 56.2, 28.4, 27.9; HRMS (ESI): Exact mass calcd for $C_{31}H_{34}F_1N_2O_4$ $[M+H]^+$ 517.25026, Found 517.25084; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 4.5min. 30.1 min. (major), 6.9 min. 14.3 min. (minor); $[a]_D^{24}$ = –128.7 (c 0.200, CH_2Cl_2).

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(4-chloro-phenyl) propionic acid *tert*-butyl ester (15ag): m.p.: 185 -186 ºC; IR (neat): 3336, 2974, 2927, 2885,



2361, 2339, 1925, 1653, 1453, 1381, 1331, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.40-7.34 (m, 4H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.20-7.15 (m, 3H), 6.33 (d, *J* = 7.8 Hz, 1H), 5.57 (d, *J* = 7.8 Hz, 1H), 5.13 (s, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.0, 167.1, 155.2, 144.1, 144.1, 141.2, 137.9, 132.9, 131.9, 131.6, 131.5, 128.4, 128.4, 128.3, 127.9, 126.5, 123.0, 120.5, 119.4, 82.9, 79.6, 68.7, 56.3, 28.4, 27.9; HRMS (ESI): Exact mass calcd for $C_{31}H_{34}Cl_1N_2O_4$ $[M+H]^+$ 533.22071, Found 533.21841; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 5.4 min. 36.9 min. (major), 8.9 min. 21.2 min. (minor); $[a]_D^{24}$ = –131.8 (c 0.200, CH_2Cl_2).

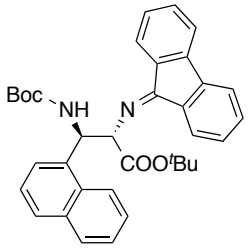
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(4-trifluoromethyl -phenyl) propionic acid *tert*-butyl ester (15ah): m.p.: 179-180 ºC; IR (neat): 3347, 2974, 2885,



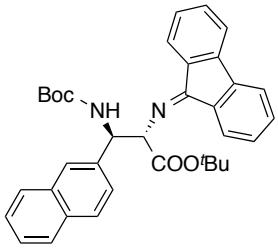
2540, 2362, 2255, 2134, 1925, 1657, 1453, 1330, 1275, 1090, 881,649; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.62-7.35 (m, 9H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.65 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 1H), 1.47 (s, 9H) 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.2, 167.5, 155.5, 145.5, 144.3, 141.5, 138.1, 132.2, 131.9, 131.8, 128.7, 128.1, 127.7, 127.6, 126.7, 125.5, 125.2, 123.3, 120.8, 119.7, 83.4, 79.9, 68. 8, 56.9, 28.6, 28.1; HRMS (ESI): Exact mass calcd for

$C_{32}H_{34}F_3N_2O_4$ $[M+H]^+$ 527.24975, Found 527.24537; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 4.6min. 35.8 min. (major), 7.9 min. 19.5 min. (minor); $[a]_D^{24}$ = –122.1 (c 0.200, CH_2Cl_2).

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(naphthalene-1-yl) propionic acid *tert*-butyl ester (15ai): m.p.: 205-206 ºC; IR (neat): 3378, 2974, 2882, 2503, 2360, 2339, 1925, 1756, 1454, 1381, 1330, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.39 (d, *J* = 9.6 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.66-7.59 (m, 3H), 7.47-7.18 (m, 3H) 7.36-7.33 (m, 2H), 7.29-7.21 (m, 3H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 1H), 1.57 (s, 9H), 1.46 (s, 9H) ; ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.7, 166.9, 155.3, 143.8, 141.1, 138.0, 136.4, 133.8, 131.6, 131.6, 131.4, 130.3, 129.0, 128.3, 127.8, 127.7, 126.5, 126.3, 125.4, 125.1, 124.0, 123.0, 122.3, 120.2, 119.2, 82.9, 79.5, 67.3, 53.2, 28.4, 28.0; HRMS (ESI): Exact mass calcd for $C_{35}H_{37}N_2O_4$ $[M+H]^+$ 549.27533, Found 549.27591; HPLC Column ADH, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 3.7 min. 4.9 min. (major), 6.6 min. 9.3 min. (minor) ; $[a]_D^{24}$ = –179.0 (c 0.200, CH_2Cl_2).



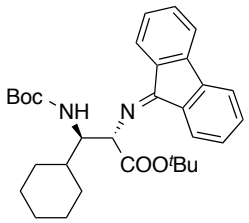
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(naphthalene-2-yl) propionic acid *tert*-butyl ester (15aj): m.p.: 200-201 ºC; IR (neat): 3344, 2974, 2927, 2885, 2360, 2339, 1925, 1381, 1331, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.92 (d, *J* = 7.2 Hz, 1H), 7.87 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.71-7.69 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.48-7.45 (m, 2H), 7.39-7.28 (m, 5H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.80 (d, *J* = 9.0 Hz, 1H), 5.28 (s, 1H), 1.51 (s, 9H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.3, 166.9, 155.3, 143.9, 141.2, 138.7, 138.0, 133.1, 132.7, 131.7, 131.6, 131.4, 128.3, 127.9, 127.8, 127.4, 126.5, 125.8, 125.6, 125.2, 123.0, 120.4, 119.3, 82.83, 79.4, 69.0, 56.9, 28.4, 27.9; HRMS (ESI): Exact mass calcd for $C_{35}H_{37}N_2O_4$ $[M+H]^+$ 549.27533, Found 549.27577; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 6.1 min. 37.7 min. (major), 11.4 min. 16.7 min. (minor); $[a]_D^{24}$ = –87.7 (c 0.200, CH_2Cl_2).



(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-(pyridine-3-yl) propionic acid *tert*-butyl ester (15ak): m.p.: 173 ºC; IR (neat): 3345, 2974, 2927, 2885, 2360, 2339, 1925, 1654, 1453, 1381, 1330, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.68 (s, 1H), 8.39 (d, *J* = 4.5 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.39-7.35 (m, 2H), 7.29 (t, *J* = 6.9 Hz, 1H), 7.18-7.13 (m, 2H), 6.35 (d, *J* = 7.9 Hz, 1H), 5.63 (d, *J* = 7.9 Hz, 1H), 5.15 (s, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 167.8, 167.4, 148.7, 148.5, 144.7, 144.1, 141.2, 139.3, 139.3, 137.8, 134.8, 132.0, 131.6, 128.4, 127.9, 126.5, 123.1, 123.0, 120.5, 119.4, 83.1, 79.8, 68.4, 55.0, 28.3, 27.8; HRMS (ESI): Exact mass calcd for $C_{30}H_{34}N_3O_4$ $[M+H]^+$ 500.25493, Found 500.25323; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 6.5min. 45.7 min. (major), 12.4 min. (minor) ; $[a]_D^{24}$ = –42.4 (c 0.200, CH_2Cl_2).

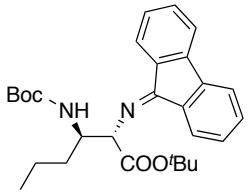
(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-5-phenyl pentanoic acid *tert*-butyl ester (15al): m.p.: 153 ºC; IR (neat): 3337, 2974, 2885, 2360, 2339, 1925, 1380, 1330, 1275, 1090, 1050; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.54-7.51 (m, 2H), 7.40-7.39 (m, 2H), 7.30-7.27 (m, 2H), 7.22-7.14 (m, 4H), 7.10 (t, *J* = 7.2 Hz, 1H), 5.70 (d, *J* = 9.6 Hz, 1H), 4.97 (d, *J* = 1.8. Hz, 1H), 4.56-4.52 (m, 1H), 2.76-2.65 (m, 2H), 1.92-1.75 (m, 2H), 1.45 (s, 9H), 1.45 (s, 9H) ; ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.7, 166.8, 155.6, 144.0, 141.9, 141.2, 138.1, 131.8, 131.6, 131.4, 128.6, 128.3, 128.3, 127.9, 126.6, 125.7, 123.1, 120.5, 119.3, 82.5, 79.0, 67.1, 53.3, 36.2, 32.6, 28.4, 27.9; HRMS (ESI): Exact mass calcd for $C_{33}H_{39}N_2O_4$ $[M+H]^+$ 527.29098, Found 527.29011; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 3.8 min. 34.5 min. (major); $[a]_D^{24}$ = –1.12 (c 0.200, CH_2Cl_2).

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-3-cyclohexyl propionic acid *tert*-butyl ester (15am): m.p.: 145 ºC; IR (neat): 3347, 2974, 2927, 2885, 2360, 2339, 2257, 1926, 1655, 1453, 1381, 1331, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.86 (d,



J = 7.2 Hz, 1H), 7.64 (*d*, *J* = 5.8 Hz, 1H), 7.57-7.54 (m, 2H), 7.42-7.36 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.63 (d, *J* = 7.9 Hz, 1H), 5.16 (brs, 1H), 4.16-4.13 (m, 1H), 1.89 (d, *J* = 7.8 Hz, 1H), 1.73 (br, 1H), 1.59-1.54 (m, 2H), 1.46 (*s*, 9H), 1.43 (*s*, 9H), 1.28-1.24 (m, 2H), 1.13-1.10 (m, 2H), 1.04-1.01 (m, 2H), 0.87 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$ 124.51 MHz): δ 169.2, 166.4, 155.8, 144.1, 141.2, 138.2, 131.8, 131.7, 131.3, 128.3, 128.0, 126.5, 123.2, 120.5, 119.3, 82.3, 78.7, 64.6, 57.2, 40.7, 29.8, 29.5, 28.4, 27.9, 26.1, 26.0; HRMS (ESI): Exact mass calcd for $C_{31}H_{41}N_2O_4$ $[M+H]^+$ 505.30663, Found 505.30736; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 3.4 min. 18.0 min. (major); $[a]_D^{24}$ = –1.22 (c 0.200, CH_2Cl_2).

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(fluoren-9-ylideneamino)-hexanoic acid *tert*-butyl ester (15an): m.p.: 138 ºC; IR (neat): 3347, 2974, 2886, 2360, 2339, 2257, 1925, 1655, 1453, 1380, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.87 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.41 (dd, *J* = 7.2 Hz, 14.4 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 4.96 (d, *J* = 1.8 Hz, 1H), 4.46-4.41 (m, 1H), 1.57-1.51 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H), 1.35-133 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 168.9, 166.5, 155.6, 144.1, 141.2, 138.2, 131.7, 131.3, 128.5, 128.3, 127.9, 126.6, 123.1, 120.5, 119.3, 82.3, 78.8, 66.9, 53.1, 36.3, 28.4, 27.9, 19.3, 13.9; HRMS (ESI): Exact mass calcd for $C_{28}H_{37}N_2O_4$ $[M+H]^+$ 465.27533, Found 465.27730; HPLC Column AD–H, eluent Hex/IPA = 4/1, flow rate 1.0 mL/min; rac 2.7 min. 37.0 min. (major); $[a]_D^{24}$ = –0.84 (c 0.200, CH_2Cl_2).

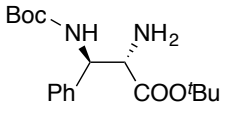


Hydrolysis of compound 15aa

To the solution of 1.0 M aq. HCl and Et_2O (4/1) was added the coupling product **15aa** (1.12 g, 2.24 mmol). The mixture was stirred for 30 min at room temperature and then diluted with water. The aqueous phase was washed with Et_2O three times and basicified with sat. $NaHCO_3$, and the aqueous phase was extracted with Et_2O. The organic layers were combined and dried

over Na_2SO_4, Filtration and evaporation under reduced pressure to afford free amine **16** (0.487 g, 1.45 mmol, 65% yield).

***Anti*-2-amino-3-*tert*-Butoxycarbonylamino propanoic acid *tert*-butyl ester (16)**

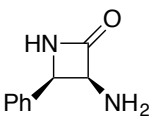


IR (neat): 3428, 2975, 1711, 1640, 1492, 1367, 1251, 1162. ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.28-7.19 (d, J = 7.2 Hz, 1H), 5.66 (s, 1H), 5.11 (s, 1H), 3.71 (s, 1H), 1.38 (s, 9H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 171.5, 155.1, 140.4, 128.5, 127.3, 126.5, 82.1, 79.3, 58.9, 56.2, 28.3, 27.9; HRMS (ESI): Exact mass calcd for $C_{18}H_{30}N_2O_4$ $[M+H]^+$ 337.21273, Found 337.21106.

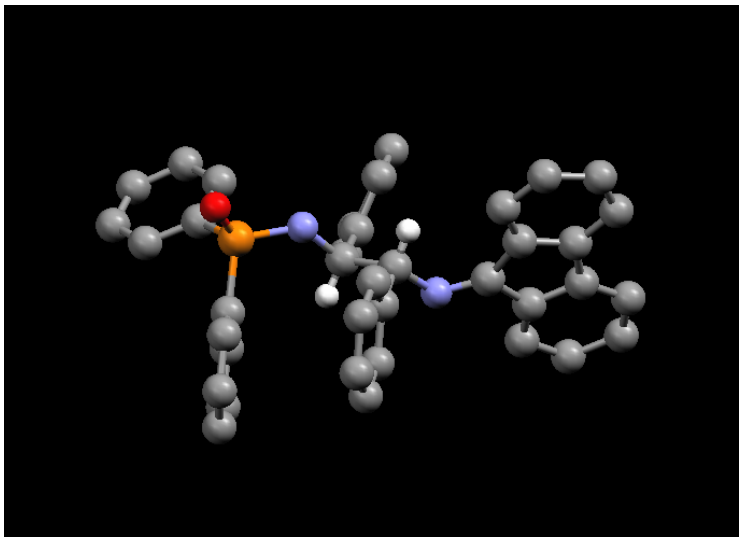
Synthesis of Monobactam 18[48]

A solution of **16** (250 mg, 0.74 mmol) in MeOH (4 mL) and conc. HCl (1 mL) was stirred at r.t. for 2 h, then diluted with H_2O (10 mL) and the aqueous phase was washed with Et_2O (10 mL × 3). The water layers were combined, and evaporated under reduced pressure to afford the corresponding hydrochloric acid salt **17** (178 mg, quant. yield). The diamine HCl salt **17** (70.0 mg, 0.230 mmol) was directly dissolved into THF, and the solution was kept at –60 ºC, and LDA in THF was added dropwise. After 24 h stirring, the reaction was quenched by sat. $NaHCO_3$. The crude mixture was extracted by CH_2Cl_2, then dried with Na_2SO_4. The residue was isolated by column chromatography using silica gel using a mixture of CH_2Cl_2/Et_2O to give the corresponding cyclized product **18** (27.2 mg, 0.167 mmol, 75% yield).

(3*S*,4*R*)-3-amino-4-phenylazetidin-2-one (18): m.p.: 172-175 ºC; IR (neat): 3347, 2974, 1275, 1090, 1050, 881; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.50 (m, 5H), 6.25 (br, 1H), 4.62 (d, J = 5.4, 1H), 4.05 (d, J = 5.5, 1H), 1.60 (br, 2H); ^{13}C NMR ($CDCl_3$ 150.92 MHz): δ 176.5, 128.8, 127.8, 126.8, 125.7, 84.9, 75.0; HRMS (ESI): Exact mass calcd for $C_9H_{10}N_2O$ $[M+H]^+$ 163.08659, Found 163.08641; $[a]_D^{24}$ = –45.1 (c 0.200, CH_2Cl_2).



X-ray Structure Report



Experimental

Data Collection

An unknown crystal of $C_{39}H_{31}N_2OP$ having approximate dimensions of 0.100 x 0.100 x 0.100 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using filtered Mo-Kα radiation.

The crystal-to-detector distance was 127.40 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive triclinic cell with dimensions:

a	=	11.795(3) Å	α	=	70.872(5)^{o}
b	=	12.193(4) Å	β	=	76.469(5)^{o}
c	=	12.323(3) Å	γ	=	71.681(5)^{o}
V	=	1572.4(7) Å^{3}			

For Z = 2 and F.W. = 574.66, the calculated density is 1.214 g/cm^{3}. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

P-1 (#2)

The data were collected at a temperature of 23 $\pm$ 1^{o}C to a maximum 2θ value of 55.0^{o}. A total of 44 oscillation images were collected. A sweep of data was done using ω scans from 130.0 to 190.0^{o} in 5.0^{o} step, at χ=45.0^{o} and ϕ = 0.0^{o}. The exposure rate was 30.0 [sec./^{o}]. A second sweep was performed using ω scans from 0.0 to 160.0^{o} in 5.0^{o} step, at χ=45.0^{o} and ϕ = 180.0^{o}. The exposure rate was 30.0 [sec./^{o}]. Readout was performed in the 0.100 mm pixel mode.

Data Reduction

Of the 15153 reflections that were collected, 7143 were unique (R_{int} = 0.0553); equivalent reflections were merged.

The linear absorption coefficient, μ, for Mo-Kα radiation is 1.207 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.082 to 0.988. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques. The non-hydrogen atoms were refined isotropically. Hydrogen atoms were refined using the

riding model. The final cycle of full-matrix least-squares refinement[2] on F^2 was based on 7143 observed reflections and 173 variable parameters and converged (largest parameter shift was 0.30 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.1293$$

$$wR2 = [\, \Sigma \, (\, w \, (Fo^2 - Fc^2)^2 \,) / \, \Sigma \, w(Fo^2)^2 \,]^{1/2} = 0.3796$$

The standard deviation of an observation of unit weight[3] was 2.12. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 1.08 and -1.19 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[4]. Anomalous dispersion effects were included in Fcalc[5]; the values for Δf' and Δf'' were those of Creagh and McAuley[6]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[7]. All calculations were performed using the CrystalStructure[8] crystallographic software package except for refinement, which was performed using SHELXL-97[9].

References

(1) SIR2002: Burla, M.C., Camalli, M., Carrozzini, B., Cascarano, G.L., Giacovazzo, C., Polidori, G., Spagna., R. (2003).

(2) Least Squares function minimized: (SHELXL97)

$\Sigma w(F_o^2 - F_c^2)^2$ where w = Least Squares weights.

(3) Standard deviation of an observation of unit weight:

$[\Sigma w(F_o^2 - F_c^2)^2/(N_o - N_v)]^{1/2}$

where: N_o = number of observations

N_v = number of variables

(4) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(5) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(6) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(7) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(8) CrystalStructure 4.0: Crystal Structure Analysis Package, Rigaku Corporation (2000-2010). Tokyo 196-8666, Japan.

(9) SHELX97: Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{39}H_{31}N_2OP$
Formula Weight	574.66
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.100 X 0.100 X 0.100 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 11.795(3) Å
	b = 12.193(4) Å
	c = 12.323(3) Å
	α = 70.872(5) ^{o}
	β = 76.469(5) ^{o}
	γ = 71.681(5) ^{o}
	V = 1572.4(7) Å^3
Space Group	P-1 (#2)
Z value	2
D_{calc}	1.214 g/cm^3
F_{000}	604.00
μ(MoKa)	1.207 cm^{-1}

B. Intensity Measurements

Diffractometer	R-AXIS RAPID
Radiation	MoKα (λ = 0.71075 Å)
Voltage, Current	50kV, 24mA
Temperature	23.0^{o}C
Detector Aperture	280 x 256 mm
Data Images	44 exposures

ω oscillation Range (χ=45.0, ϕ=0.0)	130.0 - 190.0°
Exposure Rate	30.0 sec./°
ω oscillation Range (χ=45.0, ϕ=180.0)	0.0 - 160.0°
Exposure Rate	30.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 15153
	Unique: 7143 (R_{int} = 0.0553)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.082 - 0.988)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.1000 \cdot P)^2$
	$+ 0.0000 \cdot P]$
	where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	7143
No. Variables	173
Reflection/Parameter Ratio	41.29
Residuals: R1 (I>2.00σ(I))	0.1293
Residuals: R (All reflections)	0.1742
Residuals: wR2 (All reflections)	0.3796
Goodness of Fit Indicator	2.121
Max Shift/Error in Final Cycle	0.301
Maximum peak in Final Diff. Map	1.08 $e^-/Å^3$
Minimum peak in Final Diff. Map	-1.19 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
P1	0.56245(9)	0.4533(1)	0.82168(9)	2.97(3)
O2	0.6364(3)	0.3977(3)	0.9179(3)	3.76(7)
N3	0.2758(4)	0.8740(4)	0.7271(4)	4.15(8)
N4	0.4502(3)	0.5648(4)	0.8508(3)	3.24(7)
C5	0.1111(4)	1.0513(5)	0.6976(4)	3.61(9)
C6	0.5055(4)	0.3442(5)	0.7961(4)	3.58(9)
C7	0.3651(4)	0.7809(5)	0.7980(4)	3.68(9)
C8	0.0867(5)	1.0951(5)	0.8735(4)	4.0(1)
C9	0.6475(4)	0.5146(5)	0.6848(4)	3.20(8)
C10	0.2026(4)	0.9593(5)	0.7685(4)	3.64(9)
C11	0.2500(5)	0.6423(5)	0.7848(5)	4.0(1)
C12	0.7502(5)	0.5464(6)	0.6868(5)	4.6(1)
C13	0.3754(4)	0.6629(5)	0.7714(4)	3.50(9)
C14	0.2438(5)	0.9431(6)	0.9770(5)	4.4(1)
C15	0.1840(4)	0.9937(5)	0.8788(4)	3.79(9)
C16	0.3897(5)	0.3325(6)	0.8448(5)	4.5(1)
C17	0.4864(5)	0.8099(5)	0.7629(5)	4.0(1)
C18	0.6114(5)	0.5339(5)	0.5789(5)	4.2(1)
C19	0.5567(5)	0.7883(6)	0.8480(5)	5.0(2)
C20	0.0855(5)	1.0592(6)	0.5904(5)	4.6(1)
C21	0.0424(5)	1.1329(5)	0.7614(5)	3.93(9)
C22	0.5306(5)	0.8575(6)	0.6433(5)	5.1(2)
C23	0.7790(6)	0.6182(7)	0.4778(6)	6.2(2)
C24	0.1746(5)	0.6320(6)	0.8914(5)	4.9(1)
C25	0.6424(6)	0.8834(7)	0.6169(6)	5.6(2)
C26	0.0435(5)	1.1495(6)	0.9665(5)	5.0(2)
C27	-0.0524(5)	1.2271(6)	0.7165(5)	5.2(2)
C28	0.1014(5)	1.0980(6)	1.0628(5)	5.2(2)
C29	0.2020(5)	0.9980(6)	1.0678(5)	5.1(2)
C30	-0.0088(6)	1.1535(7)	0.5440(6)	5.5(2)
C31	0.2121(6)	0.6301(7)	0.6924(6)	5.6(2)
C32	0.8167(6)	0.5973(7)	0.5851(6)	6.2(2)
C33	0.7128(6)	0.8595(7)	0.7023(6)	6.2(2)
C34	0.3500(6)	0.2354(7)	0.8336(6)	6.5(2)
C35	-0.0784(6)	1.2371(7)	0.6074(6)	5.7(2)
C36	0.5833(6)	0.2626(6)	0.7364(5)	5.3(2)
C37	0.6782(6)	0.5885(7)	0.4735(6)	5.8(2)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C38	0.0609(6)	0.6120(7)	0.9032(6)	6.1(2)
C39	0.0256(7)	0.5989(8)	0.8088(7)	7.1(2)

C40	0.4298(7)	0.1583(8)	0.7723(7)	7.3(2)
C41	0.1025(7)	0.6056(8)	0.7033(7)	6.9(2)
C42	0.6699(6)	0.8128(7)	0.8164(6)	5.8(2)
C43	0.5436(7)	0.1691(8)	0.7258(7)	7.1(2)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2. Atomic coordinates and B_{iso} involving hydrogen atoms

atom	x	y	z	B_{iso}
H7	0.3369	0.7741	0.8807	1.00
H13	0.4153	0.6671	0.6914	1.00

Table 3. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
P1	O2	1.488(4)	P1	N4	1.642(4)
P1	C6	1.804(7)	P1	C9	1.806(4)
N3	C7	1.480(6)	N3	C10	1.290(7)
N4	C13	1.463(6)	C5	C10	1.492(6)
C5	C20	1.389(9)	C5	C21	1.404(8)
C6	C16	1.390(7)	C6	C36	1.401(9)
C7	C13	1.540(9)	C7	C17	1.512(8)
C8	C15	1.393(7)	C8	C21	1.471(8)
C8	C26	1.423(9)	C9	C12	1.391(9)
C9	C18	1.391(8)	C10	C15	1.500(9)
C11	C13	1.539(8)	C11	C24	1.396(7)
C11	C31	1.382(11)	C12	C32	1.380(8)
C14	C15	1.407(8)	C14	C29	1.402(10)
C16	C34	1.457(13)	C17	C19	1.395(9)
C17	C22	1.431(7)	C18	C37	1.427(8)
C19	C42	1.399(10)	C20	C30	1.396(8)
C21	C27	1.393(7)	C22	C25	1.392(10)
C23	C32	1.412(11)	C23	C37	1.364(12)
C24	C38	1.404(10)	C25	C33	1.392(11)
C26	C28	1.374(9)	C27	C35	1.407(10)
C28	C29	1.405(8)	C30	C35	1.421(10)
C31	C41	1.384(12)	C33	C42	1.371(9)
C34	C40	1.384(11)	C36	C43	1.413(14)
C38	C39	1.393(13)	C39	C41	1.394(10)
C40	C43	1.359(11)			

Table 4. Bond lengths involving hydrogens (Å)

atom	atom	distance	atom	atom	distance
C7	H7	0.980	C13	H13	0.980

Table 5. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
O2	P1	N4	110.2(2)	O2	P1	C6	111.4(3)
O2	P1	C9	112.8(2)	N4	P1	C6	110.2(3)
N4	P1	C9	106.76(19)	C6	P1	C9	105.4(3)
C7	N3	C10	119.3(5)	P1	N4	C13	128.8(4)
C10	C5	C20	130.0(5)	C10	C5	C21	108.1(5)
C20	C5	C21	121.8(5)	P1	C6	C16	120.7(5)
P1	C6	C36	119.3(5)	C16	C6	C36	119.6(7)
N3	C7	C13	105.5(5)	N3	C7	C17	110.4(4)
C13	C7	C17	109.7(4)	C15	C8	C21	110.0(5)
C15	C8	C26	121.7(5)	C21	C8	C26	128.3(5)
P1	C9	C12	118.3(4)	P1	C9	C18	122.1(4)
C12	C9	C18	119.6(5)	N3	C10	C5	119.0(5)
N3	C10	C15	134.9(5)	C5	C10	C15	106.1(4)
C13	C11	C24	120.4(6)	C13	C11	C31	120.5(5)
C24	C11	C31	119.1(6)	C9	C12	C32	120.9(6)
N4	C13	C7	107.8(5)	N4	C13	C11	111.0(4)
C7	C13	C11	111.2(4)	C15	C14	C29	117.8(5)
C8	C15	C10	107.4(5)	C8	C15	C14	120.2(6)
C10	C15	C14	132.3(5)	C6	C16	C34	119.8(6)
C7	C17	C19	119.5(5)	C7	C17	C22	120.8(6)
C19	C17	C22	119.7(6)	C9	C18	C37	119.9(6)
C17	C19	C42	120.0(5)	C5	C20	C30	118.6(6)
C5	C21	C8	108.4(4)	C5	C21	C27	120.3(6)
C8	C21	C27	131.3(6)	C17	C22	C25	117.9(6)
C32	C23	C37	120.9(6)	C11	C24	C38	120.1(7)
C22	C25	C33	121.9(6)	C8	C26	C28	117.5(5)
C21	C27	C35	118.5(6)	C26	C28	C29	121.4(7)
C14	C29	C28	121.3(6)	C20	C30	C35	120.1(7)
C11	C31	C41	121.8(6)	C12	C32	C23	119.4(8)
C25	C33	C42	119.5(7)	C16	C34	C40	118.2(7)
C27	C35	C30	120.7(6)	C6	C36	C43	120.0(6)
C18	C37	C23	119.3(7)	C24	C38	C39	119.5(6)
C38	C39	C41	120.4(8)	C34	C40	C43	122.0(10)
C31	C41	C39	119.1(9)	C19	C42	C33	120.9(7)
C36	C43	C40	120.4(8)				

Table 6. Bond angles involving hydrogens (°)

atom	atom	atom	angle	atom	atom	atom	angle

N3	C7	H7	110.4	C13	C7	H7	110.4
C17	C7	H7	110.4	N4	C13	H13	108.9
C7	C13	H13	108.9	C11	C13	H13	108.9

Table 7. Torsion Angles(°)

(Those having bond angles > 160 or < 20 degrees are excluded.)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
O2	P1	N4	C13	162.2(4)	O2	P1	C6	C16	96.7(4)
O2	P1	C6	C36	-76.8(4)	O2	P1	C9	C12	-23.6(4)
O2	P1	C9	C18	158.2(3)	N4	P1	C6	C16	-25.9(4)
N4	P1	C6	C36	160.7(3)	C6	P1	N4	C13	-74.5(4)
N4	P1	C9	C12	97.5(4)	N4	P1	C9	C18	-80.7(4)
C9	P1	N4	C13	39.4(5)	C6	P1	C9	C12	-145.4(3)
C6	P1	C9	C18	36.5(4)	C9	P1	C6	C16	-140.7(3)
C9	P1	C6	C36	45.9(4)	C7	N3	C10	C5	-178.7(4)
C7	N3	C10	C15	1.9(9)	C10	N3	C7	C13	143.8(5)
C10	N3	C7	C17	-97.8(5)	P1	N4	C13	C7	-133.9(4)
P1	N4	C13	C11	104.1(4)	C10	C5	C20	C30	177.8(5)
C20	C5	C10	N3	3.5(9)	C20	C5	C10	C15	-176.9(6)
C10	C5	C21	C8	-0.6(6)	C10	C5	C21	C27	-178.3(5)
C21	C5	C10	N3	179.6(5)	C21	C5	C10	C15	-0.8(6)
C20	C5	C21	C8	175.9(5)	C20	C5	C21	C27	-1.8(9)
C21	C5	C20	C30	2.1(9)	P1	C6	C16	C34	-173.4(3)
P1	C6	C36	C43	173.7(4)	C16	C6	C36	C43	0.2(7)
C36	C6	C16	C34	0.1(7)	N3	C7	C13	N4	-172.5(3)
N3	C7	C13	C11	-50.7(4)	N3	C7	C17	C19	141.2(5)
N3	C7	C17	C22	-39.7(7)	C13	C7	C17	C19	-103.0(6)
C13	C7	C17	C22	76.1(6)	C17	C7	C13	N4	68.6(5)
C17	C7	C13	C11	-169.6(4)	C15	C8	C21	C5	1.9(7)
C15	C8	C21	C27	179.2(6)	C21	C8	C15	C10	-2.3(6)
C21	C8	C15	C14	178.2(5)	C15	C8	C26	C28	-0.1(9)
C26	C8	C15	C10	178.5(5)	C26	C8	C15	C14	-1.0(9)
C21	C8	C26	C28	-179.1(5)	C26	C8	C21	C5	-179.1(6)
C26	C8	C21	C27	-1.7(11)	P1	C9	C12	C32	-177.9(4)
P1	C9	C18	C37	176.7(3)	C12	C9	C18	C37	-1.5(8)
C18	C9	C12	C32	0.3(8)	N3	C10	C15	C8	-178.6(6)
N3	C10	C15	C14	0.8(11)	C5	C10	C15	C8	1.9(6)
C5	C10	C15	C14	-178.7(5)	C13	C11	C24	C38	-179.4(5)
C24	C11	C13	N4	59.6(7)	C24	C11	C13	C7	-60.4(6)
C13	C11	C31	C41	176.7(5)	C31	C11	C13	N4	-118.5(6)
C31	C11	C13	C7	121.5(6)	C24	C11	C31	C41	-1.4(9)
C31	C11	C24	C38	-1.3(8)	C9	C12	C32	C23	0.5(10)
C15	C14	C29	C28	2.0(9)	C29	C14	C15	C8	0.0(9)
C29	C14	C15	C10	-179.3(6)	C6	C16	C34	C40	-1.0(8)

Table 7. Torsion angles (°) (continued)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C7	C17	C19	C42	178.9(5)	C7	C17	C22	C25	179.4(5)
C19	C17	C22	C25	-1.6(9)	C22	C17	C19	C42	-0.2(9)
C9	C18	C37	C23	1.8(9)	C17	C19	C42	C33	0.8(10)
C5	C20	C30	C35	-1.8(10)	C5	C21	C27	C35	0.9(9)
C8	C21	C27	C35	-176.2(6)	C17	C22	C25	C33	2.8(10)
C32	C23	C37	C18	-1.0(11)	C37	C23	C32	C12	-0.1(11)
C11	C24	C38	C39	1.9(9)	C22	C25	C33	C42	-2.3(11)
C8	C26	C28	C29	2.2(10)	C21	C27	C35	C30	-0.6(10)
C26	C28	C29	C14	-3.2(11)	C20	C30	C35	C27	1.0(10)
C11	C31	C41	C39	3.3(10)	C25	C33	C42	C19	0.4(11)
C16	C34	C40	C43	1.8(10)	C6	C36	C43	C40	0.5(9)
C24	C38	C39	C41	0.0(11)	C38	C39	C41	C31	-2.6(11)
C34	C40	C43	C36	-1.5(11)					

Table 8. Intramolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
O2	C12	3.091(6)	O2	C36	3.440(10)
N3	C11	2.776(8)	N3	C14	3.361(9)
N3	C20	3.011(7)	N3	C21	3.548(7)
N3	C22	2.905(7)	N3	C24	3.377(8)
N3	C31	3.461(11)	N4	C16	3.157(9)
N4	C17	2.959(8)	N4	C18	3.518(7)
N4	C19	3.329(10)	N4	C24	3.053(7)
N4	C31	3.532(9)	C5	C35	2.774(7)
C6	C18	3.203(7)	C6	C40	2.802(13)
C7	C14	3.230(9)	C7	C15	3.083(8)
C7	C24	3.107(9)	C8	C29	2.764(8)
C9	C13	3.274(6)	C9	C23	2.789(8)
C9	C36	3.222(10)	C10	C13	3.540(7)
C10	C17	3.267(7)	C11	C16	3.515(8)
C11	C39	2.790(11)	C12	C37	2.790(10)
C13	C18	3.529(7)	C13	C19	3.428(10)
C13	C22	3.224(9)	C14	C26	2.850(8)
C15	C28	2.789(9)	C16	C43	2.795(10)
C17	C33	2.800(10)	C18	C32	2.787(11)
C18	C36	3.316(9)	C19	C25	2.775(8)
C20	C27	2.839(10)	C21	C30	2.797(10)
C22	C42	2.804(10)	C24	C41	2.790(12)
C25	C32	3.543(11)	C26	C27	3.274(9)
C31	38	2.772(9)	C34	C36	2.808(10)

Table 9. Intramolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
P1	H13	2.847	N3	H13	2.654
N4	H7	2.585	C9	H13	2.785
C10	H7	2.499	C11	H7	2.808
C14	H7	2.535	C15	H7	2.713
C17	H13	2.603	C18	H13	2.743
C19	H7	2.581	C22	H7	3.345
C22	H13	2.879	C24	H7	2.916
C24	H13	3.333	C31	H13	2.571
H7	H13	2.868			

Table 10. Intermolecular contacts less than 3.60 Å

atom	atom	distance	atom	atom	distance
O2	N4[1]	2.928(6)	O2	C7[1]	3.464(6)
O2	C24[1]	3.465(8)	N4	O2[1]	2.928(6)
C7	O2[1]	3.464(6)	C8	C26[2]	3.571(9)
C8	C28[2]	3.512(10)	C15	C26[2]	3.501(9)
C21	C28[2]	3.575(9)	C24	O2[1]	3.465(8)
C26	C8[2]	3.571(9)	C26	C15[2]	3.501(9)
C26	C38[2]	3.526(11)	C28	C8[2]	3.512(10)
C28	C21[2]	3.575(9)	C28	C38[2]	3.562(10)
C30	C41[3]	3.579(9)	C38	C26[2]	3.526(11)
C38	C28[2]	3.562(10)	C38	C38[4]	3.436(10)
C41	C30[3]	3.579(9)			

Symmetry Operators:

(1) -X+1,-Y+1,-Z+2 (2) -X,-Y+2,-Z+2

(3) -X,-Y+2,-Z+1 (4) -X,-Y+1,-Z+2

Table 11. Intermolecular contacts less than 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
O2	H7[1]	2.681	H7	O2[1]	2.681

Symmetry Operators:

(1) -X+1,-Y+1,-Z+2

VII. References

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[5] The value of the pK, of a tautomer A can be calculated by using the following equation:

$$\text{p}K_\text{a} \text{ of tautomer A} = \text{p}K_\text{a} \text{ of mixture} + \left[(\text{X of tautomer B}) \log \frac{\text{tautomer A}}{\text{tautomer B}} \right]$$

in which pK, of mixture is the equilibrium acidity of the tautomer mixture, X of tautomer B is the mole fraction of tautomer B at equilibrium with tautomer A and log (tautomer A/tautomer B) is the log of the ratio of the two tautomeric forms at equilibrium. The acidity of tautomer B can be calculated by an analogous equation.

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