博士論文

Enantioselective Synthesis of Tetrasubstituted Stereocenters via Catalytic Asymmetric Mannich-type Reaction
（触媒的不斉マンニッヒ型反応による不斉4置換炭素中心の構築）

林　紹全 (LIN SHAOQUAN)

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Acknowledgements

First and foremost, I would like to express my deep and sincere appreciation to my supervisor Prof. Masakatsu Shibasaki for giving me the opportunity to work in his group during these years and surporting me to apply for the PhD degree. His guidance, support and patience throughout the course of this research is very much appreciated and will not be forgotten. A special thanks to Dr. Naoya Kumagai for his helpful discussions and suggestions during these years. I am thankful to Prof. Motomu Kanai for allowing me as a PhD candidate. This dissertation would not have been possible without the support from all of you.

Many thanks to all the other staff that helped me in any way over my years in BIKAKEN. I thank Dr. Ryuichi Sawa, Ms. Yumiko Kubota and Ms. Kiyoko Iijima for their assistance in NMR and HRMS work. An exceptional thank you goes out to Dr. Tomoyuki Kimura for his assistance in X-ray crystallographic work. I am thankful to Ms. Yuko Suya and Ms. Mariko Okui for the kind helps they have offered.

A grateful thank you to my lab mates, including Dr. Liang Yin, Dr. Karin Weidner, Dr. Alagiri Kaliyamoorthy, Dr. Akira Saito, Dr. Youmei Bao, Dr. Hisashi Takata, Dr. Akinobu Matsuzawa, Dr. Kazuki Hashimoto, Dr. Sureshkumar Devarajulu, Dr. Makoto Furutachi, Dr. Keiji Tamura, Dr. Yuji Kawato, Dr. Ganesh Venkataraman, Dr. Christopher Opie, Mr. Hikaru Abe, Ms. Chiharu Sakashita, Dr. Lu Wang, Dr. Nilanjana Majumdar, Dr. Raphaël Oriez, Prof. Jingbo Chen, Dr. Jianyang Chen, Ms. Yui Sahara, Dr. Fernando Arteaga Arteaga, Dr. Lennart Brewitz, Mr. Zhongdong Sun, Dr. Ming Zhang, Mr. Fuyuki Amemiya, Mr. Akihito Nonoyama, Dr. Shinya Adachi, Dr. Jin Cui, Dr. Bo Sun, Dr. Toshifumi Takeuchi, Dr. Hidetoshi Noda, Dr. Zijian Liu, Dr. Akimichi Ohtsuki, and so on, thank you for being so kind and generous with your time to help me over these past few years.

A heartfelt thank you to Ting Cao, whose love and support over the years encouraged me to go this far.

Last, but not at all least, I would like to thank my parents and my brother for their love, prayers and support throughout this journey.

Abbreviations

Ac	acetyl
Ad	adamantyl
Ar	aryl
Ag	silver
aq.	aqueous
BAr^F	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat.	catalyst
Cbz	carboxybenzyl
Co	cobalt
cod	1,5-cyclooctadiene
Conv.	conversion
CPME	cyclopentyl methyl ether
Cs	cesium
Cu	copper
d	day
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dpp	diphenylphosphinoyl
dppe	ethylenebis(diphenylphosphine)
dppf	1,1’-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	ethyl ether
EtOH	ethanol
EWG	electron-withdrawing group
Fe	iron
Flu	9-fluorenylidene
h	hour
HRMS	high resolution mass spectrometry
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography

Hz	hertz
^{i}Pr	isopropyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared spectroscopy
Ir	iridium
J	coupling constant
K	potassium
KHMDS	potassium hexamethyldisilazide
Li	lithium
M	molar concentration
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute
mM	micromolar concentration
MS	mass spectrometry
MS 3A	molecular sieves 3A
MS 4A	molecular sieves 4A
MS 5A	molecular sieves 5A
Na	sodium
NHC	*N*-heterocyclic carbene
Ni	nickel
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
PG	protecting group
Ph	phenyl
*p*Ka	acid dissociation constant
PMP	4-methoxybenzyl
ppm	parts per million
quant.	quantitative
R	*rectus*
Rh	rhodium
rxn	reaction
rt	room temperature
S	*sinister*
t	time
T	temperature
^{t}Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
Ti	titanium
thioDpp	diphenylthiophosphinoyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene

Ts	*p*-toluenesulfonyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Xyl	3,5-dimethylphenyl
Zn	zinc

Abstract

The introductory section of this thesis describes the Mannich-type reaction in a broad definition, in addition to a discussion on the first metal-catalyzed and the first organo-catalyzed asymmetric Mannich-type reactions of ketimine.

The first part of the results and discussion focuses on the development of direct catalytic asymmetric Mannich-type reaction for the construction of *α*,*β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters. The use of *N*-(diphenylthiophosphinoyl)ketimine (*N*-thioDpp ketimine) as soft Lewis basic electrophile is the key to afford the excellent results. A variety of aliphatic ketimines could serve as suitable substrates, and the corresponding products could be isolated in excellent yields (up to 99%), high diastereoselectivity (up to 95/5 *dr*) and excellent enantioselectivity (up to 95% *ee*). The second part of this section details the first example of the direct catalytic asymmetric Mannich-type reaction of MeCN with acyclic ketimines. In the presence of chiral *N*-hetereocyclic carbenes (NHCs) and $[Ir(cod)OMe]_2$, the direct catalytic asymmetric coupling of MeCN with *N*-thioDpp *α*-iminoesters was achieved, giving the corresponding products in excellent yields (up to 92%) and good enantioselectivity (up to 80% *ee*). ^{31}P NMR studies and kinetic studies are also discussed. The third part of this section discusses the construction of *α*,*α*-disubstituted *α*-amino acid derivatives via *α*-addition of *α*,*β*-unsaturated *γ*-butyrolactam to *N*-thioDpp *α*-iminoesters. It has been found that using *N*-thioDpp *α*-iminoester is the key to promote the reaction. The reaction worked well for a range of *N*-thioDpp *α*-iminoesters, giving the corresponding products in excellent yields (up to 99%) and excellent enantioselectivity (up to 94% *ee*). Catalyst revovery and reuse showed that the catalyst was fairly stable and could be purified by chromatography on silica gel. The recovered catalyst showed almost the same performance compared with the original catalyst.

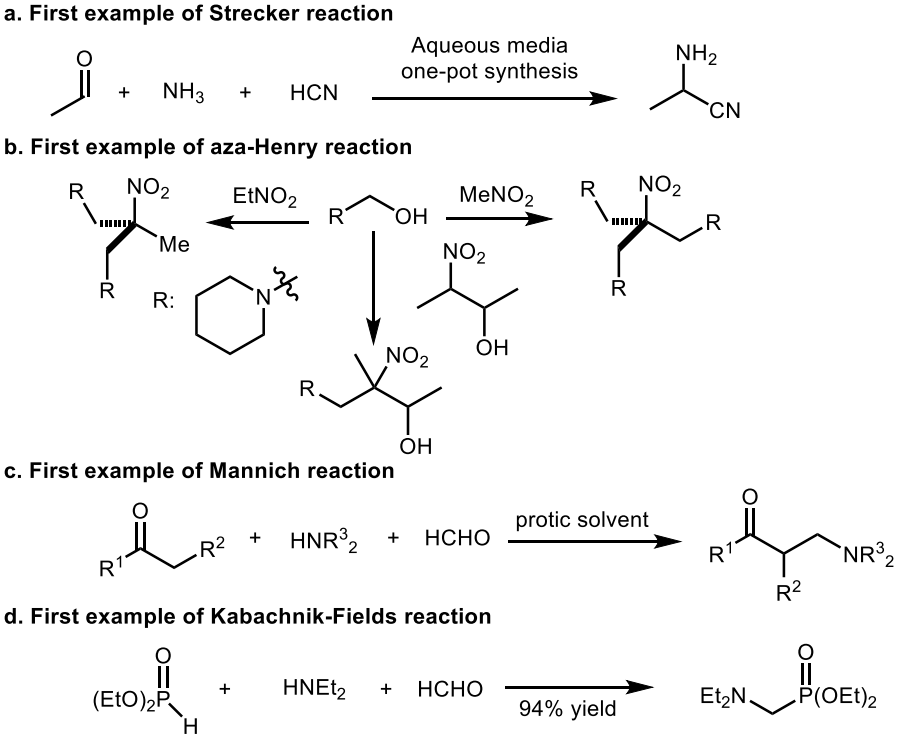
The experimental section details the experimental procedures and characterization of new compounds described in this thesis.

Finally, a comprehensive list of references referred to in this thesis is included.

1. Introduction

1.1 The Mannich-type reaction

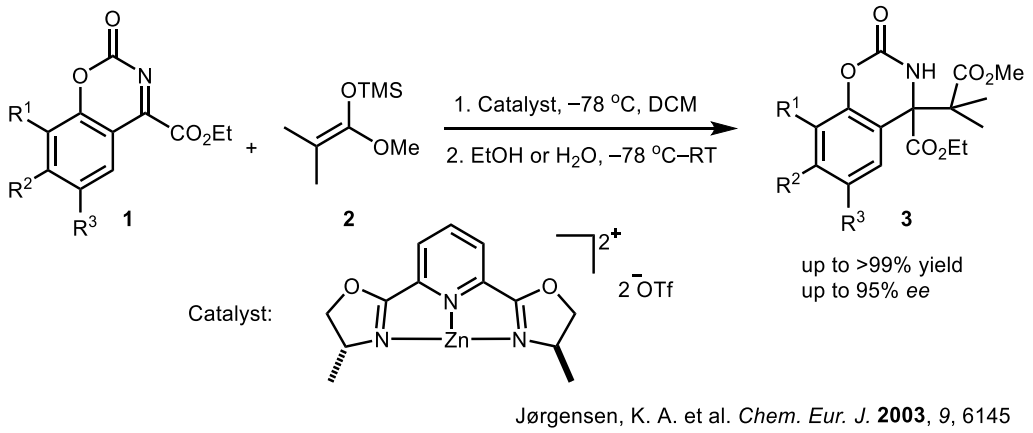
Chiral nitrogen-containing building blocks are widely embedded in natural and unnatural bioactive molecules, and these units are known to play important roles as a result of their bioactivities.[1] To construct the chiral nitrogen-containing building blocks, direct asymmetric addition of various nucleophiles to imines via the Mannich-type reaction is one of the most promising and convenient routes.[2] In a broad definition, Mannich-type reaction includes[3] 1) the Strecker reaction, named after Adolph Strecker who reported the first example of the reaction in 1850 (**Scheme 1**, **a**);[4] 2) the aza-Henry or nitro-Mannich reaction, which was reported by Henry in 1896 (**Scheme 1**, **b**);[5] 3) the Mannich reaction, which was reported by Carl Mannich in 1912 (**Scheme 1**, **c**);[6] 4) the Pudovik reaction or Kabachnik-Fields reaction (**Scheme 1**, **d**).[7] In this thesis, I was interested in the catalytic asymmetric Mannich-type reaction (**c** type) using ketimines as electrophilic partners for the construction of tetrasubstituted stereogenic centers.



Scheme 1. Mannich-type reaction

1.2 The Mannich-type reaction of ketimine

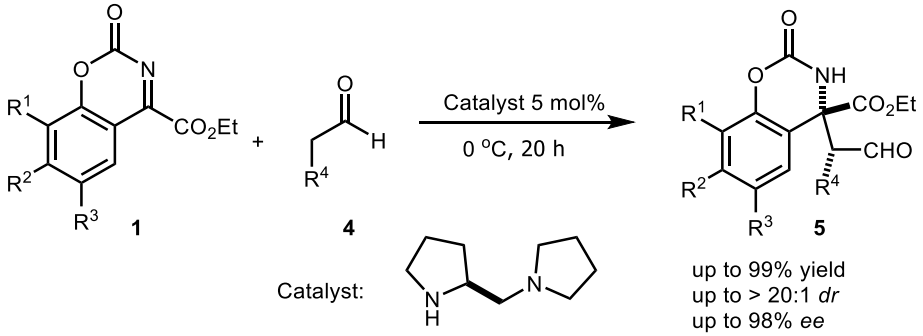
Whilst the asymmetric Mannich-type reactions of aldimine have been extensively studied, the asymmetric Mannich-type reactions of ketimine, derived from ketones, have been much less well studied because of their lower reactivity and higher steric bulk.[2] In 2003, Jørgensen et al. achieved the first example of catalytic asymmetric Mannich-type reaction of ketimines (**Scheme 2**).[8] By introducing the strategy of intrinsic protecting group anchoring, they reported a $Zn(OTf)_2 \cdot H_2O$/(*R*,*R*)-Ph-Pybox complex catalyzed Mannich-type reaction of silylketene acetals **2** with several ketimines **1**, giving the adducts **3** in high yields (up to >99%) and with high enantioselectivities (up to 95% *ee*).



Jørgensen, K. A. et al. *Chem. Eur. J.* **2003**, *9*, 6145

Scheme 2. First metal-catalyzed asymmetric Mannich-type reaction of ketimine

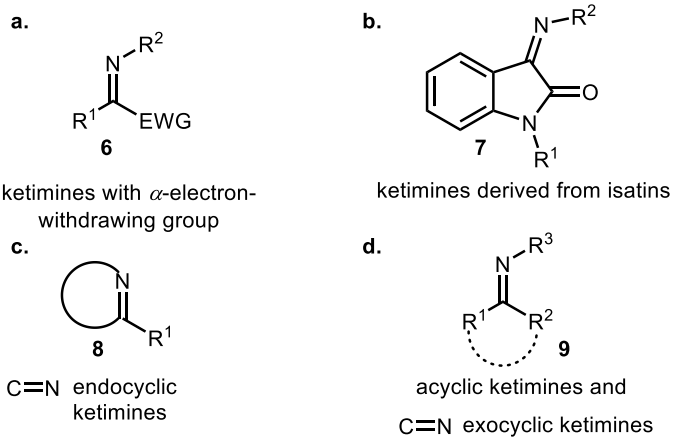
Shortly thereafter in 2004, based on the same concept, Jørgensen et al. described the first organocatalytic enantioselective Mannich-type reaction of ketimines (**Scheme 3**).[9] With chiral secondary amines, the reaction of unmodified aldehydes **4** with ketimines **1** could deliver the enantioenriched tetrasubstituted α-amino acid derivatives **5** in high yields (up to 99%), high diastereoselectivities (up to > 20:1 *dr*) and high enantioselectivities (up to 98% *ee*).



Jørgensen, K. A. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476.

Scheme 3. First organo-catalyzed asymmetric Mannich-type reaction of ketimine

From then on, the number of reports on the catalytic asymmetric Mannich-type reaction of ketimines has increased dramatically. Based on their structure, ketimines can be categorized into four types (**Scheme 4**).[2s] In this thesis, I focused on type-**a** and type-**d**.

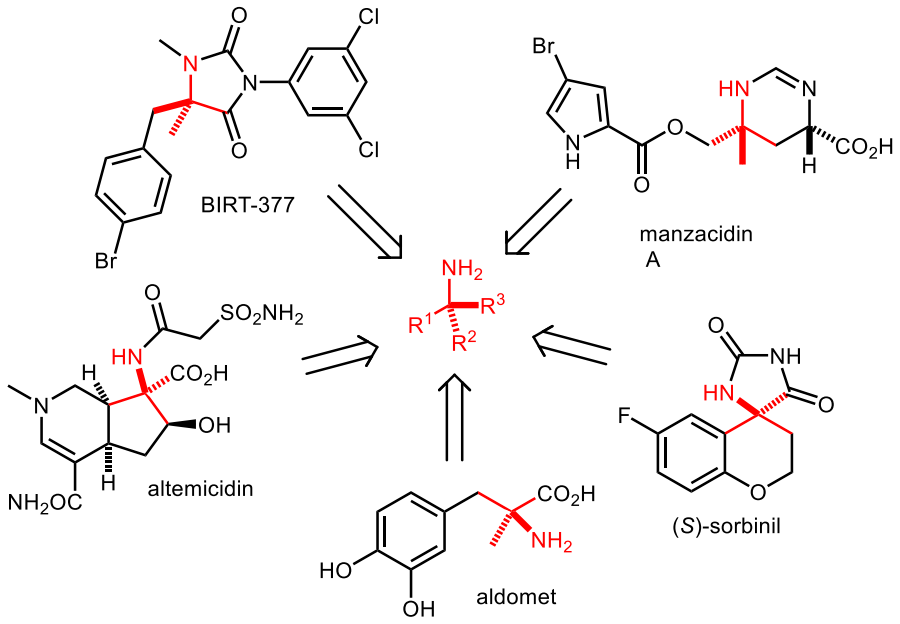


Kumagai, N.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 503

Scheme 4. Four-types of Ketimines

1.3 Overview of the research

The tetrasubstituted stereogenic centers, especially those featuring an amino group, are important structural motifs because these units are present in a number of natural products and biologically active compounds (**Scheme 5**).[10]



Zhou, J. et al. *Synthesis* **2014**, 2983

Scheme 5. Selected natural products and biologically active compounds with a nitrogen-containing tetrasubstituted stereogenic center

In the recent past, much effort has been devoted toward the enantioselective construction of tetrasubstituted stereocenters by Mannich-type reactions of various nucleophiles with ketimines.[2e–s] However, further development of methodologies for more efficient access to quaternary carbon stereocenters featuring an amino group is still highly desirable and challenging. As part of continuing interest on catalytic asymmetric C-C bond formation in Shibasaki group, I focused on the reaction of various nucleophiles with ketimines to construct the tetrasubstituted stereocenters.

This thesis can be sub-divided into three major components:

1) The construction of α,β-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters.

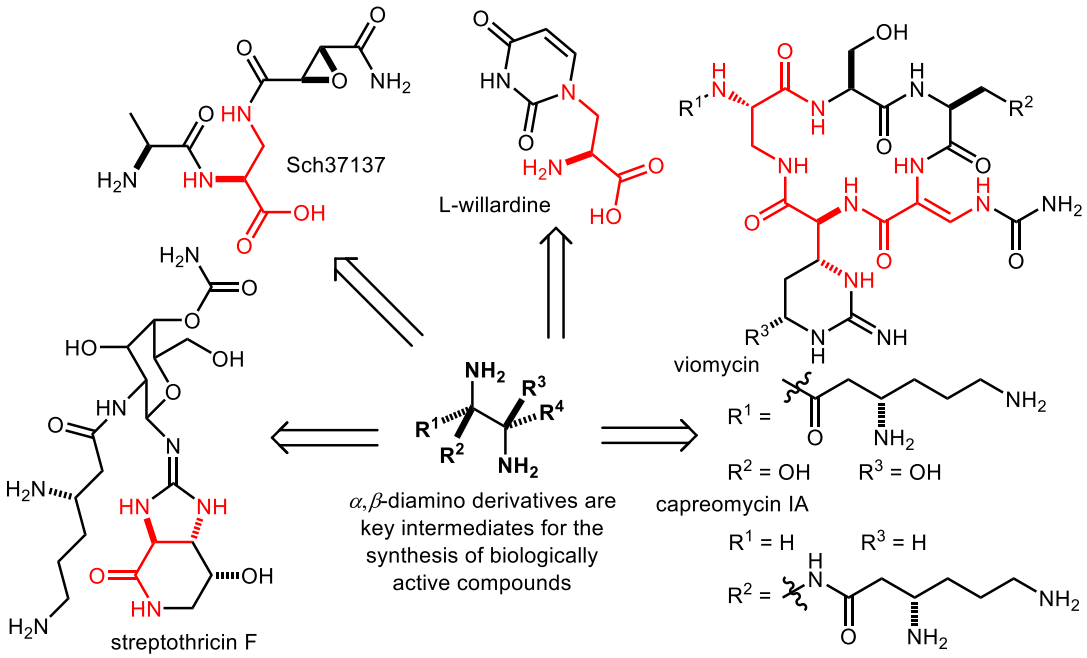
2) The construction of α,α-disubstituted α-amino acid derivatives using MeCN as nucleophile.

3) The construction of α,α-disubstituted α-amino acid derivatives with α,β-unsaturated γ-butyrolactam.

2. Results and discussion

2.1 Construction of *α,β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters

Optically active *α,β*-diamino derivatives are important structural motifs, which have been widely found in many bioactive compounds (**Scheme 6**).[11] Recently, impressive progress has been achieved in the development of catalytic protocols to *α,β*-diamino derivatives through C-C bond forming reactions.[12] Despite these achievements, only a few examples have been reported for the synthesis of *α,β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters.

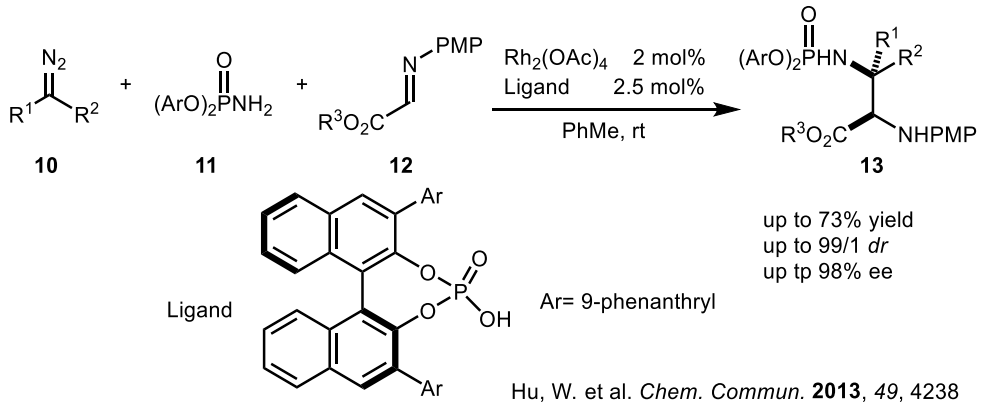


Viso. A. et al. *Chem.Rev.* **2005**,*105*, 3167

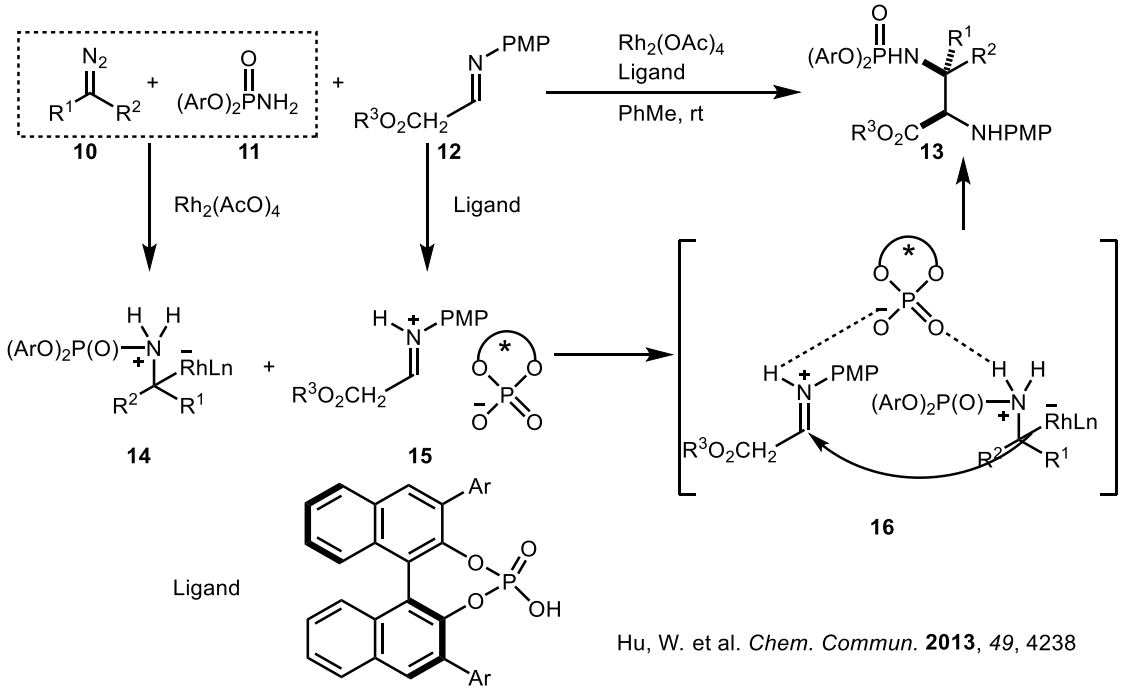
Scheme 6. Selected bioactive compounds containing *α,β*-diamino acids motifs

2.1.1 Literature known methods to access to *α,β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters

In 2013, Hu et al. disclosed a novel three-component Mannich-type reaction, to rapid and efficiently construct *α,β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters (**Scheme 7**).[13] The authors proposed that a phosphoramidate ammonium ylide derived from a phosphoramide **11** was trapped by *α*-imino ester **12** (**Scheme 8**). Only 11% yield was observed for the desired product in the absence of chiral phosphoric acids. However, the yield increased dramatically with chiral phosphoric acids, and the reaction delivered the corresponding optically active adducts **13** in moderate yields (up to 73% yield), excellent diastereoselectivities (up to 99/1 *dr*) and excellent enantioselectivities (up to 98% *ee*).



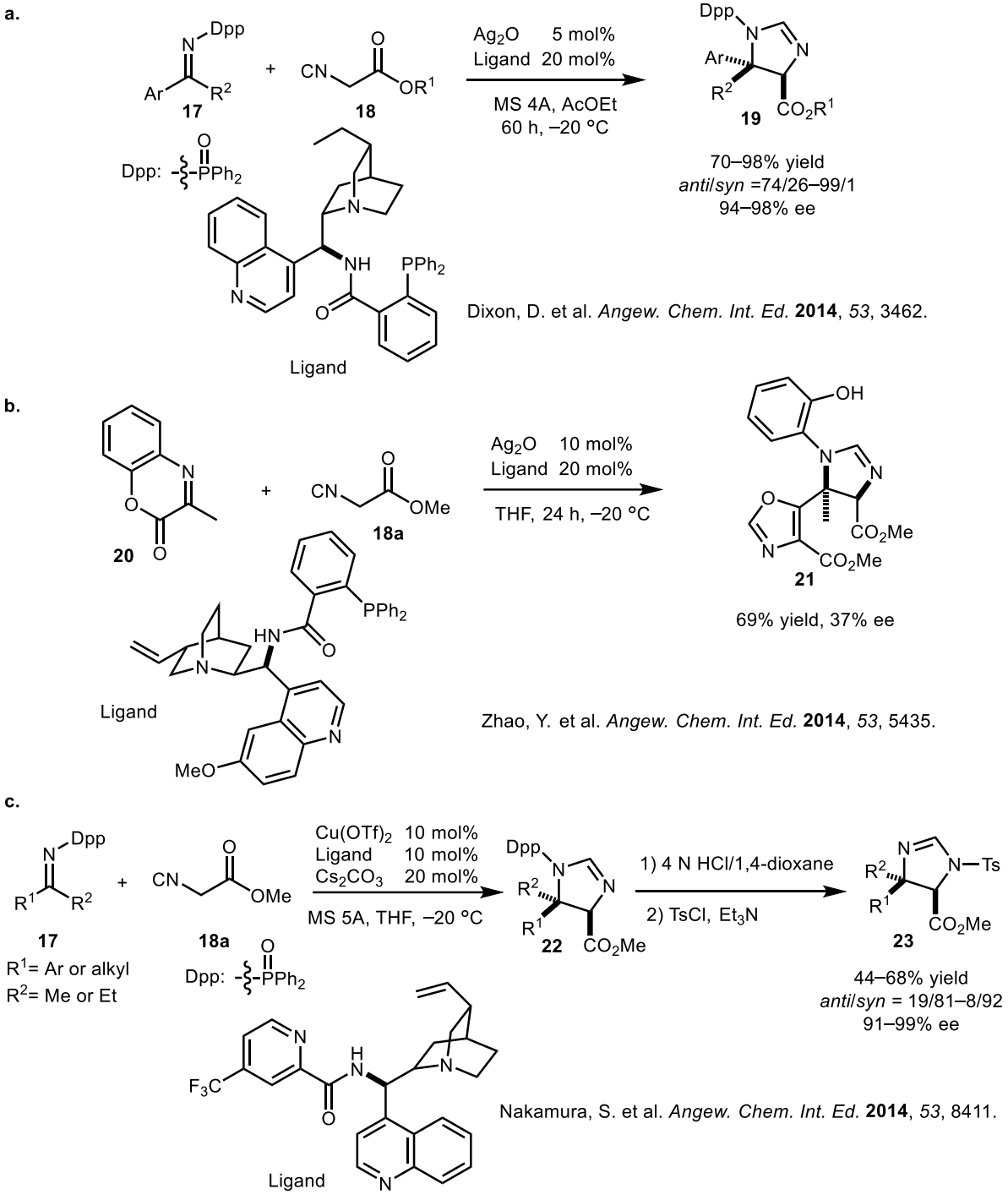
Scheme 7. Enantioselective three-component Mannich-type reaction



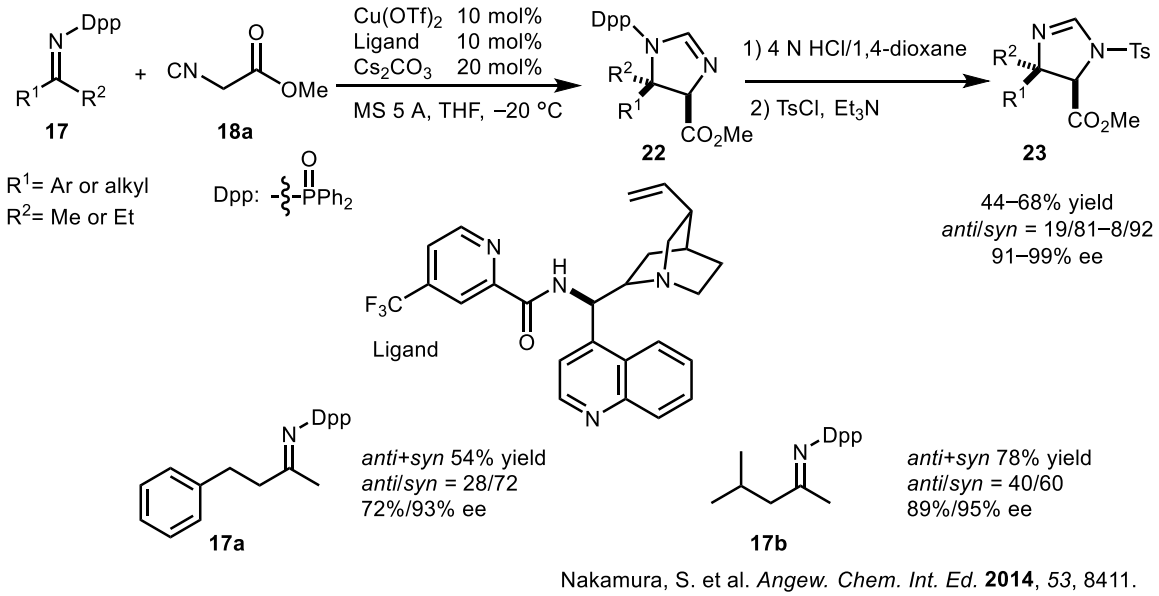
Scheme 8. Proposed mechanism: the trapping of phoshphoramidate ammonium ylides with imino esters

It is well-known that imidazoline heterocycles can be easily converted into *α*,*β*-diamino derivatives under hydrolytic or reductive conditions.[14] Thus, a potential method to access to *α*,*β*-diamino derivatives is the synthesis via imidazoline heterocycles.[15] Direct catalytic Mannich-type addition/cyclization reactions of isocyanoester pronucleophiles with imine electrophiles provide a promising strategy for the synthesis of imidazolines.[16] In 2014, the groups of Dixon, Zhao and Nakamura independently reported the cinchona alkaloid-catalyzed enantio- and diastereoselective Mannich-type reaction of isocyanoacetates **18** with ketimines **17** to build the optically active imidazoline derivatives (**Scheme 9**). Dixon et al. used cinchona alkaloid-derived aminophosphine as a chiral ligand, and in the presence of Ag_2O, the reaction provided the *anti* isomers **19** as the major products (**Scheme 9**, **a**).[17] Zhao et al. focused on cyclization of *α*-ketiminoester **20** with isocyanoacetate **18a**, reporting one ketimine substrate (**Scheme 9**, **b**).[18] Nakamura et al. employed $Cu(OTf)_2$ as a cocatalyst, obtaining *syn* isomers **22** as the major products (**Scheme 9**, **c**).[19] Among them, a few successful aliphatic substrates have been reported. Dixon and Nakamura both focused on aromatic ketimines, and

there are only two aliphatic ketimines in Nakamura's report (**Scheme 10**).[19] Base on those reports, there remains room for improvement with respect to substrate generality, in particular for aliphatic ketimines.

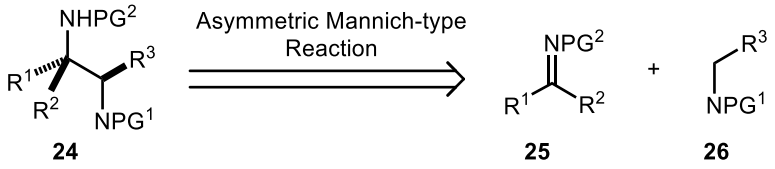


Scheme 9. Mannich-type reaction of isocyanoacetates with ketimines

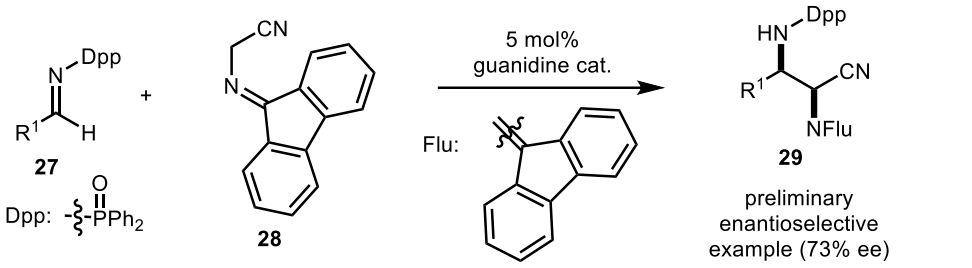


Scheme 10. Mannich-type reaction of alkyl ketimines

By utilizing soft-soft interactions,[20] the Shibasaki group recently found that diphenylthiophosphinoyl (thioDpp) protected ketimines showed high reactivity in the rapid construction of tetrasubstituted stereogenic centers, and even aliphatic ketimines gave excellent results.[21] Thus, I envisioned to employ thioDpp protected ketimines in the construction of *α*,*β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters. To construct this unit via a catalytic asymmetric Mannich-type reaction, pronucleophile **26** which contains an *α*-amino group is required (**Scheme 11**). Given the potential for divergent functional group interconversions, pronucleophile **26** containing a cyano group (R^3 = CN) is a desirable candidate, as cyano groups may be converted to other functional groups,[22] and the products, *α*,*β*-diamino nitriles, would serve as similarly versatile chiral building blocks. Catalytic enantioselective reactions of acetonitrile containing an *α*-*N*-alkylidene functionality is rare.[23] Recently, Kobayashi et al. employed *N*-(9-fluorenylidene)-*α*-aminoacetonitrile **28** as a pronucleophile in a Mannich-type reaction, and it showed high reactivities (**Scheme 12**).[24] In their report, the use of a chiral guanidine as catalyst and aldimines as electrophiles gave Mannich products with moderate enantioselectivity.



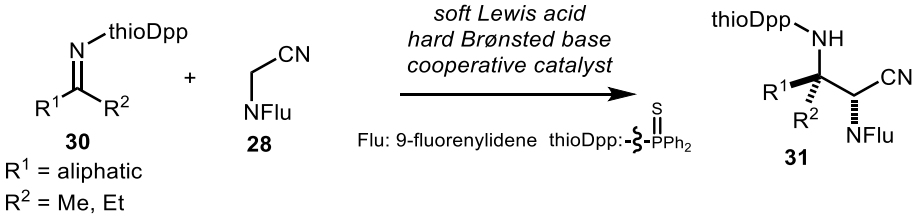
Scheme 11. Retrosynthetic analysis for **24**



Kobayashi, S. et al. *J. Am. Chem. Soc.* **2010**, *132*, 3244.
Kobayashi, S. et al. *Tetrahedron* **2012**, *68*, 7558.

Scheme 12. Mannich-type reaction of *N*-(9-fluorenylidene)-*α*-aminoacetonitrile to Dpp-aldimines

In continuing studies on a cooperative soft Lewis acid/hard Brønsted base catalysis in the Shibasaki group,[25] it has been observed that both nitrile and thioDpp functionalities can be activated by a soft Lewis acid. Based on these traits, I envisioned that *α*,*β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters could be constructed via the cooperative soft Lewis acid/hard Brøsted base catalyzed Mannich-type reaction of *N*-(9-fluorenylidene)-α-aminoacetonirtile **28** with alkyl substituted *N*-(diphenylthiophosphinoyl)ketimines **30** (**Scheme 13**).

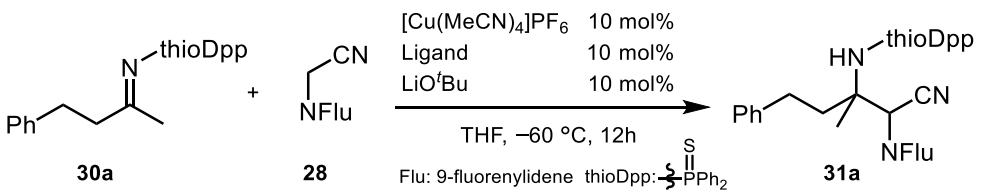


Scheme 13. Mannich-type reaction of *N*-(9-fluorenylidene)-*α*-aminoacetonitrile to thioDpp-ketimines

2.1.2 Screening of reaction conditions

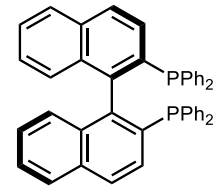
Investigations into this idea commenced with the reaction of *N*-(9-fluorenylide)-*α*-aminoacetonitrile **28** with *N*-thioDpp ketimine **30a** in the presence of commercially available $[Cu(MeCN)_4]PF_6$ and LiO^{t}Bu. Several chiral ligands were screened at –60 °C in THF (**Table 1**), and the reaction delivered the desired product **31a** with good to excellent conversion. Biaryl-type phosphine ligands (entries 1–9), (*S*,*S*)-Diop (entry 10), (*R*,*R*$_p$)-Taniaphos (entry 11) and (*S*$_p$,*S'*$_p$,*R*)-Mandyphos (entry 12) afforded the *anti* isomer as the major product. On the other hand, (*R*,*R*)-QuinoxP (entry 13) and (*S*)-Binapine (entry 14) favored the *syn* isomer. Other type of ligands almost completely failed to promote the reaction (entries 15–19). Increasing the steric bulk of the phosphine substituents on Garphos-type ligands improved diastereoselectivity significantly. However, the use of Garphos type ligands with too bulky or electron-withdrawing phosphine substituents slightly dropped the diastereoselectivity compared with medium-sized substituents (entries 4–9). For high diastereoselectivity and enantioselectivity, (*R*)-DMM-Garphos was found to be the optimal ligand, delivering the desired product **31a** in 99% Conv., 85/15 *dr*, and 88% *ee* for the *anti* isomer.

Table 1. Ligand Screening.[a]

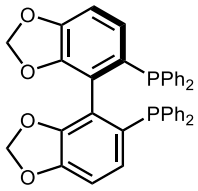


Entry	Ligand	Conv.[b] (%)	*dr*[b] (*anti*/*syn*)	ee[c] (%)
1	(*R*)-Binap	99	59/41	39/7
2	(*R*)-Segphos	72	69/31	54/35
3	(S)-DTBM-Biphep	53	53/47	–77/4
4	(*R*)-Garphos	99	62/38	38/47
5	(*R*)-Tol-Garphos	99	58/42	22/50
6	(*R*)-Xyl-Garphos	99	81/19	76/28
7	(*R*)-DMM-Garphos	99	85/15	88/43
8	(*R*)-DTBM-Garphos	95	78/22	90/–21
9	(*R*)-BTFM-Garphos	62	72/28	47/–53
10	(S,S)-Diop	70	73/27	–12/17
11	(R,R_p)-Taniaphos	47	68/32	–79/38
12	(S_p,S'_p,R)-Mandyphos	85	63/37	13/–18
13	(*R*,*R*)-QuinoxP	52	35/65	12/–28
14	(*S*)-Binapine	71	40/60	3/–25
15	(R_a,*S*,*S*)-SpriroBox	trace if any	–	–
16	(*R*,*R*)-*O*-Pinap	trace if any	–	–
17	(*R*,*R*)-Dipamp	trace if any	–	–
18	Carbophos	trace if any	–	–
19	CTH-(*S*)-P-Phos	trace if any	–	–

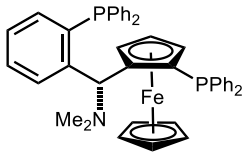
[a] **28**: 0.1 mmol, **30a**: 0.11 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis.



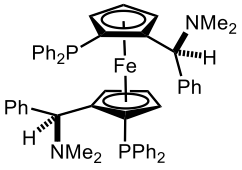
(*R*)-Binap



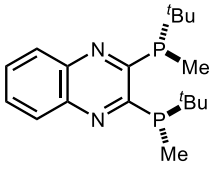
(*R*)-Segphos



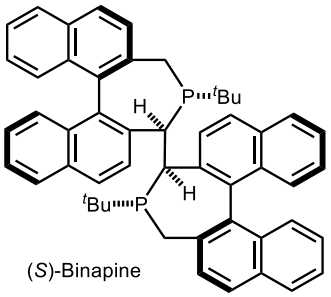
(R,R_p)-Taniaphos



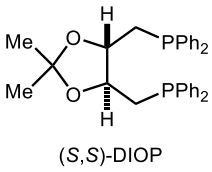
(S_p,S'_p,R)-Mandyphos



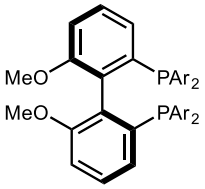
(*R*,*R*)-QuinoxP



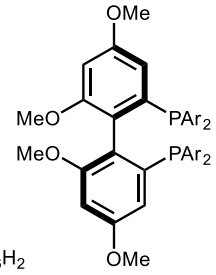
(*S*)-Binapine



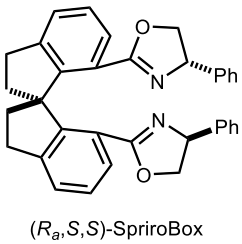
(*S*,*S*)-DIOP



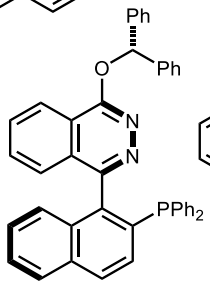
(*S*)-DTBM-Biphep
Ar= 3,5-^{t}Bu$_2$-4-MeO-C$_6$H$_2$



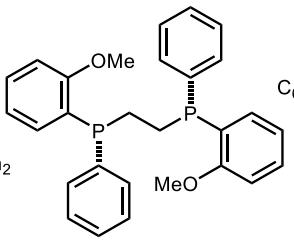
(*R*)-Garphos
Ar= Ph
(*R*)-Tol-Garphos
Ar= 4-Me-C$_6$H$_4$
(*R*)-Xyl-Garphos
Ar= 3,5-Me$_2$-C$_6$H$_3$
(*R*)-DMM-Garphos
Ar= 3,5-Me$_2$-4-MeO-C$_6$H$_2$
(*R*)-DTBM-Garphos
Ar= 3,5-^{t}Bu$_2$-4-MeO-C$_6$H$_2$
(*R*)-BTFM-Garphos
Ar= 3,5-(CF$_3$)$_2$-C$_6$H$_3$



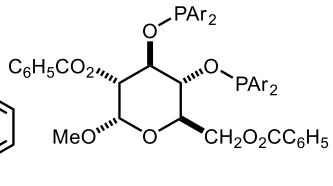
(R_a,*S*,*S*)-SpriroBox



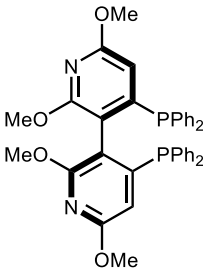
(*R*,*R*)-*O*-Pinap



(*R*,*R*)-Dipamp

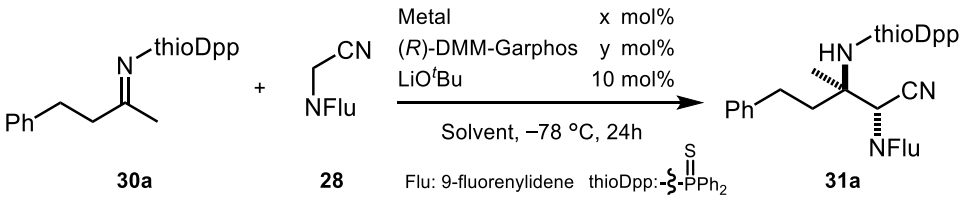


Carbophos
Ar= 3,5-Me$_2$-C$_6$H$_3$



CTH-(*S*)-P-Phos

Table 2. Metal Screening.[a]



30a **28** Flu: 9-fluorenylidene thioDpp: **31a**

Entry	Metal	x	y	Solvent	Conv.[b] (%)	*anti*/*syn*[b]	ee[c] (%)
1	$[Cu(MeCN)_4]PF_6$	10	10	THF	83	91/9	94/–
2	$[Cu(MeCN)_4]PF_6$	5	10	THF	45	42/58	90/7
3	$[Cu(MeCN)_4]PF_6$	5	10	toluene	96	91/9	94/37
4	$[Cu(MeCN)_4]ClO_4$	10	10	toluene	97	86/14	93/–
5	$CuBF_4$	10	10	toluene	95	80/20	92/–
6[d]	CuMes	10	10	toluene	77	84/16	92/–
7[e]	CuMes+Chromanol	10	10	toluene	16	80/20	–
8	CuOTf·1/2 toluene	10	10	toluene	trace if any	–	–
9	CuI	10	10	toluene	trace if any	–	–
10[f]	$CuBAr^F$	10	10	toluene	trace if any	–	–
11	$[Cu(MeCN)_4]PF_6$	5	5	toluene	96	91/9	94/–
12	$[Cu(MeCN)_4]PF_6$	2	2	toluene	73	90/10	93/–
13	$[Cu(MeCN)_4]PF_6$	1	1	toluene	59	75/25	92/–
14[g]	$[Cu(MeCN)_4]PF_6$	3	5	toluene	91	91/9	94/–

[a] **28**: 0.1 mmol, **30a**: 0.11 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis. [d] CuMes: Mesitylcopper(I). [e] Chromanol: 2,2,5,7,8-pentamethyl-6-chromanol. [f] $CuBAr^F$: Copper(I) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. [g] Isolated yield.

Further reaction condition screening wiht (*R*)-DMM-Garphos was performed (**Table 2**). Both diastereo- and enantioselectivity were improved by lowering the reaction temperature to –78 °C (entry 1). A detrimental effect on the diastereoselectivity was observed when decreasing the amount of Cu(I) complex relative to LiO^{t}Bu, while high enantioselectivity of the *anti* isomer was still maintained (entry 1 versus 2). This negative effect was suppressed by switching the solvent to toluene (entry 3). Using toluene as solvent, other Cu(I) sources were examined (entries 4–10), as was the ratio of metal to base (entries 11–14). Cu(I) sources with different counteranions slightly dropped the diastereoselectivity, while the product was obtained with similar enantioselectivities (entries 4–6). It should be noted that the additive, 2,2,5,7,8-pentamethyl-6-chromanol, which showed a positive effect in previous reports published by the Shibasaki group,[26] gave much lower conversion compared with the system without additive (entry 6 versus 7). No reaction took place when CuOTf·1/2 toluene (entry 8), CuI (entry 9) or Copper(I) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($CuBAr^F$) (entry 10) were used as Cu(I) sources. Next, the ratio between metal and base was probed (entries 11–14). Decreasing the loading of Cu(I) complex and base caused a reduction in *dr* and yield. Finally, it was found that the catalyst loading could be reduced to 3 mol% of the Cu(I)/(*R*)-DMM-Garphos complex and 5 mol% of LiO^{t}Bu without losing catalytic efficiency, and under these reaction conditions, **31a** was obtained in 91% isolated yield, 91/9 *dr*, and 94% *ee* for the *anti* isomer (entry 14).

2.1.3 Control experiments

To gain futher insight on the reaction, additional control experiments were performed (**Scheme 14**). LiO^{t}Bu alone catalyzed the reaction to give almost exclusively racemic *syn* product in THF at –78 °C (**Scheme 14**, **a**). In sharp contrast, LiO^{t}Bu completely failed to promote the reaction in toluene at –78 °C (**Scheme 14**, **b**). Thus, high *anti*/*syn* ratio was observed even with the decreased amount of Cu(I) complex relative to LiO^{t}Bu when switching the solvent from THF to toluene (**Table 2**, entry 2 versus 3). I ascribed this phenomenon to the solvent effect (**Figure 1**).

Treatment of Schiff base **28** with LiO^{t}Bu can form different ion-pairs **33** and **34** depending on the nature of the solvents. An intimate ion-pair **33** could be formed in the non-polar solvent toluene at –78 °C. Thus-formed ion-pair **33** would be less nucleophilic and therefore the reaction would take place only in the presence of Cu(I) catalyst, giving the *anti* isomer as the major product (**Path a**). In contrast, a loose ion-pair **34** could be formed in THF at –78 °C due to the complexation of THF to Li^+, making the anion more nucleophilic. In this case, the reaction could proceed without Cu(I) catalyst, and the reaction would give racemic *syn* isomer (**Path b**). Under the identified reaction conditions, in the presence of Cu(I)/(*R*)-DMM-Garphos complex and LiO^{t}Bu in toluene at –78 °C, the *anti* isomer could not be converted to *syn* isomer by epimerization. However, *anti* isomer could be partially epimerized to *syn* isomer with LiO^{t}Bu in toluene at room temperature. In the absence of base, Cu(I) complex could not promote the reaction (**Scheme 14**, **c**). Much lower conversion and stereoselectivity were observed when the *O*-analogue, *N*-diphenylphosphinoyl (Dpp) ketimine, was subjected to the identified reaction conditions (**Scheme 14**, **d**), suggesting that the specific interaction between the thioDpp group and Cu(I) complex was crucial for the C-C bond formation with high stereoselectivity.

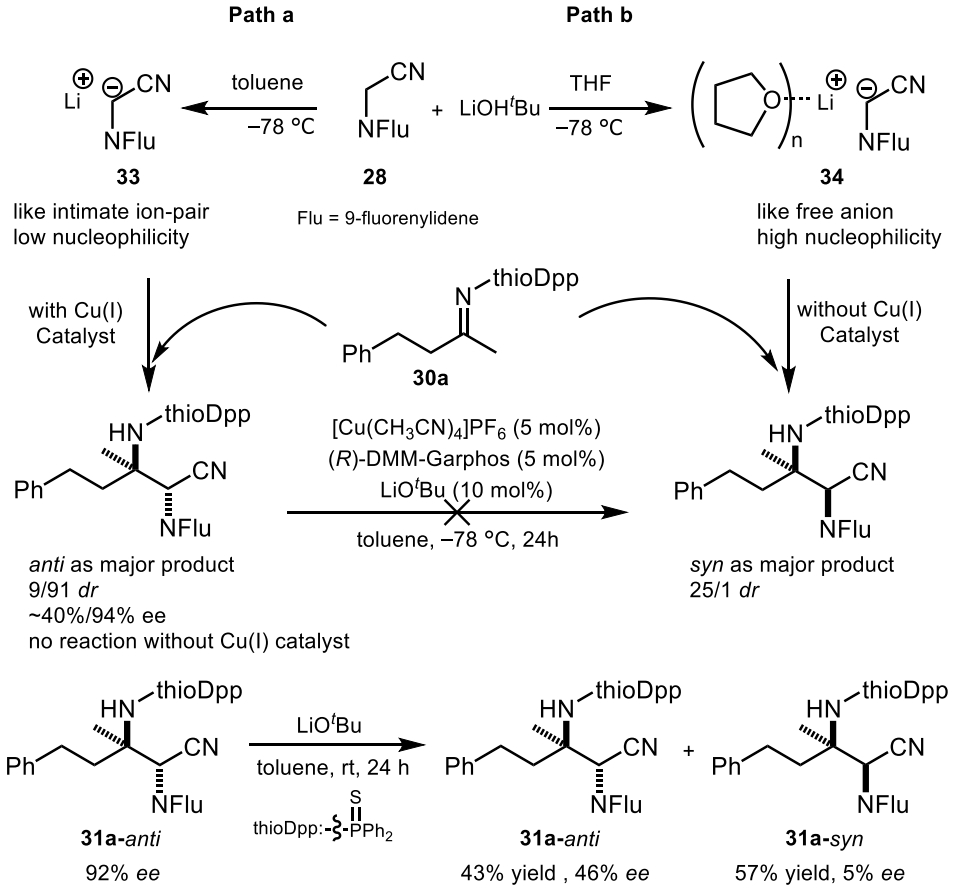
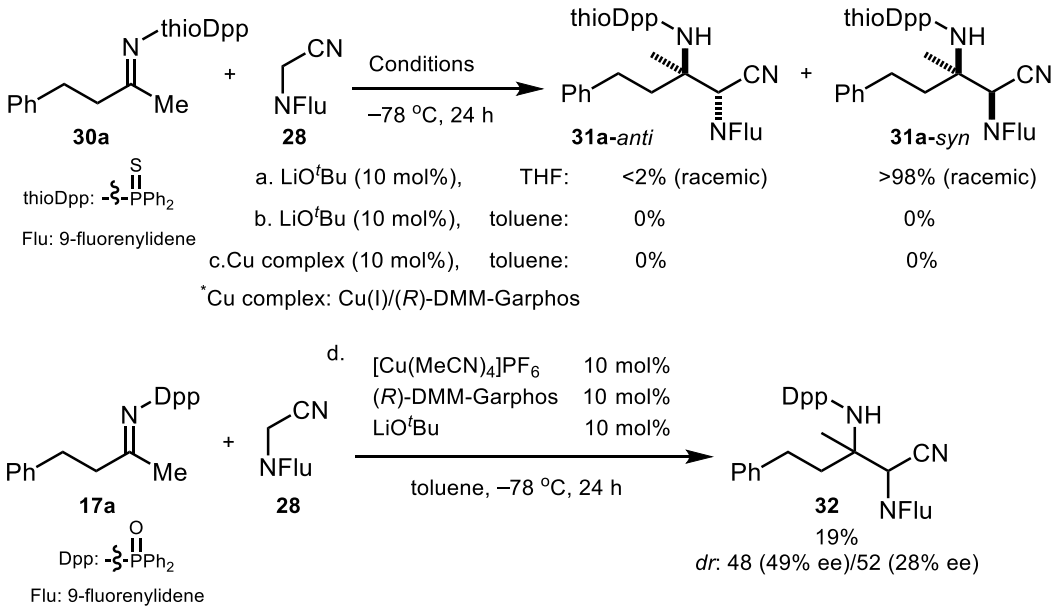


Figure 1. Solvent effect

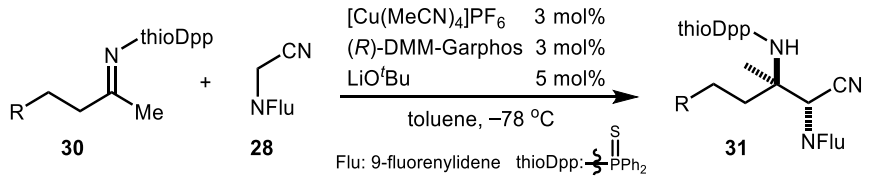


Scheme 14. Control experiments

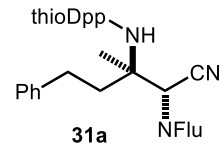
2.1.4 Investigation of substrate scope

With the optimum reaction conditions in hand, the substrate scope was further evaluated (**Table 3**). Running the reaction on gram-scale gave a similar outcome (entry 1). Ketimines bearing a 2-naphthyl group and a linear or branched alkyl chain gave products in excellent yield with high stereoselectivity (entries 2–4). Ketimines bearing unsaturated bonds, including internal alkynes, served as suitable substrates (entries 5–7). Oxygen functionalities, such as ether and ester which could coordinate to the catalyst were tolerated (entries 8,9). Cyano and xanthine groups slightly decreased the stereoselectivity (entries 10,11). This reaction system was fairly sensitive to steric hindrance, and the reaction of a ketimine bearing an ethyl group was less efficient. In this case, (R,R_p)-Taniaphos was found to give the desired product with reasonable results (entry 12). Moderate enantioselectivity was observed for the cyclic ketimine (entry 13).

Table 3. Substrate scope

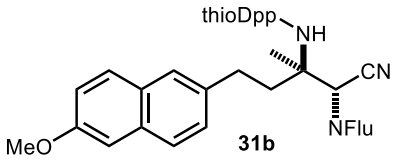


1



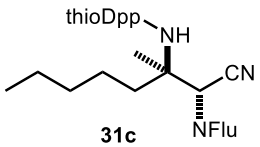
48 h, 95%
anti/syn = 91/9
93% ee *(anti)*
1.09 g scale

2



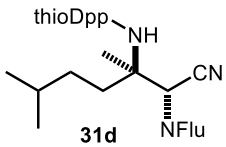
48 h, 91%
anti/syn = 93/7
94% ee *(anti)*

3



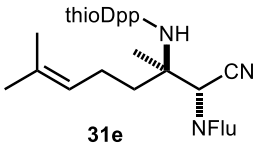
72 h, 88%
anti/syn = 90/10
91% ee *(anti)*

4



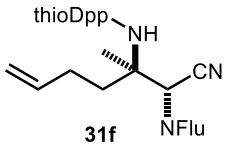
48 h, 97%
anti/syn = 95/5
95% ee *(anti)*

5



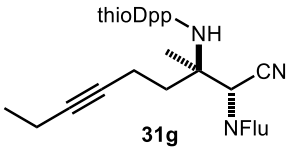
48 h, 96%
anti/syn = 91/9
90% ee *(anti)*

6



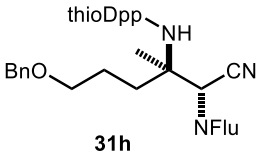
72 h, 92%
anti/syn = 90/10
90% ee *(anti)*

7



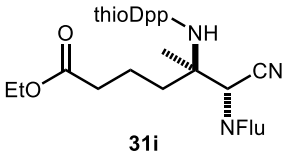
72 h, 97%
anti/syn = 83/17
88% ee *(anti)*

8



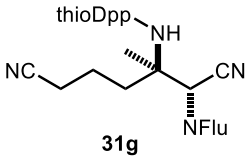
72 h, 88%
anti/syn = 88/12
90% ee *(anti)*

9



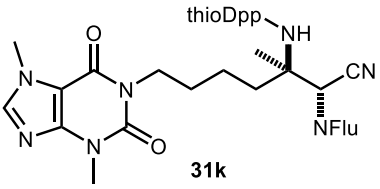
72 h, 95%
anti/syn = 92/8
92% ee *(anti)*

10



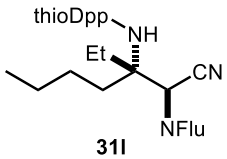
48 h, 99%
anti/syn = 85/15
87% ee *(anti)*

11



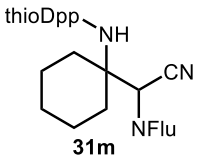
72 h, 85%
anti/syn = 83/17
84% ee *(anti)*
(6 mol% Cu(I) complex and 10 mol% LiO*t*Bu)

12



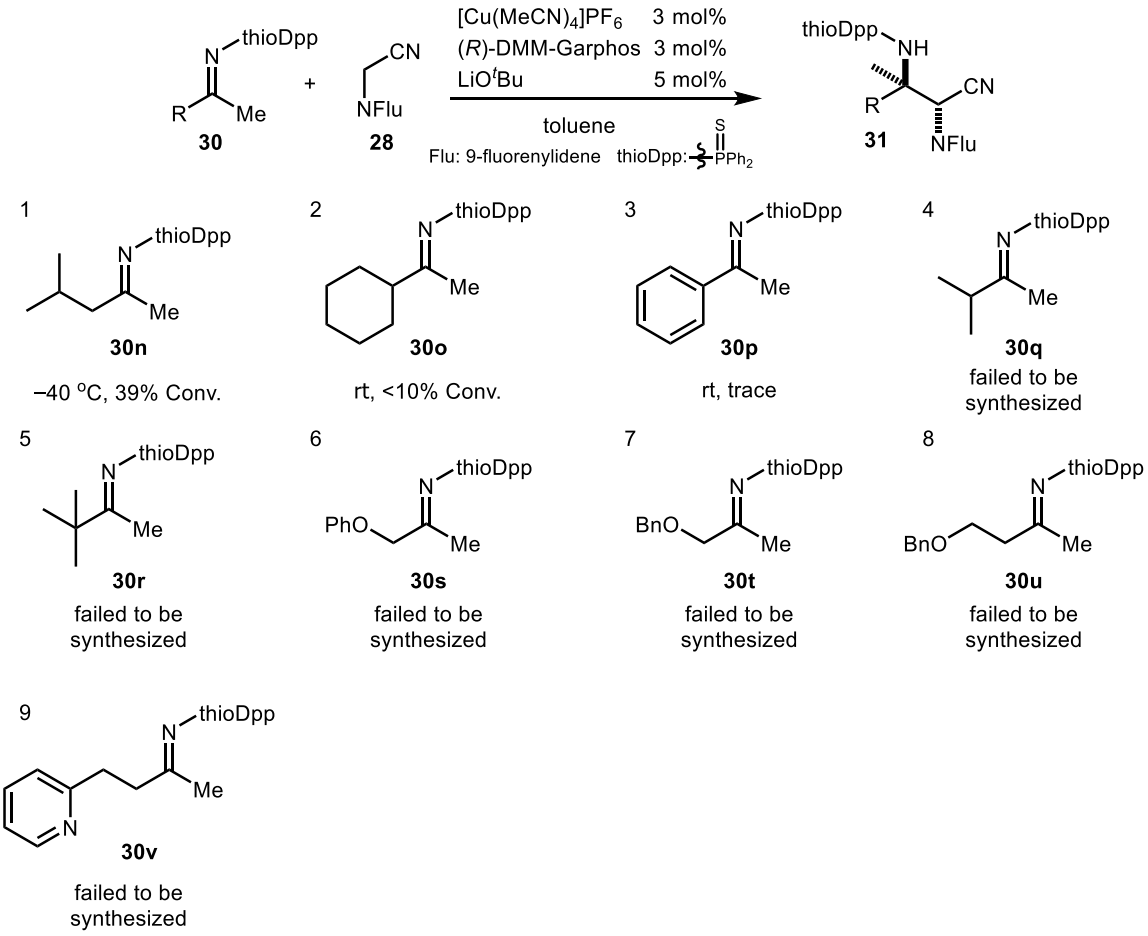
72 h, 61%
anti/syn = 77/23
83% ee *(anti)*
(Taniaphos, –60 °C,10 mol% Cu(I) complex and 30 mol% LiO*t*Bu)

13



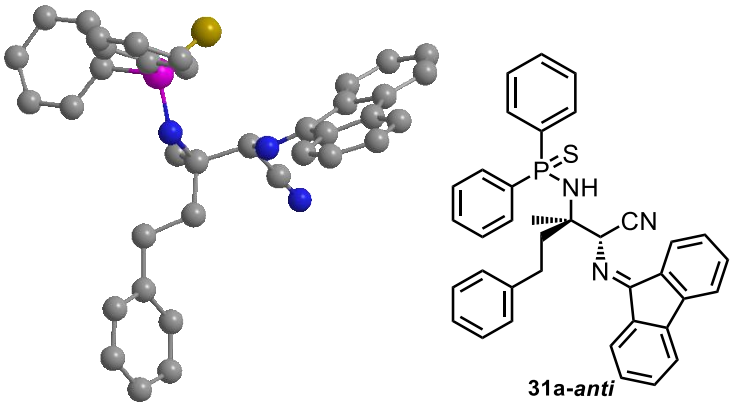
24 h, 99%
67% ee

Table 4. Unsuccessful examples

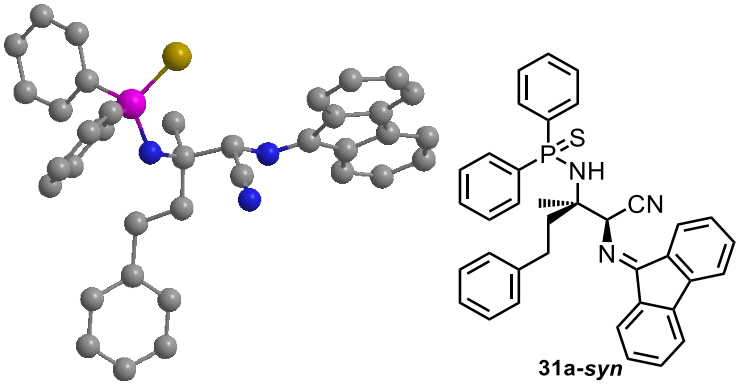


Some unsuccessful examples are described in **Table 4**. Under the identified reaction conditions, ketimines **30n** and **30o** bearing substituents at the α or β position gave much lower conversion (entries 1–2). Ketimine **30p** derived from acetophenone gave trace amount of corresponding product even at room temperature (entry 3). Some ketimines could not be prepared by standard conditions (entries 4–5). Ketimines bearing an α or β ether group also failed to be synthesized (entries 6–8). No ketimine was formed using a pyridine containing ketone (entry 9).

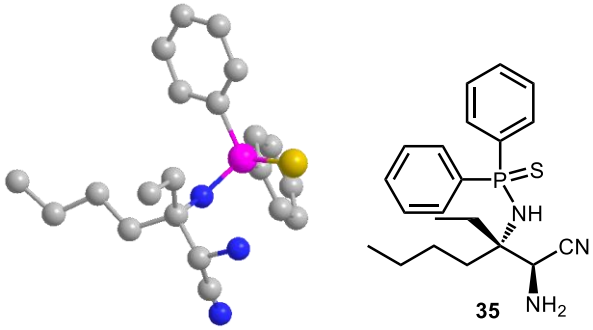
2.1.5 Determination of absolute configuration



a. X-ray crystal structure of **31a**-*anti* isomer (major)



b. X-ray crystal structure of **31a**-*syn* isomer (minor)



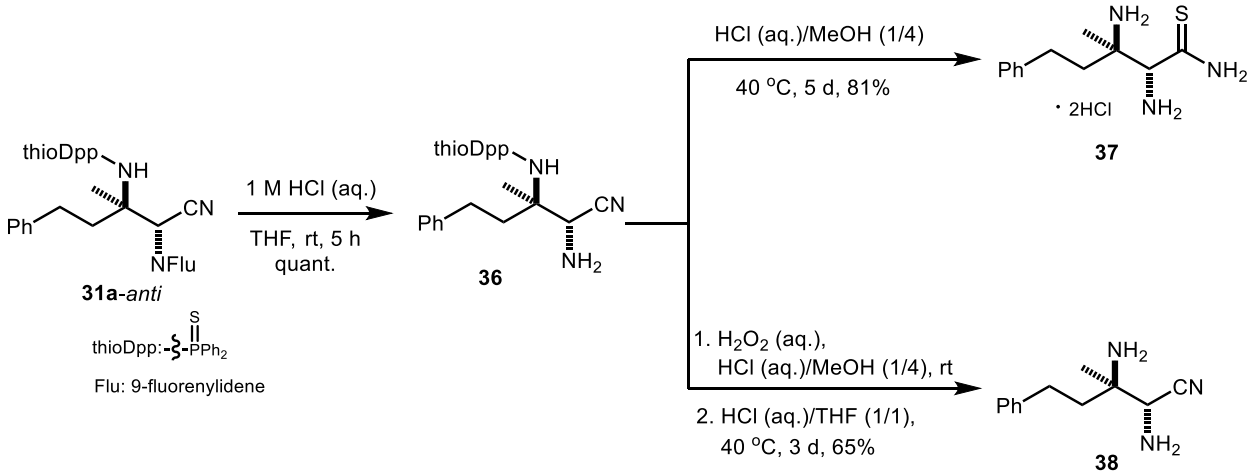
c. X-ray crystal structure of ethyl substituted product **35** (major)

Figure 2. X-ray crystal structure of the product[27]

The absolute configuration of the products, **31a**-*anti* and **31a**-*syn*, were determined by X-ray crystallographic analysis (**Figure 2, a and b**). The relative and absolute configurations of other products were deduced by analogy. The major stereoisomer of ethyl substituted product **31l** was also in the *anti*-conformation, which was revealed by X-ray crystallographic analysis of free amine **35** (**Figure 2, c**).

2.1.6 Transformation of the product

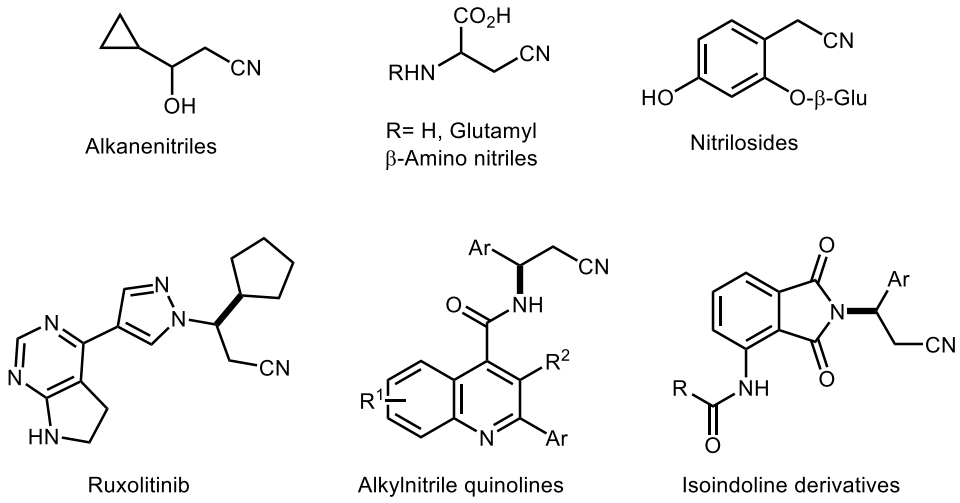
Product **31a**-*anti* was treated with 1 M HCl (aq.) to remove the 9-fluorenylimine moiety to give **36** (**Scheme 15**). A solution of the thus-obtained product in a mixture of 12 M HCl/MeOH (1:4) was heated to 40 °C, furnishing primary thioamide **37** which contains two free vicinal amine groups. The mechanism would potentially be via an intramolecular nucleophilic attack of the sulfur atom to the cyano group. The thioDpp group was converted to the Dpp group with H_2O_2, and the crude product was treated with a mixture of 12 M HCl/THF (1:1) at 40 °C to give diamino nitrile **38**.



Scheme 15. Transformation of the product

2.2 Construction of *α,α*-disubstituted *α*-amino acid derivatives using MeCN as nucleophile

Cyanoalkyl moieties are widely found in many natural products such as alkanenitriles, *β*-amino nitriles and nitrilosides, and biological active molecules such as ruxolitinib, alkylnitrile quinolones and isoindoline derivatives (**Scheme 16**).[28]



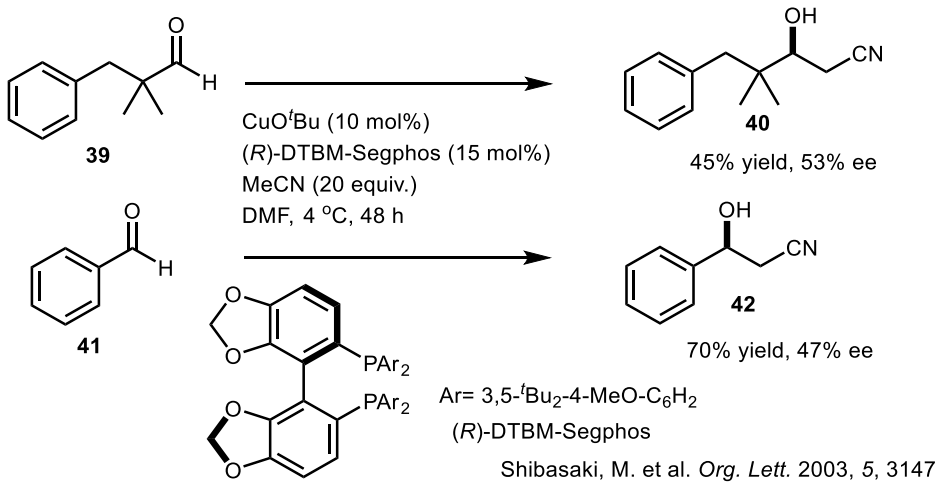
Scheme 16. Natural products and pharmaceuticals containing alkylnitrile moieties

In the previous section (see **Section 2.1**), activated nitrile **28** was used as a pronucleophile in the Mannich-type reaction. Simple alkylnitriles also represent a range of useful building blocks. Thus, I envisioned to employ simple alkylnitriles as pronucleophiles in the Mannich-type reaction with ketimines. The reaction could deliver useful nitrile containing tetersubstitued stereocenters.

2.2.1 Literature known asymmetric reaction using simple alkylnitriles as pronucleophiles

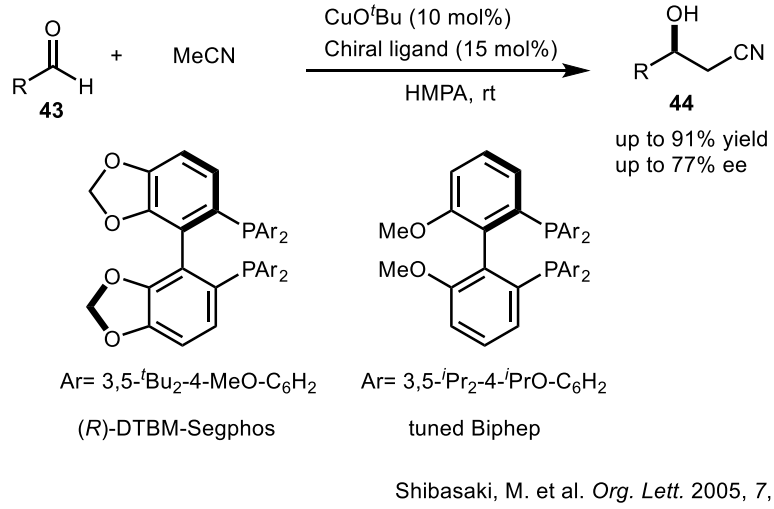
In addition to a range of nitrile-containing products, divergent functional group transformation of nitrile group further enhances the importance of the nitrile functionality.[22] Because of the high pK_a values of *α*-hydrogen of alkyl nitriles (31.3 in DMSO and 28.9 in H_2O for acetonitrile[29]), reports on catalytic asymmetric reactions directly using simple alkylnitriles as pronucleophiles are rare.[30]

The first example of direct catalytic asymmetric reaction using simple alkylnitrile as pronucleophile was achieved by Shibasaki et al. in 2003. They reported a direct catalytic asymmetric coupling of acetonitrile with aldehyde, and the reaction gave the corresponding product in moderate yield and moderate *ee* (**Scheme 17**).[31] The author mentioned that the soft-soft interaction between copper (I) and the nitrile group played key roles for catalytic generation of α-cyanocarbanion.



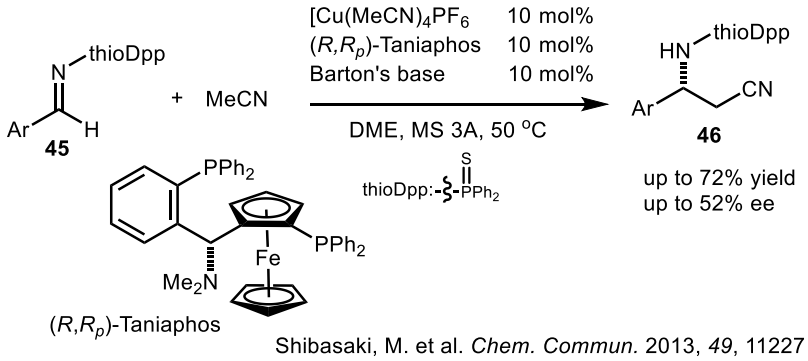
Scheme 17. Direct catalytic enantioselective cyanomethylation of aldehydes

In 2005, the same group accomplished the direct catalytic enantioselective addition of acetonitrile to a wide range of aldehydes (**Scheme 18**).[32] The use of hexamethylphosphoramide (HMPA) as solvent was crucial for inhibiting the self-condensation of aldehyde, improving the yield greatly. Together with bulky chiral phosphine ligand, the corresponding products were obtained in up to 91% yield with up to 77% *ee*.



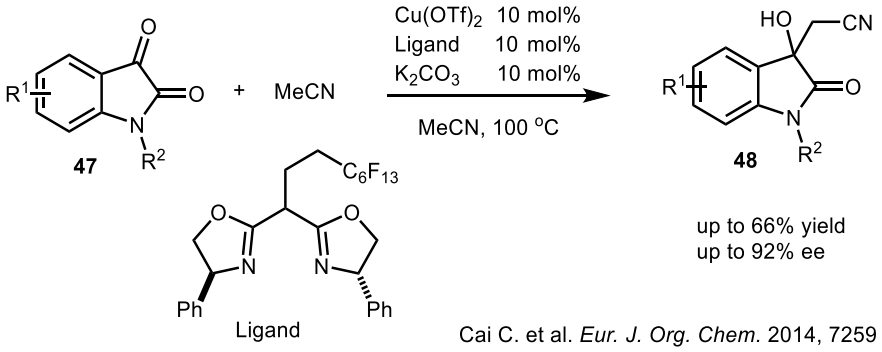
Scheme 18. Catalytic enantioselective nitrile aldol reaction

In 2013, based on their soft-soft interaction strategy, Shibasaki et al. described the first example of copper-catalyzed asymmetric addition of acentonitrile to *N*-thioDpp aldimine, affording the corresponding adducts in moderate yields (up to 72% yield) and with moderate enantioselectivities (up to 52% *ee*) (**Scheme 19**).[33] In their report, a Cu-based soft Lewis acid-hard Brønsted base cooperative catalytic system was used and the soft-soft interactions such as Cu(I)/acetonitrile and Cu(I)/*N*-thioDpp was key for promoting the reaction. The reaction did not take place when using the *O*-analogue *N*-Dpp aldimine.



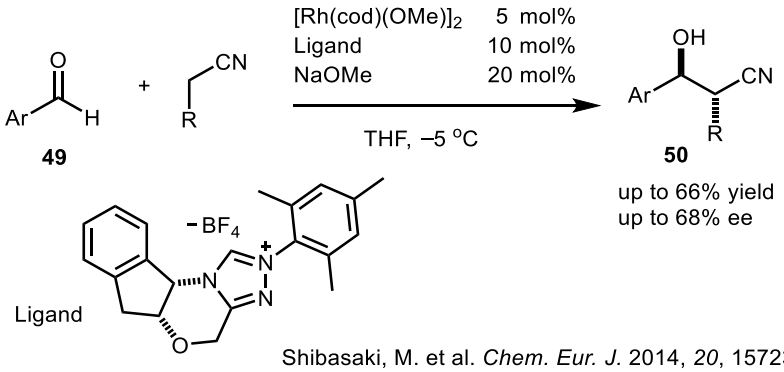
Scheme 19. Direct catalytic asymmetric addition of MeCN to *N*-thioDpp imines

The units of chiral 3-hydroxy-2-oxindole which contains a quaternary carbon center at the 3-position are widely embedded in many natural products and biological active molecules.[34] In 2014, Cai et al. reported the $Cu(OTf)_2$/bis(oxazoline) catalyzed enantioselective addition of MeCN to isatins to construct useful structural cores (**Scheme 20**),[35] obtaining the corresponding adducts in moderate yields (up to 66% yield) and with good to excellent enantioselectivities (up to 92% *ee*).



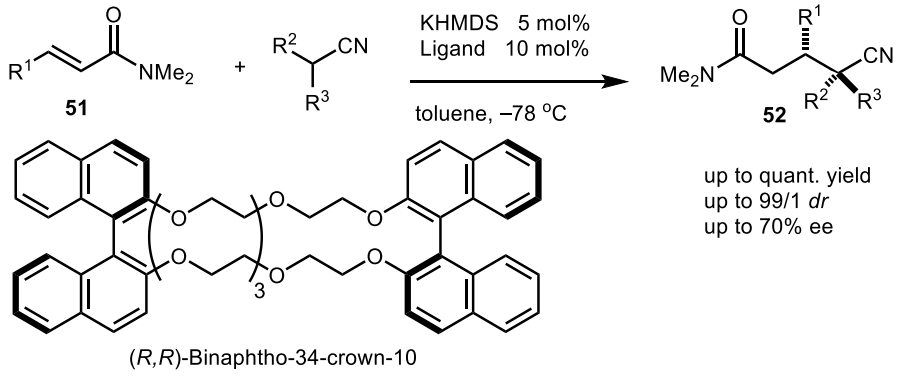
Scheme 20. Enantioselective addition of MeCN to isatins

Based on their previous reports that chiral phosphine ligands failed to give high enantioselectivity in the asymmetric nitrile chemistry, Shibasaki et al. searched for other chiral systems in the enantioselective addition of alkylnitriles. In 2014, in the presence of chiral NHCs and $[Rh(cod)OMe]_2$, they achieved the direct catalytic asymmetric addition of alkylnitriles to aldehydes (**Scheme 21**).[36] Although only moderate enantioselecitvities were observed (up to 68% *ee*), this work was yet one more chiral system employed to improve the enantioselecitvity in asymmetric nitrile chemistry.



Scheme 21. Direct catalytic asymmetric addition of alkylnitriles to aldehydes

In 2015, Kobayashi et al. reported the first example of catalytic asymmetric Michael addition of simple alkylnitriles to *α,β*-unsaturated amides **51** (**Scheme 22**).[37] Chiral crown ethers were synthesized and used in their study. Under the identified conditions, *α*-alkyl substituted nitriles could deliver the corresponding adducts **52** in moderate to excellent yields, moderate to excellent diastereoselectivities and moderate enantioselectivities. However, the simplest nitrile, MeCN, failed to give the Michael addition product **52**.



Kobayashi, S. et al. *Chem. Asian J.* 2015, *10*, 2143

Scheme 22. Catalytic asymmetric Michael addition

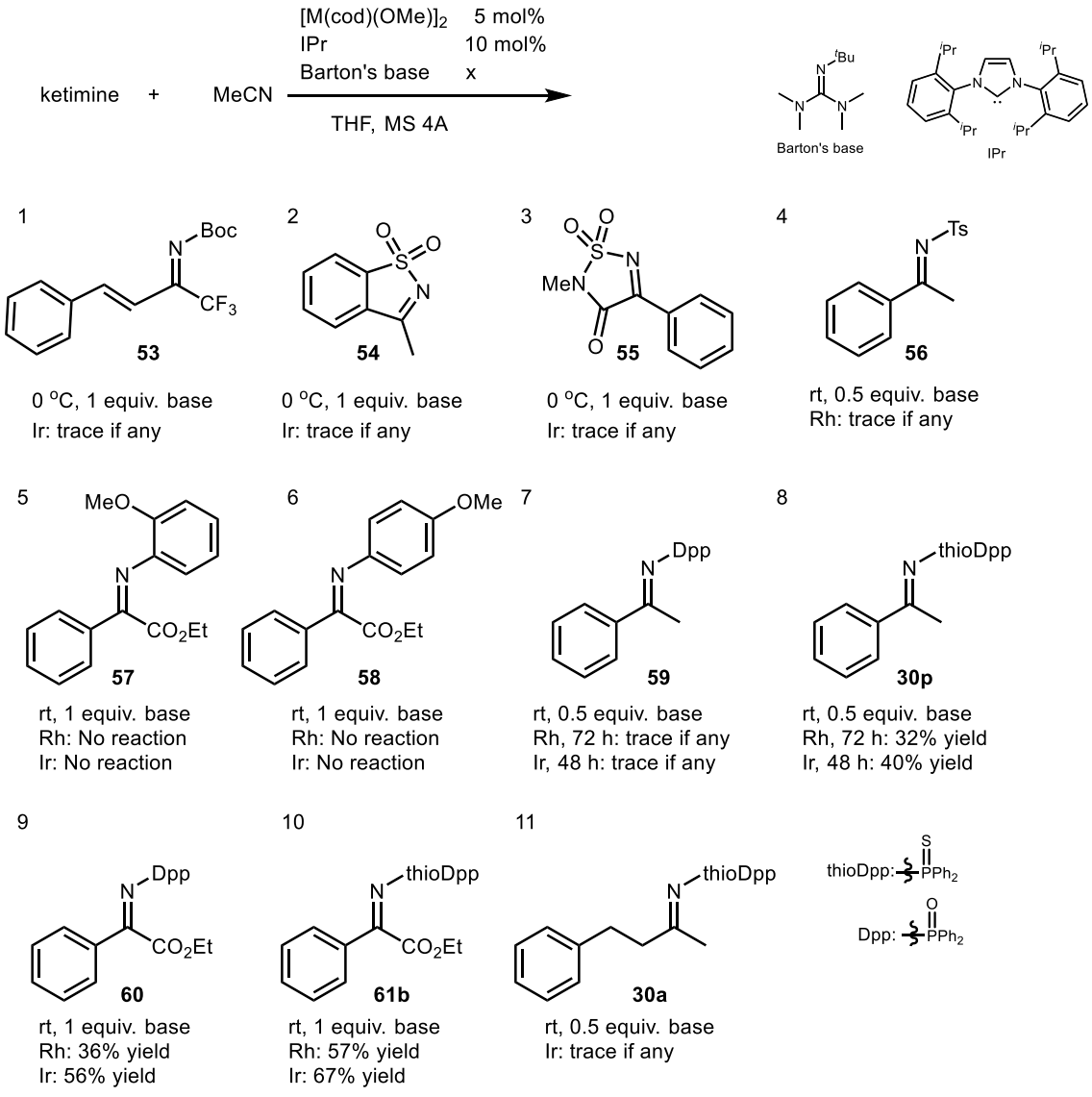
Over the past few years, despite extensive efforts, the use of simple alkylnitriles as pronucleophiles in a direct catalytic asymmetric reaction remains a challenging task. As a part of ongoing interest in the catalytic asymmetric addition of simple alkylnitriles in Shibasaki group, and also considering the utility of nitrile containing building blocks, I became interested in whether simple alkylnitriles could serve as suitable pronucleophiles in a Mannich-type reaction with ketimines to give nitrile containing tetersubstitued stereocenters.

2.2.2 Screening of reaction conditions

Ketimine screening

Based on the previously described report by the Shibasaki group,[36] *α*-cyanocarbanion could be generated from acetonitrile using a Rh/NHC complex with base. I was interested in applying this system in the testing of various ketimines in the direct coupling reaction with acetonitrile (**Table 5**). Among them, only *N*-Dpp and *N*-thioDpp protected aromatic ketimines could deliver the corresponding adducts, and the latter showed a better outcome, albeit with moderate yield (entries 8–10). Switching to an Ir/NHC complex provided a higher catalytic efficiency (entries 8–10). Other types of ketimines, including *N*-thioDpp alkyl ketimine, failed to give the corresponding products (entries 1–7,11).

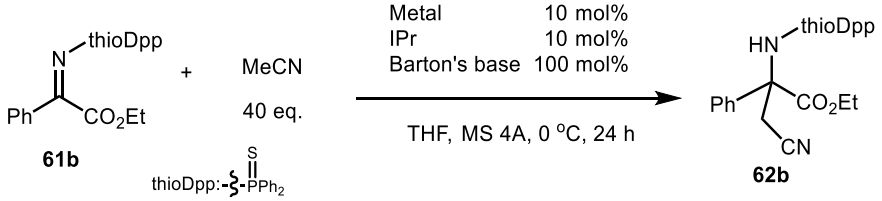
Table 5. Ketimine screening



Metal screening

Using *N*-thioDpp iminoester **61b** as electrophile and IPr as ligand, metal screening was undertaken (**Table 6**). Unfortunately, it turned out that only $[Ir(cod)(OMe)]_2$/IPr could promote the reaction at 0 °C, giving the product **62b** in 52% yield (entry 7). No detectable product was found when other metal/IPr as catalysts were used (entry 1–6).

Table 6. Metal Screening[a]

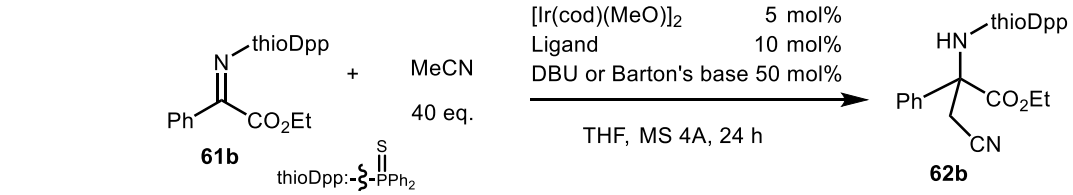


Entry	Metal	Yield (%)[b]
1	$Ti(OMe)_4$	–
2	$Fe(OTf)_2$	–
3	$Ni(cod)_2$	–
4	$Co(BF_4)_2\,6H_2O$	–
5	$AgSbF_6$	–
6	$Ni(OTf)_2$	–
7	$[Ir(cod)(OMe)]_2$	52

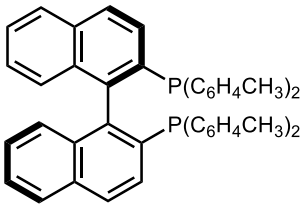
[a] **61b**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^1H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard.

Ligand screening

Table 7. Ligand screening

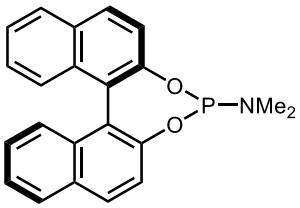


1



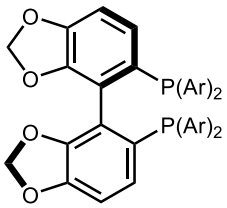
DBU, rt, No reaction

2



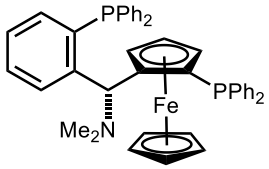
DBU, rt, No reaction

3



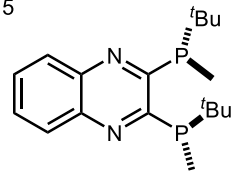
DBU, rt, No reaction

4



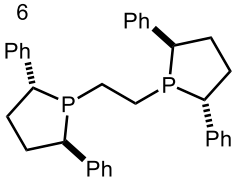
Barton's base, rt, trace

5



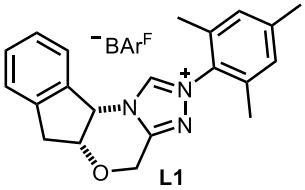
Barton's base, rt
trace

6



Barton's base, rt
14% yield, 19% ee

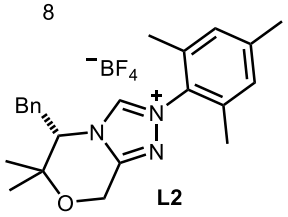
7



L1

Barton's base, 0 °C
79% yield,55% ee

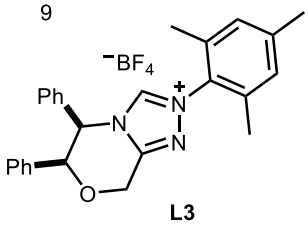
8



L2

Barton's base, 0 °C
32% yield, 14% ee

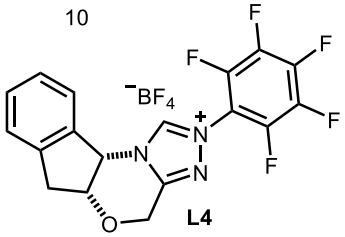
9



L3

Barton's base, 0 °C
40% yield, –8% ee

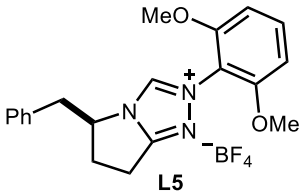
10



L4

Barton's base, 0 °C
28% yield; –28% ee

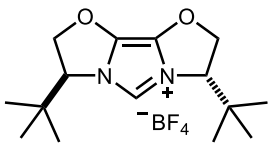
11



L5

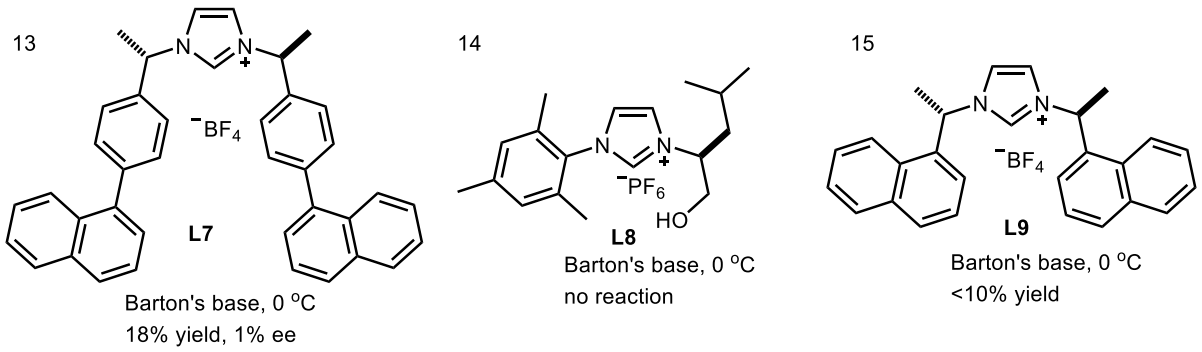
Barton's base, 0 °C
28% yield, –2% ee

12



L6

Barton's base, 0 °C
no reaction

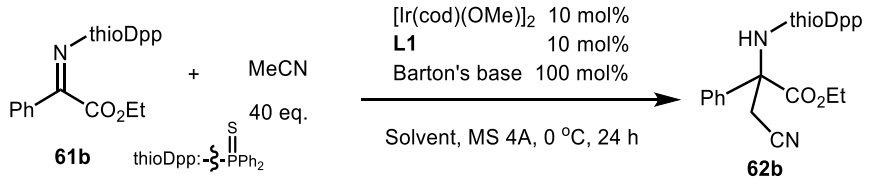


No reaction took place when chiral bisphosphine ligands were used (**Table 7**, entries 1–5), except for (*R*,*R*)-Ph-BPE which afforded the product in 14% yield with 19% ee. Most of the NHC ligands examined could promote the reaction, albeit with low convertion and enantioselectivity (**Table 7**, entries 7–15). Among them, **L1** gave the best results (**Table 7**, entry 7).

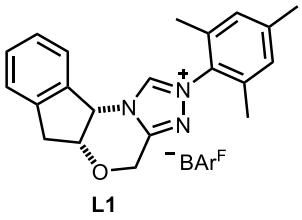
Solvent Screening

With **L1**, solvent screening was investigated (**Table 8**). Using THF as solvent, the reaction gave product **62b** in 79% yield with 55% *ee* (entry 1). With other ethereal solvents such as Et_2O, DME, and CPME, catalytic activity dropped significantly, while enantioselectivity had only slightly dropped (entries 1–4). Toluene and DCM caused both catalytic activity and enantioselectivity to drop significantly (entries 5–6). Using DMF as the solvent, there was no negative effct on catalytic activity, while enantioselectivity dropped dramatically (entry 7). A negative effect was observed when using MeCN as solvent, which gave lower *ee* (28% *ee*) (entry 8).

Table 8. Solvent screening[a]



Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	79	55
2	Et_2O	31	47
3	DME	32	46
4	CPME	42	49
5	toluene	40	20
6	DCM	49	39
7	DMF	73	40
8	MeCN	57	28

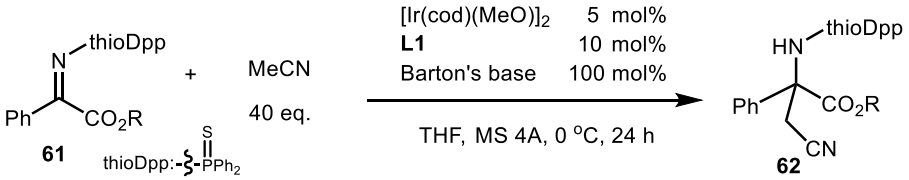


[a] **61b**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

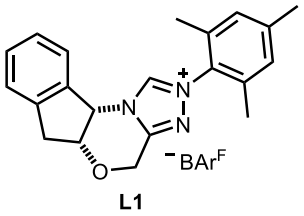
Ester moiety screening

A brief investigation of the ester moiety (**Table 9**) showed that the highest enantioselectivity was observed with ethyl ester (entry 2). Enantioselectivity progressively dropped when increasing the steric bulk from the ethyl group to the 1-adamantyl group (entries 2–5). Benzyl and neopentyl group afforded the adducts **62** with similar enantioselectivity to ethyl substrate (entries 2 versus 6–7). This shows that the steric bulk of alkyl groups on the ester has an important effect on enantioselectivity.

Table 9. Ester moiety screening[a]

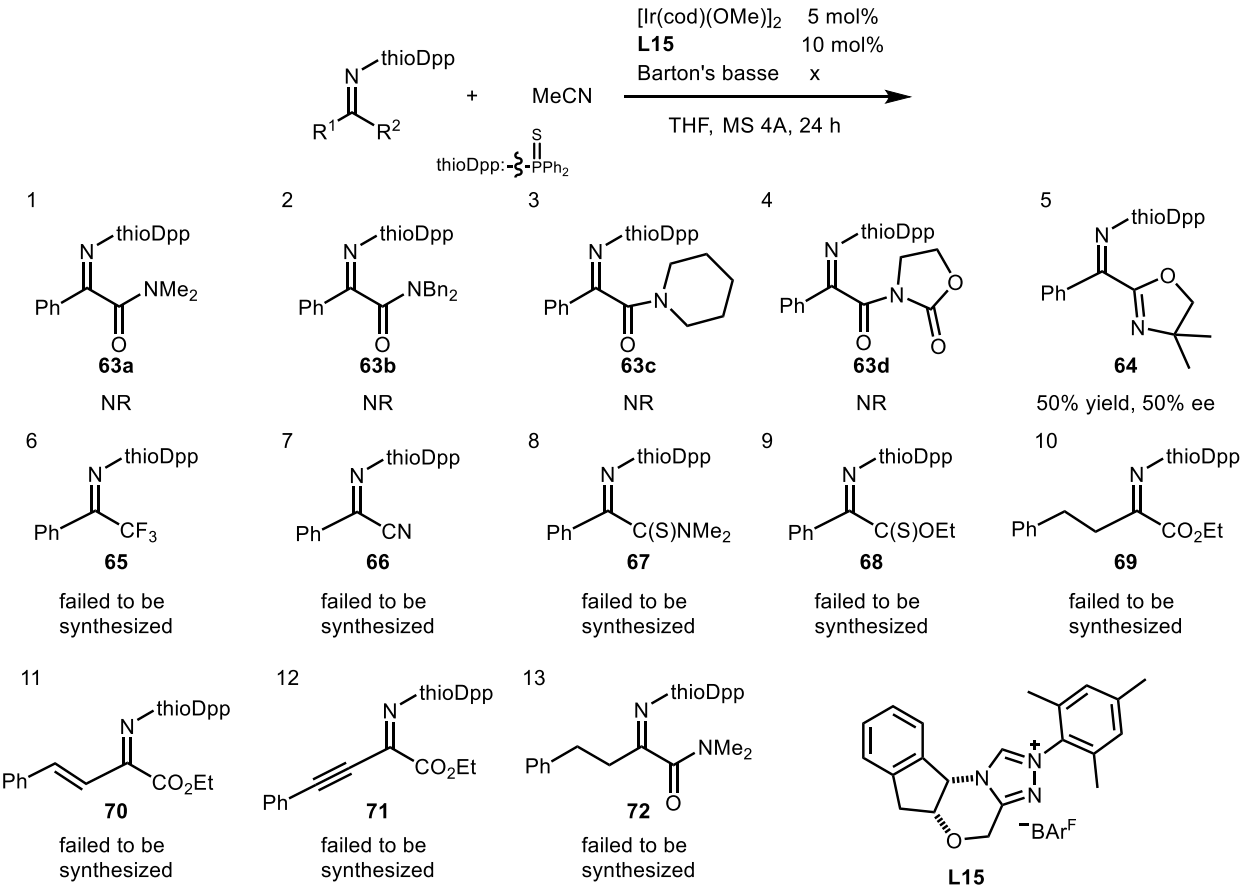


entry	R		Yield (%)[b]	ee (%)[c]
1	Me	**a**	44	49
2	Et	**b**	79	55
3	^{i}Pr	**c**	59	43
4	^{t}Bu	**d**	75	21
5	1-Ad	**e**	68	15
6	Bn	**f**	63	54
7	CH_2 ^{t}Bu	**g**	49	51



[a] **61**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

Table 10. Unsuccessful examples

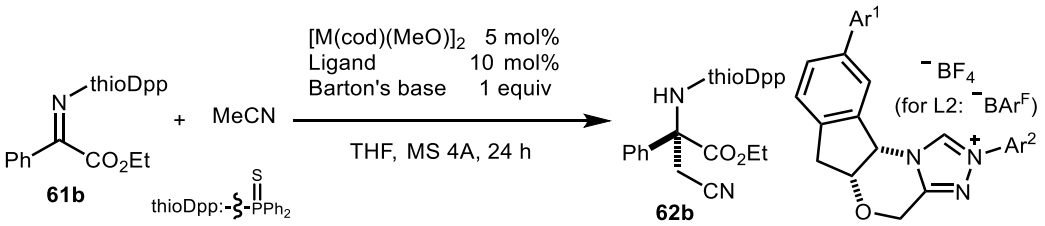


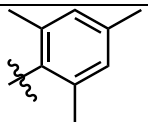
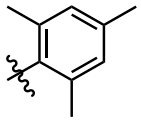
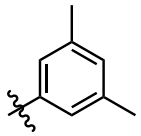
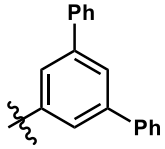
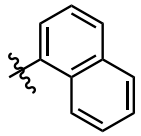
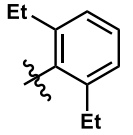
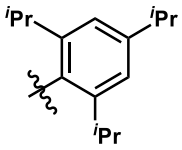
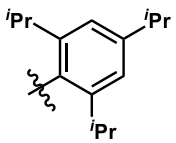
Based on the ester effect observed above, other *N*-thioDpp ketimines were synthesized (**Table 10**). No corresponding products were observed with *α*-iminoamides **63a-d** which contained different substituents on nitrogen (entries 1–4). Ketimine bearing an *α*-oxazoline substituent could deliver the corresponding adduct in 50% yield with 50% *ee* (entry

5). Ketimines bearing α-CF_3, α-CN, α-thioamide, α-thioester, α-alkyl, α-alkene and α-alkyne substituents failed to be synthezised (entries 6–13).

Ligand modification

Table 11. Ligand modification[a]



Entry	Ligand			Temp. (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
	Ar[1]		Ar[2]				
1	**L1**	H		0	24	79	54
2	**L10**	Ph		0	24	61	43
3	**L11**	H		0	24	26	22
4	**L12**	H		0	24	27	18
5	**L13**	H		0	24	30	38
6	**L14**	H		0	24	63	56
7	**L15**	H		0	24	54	65
8	**L15**	H		–5	72	79	68

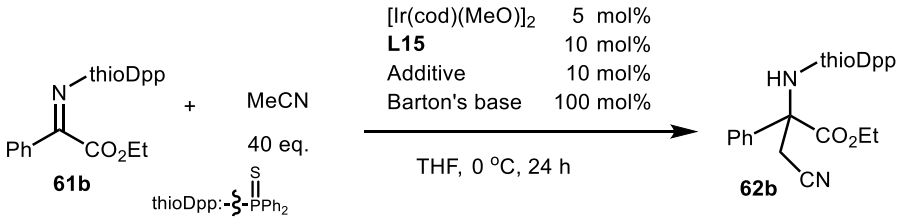
[a] **61b**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

In order to improve the enantioselectivity, modifications to the ligand were explored (**Table 11**). A negative effect on catalytic activity and enantioselectivity was observed when a phenyl group on the indanyl group was introduced (entry 1 versus 2). Ligands with *meta*-disubstituted aromatics (entries 3–4) or 1-naphthyl group (entry 5) gave the product with low yield and enantioselectivity. Ligands with *ortho*-disubstituted aromatics had a positive effect, giving the desired product with higher enantioselectivity (entries 6–7). With optimal NHC precursor **L15**, the reaction gave the product **62b** in 79% yield with 68% ee at –5 °C with a prolonged reaction time.

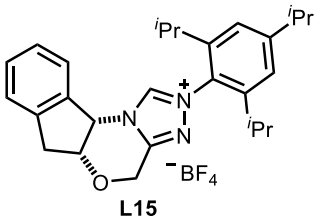
Additive screening

Employing monodentate ligands as additives gave similar results for the reaction (**Table 12**, entries 1–3). The addition of bidentate ligand dppe and dppp gave a negative effect on catalytic activity (entries 4–5). However bidentate ligands with bulky backbones e.g. dppf and Xantphos, had no negative effect on the catalytic activity (entries 6–7).

Table 12. Additive screening[a]



Entry	Additive	Yield (%)[b]	ee (%)[c]
1	PPh_3	55	64
2	P^tBu_3	56	65
3	$P(S)Ph_3$	57	65
4	dppe	15	64
5	dppp	13	62
6	dppf	54	65
7	Xantphos	62	65

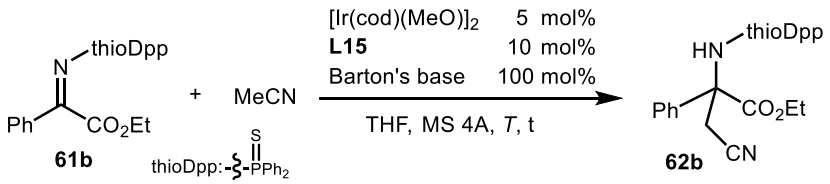


[a] **61b**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^1H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

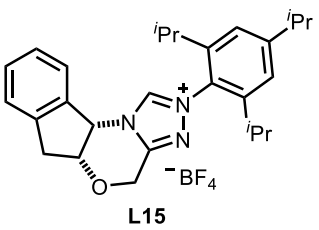
Screening of reaction conditions

Decreasing the MeCN loading gave slightly improved enantioselectivtity, while the yield dropped (**Table 13**, entries 1–5). Considering the enantioselectivity and catalytic activity, the effect of concentration was investigated with 10 eq. of MeCN (entries 3, 6–8). Around 38% yield and 66% *ee* was observed with different concentrations. Finally, the optimal reaction conditions was found to be 0.1 M, 40 eq. of MeCN with the reaction carried out at –5 °C and with a longer reaction time (entry 9).

Table 13. Condition Screening[a]



Entry	MeCN (eq.)	Conc. (M)	*T* (°C)	t (h)	Yield[b] (%)	ee[c] (%)
1	40	0.1	0	24	54	65
2	20	0.1	0	24	37	67
3	10	0.1	0	24	17	69
4	5	0.1	0	24	6	70
5	2	0.1	0	24	trace	–
6	10	0.2	0	24	39	66
7	10	0.25	0	24	38	67
8	10	0.29	0	24	35	66
9	40	0.1	–5	72	79	68
10	40	0.1	–10	72	57	70



L15

[a] **61b**: 0.1 mmol, MeCN: 4 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

2.2.3 ^{31}P NMR studies

To gain an insight in the mechanism, ^{31}P NMR studies were conducted (**Figures 3–7**).

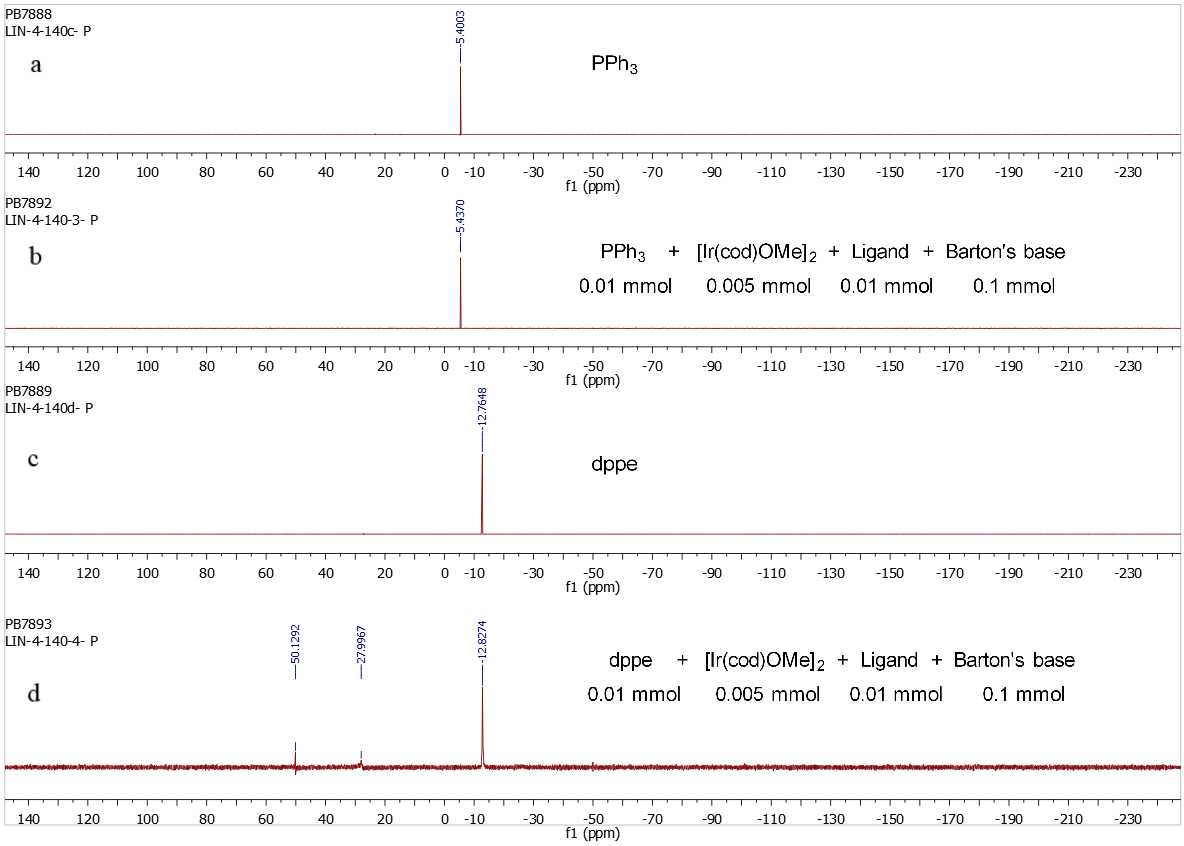


Figure 3. ^{31}P NMR studies on additive effect

^{31}P NMR studies showed that no new peaks were generated when monodentate ligand, PPh_3 was used as an additive (**Figure 3**. **a** vs **b**). On the other hand, using dppe as additive, two new peaks located at downfield were observed (**c** vs **d**), indicating that dppe coordinated to Ir center, and thus-formed complex may have no catalytic activity. This is in line with the experimental results using dppe as additive, in which the catalytic efficiency decreased.

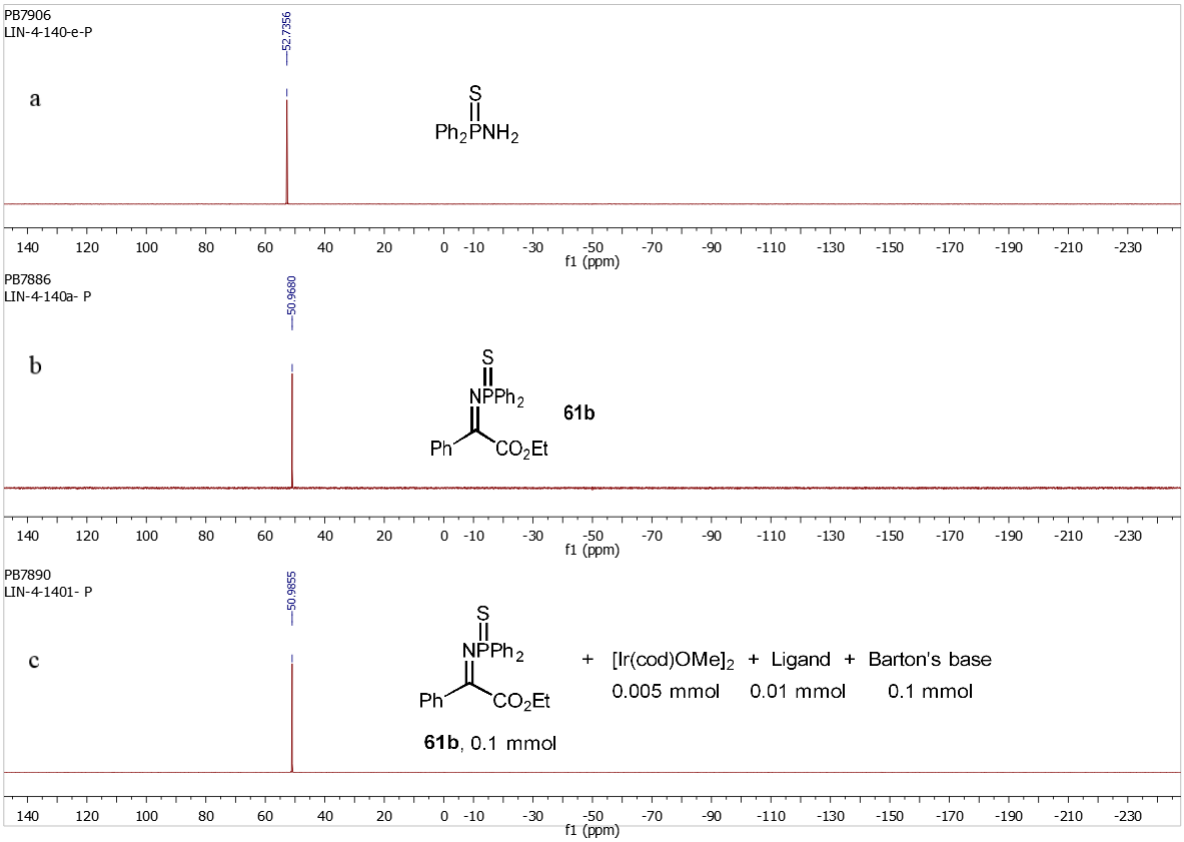


Figure 4. ^{31}P NMR studies on coordination effect between substrates and Ir/NHC complex

Sulfur has the potential to form a strong dative bond with transition metals, however, ^{31}P NMR studies showed that there was no interaction between the *N*-thioDpp group and Ir/NHC complex (**Figure 4**).

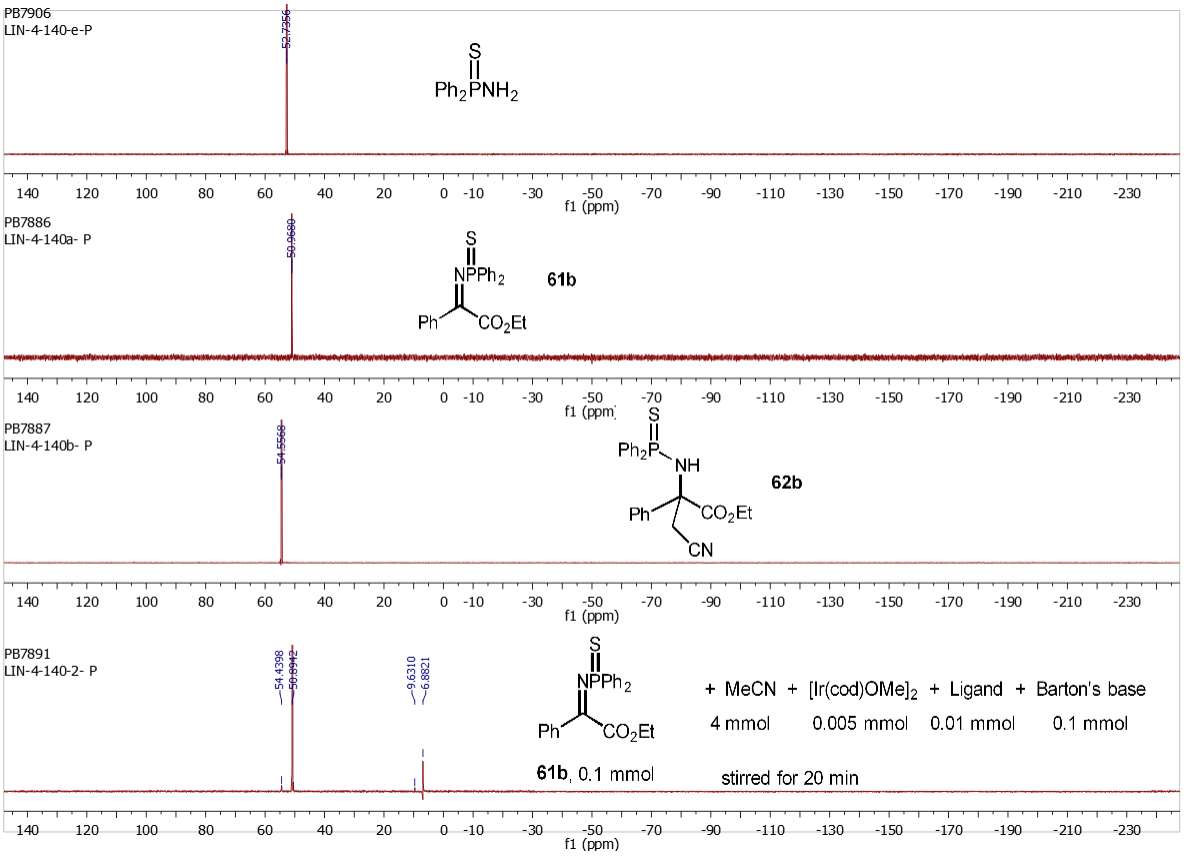


Figure 5. ^{31}P NMR studies of the reaction mixture (1)

^{31}P NMR studies of the complete reaction mixture showed that two new peaks appeared at around 7 and 10 ppm (**Figure 5**). However, these peaks disappeared when the reaction was quenched with acid.

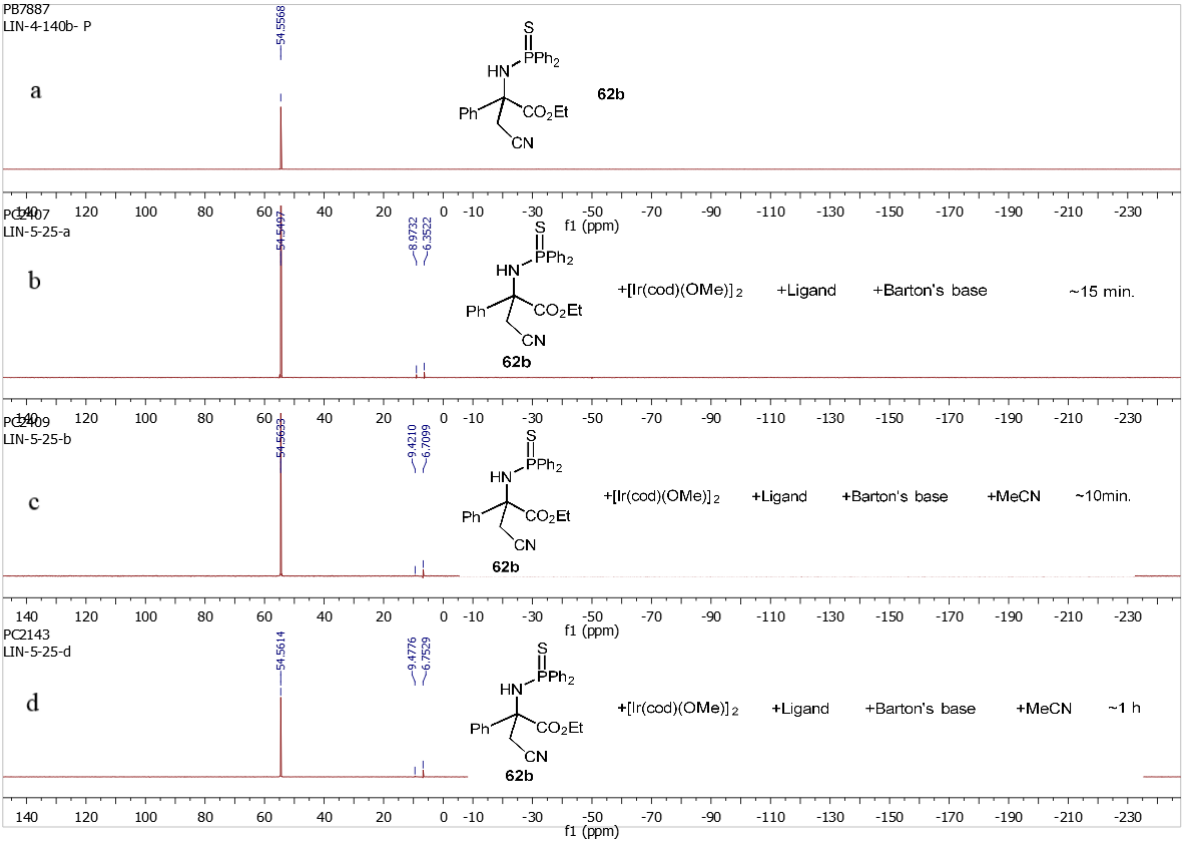


Figure 6. ^{31}P NMR studies of the reaction mixture (2)

The two new peaks at around 7 and 10 ppm appeared, upon mixing product **62b** with Ir/**L15** complex and Barton's base (**Figure 6**, **b**), and they became more prominent after either MeCN was added (**Figure 6**, **b** versus **c**) or with prolonged time (**Figure 7**, **a** versus **b**). Treatment of product **62b** with Barton's base gave no new peaks (**Figure 7**, **c**). Using MeONa instead of Barton's base, a new peak at 31 ppm was observed (**Figure 7**, **d**). Based on the literature,[38] the new peaks which appeared at around 7 and 10 ppm can be assigned to thiophosphinimide **62b'**.

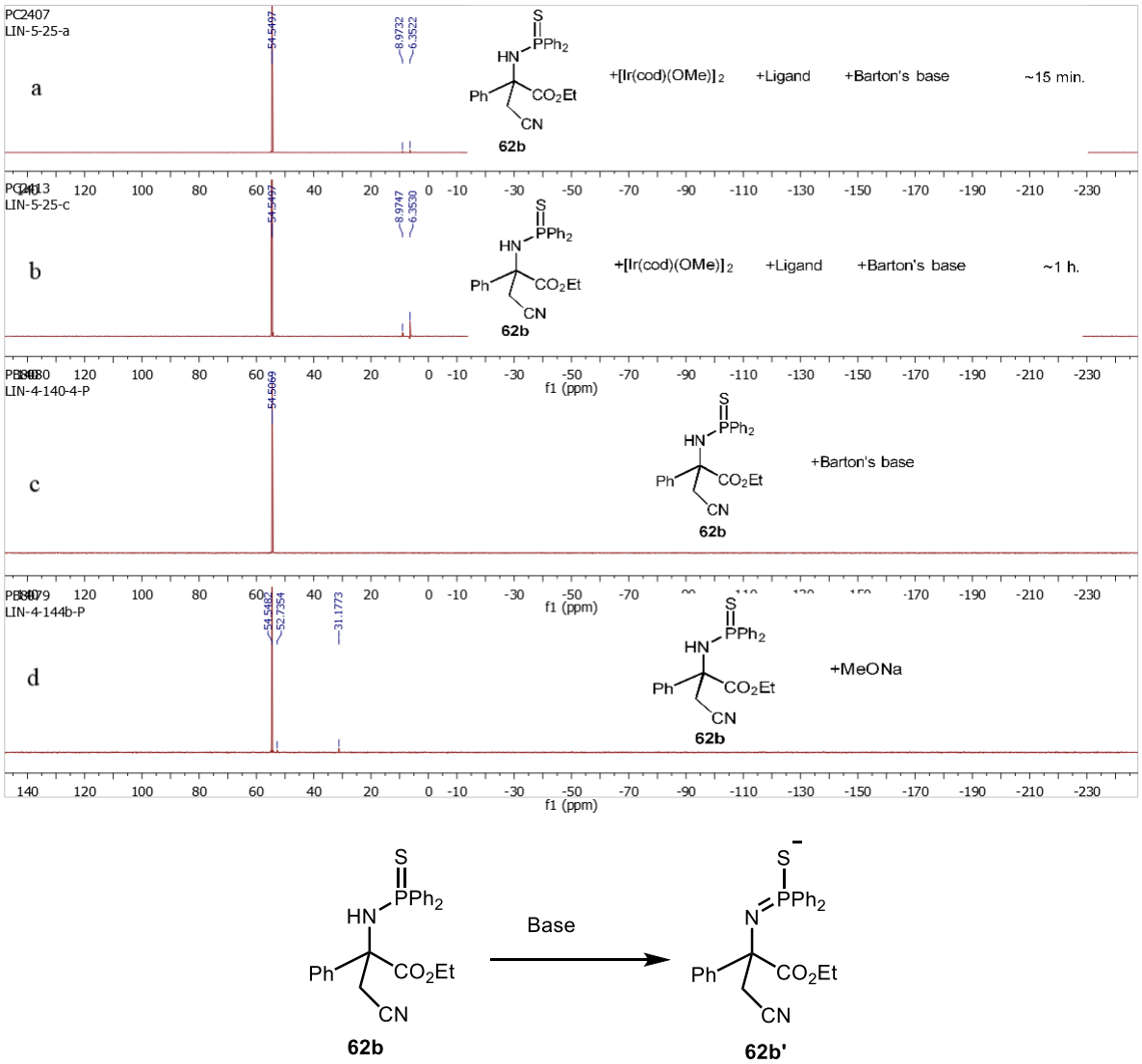


Figure 7. ^{31}P NMR studies of the reaction mixture (3)

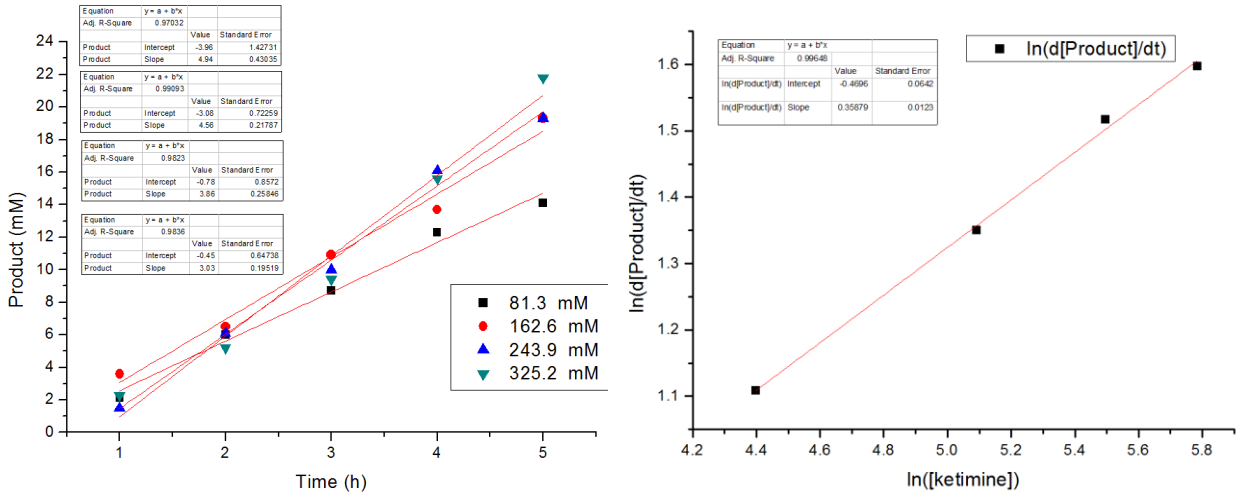
2.2.4 Kinetic studies

Determination of the reaction order in ketimine.

The reactions with different concentrations of ketimine **61b** (0.1 mmol, 0.2 mmol, 0.3 mmol and 0.4 mmol) 81.3, 162.6, 243.9 and 325.2 mM were performed according to the general procedure[39], and the results were summarized in the **Table 14** and **Figure 8**. The results showed that the reaction order in ketimine is 0.4.

Table 14. Initial rate of reaction with varied concentration of ketimine

[ketimine] (mM)	d[Product]/dt (mM/h)
81.3	3.03
162.6	3.86
243.9	4.56
325.2	4.94



(a). Initial rate kinetic experiments for ketimine. **(b)**. Plot of ln(d[Product]/dt) versus ln([ketimine])

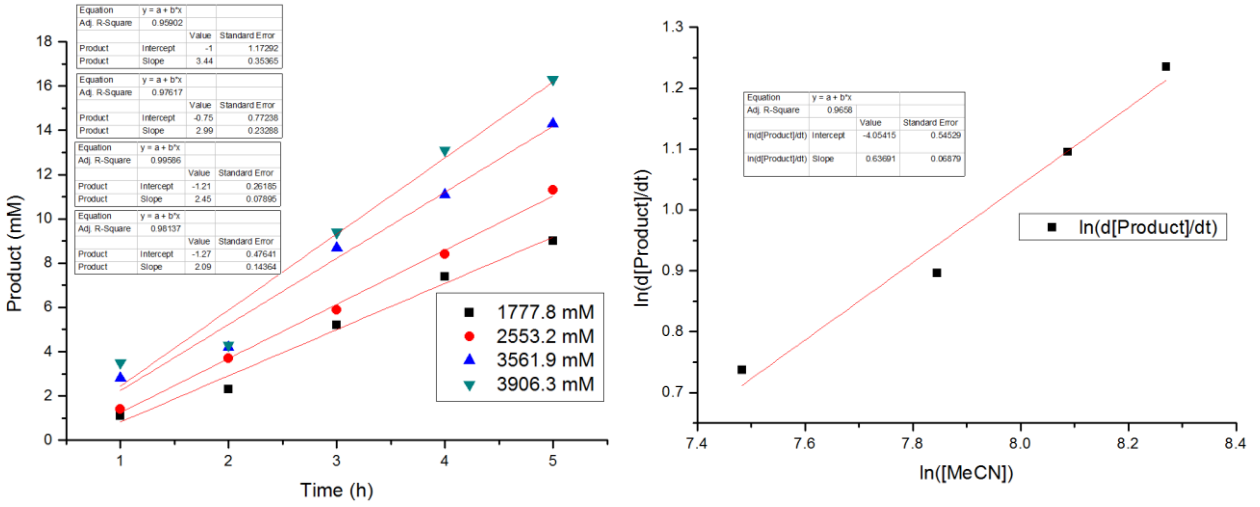
Figure 8. (a) Initial rate kinetic experiments for ketimine. **(b)** Plot of ln(d[Product]/dt) versus ln([ketimine])

Determination of the reaction order in MeCN.

The reactions with different concentrations of MeCN (2 mmol, 3 mmol, 4 mmol and 5 mmol) 1777.8, 2553.2, 3561.9 and 3906.3 mM were performed according to the general procedure[39], and the results were summarized in the **Table 15** and **Figure 9**. The results showed that the reaction order in MeCN is 0.6.

Table 15. Initial rate of reaction with varied concentration of MeCN

[MeCN] (mM)	d[Product]/dt (mM/h)
1777.8	2.09
2553.2	2.45
3561.9	2.99
3906.3	3.44



(a). Initial rate kinetic experiments for MeCN. **(b)**. Plot of ln(d[Product]/dt) versus ln([MeCN])

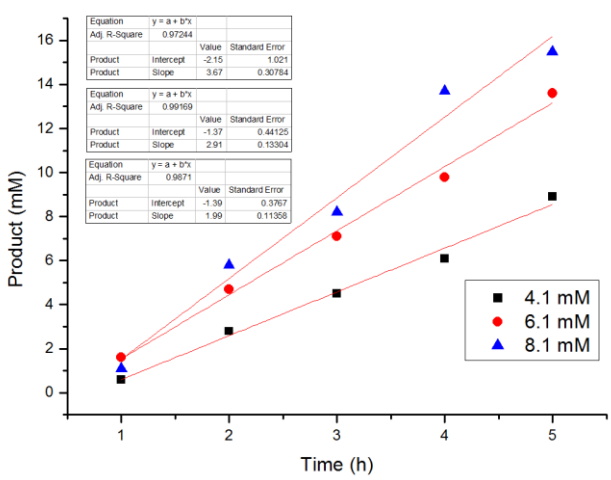
Figure 9. (a) Initial rate kinetic experiments for MeCN **(b)** Plot of ln(d[Product]/dt) versus ln([MeCN])

Determination of the reaction order in catalyst.

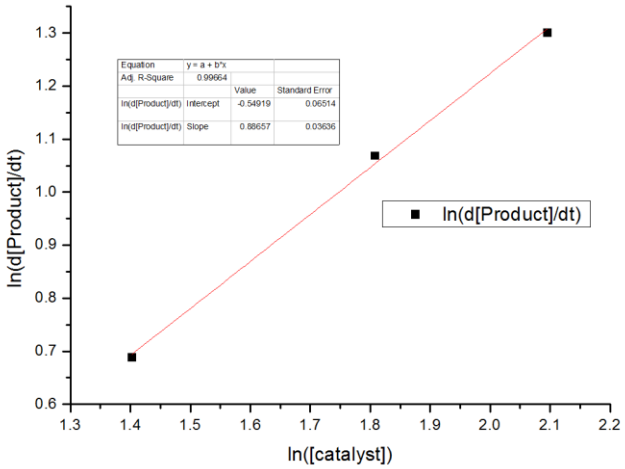
The reactions with different concentrations of catalyst (5 mol%, 7.5 mol% and 10 mol%) 4.1, 6.1 and 8.1 mM were performed according to the general procedure[39], and the results were summarized in the **Table 16** and **Figure 10**. The results showed that the reaction order in catalyst is 0.9.

Table 16. Initial rates of reaction with varied concentration of catalyst

[Catalyst] (mM)	d[Product]/dt (mM/h)
4.1	1.99
6.1	2.91
8.1	3.67



(a). Initial rate kinetic experiments for catalyst.

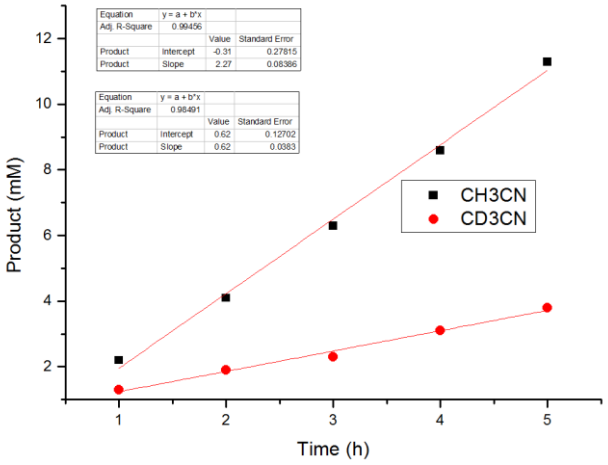


(b). Plot of ln(d[Product]/dt) versus ln([catalyst])

Figure 10. (a) Initial rate kinetic experiments for catalyst. **(b)** Plot of ln(d[Product]/dt) versus ln([catalyst])

Kinetic isotope effects[39]

Table 17. Comparison of initial rates of CH_3CN and CD_3CN



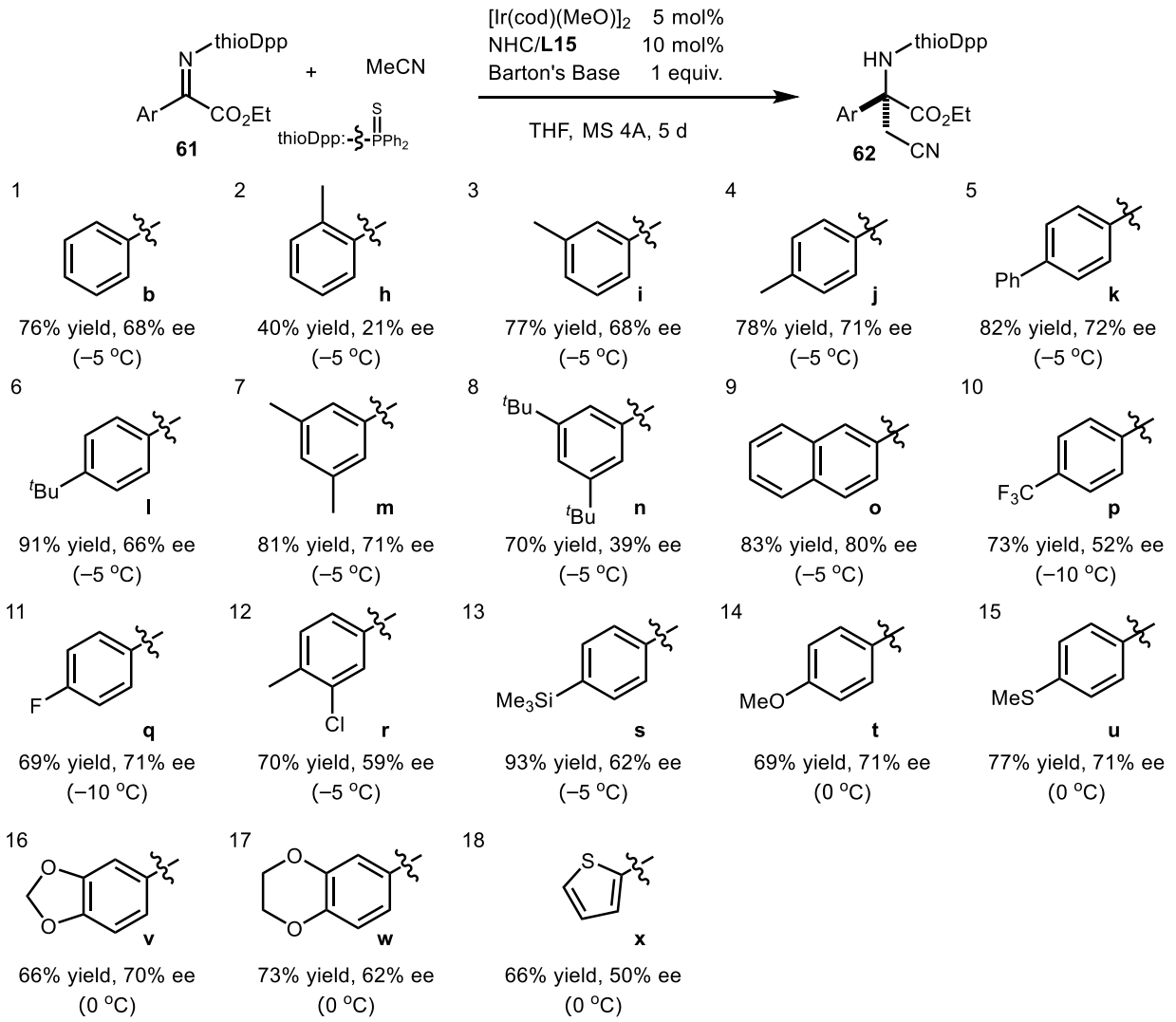
Time (h)	[Product] (mM)/ CH_3CN	[Product] (mM)/ CD_3CN
1h	2.2	1.3
2h	4.1	1.9
3h	6.3	2.3
4h	8.6	3.1
5h	11.3	3.8

Figure 11. Initial rate kinetic experiments for CH_3CN and CD_3CN

The reaction with CD_3CN was performed independently under the identical reaction conditions. The results were summarized in the **Table 17** and **Figure 11**. Based on the slopes in **Figure 11**, the value of kinetic isotope effect was calculated to be k_H/k_D = 2.27/0.62 = 3.7, suggesting the presence of primary kinetic isotope effects.

2.2.5 Investigation of substrate scope

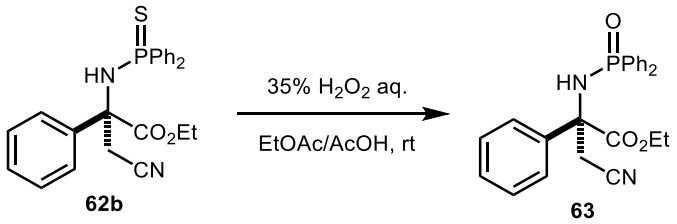
Table 18. Substrate scope



The substrate scope was investigated using the optimized reaction conditions described above (**Table 18**). Aromatic *α*-iminoesters bearing alkyl substituents on the aromatic ring gave the corresponding products **62** with good to excellent yield and moderate enantioselectivity (entries 1,3–7,9), with the exception of the substituents having *ortho*-methyl (entry 2) and the excessively bulky *meta*-di-*tert*-butyl groups (entry 8). Substrates with electron-withdrawing groups had no detrimental effects (entries 10,11). Ketimines bearing electron-donating groups on the aromatic ring gave similar enantioselectivity (entries 14–17). Lower enantioselectivity was observed for the ketimine bearing the heteroaromatic 2-thienyl group (entry 18).

2.2.6 Determination of absolute configuration

Although crystals of the product **62b** were unable to be obtained, transformation to *O*-analogue **63** was performed (**Scheme 23**), which showed a highly crystalline nature. The absolute configuration of the product was determined by analogy to the X-ray crystal structure of the **63**, which provided proof of the absolute configuration of the stereogenic center. The absolute configuration of other products were deduced by analogy.



Scheme 23. Product transformation

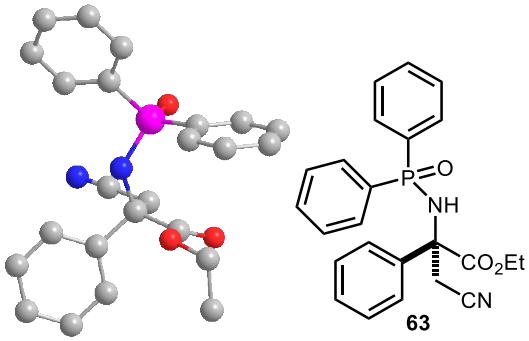
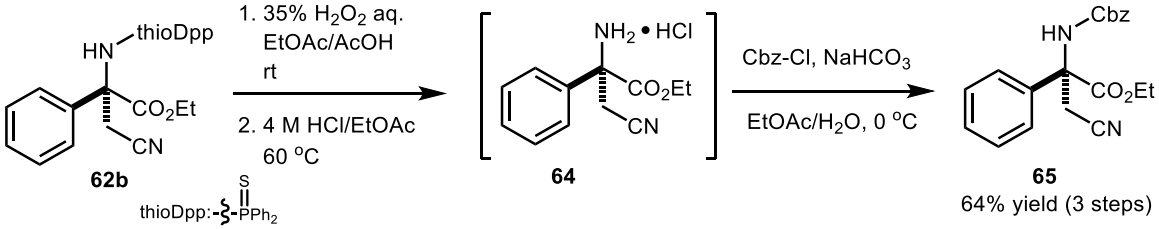


Figure 12. X-ray crystal structure of product[40]

2.2.7 Transformation of the product

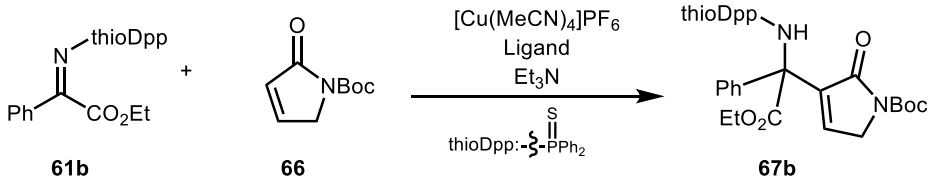


Scheme 24. Product transformation

α-Alkylnitrile-substiteted amino ester analogue **65** was synthesized via a short transformation sequence. Product **62b** was treated with aqueous H_2O_2, and the crude product was dissolved in a mixture of 4 M HCl/EtOAc (1:1) and heated to 60 °C. Thus-obtained amine hydrochloride **64** reacted with Cbz-Cl under basic conditions to give the Cbz-protected amine **65**.

2.3 Construction of *α,α*-disubstituted *α*-amino acid derivatives with *α,β*-unsaturated *γ*-butyrolactam

In **Section 2.2**, *N*-thioDpp *α*-iminoesters **61b** showed high reactivity in the construction of *α,α*-disubstituted *α*-amino acid derivatives via a catalytic asymmetric Mannich-type reaction. Considering the utility of *α,α*-disubstituted *α*-amino acid derivatives,[41] I searched for other pronucleophiles using *N*-thioDpp *α*-iminoester **61b** as electrophile. As a result, I found *α,β*-unsaturated *γ*-butyrolactam **66** could serve as suitable candidate, which gave the *α*-addition product **67b** (**Scheme 25**).



Scheme 25. *α*-Addition of *α,β*-unsaturated *γ*-butyrolactam

2.3.1 Literature known *α*-addition of *α,β*-unsaturated *γ*-butyrolactam

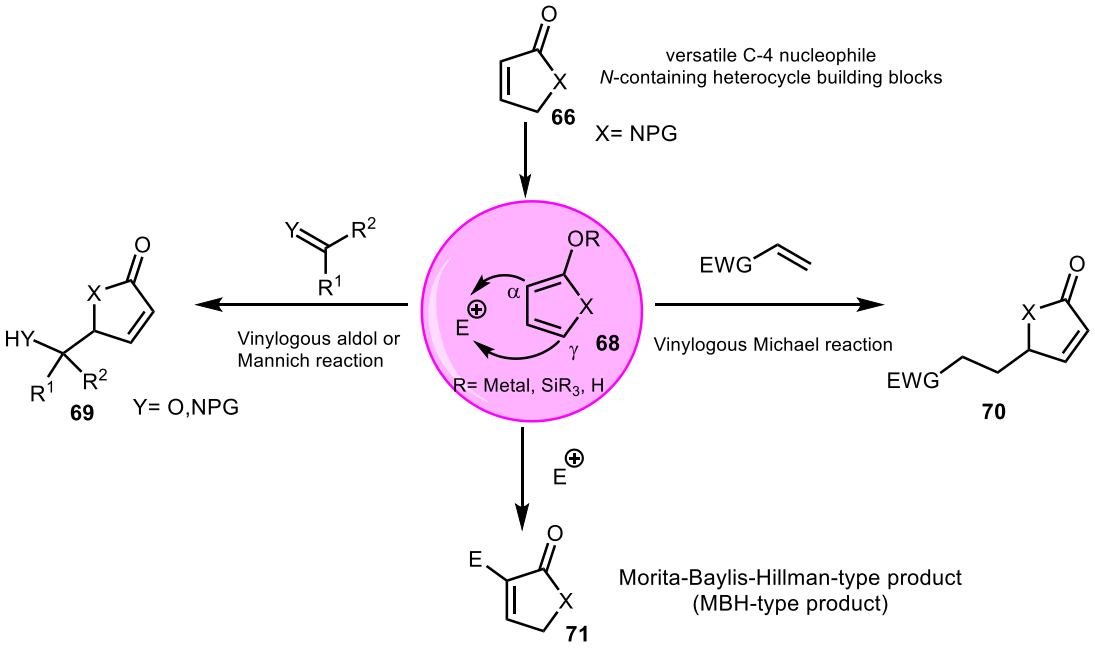
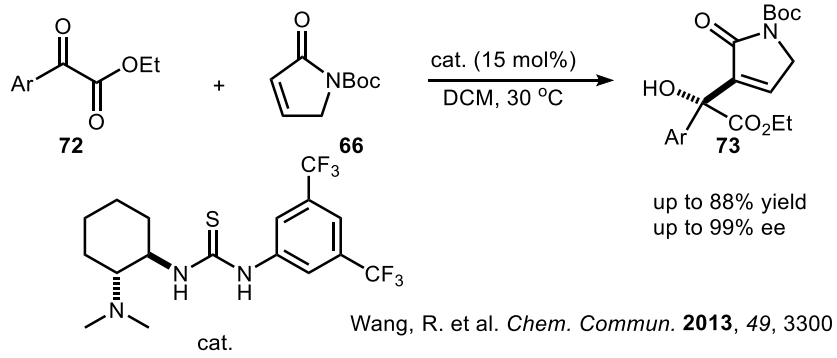


Figure 13. Construction of *γ*-butenolide and *α,β*-unsaturated *γ*-butyrolactams by addition of cyclic dienolate-type nucleophiles

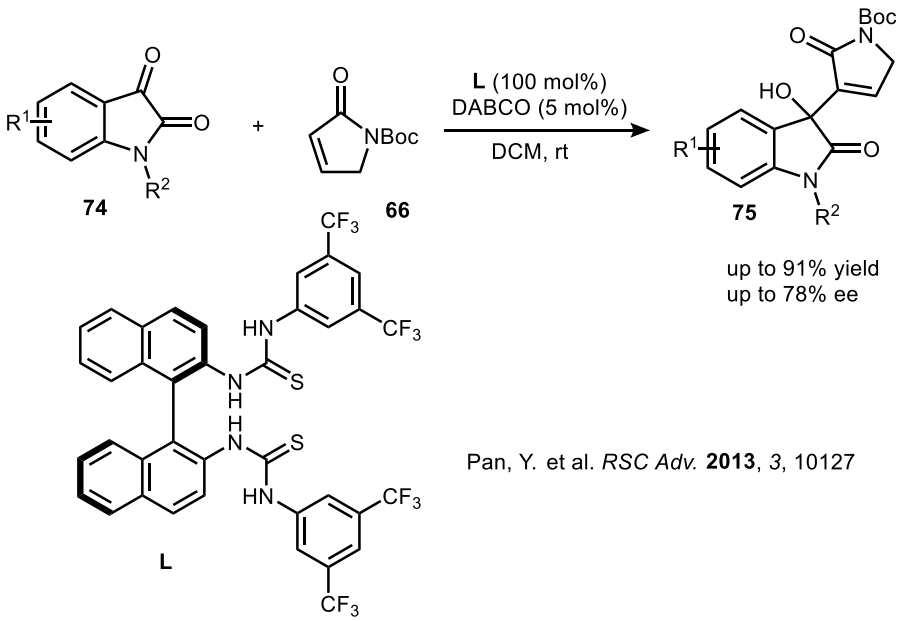
Nitrogen-containing heterocycles are important structural motifs because such units are present in numerous natural and non-natural compounds with significant biological activities and pharmacological properties.[42] Recently, *α,β*-unsaturated *γ*-butyrolactam **66** has received much attention because this unit is embedded in a number of bioactive compounds[43] and it can be used as a versatile C-4 nucleophile for delivering *N*-containing heterocyclic building blocks.[44] In this regard, efforts have been made for using *α,β*-unsaturated *γ*-butyrolactam **66** as a nucleophile in catalytic asymmetric reactions.[45] Deprotonation at the *γ*-position leads to dienolate intermediate **68** which can undergo either *α*-addition or *γ*-addition (**Figure 13**). Asymmetric *γ*-addition, including vinylogous aldol reactions, Mannich reactions and Michael reactions, have been well-studied, whereas only a few successful examples have been described for the *α*-addition which afforded Morita-Baylis-Hillman (MBH)-type product **71**.[46]

The first example of MBH-type addition of *α*,*β*-unsaturated *γ*-butyrolactam **66** was reported by Wang et al. in 2013 (**Scheme 26**).[47] They showed that a simple bifunctional thiourea catalyst was able to promote the reaction of *α*,*β*-unsaturated *γ*-butyrolactam **66** with a series of aryl *α*-ketoesters **72**. The authors proposed that the reaction proceeded via a direct asymmetric aldol addition-isomerization pathway to give the chiral *α*-hydroxy esters **73**.



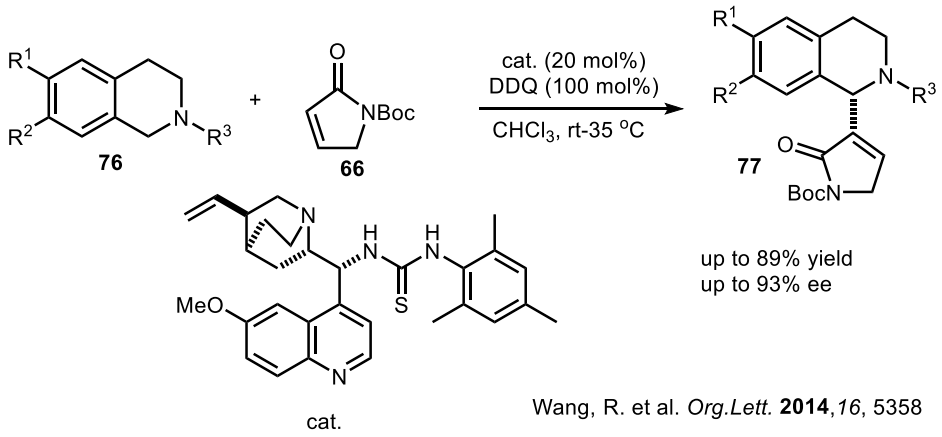
Scheme 26. Catalytic asymmetric aldol additon-isomerization

In the same year, Pan and Han et al. achieved the first enantioselective MBH reaction of *α*,*β*-unsaturated *γ*-butyrolactam **66** to isatins **74** (**Scheme 27**).[48] The reaction, catalyzed by chiral bisthiourea and DABCO, afforded the corresponding products **75** in good to excellent yields (up to 91%) and with moderate enantioselectivities (up to 78% ee).



Scheme 27. The MBH reaction of isatins with *α*,*β*-unsaturated *γ*-butyrolactam

In 2014, an alternative strategy based on the direct *α*-addition of *α*,*β*-unsaturated *γ*-butyrolactam **66** emerged. Wang et al. coupled *α*,*β*-unsaturated *γ*-butyrolactam **66** with *N*-aryl tetrahydroisoquinolines **76** via an organocatalyzed asymmetric oxidative coupling to the *α*-C(*sp*^{3})-H bond of tertiary amines (**Scheme 28**).[49] A wide range of tetrahydroisoquinolines **76** were employed in this reaction, delivering the products in good to excellent yields (up to 89%) and with good to excellent enantioselectivities (up to 93% ee).

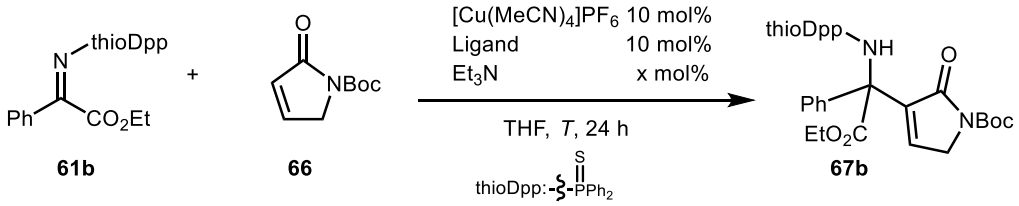


Scheme 28. Oxidative coupling of *α*,*β*-unsaturated *γ*-butyrolactam to tetrahydroisoquinolines

Given that butyrolactam containing motifs are present in a variety of bioactive compounds and can serve as versatile synthetic intermediates in the construction of many biologically and pharmacologically active compounds, I focused on the catalytic asymmetric coupling of *α*,*β*-unsaturated *γ*-butyrolactam **66** with *N*-thioDpp *α*-iminoesters **61** to give *α*,*α*-disubstituted *α*-amino acid derivatives.

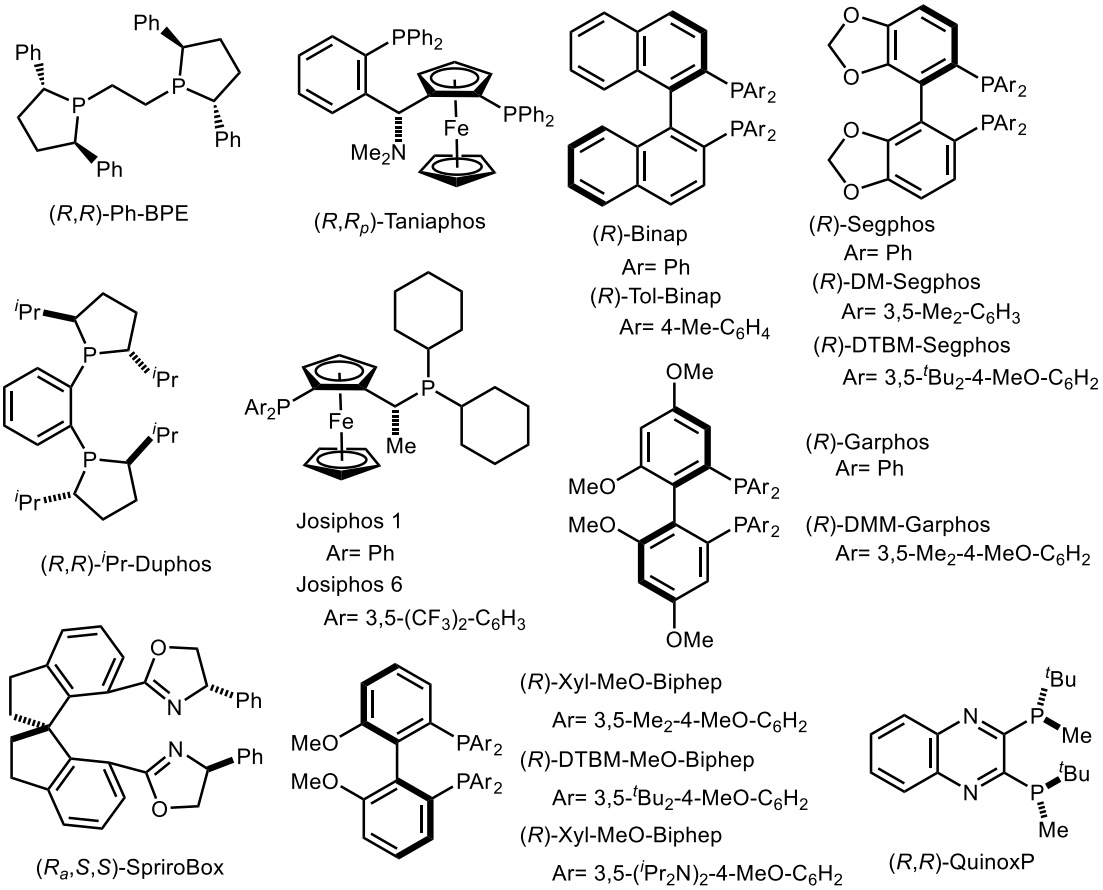
2.3.2 Screening of reaction conditions

Table 19. Ligand Screening[a]



Entry	Ligand	x	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	(*R*,*R*)-Ph-BPE	20	0	78	51
2	(*R*,R_p)-Taniaphos	20	0	28	5
3	(*R*)-Tol-Binap	20	0	69	–32
4	(*R*)-DM-Segphos	20	0	31	–24
5	(*R*,*R*)-^{i}Pr-Duphos	50	–20	90	34
6	Josiphos-1	50	–20	38	21
7	Josiphos-2	50	–20	94	–22
8	(*R*)-DMM-Garphos	50	–20	19	–49
9	(*R*,R_p)-Taniaphos	50	–20	39	16
10	(*R*)-Segphos	50	–20	27	–40
11	(*R*)-Binap	50	–20	37	–32
12	(*R*,*R*)-QuinoxP	50	–20	24	–74
13	(*R*)-Garphos	50	–20	38	–22
14	(*R*,*R*)-Ph-BPE	50	–20	55	76
15	(*R*)-DTBM-Segphos	50	–20	–	–
16	(R_a,*S*,*S*)-SpiroBox	50	–20	–	–
17	(*R*)-DTBM-Biphep	50	–20	–	–
18	(*R*)-Xyl-MeO-Biphep	50	–20	16	–
19	(*R*)-DIPA-MeO-Biphep	50	–20	–	–

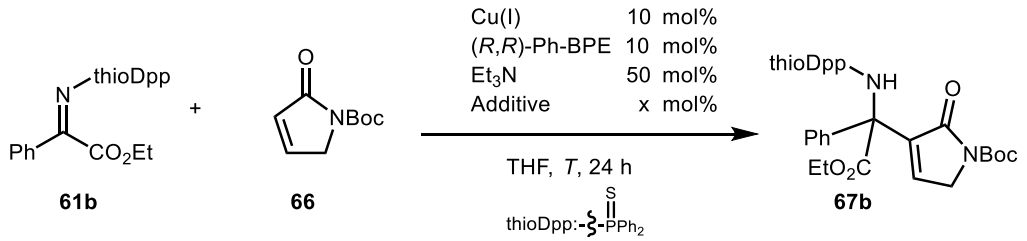
[a] **61b**: 0.1 mmol, **66**: 0.15 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.



A variety of bisphosphine ligands were evaluated for the reaction of α-iminoesters **61b** with α,β-unsaturated γ-butyrolactam **66** as the representative reaction, in the presence of $[Cu(MeCN)_4]PF_6$ and Et_3N as base (**Table 19**). The reaction proceeded with bisphosphine ligands in THF at 0 °C, delivering the MBH-type product **67b**, albeit with low enantioselectivity (entries 1–4). Ligand screening at –20 °C in THF (entries 5–19) showed that (*R*,*R*)-QuinoxP and (*R*,*R*)-Ph-BPE provided the product with the highest enantioselectivity, and the latter showed higher catalytic activity. (*R*)-DTBM-Segphos, (R_a,*S*,*S*)-SpiroBox and Biphep-type ligands almost completely failed to promote the reaction (entries 15–19).

With the optimal ligand, (*R*,*R*)-Ph-BPE, the effect of Cu(I) sources was investigated (**Table 20**). Cu(I) species with different counteranions afforded similar results, with the exception of mesitylcopper which failed to provide the desired product (entries 1–4). To improve the catalytic efficiency, some additives were investigated (entries 5–9). A trace amount of H_2O may have an effect on the reaction, however, no obvious effect was observed when using MS 4A as an additive (entries 5–6). $LiBF_4$ is a strong Lewis acid which can coordinate to α,β-unsaturated γ-butyrolactam **66**. While the addition of $LiBF_4$ improved the yield significantly, the enantioselectivity dropped significantly (entries 7–9). It was determined that even in the absence of Cu(I) complex, NEt_3 and $LiBF_4$ alone could promote the reaction, giving a low yield of product (entry 10).

Table 20. Condition Screening[a]

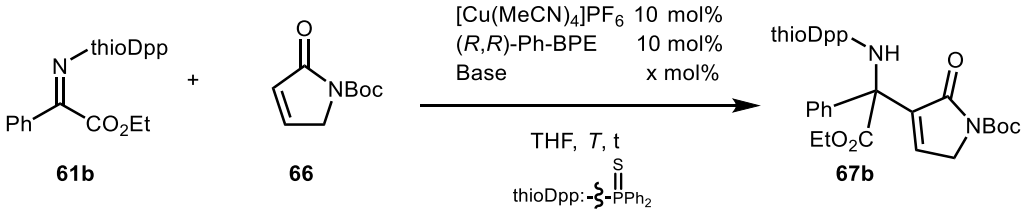


Entry	Cu(I)	Additive	t (h)	*T* (°C)	Yield.[b] (%)	ee[c] (%)
1	$[Cu(MeCN)_4]PF_6$	–	72	–50	16	91
2	Mesitylcopper	–	48	–40	–	–
3	$[Cu(MeCN)_4]SbF_6$	–	72	–50	24	87
4	$[Cu(MeCN)_4]ClO_4$	–	72	–50	11	91
5	$[Cu(MeCN)_4]PF_6$	MS 4A	72	–40	–	69
6	$[Cu(MeCN)_4]PF_6$	MS 4A	72	–50	19	74
7	$[Cu(MeCN)_4]PF_6$	$LiBF_4$ (0.3 eq)	48	–50	95	59
8	$[Cu(MeCN)_4]PF_6$	$LiBF_4$ (0.5 eq)	48	–50	95	59
9	$[Cu(MeCN)_4]ClO_4$	$LiBF_4$ (1.0 eq)	72	–50	97	58
10	–	$LiBF_4$ (0.5 eq)	72	–40	13	–

[a] **61b**: 0.1 mmol, **66**: 0.15 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

A brief survey on the effect of bases was next conducted (**Table 21**). Using LiO(*p*-$OMeC_6H_4$) as base in THF at –40 °C, enantioselectivity decreased when increasing the base loading (entries 1–3). Using Et_3N as base, lowering the reaction temperature improved the enantioselectivity, but catalytic activity decreased (entries 4–7). Increasing the loading of Et_3N could improve the yield (entry 8). Quinuclidine could promote the reaction in THF at –20 °C, and giving product with low yield and *ee* (entry 9), however, no product was detected when the reaction was carried out at –40 °C (entry 10). No corresponding product was observed when proton-sponge or DIPEA was used as base (entries 11–14). Although an excellent yield was observed when using DBU as base at –20 °C, the enantioselectivity was only 14% (entry 15). DBU displayed both low yield and *ee* when the reaction was carried out at –40 °C (entries 16,17).

Table 21. Base Screening[a]



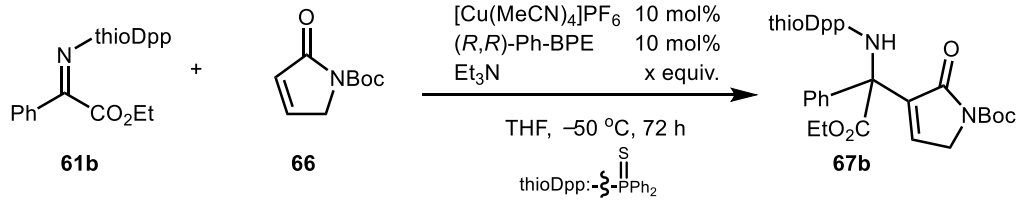
Entry	Base	X	t (h)	*T* (°C)	Yield.[b] (%)	ee[c] (%)
1	LiO(*p*-$OMeC_6H_4$)	10	48	–40	62	52
2	LiO(*p*-$OMeC_6H_4$)	20	48	–40	75	31
3	LiO(*p*-$OMeC_6H_4$)	50	48	–40	24	29
4	Et_3N	50	24	–20	55	76
5	Et_3N	50	24	–30	70	83
6	Et_3N	50	72	–40	48	87
7	Et_3N	50	72	–50	16	91
8	Et_3N	100	72	–50	30	91

9	Quinuclidine	50	24	–20	32	17
10	Quinuclidine	50	24	–40	–	–
11	Proton-sponge	50	24	–40	–	–
12	DIPEA	10	24	–40	–	–
13	DIPEA	50	24	–40	–	–
14	DIPEA	50	48	–40	–	–
15	DBU	50	24	–20	85	14
16	DBU	10	24	–40	–	–
17	DBU	20	24	–40	31	75

[a] **61b**: 0.1 mmol, **66**: 0.15 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis.

The base screening showed that Et_3N was the optimal base examined for this reaction. Increasing the base loading to 2 eq. improved the yield to 59% whilst maintaining high enantioselectivity (**Table 22,** entry 1 versus 2). Using 2 eq. of nucleophile at a high concentration (0.2 M) improved the yield significantly: 81% yield and 90% *ee* was obtained (entry 5). However, higher concentrations decreased the enantioselectivity (entries 6–8). Under the optimal reaction conditions, product **67b** was obtained in 94% yield with 90% *ee* (entry 9).

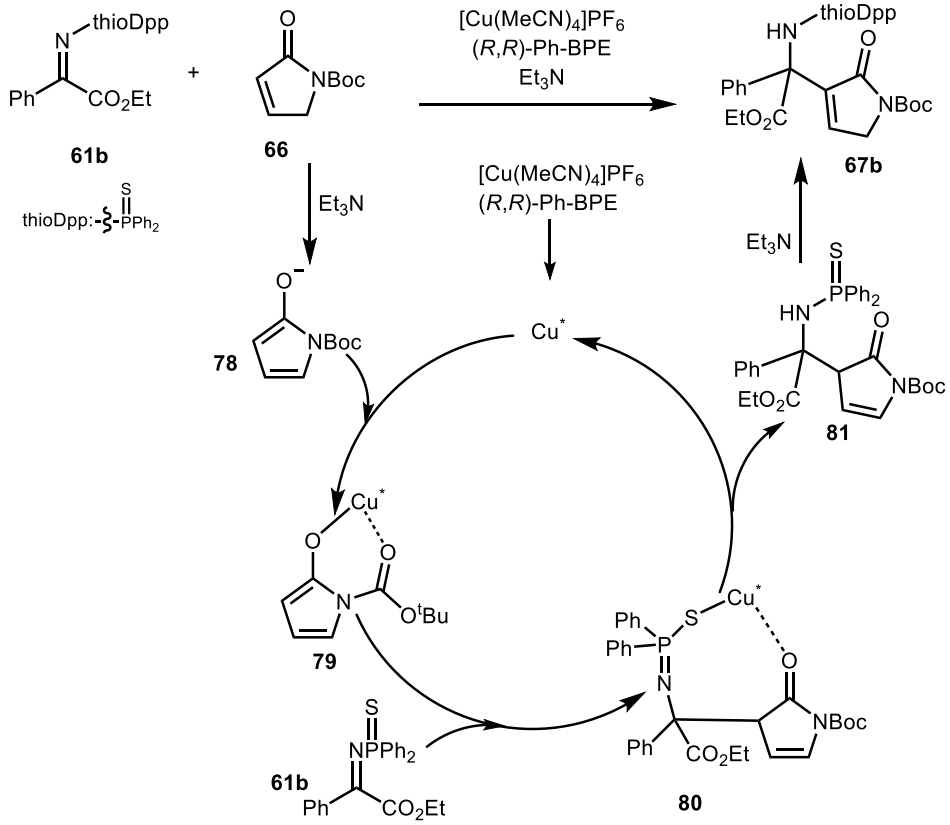
Table 22. Condition Screening[a]



Entry	Nu (eq.)	x	Conc. (M)	Yield[b] (%)	ee[c] (%)
1	1.5	1	0.1	30	91
2	1.5	2	0.1	59	92
3	1.5	5	0.1	52	90
4	1.5	10	0.1	48	91
5	2	2	0.2	81	90
6	2	1	0.5	48	86
7	2	1	0.4	57	88
8	2	1	0.33	69	88
9[d]	2	2	0.2	94	90

[a] **61b**: 0.1 mmol. [b] Determined by ^{1}H NMR analysis of the crude mixture using 3,4,5-trichloropyridine as an internal standard. [c] Determined by HPLC analysis. [c] 96 h, Isolated yield.

2.3.3 Proposed mechanism



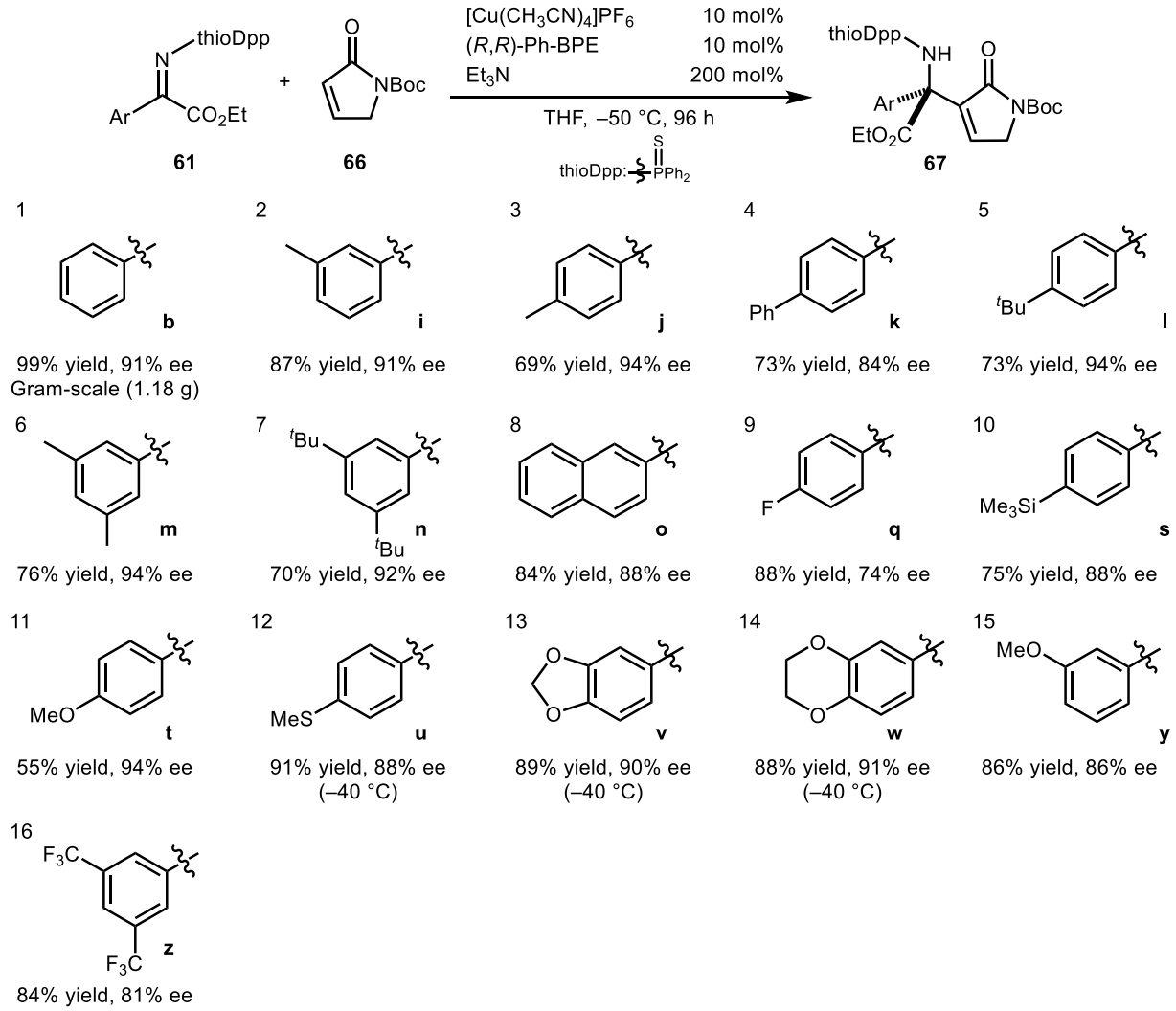
Scheme 29. Proposed mechanism

Based on Wang's report[45] on the addition-isomerization sequence, I propose the reaction mechanism as shown in **Scheme 29**. Deprotonation of **66** by Et_3N at the γ-position gave dienolate intermediate **78**, which formed complex **79** with Cu(I)/(*R*,*R*)-Ph-BPE. Then, a direct Mannich-type addition to *N*-thioDpp α-iminoesters **61b** furnished **81** which isomerized to give the final product.

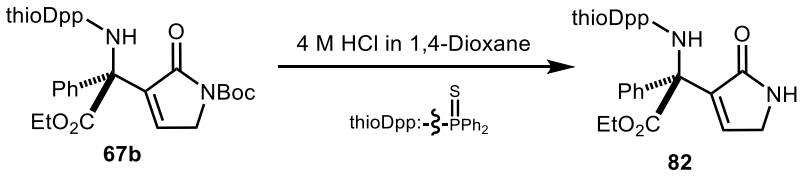
2.3.4 Investigation of substrate scope

Table 23. Substrate scope

With optimized conditions being established, the scope of the reaction was evaluated (**Table 23**). The reaction could be carried out on a gram scale (entry 1). High enantioselectivity was observed for the ketimines bearing small and bulky alkyl groups at the *meta* and *para* positons (entries 2–3,5–7), however enantioselectivity dropped slightly with *para*-phenyl substituted substrate (entry 4). Lower enantioselectivity was observed for the ketimines bearing electron-withdrawing groups (entries 9,10,16). Ketimines bearing electron-donating groups on the aromatic ring gave similar enantioselectivity (entries 11–15).



2.3.5 Determination of absolute configuration



Scheme 30. Product transformation

Crystals of the product **67b** were not able to be obtained. Thus, product **67b** was transformed into **82** (**Scheme 30**) which showed a highly crystalline nature. The absolute configuration of the product was determined by the X-ray crystal structure as shown in **Figure 14**. The absolute configuration of other products were deduced by analogy.

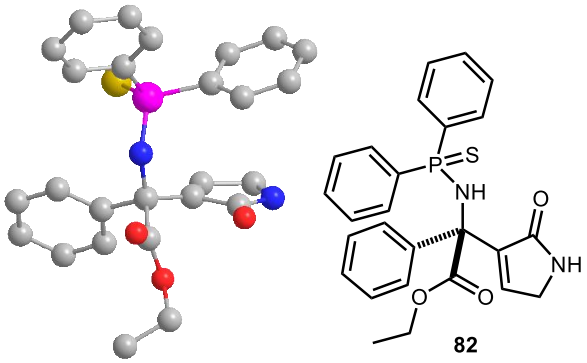
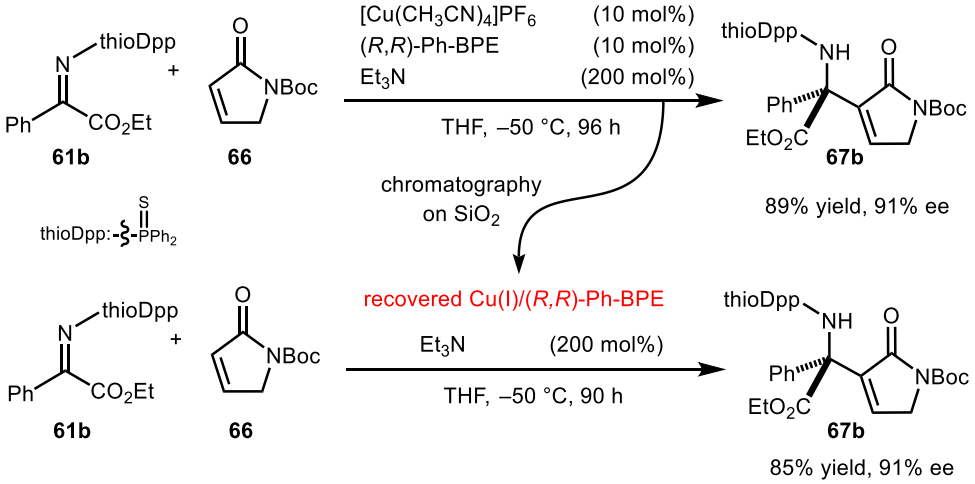


Figure 14. X-ray crystal structure of the product[50]

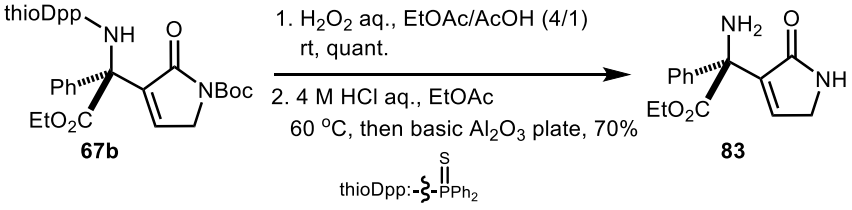
2.3.6 Catalyst recovery and reuse

Recovery and reuse of the Cu(I)/(*R*,*R*)-Ph-BPE complex was attempted (**Scheme 29**). It was found that the catalyst was fairly stable and could be purified by chromatography on silica gel. The recovered catalyst showed almost the same performance compared with new catalyst to give the product in high yield and with high enantioselectivity.



Scheme 31. Recovery and reuse of Cu(I)/(*R*,*R*)-Ph-BPE

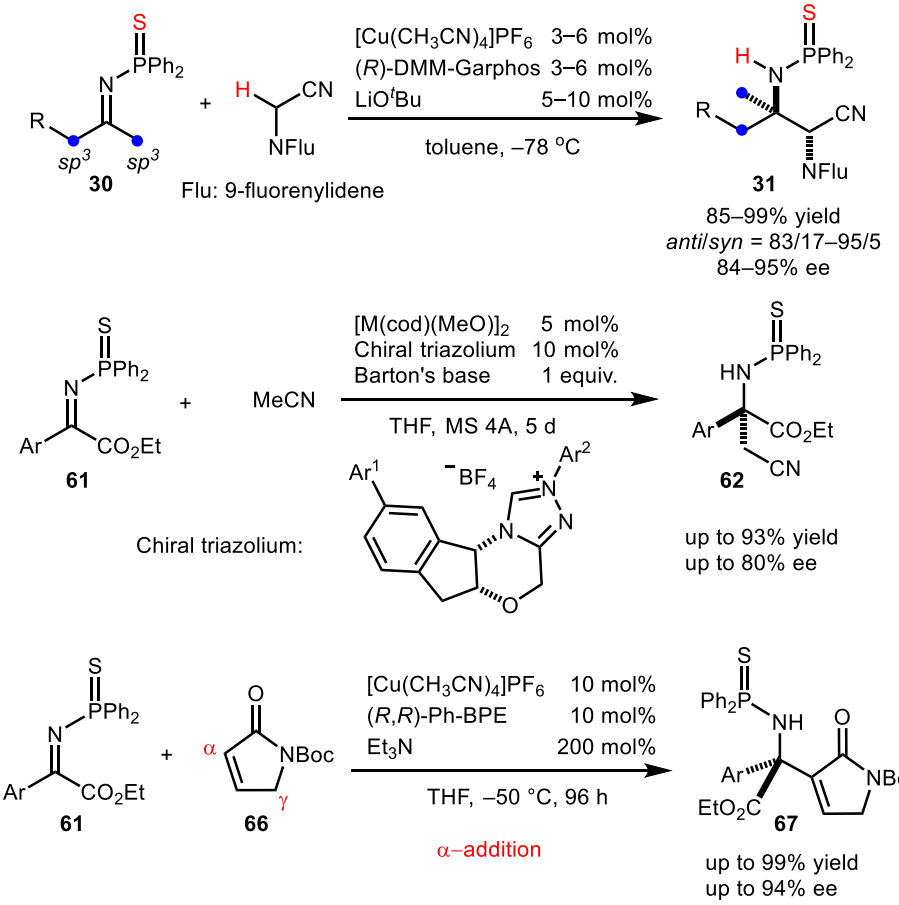
2.3.7 Transformation of the product



Scheme 32. Product transformation

Product **67b** was treated with aqueous H_2O_2, and the crude product was dissolved in a mixture of 4 M HCl/EtOAc and heated to 60 °C to give *α*,*α*-disubstituted *α*-amino ester **83**.

3. Research summary and conclusion



In summary, by using *N*-(diphenylthiophosphinoyl)ketimines as soft Lewis basic electrophiles in Mannich reactions, I developed 1) a highly diastereo- and enantioselective method to access to *α*,*β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters; 2) the first example of a catalytic asymmetric Mannich-type reaction of MeCN with acyclic ketimines; 3) asymmetric *α*-addition of *α*,*β*-unsaturated *γ*-butyrolactam to ketimines for the construction of *α*,*α*-disubstituted *α*-amino acid derivatives.

4. Experimental

4.1 General experimental

4.1.1 General

All reactions were performed in a flame-dried glassware with a Teflon-coated magnetic stirring bar unless otherwise noted. The flasks or test tubes were fitted with a 3-way glass stopcock and reactions were run under Ar atmosphere. Air- and moisture-sensitive liquids were transferred via a gas-tight syringe and a stainless-steel needle. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

4.1.2 Instrumentation

Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR was recorded on JEOL ECS-400 or Bruker AVANCE III HD400. Chemical shifts for proton were reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ppm or TMS in $CDCl_3$: δ 0.00 ppm; DMSO-d_6: δ 2.49; CD_3OD: δ 3.30 ppm or TMS in CD_3OD: δ 0.00 ppm; CD_3CN: δ 1.94 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$: δ 77.0 ppm; DMSOd_6: δ 39.5; CD_3OD: δ 49.0 ppm; CD_3CN: δ 118.26 ppm) as an internal reference. For ^{31}P NMR, chemical shifts were reported in the scale relative to H_3PO_4 (δ 0.0 ppm in D_2O) or $OP(OPh)_3$ (δ –17.6035 ppm in $CDCl_3$) as an external reference. For ^{19}F NMR, chemical shifts were reported in the scale relative to $PhCF_3$(δ –62.7680 ppm in $CDCl_3$) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 1 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra (ESI TOF (+)) was measured on Thermo Fisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (ø 0.46 cm x 25 cm).

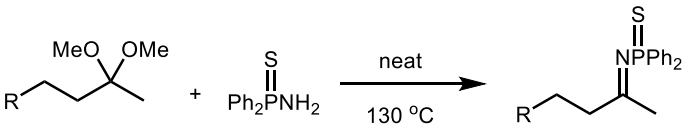
4.1.3 Materials

Unless otherwise noted, materials were purchased from commercial suppliers and were used without further purification. Solvents were purified by passing through a solvent purification system (Glass Contour). Et_3N was distilled from CaH_2. MS 4A was purchased from Nacalai Tesque Co. Ltd. and dried by microwave oven heating three times. Barton's base was purchased from Aldrich. All the metals or chiral phosphine ligands were purchased from TCI Co. Ltd., Aldrich or Strem Chemical Co. Ltd. and used as received (opened and handled in a dry box). Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM) or silicagel 60 N (spherical, neutral, 40-50 □m) from Kanto Chemical Co. Ltd. Preparative TLC plates (1.05788.0001, PLC Aluminium Oxide 60 F_{254}, 1.5 mm) and preparative TLC plates (1.05744.0001, PLC Silica gel 60 F_{254}, 0.5 mm) were purchased from Merck.

4.2 Synthetic procedures

4.2.1 Procedures for preparation of ketimine

Procedure A:[51]

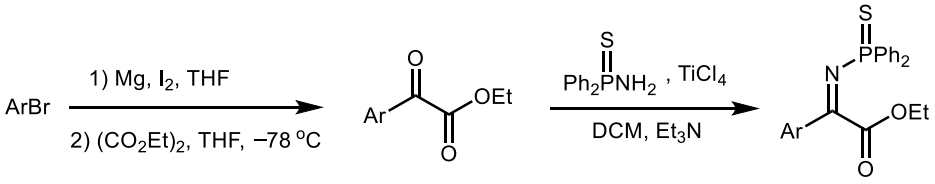


A 50 mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with diphenylthiophosphinamide (5 mmol, 1.0 equiv.) and acetal (5 mmol, 1.0 equiv.). The flask was equipped with a reflux condenser without flow of tap water (air-cooling), and the mixture was heated to 130 °C (oil bath temperature) under

ambient atmosphere. After stirring for 1 h, another portion of acetal (5 mmol, 1.0 equiv.) was added. After stirring for an additional 1 h, the mixture was cooled to room temperature. The mixture was diluted with 10 mL EtOAc, and Et_3N (1 mL), then neutral silica gel was added. The volatiles were removed under reduce pressure. The crude mixture was purified by column chromatography.

Procedure B:[52]

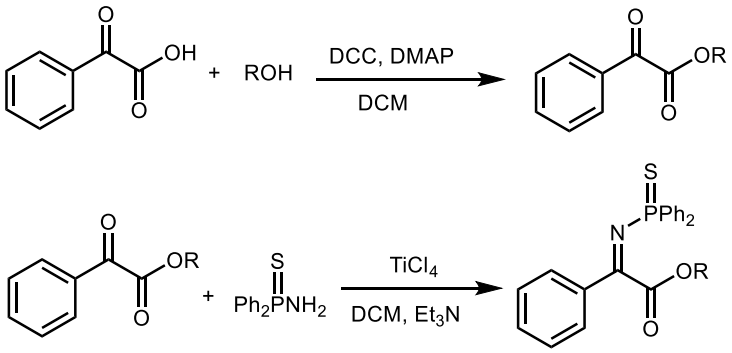
Magnesium (22 mmol, 1.1 equiv.) was heated at reduced pressure for 10 min in a three neck round flask with condenser and dropping funnel. A catalytic amount of I_2 followed by THF (30 mL) were added after cooling to room temperature and aryl bromide (20 mmol, 1 equiv.) in THF (5 mL) was added dropwise and the reaction mixture was stirred for 1h. The formed Grignard reagent was added over 1h to a solution of diethyl oxalate (20 mmol, 1 equiv.) in THF (10 mL) at –78 °C. After 1h at –78 °C, the mixture was warmed to 0 °C. The mixture was quenched with aqueous saturated NH_4Cl, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered off, and the solvents were evaporated. The crude product was purified by flash column chromatography to afford pure *α*-keto esters.



A flame-dried flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with α-keto esters (5 mmol, 1 equiv.) and phosphinothioic amide (5 mmol, 1 equiv) under Ar atmosphere. DCM (30 mL) was added, and the solution was stirred for 1 min at rt, then cooled to 0 °C. Et_3N (5 mL) was added and the resulting solution was stirred at the same temperature for another 5 min. Then $TiCl_4$ (5 mL) solution (1 M in DCM) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with sat. $NaHCO_3$ and extracted with DCM. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product.

Procedure C:

A mixture of keto acid (40 mml, 1 equiv.), alcohol (40 mmol, 1 equiv.) and DMAP (6 mmol, 0.15 equiv.) in DCM (200 mL) was cooled to 0 °C. DCC (60 mmol, 1.5 equiv.) was added, and the resulting mixture was warmed to room temperature and stirred overnight. The mixture was quenched with aqueous saturated NH_4Cl, extracted with DCM, washed with brine, dried over $MgSO_4$, filtered off, and the solvents were evaporated. The crude product was purified by flash column chromatography to afford pure *α*-keto esters.

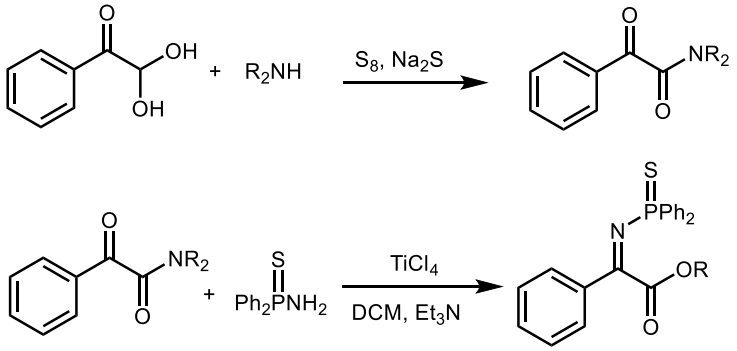


A flame-dried flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with α-keto esters (5

mmol, 1 equiv.) and phosphinothioic amide (5 mmol, 1 equiv) under Ar atmosphere. DCM (30 mL) was added, and the solution was stirred for 1 min at rt, then cooled to 0 °C. Et_3N (5 mL) was added and the resulting solution was stirred at the same temperature for another 5 min. Then $TiCl_4$ (5 mL) solution (1 M in DCM) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with sat. $NaHCO_3$ and extracted with DCM. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product.

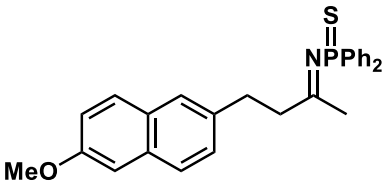
Procedure D: [53]

Arylglyoxal (10 mml, 1 equiv.) was added to a mixture of amine (20 mml, 2 equiv.), elemental sulfur (20 mml, 2 equiv.) and Na_2S (0.1 mml, 0.01 equiv.).The mixture was heated to 60 °C for 4 h. The obtained solid was removed by filtration. EtOH (45 mL) was added to the mixture and then heating, followed by hot filtration. The solvents were evaporated. The crude product was purified by flash column chromatography to afford *α*-keto amides.



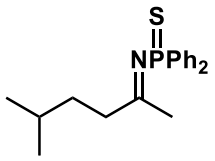
A flame-dried flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with α-keto esters (5 mmol, 1 equiv.) and phosphinothioic amide (5 mmol, 1 equiv) under Ar atmosphere. DCM (30 mL) was added, and the solution was stirred for 1 min at rt, then cooled to 0 °C. Et_3N (5 mL) was added and the resulting solution was stirred at the same temperature for another 5 min. Then $TiCl_4$ (5 mL) solution (1 M in DCM) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched with sat. $NaHCO_3$ and extracted with DCM. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product.

***N*-(4-(6-Methoxynaphthalen-2-yl)butan-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30b)**



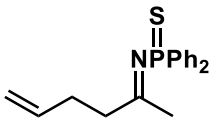
Procedure A: Colorless crystal; M. p.97–98 °C; IR (KBr): *v* 1650, 1633, 1606 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.77–7.65 (m, 7H), 7.47–7.33 (m, 7H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.13 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.85 (s, 3H), 3.12–3.04 (m, 4H), 2.28 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.1 (d, *J* = 11.4 Hz), 156.8, 136.6, 135.9, 135.6, 132.8, 131.2 (d, *J* = 2.9 Hz), 130.5 (d, *J* = 10.5 Hz), 128.8, 128.6, 128.4 (d, *J* = 12.4 Hz), 127.7, 126.7, 126.0, 118.6, 105.8, 55.1, 44.4 (d, *J* = 22.9 Hz), 30.7, 26.2 (d, *J* = 19.1 Hz); ^{31}P NMR (DMSO-d_6): δ 44.9; HRMS (ESI) Anal. calcd. for $C_{27}H_{26}ONNaPS$ *m/z* 466.1365 $[M+Na]^+$, found 466.1371.

***N*-(5-Methylhexan-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30d)**



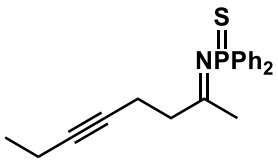
Procedure A: Yellow oil; IR (neat): *v* 1645 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90–7.85 (m, 4H), 7.52–7.46 (m, 6H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.27 (d, *J* = 1.4 Hz, 3H), 1.54–1.43 (m, 3H), 0.85 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.3 (d, *J* = 10.5 Hz), 136.7, 135.7, 131.3 (d, *J* = 3.8 Hz), 130.5, 128.5 (d, *J* = 12.4 Hz), 41.5 (d, *J* = 20.0 Hz), 34.0, 27.2, 26.3 (d, *J* = 19.1 Hz), 22.3; ^{31}P NMR (DMSO-d_6): δ 44.5; HRMS (ESI) Anal. calcd. for $C_{19}H_{24}NNaPS$ *m/z* 352.1259 $[M+Na]^+$, found 352.1270.

***N*-(Hex-5-en-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide amide (30f)**



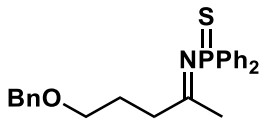
Procedure A: Yellow solid; M. p. 69–71 °C; IR (KBr): *v* 1726, 1639 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92–7.86 (m, 4H), 7.50–7.45 (m, 6H), 5.88–5.78 (m, 1H), 5.06–4.96 (m, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.41–2.35 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.1 (d, *J* = 11.4 Hz), 137.4, 136.7, 135.6, 131.3 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 115.4, 42.6 (d, *J* = 20.0 Hz), 29.0, 26.1 (d, *J* = 18.1 Hz); ^{31}P NMR (DMSO-d_6): δ 44.9; HRMS (ESI) Anal. calcd. for $C_{18}H_{20}NNaPS$ *m/z* 336.0946 $[M+Na]^+$, found 336.0952.

***N*-(Oct-5-yn-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30g)**



Procedure A: Yellow crystal; M. p. 38–40 °C; IR (KBr): *v* 2349, 1643 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97–7.91 (m, 4H), 7.52–7.46 (m, 6H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.52–2.48 (m, 2H), 2.27 (d, *J* = 1.4 Hz, 3H), 2.15–2.08 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.9 (d, *J* = 10.5 Hz), 136.7, 135.7, 131.3 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 81.9, 79.0, 42.8 (d, *J* = 21.0 Hz), 25.8 (d, *J* = 17.2 Hz), 14.4, 14.1, 11.8; ^{31}P NMR (DMSO-d_6): δ 45.0; HRMS (ESI) Anal. calcd. for $C_{20}H_{22}NNaPS$ *m/z* 362.1103 $[M+Na]^+$, found 362.1113.

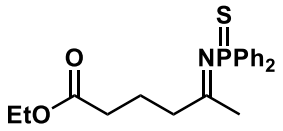
***N*-(Oct-5-yn-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30h)**



Procedure A: Yellow oil; IR (neat): *v* 1714, 1644 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90–7.84 (m, 4H), 7.52–7.44 (m, 6H), 7.34–7.24 (m, 5H), 4.43 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.27 (d, *J* = 1.1 Hz, 3H), 1.94–1.87 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.6 (d, *J* = 11.5 Hz), 138.5, 136.7, 135.7, 131.3 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 128.2, 127.43, 127.35, 71.9, 68.8, 40.5 (d, *J* = 21.9 Hz), 26.1 (d, *J* = 18.1 Hz), 25.3; ^{31}P NMR (DMSO-d_6): δ 44.8; HRMS (ESI) Anal. calcd. for $C_{24}H_{26}ONNaPS$ *m/z* 430.1365

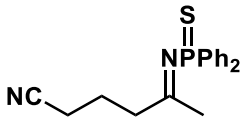
[M+Na]$^+$, found 430.1375.

Ethyl-5-((diphenylphosphorothioyl)imino)hexanoate (30i)



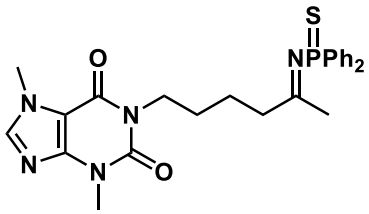
Procedure A: Yellow oil; IR (neat): *v* 1732, 1646 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92–7.86 (m, 4H), 7.53–7.45 (m, 6H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.27 (d, *J* = 1.4 Hz, 3H), 1.92–1.85 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.1 (d, *J* = 11.5 Hz), 172.6, 136.6, 135.6, 131.3 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 59.8, 42.7 (d, *J* = 20.0 Hz), 32.6 (d, *J* = 4.8 Hz), 25.9 (d, *J* = 18.1 Hz), 20.3, 14.1; ^{31}P NMR (DMSO-d_6): δ 44.9; HRMS (ESI) Anal. calcd. for $C_{20}H_{24}O_2NNaPS$ *m/z* 396.1158 [M+Na]$^+$, found 396.1161.

***N*-(5-Isocyanopentan-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30j)**



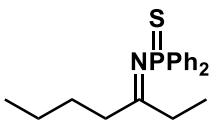
Procedure A: Colorless crystal; M. p. 82–83 °C; IR (KBr): *v* 2246, 1639 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88–7.83 (m, 4H), 7.49–7.42 (m, 6H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.24 (d, *J* = 1.4 Hz, 3H), 1.94–1.86 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.3 (d, *J* = 11.4 Hz), 136.5, 135.5, 131.4 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.6 (d, *J* = 12.4 Hz), 120.4, 42.3 (d, *J* = 21.9 Hz), 25.9 (d, *J* = 18.1 Hz), 20.8, 15.6; ^{31}P NMR (DMSO-d_6): δ 45.3; HRMS (ESI) Anal. calcd. for $C_{18}H_{19}N_2NaPS$ *m/z* 349.0899 [M+Na]$^+$, found 349.0907.

***N*-(6-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)hexan-2-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30k)**



Procedure A: Amorphous solid; IR (KBr): *v* 1703, 1659 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (s, 1H), 7.95–7.90 (m, 4H), 7.50–7.47 (m, 6H), 3.93–3.89 (m, 5H), 3.44 (s, 3H), 2.68 (d, *J* = 6.4 Hz, 2H), 2.31 (s, 3H), 1.70–1.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.7 (d, *J* = 11.4 Hz), 154.4, 150.8, 148.2, 142.9, 136.7, 135.7, 131.2 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 106.6, 43.2 (d, *J* = 21.0 Hz), 33.1, 29.4, 27.0, 26.1 (d, *J* = 18.1 Hz), 22.4; ^{31}P NMR (DMSO-d_6): δ 44.6; HRMS (ESI) Anal. calcd. for $C_{25}H_{28}O_2N_5NaPS$ *m/z* 516.1594 [M+Na]$^+$, found 516.1581.

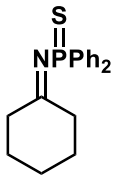
***N*-(Heptan-3-ylidene)-*P*,*P*-diphenylphosphinothioic amide (30l)**



Procedure A: Yellow oil; IR (neat): *v* 1645 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94–7.89 (m, 4H), 7.51–7.46

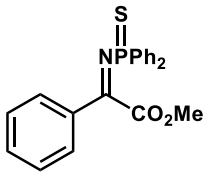
(m, 6H), 2.70–2.63 (m, 4H), 1.46–1.38 (m, 2H), 1.22–1.13 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.6 (d, *J* = 11.4 Hz), 137.2, 136.1, 131.2 (d, *J* = 2.9 Hz), 130.6 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 33.6 (d, *J* = 20.0 Hz), 27.6, 21.9, 13.7, 10.2; ^{31}P NMR (DMSO-d_6): δ 43.4; HRMS (ESI) Anal. calcd. for $C_{19}H_{24}NNaPS$ *m/z* 352.1259 $[M+Na]^+$, found 352.1254.

_N_-Cyclohexylidene-_P_,_P_-diphenylphosphinothioic amide (30m)



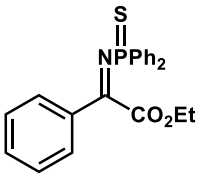
Procedure A: White solid; M. p. 95–97 °C; IR (KBr): *v* 1633 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91–7.85 (m, 4H), 7.52–7.46 (m, 6H), 2.62–2.59 (m, 4H), 1.60–1.53 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.4 (d, *J* = 11.4 Hz), 136.8, 135.8, 131.2 (d, *J* = 2.9 Hz), 130.5 (d, *J* = 10.5 Hz), 128.5 (d, *J* = 12.4 Hz), 27.3, 24.2; ^{31}P NMR (DMSO-d_6): δ 44.2; HRMS (ESI) Anal. calcd. for $C_{18}H_{20}NNaPS$ *m/z* 336.0946 $[M+Na]^+$, found 336.0944.

Methyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61a)



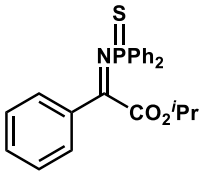
Procedure C: Yellow crystal; M. p.144–145 °C; IR (KBr): *v* 1735, 1631, 1591 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 4H), 7.95–7.93 (m, 2H), 7.61–7.57 (m, 1H), 7.51–7.71 (m, 8H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (d, *J* = 9.0 Hz), 165.0 (d, *J* = 17.1 Hz), 135.6, 134.5, 134.2, 134.0, 133.8, 131.51, 131.48, 131.4, 131.3, 129.0, 128.9, 128.5, 128.3, 52.4; ^{31}P NMR ($CDCl_3$): δ 52.0; HRMS (ESI) Anal. calcd. for $C_{21}H_{18}O_2NNaPS$ *m/z* 402.0688 $[M+Na]^+$, found 402.0680.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61b)



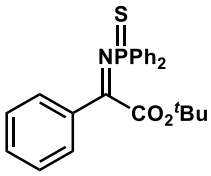
Procedure B: Pale yellow crystal; M. p.110–112 °C; IR (KBr): *v* 1731, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 4H), 7.97–7.95 (m, 2H), 7.61–7.57 (m, 1H), 7.51–7.41 (m, 8H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (d, *J* = 8.8 Hz), 164.5 (d, *J* = 16.9 Hz), 135.7, 134.7, 134.4, 134.2, 133.7, 131.44, 131.41, 131.4, 131.3, 129.0, 128.9, 128.4, 128.3, 62.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.8; HRMS (ESI) Anal. calcd. for $C_{22}H_{20}O_2NNaPS$ *m/z* 416.0845 $[M+Na]^+$, found 416.0842.

Isopropyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61c)



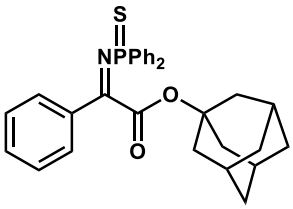
Procedure C: Yellow crystal; M. p.105–106 ºC; IR (KBr): *v* 1726, 1631, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.01 (m, 4H), 7.95–7.93 (m, 2H), 7.60–7.56 (m, 1H), 7.50–7.41 (m, 8H), 5.43–5.34 (m, 1H), 1.39 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (d, *J* = 8.7 Hz), 164.0 (d, *J* = 16.8 Hz), 135.9, 134.8, 134.6, 134.4, 133.6, 131.39, 131.36, 131.28, 129.0, 128.9, 128.4, 128.3, 71.2, 21.6; ^{31}P NMR ($CDCl_3$): δ 51.5; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_2NNaPS$ *m/z* 430.1001 $[M+Na]^+$, found 430.0997.

***tert*-Butyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61d)**



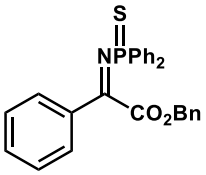
Procedure C: Yellow crystal; M. p.138–140 ºC; IR (KBr): *v* 1725, 1682, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.01 (m, 4H), 7.98–7.96 (m, 2H), 7.59–7.55 (m, 1H), 7.50–7.40 (m, 8H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (d, *J* = 8.5 Hz), 163.2 (d, *J* = 16.3 Hz), 136.2, 135.2, 135.1, 135.0, 133.3, 131.36, 131.28, 131.25, 129.0, 128.8, 128.4, 128.2, 85.6, 28.2; ^{31}P NMR ($CDCl_3$): δ 50.9; HRMS (ESI) Anal. calcd. for $C_{24}H_{24}O_2NNaPS$ *m/z* 444.1158 $[M+Na]^+$, found 444.1155.

Adamantan-1-yl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61e)



Procedure C: Yellow crystal; M. p.187–189 ºC; IR (KBr): *v* 1726, 1639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–7.97 (m, 6H), 7.59–7.55 (m, 1H), 7.50–7.40 (m, 8H), 2.32 (d, *J* = 2.7 Hz, 6H), 2.21 (s, 3H), 1.73–1.74 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (d, *J* = 8.4 Hz), 163.1 (d, *J* = 16.4 Hz), 136.1, 135.2, 135.1, 134.9, 133.3, 131.4, 131.29, 131.28, 131.24, 139.1, 128.7, 128.4, 128.2, 85.9, 41.5, 36.0, 31.1; ^{31}P NMR ($CDCl_3$): δ 51.0; HRMS (ESI) Anal. calcd. for $C_{30}H_{31}O_2NPS$ *m/z* 500.1808 $[M+H]^+$, found 500.1805.

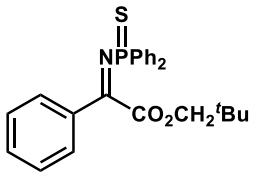
Benzyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61f)



Procedure B: Yellow solid; IR (KBr): *v* 1734, 1637, 1592, 1577 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–7.99 (m, 4H), 7.92–7.89 (m, 2H), 7.58–7.54 (m, 1H), 7.46–7.38 (m, 10H), 7.33–7.30 (m, 3H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (d, *J* = 8.9 Hz), 164.3 (d, *J* = 17.1 Hz), 135.6, 134.53, 134.5, 134.2, 134.0, 133.8, 131.5, 131.44,

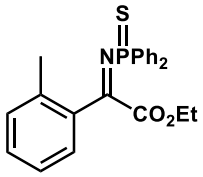
131.4, 131.3, 129.1, 129.0, 128.9, 128.49, 128.46, 128.44, 128.3, 68.0; ^{31}P NMR ($CDCl_3$): δ 52.0; HRMS (ESI) Anal. calcd. for $C_{27}H_{22}O_2NNaPS$ *m/z* 478.1001 $[M+Na]^+$, found 478.0996.

Neopentyl 2-((diphenylphosphorothioyl)imino)-2-phenylacetate (61g)



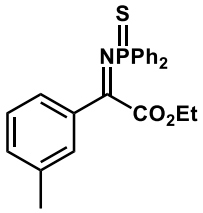
Procedure B: Yellow solid; IR (KBr): *v* 2958, 1733, 1642, 1592, 1577 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–7.95 (m, 6H), 7.62–7.58 (m, 1H), 7.52–7.41 (m, 8H), 4.12 (s, 2H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (d, *J* = 8.7 Hz), 164.9 (d, *J* = 17.0 Hz), 135.8, 134.7, 134.4, 134.2, 133.7, 131.41, 131.39, 131.3, 129.0, 128.9, 128.4, 128.3, 75.4, 31.0, 26.5; ^{31}P NMR ($CDCl_3$): δ 51.7; HRMS (ESI) Anal. calcd. for $C_{25}H_{26}O_2NNaPS$ *m/z* 458.1314 $[M+Na]^+$, found 458.1308.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(*o*-tolyl)acetate (61h)



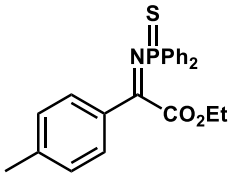
Procedure B: Yellow crystal; M. p.111–112 ºC; IR (KBr): *v* 1734, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01–7.96 (m, 4H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.47–7.36 (m, 7H), 7.27–7.22 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (d, *J* = 10.5 Hz), 164.5 (d, *J* = 19.0 Hz), 138.9, 135.4, 134.4, 134.2, 134.0, 132.0, 131.77, 131.51, 131.42, 131.40, 130.2, 128.4, 128.2, 126.0, 62.2, 21.7, 13.7; ^{31}P NMR ($CDCl_3$): δ 52.6; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_2NNaPS$ *m/z* 430.1001 $[M+Na]^+$, found 430.0993.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(*m*-tolyl)acetate (61i)



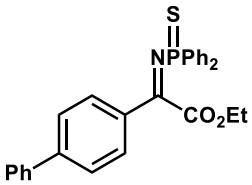
Procedure B: Yellow crystal; M. p.65–67 ºC; IR (KBr): *v* 1736, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 4H), 7.78–7.76 (m, 1H), 7.72 (s, 1H), 7.49–7.35 (m, 8H), 4.46 (q, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, *J* = 8.9 Hz), 164.5 (d, *J* = 17.1 Hz), 138.7, 135.8, 134.7, 134.6, 134.4, 134.2, 131.40, 131.38, 131.3, 129.5, 128.8, 128.4, 128.3, 126.3, 62.2, 21.4, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.7; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_2NNaPS$ *m/z* 430.1001 $[M+Na]^+$, found 430.1000.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(*p*-tolyl)acetate (61j)



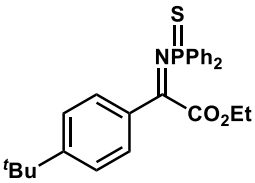
Procedure B: Yellow crystal; M. p.122–124 ºC; IR (KBr): *v* 1732, 1638, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.00 (m, 4H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.48–7.40 (m, 6H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (d, *J* = 8.7 Hz), 164.6 (d, *J* = 17.0 Hz), 144.9, 136.0, 134.9, 131.9, 131.6, 131.4, 131.32, 131.26, 129.6, 129.1, 128.4, 128.2, 62.2, 21.8, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_2NNaPS$ *m/z* 430.1001 $[M+Na]^+$, found 430.0997.

Ethyl 2-([1,1'-biphenyl]-4-yl)-2-((diphenylphosphorothioyl)imino)acetate (61k)



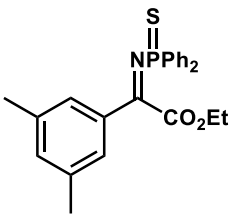
Procedure B: Yellow crystal; M. p.108–110 ºC; IR (KBr): *v* 1738, 1631, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.02 (m, 6H), 7.72–7.70 (m, 2H), 7.63–7.61 (m, 2H), 7.49–7.38 (m, 9H), 4.49 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (d, *J* = 8.7 Hz), 164.5 (d, *J* = 16.9 Hz), 146.5, 139.6, 135.8, 134.8, 133.2, 133.0, 131.42, 131.38, 131.28, 129.6, 129.0, 128.5, 128.4, 128.3, 127.5, 127.2, 62.3, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.8; HRMS (ESI) Anal. calcd. for $C_{28}H_{25}O_2NPS$ *m/z* 470.1338 $[M+H]^+$, found 470.1334.

Ethyl 2-(4-(*tert*-butyl)phenyl)-2-((diphenylphosphorothioyl)imino)acetate (61l)



Procedure B: Yellow crystal; M. p.115–118 ºC; IR (KBr): *v* 1734, 1633, 1598 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 4H), 7.80 (d, *J* = 1.8 Hz, 2H), 7.67 (t, *J* = 1.8 Hz, 2H), 7.49–7.42 (m, 6H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.35–1.31 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (d, *J* = 8.8 Hz), 164.6 (d, *J* = 17.0 Hz), 157.9, 136.0, 134.9, 131.8, 131.5, 131.4, 131.3, 131.2, 129.0, 128.4, 128.2, 125.9, 62.1, 35.2, 31.0, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{26}H_{29}O_2NPS$ *m/z* 450.1651 $[M+H]^+$, found 450.1646.

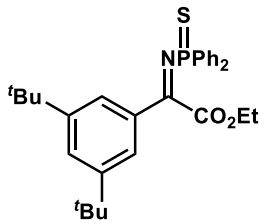
Ethyl 2-(3,5-dimethylphenyl)-2-((diphenylphosphorothioyl)imino)acetate (61m)



Procedure B: Yellow crystal; M. p.142–144 ºC; IR (KBr): *v* 1733, 1644, 1594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.00 (m, 4H), 7.54 (s, 2H), 7.47–7.41 (m, 6H), 7.22 (s, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 6H), 1.33 (t, *J* =

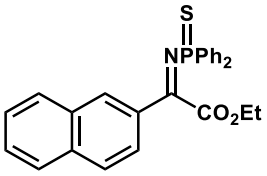
7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (d, *J* = 9.1 Hz), 164.6 (d, *J* = 17.2 Hz), 138.6, 135.9, 135.6, 134.8, 134.4, 134.2, 131.4, 131.32, 131.26, 128.4, 128.3, 126.8, 62.1, 21.3, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.7; HRMS (ESI) Anal. calcd. for $C_{24}H_{24}O_2NNaPS$ *m/z* 444.1158 $[M+Na]^+$, found 444.1155.

Ethyl 2-(3,5-di-*tert*-butylphenyl)-2-((diphenylphosphorothioyl)imino)acetate (61n)



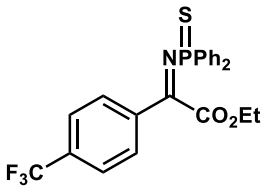
Procedure B: Yellow crystal; M. p.143–145 ºC; IR (KBr): *v* 1741, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–8.01 (m, 4H), 7.92–7.90 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.40 (m, 6H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.38–1.35 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (d, *J* = 9.0 Hz), 164.7 (d, *J* = 17.0 Hz), 151.5, 136.0, 134.9, 134.0, 133.8, 131.39, 131.35, 131.32, 131.29, 128.38, 128.35, 128.3, 123.3, 62.0, 35.0, 31.2, 13.9; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{30}H_{37}O_2NPS$ *m/z* 506.2277 $[M+H]^+$, found 506.2274.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(naphthalen-2-yl)acetate (61o)



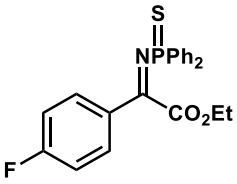
Procedure B: Yellow crystal; M. p.145–147 ºC; IR (KBr): *v* 1733, 1635, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.16 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.10–8.04 (m, 4H), 7.94–7.87 (m, 3H), 7.63–7.53 (m, 2H), 7.50–7.42 (m, 6H), 4.53 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (d, *J* = 8.7 Hz), 164.6 (d, *J* = 16.9 Hz), 135.9, 134.8, 132.5, 131.9, 131.8, 131.6, 131.43, 131.40, 131.3, 129.7, 129.0, 128.9, 128.4, 128.3, 127.9, 127.1, 123.7, 62.3, 13.8; ^{31}P NMR ($CDCl_3$): δ 51.8; HRMS (ESI) Anal. calcd. for $C_{26}H_{23}O_2NPS$ *m/z* 444.1182 $[M+H]^+$, found 444.1178.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(4-(trifluoromethyl)phenyl)acetate (61p)



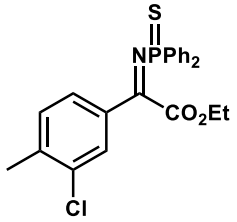
Procedure B: Yellow crystal; M. p.146–148 ºC; IR (KBr): *v* 1733, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–7.99 (m, 6H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.51–7.43 (m, 6H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (d, *J* = 8.4 Hz), 164.0 (d, *J* = 16.5 Hz), 137.4, 137.2, 135.2, 135.0, 134.6, 134.1, 131.69, 131.66, 131.4, 131.3, 129.2, 128.5, 128.4, 127.5, 125.90, 125.86, 125.82, 124.8, 122.1, 119.4, 62.6, 13.7; ^{19}F NMR (375 MHz, $CDCl_3$): δ –63.2; ^{31}P NMR ($CDCl_3$): δ 52.9; HRMS (ESI) Anal. calcd. for $C_{23}H_{19}O_2NF_3NaPS$ *m/z* 484.0718 $[M+Na]^+$, found 484.0716.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(4-fluorophenyl)acetate (61q)



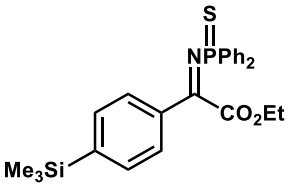
Procedure B: Yellow crystal; M. p.94–96 °C; IR (KBr): *v* 1737, 1644, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–7.51 (m, 6H), 7.48–7.41 (m, 6H), 7.20–7.14 (m, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (d, *J* = 8.4 Hz), 167.4, 164.9, 164.3 (d, *J* = 16.7 Hz), 135.6, 134.6, 131.6, 131.53, 131.50, 131.47, 131.4, 131.2, 130.8, 130.7, 130.55, 130.52, 128.4, 128.3, 116.3, 116.1, 62.4, 13.7; ^{19}F NMR (375 MHz, $CDCl_3$): δ –103.5; ^{31}P NMR ($CDCl_3$): δ 52.0; HRMS (ESI) Anal. calcd. for $C_{22}H_{19}O_2NFNaPS$ *m/z* 434.0750 $[M+Na]^+$, found 434.0744.

Ethyl 2-(3-chloro-4-methylphenyl)-2-((diphenylphosphorothioyl)imino)acetate (61r)



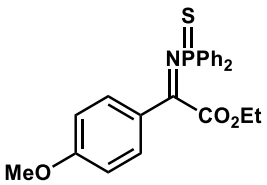
Procedure B: Yellow crystal; M. p.112–114 °C; IR (KBr): *v* 1742, 1639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04–7.98 (m, 4H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.70 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.50–7.42 (m, 6H), 7.34 (d, *J* = 8.0 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (d, *J* = 8.5 Hz), 164.2 (d, *J* = 16.7 Hz), 142.6, 135.5, 135.3, 134.5, 133.7, 133.5, 131.51, 131.49, 131.38, 131.33, 131.27, 129.2, 128.5, 128.3, 127.3, 62.4, 20.5, 13.7; ^{31}P NMR ($CDCl_3$): δ 52.2; HRMS (ESI) Anal. calcd. for $C_{23}H_{21}O_2NClNaPS$ *m/z* 464.0611 $[M+Na]^+$, found 464.0602.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(4-(trimethylsilyl)phenyl)acetate (61s)



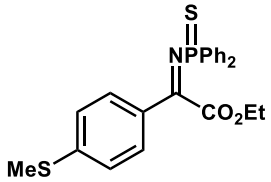
Procedure B: Yellow crystal; M. p.117–119 °C; IR (KBr): *v* 1736, 1628, 1592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 4H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.49–7.40 (m, 6H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (d, *J* = 8.9 Hz), 164.5 (d, *J* = 17.0 Hz), 148.4, 135.8, 134.7, 134.5, 134.3, 133.7, 131.41, 131.38, 131.27, 128.4, 128.3, 127.9, 62.2, 13.8, -1.4; ^{31}P NMR ($CDCl_3$): δ 51.7; HRMS (ESI) Anal. calcd. for $C_{25}H_{29}O_2NPSSi$ *m/z* 466.1420 $[M+H]^+$, found 466.1422.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(4-methoxyphenyl)acetate (61t)



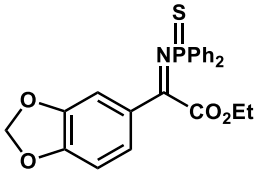
Procedure B: Yellow crystal; M. p.92–94 ºC; IR (KBr): *v* 1734, 1627, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05–7.99 (m, 4H), 7.95–7.92 (m, 2H), 7.48–7.40 (m, 6H), 6.99–6.95 (m, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (d, *J* = 8.4 Hz), 164.7 (d, *J* = 17.0 Hz), 164.3, 136.2, 135.1, 131.37, 131.33, 131.27, 131.24, 131.22, 128.3, 128.2, 127.2, 127.0, 114.3, 62.1, 55.6, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.0; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_3NNaPS$ *m/z* 446.0950 $[M+Na]^+$, found 446.0942.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(4-(methylthio)phenyl)acetate (61u)



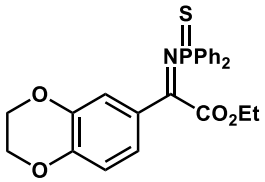
Procedure B: Yellow crystal; M. p.121–123 ºC; IR (KBr): *v* 1733, 1628, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.99 (m, 4H), 7.87–7.85 (m, 2H), 7.48–7.40 (m, 6H), 7.30–7.27 (m, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.52 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (d, *J* = 8.5 Hz), 164.5 (d, *J* = 16.8 Hz), 147.4, 136.0, 134.9, 131.34, 131.23, 130.6, 130.4, 129.3, 128.4, 128.2, 125.2, 62.2, 14.7, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.4;HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_2NnaPS_2$ *m/z* 462.0722 $[M+H]^+$, found 462.0717.

Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-((diphenylphosphorothioyl)imino)acetate (61v)



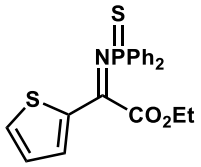
Procedure B: Yellow crystal; M. p.117–119 ºC; IR (KBr): *v* 1734, 1636, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.98 (m, 4H), 7.55 (d, *J* = 1.7 Hz, 1H), 7.48–7.41 (m, 7H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.07 (s, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (d, *J* = 8.2 Hz), 164.5 (d, *J* = 16.6 Hz), 152.7, 148.5, 136.0, 135.0, 131.33, 131.32, 131.2, 129.1, 128.7, 128.4, 128.2, 126.4, 108.3, 107.8, 102.1, 62.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.3; HRMS (ESI) Anal. calcd. for $C_{23}H_{21}O_4NPS$ *m/z* 438.0923 $[M+H]^+$, found 438.0922.

Ethyl 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-((diphenylphosphorothioyl)imino)acetate (61w)



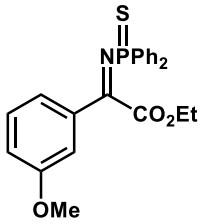
Procedure B: Yellow solid; IR (KBr): *v* 1733, 1634, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.98 (m, 4H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.47–7.39 (m, 7H), 6.93 (d, *J* = 8.6 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 4.34–4.27 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (d, *J* = 8.3 Hz), 164.6 (d, *J* = 16.8 Hz), 148.9, 143.7, 135.0, 131.32, 131.29, 131.26, 131.22, 128.4, 128.2, 123.6, 118.1, 117.7, 64.8, 64.1, 62.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{24}H_{22}O_4NNaPS$ *m/z* 474.0899 $[M+Na]^+$, found 474.0895.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(thiophen-2-yl)acetate (4v)



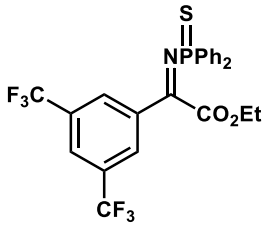
Procedure B: White crystal; M. p.114–115 °C; IR (KBr): *v* 1731, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.98 (m, 4H), 7.69 (dd, *J* = 0.8, 5.0 Hz, 1H), 7.59 (dd, *J* = 0.9, 3.8 Hz, 1H), 7.46–7.41 (m, 6H), 7.16–7.14 (m, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (d, *J* = 9.2 Hz), 163.4, 142.3 (d, *J* = 25.9 Hz), 136.0, 135.0, 134.9, 134.5, 131.35, 131.32, 131.29, 131.18, 128.8 (d, *J* = 1.4 Hz), 128.4, 128.2, 62.5, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{20}H_{18}O_2NNaPS_2$ *m/z* 422.0409 $[M+Na]^+$, found 422.0407.

Ethyl 2-((diphenylphosphorothioyl)imino)-2-(3-methoxyphenyl)acetate (61y)



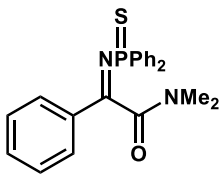
Procedure B: Yellow crystal; M. p.72–74 °C; IR (KBr): *v* 1741, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05–7.99 (m, 4H), 7.51–7.38 (m, 9H), 7.14–7.12 (m, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (d, *J* = 8.8 Hz), 164.4 (d, *J* = 16.8 Hz), 159.8, 135.8, 135.7, 135.5, 134.6, 131.44, 131.41, 131.37, 131.3, 129.9, 128.4, 128.3, 121.8, 119.4, 113.9, 62.2, 55.4, 13.7; ^{31}P NMR ($CDCl_3$): δ 51.8; HRMS (ESI) Anal. calcd. for $C_{23}H_{22}O_3NNaPS$ *m/z* 446.0950 $[M+Na]^+$, found 446.0944.

Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-((diphenylphosphorothioyl)imino)acetate (61z)



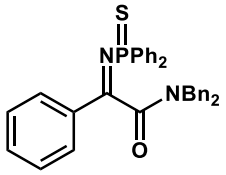
Procedure B: Yellow crystal; M. p.125–127 °C; IR (KBr): *v* 1735, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 2H), 8.07 (s, 1H), 8.04–7.98 (m, 4H), 7.54–7.46 (m, 6H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (d, *J* = 7.9 Hz), 163.4 (d, *J* = 16.0 Hz), 136.5, 136.3, 134.6, 133.6, 133.2, 132.8, 132.5, 132.1, 131.92, 131.90, 131.4, 131.3, 128.7, 128.6, 128.5, 126.8, 126.64, 126.61, 126.57, 126.53, 126.5, 124.1, 121.4, 118.7, 63.0, 13.7; ^{19}F NMR (375 MHz, $CDCl_3$): δ –63.1; ^{31}P NMR ($CDCl_3$): δ 54.1; HRMS (ESI) Anal. calcd. for $C_{24}H_{18}O_2NF_6NaPS$ *m/z* 552.0592 $[M+Na]^+$, found 552.0580.

2-((Diphenylphosphorothioyl)imino)-*N*,*N*-dimethyl-2-phenylacetamide (63a)



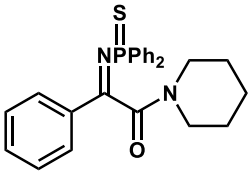
Procedure D: Yellow solid; IR (KBr): *v* 1645, 1590, 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–7.99 (m, 6H), 7.60–7.56 (m, 1H), 7.51–7.41 (m, 8H), 3.06 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (d, *J* = 8.0 Hz), 165.9 (d, *J* = 14.7 Hz), 135.8, 134.8, 134.7, 134.5, 133.6, 131.46, 131.38, 131.35, 129.0, 128.9, 128.4, 128.3, 37.7, 34.0; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{22}H_{21}ON_2NaPS$ *m/z* 415.1004 $[M+Na]^+$, found 415.1002.

***N*,*N*-Dibenzyl-2-((diphenylphosphorothioyl)imino)-2-phenylacetamide (63b)**



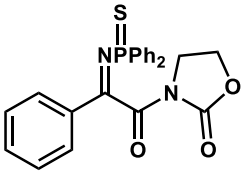
Procedure D: Brown solid; IR (KBr): *v* 1631, 1594, 1577 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.05 (m, 4H), 7.98–7.95 (m, 2H), 7.58–7.54 (m, 1H), 7.46–7.42 (m, 8H), 7.24–7.23 (m, 5H), 7.13–7.09 (m, 1H), 7.05–7.03 (m, 2H), 6.83–6.81 (m, 2H), 4.62 (s, 2H), 4.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9 (d, *J* = 8.4 Hz), 166.7 (d, *J* = 14.6 Hz), 136.0, 135.8, 135.5, 135.3, 134.8, 134.6, 133.4, 131.49, 131.42, 131.39, 129.8, 129.1, 128.9, 128.5, 128.32, 128.27, 128.1, 127.8, 127.3, 53.2, 48.1; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{34}H_{29}ON_2NaPS$ *m/z* 567.1630 $[M+Na]^+$, found 567.1625.

***N*-(2-Oxo-1-phenyl-2-(piperidin-1-yl)ethylidene)-*P*,*P*-diphenylphosphinothioic amide (63c)**



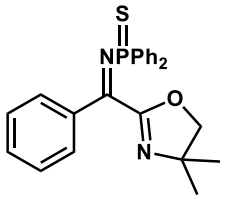
Procedure D: Yellow solid; IR (KBr): *v* 2937, 2855, 1643, 1590, 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.02 (m, 6H), 7.61–7.56 (m, 1H), 7.51–7.42 (m, 8H), 3.69 (brs, 2H), 3.13 (t, *J* = 5.7 Hz, 2H), 1.71–1.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2 (d, *J* = 8.0 Hz), 164.2 (d, *J* = 14.6 Hz), 135.9, 135.0, 134.8, 134.7, 133.6, 131.5, 131.4, 131.37, 131.30, 129.0, 128.9, 128.4, 128.3, 47.4, 41.8, 25.1, 24.7, 24.2; ^{31}P NMR ($CDCl_3$): δ 51.0; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}ON_2NaPS$ *m/z* 455.1317 $[M+Na]^+$, found 455.1310.

***N*-(2-Oxo-2-(2-oxooxazolidin-3-yl)-1-phenylethylidene)-*P*,*P*-diphenylphosphinothioic amide (63d)**



Procedure D: Yellow solid; IR (KBr): *v* 1786, 1692, 1685, 1626, 1588, 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.01 (m, 2H), 7.95–7.90 (m, 4H), 7.59–7.55 (m, 1H), 7.49–7.39 (m, 8H), 4.61–4.55 (m, 1H), 4.51–4.45 (m, 1H), 4.36–4.29 (m, 1H), 4.18–4.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (d, *J* = 9.6 Hz), 16.7 (d, *J* = 17.1 Hz), 153.1, 135.4, 135.2, 134.7, 134.5, 134.3, 134.2, 133.5, 131.55, 131.51, 131.48, 131.45, 131.3, 131.2, 131.1, 128.9, 128.6, 128.5, 128.4, 63.6, 41.5; ^{31}P NMR ($CDCl_3$): δ 51.8; HRMS (ESI) Anal. calcd. for $C_{23}H_{19}O_3N_2NaPS$ *m/z* 457.0746 $[M+Na]^+$, found 457.0742.

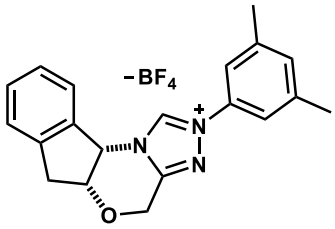
***N*-((4,4-Dimethyl-4,5-dihydrooxazol-2-yl)(phenyl)methylene)-*P*,*P*-diphenylphosphinothioic amide (64)**



Yellow solid; IR (KBr): *v* 1673, 1636, 1616, 1589, 1576 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06–8.00 (m, 6H), 7.58–7.54 (m, 1H), 7.48–7.40 (m, 8H), 4.19 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2 (d, *J* = 10.3 Hz), 156.0 (d, *J* = 15.6 Hz), 136.4, 136.3, 136.2, 135.2, 133.5, 131.4, 131.3, 131.23, 131.20, 129.3, 128.7, 128.3, 128.2, 79.1, 69.0, 27.8; ^{31}P NMR ($CDCl_3$): δ 51.6; HRMS (ESI) Anal. calcd. for $C_{24}H_{24}ON_2PS$ *m/z* 419.1341 $[M+Na]^+$, found 419.1339.

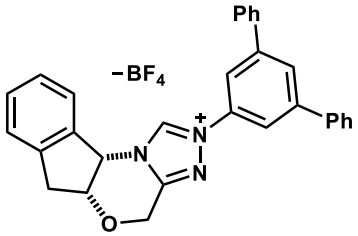
4.2.2 Procedures for preparation of NHC precursor[54]

(5a*R*,10b*S*)-2-(3,5-Dimethylphenyl)-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate (L11)



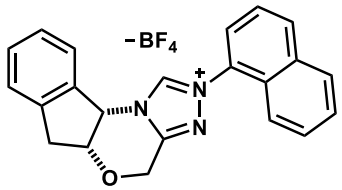
White solid; M. p.249–252 °C; IR (KBr): *v* 3421, 3130, 3102, 3055, 3016, 2923, 1621, 1584, 1540, 1483, 1461, 1447, 1427, 1104, 1084, 1006 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 10.28 (s, 1H), 7.62–7.60 (m, 1H), 7.52 (t, *J* = 0.6 Hz, 2H), 7.42–7.32 (m, 4H), 5.93 (d, *J* = 4.2 Hz, 1H), 5.17 (d, *J* = 16.4 Hz, 1H), 5.03 (dd, *J* = 0.2, 16.4 Hz, 1H), 4.95–4.93 (m, 1H), 3.45 (dd, *J* = 5.0, 17.2 Hz, 1H), 3.23 (d, *J* = 17.2 Hz, 1H), 2.45 (d, *J* = 0.6 Hz, 6H); ^{13}C NMR (100 MHz, CD_3CN): δ 151.1, 141.68, 141.65, 140.3, 136.0, 133.5, 130.6, 128.2, 126.6, 125.5, 119.6, 78.2, 62.6, 60.9, 37.8, 21.2; HRMS (ESI) Anal. calcd. for $C_{20}H_{20}ON_3$ *m/z* 318.1601 $[M\text{-}BF_4]^+$, found 318.1602. $[\alpha]_D^{25}$ 246.0 (*c* 0.59, CH_3CN).

(5a*R*,10b*S*)-2-([1,1':3',1''-Terphenyl]-5'-yl)-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate (L12)



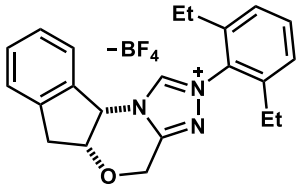
Pale yellow solid; IR (KBr): *v* 3418, 3054, 2931, 1732, 1614, 1593, 1578, 1535, 1499, 1473, 1462, 1438, 1102, 1083, 1063 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 10.47 (s, 1H), 8.16 (t, *J* = 1.6 Hz, 1H), 8.09 (d, *J* = 1.6 Hz, 2H), 7.85–7.82 (m, 4H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.59–7.55 (m, 4H), 7.52–7.48 (m, 2H), 7.44–7.38 (m, 3H), 5.98 (d, *J* = 4.2 Hz, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 5.05 (d, *J* = 16.4 Hz, 1H), 4.99–4.97 (m, 1H), 3.47 (dd, *J* = 5.0, 17.2 Hz, 1H), 3.25 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ 151.1, 144.6, 141.6, 140.9, 139.5, 137.0, 135.9, 130.6, 130.0, 129.6, 128.2, 128.1, 126.6, 125.4, 119.3, 78.1, 62.7, 60.8, 37.7; HRMS (ESI) Anal. calcd. for $C_{30}H_{24}ON_3$ *m/z* 442.1914 $[M\text{-}BF_4]^+$, found 442.1912. $[\alpha]_D^{25}$ 212.4 (*c* 0.76, CH_3CN).

(5a*R*,10b*S*)-2-(Naphthalen-1-yl)-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate (L13)



Purple solid; M. p.224–227 °C; IR (KBr): *v* 3421, 3112, 3077, 3032, 2940, 1600, 1577, 1527, 1514, 1486, 1461, 1427, 1120, 1101, 1084, 1019, 1005 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 10.24 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.16–8.13 (m, 1H), 7.90–7.85 (m, 2H), 7.77–7.69 (m, 3H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.45–7.36 (m, 3H), 6.03 (d, *J* = 4.2 Hz, 1H), 5.24 (d, *J* = 16.4 Hz, 1H), 5.09 (d, *J* = 16.4 Hz, 1H), 5.03–5.01 (m, 1H), 3.51 (dd, *J* = 5.1, 17.2 Hz, 1H), 3.28 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ 151.5, 143.9, 141.8, 136.1, 135.1, 133.5, 132.1, 130.6, 129.6, 129.5, 128.7, 128.4, 128.2, 126.7, 126.2, 126.1, 125.5, 122.6, 78.3, 62.7, 61.1, 37.9; HRMS (ESI) Anal. calcd. for $C_{22}H_{18}ON_3$ *m/z* 340.1444 $[M\text{-}BF_4]^+$, found 340.1446. $[\alpha]_D^{25}$ 138.5 (*c* 0.76, CH_3CN).

(5a*R*,10b*S*)-2-(2,6-Diethylphenyl)-5a,10b-dihydro-4*H*,6*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate (L14)

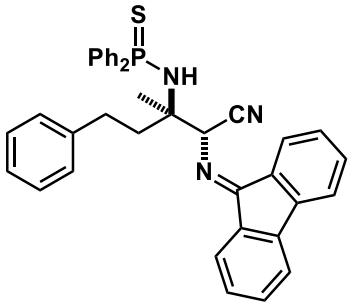


White solid; M. p.204–206 °C; IR (KBr): *v* 3421, 3124, 3088, 3049, 2973, 2938, 2905, 2880, 1579, 1531, 1485, 1463, 1432, 1105, 1086, 1058, 1001 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 10.11 (s, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.45–7.36 (m, 6H), 6.02 (d, *J* = 4.2 Hz, 1H), 5.17 (d, *J* = 16.2 Hz, 1H), 5.05–5.01 (m, 2H), 3.50 (dd, *J* = 5.0, 17.3 Hz, 1H), 3.25 (d, *J* = 17.3 Hz, 1H), 2.42 (brs, 4H), 1.14 (S, 6H); ^{13}C NMR (100 MHz, CD_3CN): δ 151.8, 143.9, 142.5, 141.8, 136.5, 133.4, 130.6, 128.44, 128.40, 126.8, 124.5, 78.1, 62.8, 61.1, 38.0, 24.6, 15.4; HRMS (ESI) Anal. calcd. for $C_{22}H_{24}ON_3$ *m/z* 346.1914 $[M\text{-}BF_4]^+$, found 346.1911. $[\alpha]_D^{24}$ 89.9 (*c* 0.55, CH_3CN).

4.2.3 Procedures for construction of *α,β*-diamino derivatives bearing contiguous tri- and tetrasubstituted stereocenters

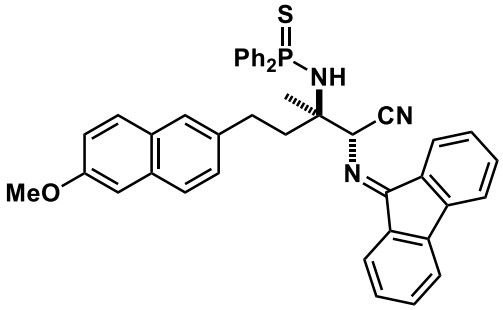
A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 9-Fluorenylidene-protected α-iminoacetonitrile (43.7 mg, 0.2 mmol), corresponding *N*-thioketimine (0.22 mmol, 1.1 equiv), (*R*)-2,2'-Bis[Bis(4–methoxyl-3,5-dimethylphenyl)phosphino]-,4',6,6',tetramethoxylbiphenyl (5.2 mg, 0.006 mmol, 3 mol%) and $[Cu(CH_3CN)_4]PF_6$ (2.2 mg, 0.006 mmol, 3 mol%) in a glove box under Ar atmosphere. After evacuating for 5 min, the tube was backfilled with Ar and anhydrous PhMe was added at rt. The mixture solution was stirred for 20min at rt, then cooled to –78 °C and LiO^tBu (10 μL, 0.01 mmol, 5 mmol%) was added, then the resulting solution was stirred at the same temperature. The reaction was quenched with AcOH (0.2 mL) (0.1N in PhMe), then sat. NH_4Cl solution was added. The mixture was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product.

***N*-((1*R*,2*R*)-1-((9*H*-Fluoren-9-ylidene)amino)-1-cyano-2-methyl-4-phenylbutan-2-yl)-*P*,*P*-diphenylphosphinothioic amide (31a)**



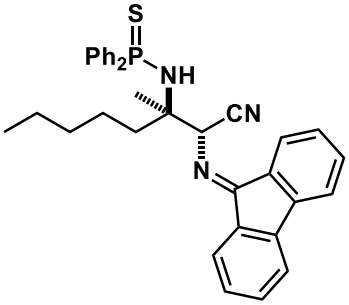
Yellow crystal; M. p. 152–153 ºC; IR ($CHCl_3$): *v* 2237, 1730, 1711, 1648, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19–8.14 (m, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.3 Hz, 2H), 7.59–7.49 (m, 7H), 7.47–7.42 (m, 1H), 7.39–7.33 (m, 2H), 7.29–7.17 (m, 8H), 6.55 (s, 1H), 3.50 (d, *J* = 2.3 Hz, 1H), 2.93 (dt, *J* = 4.6, 13.5 Hz, 1H), 2.79 (dt, *J* = 5.5, 12.4 Hz, 1H), 2.57 (dt, *J* = 4.8, 14.0 Hz, 1H), 2.21–2.12 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 144.1, 141.7, 141.4, 137.7, 136.8, 135.8, 134.9, 133.9, 132.8, 132.54, 132.43, 132.1, 131.9 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 2.9 Hz), 131.1, 130.2, 130.1, 128.62, 128.57, 128.4, 128.31, 128.29, 128.24, 126.0, 122.7, 120.6, 119.7, 117.2, 61.6 (d, *J* = 3.8 Hz), 57.8 (d, *J* = 1.9 Hz), 39.6 (d, *J* = 7.6 Hz), 30.0, 20.9 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 54.0; HRMS (ESI) Anal. calcd. for $C_{37}H_{32}N_3NaPS$ *m/z* 604.1947 $[M+Na]^+$, found 604.1942; $[\alpha]_D^{28}$ 3.9 (*c* 2.53, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 2.0 mL/min, detection at 254 nm, t_R = 10.9 min (minor), 14.4 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-4-(6-methoxynaphthalen-2-yl)-2-methylbutan-2-yl)-_P,P_-diphenylphosphinothioic amide (31b)



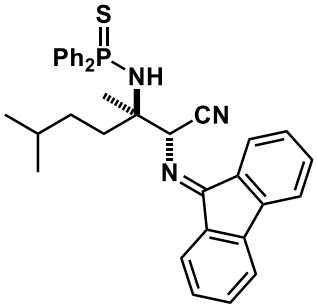
Amorphous yellow powder; IR ($CHCl_3$): *v* 2363, 1728, 1649, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21–8.15 (m, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.67–7.62 (m, 4H), 7.59–7.50 (m, 8H), 7.49–7.41 (m, 2H), 7.36–7.24 (m, 3H), 7.22–7.16 (m, 2H), 7.12–7.09 (m, 2H), 6.51 (s, 1H), 3.90 (s, 3H), 3.54 (d, *J* = 2.3 Hz, 1H), 3.09–3.01 (m, 1H), 2.96–2.88 (m, 1H), 2.69–2.61 (m, 1H), 2.30–2.21 (m, 1H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 157.2, 144.1, 141.8, 137.8, 136.8, 136.6, 135.8, 135.1, 134.0, 133.0, 132.8, 132.6, 132.5, 132.2, 131.9 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 1.9 Hz), 131.2, 130.3, 130.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.45, 128.35, 128.3, 127.6, 127.0, 126.2, 122.8, 120.6, 119.7, 118.8, 117.3, 105.6, 61.8 (d, *J* = 3.8 Hz), 58.0, 55.3, 39.4 (d, *J* = 6.7 Hz), 30.0, 21.1 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 53.9; HRMS (ESI) Anal. calcd. for $C_{42}H_{36}ON_3NaPS$ *m/z* 684.2209 $[M+Na]^+$, found 684.2200; $[\alpha]_D^{27}$ –15.8 (*c* 0.83, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by chiral stationary phase HPLC); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK AD3 (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane/diethylamine = 1/17/0.1, flow rate 0.8 mL/min, detection at 254 nm, t_R = 52.9 min (major), 57.3 min (minor)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-2-methylheptan-2-yl)-_P,P_-diphenylphosphinothioic amide (31c)



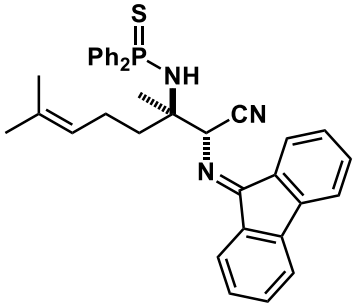
Amorphous yellow powder; IR ($CHCl_3$): *v* 2237, 1711, 1649, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–8.11 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 9.4 Hz, 2H), 7.60–7.42 (m, 8H), 7.40–7.32 (m, 2H) 7.27–7.24 (m, 1H), 7.21–7.17 (m, 2H), 6.53 (s, 1H), 3.39 (d, *J* = 1.4 Hz, 1H), 2.17 (dt, *J* = 3.4, 13.5 Hz, 1H), 1.83–1.74 (m, 1H), 1.52 (s, 3H), 1.43–1.21 (m, 6H), 0.88 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 144.1, 141.7, 137.8, 136.9, 135.9, 135.1, 134.0, 132.7, 132.5, 132.4, 132.1, 131.8 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.2, 130.3, 130.2, 128.7, 128.5, 128.4, 128.35 (d, *J* = 1.9 Hz), 128.2 (d, *J* = 1.9 Hz), 122.7, 120.6, 119.7, 117.4, 61.6 (d, *J* = 3.8 Hz), 58.0, 37.8 (d, *J* = 7.6 Hz), 32.0, 23.3, 22.6, 20.8 (d, *J* = 2.9 Hz), 14.0; ^{31}P NMR ($CDCl_3$): δ 53.7; HRMS (ESI) Anal. calcd. for $C_{34}H_{34}N_3NaPS$ *m/z* 570.2103 $[M+Na]^+$, found 570.2101; $[\alpha]_D^{27}$ 48.7 (*c* 3.40, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 91% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 2.0 mL/min, detection at 254 nm, t_R = 7.6 min (minor), 10.5 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-2,5-dimethylhexan-2-yl)-_P_,_P_-diphenylphosphinothioic amide (31d)



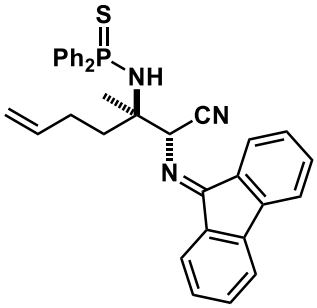
Amorphous yellow powder; IR ($CHCl_3$): *v* 2361, 1732, 1648, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17–8.12 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 13.0 Hz, 2H), 7.60–7.33 (m, 10H), 7.28–7.18 (m, 3H), 6.47 (s, 1H), 3.43 (d, *J* = 1.8 Hz, 1H), 2.19 (dt, *J* = 3.0, 13.0 Hz, 1H), 1.84–1.76 (m, 1H), 1.52–1.40 (m, 5H), 1.28–1.21 (m, 1H), 0.86 (t, *J* = 5.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 144.2, 141.8, 137.9, 137.0, 136.0, 135.2, 134.2, 132.8, 132.6, 132.5, 132.1, 131.8 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 2.9 Hz), 131.2, 130.3, 130.2, 128.8, 128.6, 128.5, 128.44, 128.37, 128.3, 128.2, 122.8, 120.6, 119.7, 117.3, 61.7 (d, *J* = 3.8 Hz), 58.1, 35.8 (d, *J* = 7.6 Hz), 32.5, 28.4, 22.8, 22.4, 21.0 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 53.6; HRMS (ESI) Anal. calcd. for $C_{34}H_{34}N_3NaPS$ *m/z* 570.2103 $[M+Na]^+$, found 570.2093; $[\alpha]_D^{24}$ 48.2 (*c* 0.57, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by chiral stationary phase HPLC); Enantiomeric excess of the product was determined to be 95% ee by chiral stationary phase HPLC analysis (CHIRALPAK OD3 (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane/diethylamine = 1/17/0.1, flow rate 0.8 mL/min, detection at 254 nm, t_R = 61.1 min (minor), 69.4 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-2,6-dimethylhept-5-en-2-yl)-_P_,_P_-diphenylphosphinothioic amide (31e)



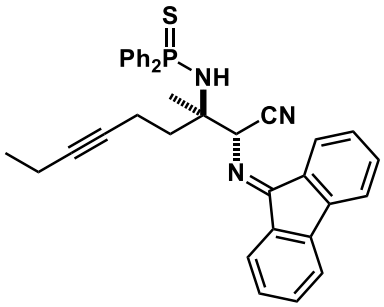
Amorphous yellow powder; IR ($CHCl_3$): *v* 2323, 1732, 1648, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18–8.13 (m, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 2H), 7.58–7.41 (m, 8H), 7.39–7.31 (m, 2H), 7.27–7.23 (m, 1H), 7.20–7.15 (m, 2H), 6.50 (s, 1H), 5.11 (t, *J* = 6.4 Hz 1H), 3.45 (d, *J* = 2.3 Hz, 1H), 2.29–2.16 (m, 3H), 1.89–1.83 (m, 1H), 1.67 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 144.0, 141.6, 137.7, 136.8, 135.8, 135.0, 133.9, 132.7, 132.5, 132.4, 132.2, 132.0, 131.8 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.1, 130.1, 130.0, 128.53, 128.46, 128.3 (d, *J* = 19.1 Hz), 128.31, 128.2, 123.7, 122.6, 120.6, 119.7, 117.2, 61.5 (d, *J* = 3.8 Hz), 57.8 (d, *J* = 1.9 Hz), 37.9 (d, *J* = 7.6 Hz), 25.6, 22.3, 20.7 (d, *J* = 3.8 Hz), 17.7; ^{31}P NMR ($CDCl_3$): δ 53.8; HRMS (ESI) Anal. calcd. for $C_{35}H_{34}N_3NaPS$ *m/z* 582.2103 $[M+Na]^+$, found 582.2098; $[\alpha]_D^{27}$ 25.3 (*c* 5.78, $CHCl_3$, 98% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 90% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 1.0 mL/min, detection at 254 nm, t_R = 14.0 min (minor), 18.5 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-2-methylhex-5-en-2-yl)-_P,P_-diphenylphosphinothioic amide (31f)



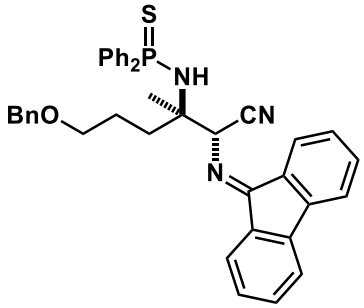
Amorphous yellow powder; IR ($CHCl_3$): *v* 2361, 1737, 1647, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–8.11 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.67 (dd, *J* = 7.3, 12.6 Hz, 2H), 7.59–7.32 (m, 10H), 7.27–7.24 (m, 1H), 7.19–7.15 (m, 2H), 6.60 (s, 1H), 5.86–5.76 (m, 1H), 5.06–4.96 (m, 2H), 3.41 (s, 1H), 2.36–2.30 (m, 2H), 2.25–2.19 (m, 1H), 1.95–1.86 (m, 1H), 1.54–1.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 144.2, 141.8, 138.0, 137.9, 136.9, 135.9, 134.8, 133.8, 132.8, 132.7, 132.5, 132.2, 131.9 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 2.9 Hz), 131.2, 130.2, 130.1, 128.7, 128.6, 128.54, 128.47, 128.45, 128.32, 128.30, 122.8, 120.6, 119.8, 117.3, 115.1, 61.5 (d, *J* = 3.8 Hz), 57.8, 37.1 (d, *J* = 8.6 Hz), 27.9, 20.7 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 54.0; HRMS (ESI) Anal. calcd. for $C_{33}H_{30}N_3NaPS$ *m/z* 554.1790 $[M+Na]^+$, found 554.1780; $[\alpha]_D^{27}$ 25.7 (*c* 0.35, $CHCl_3$, 92% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 90% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 2.0 mL/min, detection at 254 nm, t_R = 8.3 min (minor), 10.9 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-2-methyloct-5-yn-2-yl)-_P,P_-diphenylphosphinothioic amide (31g)



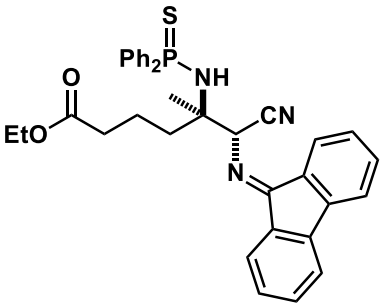
Amorphous yellow powder; IR ($CHCl_3$): *v* 2359, 1728, 1649, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18–8.12 (m, 2H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60–7.43 (m, 8H), 7.39–7.35 (m, 1H), 7.33–7.24 (m, 2H), 7.16–7.11 (m, 2H), 6.61 (s, 1H), 3.68 (d, *J* = 1.8 Hz, 1H), 2.52–2.42 (m, 3H), 2.09–1.98 (m, 3H), 1.52 (s, 3H), 1.01 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 144.1, 141.7, 137.8, 136.9, 135.8, 134.8, 133.7, 132.7, 132.6, 132.5, 132.1, 131.9 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.1, 130.0, 129.9, 128.6, 128.5, 128.4, 128.2, 122.8, 120.6, 119.7, 117.1, 82.6, 79.0, 61.3 (d, *J* = 3.8 Hz), 57.3, 37.3 (d, *J* = 8.6 Hz), 20.8 (d, *J* = 3.8 Hz), 14.0, 13.7, 12.2; ^{31}P NMR ($CDCl_3$): δ 54.0; HRMS (ESI) Anal. calcd. for $C_{35}H_{32}N_3NaPS$ *m/z* 580.1947 $[M+Na]^+$, found 580.1937; $[\alpha]_D^{28}$ 42.3 (*c* 2.34, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 88% ee by chiral stationary phase HPLC analysis (CHIRALPAK IB3 (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane/diethylamine = 1/17/0.1, flow rate 1.0 mL/min, detection at 254 nm, t_R = 7.9 min (minor), 29.4 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-5-(benzyloxy)-1-cyano-2-methylpentan-2-yl)-_P_,_P_-diphenylphosphinothioic amide (31h)



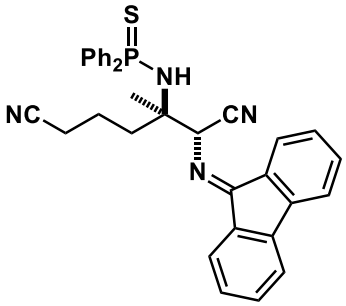
Amorphous yellow powder; IR ($CHCl_3$): *v* 2361, 1728, 1649, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.10 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.69–7.64 (m, 2H), 7.59–7.42 (m, 9H), 7.39–7.23 (m, 7H), 7.18–7.13 (m, 2H), 6.62 (s, 1H), 4.45 (s, 2H), 3.52–3.38 (m, 3H), 2.37–2.31 (m, 1H), 1.96–1.84 (m, 2H), 1.82–1.72 (m, 1H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 144.1, 141.8, 138.2, 137.9, 136.9, 135.8, 134.9, 133.9, 132.7, 132.6, 132.5, 132.1, 131.9 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.2, 130.3, 130.1, 128.7, 128.5, 128.41, 128.37, 128.3 (d, *J* = 1.9 Hz), 127.7, 127.6, 122.8, 120.6, 119.7, 117.3, 73.1, 70.3, 61.4 (d, *J* = 3.8 Hz), 57.7, 34.7 (d, *J* = 7.6 Hz), 24.1, 20.8 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 53.9; HRMS (ESI) Anal. calcd. for $C_{39}H_{36}ON_3NaPS$ *m/z* 648.2209 $[M+Na]^+$, found 648.2201; $[\alpha]_D^{27}$ 25.8 (*c* 1.05, $CHCl_3$, 92% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 91% ee by chiral stationary phase HPLC analysis (CHIRALPAK IB3 (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane/diethylamine = 1/17/0.1, flow rate 1.0 mL/min, detection at 254 nm, t_R = 11.0 min (minor), 54.0 min (major)).

Ethyl (5_R_,6_R_)-6-((9_H_-fluoren-9-ylidene)amino)-6-cyano-5-((diphenylphosphorothioyl)amino)-5-methylhexanoate (31i)



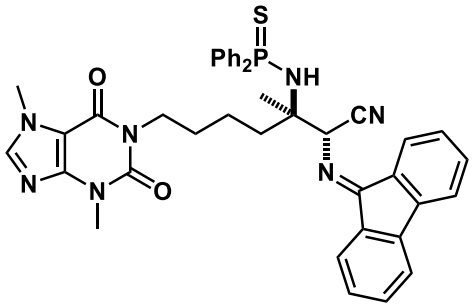
Amorphous yellow powder; IR ($CHCl_3$): *v* 2359, 1727, 1649, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–8.10 (m, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 6.4 Hz, 2H), 7.59–7.42 (m, 8H), 7.40–7.31 (m, 2H), 7.27–7.24 (m, 1H), 7.20–7.15 (m, 2H), 6.60 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.42 (d, *J* = 2.0 Hz, 1H), 2.35–2.20 (m, 3H), 1.96–1.87 (m, 1H), 1.85–1.73 (m, 2H), 1.54 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.1, 144.0, 141.6, 137.6, 136.6, 135.6, 134.8, 133.8, 132.7, 132.4, 132.3, 132.0, 131.8 (d, *J* = 1.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.0, 130.2, 130.1, 128.6, 128.4, 128.34, 128.31, 128.20, 128.15, 122.6, 120.5, 119.6, 117.1, 61.4 (d, *J* = 2.9 Hz), 60.2, 57.6, 37.1 (d, *J* = 7.6 Hz), 34.0, 20.6 (d, *J* = 3.8 Hz), 19.0, 14.1; ^{31}P NMR ($CDCl_3$): δ 53.9; HRMS (ESI) Anal. calcd. for $C_{35}H_{34}O_2N_3NaPS$ *m/z* 614.2002 $[M+Na]^+$, found 614.1995; $[\alpha]_D^{28}$ 38.3 (*c* 3.88, $CHCl_3$, 93% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 92% ee by chiral stationary phase HPLC analysis (CHIRALPAK IB3 (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane/diethylamine = 1/17/0.1, flow rate 0.8 mL/min, detection at 254 nm, t_R = 11.1 min (minor), 63.6 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-5-isocyano-2-methylpentan-2-yl)-_P_,_P_-diphenylphosphinothioic amide (31j)



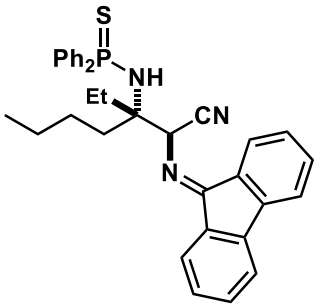
Amorphous yellow powder; IR ($CHCl_3$): *v* 2249, 1730, 1648, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11–8.05 (m, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 2H), 7.59–7.42 (m, 8H), 7.40–7.36 (m, 2H), 7.28–7.19 (m, 3H), 6.63 (s, 1H), 3.40 (d, *J* = 2.1 Hz, 1H), 2.36–2.18 (m, 3H), 1.99–1.79 (m, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 144.1, 141.7, 137.6, 136.3, 135.3, 134.6, 133.6, 132.9, 132.30, 132.26, 132.2, 132.1 (d, *J* = 2.9 Hz), 131.6 (d, *J* = 3.8 Hz), 131.1, 130.4, 130.3, 128.7, 128.64, 128.57, 128.5, 128.44, 128.37, 122.8, 120.7, 119.8, 119.3, 117.0, 61.2 (d, *J* = 3.8 Hz), 57.7, 37.0 (d, *J* = 6.7 Hz), 20.7 (d, *J* = 3.8 Hz), 20.3, 17.3; ^{31}P NMR ($CDCl_3$): δ 54.1; HRMS (ESI) Anal. calcd. for $C_{33}H_{29}N_4NaPS$ *m/z* 567.1743 $[M+Na]^+$, found 567.1733; $[\alpha]_D^{26}$ 50.9 (*c* 1.78, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 87% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 24.0 min (minor), 27.3 min (major)).

_N_-((1_R_,2_R_)-1-((9_H_-Fluoren-9-ylidene)amino)-1-cyano-6-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1_H_-purin-1-yl)-2-methylhexan-2-yl)-_P_,_P_-diphenylphosphinothioic amide (31k)



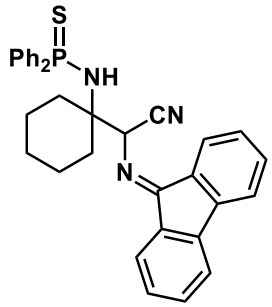
Amorphous yellow powder; IR ($CHCl_3$): *v* 2359, 1732, 1656, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13–8.08 (m, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.54–7.40 (m, 8H), 7.36 (dt, *J* = 1.2, 6.2 Hz, 1H), 7.31–7.26 (m, 2H), 7.13 (dt, *J* = 3.2, 7.8 Hz, 2H), 6.60 (s, 1H), 4.12–3.99 (m, 2H), 3.88 (s, 3H), 3.47 (s, 4H), 2.39 (t, *J* = 10.3 Hz, 1H), 1.84–1.52 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 155.3, 151.6, 148.7, 144.1, 141.8, 141.4, 137.9, 137.0, 136.0, 135.1, 134.0, 132.7, 132.5, 132.0, 131.8 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.2, 130.2, 130.1, 128.7, 128.5, 128.39, 128.37, 128.27, 128.24, 122.9, 120.6, 119.6, 117.3, 107.6, 61.5 (d, *J* = 3.8 Hz), 57.6, 41.1, 37.5 (d, *J* = 7.6 Hz), 33.5, 29.6, 28.2, 21.0, 20.7 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 53.7; HRMS (ESI) Anal. calcd. for $C_{40}H_{38}O_2N_7NaPS$ *m/z* 734.2438 $[M+Na]^+$, found 734.2424; $[\alpha]_D^{25}$ 52.7 (*c* 1.09, $CHCl_3$, 99% ee sample after separation of *anti* diastereomer by chiral stationary phase HPLC); Enantiomeric excess of the product was determined to be 84% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA3 and OD3 (ø 0.46 cm x 25 cm each), 2–propanol/*n*–hexane/diethylamine = 50/50/0.1, flow rate 0.5 mL/min, detection at 254 nm, t_R = 58.8 min (minor), 97.3 min (major)).

_N_-((_S_)-3-((_R_)-((9_H_-Fluoren-9-ylidene)amino)(cyano)methyl)heptan-3-yl)-_P,P_-diphenylphosphinothioic amide (31l)



Amorphous yellow powder; IR ($CHCl_3$): *v* 2369, 1731, 1646, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12–8.06 (m, 2H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.71 (dd, *J* = 7.3, 13.5 Hz, 2H), 7.65–7.56 (m, 3H), 7.53–7.35 (m, 7H), 7.26–7.21 (m, 3H), 6.40 (s, 1H), 3.60 (d, *J* = 3.4 Hz, 1H), 2.38–2.29 (m, 1H), 2.00–1.91 (m, 3H) 1.50–1.31 (m, 2H), 1.17–1.08 (m, 2H), 1.04 (t, *J* = 7.6 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 144.1, 141.7, 137.9, 136.9, 135.9 (d, *J* = 3.8 Hz), 134.8, 132.7, 132.2, 132.1, 131. (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 131.1, 130.9, 130.8, 128.8, 128.5, 128.4, 128.3, 122.9, 120.6, 119.7, 117.9, 64.3 (d, *J* = 3.8 Hz), 57.9, (d, *J* = 2.9 Hz), 34.9 (d, *J* = 6.7 Hz), 28.4 (d, *J* = 3.8 Hz, 1H), 25.6, 23.0, 13.8, 8.9; ^{31}P NMR ($CDCl_3$): δ 53.3; HRMS (ESI) Anal. calcd. for $C_{34}H_{34}N_3NaPS$ *m/z* 570.2103 $[M+Na]^+$, found 570.2103; $[\alpha]_D^{24}$ –95.1 (*c* 0.49, $CHCl_3$, 97% ee sample after separation of *anti* diastereomer by recrystallizaton); Enantiomeric excess of the product was determined to be 83% ee by chiral stationary phase HPLC analysis (CHIRALPAK IE (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 2.0 mL/min, detection at 254 nm, t_R = 7.7 min (major), 9.8 min (minor)).

_N_-(1-(((9_H_-Fluoren-9-ylidene)amino)(cyano)methyl)cyclohexyl)-_P,P_-diphenylphosphinothioic amide (31m)

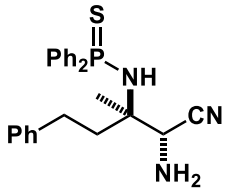


Amorphous yellow powder; IR ($CHCl_3$): *v* 2238, 1711, 1648, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20–8.15 (m, 2H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.82 (dd, *J* = 7.6 Hz, 13.5 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.53–7.36 (m, 7H), 7.30–7.22 (m, 3H), 6.34 (s, 1H), 3.68 (s, 1H), 2.62–2.59 (m, 1H), 2.35–2.31 (m, 1H), 2.03–1.99 (m, 1H), 1.82–1.77 (m, 1H), 1.44–1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 144.1, 141.5, 137.7, 136.9, 136.1, 135.9, 135.1, 132.8, 132.3, 132.2, 132.1, 131.7 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 2.9 Hz), 131.0, 130.9, 130.7, 128.7, 128.5, 128.38, 128.36, 128.3, 128.2, 128.1, 122.8, 120.7, 119.7, 117.5, 61.9 (d, *J* = 2.9 Hz), 57.2, 32.6 (d, *J* = 5.7 Hz), 32.2 (d, *J* = 1.9 Hz), 24.8, 21.9, 21.6; ^{31}P NMR ($CDCl_3$): δ 52.0; HRMS (ESI) Anal. calcd. for $C_{33}H_{30}N_3NaPS$ *m/z* 554.1790 $[M+Na]^+$, found 554.1782; $[\alpha]_D^{27}$ 62.7 (*c* 1.88, $CHCl_3$, 67% ee sample); Enantiomeric excess of the product was determined to be 67% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/17, flow rate 1.0 mL/min, detection at 254 nm, t_R = 9.5 min (minor), 10.9 min (major)).

Transformation of the product

To a solution of **31a-***anti* (581.7 mg, 1 mmol) in THF (20 mL) at 0 °C, then 1 M HCl (5 mL) was added dropwise. The resulting solution was warmed to rt and stirred for 5 h. The reaction was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product in quant. yield.

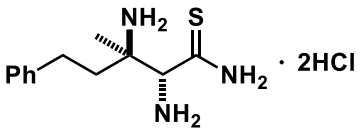
***N*-((1*R*,2*R*)-1-Amino-1-cyano-2-methyl-4-phenylbutan-2-yl)-*P*,*P*-diphenylphosphinothioic amide (36)**



Amorphous yellow powder; IR ($CHCl_3$): *v* 2231, 1734, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24–8.19 (m, 2H), 7.97–7.92 (dd, *J* = 8.4, 13.3 Hz, 2H), 7.58–7.45 (m, 6H), 7.35–7.32 (m, 2H), 7.28–7.22 (m, 3H), 5.09 (s, 1H), 3.48 (s, 1H), 2.92 (dt, *J* = 6.0, 13.0 Hz, 1H), 2.72 (dt, *J* = 6.0, 12.6 Hz, 1H), 1.98–1.86 (m, 2H), 1.83 (d, *J* = 6.9 Hz, 2H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 136.3, 135.3, 135.2, 134.1, 132.4, 132.2, 131.9 (d, *J* = 2.9 Hz), 131.7 (d, *J* = 15.3 Hz), 130.5, 130.4, 128.7, 128.6, 128.5, 128.34, 128.32, 126.2, 120.8, 60.6 (d, *J* = 3.8 Hz), 49.8, 39.5 (d, *J* = 8.6 Hz), 30.0, 20.1 (d, *J* = 3.8 Hz); ^{31}P NMR ($CDCl_3$): δ 53.3; HRMS (ESI) Anal. calcd. for $C_{24}H_{27}N_3PS$ *m/z* 420.1658 $[M+H]^+$, found 420.1657; $[\alpha]_D^{25}$ –15.3 (*c* 0.76, $CHCl_3$).

A solution of **36** (42.0 mg, 0.1 mmol) in a mixture of *Conc*. HCl/MeOH (v/v:1/4)(2 mL) was heated to 40 °C and stirred for 5 d. The reaction was diluted with water (10 mL), then washed with ethyl acetate(10 mL) four times. The aqueous phase was evaporated under reduced pressure to afford **37** (25.2 mg, 81% yield)

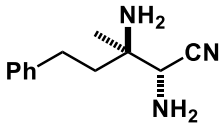
(2*R*,3*R*)-2,3-Diamino-3-methyl-5-phenylpentanethioamide dihydrochloride (37)



Colorless crystal; M. p. 117–118 °C; IR (KBr): *v* 2927 (brm), 1629 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.25–7.24 (m, 4H), 7.19–7.14 (m, 1H), 4.59 (s, 1H), 3.27–3.25 (m, 1H), 2.84 (dt, *J* = 4.8, 13.0 Hz, 1H), 2.72 (dt, *J* = 4.8, 12.8 Hz, 1H), 2.19 (dt, *J* = 4.8, 12.8 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 197.6, 141.2, 129.7, 129.5, 127.6, 62.4, 58.1, 39.6, 29.9, 20.9; HRMS (ESI) Anal. calcd. for $C_{12}H_{20}N_3S$ [M–H–2Cl] *m/z* 238.1372 $[M–H–2Cl]^+$, found 238.1370; $[\alpha]_D^{24}$ –48.4 (*c* 0.89, MeOH).

To a solution of **36** (42.0 mg, 0.1 mmol) in a mixture of *Conc*. HCl/MeOH (v/v: 1/4)(2 mL), H_2O_2 (35 wt %)(0.2 mL) was added dropwise at room temperature. The reaction was quenched with sat. $NaHCO_3$ solution after stirred for 30 min at room temperature. The mixture was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude mixture was dissolved in *Conc*. HCl/THF (v/v:1/1)(2 mL). The mixture was heated to 40 °C and stirred for 3 d. The reaction was diluted with water (10 mL), then washed with ethyl acetate(10 mL) four times. The aqueous phase was evaporated under reduced pressure. Crude product was passed through a short column of Dowex® 50×8 hydrogen form (200 – 400 mesh) using ammonium hydroxide (2 M) as eluent to give the desired product as colorless oil in 65% yield.

(2*R*,3*R*)-2,3-Diamino-3-methyl-5-phenylpentanenitrile (38)

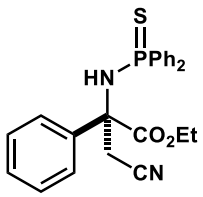


Colorless oil; IR (KBr): *v* 3385 (brm), 2359 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.27–7.219 (m, 4H), 7.17–7.12 (m, 1H), 3.67 (s, 1H), 2.74–2.61 (m, 2H), 1.85–1.74 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.5, 129.5, 129.4, 126.9, 122.1, 55.4, 54.5, 41.9, 30.9, 23.3; HRMS (ESI) Anal. calcd. for $C_{12}H_{18}N_3$ *m/z* 204.1495 $[M+H]^+$, found 204.1493; $[\alpha]_D^{22}$ 3.4 (*c* 0.66, $CHCl_3$).

4.2.4 Procedures for construction of *α*,*α*-disubstituted *α*-amino acid derivatives using MeCN as nucleophile

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $[Ir(cod)(OMe)]_2$ (3.3 mg, 0.005 mmol) and NHC precursor (5.0 mg, 0.01 mmol) and MS 4A (100 mg) under Ar atmosphere, then THF (0.5 mL) and Barton's base (20.0 □L, 0.1 mmol) was added at room temperature. The mixture was stirred at room temperature for 0.5 h and then cooled to –5 °C. Ketimine (0.1 mmol) in THF (0.5 mL) was added followed by MeCN (210 □L, 4 mmol). The resulting reaction mixture was stirred at –5 °C for 5 d. Reaction was quenched with AcOH (0.2 ml, 1.0 M in THF). After diluting the mixture with EtOAc and passed through a shot pad of silica gel column (eluted with EtOAc). After evaporation, the residue was purified by preparative TLC (*n*-hexane/ethyl acetate) to give the product.

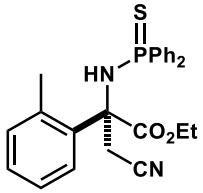
Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-phenylpropanoate (62b)



White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94–7.81 (m, 4H), 7.51–7.40 (m, 6H),

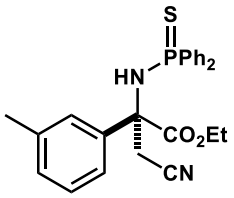
7.37–7.34 (m, 2H), 7.26–7.23 (m, 3H), 4.35–4.28 (m, 1H), 4.23–4.11 (m, 3H), 3.66 (d, *J* = 16.6 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 5.8 Hz), 137.6 (d, *J* = 7.1 Hz), 136.3, 135.2, 134.5, 133.5, 132.2, 132.0, 131.8 (d, *J* = 2.7 Hz), 130.8, 130.7, 128.9, 128.7, 128.65, 128.61, 128.4, 128.2, 125.9, 117.0, 65.0, 63.0, 28.1, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.7; HRMS (ESI) Anal. calcd. for $C_{24}H_{23}O_2N_2NaPS$ *m/z* 457.1110 $[M+Na]^+$, found 457.1105; $[\alpha]_D^{25}$ –6.3 (*c* 0.66, $CHCl_3$, 68% ee sample); Enantiomeric excess of the product was determined to be 68% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 18.0 min (major), 23.7 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(*o*-tolyl)propanoate (62h)



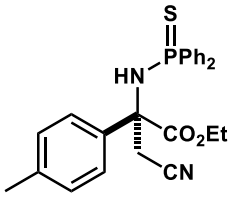
White powder; IR (KBr): *v* 2246, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84 (m, 2H), 7.55–7.45 (m, 5H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.32–7.28 (m, 1H), 7.17–7.11 (m, 3H), 6.99 (dt, *J* = 0.9, 7.4 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 4.92 (d, *J* = 15.9 Hz, 1H), 4.74 (d, *J* = 8.3 Hz, 1H), 4.29–4.37 (m, 1H), 4.23–4.16 (m, 1H), 3.55 (d, *J* = 15.8 Hz, 1H), 1.86 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (d, *J* = 11.7 Hz), 136.9, 136.1, 135.1, 133.0, 132.8 (d, *J* = 1.7 Hz), 131.95, 131.93, 131.90, 131.8, 131.72, 131.68, 131.0 (d, *J* = 3.0 Hz), 130.5, 130.4, 129.0, 128.8, 127.6, 127.5, 127.4, 125.5, 116.8, 64.3 (d, *J* = 1.3 Hz), 63.6, 29.1, 20.4, 13.9; ^{31}P NMR ($CDCl_3$): δ 51.5; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}O_2N_2NaPS$ *m/z* 471.1267 $[M+Na]^+$, found 471.1260; $[\alpha]_D^{24}$ 1.9 (*c* 0.75, $CHCl_3$, 21% ee sample); Enantiomeric excess of the product was determined to be 21% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.0 min (minor), 11.3 min (major)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(*m*-tolyl)propanoate (62i)



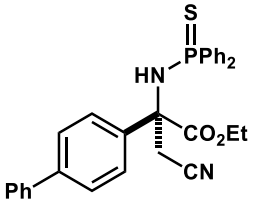
White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.80 (m, 4H), 7.52–7.39 (m, 6H), 7.19–7.12 (m, 2H), 7.06–7.02 (m, 2H), 4.35–4.27 (m, 1H), 4.23–4.15 (m, 3H), 3.64 (d, *J* = 10.8 Hz, 1H), 2.21 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 5.8 Hz), 138.4, 137.3 (d, *J* = 6.7 Hz), 136.4, 135.4, 134.5, 133.5, 132.2, 132.0, 131.81, 131.78, 131.75, 130.7, 130.6, 129.6, 128.7, 128.6, 128.5, 128.2, 128.1, 126.7, 117.1, 65.0, 63.0, 28.1, 21.5, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}O_2N_2NaPS$ *m/z* 471.1267 $[M+Na]^+$, found 471.1257; $[\alpha]_D^{25}$ –7.3 (*c* 0.82, $CHCl_3$, 68% ee sample); Enantiomeric excess of the product was determined to be 68% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 15.0 min (major), 20.1 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(p-tolyl)propanoate (62j)



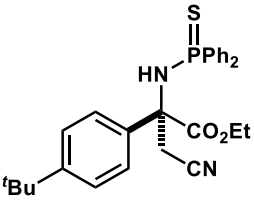
White powder; IR (KBr): *v* 2251, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.81 (m, 4H), 7.52–7.38 (m, 6H), 7.24–7.22 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.34–4.26 (m, 1H), 4.22–4.08 (m, 3H), 3.64 (d, *J* = 16.6 Hz, 1H), 2.27 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, *J* = 5.8 Hz), 138.9, 136.3, 135.3, 134.74, 134.66, 134.5, 133.5, 132.2, 132.1, 131.8 (d, *J* = 3.0 Hz), 131.7 (d, *J* = 3.0 Hz), 130.8, 130.7, 129.3, 128.7, 128.6, 128.3, 128.1, 125.8, 117.1, 64.8, 62.9, 28.2, 21.0, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.6; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}O_2N_2NaPS$ *m/z* 471.1267 $[M+Na]^+$, found 471.1261; $[\alpha]_D^{25}$ –2.5 (*c* 0.69, $CHCl_3$, 71% ee sample); Enantiomeric excess of the product was determined to be 71% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 18.2 min (major), 23.4 min (minor)).

Ethyl (*R*)-2-([1,1'-biphenyl]-4-yl)-3-cyano-2-((diphenylphosphorothioyl)amino)propanoate (62k)



White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.82 (m, 4H), 7.53–7.33 (m, 15H), 4.38–4.18 (m, 4H), 3.68 (d, *J* = 16.5 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 6.6 Hz), 141.7, 139.9, 136.3, 136.2, 136.1, 135.2, 134.4, 133.4, 132.2, 132.1, 131.8 (d, *J* = 3.0 Hz), 131.7 (d, *J* = 3.0 Hz), 130.7, 130.6, 128.79, 128.76, 128.6, 128.2, 128.1, 127.7, 127.1, 127.0, 126.5, 117.0, 64.9, 63.2, 28.0, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{30}H_{27}O_2N_2NaPS$ *m/z* 533.1423 $[M+Na]^+$, found 533.1415; $[\alpha]_D^{25}$ 7.2 (*c* 0.93, $CHCl_3$, 72% ee sample); Enantiomeric excess of the product was determined to be 72% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 13.8 min (major), 16.5 min (minor)).

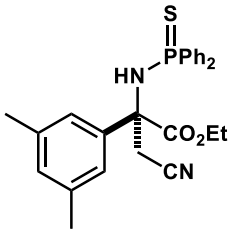
Ethyl (*R*)-2-(4-(*tert*-butyl)phenyl)-3-cyano-2-((diphenylphosphorothioyl)amino)propanoate (62l)



White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.79 (m, 4H), 7.50–7.37 (m, 6H), 7.28–7.21 (m, 4H), 4.36–4.28 (m, 1H), 4.24–4.14 (m, 3H), 3.65 (d, *J* = 16.6 Hz, 1H), 1.25 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, *J* = 5.9 Hz), 151.9, 136.4, 135.4, 134.4 (d, *J* = 3.3 Hz), 134.3, 133.4, 132.2, 132.1, 131.8, 131.78, 131.76, 131.73, 130.7, 130.6, 128.7, 128.6, 128.3, 128.1, 125.7, 125.5, 117.2, 64.8, 63.0, 34.5, 31.1, 28.1, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{28}H_{31}O_2N_2NaPS$ *m/z* 513.1736 $[M+Na]^+$, found 513.1729; $[\alpha]_D^{25}$ 1.2 (*c* 0.53, $CHCl_3$, 66% ee sample); Enantiomeric excess of the product was determined to be 66% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–

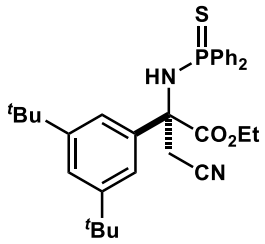
propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 14.7 min (major), 17.7 min (minor)).

Ethyl (*R*)-3-cyano-2-(3,5-dimethylphenyl)-2-((diphenylphosphorothioyl)amino)propanoate (62m)



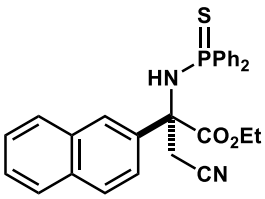
White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.79 (m, 4H), 7.48–7.40 (m, 6H), 6.89 (s, 2H), 6.82 (s, 1H), 4.36–4.28 (m, 1H), 4.23–4.14 (m, 3H), 3.61 (d, *J* = 16.5 Hz, 1H), 2.19 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, *J* = 6.5 Hz), 138.2, 137.1 (d, *J* = 6.3 Hz), 136.5, 135.5, 134.5, 133.5, 132.2, 132.0, 131.77, 131.74, 131.7, 130.7, 130.6, 130.5, 128.7, 128.6, 128.1, 128.0, 123.8, 117.2, 64.9, 63.0, 28.1, 21.4, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.2; HRMS (ESI) Anal. calcd. for $C_{26}H_{27}O_2N_2NaPS$ *m/z* 485.1423 $[M+Na]^+$, found 485.1410; $[\alpha]_D^{25}$ –4.9 (*c* 0.57, $CHCl_3$, 71% ee sample); Enantiomeric excess of the product was determined to be 71% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 14.0 min (major), 18.5 min (minor)).

Ethyl (*R*)-3-cyano-2-(3,5-di-*tert*-butylphenyl)-2-((diphenylphosphorothioyl)amino)propanoate (62n)



White powder; IR (KBr): *v* 2254, 1734, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86–7.80 (m, 4H), 7.50–7.40 (m, 4H), 7.37–7.33 (m, 2H), 7.28–7.27 (m, 3H), 4.34–4.13 (m, 4H), 3.71 (d, *J* = 16.6 Hz, 1H), 1.26 (s, 18H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, *J* = 6.1 Hz), 151.1, 136.9 (d, *J* = 6.3 Hz), 136.7, 135.6, 134.9, 133.9, 132.0, 131.9, 131.74, 131.71, 131.69, 131.66, 130.8, 130.7, 128.7, 128.5, 128.3, 128.2, 123.0, 120.6, 117.5, 65.7, 62.8, 35.0, 31.3, 28.1, 13.8; ^{31}P NMR ($CDCl_3$): δ 54.2; HRMS (ESI) Anal. calcd. for $C_{32}H_{40}O_2N_2PS$ *m/z* 547.2543 $[M+H]^+$, found 547.2537; $[\alpha]_D^{24}$ –3.1 (*c* 1.57, $CHCl_3$, 39% ee sample); Enantiomeric excess of the product was determined to be 39% ee by chiral stationary phase HPLC analysis (CHIRALPAK ID (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.5 min (major), 12.9 min (minor)).

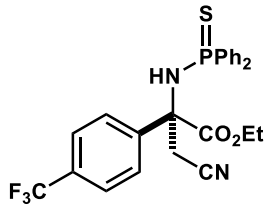
Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(naphthalen-2-yl)propanoate (62o)



White powder; IR (KBr): *v* 2251, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.78 (m, 5H), 7.75–7.72 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.51–7.45 (m, 5H), 7.37–7.31 (m, 2H), 7.29–7.24 (m, 2H), 4.42–4.29 (m, 3H), 4.23–4.15 (m, 1H), 3.76 (d, *J* = 16.4 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 6.9 Hz), 136.3,

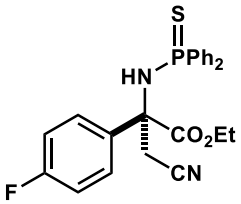
135.3, 134.4 (d, J = 6.2 Hz), 134.3, 133.3, 133.0, 132.5, 132.0, 131.9, 131.8 (d, J = 3.0 Hz), 131.6 (d, J = 3.0 Hz), 130.8, 130.7, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.4, 126.9, 126.5, 125.8, 123.2, 117.0, 65.1, 63.2, 28.1, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.3; HRMS (ESI) Anal. calcd. for $C_{28}H_{25}O_2N_2NaPS$ *m/z* 507.1267 $[M+Na]^+$, found 507.1257; $[\alpha]_D^{25}$ 3.7 (*c* 0.77, $CHCl_3$, 80% ee sample); Enantiomeric excess of the product was determined to be 80% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 20.0 min (major), 22.5 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(4-(trifluoromethyl)phenyl)propanoate (62p)



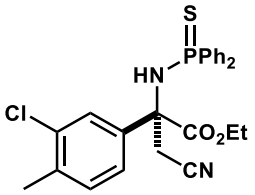
White powder; IR (KBr): *v* 2251, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.75 (m, 4H), 7.54–7.43 (m, 4H), 7.41–7.34 (m, 6H), 4.44–4.30 (m, 3H), 4.25–4.19 (m, 1H), 3.63 (d, J = 16.4 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (d, J = 7.7 Hz), 140.6, 140.5, 136.0, 135.0, 133.9, 132.9, 132.11, 132.05 (d, J = 3.0 Hz), 132.00, 131.9 (d, J = 3.0 Hz), 131.4, 131.1, 130.74, 130.70, 130.6, 130.4, 128.9, 128.7, 128.3, 128.2, 127.6, 126.9, 125.40, 125.36, 125.32, 125.28, 124.9, 122.2, 119.5, 116.7, 64.8, 63.6, 27.7, 13.7; ^{19}F NMR (375 MHz, $CDCl_3$): –63.0; ^{31}P NMR ($CDCl_3$): δ 54.2; HRMS (ESI) Anal. calcd. for $C_{25}H_{22}O_2N_2F_3NaPS$ *m/z* 525.0984 $[M+Na]^+$, found 525.0977; $[\alpha]_D^{25}$ –3.1 (*c* 0.62, $CHCl_3$, 52% ee sample); Enantiomeric excess of the product was determined to be 52% ee by chiral stationary phase HPLC analysis (CHIRALPAK ID (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 28.5 min (major), 30.8 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(4-fluorophenyl)propanoate (62q)



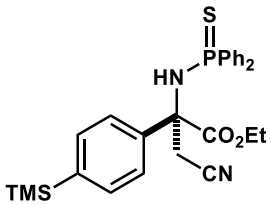
White powder; IR (KBr): *v* 2251, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.79 (m, 4H), 7.51–7.40 (m, 6H), 7.30–7.26 (m, 2H), 6.90–6.84 (m, 2H), 4.36–4.16 (m, 4H), 3.62 (d, J = 16.5 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (d, J = 7.8 Hz), 163.8, 161.3, 136.1, 135.1, 134.3, 133.3, 133.12, 133.09, 133.06, 133.03, 132.2, 132.0, 131.93 (d, J = 3.0 Hz), 131.86 (d, J = 3.0 Hz), 130.7, 130.6, 128.8, 128.7, 128.3, 128.21, 128.19, 128.13, 116.9, 115.5, 115.3, 64.6, 63.3, 28.1, 13.7; ^{19}F NMR (375 MHz, $CDCl_3$): δ –112.4; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{24}H_{22}O_2N_2FNaPS$ *m/z* 475.1016 $[M+Na]^+$, found 475.1009; $[\alpha]_D^{25}$ –5.5 (*c* 0.66, $CHCl_3$, 71% ee sample); Enantiomeric excess of the product was determined to be 71% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 13.6 min (major), 16.4 min (minor)).

Ethyl (*R*)-2-(3-chloro-4-methylphenyl)-3-cyano-2-((diphenylphosphorothioyl)amino)propanoate (62r)



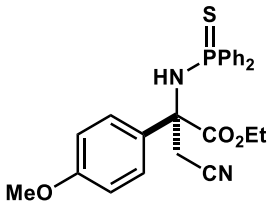
White powder; IR (KBr): *v* 2252, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.79 (m, 4H), 7.51–7.39 (m, 6H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.11 (dd, *J* = 2.1, 8.0 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 4.37–4.16 (m, 4H), 3.60 (d, *J* = 16.5 Hz, 1H), 2.26 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (d, *J* = 7.1 Hz), 136.9, 136.42, 136.36, 135.1, 134.6, 134.1, 133.1, 132.1, 132.0, 131.9 (d, *J* = 3.0 Hz), 131.8 (d, *J* = 3.0 Hz), 130.8, 130.7, 130.6, 128.8, 128.7, 128.2, 128.1, 127.1, 124.3, 116.8, 64.5, 63.3, 27.9, 19.6, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.3; HRMS (ESI) Anal. calcd. for $C_{25}H_{24}O_2N_2ClNaPS$ *m/z* 505.0877 $[M+Na]^+$, found 505.0876; $[\alpha]_D^{25}$ –3.1 (*c* 0.85, $CHCl_3$, 59% ee sample); Enantiomeric excess of the product was determined to be 59% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/20, flow rate 1.0 mL/min, detection at 254 nm, t_R = 13.8 min (major), 15.5 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(4-(trimethylsilyl)phenyl)propanoate (62s)



White powder; IR (KBr): *v* 2251, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.79 (m, 4H), 7.50–7.41 (m, 4H), 7.40–7.30 (m, 6H), 4.36–4.28 (m, 1H), 4.24–4.16 (m, 3H), 3.65 (d, *J* = 16.6 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (d, *J* = 6.1 Hz), 141.6, 137.7 (d, *J* = 6.8 Hz), 136.3, 135.3, 134.4, 133.6, 133.3, 132.2, 132.1, 131.8 (d, *J* = 3.0 Hz), 131.7 (d, *J* = 3.0 Hz), 130.7, 130.6, 128.7, 128.6, 128.3, 128.1, 125.2, 117.1, 65.0, 63.1, 28.0, 13.7, -1.3; ^{31}P NMR ($CDCl_3$): δ 54.5; HRMS (ESI) Anal. calcd. for $C_{27}H_{31}O_2N_2NaPSSi$ *m/z* 529.1505 $[M+Na]^+$, found 529.1488; $[\alpha]_D^{25}$ 1.9 (*c* 1.21, $CHCl_3$, 62% ee sample); Enantiomeric excess of the product was determined to be 62% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/20, flow rate 1.0 mL/min, detection at 254 nm, t_R = 8.1 min (major), 9.2 min (minor)).

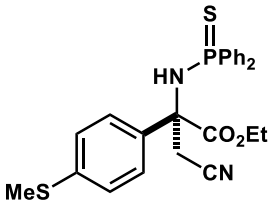
Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(4-methoxyphenyl)propanoate (62t)



White powder; IR (KBr): *v* 2251, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.80 (m, 4H), 7.48–7.40 (m, 6H), 7.26–7.23 (m, 2H), 6.74–6.70 (m, 2H), 4.34–4.26 (m, 1H), 4.22–4.12 (m, 3H), 3.75 (s, 3H), 3.63 (d, *J* = 16.6 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, *J* = 6.1 Hz), 159.7, 136.3, 135.3, 134.6, 133.5, 132.2, 132.1, 131.8 (d, *J* = 3.0 Hz), 131.7 (d, *J* = 3.0 Hz), 130.8, 130.6, 129.5, 129.4, 128.7, 128.6, 128.3, 128.2, 127.4, 117.2, 113.9, 64.6, 63.0, 55.2, 28.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}O_3N_2NaPS$ *m/z* 487.1216 $[M+Na]^+$, found 487.1209; $[\alpha]_D^{25}$ –1.5 (*c* 0.65, $CHCl_3$, 71% ee sample); Enantiomeric excess of the product was determined to be 71% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25

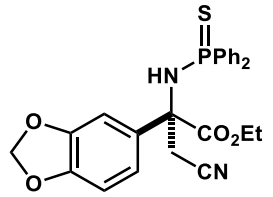
cm), 2–propanol/*n*–hexane = 1/5, flow rate 1.0 mL/min, detection at 254 nm, t_R = 23.7 min (major), 29.3 min (minor)).

Ethyl (*R*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(4-(methylthio)phenyl)propanoate (62u)



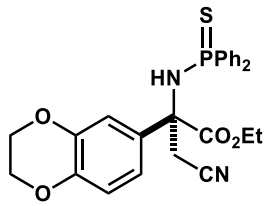
White powder; IR (KBr): *v* 2251, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.80 (m, 4H), 7.51–7.39 (m, 6H), 7.22–7.19 (m, 2H), 7.05–7.02 (m, 2H), 4.34–4.26 (m, 1H), 4.22–4.14 (m, 3H), 3.63 (d, *J* = 16.5 Hz, 1H), 2.42 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (d, *J* = 6.5 Hz), 139.9, 136.1, 135.2, 134.4, 133.8, 133.7, 133.4, 132.1, 132.0, 131.8 (d, *J* = 3.0 Hz), 131.7 (d, *J* = 3.0 Hz), 130.7, 130.6, 128.7, 128.6, 128.3, 128.1, 126.5, 125.9, 117.0, 64.7, 63.1, 28.0, 15.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{25}H_{25}O_2N_2NaPS_2$ *m/z* 503.0987 $[M+Na]^+$, found 503.0983; $[\alpha]_D^{25}$ 4.9 (*c* 1.05, $CHCl_3$, 71% ee sample); Enantiomeric excess of the product was determined to be 71% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 42.2 min (major), 49.0 min (minor)).

Ethyl (*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-3-cyano-2-((diphenylphosphorothioyl)amino)propanoate (62v)



White powder; IR (KBr): *v* 2252, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93–7.80 (m, 4H), 7.49–7.42 (m, 6H), 6.83 (dd, *J* = 2.1, 8.2 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 5.90 (dd, *J* = 1.4, 14.7 Hz, 2H), 4.36–4.28 (m, 1H), 4.24–4.14 (m, 3H), 3.59 (d, *J* = 16.5 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 6.4 Hz), 147.9, 147.8, 136.2, 135.1, 134.4, 133.3, 132.2, 132.1, 131.9 (d, *J* = 3.0 Hz), 131.8 (d, *J* = 3.0 Hz), 131.2, 131.1, 130.7, 130.6, 128.8, 128.6, 128.2, 128.1, 119.8, 117.0, 107.9, 106.8, 101.4, 64.8, 63.1, 28.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.3; HRMS (ESI) Anal. calcd. for $C_{25}H_{23}O_4N_2NaPS$ *m/z* 501.1008 $[M+Na]^+$, found 501.1004; $[\alpha]_D^{25}$ –7.5 (*c* 0.84, $CHCl_3$, 70% ee sample); Enantiomeric excess of the product was determined to be 70% ee by chiral stationary phase HPLC analysis (CHIRALPAK IC (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 50.7 min (major), 57.5 min (minor)).

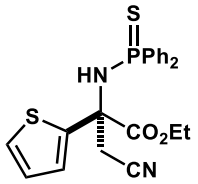
Ethyl (*R*)-3-cyano-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-((diphenylphosphorothioyl)amino)propanoate (62w)



White powder; IR (KBr): *v* 2251, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94–7.89 (m, 2H), 7.85–7.80 (m, 2H), 7.50–7.42 (m, 6H), 6.85–6.80 (m, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.35–4.27 (m, 1H), 4.23–4.15 (m, 5H), 4.12–4.09 (m, 2H), 3.59 (d, *J* = 16.6 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (d, *J* = 6.0 Hz), 143.9,

143.2, 136.3, 135.2, 134.4, 133.4, 132.3, 132.1, 131.8 (d, J = 3.0 Hz), 131.7 (d, J = 3.0 Hz), 130.73, 130.69, 130.6, 128.7, 128.6, 128.3, 128.1, 119.0, 117.3, 117.1, 115.4, 64.5, 64.24, 64.21, 63.0, 28.2, 13.7; ^{31}P NMR ($CDCl_3$): δ 54.4; HRMS (ESI) Anal. calcd. for $C_{26}H_{25}O_4N_2NaPS$ *m/z* 515.1165 $[M+Na]^+$, found 515.1156; $[\alpha]_D^{25}$ –0.3 (*c* 1.05, $CHCl_3$, 62% ee sample); Enantiomeric excess of the product was determined to be 62% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 21.0 min (major), 26.2 min (minor)).

Ethyl (*S*)-3-cyano-2-((diphenylphosphorothioyl)amino)-2-(thiophen-2-yl)propanoate (62x)



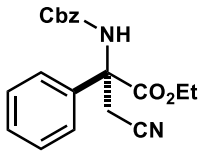
White powder; IR (KBr): *v* 2252, 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.88 (m, 4H), 7.53–7.43 (m, 6H), 7.27–7.25 (m, 1H), 7.07 (dd, J = 1.2, 3.7 Hz, 1H), 6.91 (dd, J = 3.7, 5.1 Hz, 1H), 4.29–4.21 (m, 1H), 4.16–4.01 (m, 3H), 3.84 (d, J = 16.8 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, J = 4.0 Hz), 142.4, 142.3, 135.9, 135.0, 134.8, 134.0, 132.0 (d, J = 3.0 Hz), 131.84 (d, J = 3.0 Hz), 131.80, 131.7, 131.1, 131.0, 128.63, 128.59, 128.50, 128.46, 127.2, 126.5, 126.1, 116.8, 63.2, 63.1, 29.4, 13.5; ^{31}P NMR ($CDCl_3$): δ 55.3; HRMS (ESI) Anal. calcd. for $C_{22}H_{21}O_2N_2NaPS_2$ *m/z* 463.0674 $[M+Na]^+$, found 463.0667; $[\alpha]_D^{25}$ –11.5 (*c* 0.69, $CHCl_3$, 50% ee sample); Enantiomeric excess of the product was determined to be 50% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/20, flow rate 1.0 mL/min, detection at 254 nm, 18.3 min (minor), t_R = 20.5 min (major)).

Transformation of the Mannich product

To a solution of **62b** (400 mg, 0.92 mmol) in a mixture of EtOAc/AcOH (v/v: 4/1), (5 mL), H_2O_2 (35 wt %), (1.0 mL) was added dropwise at room temperature. The reaction was quenched with sat. $NaHCO_3$ solution after complete consumption of **62b** based on TLC monitoring. The mixture was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude mixture was purified by silica gel column chromatography to afford the desired product in quantitative yield.

To a solution of the thus-obtained *N*-phosphinoylamide (41.8 mg, 0.1 mmol) in EtOAc (0.5 mL), 4 N HCl (1.5 mL) was added dropwise at room temperature. After stirring at 60 °C for 2.5 h, the resulting mixture was concentrated, and redissolved in EtOAc (1.5 mL), H_2O (1.5 mL) was added and cooled to 0 °C. To the biphase mixture, $NaHCO_3$ (420 mg, 5 mmol) and Cbz-Cl (72 µL, 0.5 mmol) were added and the solution was stirred for 4 h. The solution was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried ($NaSO_4$) and concentrated. The reaction mixture was purified by preparative TLC (hexane/acetone = 5/1) to give product **65** (22.4 mg, 64% yield).

Ethyl (*R*)-2-(((benzyloxy)carbonyl)amino)-3-cyano-2-phenylpropanoate (65)



White powder; IR ($CHCl_3$): *v* 2257, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.26 (m, 10H), 6.21 (s, 1H), 5.16–5.06 (m, 2H); 4.26–4.20 (m, 2H), 3.80–3.70 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

169.6, 154.7, 136.5, 135.8, 129.21, 129.18, 128.6, 128.3, 128.1, 125.2, 116.6, 67.3, 63.2, 63.1, 25.2, 13.8; HRMS (ESI) Anal. calcd. for $C_{20}H_{20}O_4N_2Na$ *m/z* 375.1315 $[M+Na]^+$, found 375.1314; $[\alpha]_D^{25}$ 1.4 (*c* 0.88, $CHCl_3$, from 65% ee sample).

General procedure for initial rate kinetic experiments

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $[Ir(cod)(OMe)]_2$ (3.3 mg, 0.005 mmol) and NHC precursor (5.0 mg, 0.01 mmol) under Ar atmosphere, then THF (0.5 mL) and Barton's base (20.0 μL, 0.1 mmol) were added at room temperature. The mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C. Ketimine (0.1 mmol) in THF (0.5 mL) was added, followed by MeCN (210 μL, 4 mmol). Aliquots were taken at 1 h intervals by removing a small amount (ca. 0.1 mL) of the reaction solution, which were quenched it immediately with AcOH (0.1 mL, 0.1 M in THF), then passed through a small silica gel plug, eluting with THF. After evaporation, the residue was analyzed by ^{1}H NMR spectroscopy to determine the yield based on the relative integration values of the peaks at 4.47 ppm (for ketimine) and 3.66 ppm (for product).

General procedure for kinetic isotope effects

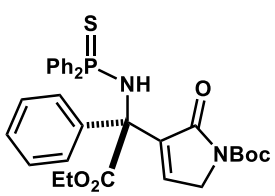
A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $[Ir(cod)(OMe)]_2$ (3.3 mg, 0.005 mmol) and NHC precursor (5.0 mg, 0.01 mmol) under Ar atmosphere. THF (0.5 mL) then Barton's base (20.0 μL, 0.1 mmol) were added at room temperature. The mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C. *para-F* Substituted ketimine (0.1 mmol) in THF (0.5 mL) followed by MeCN (210 μL, 4 mmol) were added. Aliquots were taken at 1 h intervals by removing a small amount (ca. 0.1 mL) of the reaction solution, which were quenched it immediately with AcOH (0.1 mL, 0.1 M in THF), then passed through a small silica gel plug, eluting with THF. After evaporation, the residue was analyzed by ^{1}F NMR spectroscopy to determine the yield based on the relative integration values of the peaks at –103.5 ppm (for ketimine) and –112.4 (for product).

4.2.5 Procedures for construction of *α,α*-disubstituted *α*-amino acid derivatives with *α,β*-unsaturated *γ*-butyrolactam

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with (*R,R*)-Ph-BPE (25.3 mg, 0.05 mmol), $[Cu(CH_3CN)_4]PF_6$ (18.6 mg, 0.05 mmol) and THF (0.5 mL) under Ar atmosphere. The mixture was stirred for 30 min to form the complex, which was stored at room temperature and used within one day.

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with ketimine (0.1 mmol) and *α,β*-unsaturated *γ*-butyrolactam (0.2 mmol) under Ar atmosphere and THF (0.4 mL) was added at room temperature, then the mixture was cooled to –50 °C. The catalyst solution (0.1 mL) containing copper (I) complex (0.01 mmol) then Et_3N (28 μL, 0.2 mmol) were added. The resulting reaction mixture was stirred at –50 °C for 96 h. After diluting the mixture with EtOAc and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product.

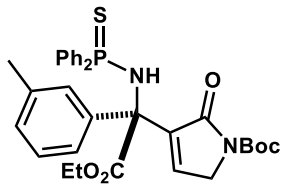
***tert*-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxo-1-phenylethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67b)**



White solid; IR (KBr): *ν* 1777, 1736, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.87–7.82 (m,

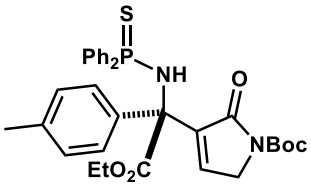
2H), 7.73 (d, *J* = 7.0 Hz, 2H), 7.47–7.41 (m, 6H), 7.37–7.31 (m, 4H), 5.05 (d, *J* = 9.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 1.7, 20.2 Hz, 1H), 3.53 (dd, *J* = 1.7, 20.2 Hz, 1H), 1.51 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 171.2, 166.9, 148.6, 145.9, 138.1, 136.9 (d, *J* = 2.6 Hz), 136.4, 135.4, 134.8, 133.8, 132.1, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 3.0 Hz), 130.5, 130.4, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.5, 82.4, 63.7, 62.8, 49.2, 28.1, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.3; HRMS (ESI) Anal. calcd. for $C_{31}H_{33}O_5N_2NaPS$ *m/z* 599.1740 $[M+Na]^+$, found 599.1733; $[\alpha]_D^{26}$ –16.1 (*c* 0.37, $CHCl_3$, 90% ee sample); Enantiomeric excess of the product was determined to be 90% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.3 min (major), 13.7 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxo-1-(m-tolyl)ethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67i)



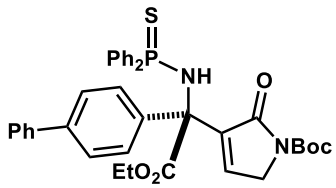
White solid; IR (KBr): *v* 1776, 1737, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.87–7.81 (m, 2H), 7.54–7.50 (m, 2H), 7.45–7.41 (m, 6H), 7.36 (t, *J* = 2.0 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 5.00 (d, *J* = 9.5 Hz, 1H), 4.12 (dq, *J* = 2.0, 7.1 Hz, 2H), 4.05 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.56 (dd, *J* = 2.0, 20.2 Hz, 1H), 2.36 (s, 3H), 1.51 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.3, 167.0, 148.5, 145.9, 138.0 (d, *J* = 1.4 Hz), 137.0, 136.94, 136.91, 136.5, 135.4, 135.0, 134.0, 132.1, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 3.0 Hz), 130.6, 130.5, 128.9, 128.8, 128.6, 128.5, 127.9, 127.8, 127.4, 125.3, 82.3, 63.7 (d, *J* = 1.3 Hz), 62.7, 49.3, 28.1, 21.7, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{32}H_{35}O_5N_2NaPS$ *m/z* 613.1897 $[M+Na]^+$, found 613.1888; $[\alpha]_D^{26}$ –23.1 (*c* 0.38, $CHCl_3$, 91% ee sample); Enantiomeric excess of the product was determined to be 91% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 8.2 min (major), 10.1 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxo-1-(p-tolyl)ethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67j)



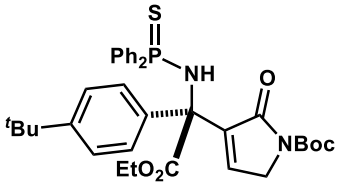
White solid; IR (KBr): *v* 1778, 1736, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.87–7.82 (m, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.47–7.40 (m, 6H), 7.34 (t, *J* = 1.9 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.13–4.07 (m, 2H), 4.03 (dd, *J* = 2.0, 20.1 Hz, 1H), 3.53 (dd, *J* = 2.0, 20.2 Hz, 1H), 2.35 (s, 3H), 1.51 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.3, 166.9, 148.5, 145.9, 137.8, 137.0 (d, *J* = 2.7 Hz), 136.5, 135.4, 135.1, 134.9, 133.9, 132.2, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 3.0 Hz), 130.6, 130.5, 128.7, 128.5, 128.3, 128.1, 127.9, 127.7, 82.3, 63.5, 62.7, 49.2, 28.1, 21.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{32}H_{35}O_5N_2NaPS$ *m/z* 613.1897 $[M+Na]^+$, found 613.1898; $[\alpha]_D^{26}$ –27.8 (*c* 0.32, $CHCl_3$, 94% ee sample); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.3 min (major), 21.5 min (minor)).

tert-Butyl (_S_)-3-(1-([1,1'-biphenyl]-4-yl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1_H_-pyrrole-1-carboxylate (67k)



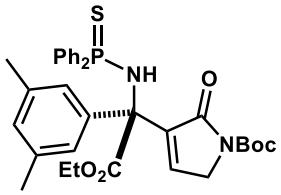
White solid; IR (KBr): *v* 1777, 1736, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01–7.95 (m, 2H), 7.89–7.84 (m, 2H), 7.80–7.78 (m, 2H), 7.63–7.57 (m, 4H), 7.48–7.39 (m, 9H), 7.36–7.32 (m, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 4.19–4.11 (m, 2H), 4.06 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.58 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 171.2, 166.9, 148.5, 146.0, 140.8, 140.4, 137.2, 137.0 (d, *J* = 2.5 Hz), 136.4, 135.4, 134.9, 133.9, 132.2, 132.1, 131.6 (d, *J* = 2.8 Hz), 131.3 (d, *J* = 2.9 Hz), 130.6, 130.5, 128.7, 128.6, 127.9, 127.8, 127.4, 127.1, 126.3, 82.4, 63.7, 62.9, 49.3, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{37}H_{37}O_5N_2NaPS$ *m/z* 675.2053 $[M+Na]^+$, found 675.2043; $[\alpha]_D^{25}$ –32.0 (*c* 0.32, $CHCl_3$, 84% ee sample); Enantiomeric excess of the product was determined to be 84% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 11.6 min (major), 23.7 min (minor)).

tert-Butyl (_S_)-3-(1-(4-(_tert_-butyl)phenyl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1_H_-pyrrole-1-carboxylate (67l)



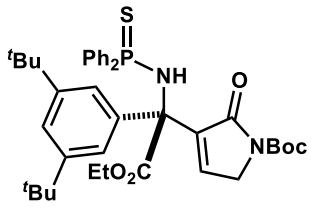
White solid; IR (KBr): *v* 1778, 1737, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.87–7.81 (m, 2H), 7.62–7.60 (m, 2H), 7.46–7.38 (m, 6H), 7.37–7.31 (m, 3H), 4.98 (d, *J* = 9.2 Hz, 1H), 4.16–4.08 (m, 2H), 4.04 (dd, *J* = 2.0, 20.1 Hz, 1H), 3.62 (dd, *J* = 2.0, 20.1 Hz, 1H), 1.51 (s, 9H), 1.31 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.3, 167.0, 150.8, 148.6, 145.8, 137.0 (d, *J* = 2.2 Hz), 136.5, 135.4, 135.1, 134.9 (d, *J* = 2.1 Hz), 134.1, 132.1, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.0 Hz), 130.7, 130.6, 128.6, 128.5, 127.9, 127.75, 127.74, 124.6, 82.3, 63.7, 62.6, 49.2, 34.5, 31.3, 28.1, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.5; HRMS (ESI) Anal. calcd. for $C_{35}H_{41}O_5N_2NaPS$ *m/z* 655.2366 $[M+Na]^+$, found 655.2364; $[\alpha]_D^{25}$ –31.7 (*c* 0.31, $CHCl_3$, 94% ee sample); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 6.7 min (major), 12.4 min (minor)).

tert-Butyl (_S_)-3-(1-(3,5-dimethylphenyl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1_H_-pyrrole-1-carboxylate (67m)



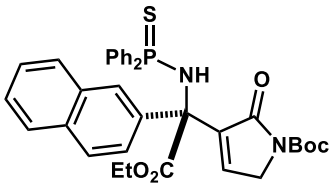
White solid; IR (KBr): *v* 1775, 1736, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.87–7.81 (m, 2H), 7.46–7.41 (m, 6H), 7.36 (t, *J* = 2.0 Hz, 1H), 7.29 (s, 2H), 6.92 (s, 1H), 4.95 (d, *J* = 9.2 Hz, 1H), 4.12 (dq, *J* = 1.8, 7.1 Hz, 2H), 4.05 (dd, *J* = 2.0, 20.1 Hz, 1H), 3.59 (dd, *J* = 2.0, 20.2 Hz, 1H), 2.31 (s, 6H), 1.51 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.3, 167.0, 148.6, 145.7, 137.8 (d, *J* = 2.1 Hz), 137.0 (d, *J* = 2.4 Hz), 136.8, 136.5, 135.5, 135.1, 134.1, 132.1, 132.0, 131.4 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 3.2 Hz), 130.7, 130.6, 129.7, 128.6, 128.4, 127.9, 127.8, 126.0, 82.3, 63.8, 62.6, 49.3, 28.1, 21.5, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.6; HRMS (ESI) Anal. calcd. for $C_{33}H_{37}O_5N_2NaPS$ *m/z* 627.2053 $[M+Na]^+$, found 627.2043; $[\alpha]_D^{25}$ –25.5 (*c* 0.38, $CHCl_3$, 94% ee sample); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 6.6 min (major), 8.1 min (minor)).

tert-Butyl (*S*)-3-(1-(3,5-di-_tert_-butylphenyl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67n)



White solid; IR (KBr): *v* 1777, 1739, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01–7.94 (m, 2H), 7.88–7.82 (m, 2H), 7.59 (d, *J* = 1.7 Hz, 2H), 7.49–7.39 (m, 6H), 7.33 (t, *J* = 1.7 Hz, 1H), 7.21 (t, *J* = 1.9 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.17–4.04 (m, 3H), 3.52 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.33 (s, 18H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 171.5, 167.1, 149.3, 148.5, 145.8, 137.8 (d, *J* = 2.3 Hz), 137.0, 136.6, 135.9, 134.7, 133.7, 132.4, 132.3, 131.6 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 3.0 Hz), 131.18, 131.1, 130.5, 130.4, 128.7, 128.53, 128.46, 128.3, 127.8, 127.7, 123.3, 121.6, 82.3, 64.2, 62.6, 49.2, 35.0, 31.5, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 50.8; HRMS (ESI) Anal. calcd. for $C_{39}H_{49}O_5N_2NaPS$ *m/z* 711.2992 $[M+Na]^+$, found 711.2991; $[\alpha]_D^{26}$ –21.1 (*c* 0.35, $CHCl_3$, 92% ee sample); Enantiomeric excess of the product was determined to be 92% ee by chiral stationary phase HPLC analysis (CHIRALPAK ID (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 8.8 min (major), 10.5 min (minor)).

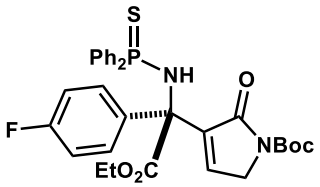
tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-1-(naphthalen-2-yl)-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67o)



White solid; IR (KBr): *v* 1775, 1736, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.02–7.96 (m, 2H), 7.94–7.81 (m, 6H), 7.49–7.41 (m, 8H), 7.39 (t, *J* = 1.9 Hz, 1H), 5.16 (d, *J* = 9.7 Hz, 1H), 4.14–4.06 (m, 3H), 3.55 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 171.2, 166.9, 148.5, 146.1, 136.6 (d, *J* = 2.4 Hz), 136.5, 135.5, 135.4, 134.9, 133.9, 133.0, 132.5, 132.2, 132.1, 131.6 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 130.6, 130.5, 128.7, 128.6, 128.5, 128.1, 127.9, 127.8, 127.4, 127.1, 126.4, 126.0, 125.7, 82.4, 63.9, 62.9, 49.3, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.3; HRMS (ESI) Anal. calcd. for $C_{35}H_{35}O_5N_2NaPS$ *m/z* 649.1897 $[M+Na]^+$, found 649.1894; $[\alpha]_D^{26}$ –39.5 (*c* 1.06, $CHCl_3$, 88% ee sample); Enantiomeric excess of the product was determined to be 88% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–

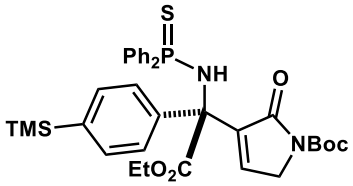
propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.4 min (major), 26.3 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-1-(4-fluorophenyl)-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67q)



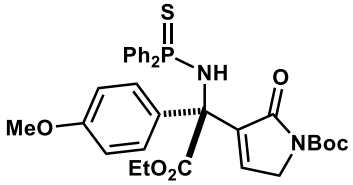
White solid; IR (KBr): *v* 1777, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.92 (m, 2H), 7.86–7.80 (m, 2H), 7.73–7.70 (m, 2H), 7.48–7.41 (m, 6H), 7.31 (t, *J* = 2.0 Hz, 1H), 7.05–7.01 (m, 2H), 5.06 (d, *J* = 9.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.51 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 171.0, 166.8, 163.8, 161.3, 148.4, 145.9, 136.9 (d, *J* = 2.7 Hz), 136.3, 135.3, 134.6, 133.8 (d, *J* = 4.1 Hz), 133.6, 132.1, 132.0, 131.6 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.2 Hz), 130.5, 130.4, 130.2, 130.1, 128.7, 128.6, 127.9, 127.8, 114.6, 114.3, 82.5, 63.3, 62.9, 49.3, 28.1, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.2; ^{19}F NMR (375 MHz, $CDCl_3$): δ -114.5; HRMS (ESI) Anal. calcd. for $C_{31}H_{32}O_5N_2FNaPS$ *m/z* 617.1646 $[M+Na]^+$, found 617.1643; $[\alpha]_D^{26}$ –15.5 (*c* 0.35, $CHCl_3$, 74% ee sample); Enantiomeric excess of the product was determined to be 74% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 9.2 min (major), 13.9 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxo-1-(4-(trimethylsilyl)phenyl)ethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67s)



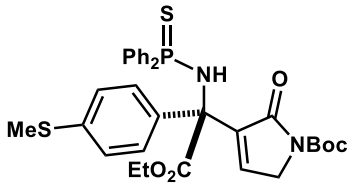
White solid; IR (KBr): *v* 1779, 1737, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.87–7.82 (m, 2H), 7.66–7.62 (m, 2H), 7.49–7.40 (m, 8H), 7.36 (t, *J* = 2.0 Hz, 1H), 5.00 (d, *J* = 9.3 Hz, 1H), 4.16–4.01 (m, 3H), 3.60 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); 0.26 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 171.1, 166.9, 148.5, 146.0, 140.2, 138.6, 136.9 (d, *J* = 2.4 Hz), 136.4, 135.4, 134.0, 132.7, 132.1, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.0 Hz), 130.7, 130.5, 128.7, 128.5, 127.9, 127.8, 127.3, 82.4, 63.9, 62.8, 49.2, 28.1, 13.5, –1.1; ^{31}P NMR ($CDCl_3$): δ 51.5; HRMS (ESI) Anal. calcd. for $C_{34}H_{41}O_5N_2NaPSSi$ *m/z* 671.2135 $[M+Na]^+$, found 671.2137; $[\alpha]_D^{25}$ –28.1 (*c* 0.37, $CHCl_3$, 88% ee sample); Enantiomeric excess of the product was determined to be 88% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 5.7 min (major), 7.4 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67t)



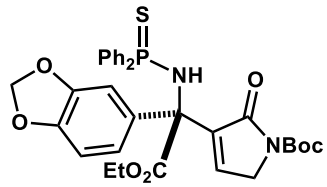
White solid; IR (KBr): *v* 1777, 1735, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.93 (m, 2H), 7.87–7.82 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.47–7.41 (m, 6H), 7.33 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.04 (d, *J* = 20.1 Hz, 1H), 3.82 (s, 3H), 3.53 (d, *J* = 20.1 Hz, 1H), 1.51 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 171.4, 166.9, 148.5, 145.8, 137.1, 136.5, 135.5, 134.9, 133.8, 132.2, 132.0, 131.5 (d, *J* = 2.8 Hz), 131.3 (d, *J* = 2.8 Hz), 130.5, 130.4, 129.9, 129.5, 128.7, 128.5, 127.9, 127.7, 112.9, 82.4, 63.3, 62.7, 55.2, 49.2, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.0; HRMS (ESI) Anal. calcd. for $C_{32}H_{35}O_6N_2NaPS$ *m/z* 629.1846 $[M+Na]^+$, found 629.1838; $[\alpha]_D^{26}$ –26.3 (*c* 0.35, $CHCl_3$, 94% ee sample); Enantiomeric excess of the product was determined to be 94% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 12.8 min (major), 25.2 min (minor)).

tert-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-1-(4-(methylthio)phenyl)-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67u)



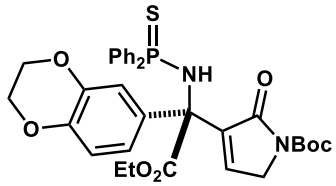
White solid; IR (KBr): *v* 1777, 1736, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.92 (m, 2H), 7.87–7.81 (m, 2H), 7.66–7.62 (m, 2H), 7.47–7.40 (m, 6H), 7.32 (t, *J* = 1.9 Hz, 1H), 7.22–7.19 (m, 2H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.16–4.08 (m, 2H), 4.03 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.52 (dd, *J* = 2.0, 20.2 Hz, 1H), 2.49 (s, 3H), 1.51 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 171.1, 166.9, 148.5, 146.0, 138.6, 136.9 (d, *J* = 2.4 Hz), 136.4, 135.4, 134.7 (d, *J* = 1.2 Hz, 1H), 133.8, 132.2, 132.0, 131.6 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.0 Hz), 130.6, 130.4, 128.8, 128.7, 128.6, 127.9, 127.8, 125.2, 82.4, 63.4, 62.9, 49.3, 28.1, 15.4, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.1; HRMS (ESI) Anal. calcd. for $C_{32}H_{35}O_5N_2NaPS_2$ *m/z* 645.1617 $[M+Na]^+$, found 645.1619; $[\alpha]_D^{26}$ –34.3 (*c* 0.42, $CHCl_3$, 88% ee sample); Enantiomeric excess of the product was determined to be 88% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 10.6 min (major), 22.1 min (minor)).

tert-Butyl (*S*)-3-(1-(benzo[*d*][1,3]dioxol-5-yl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67v)



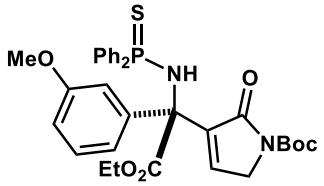
White solid; IR (KBr): *v* 1776, 1736, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–7.93 (m, 2H), 7.85–7.79 (m, 2H), 7.47–7.38 (m, 7H), 7.27–7.34 (m, 1H), 7.14 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.98 (d, *J* = 3.8 Hz, 2H), 5.00 (d, *J* = 9.5 Hz, 1H), 4.13 (dq, *J* = 2.2, 7.2 Hz, 2H), 4.04 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.56 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.51 (s, 9H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 171.1, 166.8, 148.5, 147.4, 147.1, 145.9, 136.9 (d, *J* = 2.2 Hz), 136.3, 135.3, 134.8, 133.8, 132.1, 132.0, 131.9 (d, *J* = 1.4 Hz), 131.5 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.0 Hz), 130.5, 130.4, 128.7, 128.5, 127.9, 127.8, 122.0, 108.8, 107.3, 101.2, 82.4, 63.5, 62.8, 49.2, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.3; HRMS (ESI) Anal. calcd. for $C_{32}H_{33}O_7N_2NaPS$ *m/z* 643.1638 $[M+Na]^+$, found 643.1634; $[\alpha]_D^{26}$ –21.8 (*c* 0.33, $CHCl_3$, 90% ee sample); Enantiomeric excess of the product was determined to be 90% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 14.3 min (major), 22.1 min (minor)).

***tert*-butyl (*S*)-3-(1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67w)**



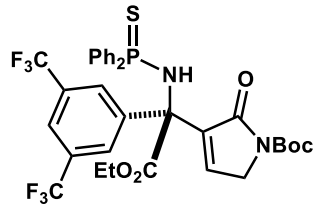
White solid; IR (KBr): *v* 1775, 1735, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H), 7.85–7.79 (m, 2H), 7.45–7.38 (m, 7H), 7.21–7.18 (m, 2H), 6.83–6.81 (m, 1H), 4.97 (d, *J* = 9.4 Hz, 1H), 4.25 (s, 4H), 4.16–4.08 (m, 2H), 4.03 (dd, *J* = 2.0, 20.1 Hz, 1H), 3.58 (dd, *J* = 2.0, 20.2 Hz, 1H), 1.50 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 171.2, 166.9, 148.5, 145.8, 143.4, 142.6, 136.8 (d, *J* = 2.4 Hz), 136.4, 135.4, 134.9, 133.9, 132.1, 132.0, 131.5 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 3.0 Hz), 131.2 (d, *J* = 1.7 Hz), 130.6, 130.5, 128.6, 128.5, 127.9, 127.7, 121.3, 117.5, 116.3, 82.4, 64.32, 64.25, 63.2, 62.9, 49.2, 28.1, 13.6; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{33}H_{35}O_7N_2NaPS$ *m/z* 657.1795 $[M+Na]^+$, found 657.1791; $[\alpha]_D^{26}$ –24.8 (*c* 0.84, $CHCl_3$, 91% ee sample); Enantiomeric excess of the product was determined to be 91% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 14.9 min (major), 22.1 min (minor)).

***tert*-Butyl (*S*)-3-(1-((diphenylphosphorothioyl)amino)-2-ethoxy-1-(3-methoxyphenyl)-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67y)**



White solid; IR (KBr): *v* 1776, 1737, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2H), 7.87–7.81 (m, 2H), 7.47–7.40 (m, 6H), 7.37 (t, *J* = 2.0 Hz, 1H), 7.33–7.31 (m, 1H), 7.29–7.24 (m, 2H), 6.87–6.84 (m, 1H), 5.02 (d, *J* = 9.7 Hz, 1H), 4.13 (dq, *J* = 1.8, 7.2 Hz, 2H), 4.04 (dd, *J* = 2.0, 20.2 Hz, 1H), 3.83 (s, 3H), 3.55 (dd, *J* = 2.1, 20.1 Hz, 1H), 1.51 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 171.1, 166.9, 158.8, 148.5, 146.0, 139.7 (d, *J* = 1.3 Hz), 136.8 (d, *J* = 2.2 Hz), 136.4, 135.4, 134.8, 133.8, 132.1, 132.0, 131.5 (d, *J* = 3.0 Hz), 131.3 (d, *J* = 2.9 Hz), 130.6, 130.4, 128.7, 128.53, 128.45, 127.9, 127.8, 120.7, 114.6, 113.4, 82.4, 63.7, 62.8, 55.3, 49.2, 28.1, 13.5; ^{31}P NMR ($CDCl_3$): δ 51.4; HRMS (ESI) Anal. calcd. for $C_{32}H_{35}O_6N_2NaPS$ *m/z* 629.1846 $[M+Na]^+$, found 629.1841; $[\alpha]_D^{25}$ –20.9 (*c* 0.34, $CHCl_3$, 86% ee sample); Enantiomeric excess of the product was determined to be 86% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 11.6 min (major), 13.3 min (minor)).

***tert*-Butyl (*S*)-3-(1-(3,5-bis(trifluoromethyl)phenyl)-1-((diphenylphosphorothioyl)amino)-2-ethoxy-2-oxoethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (67z)**



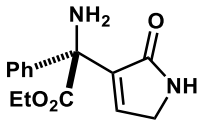
White solid; IR (KBr): *v* 1779, 1742, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 2H), 7.98–7.92 (m, 2H), 7.86–7.78 (m, 3H), 7.52–7.43 (m, 6H), 7.21 (t, *J* = 2.0 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.21–4.08 (m, 3H), 3.44 (dd, *J* = 2.0, 20.4 Hz, 1H), 1.52 (s, 9H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.9, 166.6, 148.2, 146.0, 141.2, 136.5 (d, *J* = 2.8 Hz), 135.8, 134.8, 133.7, 138.8, 132.3, 132.1, 131.9 (d, *J* = 2.9 Hz), 131.6 (d, *J* = 2.9 Hz), 130.7 (q, *J* = 125.2 Hz), 130.5, 130.3, 129.2, 128.9, 128.8, 128.0, 127.9, 127.4, 124.7, 122.2, 122.1, 121.9, 119.2, 82.7, 63.59, 63.55, 49.4, 28.1, 13.4; ^{31}P NMR ($CDCl_3$): δ 51.9; ^{19}F NMR (375 MHz, $CDCl_3$): δ -62.8; HRMS (ESI) Anal. calcd. for $C_{33}H_{31}O_5N_2F_6NaPS$ *m/z* 735.1488 $[M+Na]^+$, found 735.1472; $[\alpha]_D^{26}$ –1.1 (*c* 0.41, $CHCl_3$, 82% ee sample); Enantiomeric excess of the product was determined to be 82% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA/ID (*ø* 0.46 cm x 25 cm), 2–propanol/*n*–hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, t_R = 11.0 min (major), 11.8 min (minor)).

Transformation of the Mannich product

To a solution of **77b** (576.3 mg, 1 mmol) in a mixture of EtOAc/AcOH (v/v: 4/1) (10.0 mL), H_2O_2 (35 wt %) (1.0 mL) was added dropwise at room temperature. The reaction was quenched with sat. $NaHCO_3$ solution after TLC showed complete consumption of **77b**. The mixture was extracted with ethyl acetate, and the organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the obtained crude mixture was purified by silica gel column chromatography to afford the desired product in quantitative yield.

The obtained product (56.1 mg, 0.1 mmol) was dissolved in EtOAc (0.5 mL), before 4 M HCl (1.5 mL) was added dropwise at room temperature. The mixture was heated to 60 °C and stirred for 40 min. Then solvent was evaporated under reduced pressure. The reaction mixture was purified by preparative TLC (Al_2O_3 plate)($CHCl_3$/MeOH = 30/1) to give the pure product **83** (18.1 mg, 70% yield).

Ethyl (*S*)-2-amino-2-(2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-2-phenylacetate (83)



Yellow oil; IR ($CHCl_3$): *v* 3363 (brm), 1730, 1697, 1602 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.57–7.54 (m, 2H), 7.42–7.33 (m, 3H), 6.54 (t, *J* = 1.8 Hz, 1H), 4.23 (dq, *J* = 0.6, 7.2 Hz, 2H); 3.95 (dd, *J* = 1.8, 9.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 174.9, 174.7, 142.6, 140.6, 129.5, 129.2, 127.5, 64.0, 63.1, 47.8, 14.3; HRMS (ESI) Anal. calcd. for $C_{14}H_{16}O_3N_2Na$ *m/z* 283.1059 $[M+Na]^+$, found 283.1054; $[\alpha]_D^{26}$ 20.6 (*c* 0.54, $CHCl_3$, from 91% ee sample).

Recovery and Reuse of Catalyst

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with (*R,R*)-Ph-BPE (25.3 mg, 0.05 mmol), $[Cu(CH_3CN)_4]PF_6$ (18.6 mg, 0.05 mmol) and THF (1.0 mL) under Ar atmosphere. The mixture was stirred for 30 min to form the complex, which was stored at room temperature.

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with ketimine **61b** (157.4 mg, 0.4 mmol) and *α,β*-unsaturated *γ*-butyrolactam **66** (146.6 mg, 0.8 mmol) under Ar atmosphere and THF (1.2 mL) was added at room temperature, then the mixture was cooled to –50 °C. The catalyst solution (0.8 mL) containing copper (I) complex (0.04 mmol) followed by Et_3N (111.5 µL, 0.8 mmol) was added. The resulting reaction mixture was stirred at –50 °C for 96 h. After diluting the mixture with MeCN, neutral silica gel (1.0 g) was added. Volatiles were removed under reduced pressure and the resulting crude products absorbed on neutral silica were loaded on a silica gel column. Elution with a mixture of DCM and MeCN (from 20/1 to 4/1) gave the product (205.0 mg, 89% yield) and Cu/Ph-BPE complex. Enantioselectivity was determined to be 91% ee by chiral stationary

phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, tR = 10.1 min (major), 13.3 min (minor)).

The recovered complex was dried under vacuum, washed with dry THF in a 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock. THF (0.5 mL) was added and the mixture was cooled to –50 °C. Ketimines **61b** (157.4 mg, 0.4 mmol) and *α*,*β*-unsaturated *γ*-butyrolactam **66** (146.6 mg, 0.8 mmol) dissolved in 1.5 mL THF were added at –50 °C. Then Et_3N (111.5 µL, 0.8 mmol) was added. The resulting reaction mixture was stirred at –50 °C for 90 h. After diluting the mixture with EtOAc and concentration under reduced pressure, the obtained crude product was purified by silica gel column chromatography (*n*–Hexane/Ethyl acetate) to afford the desired product (195.5 mg, 85% yield). Enantioselectivity was determined to be 91% ee by chiral stationary phase HPLC analysis (CHIRALPAK IA (ø 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm, tR = 9.9 min (major), 12.9 min (minor)).

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