PHOSPHORUS LIGAND DEVELOPMENT FOR TRANSITION METAL CATALYZED REACTIONS

By

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written under the direction of

Professor Xumu Zhang

and approved by

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New Brunswick, New Jersey
January, 2014

ABSTRACT OF THE DISSERTATION

PHOSPHORUS LIGAND DEVELOPMENT FOR TRANSITION METAL CATALYZED REACTIONS

By KEXUAN HUANG

Dissertation Director:

Professor Xumu Zhang

This thesis summarizes the author's graduate research on phosphorus ligands synthesis and catalytic asymmetric. The first chapter describes the design and synthesis of novel *P*-chiral ligands and their applications in asymmetric hydrogenation. Those ligands exhibit extremely high enantioselectivities (up to 99% ee) and reactivities (up to 50 000 TON) for rhodium-catalyzed hydrogenation of a wide range of functionalized olefin derivatives. Chapter 2 delineates asymmetric hydrogenation of oxime esters and ketoenamides, which affords new approaches for the synthesis of optically pure chiral amines. In Chapter 3, the development of two tetraphosphorous ligands (TPPB and Tetrabi) is discussed. Those ligands are based on a biphenyl backbone and can be successfully applied in the highly regioselective hydroformylation of terminal olefins and internal olefins.

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Chapter 1

Design and synthesis of novel *P*-chiral ligands and their applications in asymmetric hydrogenation

1.1 Introduction

Phosphorus ligands development for asymmetric hydrogenation

In the 1960s, Knowles[1a] and Horner[1b] first reported that the enantioselective hydrogenation of prochiral double bonds is possible by using chiral versions of Wilkinson's catalyst. Since then, the development of methods to prepare chiral phosphine ligands has never stopped. To date, hundreds of chiral phosphine ligands have been created for asymmetric hydrogenation. We have to mention some of them because of their long-lasting impact on the history of asymmetric hydrogenation. In the early 1970s, Kagan developed the first C_2-symmetric chelating bisphosphine DIOP (**1**)[2] (Figure 1-1-1). This work showed that a chelating ligand with backbone chirality is capable of inducing high enantioselectivity without *P*-chirality. Meanwhile, Knowles continued to develop an improved *P*-chiral bidentate ligand DIPAMP (**2**) which led to the first industrial scale synthesis of L-DOPA via asymmetric hydrogenation.[3] In 1980, A major breakthrough was made by Noyori and co-workers when they carried out pioneering studies on axially chiral BINAP (**3**).[4] The Ru-BINAP catalytic system was confirmed to show unprecedented substrate scope for both functionalized olefins and functionalized ketones.[5] Later, a Ru-BINAP-diamine system was discovered to show extremely high activity and selectivity to unfunctionalized simple ketones through a novel bifunctional mechanism.[5] Parallel to Noyori's research, significant progress was also made in the synthesis many efficient chiral phosphorus ligands for the Rh-catalyzed asymmetric hydrogenation. In 1991, Burk developed conformationally rigid electron-rich bis(phospholane) DuPhos (**4**) and BPE (**5**) for Rh-catalyzed

hydrogenation of various functional olefins.[6] Those ligands could change their chiral environment through structural modification of the R group. A C_1-symmetric planar chiral ferrocene-based Josiphos (**6**) ligand was also developed later by Togni.[7] With modification of the two different chelating phosphine parts, a large ligand series has been prepared to fit the steric and electronic requirements of different substrates.[7b] Novel *P*-chiral trialkyl phosphine ligands such as BisP*(**7**) were also reported to with impressive results by Imamoto. [8]

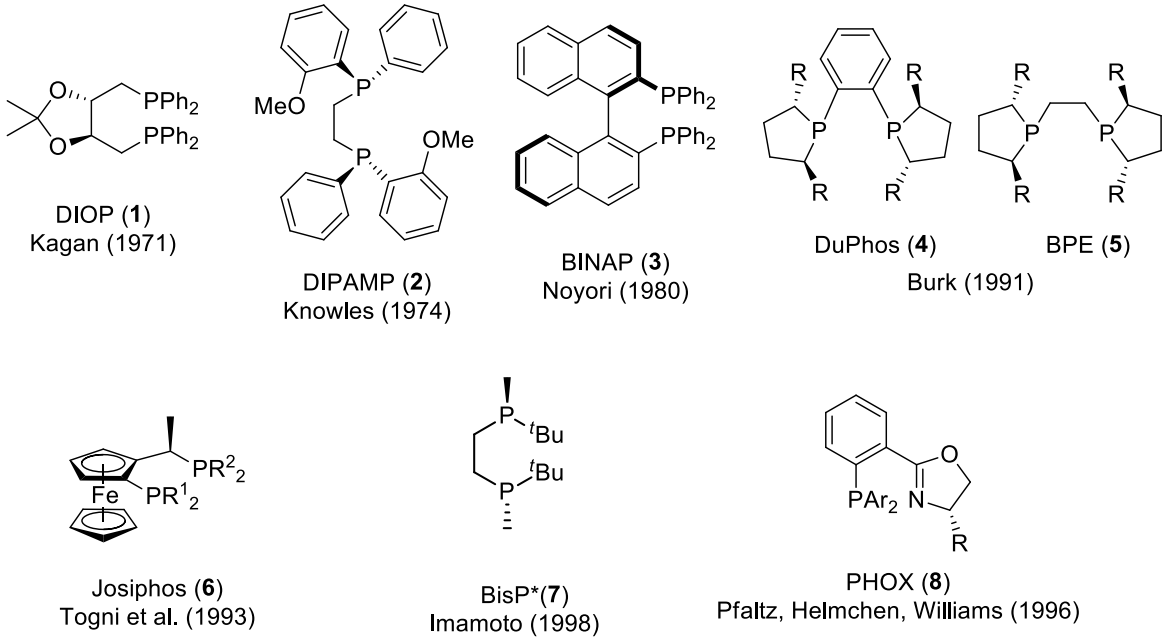


Figure 1-1-1. Historically important ligands for asymmetric hydrogenation

For Ir-catalyzed hydrogenation, the most important class of chiral modular ligands is P, N-ligand PHOX (**8**) developed by Pfaltz and others, which was designed to mimic Crabtree's catalyst for the hydrogenation of multi-substituted olefins.[9] Its two chelating donors are both sterically and electronically tunable, allowing Ir-catalyzed asymmetric hydrogenation of imines and unfunctionalized olefins to afford excellent enantioselectivities.

Mechanism of Rh-catalyzed asymmetric hydrogenation.

The generally accepted mechanism of Rh-catalyzed asymmetric hydrogenation of enamides was proposed by Halpern[10] and Brown[11] in the 1980s, which was established by using Rh-catalysts generated from ligands such as DIPAMP and ChiraPhos. The so-called "unsaturated" mechanism is depicted in Figure 1-1-2 and encompasses four elemental steps:

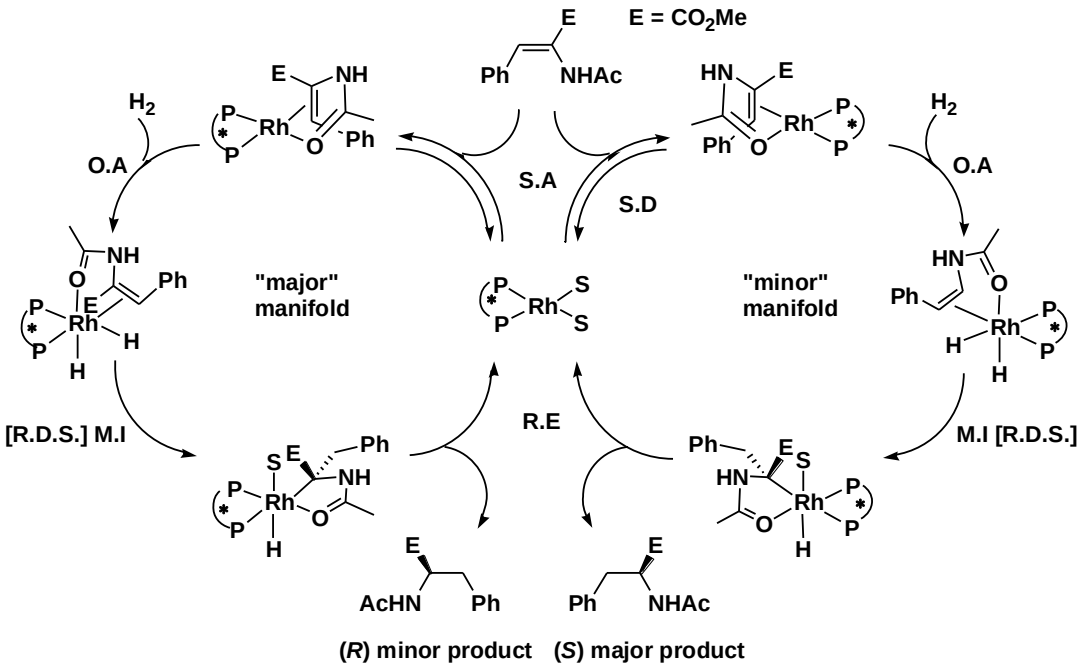


Figure 1-1-2. "Unsaturated" mechanism of Rh-catalyzed asymmetric hydrogenation.

(a) reversible binding of the substrate to the catalyst affording a mixture of two diastereomeric Rh-substrate complexes. One of them is predominant as the major isomer; (b) irreversible oxidative addition of H_2 to the Rh-substrate complex, in which two manifolds are available from the diastereomeric Rh-substrate complexes; (c) irreversible migratory insertion of the alkene which is the rate determining step， providing a Rh-hydridoalkyl complex; and (d) irreversible reductive elimination leading to the product and regenerating the catalyst. The enantioselectivity in this reaction is confirmed to originate not from the predominance of the major diastereomeric Rh-substrate complex, but from the much higher relative reactivity toward H_2 of the minor

complex, which eventually gives the product with the experimentally observed configuration. A new mechanistic pathway has been observed by Gridnev and Imamoto when using electron-rich BisP* as the ligand for Rh-catalyzed asymmetric hydrogenation of functionalized olefins (Figure 1-1-3).[12] The so called "dihydride pathway" involves the oxidative addition of a hydrogen molecule prior to the coordination of the substrate to the Rh metal; subsequent migratory insertion followed by reductive elimination provides the hydrogenation product. This mechanism is in contrast to the classic "unsaturated pathway" (Figure 1-1-3) and is in effect only when electron-rich phosphanes are employed as ligands. Thus, it is worth the effort to develop novel highly electron-rich trialkyl phosphine ligands for asymmetric hydrogenation from both practical and mechanistic points of view.

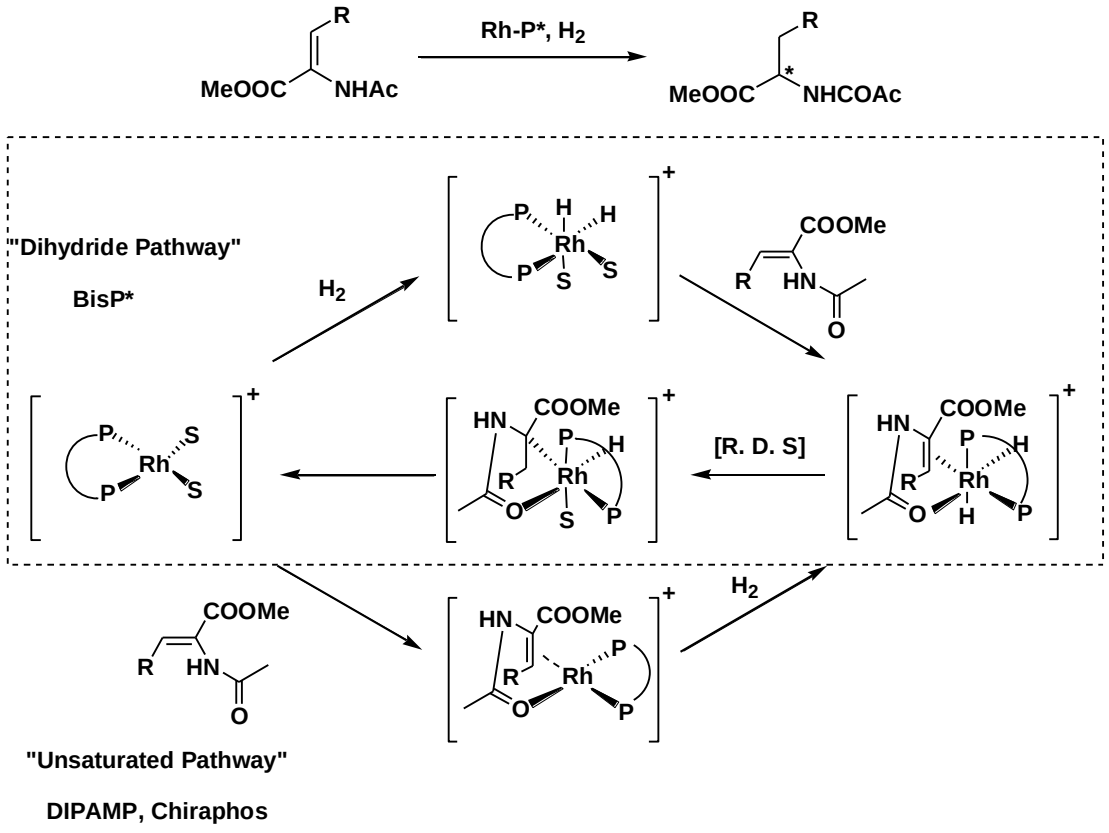


Figure 1-1-3. Two possible reaction pathways for Rh-catalyzed hydrogenation.

Ligand design strategy

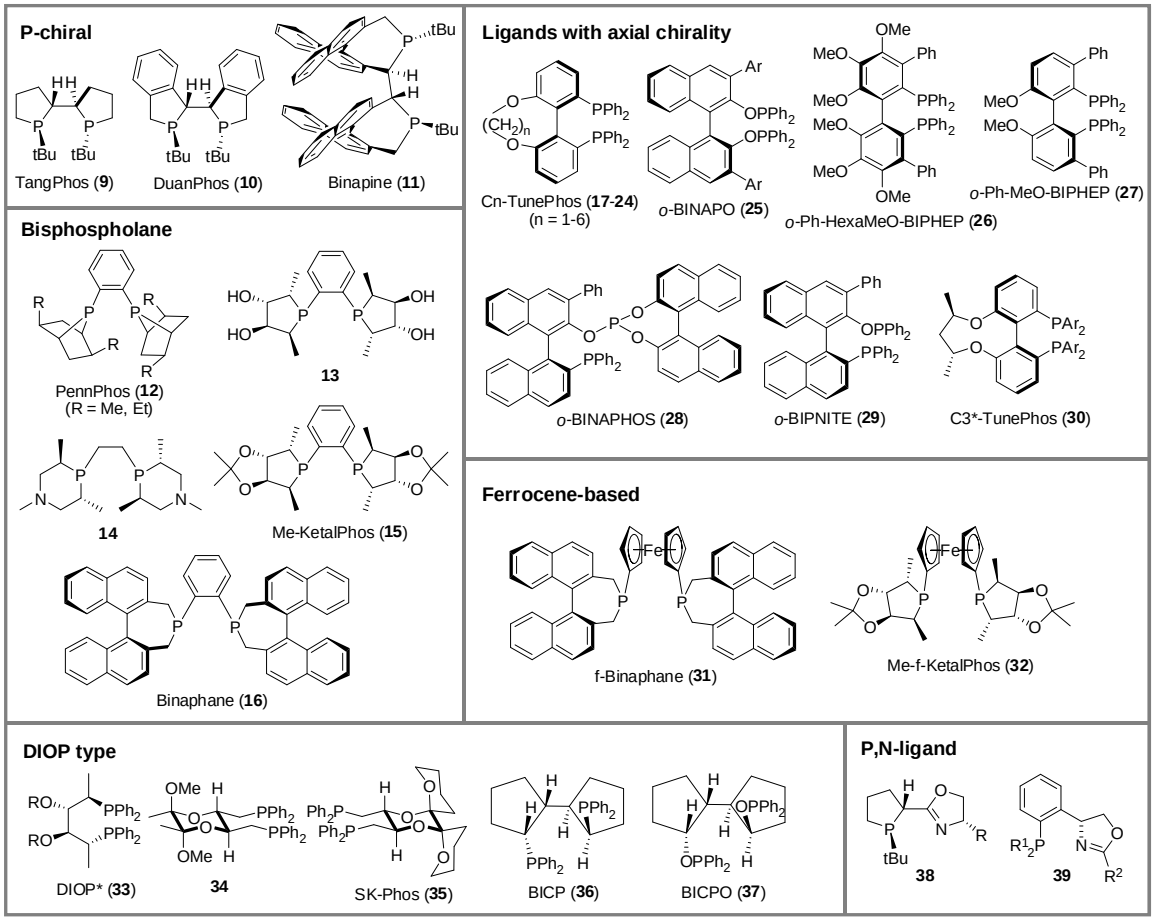


Figure 1-1-4. A chiral ligand toolbox developed by Zhang's lab for asymmetric hydrogenation.

Over the last decade, our group has developed a large variety of chiral ligands, including *P*-chiral ligands **9**-**11**, bisphospholanes **12**-**16**, axially chiral ligands **17**-**30**, ferrocene-based ligands **31** and **32**, and P, N-ligands **38** and **39** (Figure 1-1-4).[13] They have been proved to be remarkable in highly enantioselective hydrogenation of various olefins, ketones, and imines. Although the structures of these ligands are diversified, they have shared some common design spirit in terms of steric and electronic factors. For example, the flexible conformation of DIOP (**1**) can be rigidified via either cyclization of its backbone or introduction of additional chiral centers near the chelating sites (Figure 1-1-5). The resultant ligands BICP (**36**)[14] and DIOP* (**33**)[15] showed better enantioselectivity than DIOP **1** in Rh-catalyzed asymmetric hydrogenation of enamides.

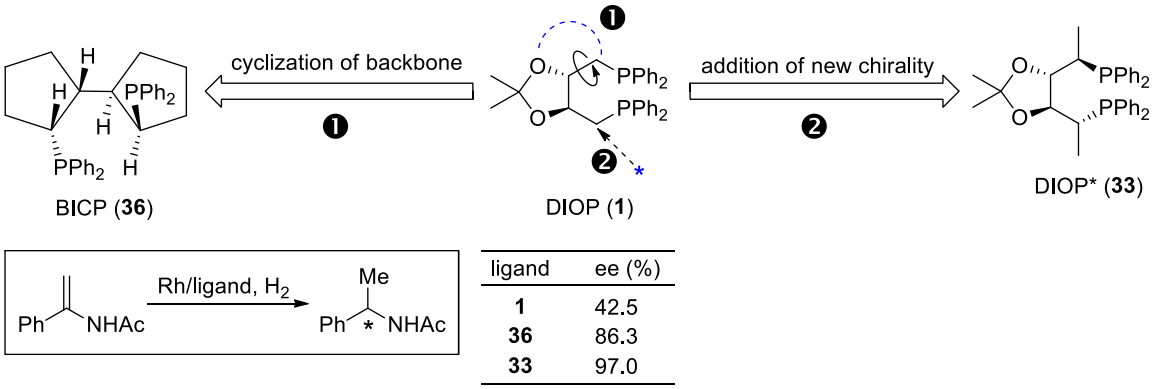


Figure 1-1-5. Develop conformationally rigid BICP and DIOP* based on DIOP.

As described above, one primary design principle is increasing conformational rigidity of a flexible ligand structure. Same idea was used in the development of TunePhos. Following the success of Noyori's BINAP (**3**) in Ru-catalyzed asymmetric hydrogenation,[3] a large number of atropisometic biaryl diphosphine ligands have been reported.[16] Generally, all these ligands possess a C(sp^2)-C(sp^2) single bond around which the two aryl moieties can rotate with little restriction (Figure 1-1-6). This rotational flexibility can sometimes afford a less effective steric environment for chiral induction, especially at elevated temperatures.

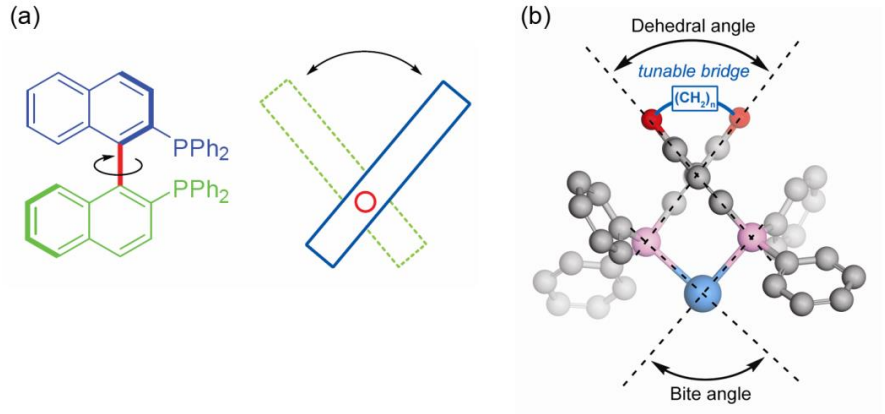
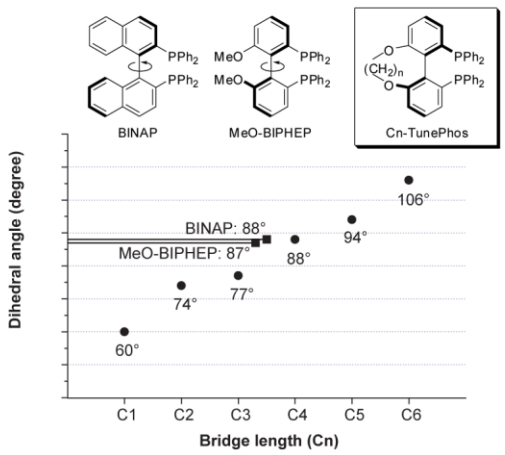


Figure 1-1-6. Top view of Cn-TunePhos model showing the dual functions of restrictive bridge.

Applying our principle, we designed modular TunePhos (**17-24**) by connecting the two aryl moieties with a tunable bridge.[17a] The additional linkage reduces its conformational rotation and

defines the dihedral angle with better precision. Now we can adjust the length of the linking bridge from C1 to C6 to optimize the dihedral angle (Figure 1-1-6). Hydrogenation of various substrates allowed us to test the effect of dihedral angle on enantioselectivity in a systematic way.[17] Ru-catalyzed hydrogenation of four different substrates with **17**-**24** confirmed the existence of an optimal dihedral angle. Excellent results have been achieved which are superior to the previous BINAP (**3**) and BIPHEP (Figure 1-1-7) ligand. Another example includes the design and synthesis of TangPhos based on the structure of BisP*. The five-membered phospholane rings restrict the conformational flexibililty, which lead to better enantioselectivity in some asymmetric hydrogenation reactions (Figure 1-1-8).[18]



Comparative hydrogenation results (ee%)

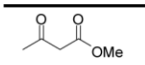
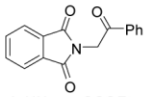
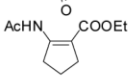
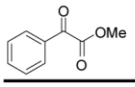
Ligand	Cn-TunePhos C1	C2	C3	C4	C5	C6	BINAP	MeO-BIPHEP
	91	91	98	**99**	97	97	98	98
	91	90	**99**	95	95	91	94	96
	98	**99**	**99**	**99**	**99**	97	99	99
	91	93	**97**	93	93	92	72	90

Figure 1-1-7. Effect of dihedral angle on enantioselectivity.

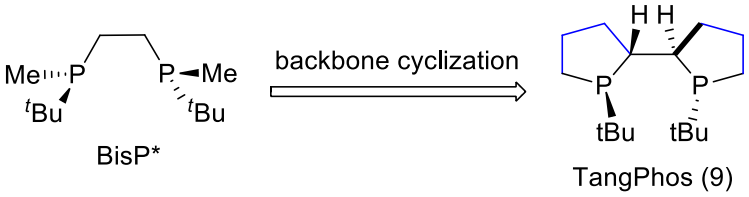


Figure 1-1-8. Design of TangPhos

Conclusions

The past has witnessed tremendous progress in asymmetric hydrogenation because of the development of chiral phosphorus ligands. The exceptional catalytic activities and outstanding enantioselectivities of those ligands have extended their applications far beyond asymmetric hydrogenation and laboratory research. Our group will continue to develop new phosphorus ligands with our own design spirit.

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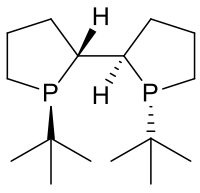
1.2 Novel *P*-stereogenic bisphospholane ligands for highly enantioselective rhodium-catalyzed asymmetric hydrogenations

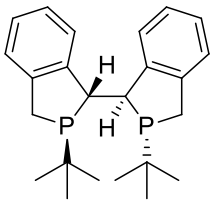
Background

In 2002, Our research group has reported a *P*-stereogenic ligand, TangPhos to be one of the most efficient ligands for asymmetric hydrogenation.[1] Recently, many other research groups found that TangPhos exhibited the excellent enantioselectivities for asymmetric reactions other than hydrogenation, such as arylcyanation and alkylation.[2] However, only one enantiomer of TangPhos (*1S,1S',2R,2R'*) is readily available owing to the requisition of chiral induction from (-)-sparteine. Following the success of TangPhos (**1**), we introduced another *P*-stereogenic ligand DuanPhos (**2**) with both enantiomers available by optical resolution. The wide applications of TangPhos and Duan-Phos[3] encourage us to develop a new synthetically practical and conformationally rigid *P*-stereogenic bisphospholane scaffold **3**. We predicted that the chiral cyclohexane structure of the ligand would facilitate the lithiation step to afford one single stereoisomer. The two five-membered phospholane rings in the backbone of **3** are believed to restrict the conformational flexibility and lead to high enantioselectivity. In addition to the enantioselective induction, the two chiral cyclohexane rings on the backbone are expected to further increase the conformational rigidity of the ligand.



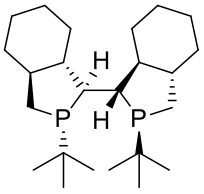
(*S,S',R,R'*)-TangPhos
1

only one enantiomer avaliable



(*S,S',R,R'*)-DuanPhos
2

resolution is needed

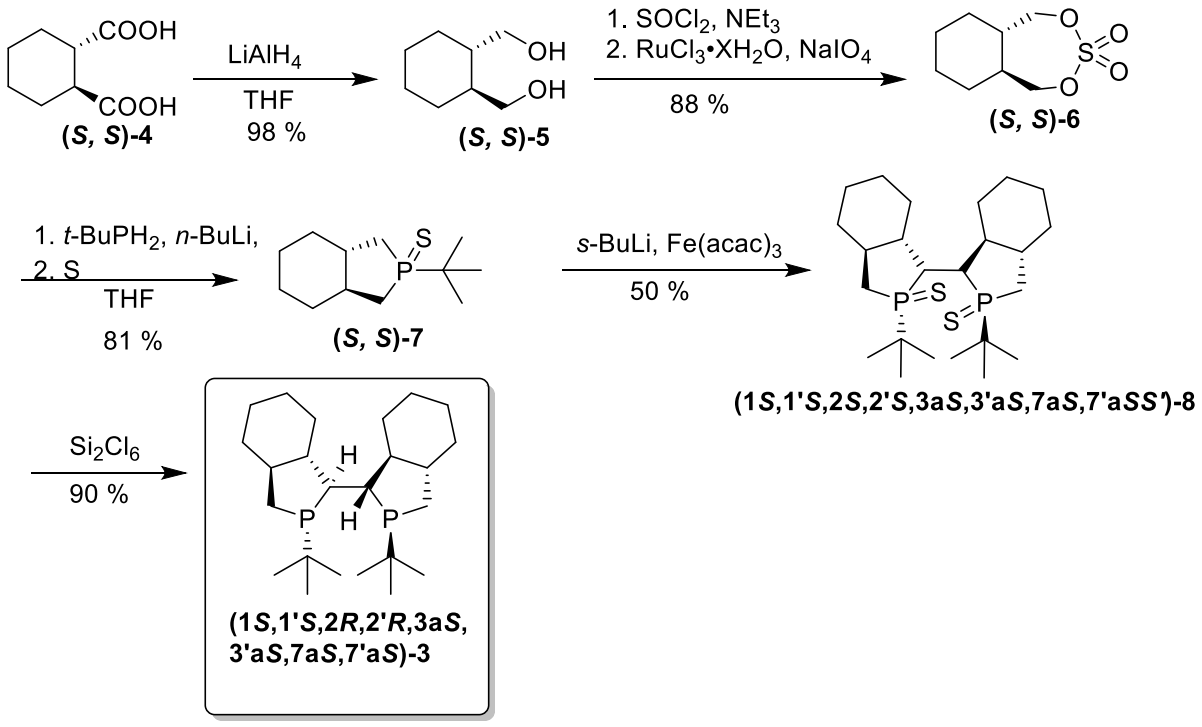


3

Both enantiomer are available through asymmetric synthesis

Scheme 1-2-1. Structure of three *P*-stereogenic phosphorus ligands.

Results and discussion

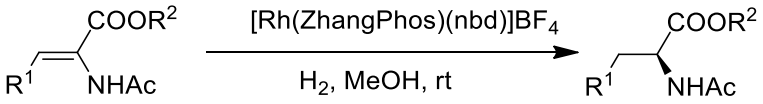


Scheme 1-2-2. Synthesis of ligand 3.

Ligand 3 was synthesized in a straightforward manner in five steps from a commercially available (*1S,2S*)-1,2-cyclohexanedicarboxylic acid **4**, which was reduced to chiral diol **5** quantitatively (Scheme 1-2-2). Cyclic sulfate **6** was synthesized according to a known procedure and was obtained in 88% yield.[4] Reaction of **6** with lithiated tert-butylphosphane and subsequent in situ protection with sulfur powder afforded enantiomerically pure phosphane sulfide **7**. A homocoupling mediated by $Fe(acac)_3$ in the presence of sec-butyllithium provided the C_2-symmetric bisphosphane sulfide **8** in 50% yield, along with recovered starting material **7** (25%). The absolute configuration of **8** was determined by X-ray crystallographic analysis. Desulfuration of **8** with hexachlorodisilane afforded ligand **3** as a white crystalline solid in 90% yield. Ligand **3** was then used in the rhodium-catalyzed hydrogenation of various prochiral

alkene derivatives. The cationic Rh complex, [Rh(ZhangPhos)(nbd)]BF_4 (**9**; nbd=3,5-norbornadiene), was prepared and used directly as the catalyst precursor.

Table 1-2-1. Rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)-acrylic acids and esters.[a]



10a-n 11a-n

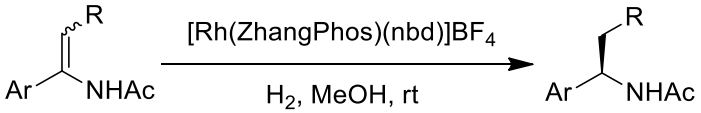
Entry	10	R^1	R^2	ee [%] [b]
1	a	H	Me	>99
2	b	*n*Pr	Me	>99
3	c	*i*Pr	H	>99
4	d	Ph	H	>99
5	e	Ph	Me	>99
6	f	*p*-FC_6H_4	H	>99
7	g	*p*-FC_6H_4	Me	>99
8	h	*p*-$MeOC_6H_4$	Me	>99
9	i	*p*-$CF_3C_6H_4$	Me	>99
10	j	*m*-BrC_6H_4	Me	>99
11	k	*o*-ClC_6H_4	Me	>99
12	l	2-thienyl	Me	>99
13	m	2-naphthyl	H	>99
14[c]	n	Ph	Me	>99

[a] The reactions were carried out at room temperature under 20 psi of H_2 in MeOH for 12 hours with 9 (1 mol%) as the catalyst precursor. Conversions were 100%. [b] The ee values were determined by GC or HPLC on a chiral stationary phase using a Chiralsil-VAL III FSOT or a Chiralcel OJ column, respectively. The ee values of the acids were determined for the corresponding methyl ester by treatment with $TMSCHN_2$. The absolute configurations of the products were determined as S by comparison of the retention times of two enantiomers with reported data, see reference 1a. [c] The protecting group on N was changed from Ac to Bz for this reaction. Bz=benzoyl, TMS=trimethylsilyl.

α-(Acylamino)acrylic acids and esters were hydrogenated under very mild conditions (in methanol at room temperature under 20 psi of H_2 for 12 h). Full conversions and extremely high enantioselectivities (>99% ee exclusively) were obtained in the hydrogenation of both α-(acylamino)acrylic acids and their ester derivatives (Table 1-2-1). The catalyst can tolerate a wide array of substituted phenyl rings and thio ring (Table 1-2-1, entries 5–12), as well as the *N*-

benzoyl derivative (Table 1-2-1, entry 14). To further evaluate the catalytic efficiency of the Rh–ZhangPhos system in asymmetric hydrogenation, methyl 2-acetamido-3-(4-fluorophenyl)acrylate (**10g**) was hydrogenated using 0.002 mol% of complex **9** under the same reaction conditions. In this way, (S)-11g was obtained with >99% ee in quantitative yield within 4 hours, thus indicating a high turnover number (TON= 50000) and a high turnover frequency (TOF=12 500 h^{-1}) for the Rh–ZhangPhos catalyst.

Table 1-2-2. Rhodium-catalyzed asymmetric hydrogenation of α-arylenamide.[a]



12a-k 13a-k

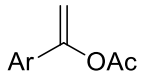
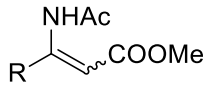
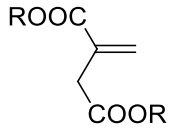
Entry	12	Ar	R	ee [%][b]
1	a	Ph	H	>99
2	b	*m*-MeC_6H_4	H	>99
3	c	*m*-$MeOC_6H_4$	H	>99
4	d	*m*-BrC_6H_4	H	>99
5	e	*p*-MeC_6H_4	H	>99
6	f	*p*-ClC_6H_4	H	>99
7	g	*p*-BrC_6H_4	H	>99
8	h	*p*-$MeOC_6H_4$	H	>99
9	i	2-naphthyl	H	>99
10	j	Ph	Me	>99
11	k	*p*-$CF_3C_6H_4$	Me	>99

[a] The reactions were carried out at room temperature under 20 psi of H_2 in MeOH for 12 hours with 9 (1 mol%) as the catalyst precursor. Conversions were 100%. For the E/Z ratio of 12j–k, see reference 5. [b] The ee values were determined by GC or HPLC on a chiral stationary phase using a Chiral Selective 1000 or a Chiralcel OD-H column, respectively. The absolute configurations of the products were determined as S by comparison of their retention times of two enantiomers with reported data.[1a]

A variety of β-arylenamides **12** were also hydrogenated with the Rh–ZhangPhos catalyst to afford enantiomerically pure amides (Table 1-2-2). Ee values of more than 99% were achieved exclusively in the hydrogenation of enamides **12**, regardless of the substituents on the phenyl ring (Table 1-2-2, entries 1–8). Rh–ZhangPhos also showed tolerance to the E/Z mixture of trisubstituted enamides and gave excellent enantioselectivity (Table 1-2-2, entries 10 and 11).

High turnover (10 000) was also obtained in the hydrogenation of N-(1-(4-bromophenyl)vinyl)-acetamide (**12g**) with > 99% ee in quantitative yield. These results are among the best reported todate.

Table 1-2-3. Rhodium-catalyzed asymmetric hydrogenation of enol acetates, *β*-(acetylamino)acrylates and itaconic acid derivatives.[a]

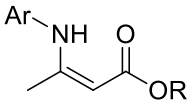
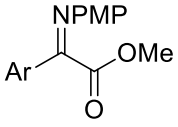
Entry	Substrate	ZhangPhos ee [%][b]	TangPhos [%][b]
			
1	14a Ar = Ph	97 (*S*)	96 (*R*)
2	14b Ar= *p*-FC_6H_4	98 (*S*)	92 (*R*)
3	14c Ar= *p*-ClC_6H_4	97 (*S*)	97 (*R*)
4	14d Ar= *p*-$NO_2C_6H_4$	>99 (*S*)	99 (*R*)
5	14e Ar= 2-naphthyl	99 (*S*)	97 (*R*)
			
6	15a R= Me (*E*)	>99 (*S*)	99 (*R*)
7	15b R= Me (*Z*)	97 (*S*)	97 (*R*)
8	15c R= Et (*E*)	>99 (*S*)	99 (*R*)
9	15d R= Ph (*Z*)	95 (*R*)	94 (*S*)
10	15e R= *o*-MeC_6H_4 (*Z*)	92 (*R*)	74 (*S*)
			
11	16a R= Me	>99 (*R*)	99 (*S*)
12	16b R= H	>99 (*R*)	99 (*S*)

[a] The reactions were carried out at room temperature under 20 psi of H_2 for 12 hours with 9 (1 mol%) as the catalyst precursor. Conversions were 100%. Solvent was ethyl acetate for 14, THF for 15 and 16. [b] The ee values were determined by GC or HPLC on a chiral stationary phase.

The two chiral cyclohexane rings fused on the phospholane rings are expected to make ZhangPhos more conformationally rigid and electron-rich than TangPhos. It has been demonstrated that high rigidity and a well-defined structure are beneficial to achieving high enantioselectivity.[6] As shown in Table 1-2-3, Rh–ZhangPhos gave higher or comparable

enantioselectivities compared to Rh–TangPhos in the hydrogenation of another three types of prochiral olefins: enol acetates **14** (Table 1-2-3, entries 1–5), *β*-(acetylamino)acrylates **15** (Table 1-2-3, entries 6–10), and itaconic acid derivatives **16** (Table 1-2-3, entries 11 and 12). For the hydrogenation of aromatic enol acetates, which serves as an alternative to direct hydrogenation of ketones, increase of enantioselectivity was observed by using Rh–ZhangPhos as the catalyst, especially for **14b** (from 92% to 98% ee; Table 1-2-3, entry 2). *β* -(Acetylamino) acrylates remain challenging substrates for asymmetric hydrogenation, which can form nonnatural chiral *β* -aminoacids. With Rh–ZhangPhos, the hydrogenation of both E and Z isomers of *β* -(acetylamino)acrylates derivatives **15** gave high enantioselectivities (from 92% to more than 99% ee). In particular, for ortho-substituted substrate **15e**, a significant increase in enantioselectivity (from 74% to 92% ee) was obtained with the Rh–ZhangPhos complex (Table 1-2-3, entry 10).

Table 1-2-4. Rhodium-catalyzed asymmetric hydrogenation of *N*-aryl *β*- enamino esters and *α*-aryl imino esters.[a]

Entry	Substrate	ZhangPhos ee [%][b]	TangPhos ee [%][b]
			
1	17a Ar= Ph, R= Me	93 (+)	91 (-)
2	17b Ar= Ph, R= Et	96 (+)	95 (-)
3	17c Ar= *p*-FC_6H_4, R= Et	98 (+)	96 (-)
			
4	18a Ar= Ph	97 (*R*)	95 (*S*)
5	18b Ar= *o*-$MeOC_6H_4$	97 (+)	95 (-)

[a]For 17, the reactions were carried out at 50 ^oC in TFE under 6 atm of H_2 for 18 hours with 9 (1 mol%). For 18, the reactions were carried out at 50 ^oC in CH_2Cl_2 under 50 atm of H_2 for 24 hours with 9 (1 mol%). Conversions were 100%. [b] The ee values were determined by GC or HPLC on a chiral stationary phase. PMP=para-methoxyphenyl, TFE=trifluoroethanol.

In asymmetric catalysis, the enantioselectivity generally decreases at high temperature as a result of the ligand flexibility. The conformationally rigid cyclohexane rings were expected to reduce the flexibility of ligand **3** and sustain high enantioselectivity at high temperature. Indeed, some preliminary results of hydrogenations requiring higher temperature showed that ZhangPhos has better tolerance to high temperature than TangPhos. As shown in Table 1-2-4, the hydrogenation of *N*-aryl *β*-enamino esters **17** (Table 1-2-4, entries 1–3) and *α*-aryl imino esters **18** (Table 1-2-4, entries 4 and 5), where a temperature of 50^{o}C was needed, Rh–ZhangPhos delivered higher enantioselectivities than Rh–TangPhos. Thus it is expected that ZhangPhos will have promising applications in asymmetric catalytic processes at elevated temperatures.

Conclusion

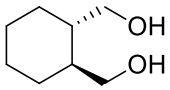
We have designed and developed a new highly electron-rich, *P*-stereogenic bisphospholane ligand (ZhangPhos), which can be synthesized practically and highly enantioselectively from a commercially available chiral reagent. Ligand **3** exhibited extremely high enantioselectivities (up to 99% ee) and reactivities (up to 50 000 TON) for rhodium-catalyzed hydrogenation of a wide range of functionalized olefin derivatives.

Experiment section

General Methods. Starting materials, reagents and solvents were purchased from commercial sources and were used as received**.** All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents

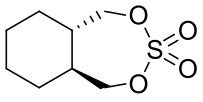
0.25 mm silica 60-F plates. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns. HPLC analysis was carried out on Agilent 1200 series. Compound **3** ((1*S*,2*S*)-1,2-cyclohexanedicarboxylic acid**)** is commercial available from TCI America or synthesized according reference.[7]

Ligand synthesis procedure



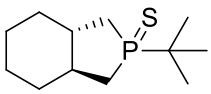
(*S, S*)-5

(1S,2S)-Cyclohexane-1,2-diyldimethanol (5). To a suspension of $LiAlH_4$ (6.76 g, 178.0 mmol) in anhydrous THF (150 mL) was added (*S, S*)-**4** (12.25 g, 71.2 mmol) in portions at 0 ˚C. The mixture was stirred at room temperature overnight and then heated at 60 ˚C for 5 h. The reaction was cooled to r.t. and quenched with H_2O (10 mL) slowly at 0 ˚C (Caution: vigorous gas evolved). An aqueous solution of NaOH (40 mL, 15 % w/w) was added and stirred for 1h. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (150 mL) for three times. The combined organic extracts were dried over Na_2SO_4. Removing the solvent under vacuum afforded (*S, S*)-**4** as a white solid (9.85 g, 98 % yield, pure enough for next use). $[\alpha]^{24}_{D}$ = -21.7 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.09 (s, 2H), 3.61 (dd, *J* = 10.9, 6.4 Hz, 2H), 3.53 (dd, *J* = 10.9, 6.4 Hz, 2H), 1.75-1.73 (m, 2H), 3.61 (dd, *J* = 16.8, 1.6 Hz, 2H), 1.35-1.31 (m, 2H), 1.27-1.22 (m, 2H), 1.08-1.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.8, 44.6, 29.9, 26.1 ppm.



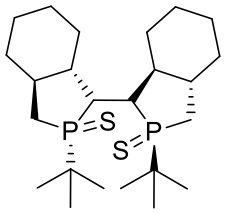
(*S*, *S*)-6

(5a*S*,9a*S*)-octahydrobenzo[*e*][1,3,2]dioxathiepine 3,3-dioxide (6). To a solution of (*S*, *S*)-**5** (5.16 g, 35.8 mmol) and triethylamine (19.95 mL, 143.2 mmol) in 120 mL of CH_2Cl_2 was added thionyl chloride (3.94 mL, 53.7 mmol) dropwise at 0 ˚C. The resulting dark brown solution was stirred at 0 ˚C for 1 h. The reaction was then quenched with water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was passed a short silica gel plug (CH_2Cl_2 as eluent) to afford crystalline crude cyclic sulfite (6.61 g. 34.7 mmol). The crude product was dissolved in a mixture of acetonitrile, chloroform and water (50, 50, 75 mL respectively). $NaIO_4$ (11.50 g, 53.7 mmol) and $RuCl_3 \cdot xH_2O$ (120 mg) were added at 0 ˚C. After vigorous stirring at 0 ˚C for 1.5 h, the reaction mixture was added brine (75 mL) and filtered. The organic layer of the filtrate was separated. The aqueous layer was washed with CH_2Cl_2 (50 mL) twice. The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting solid residue was purified by passing through a short silica gel plug (CH_2Cl_2 as eluent) to give (*S*, *S*)-**6** as a white solid (6.47 g, 88%). $[\alpha]^{24}_D$ = +64.6 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.30 (dd, *J* = 12.0, 9.6 Hz, 2H), 4.10 (dd, *J* = 12.0, 2.4 Hz, 2H), 1.91-1.82 (m, 2H), 1.78-1.68 (m, 2H), 1.65-1.62 (m, 2H), 1.40-1.26 (m, 2H), 1.06-0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.6, 44.0, 27.4, 25.5 ppm; HRMS (ESI): *m*/*z*: calcd for $C_8H_{14}O_4NaS$ ($[M+Na]^+$): 229.0510; found: 229.0505.



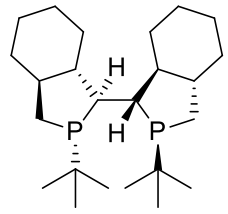
(*S*, *S*)-7

(3a*S*,7a*S*)-2-(*tert*-butyl)octahydro-1*H*-isophosphindole 2-sulfide (7). To a mixture of *tert*-butyl phosphine solution (24.48 mL, 20 % v/v in octane, 30.0 mmol) and THF (80 mL) was added *n*-BuLi (12.0 mL, 2.5 M in hexane, 30.0 mmol) dropwise at -78 ˚C. The resulting yellow solution was allowed to warm to r.t. and stirred for 1 h. The reaction mixture was then cooled back to -78 ˚C and was added a solution of (*S*, *S*)-**6** (6.19 g, 30.0 mmol) in THF (50 mL) dropwise. The resulting solution was allowed to warm to r.t. and stirred for 4 h. After being cooled to -78 ˚C again, *n*-BuLi (12.0 mL, 2.5 M in hexane, 30.0 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred overnight. After being quenched with degassed water (5.0 mL), sulfur powder (1.44 g, 45 mmol) was added as a portion. After being stirred for 2 h, the solvent was removed and the residue was dissolved in 200 mL ethyl acetate. The organic layer was washes with water (100 mL) and brine (100 mL) subsequently, and then dried over Na_2SO_4 and concentrated. The residue was passed a short alumina plug (ethyl acetate as eluent) and followed by recrystallization from hexane to give (*S*, *S*)-**7** as white crystals (5.59 g, 81%). $[\alpha]^{24}_D$ = -45.2 (c = 1.0, $CHCl_3$) at > 99 % *ee*; Enantiomeric excess was determined by HPLC analysis: Daicel ChiralPak AD, hexane/*i*PrOH = 99:1, flow rate = 1.0 mL/min, λ = 205 nm, t_{major} = 11.4 min, t_{minor} = 13.2 min; ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.53 (ddd, *J* = 14.8, 6.8, 2.8 Hz, 1H), 2.01-1.76 (m, 7H), 1.57-1.46 (m, 1H), 1.37-1.10 (m, 14H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 46.8 (d, J_{CP} = 3.3 Hz), 43.7 (d, J_{CP} = 4.4 Hz), 38.5 (d, J_{CP} = 47.1 Hz), 36.9 (d, J_{CP} = 48.5 Hz), 33.7 (d, J_{CP} = 14.3 Hz), 33.4 (d, J_{CP} = 13.2 Hz), 33.1 (d, J_{CP} = 15.6 Hz), 26.4 (d, J_{CP} = 1.5 Hz), 26.3 (d, J_{CP} = 1.5 Hz), 25.1 (d, J_{CP} = 2.1 Hz) ppm; ^{31}P NMR (162 MHz, CD_2Cl_2) δ: 75.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{23}NaPS$ ($[M+Na]^+$): 253.1156; found: 253.1151.



(1*S*,1'*S*,2*S*,2'*S*,3a*S*,3'a*S*,7a*S*,7'a*SS'*)-8

(1*S*,1'*S*,2*S*,2'*S*,3a*S*,3'a*S*,7a*S*,7'a*S*)-2,2'-di-*tert*-butylhexadecahydro-1*H*,1'*H*-[1,1'-bi isophosphindole] 2,2'-disulfide (8). To a solution of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (3.03 mL, 20.2 mmol) in Et_2O (35 mL) was added *s*-BuLi (14.4 mL, 1.4 M in hexane, 20.2 mmol) dropwise at -78 °C. After being stirred for 0.5 h, a solution of (*S*, *S*)-**7** (3.87 g, 16.8 mmol) in toluene (25 mL) was added dropwise. The reaction mixture was then stirred at -78 °C for 5 h. A solution of $Fe(acac)_3$ (8.91g, 25.2 mmol) in toluene (45 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 12 h. After washing with 100 mL aqueous HCl (2N) three times, the organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography with ethyl acetate and hexane as eluent (1:20 v/v) to afford **(1*S*,1'*S*,2*S*,2'*S*,3a*S*,3'a*S*,7a*S*,7'a*S*)-8** as white solid (1.93 g, 50.0 %). The crystalline product was obtained by recrystallization from ethyl acetate and hexane. $[\alpha]^{24}_D$ = -48.2 (c = 0.9, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.19 (dd, *J* = 12.8, 10.4 Hz, 2H), 2.57-2.54 (m, 2H), 2.02-2.00 (m, 4H), 1.87-1.76 (m, 4H), 1.64-1.52 (m, 4H), 1.34-0.86 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 47.6 (t, J_{CP} = 4.2 Hz), 42.4 (t, J_{CP} = 2.4 Hz), 37.5 (m), 37.1 (m), 35.1 (t, J_{CP} = 1.3 Hz), 34.6 (m), 34.4 (m), 26.7, 26.4, 26.2, 25.3 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 85.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{45}P_2S_2$ ([*M*+H]+): 459.2438; found: 459.2432.



(1*S*,1'*S*,2*R*,2'*R*,3a*S*,
3'a*S*,7a*S*,7'a*S*)-3

(1*S*,1'*S*,2*R*,2'*R*,3a*S*,3'a*S*,7a*S*,7'a*S*)-2,2'-di-*tert*-butylhexadecahydro-1*H*,1'*H*-1,1'-bi isophosphindole (3) (ZhangPhos).

To a solution of **8** (0.61 g, 1.33 mmol) in anhydrous degassed benzene (25 mL) was added Si_2Cl_6 (3.42 mL, 19.9 mmol) dropwise. The mixture was stirred under reflux and monitored by ^{31}P NMR . 12h later, the solution was cooled to r.t. and added degassed aqueous NaOH solution (50 mL, 30 % w/w) in an ice bath (caution: vigorous HCl gas evolved). The resulting mixture was then stirred at 50 °C until the queous layer became clear (about 2 h). The aqueous layer was washed twice with degassed benzene (30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum to around 1 mL. The solution was subjected a basic alumina plug with a mixture of Et_2O (10 mL) and hexanes (50 mL) as eluent under N_2. Concentration the resulted solution in vacuum afforded white crystalline **(1*S*,1'*S*,2*R*,2'*R*,3a*S*,3'a*S*,7a*S*,7'a*S*)-ZhangPhos** (0.47 g, 90 %). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.98-1.95 (m, 2H), 1.90-1.87 (m, 4H), 1.75-1.68 (m, 6H), 1.53-1.30 (m, 4H), 1.19-0.85 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.3 (t, J_{CP} = 4.3 Hz), 47.1 (m), 445.3 (t, J_{CP} = 3.4 Hz), 34.7, 31.9, 29.3 (t, J_{CP} = 7.1 Hz), 29.0 (t, J_{CP} = 7.1 Hz), 28.6 (t, J_{CP} = 6.8 Hz), 26.3, 25.9 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 11.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{45}P_2$ ([*M*+H]+): 395.2996; found: 395.2991.

Preparation of Rh complex {Rh[(1*S*,1'*S*,2*R*,2'*R*,3a*S*,3'a*S*,7a*S*,7'a*S*)-3](nbd)}BF_4 (**9**). To a solution of $[Rh(nbd)_2]BF_4$ (67.3 mg, 0.18 mmol) in degassed THF (1 mL) at -10 °C was added a solution of **(1*S*,1'*S*,2*R*,2'*R*,3a*S*,3'a*S*,7a*S*,7'a*S*)-3** (ZhangPhos) (74.6 mg, 0.189 mmol) in THF (2

mL). The resulting red solution was allowed to warm to r.t. and stirred for 15 min. The solution was concentrated to about 1 mL and then was added degassed Et_2O (12 mL) under vigorous stirring. The resulting precipitate was filtered, further washed with ether (3 x 10 mL) for three times, and dried under vacuum to afford **9** as an brown solid (79.1 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.69 (s, 2H), 5.60 (s, 2H), 4.20 (m, 2H), 2.43-2.38 (m, 2H), 2.08-2.01 (m, 4H), 1.87-1.75 (m, 8H), 1.43-1.38 (m, 2H), 1.22-0.90 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 100.0, 91.0 (m), 80.4 (m), 77.2, 71.8 (m), 65.8, 55.4, 50.5, 47.5 (m), 45.4, 33.6 (m), 33.0 (m), 31.4 (m), 31.0 (m), 28.7 (m), 25.8, 25.6, 15.35 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 96.9 (d, J_{Rh-P} = 153.3 Hz) ppm; HRMS (ESI): *m*/*z*: calcd for $C_{31}H_{52}P_2Rh$ ([*M*]+): 589.2599; found: 589.2587.

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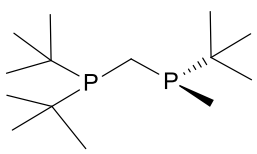
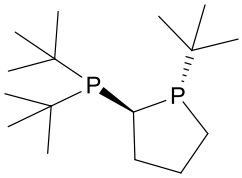
1.3 Synthesis of a novel three indered quadrant bisphosphine ligand

Background

As a result of the huge success of ligands such as DIPAMP and BINAP, C_2-symmetry has remained a popular design for chiral bisphosphine ligands. On the other hand, the development of C_1-symmetrical bisphosphine ligands and their corresponding hydrogenation catalysts has been delayed to some extent.[1] Recently, Hoge reported the synthesis of a bisphosphine ligand **1** (trichickenfootphos) with a three hindered quadrant diagram feature.[2] The corresponding rhodium complex showed good enantioselectivity and activity towards a variety of prochiral alkenes in asymmetric hydrogenation. However, the ligand synthesis relies on HPLC chiral separation, which could limit its large scale production and application in industry. We envision that three blocked quadrant bisphosphorus ligands based on *P*-chiral phosphocyclic motif could also be a good C_1-symmetric design.[3] By using the ZhangPhos monomer discribed in the last section, we should be able to get one single stereoisomer so that a preparative HPLC purification would not be necessary for the ligand synthesis.



1 trichickenfootphos

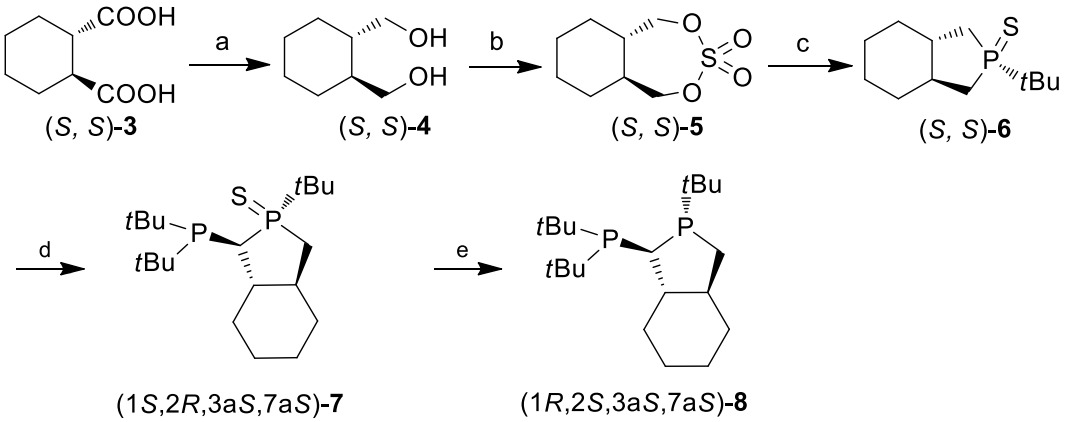


2 Ligand design based on phospholane rings

Results and discussion

The synthesis of ligand started from the synthesis of the ZhangPhos monomer (Scheme 1-3-1). Subsequent ortho-lithiation with *t*BuLi/TMEDA at -78˚C in HMPA/THF, followed by phosphinylation with di(*tert*-butyl)chlorophosphine provided **7** as a single diastereomer. The stereospecific phosphinylation was due to the induction of the chiral cyclohexane ring

structure. The di-*tert*butyl phosphine group is stable to air in this case. The absolute configuration of **7** was confirmed by its X-ray crystallographic structure (Fig. 1-3-1). Desulfurization of **7** with hexachlorodisilane in toluene provided ligand **8** in 91% yield. [4]



Scheme 1-3-1. Synthesis of ligand **8**. Reagents and conditions: a) $LiAlH_4$, 98 %; b) i. $SOCl_2$, NEt_3, ii. $RuCl_3$•XH_2O, $NaIO_4$, 88 %; c) *t*BuPH$_2$, *n*BuLi, S, 81 %; d) *t*BuLi, TMEDA, *t*Bu$_2$PCl, 52 %, e) Si_2Cl_6, toluene, 91 %.

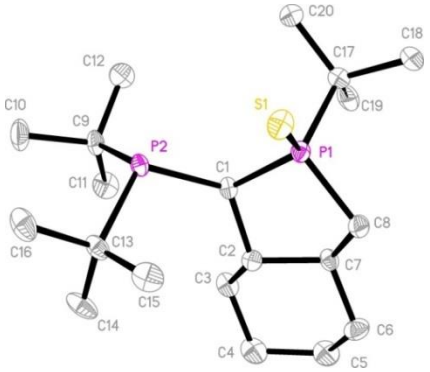
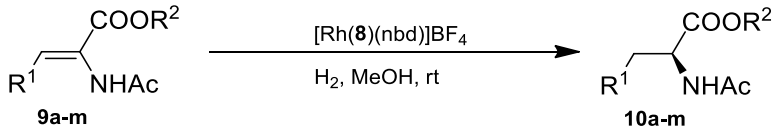


Fig. 1-3-1. ORTEP view (50% probability thermal ellipsoids) of **7**.

In order to examine the catalytic properties of **8**, a cationic Rh complex Rh[(**8**)(nbd)]BF_4 (nbd = norbornadiene) was prepared and used as the catalyst precursor in the hydrogenation of various prochiral alkenes. α-(Acylamino)acrylic acids and esters were hydrogenated at rt in methanol under 50 psi of hydrogen (Table 1-3-1).

Table 1-3-1. Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters.[a]



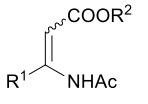
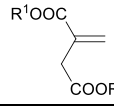
Entry	R^1 , R^2	s/c ratio	t (h)	ee [%][b]
1	Ph, Me (**9a**)	500	0.5	>99
2	Ph, Me (**9a**)	1000	12	>99
3	Ph, Me (**9a**)	5000	12	99
4	Ph, Me (**9a**)	10000	24	98
5	Ph, H (**9b**)	1000	12	>99
6	4-F-Ph, Me (**9c**)	1000	12	>99
7	4-Cl-Ph, Me (**9d**)	1000	12	>99
8	4-Br-Ph, Me (**9e**)	1000	12	>99
9	4-MeO-Ph, Me (**9f**)	1000	12	>99
10	3-Br-Ph, H (**9g**)	1000	12	>99
11	3-Br-Ph, Me (**9h**)	1000	12	>99
12	3,5-F_2-Ph, Me (**9i**)	1000	12	>99
13	2-Cl-Ph, Me (**9j**)	1000	12	99
14	2-Thienyl, Me (**9k**)	1000	12	>99
15	H, H (**9l**)	1000	12	>99
16	*n*-Pr, Me (**9m**)	1000	12	99

[a] The reactions were carried out at rt under 50 psi H_2 in MeOH. Conversions were 100 %. [b] The ee values were determined by chiral GC (Chiralsil-VAL III FSOT). The ee values of the acids were determined on the corresponding methyl ester by treatment with $TMSCHN_2$. The absolute configurations of the products were determined as *S* by comparison of their retention times of two enantiomers with reported data.

Excellent enantioselectivities and full conversion were achieved for an array of α–acetamidocinnamic acids and their esters with different substituted groups (entry 5-13). To further test the catalytic reactivity of Rh-**8**, methyl α-(acetamido)-2-phenylacrylate (**9a**) was

hydrogenated with 0.02 mol % complex Rh-**8** under the same reaction conditions without compromising the enantioselectivity (entry 3). High turnover (10000 TON) was also achieved with an excellent ee (98%) for the same substrate (entry 4). Moreover, the hydrogenation of **9a** proceeded to completion within 30min at a S/C ratio of 500 under the same reaction conditions (entry 1).

Table 1-3-2. Rh-catalyzed asymmetric hydrogenation of β-(acetylamino) acrylates and itaconic acid derivatives.[a]

Entry	Substrate (geometry)	R^1, R^2	ee[b] [%]	config
1		Me, Me ((E)-**11a**)	98	*S*
2		Me, Me ((Z)-**11a**)	97	*S*
3		Me, Et ((Z)-**11b**)	97	*S*
4		Ph, Me ((E/Z)-**11c**)	95	*R*
5		4-F-Ph, Me ((E/Z)-**11d**)	94	*R*
6		4-Me-Ph, Me ((E/Z)-**11e**)	94	*R*
7		H, H (**12a**)	97	*R*
8		Me, H (**12b**)	98	*R*
9		Me, Me (**12c**)	98	*R*

[a] The reactions were carried out at rt under 50 psi H_2 in MeOH for 12 h in the presence of 0.2 mol % Rh[(**8**)(nbd)]BF_4 as the catalyst precursor. Conversions were 100 %. For the *E*/*Z* ratio of 11c-e, see reference 5. [b] The ee values were determined by chiral GC (betadex-390 or gamadex-225). The absolute configurations of the products were determined by comparison of their retention times of two enantiomers with reported data.

Asymmetric hydrogenation of β-(acetamido)acrylate derivatives is one of the most efficient and practical ways to obtain unnatural enantiomerically enriched β-amino acids. But it still remains much less successful compared to the hydrogenation of their α-analogues.[6] The hydrogenation with Rh-**8** complex was carried out at rt in methanol for 12h under 50 psi of hydrogen with a 0.2 mol % catalyst loading. High enantioselectivities (97-98% ee's) were achieved for both (*Z*) and (*E*)-methyl β-(acetylamino)acrylates (Table 1-3-2, entry 1-2). An

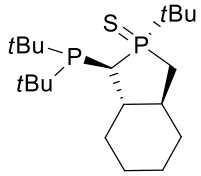
E/*Z* mixture of *β*-phenyl-*β*-(acylamino)acrylate substrate was also hydrogenated with the Rh-**8** catalyst to provide the chiral *β*-amino acid derivative in 95% ee (entry 4). Itaconic acid and its methyl esters were also hydrogenated under the same reaction conditions to afford excellent ee's (up to 98%, entry 7-9).

Conclusion

We have designed and synthesized a new rigid three hindered quadrant bisphosphine ligand based on the phosphocyclic motif. The ligand is proved to be a practical ligand for the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins, with high enantioselectivities (up to 99 % ee) and reactivities (up to 10,000 TON).

Experiment section

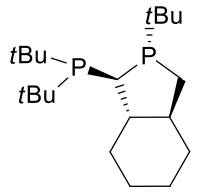
Ligand synthesis procedure



(1*S*,2*R*,3a*S*,7a*S*)-**7**

(1*S*,2*R*,3a*S*,7a*S*)-2-(*tert*-butyl)-1-(di-tert-butylphosphino)octahydro-1*H*-isophosphindole 2-sulfide (7). At -78 ˚C, to a solution of **6** (0.7 g, 3 mmol), TMEDA (0.55 mL,3.6 mmol), HMPA (0.62 mL, 3.6 mmol) in THF (35 mL) was added dropwise *t*BuLi (2.1 mL, 1.7 M in pentane, 3.6 mmol). The reaction mixture was stirred at -78 ˚C for 1 h, followed by slow addition of a solution of P*t*Bu$_2$Cl (0.59 mL, 3.1 mmol) in 10 mL of THF at the same temperature in 10 min. The resulting mixture was stirred at -78 ˚C for another 10 min, then allowed to slowly warm to rt and stirred overnight before quenching with NH_4Cl (aq). The organic layer was extracted with ether (3×15 mL) and washed with brine (10 mL), dried over Na_2SO_4, and concentrated under

reduced pressure. The residue was purified by flash column chromatography on silica gel (hexenes/EtOAc, 90:10) to afford **7** as a white solid (0.56g, 52%).$[\alpha]^{24}_{D}$ = -37.8(c = 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (ddd, *J* =22.1, 11.6, 1.5 Hz, 1H), 2.17-2.14(m, 1H), 1.98-1.94 (m, 2H), 1.83-1.69 (m, 5H), 1.42-1.38 (m, 10H), 1.24-1.18 (m, 23H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.0 (q, *J* = 63.5, 39.3 Hz), 48.5 (t, *J* = 4.4 Hz), 42.2 (d, *J* = 6.2 Hz), 37.0 (d, *J* = 1.1 Hz), 36.6 (d, *J* = 1.2 Hz), 36.1 (d, *J* = 3.2 Hz), 35.6 (d, *J* = 3.5 Hz), 35.5 (d, *J* = 6.4 Hz), 35.1 (d, *J* = 6.5 Hz), 34.5 (d, *J* = 14.1 Hz), 33.6 (d, *J* = 15.5 Hz), 33.0 (d, *J* = 7.2 Hz), 32.8(d, *J* = 16.1 Hz), 30.5 (d, *J* = 15.2 Hz), 26.4 (d, *J* = 1.9 Hz), 25.8 (d, *J* = 1.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 80.1(d, *J* = 103.6 Hz), 33.4 (d, *J* = 103.6 Hz); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{40}P_2S$ ($[M+H]^+$): 375.2404; found: 375.2411.



(1*R*,2*S*,3a*S*,7a*S*)-**8**

(1*S*,2*R*,3a*S*,7a*S*)-2-(*tert*-butyl)-1-(2,2,4,4-tetramethylpentan-3-yl)octahydro-1*H*-isophosphindole (8). To a solution of **7** (0.36 g, 1 mmol) in anhydrous degassed toluene (10 mL) was added Si_2Cl_6 (0.86 mL, 5.0 mmol) dropwise. The mixture was stirred at 70 ˚C for 10h. The solution was cooled to r.t. and added degassed aqueous NaOH solution (20 mL, 30 % w/w) in an ice bath. The resulting mixture was then stirred at 50 ˚C until the aqueous layer became clear. The aqueous layer was washed twice with degassed toluene (15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by passing through a basic alumina plug with a mixture of Et_2O (10 mL) and hexanes (50 mL) as eluent under N_2. Concentration the resulted solution in vacuum afforded **8** as colorless oil (0.29g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16-2.14 (m, 1H), 1.99-1.94 (m, 2H), 1.87-1.82 (m, 2H), 1.81-1.67(m, 5H), 1.36-1.28 (m, 13H), 1.25-1.1.09 (m, 13H), 1.08-0.97 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.4, 49.7, 49.5, 44. (d, *J* = 2.4 Hz), 34.3 (d, *J* = 2.5 Hz), 34.2, 33.7, 33.3, 31.9 (m), 31.5 (m), 30.5, 30.4 (d, *J* = 2.2 Hz), 30.3, 30.0, 29.7 (m), 29.4, 28.2 (m), 27.6, 27.5, 25.6 (d, *J* = 2.0 Hz),24.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 36.3 (br s), 10.1(br s); HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{40}P_2$ ([*M*+H]$^+$): 343.2684; found: 343.2682.

Preparation of Rh[(8)(NBD)]BF_4. To a solution of $[Rh(nbd)_2]BF_4$ (37.4 mg, 0.1 mmol) in degassed MeOH (1 mL) at 0 ˚C was added a solution of **8** (37.6 mg, 0.11 mmol) in THF (1 mL). The resulting red solution was allowed to warm to r.t. and stirred for 20 min. The solution was concentrated to about 1 mL and then was added degassed Et_2O (12 mL) under vigorous stirring. The resulting precipitate was filtered, further washed with ether (2×5 mL) twice, and dried under vacuum to afford red solid (43.6 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.65 (m, 4H), 4.23 (br s, 2H), 2.45-2.40 (m, 2H), 2.20-1.95 (m, 6H), 1.93-0.96 (m, 34H); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.1 (dd J = 128.7, 51.7Hz), -1.8 (dd J = 128.9, 52.1Hz) ;*m/z* (ESI-MS) 625.1 [M+H]$^+$.

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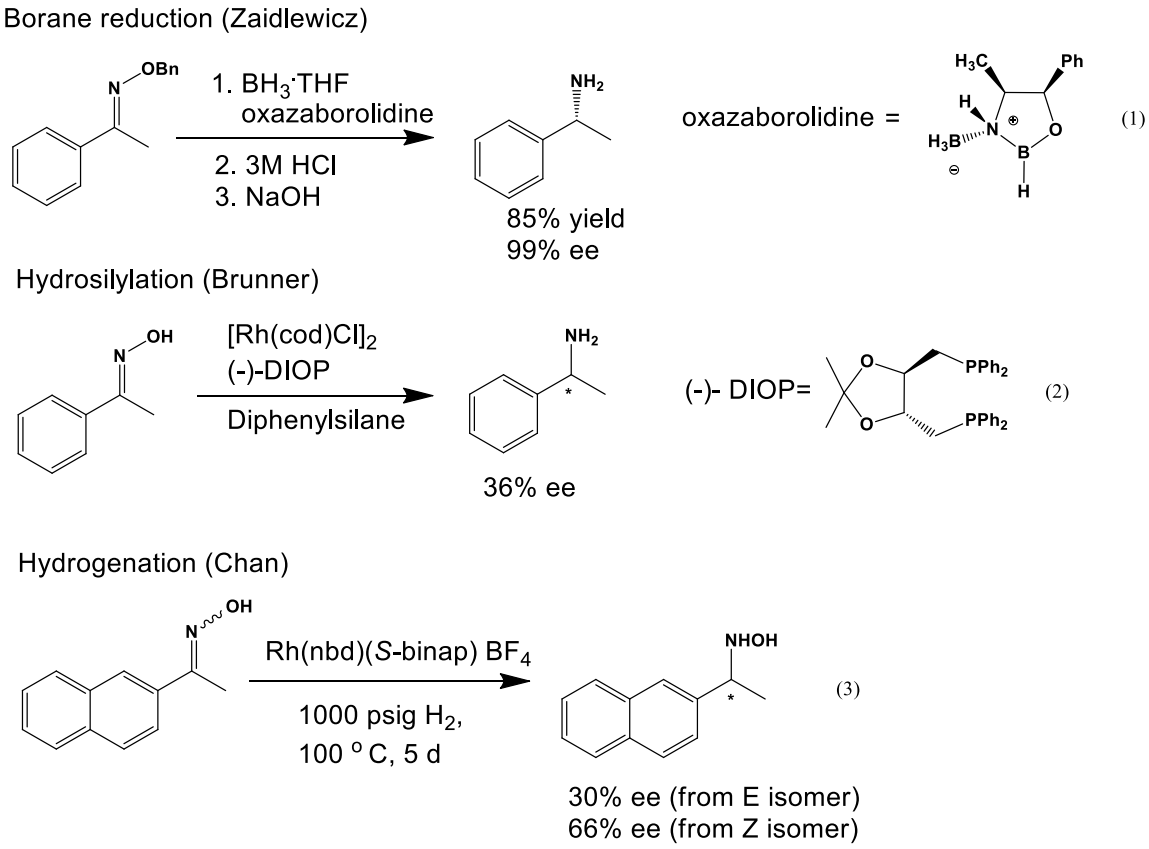
Chapter 2 Asymmetric hydrogenation of some novel substrates

2.1 Rhodium catalyzed enantioselective hydrogenation of oxime acetates

Introduction and background

Chiral amines and their derivatives are important synthetic targets and powerful pharmacophores for defining new pharmaceutical drugs.[1] In the past decade, many researchers have focused their efforts on the enantioselective synthesis of amines and tremendous progress has been made towards truly practical methods.[2] New concepts and optimized methods are still needed to achieve both the complete enantiocontrol and efficiency under different circumstances. The asymmetric reduction of oximes and their derivatives has been considered to be a facile and direct approach to chiral amine due to the ease of preparation and stability of oxime substrates.[3] However, this area has been less explored over the last 10 years and limited results have been achieved. Successful examples include borane-mediated reduction of oxime ethers.[4] Itsuno and co-workers reported the first catalytic borane reduction of *O*-benzyl oxime in 1987.[5] Recent research results from Fontaine, Zaidlewicz and Ortiz-Marciales's groups showed that chiral diphenylvalinolborane, oxazaborolidine and spiroborate esters could serve as remarkable catalysts to afford chiral amines with high enantioselectivities (Scheme 2-1-1, eq1).[6] Asymmetric hydrosilylation of ketoximes is another reliable approach for this transformation. Brunner and co-workers developed the rhodium-catalyzed asymmetric hydrosilylation of ketoximes using DIOP as ligand (up to 36% ee)[7] (Scheme 2-1-1, eq 2) Recently, Hidai reported asymmetric reduction of cyclic oximes by using Ph_2SiH_2 and a Ru-oxazolinylferrocenylphosphine catalyst.[8] Lipase/palladium-catalyzed asymmetric transformations of ketoximes to chiral amines were also reported by Park and Kim. [9]

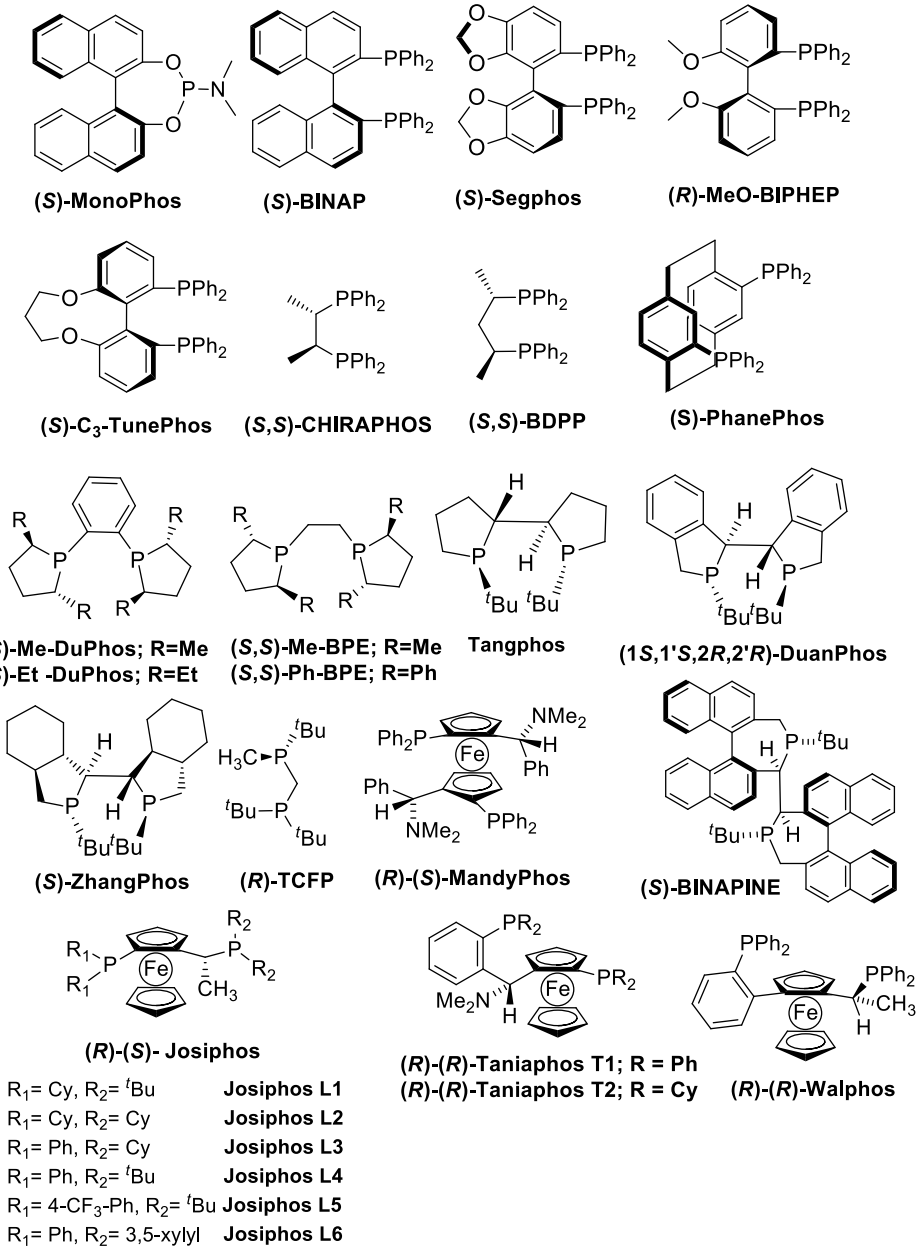


Scheme 2-1-1. Previous strategy for asymmetric reduction of oximes and oxime derivatives.

Prior to our work, reports of direct hydrogenation of simple ketoneoximes and their derivatives were rare.[10] A typical example was reported by Chan in 1995 for the catalytic asymmetric hydrogenation of 1-acetonaphthone oxime with Rh chiral phosphine catalysts (Scheme 2-1-1, eq 3). It should be noted that the reaction can only proceed under high temperature (100 ^{o}C) and with long reaction time (5 days).[10c] Inspired by the success of *N*-acetyl enamides and enol acetates as substrates for asymmetric hydrogenation, we envisioned that ketoneoxime acetates might be significant substrates for hydrogenation.[11] Recently, oxime esters have already gained much attention especially for their applications in coupling reactions.[12] Our report is the first enantioselective hydrogenation of ketoneoxime acetates.

Results and discussion

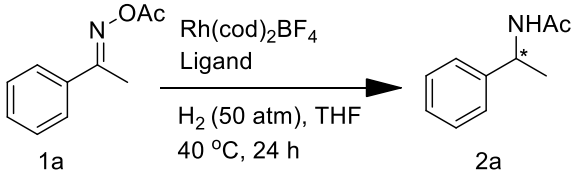
We began our study by investigating the hydrogenation of **1a** as the model substrate. After initial screening of different combinations of metal complexes and ligands (Figure 2-1-1), we were surprised to find that using Rh(I)/phosphine complexes as catalyst afforded the corresponding chiral acetamide as the major product, rather than *O*-acetyl-*N*-(1-phenylethyl)-hydroxylamine[11] (Table 2-1-1).



R_1= Cy, R_2= ^{t}Bu	**Josiphos L1**
R_1= Cy, R_2= Cy	**Josiphos L2**
R_1= Ph, R_2= Cy	**Josiphos L3**
R_1= Ph, R_2= ^{t}Bu	**Josiphos L4**
R_1= 4-CF_3-Ph, R_2= ^{t}Bu	**Josiphos L5**
R_1= Ph, R_2= 3,5-xylyl	**Josiphos L6**

Figure 2-1-1. Selected phosphine ligands tested for the reaction.

Table 2-1-1. Selected results from initial screening of chiral ligands for Rhodium-catalyzed hydrogenation of **1a.**[a]

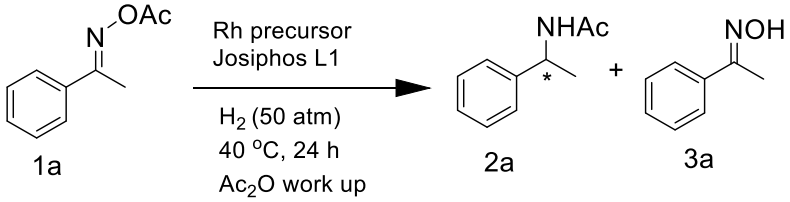


entry	ligand	conv[b] (%)	ee[c] (%)
1[e]	(*S*)-MonoPhos	<10	63
2	(*S*)-BINAP	10	14
3	(*R*)-MeO-BIPHEP	<5	n.d.
4	(*S*)- Segphos	15	3
5	(*S*)-C_3-TunePhos	17	5
6	(*S*,*S*)-CHIRAPHOS	10	35
7	(*S*,*S*)-BDPP	12	7
8	(*S*)-PhanePhos	14	19
9	(*S*,*S*)-Me-DuPhos	55	12
10	(*S*,*S*)-Et- DuPhos	52	27
11[d]	(*S*,*S*)-Me-BPE	55	37
12	(*S*,*S*)-Ph-BPE	18	64
13[d]	TangPhos	88	23
14[d]	(1*S*,1'*S*,1*R*,1*R*')-DuanPhos	82	15
15[d]	(*S*)-ZhangPhos	85	12
16[d]	(*S*)-BINAPINE	74	9
17[d]	(*R*)-TCFP	>95	2
18	(*R*)-(*S*)-Mandyphos	<5	2
19	(*R*)-(*R*)-Walphos	<5	9
20	(*R*)-(*R*)-Ph-Taniaphos T1	13	14
21	(*R*)-(*R*)-Cy-Taniaphos T2	90	1
22	**Josiphos L1**	**82**	**65**
23	Josiphos L2	78	61
24	Josiphos L3	40	17
25	Josiphos L4	35	47
26	Josiphos L5	20	3
27	Josiphos L6	<5	n.d.

[a]Unless otherwise mentioned, reaction conditions: $Rh(cod)_2BF_4$/ligand/substrate =1:1.1:10, at 40 ℃, under 50 atm of hydrogen for 24 h. [b] Conversions were determined by ^1H NMR of the crude product. [c] Determined by GC on a chiral phase. [d] $[Rh(cod)L]BF_4$ complex was used directly. [e] $Rh(cod)_2BF_4$/ligand = 1:2.1.

The MonoPhos ligand family was first tested and (*S*)- MonoPhos was found to afford the highest ee (63%). (Figure 2-1-1) However, low catalytic activity was observed under our screening conditions (conversions <10%). Atropisomeric bisphosphine ligands such as BINAP, SEGPHOS, MeO-BIPHEP and TunePhos were tested with up to 14% ee albeit with low conversions. Low catalytic activity was also observed with ligands such as BDPP, CHIRAPHOS and PhanePhos. Chiral bisphosphane ligands such as Me-DuPhos and Et-BPE improved the reaction conversions (up to 55%) and enantioselectivities (37% ee). Based on the ligand effect observed, we hypothesized that election rich phosphine ligands are more favored for this reaction. We then performed screening of some electron rich *P*-chiral ligands such as TangPhos, DuanPhos, ZhangPhos and BINAPINE. Up to 88% conversions were achieved by TangPhos and DuanPhos, however, only about 20% ee was provided. A three-hindered quadrant ligand TCFP gave almost complete conversion with low enantioselectivity (2% ee). We then focused on ferrocene-based ligands. Walphos and Mandyphos showed little activity for the reaction. Cy-Taniaphos ligand afforded good conversions, however, almost racemic products were observed. To our delight, when Josiphos L1 was tested in the reaction, 65% ee was achieved in THF with 82% conversion (Table 2-1-1, entry 22).

Table 2-1-2. Optimization of the reaction conditions. [a]



entry	Rh precursor	solvent	yield of **2a** (%)[b]	ee (%)[c]
1	$Rh(cod)_2BF_4$	CH_2Cl_2	78	25

2	$Rh(cod)_2BF_4$	THF	61	65
3	$Rh(cod)_2BF_4$	Toluene	57	45
4	$Rh(cod)_2BF_4$	Ethyl acetate	47	55
5	$Rh(cod)_2BF_4$	1,4-dioxane	63	62
6	$Rh(cod)_2BF_4$	MeOH	<5	n.d.
7	$Rh(cod)_2BF_4$	^{i}PrOH	<5	n.d.
8	$Rh(nbd)_2BF_4$	THF	59	65
9	$[Rh(cod)Cl]_2$ [d]	THF	48	68
10	$Rh(cod)_2SbF_6$	THF	65	75
11	**$Rh(cod)_2SbF_6$**	**1,4-dioxane**	**69**	**81**

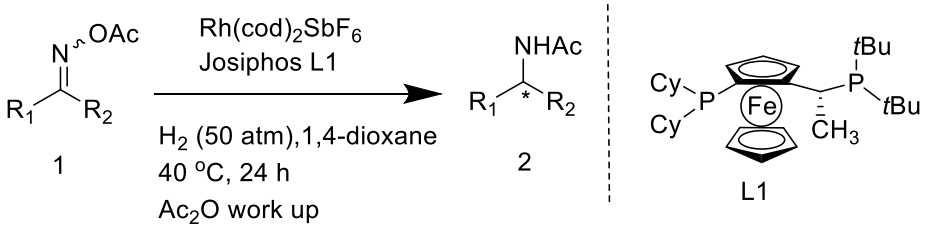
[a] Unless otherwise mentioned, reaction conditions: Rh precursor/ligand/substrate =1:1.1:10, at 40 ℃, under 50 atm of hydrogen for 24 h. [b] Determined by ^{1}H NMR of the crude product after acylation with Ac_2O. [c] Determined by GC on a chiral phase. [d] $[Rh(cod)Cl]_2$/L1 = 1: 2.2.

Solvent screening revealed that the reaction was most efficient when conducted in THF or 1,4-dioxane (Table 2-1-2). Moreover, protic solvents such as MeOH and ^{i}PrOH would completely lead to the corresponding oxime **3a** as final product. Further optimization showed that the enantioselectivity could be improved by using $Rh(cod)_2SbF_6$ as the Rh precursor in 1,4-dioxane. (81% ee)(Table 2-1-2, entry 11). The yield could be improved by acylation of the product with Ac_2O due to some primary amine remained during the process (no ee value change observed after acylation).

To further explore the efficiency and tolerance of the reaction, we subjected a series of substrates to asymmetric hydrogenation under the optimized conditions. Substrates bearing para-substituted methyl or ethyl groups gave 91% ee with moderate yields. (Table 2-1-3, entry 2-3) Substrates with para-substituted electron withdrawing groups on the aromatic ring were hydrogenated with good to high enantioselectivities (ee's up to 90%, entries 4-7). Methoxy group on the para-position caused dramatic loss of enantioselectivity (entry 8). Substrates with meta-substituted moiety on the aromatic ring also gave comparable results with up to 89% ee.

(entries 9-13). However, ortho-substituted groups on the aromatic ring dramatically lower the reactivity and enantioselectivities of the substrates (entries 15-17). Moreover, E/Z conformers of ortho-substituted substrates were often obtained as a mixture and difficult to separate them from each other. Loss of enantioselectivities and activities were also observed when substrates with bulkier R_2 groups were tested (entries 19-20).

Table 2-1-3. Substrate scope and limitations. [a]



entry	R_1	R_2	E/Z of **1**	yield [%][b]	ee [cd]
1	C_6H_4	Me	E (1a)	69	81 (*S*)
2	4-MeC_6H_4	Me	E (1b)	72	91 (*S*)
3	4-EtC_6H_4	Me	E (1c)	76	91
4	4-FC_6H_4	Me	E (1d)	80	90 (*S*)
5	4-ClC_6H_4	Me	E (1e)	72	86 (*S*)
6	4-BrC_6H_4	Me	E (1f)	76	85 (*S*)
7	4-$CF_3C_6H_4$	Me	E (1g)	71	73 (*S*)
8	4-MeOC_6H_4	Me	E (1h)	58	47 (*S*)
9	3-FC_6H_4	Me	E (1i)	70	84
10	3-$CF_3C_6H_4$	Me	E (1j)	65	82
11	3-ClC_6H_4	Me	E (1k)	66	89
12	3-BrC_6H_4	Me	E (1l)	74	83
13	3-MeC_6H_4	Me	E (1m)	63	76

14	3-$MeOC_6H_4$	Me	E (1n)	52	74
15	2-$MeOC_6H_4$	Me	E (1o)	48	41
16	2-$MeOC_6H_4$	Me	E/Z=5:1	51	39
17	2-Cl C_6H_4	Me	E/Z=3:1 (1p)	37	44
18	2-naphthyl	Me	E (1q)	68	60
19	C_6H_5	Et	E (1r)	41	61
20	C_6H_5	^{n}Pr	E (1s)	45	53

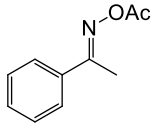
[a] Conditions: $Rh(cod)_2SbF_6$/ligand/substrate =1:1.1:10, in 1,4-dioxane, at 40 ℃, under 50 atm of hydrogen for 24 h. [b] Determined by ^1H NMR of the crude product after acylation with Ac_2O. [c] Determined by GC on a chiral phase. [d] Absolute configuration determined by comparison with literature.

The reaction mechanism is still not clear. Similar enantioselectivities given by the E/Z substrate conformers may suggest the N-O bond cleavage before the hydrogenation process (Table 2-1-3, entries 15-16). Cleavage of the N-O bond in oxime carboxylates has been established for Pd and Cu catalyzed systems,[12ab] but studies still remain rare for Rh(I) involved reactions. Moreover, acylation of chiral primary amine with oxime acetates were observed and considered responsible for the final amides formation.

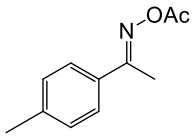
Conclusion

We have successfully applied Rh-catalyzed enantioselective hydrogenation of oxime acetates to give chiral acetamides, which afforded a new approach for the synthesis of chiral amines from oxime derivatives. Commercially available phosphorus-based ligands were screened and the highest enantioselectivities were achieved by the Josiphos ligand family.

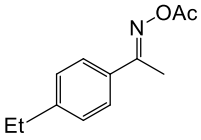
Experiment section



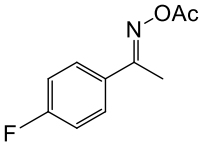
(*E*)-Acetophenone *O*-acetyloxime (1a) ^{1}H NMR (400 MHz, CDCl3) δ 2.27 (3H, s), 2.39 (3H, s), 7.42 (3H, m), 7.74 (2H, d, *J* = 8.2 Hz).



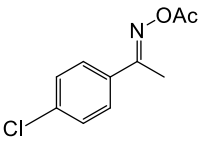
(*E*)-1-(4-Methylphenyl)ethanone *O*-acetyl oxime (1b) ^{1}H NMR (400 MHz, CDCl3) δ 2.26 (3H, s), 2.36 (6H, bs), 7.20 (2H, d, *J* = 8.0), 7.64 (2H, d, *J* = 8.4); ^{13}C NMR (100 MHz, CDCl3) δ 14.2, 19.8, 21.3, 126.9, 129.2, 131.9, 140.8, 162.3, 169.0.



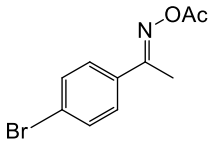
(*E*)-1-(4-Ethylphenyl)ethanone *O*-acetyl oxime (1c) ^{1}H NMR (400 MHz, CDCl3) δ 1.15 (3H, t, *J* =7.6 Hz) 2.17 (3H, s), 2.27 (3H, s), 2.58(2H, q, *J* =7.6 Hz), 7.14 (2H, d, *J*= 8.4 Hz), 7.58 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 13.2, 14.3, 18.8, 27.6, 125.9, , 127.0, 131.2, 146.1, 161.3, 168.0.



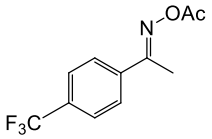
(*E*)-1-(4-Fluorophenyl)ethanone *O*-acetyl oxime (1d) ^{1}H NMR (400 MHz, CDCl3) δ 2.25 (3H, s), 2.36 (3H, s), 7.09 (2H, m), 7.74 (2H, m); ^{13}C NMR (100 MHz, CDCl3) δ 14.2, 19.7, 115.4, 115.7, 128.9, 129.0, 161.3, 162.9, 165.4, 168.7.



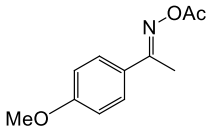
(*E*)-1-(4-Chlorophenyl)ethanone *O*-acetyl oxime (1e) ^{1}H NMR (400 MHz, CDCl3) δ 2.16 (3H, s), 2.26 (3H, s), 7.27 (2H, d, *J* = 8.4 Hz), 7.59 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 13.1, 18.7, 127.2, 127.7, 132.2, 135.6, 160.2, 167.6.



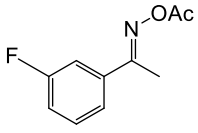
(*E*)-1-(4-Bromophenyl)ethanone *O*-acetyl oxime (1f) ^{1}H NMR (400 MHz, CDCl3) δ 2.26 (3H, s), 2.36 (3H, s), 7.53 (2H, d, *J* = 8.8 Hz), 7.62 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 14.1, 19.7, 125.1, 128.5, 131.8, 133.7, 161.3, 168.6.



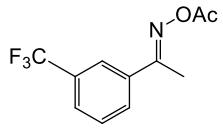
(*E*)-1-(4-trifluoromethyl)ethanone *O*-acetyl oxime (1g) ^{1}H NMR (400 MHz, CDCl3) δ 2.19 (3H, s), 2.32 (3H, s), 7.57 (2H, d, *J* = 8.4 Hz), 7.78 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 13.2, 18.6, 124.5, 126.3, 137.3, 160.1, 167.5.



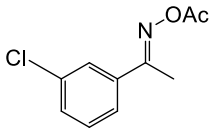
(*E*)-1-(4-Methoxyphenyl) ethanone *O*-acetyl oxime (1h) ^{1}H NMR (400 MHz, CDCl3) δ 2.23 (3H, s), 2.33 (3H, s), 6.89 (2H, d, *J* = 8.8 Hz), 7.70 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 13.1, 19.7,55.2, 113.5 , 113,8, 127.0, 128.2, 128.4, 129.6, 161.5, 161.8, 169.0, 171.0.



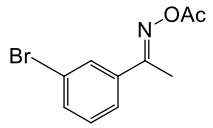
(*E*)-1-(3-Fluorophenyl)ethanone *O*-acetyl oxime (1i) ^{1}H NMR (400 MHz, CDCl3) δ 2.14 (3H, s), 2.24 (3H, s), 7.00 (1H, m), 7.25 (1H, m), 7.37 (2H, m); ^{13}C NMR (100 MHz, CDCl3) δ 14.1, 19.5, 21.3, 113.7,113.9, 117.2, 117.4, 122.6, 130.1, 136.9, 137.0, 161.1, 163.8,168.6.



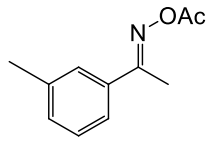
(*E*)-1-(3-trifluoromethyl)ethanone *O*-acetyl oxime (1j) ^{1}H NMR (400 MHz, CDCl3) δ 2.28 (3H, s), 2.42 (3H, s), 7.55 (1H, m), 7.70 (1H, m), 7.96 (2H, m); ^{13}C NMR (100 MHz, CDCl3) δ 14.3, 19.6, 122.4,123.7, 125.1, 127.1, 129.1, 130.2, 135.7, 161.1, 168.5.



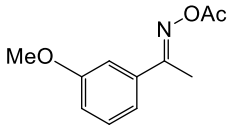
(*E*)-1-(3-Chlorophenyl)ethanone *O*-acetyl oxime (1k) ^{1}H NMR (400 MHz, CDCl3) δ 2.26 (3H, s), 2.36 (3H, s), 7.35 (1H, d, *J* = 8.0 Hz), 7.40(1H, s) 7.61 (1H, d, *J* = 8.0 Hz); 7.74(1H,bs).; ^{13}C NMR (100 MHz, CDCl3) δ 14.2, 19.7, 125.1, 127.0, 129.8, 130.5, 134.6, 136.6, 161.2, 168.6.



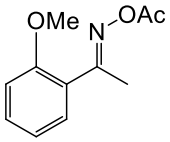
(*E*)-1-(3-Bromophenyl)ethanone *O*-acetyl oxime (1l) ^{1}H NMR (400 MHz, CDCl3) δ 2.26 (3H, s), 2.36 (3H,s), 7.27 (1H, dd, *J* = 7.6, 2.8 Hz), 7.55 (1H, dd, *J* = 8.4, Hz), 7.65 (1H, d, *J* = 7.8 Hz), 7.67 (1H, s); ^{13}C NMR (100 MHz, CDCl3) δ 14.3, 19.7, 122.7, 125.6, 129.9, 130.0, 133.5, 136.8, 161.1, 168.6.



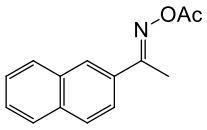
(*E*)-1-(3-Methylphenyl)ethanone *O*-acetyl oxime (1m) ^{1}H NMR (400 MHz, CDCl3) δ 2.26 (3H, s), 2.37 (3H, s), 7.27 (2H, m), 7.50 (1H, m), 7.57 (1H, s); ^{13}C NMR (100 MHz, CDCl3) δ 14.4, 19.8, 21.3, 124.1, 127.5, 128.4, 131.3, 134.8, 138.3, 162.6, 168.9.



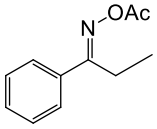
(*E*)-1-(3-Methoxyphenyl) ethanone *O*-acetyl oxime (1n) ^{1}H NMR (400 MHz, CDCl3) δ 2.18 (3H, s), 2.28 (3H, s), 3.75 (3H, s),6.88-6. 91 (1H, m), 7.19-7.23 (3H, m); ^{13}C NMR (100 MHz, CDCl3) δ 14.4, 18.7, 54.3, 111.2, 115.3, 118.5, 128.5, 135.2, 158.6, 161.4, 167.9.



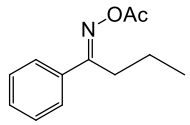
(*E*)-1-(2-Methoxyphenyl) ethanone *O*-acetyl oxime (1o) ^{1}H NMR (400 MHz, CDCl3) δ 2.23 (3H, s), 2.33 (3H, s), 3.83 (3H, s), 6.93 (2H, m), 7.37 (2H, m); ^{13}C NMR (100 MHz, CDCl3) δ 17.4, 19.8, 55.4, 111.0, 120.6, 125.2, 129.8, 131.1, 157.5, 164.8, 168.9.



(*E*)-1-(naphthalen-2-yl)ethanone *O*-acetyl oxime (1q) ^{1}H NMR (400 MHz, CDCl3) δ 2.25 (3H, s), 2.42 (3H, s), 7.47 (2H, m), 7.82 (3H, m); 7.92(1H, m) 8.10 (1H, s); ^{13}C NMR (100 MHz, cDCl3) δ 14.1, 19.8, 123.6, 126.5, 127.3, 127.4, 127.6, 128.2, 128.7, 132.1, 132.8, 134.3, 162.1, 168.9.



(*E*)-propiophenone *O*-acetyl oxime (1r) ^{1}H NMR (400 MHz, CDCl3) δ 1.18(3H, t, *J* = 8.0), 2.26 (3H, s), 2.85 (3H, q, *J* = 7.6), 7.42 (3H, m), 7.71 (2H, m), ^{13}C NMR (100 MHz, CDCl3) δ 11.2, 19.8, 21.7, 127.2, 128.6, 130.4, 133.8, 167.2, 169.1.



(*E*)-1-phenylbutan-1-one *O*-acetyl oxime (1s) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.2), 1.59(2H, m), 2.25 (3H, s), 2.82 (2H, t, *J* = 7.6), 7.41 (3H, m), 7.70 (2H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.8, 20.1, 29.9, 127.2, 128.5, 130.4, 134.1, 166.2, 169.0.

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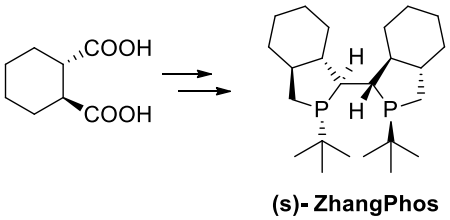
2.2 Highly enantioselective hydrogenation of *β*-ketoenamides with the Rh-ZhangPhos catalyst

Introduction and backgound

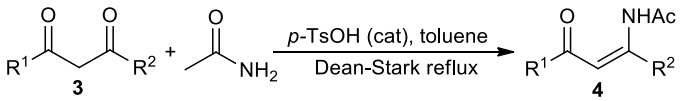
The synthesis of *β*-amino ketones has drawn great attention due to its importance in biomedical research [1] and the pharmaceutical industry.[2] *β*-Amino ketones can also serve as key precursors for the synthesis of amino alcohols, 1,3-diamines and *β*-amino acids.[3] Several stoichiometric and catalytic methods have already been reported for the synthesis of *β*-amino ketones.[4] Notable examples include Lewis acid mediated hetero-Michael addition reactions [5] and Mannich-type reactions.[6] Asymmetric synthesis of *β*-amino ketones from sulfinimines was also reported by Davis' group.[7] Our work focused on the enantioselective hydrogenation of *β*-ketoenamides with the Rh-ZhangPhos catalyst (Scheme 2-2-1). [8]



Scheme 2-2-1. Synthesis of ZhangPhos.

Results and discussion

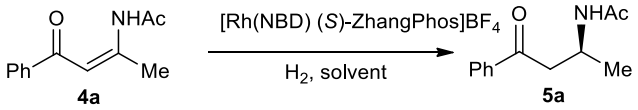
β-ketoenamides were prepared in one step on multigram scale via direct condensation of readily accessible 1,3-diketones with acetamide (Scheme 2-2-2)**.** Only (*Z*)-enamide (**4**) was observed in all cases.[9]



Scheme 2-2-2. Preparation of *β*-ketoenamides

Our initial study began with the hydrogenation of **4a** as the model substrate in MeOH under ambient hydrogen pressure with 0.5 mol% Rh-ZhangPhos complex (Table 2-2-1). To our delight, the reaction can be finished within 30 min with complete conversion into chiral *β*-amino ketone **5a** and with high enantioselectivity (96% ee). Solvent screening revealed that ethanol and isopropanol are also reliable solvents under the same reaction conditions. Aprotic solvents such as toluene and THF caused dramatic loss of the reactivity (entry 5 and entry 8). Further increasing hydrogen pressure caused a slight drop in enantioselectivity (entry 11). Lowering the catalyst loading to 0.2 mol% resulted in lower conversion (entry 12).

Table 2-2-1. Rhodium-catalyzed asymmetric hydrogenation of **4a** under various conditions.



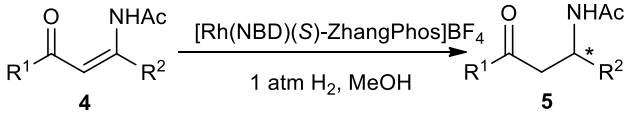
Entry [a]	P_{H2}[atm]	Solvent	Conv. [%][b]	*ee* [%][c]
1	**1.0**	**MeOH**	**>99**	**96**
2	1.0	EtOH	>99	94
3	1.0	^{i}PrOH	>99	95
4	1.0	EtOAc	86	95
5	1.0	Toluene	<5	n.d.
6	1.0	CH_2Cl_2	64	96
7	1.0	$ClCH_2CH_2Cl$	13	91
8	1.0	THF	<5	n.d.
9	1.0	1,4-dioxane	35	93
10	2.0	MeOH	>99	96
11	5.0	MeOH	>99	95
12[d)]	1.0	MeOH	68	95

[a] Unless otherwise noted, all reactions were carried out with a substrate/catalyst ratio of 200:1 at room temperature for 30 min. [b] Conversions were based on ^{1}H NMR spectroscopy of the crude product. [c] The *ee* value of **5a** was determined by chiral GC analysis. The absolute configuration of **5a** was assigned by comparison of the observed optical rotation with reported data. [d] The reaction was carried out with a substrate/catalyst ratio of 500:1 at room temperature for 30 min.

To further explore the efficiency of the Rh-ZhangPhos catalytic system, we attempted the asymmetric hydrogenation of a series of substrates (**4b**–**4m**) under the optimized conditions in MeOH (Table 2-2-2). All substrates were hydrogenated in full conversions with excellent

enantioseletivities. For example, substrates bearing both *para*-substituted electron-donating and withdrawing groups on the aromatic ring were hydrogenated with uniformly high enantioselectivities (95-98%, entries 2-8). *Meta*-substituted moiety on the aromatic ring further increased the enantioselectivity (entry 9). Substrates with thienyl and naphthyl groups also afforded the hydrogenation products with up to 99% ee (entry 10 and 11). Simple aliphatic substrate like **4l** could be hydrogenated under the same reaction conditions with 99% ee. However, increasing the steric bulkiness of R^2 group resulted in significant erosion of the reactivity and enantioselectivity (entry 13). Chiral 1,3-amino alcohol was observed as the hydrogenation product when increasing the hydrogen pressure to 20 atm and reaction time to 24 hours. Excellent enantioselectivity and diastereoselectivity were recorded with **4a** as substrate in EtOAc (Scheme 2-2-3).

Table 2-2-2. Asymmetric hydrogenation of **4** with the Rh-ZhangPhos catalyst.



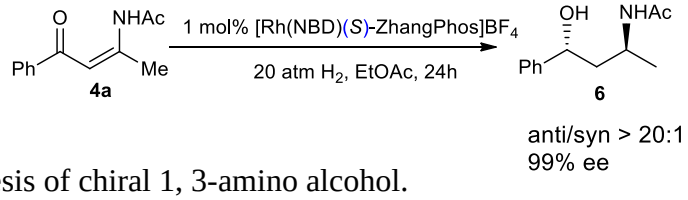
4 **5**

Entry [a]	Substrate	R^1	R^2	*ee*(%) [b] (config.) [c]
1	**4a**	C_6H_5	Me	96(S)
2	**4b**	*p*-MeC_6H_4	Me	96 (-)
3	**4c**	*p*-FC_6H_4	Me	98 (-)
4	**4d**	*p*-ClC_6H_4	Me	98 (+)
5	**4e**	*p*-BrC_6H_4	Me	97 (+)
6	**4f**	*p*-$MeOC_6H_4$	Me	98 (+)
7	**4g**	*p*-$^tBuC_6H_4$	Me	96 (-)
8	**4h**	*p*-CyC_6H_4	Me	95 (-)
9	**4i**	*m*-MeC_6H_4	Me	98 (-)
10	**4j**	2-thienyl	Me	99 (+)
11	**4k**	2-naphthyl	Me	93 (-)
12	**4l**	Me	Me	99 (-)
13[d)]	**4m**	C_6H_5	Et	90 (-)

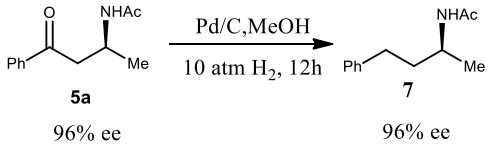
[a] Unless otherwise noted, all reactions were carried out with a substrate/catalyst ratio of 200:1 in MeOH at room temperature under 1 atm of H_2 for 30 min. In all cases, 100% conversion was observed. [b] Determined by chiral GC or HPLC analysis. [c] The absolute configurations of **5b**-**5m** were not determined. [d] *t* = 24h.

Chiral *β*-amino ketones such as **5a** could simply be converted to *γ*-arylamine by Pd/C-catalyzed hydrogenation without loss of enantioselectivity (scheme 2-2-4).[10] This transformation provided

an reliable catalytic approach to chiral γ-arylamines, which is highly pharmaceutically and biologically valuable.[11]



Scheme 2-2-3. Synthesis of chiral 1, 3-amino alcohol.



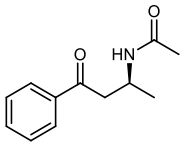
Scheme 2-2-4. Synthesis of chiral γ-arylamine.

Conclusion

We have developed an efficient enantioselective hydrogenation of a wide range of β-ketoenamides using the Rh-ZhangPhos catalyst system. This method provided an efficient access to a variety of optically active β-amino ketones with excellent enantioselectivities. Further reduction of β-amino ketones could give a variety of protected chiral γ-aryl amines.

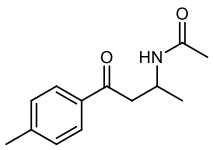
Experiment section

NMR characterization and enantioselectivity analysis of products



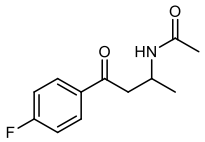
(*S*)-N-(4-oxo-4-phenylbutan-2-yl)acetamide 5a

96.5% *ee*. Enantiomeric excess was determined by GC, Chiral Beta Dex 225 column, 160℃, 1.0 mL/min, *t*minor = 59.7 min, *t*major = 60.8 min. $[\alpha]^{20}_{D}$ = -7.0 (*c* = 1.0, EtOAc).



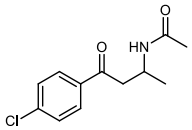
N-(4-oxo-4-p-tolylbutan-2-yl)acetamide 5b

96.1% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column, Hex/IPA = 95:5, 1.0 mL/min, *t*major = 18.0 min, *t*minor = 22.1 min. $[\alpha]^{20}_{D}$ = -5.1



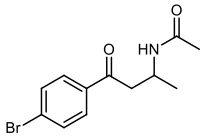
N-(4-(4-fluorophenyl)-4-oxobutan-2-yl)acetamide 5c

98.1% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column, Hex/IPA = 90:10, 1.0 mL/min, *t*major = 9.0 min, *t*minor = 10.5 min. $[\alpha]^{20}_{D}$ = -2.0 (*c* = 1.0,EtOAc).



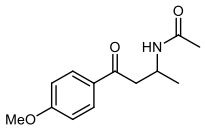
N-(4-(4-chlorophenyl)-4-oxobutan-2-yl)acetamide 5d

97.7% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column ,Hex/IPA = 90:10, 1.0 mL/min, *t*major = 9.3 min, *t*minor = 11.5 min. $[\alpha]^{20}_{D}$ = 1.9 (*c* = 1.0, EtOAc).



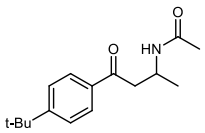
N-(4-(4-bromophenyl)-4-oxobutan-2-yl)acetamide 5e

96.5% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column,Hex/IPA = 90:10, 1.0 mL/min, *t*major = 10.4 min, *t*minor = 12.2 min. $[\alpha]^{20}_{D}$ = 1.8 (*c* = 1.0, EtOAc).



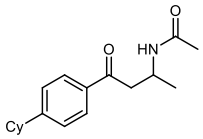
N-(4-(4-methoxyphenyl)-4-oxobutan-2-yl)acetamide 5f

97.9% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column,Hex/IPA = 90:10, 1.0 mL/min, *t*major = 13.8min, *t*minor = 16.8 min. $[\alpha]^{20}_{D}$ = 4.6 (*c* = 1.0, EtOAc).



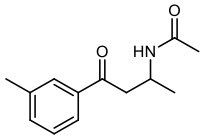
N-(4-(4-tert-butylphenyl)-4-oxobutan-2-yl)acetamide 5g

95.5% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column,Hex/IPA = 90:10, 1.0 mL/min, *t*major = 7.3 min, *t*minor = 9.9 min. $[\alpha]^{20}_{D}$=-1.8 (*c* = 1.0, EtOAc).



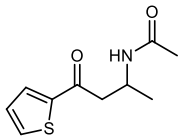
N-(4-(4-cyclohexylphenyl)-4-oxobutan-2-yl)acetamide 5h

94.5% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OD-H column, Hex/IPA = 90:10, 1.0 mL/min, *t*major = 8.1 min, *t*minor = 11.2 min. $[\alpha]^{20}_{D}$ = -3.2 (*c* = 1.0, EtOAc).



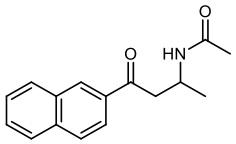
N-(4-oxo-4-m-tolylbutan-2-yl)acetamide 5i

98.2% *ee*. Enantiomeric excess was determined by GC, Chira Beta Dex 225 column,160℃, 1.0 mL/min, *t*minor = 93.6 min, *t*major = 95.6 min. $[\alpha]_{20}^{D}$ = -5.2 (*c* = 1.0, EtOAc).



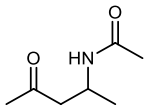
N-(4-oxo-4-(thiophen-2-yl)butan-2-yl)acetamide 5j

99.1% *ee*. Enantiomeric excess was determined by GC, Chiral Beta Dex 225 column,160℃, 1.0 mL/min, *t*minor = 81.7 min, *t*major= 82.7 min. $[\alpha]^{20}_{D}$ = 3.9 (*c* = 1.0, EtOAc).



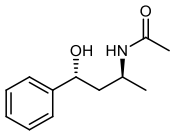
N-(4-(naphthalen-2-yl)-4-oxobutan-2-yl)acetamide 5k

93.3% *ee*. Enantiomeric excess was determined by HPLC, Chiralpak OJ-H column,Hex/IPA = 90:10, 1.0 mL/min, *t*major = 35.4 min, *t*minor = 24.9 min. $[\alpha]^{20}_{D}$ = -6.1 (*c* = 1.0, EtOAc).



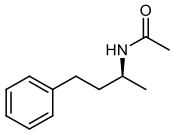
N-(4-oxopentan-2-yl)acetamide 5l

>99.9% *ee*. Enantiomeric excess was determined by GC, Chiral Beta Dex 390 column, 100℃, 1.0 mL/min, *t*major = 62.4 min. *tminor* = 67.1 min. $[\alpha]^{20}_{D}$=-27.1 (*c* = 1.0, EtOAc).



N-((2S,4R)-4-hydroxy-4-phenylbutan-2-yl)acetamide 6

>99% *ee*. Enantiomeric excess was determined by GC, Chiral Beta Dex 390 column, 170℃, 1.0 mL/min, tmajor=92.1min, tminor=87.4min. $[\alpha]^{20}_{D}$ =29.8° (c =1.0, EtOAc)



(*S*)-N-(4-phenylbutan-2-yl)acetamide 7

96.1% *ee*. Enantiomeric excess was determined by HPLC, Chiral pak OD-H column, Hex/IPA = 96:4, 0.5 mL/min, *t*major = 67.6 min, *t*minor = 56.2 min. $[\alpha]^{20}_{D}$ = -31.3 (*c* = 1.0, EtOAc).

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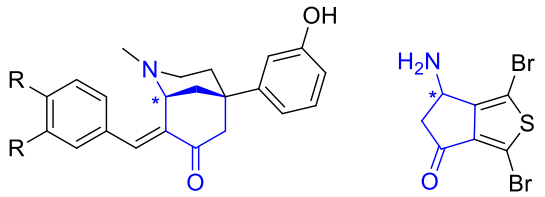
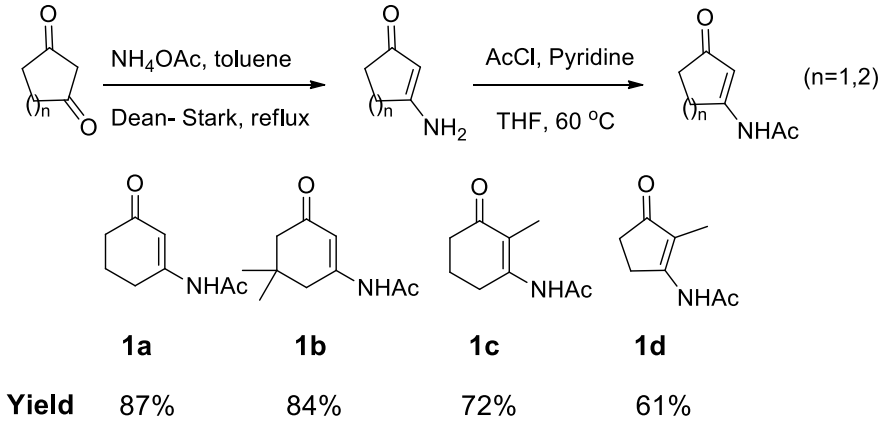
2.3 Synthesis of chiral cyclic *β*-Amino ketones by Ru-catalyzed asymmetric hydrogenation



Scheme 2-3-1. Examples of commercial available antitumor agents.

Following our work of Rh-catalyzed enantioselective hydrogenation of *β*- keto enamides, we later envisioned that chiral cyclic *β*-Amino ketones are also interesting structural motifs. For example, these amino ketones can serve as key synthetic precursors for some antitumor agents (Scheme 2-3-1).[1,2]

Results and discussion

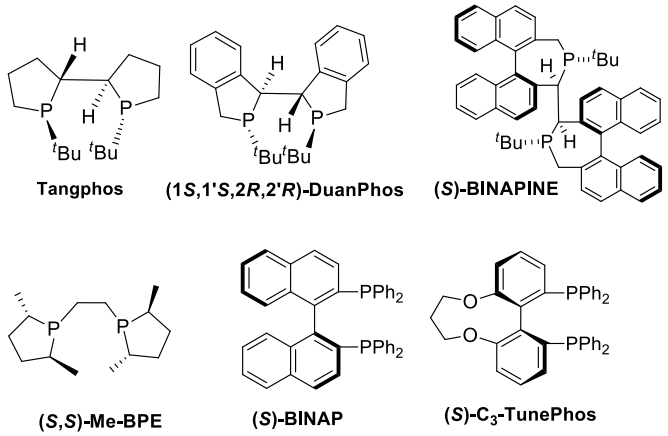


Scheme 2-3-2. Preparation of cyclic *β*-keto enamide substrates.

Preparation of cyclic *β*-keto enamide substrates were tried though the direct condensation of commercial available cyclic 1,3-diketones with acetamide.[3] However, all attempts afforded low yields (< 30%). Thus, a two-step procedure was applied. Cyclic 1,3 -diketones were first converted to the corresponding cyclic *β*-enaminones,[4] followed by acylation with acyl chloride to give the enamide substrates in moderate to good yields (up to 87%, scheme 2-3-2).We have to

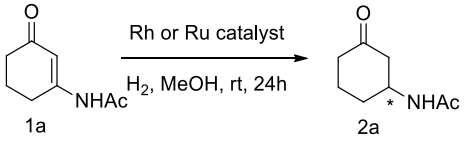
mention that aromatic cyclic 1,3-diketones such as 1,3-indanediones didn't give any desired products following this procedure, which dramatically narrowed the substrate scope.

We began our study by investigating the asymmetric hydrogenation of **1a** as the model substrate. Rh/TangPhos and Rh/DuanPhos catalysts developed by our group were initially tested. Neither of them gave satisfactory enantioselectivities under various reaction conditions (Table 2-3-1, entries 1-2). Other commercial available Rh complexes such as Rh/DuPhos and Rh/BINAPINE were also tested to give lower than 60% ee's (Table 2-3-1, entries 3-4). After catalyst screening, to our surprise, we found that commercial available $Ru(OAc)_2$/Binap catalyst gave the highest 92% ee. Later on, our results showed that $Ru(OAc)_2$/C_3-Tunephos give better enantioselectivities as well as good conversions (94% ee, Table 2-3-1, entries 6-7).



Picture 2-3-1. Selected structure of screened phosphine ligands.

Table 2-3-1. Selected results from initial screening of catalysts for hydrogenation of **1a**[a]



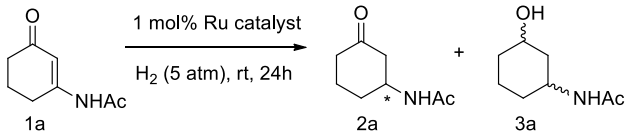
Entry	Catalyst	Conv[b] (%)	ee[c] (%)
1	TangPhos-Rh(cod)BF_4	90	61
2	DuanPhos-Rh(cod)BF_4	86	44

3	BINAPINE- $Rh(cod)BF_4$	68	35
4	Me-BPE-$Rh(cod)BF_4$	76	52
5	BINAP-$Ru(OAc)_2$	70	92
6	C_3-TunePhos- $Ru(OAc)_2$	53	94
7[d]	C_3-TunePhos- $Ru(OAc)_2$	86	94

[a] Unless otherwise mentioned, reaction conditions: Catalyst/substrate =1:100, at room temperature, under 1 atm of hydrogen for 24 h. [b] Conversions were determined by ^1H NMR of the crude product. [c] Determined by GC on a chiral phase. [d] Under 5 atm of hydrogen.

Different Ru precursors were also systematically investigated. [8] As showed in Table 2-3-2, $Ru(OAc)_2/C_3$-TunePhos complex still gave the highest enantioselectivities (Table 2-3-2, entries 1-4). Further solvent screening indicated that MeOH served as the best solvent (Table 2-3-2, entries 5-11). Increasing the hydrogen pressure or catalyst loading would cause more formation of the corresponding amino-alcohol **3a** as side product.

Table 2-3-2. Selected results from initial screening of Ru-catalysts for hydrogenation of **1a**[a]



1a 2a 3a

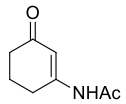
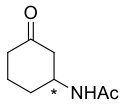
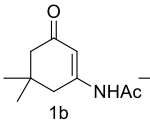
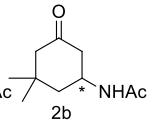
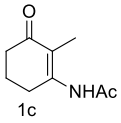
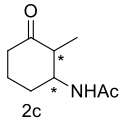
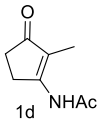
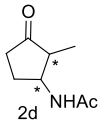
Entry	{Ru}	Solvent	Yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	$[NH_2Me_2][\{RuCl(L)\}_2(\mu\text{-}Cl)_3]$	MeOH	22	42
2	[RuCl(*p*-pymene)L]Cl	MeOH	36	51
3	[RuCl(benzene)L]Cl	MeOH	31	55
4	$RuCl_2L(DMF)_n$	MeOH	<5	n.d.
5	$Ru(OAc)_2L$	THF	31	82
6	$Ru(OAc)_2L$	1,4-dioxane	34	83
7	$Ru(OAc)_2L$	toluene	29	42
8	$Ru(OAc)_2L$	ethyl acetate	47	75
9	$Ru(OAc)_2L$	EtOH	69	91
10	$Ru(OAc)_2L$	^{i}PrOH	63	85

11	$Ru(OAc)_2L$	**MeOH**	**73**	**94**

[a] Unless otherwise mentioned, reaction conditions: Catalyst/substrate =1:100, at room temperature, under 5 atm of hydrogen for 24 h. L= (*S*)-C_3-TunePhos. Ru complexes were prepared according to reported procedure.[5] [b] Conversions were determined by ^{1}H NMR of the crude product. [c] Determined by GC on a chiral phase.

With the optimized reaction conditions, 5,5-dimethyl substituted substrate **1b** was tested to give moderate hydrogenation results (Table 2-3-3, entry 2). However, hydrogenation of tetra-substituted olefin substrates **1c** showed dramatic loss of reactivities and enantioselectivities (Table 2-3-3, entry 3). Low reactivity and enantioselectivity were also observed when cyclopentyl substrate **1d** was tested (Table 2-3-3, entry 4).

Table 2-3-3. Substrate scope and limitations.[a]

Entry	Substrate	Product	Yield[b]	ee[c]
1	 1a	 2a	73	94
2	 1b	 2b	68	88
3	 1c	 2c	36	67
4	 1d	 2d	45	61

[a] Unless otherwise mentioned, reaction conditions: $Ru(OAc)_2/C_3$-TunePhos as catalyst, Catalyst/substrate =1:100, Methanol as solvent, at room temperature, under 5 atm of hydrogen for 24 h. [b] Conversions were determined by ^{1}H NMR of the crude product. [c] Determined by GC on a chiral phase.

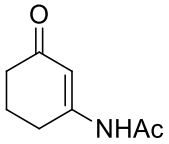
Conclusion

We reported a Ru-catalyzed asymmetric hydrogenation of cyclic *β*-keto enamides to afford chiral cyclic *β*-amino ketones, which afforded a new approach for the synthesis of optically pure cyclic *β*-amino ketones.

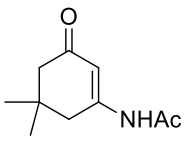
Experiment section

General Procedure for substrate synthesis

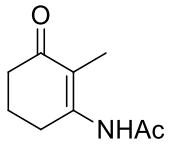
10 mmol cyclic 1,3-diketone was added to a mixture of 10 mmol ammonium acetate in dry toluene (20 mL). The mixture was heated for 3 h under reflux using a Dean–Stark water separator. The resulting oily product was separated and recrystallized with ethyl acetate to give the corresponding enaminone as crystals. The enaminone product was dissolved in 50ml THF and 2 equiv. of pyridine were added. To the mixed solution, acetyl chloride (2 equiv.) in 5ml THF was added dropwise at 0 °C. The reaction mixture was warmed up to ambient temperature and stirred additional 12 h. The solvent was removed under vacuum and the crude product purified by flash chromatography.



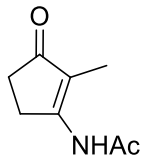
***N*-(3-oxocyclohex-1-en-1-yl)acetamide (1a)** ^{1}H NMR (400 MHz, CDCl3) δ 7.61 (1H, br), 6.49 (1H, s), 2.51 (2H, t, *J* = 6.0), 2.30 (2H, t, *J* = 6.3), 2.07 (3H, s), 1.96 (2H, q, *J* = 6.4); ^{13}C NMR (100 MHz, CDCl3) δ 21.4, 24.7, 28.2, 36.6, 111.2, 158.9, 170.1, 201.1



***N*-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)acetamide (1b)** ^{1}H NMR (400 MHz, CDCl3) δ 8.67 (1H, br), 6.74 (1H, s), 2.51 (2H, t, *J* = 6.0), 2.37 (2H, s), 2.19 (2H, s), 2.11 (3H, s), 1.05 (6H, s); ^{13}C NMR (100 MHz, CDCl3) δ 24.7, 28.1, 32.7, 42.1, 50.5, 110.1, 154.7, 170.1, 201.0



***N*-(2-methyl-3-oxocyclohex-1-en-1-yl)acetamide (1c)** ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.24 (1H, br), 2.77 (2H, t, *J* = 6.0), 2.33 (2H, t, *J* = 6.2), 2.10 (3H, s), 1.88 (2H, q, *J* = 6.4), 1.67 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ 7.95, 23.72, 23.75, 26.9, 36.04, 117.1, 152.0, 167.9, 197.8



***N*-(2-methyl-3-oxocyclopent-1-en-1-yl)acetamide (1d)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, br), 3.13 (2H, t, *J* = 2.4), 2.34 (2H, t, *J* = 2.5), 2.16 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ 6.69, 24.5, 27.7, 33.6, 118.3, 165.1, 168.9, 206.7

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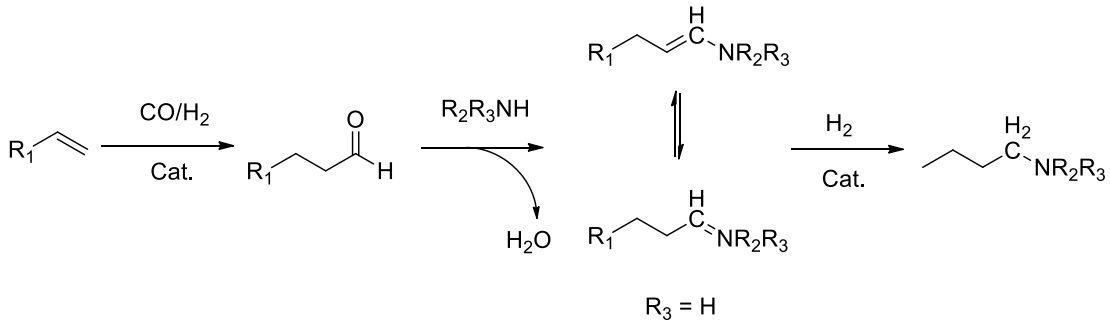
Chapter 3

Regioselective hydroaminomethylation with tetradentate phosphorus ligands

3.1 Introduction

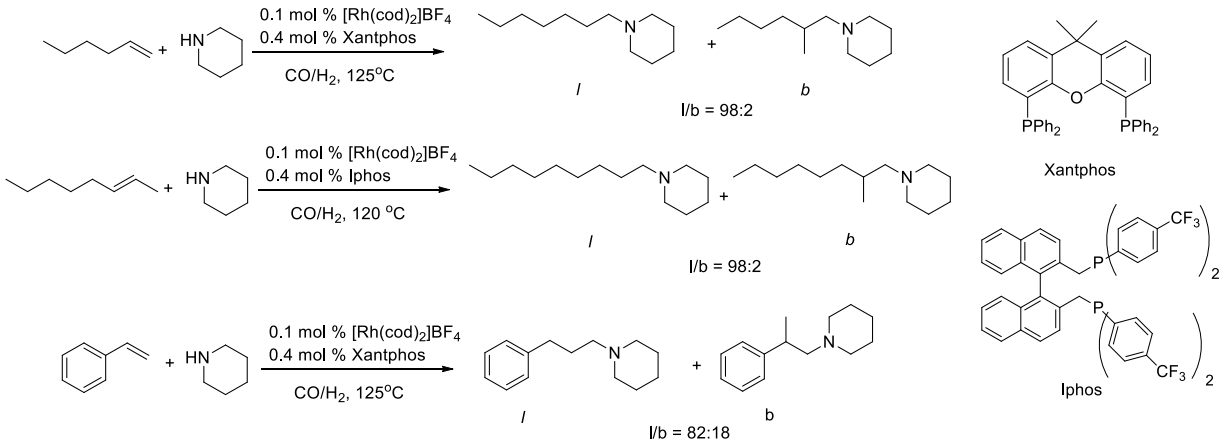
With a production on million-ton scale per year, amines are of significant importance for both the bulk and the fine chemical industries. They can serve as solvents, biologically active compounds and pharmaceutical intermediates.[1] We have several classic methods to prepare amines, but most of them are inappropriate for large-scale production, such as the nucleophilic substitution reactions of amines with alkyl halides. From both the economic and environmental points of view, an ideal chemical synthesis of amines should make use of inexpensive raw materials. Besides, minimum reaction steps should be performed to save solvents and energy and produce less waste. In such respects, hydroaminomethylation[2] (Scheme 3-1-1) should be perfectly suited to fulfilling today's need for "green chemistry".[3]



Scheme 3-1-1. Reaction sequence for hydroaminomethylation.

Hydroaminomethylation is an environmentally benign (atom-efficient, one-pot) synthesis of amines from olefins. This domino reaction consists of initial hydroformylation of the olefin to the corresponding aldehyde, which then reacts with the amine to form the enamine or imine followed by hydrogenation to provide the desired amine. Since its discovery by Reppe at BASF, the hydroaminomethylation reaction has been mainly studied in industry. [4] In the last decade, work by Eilbracht and co-workers has shown how to prepare functionalized amines by

"ligandfree" (phosphine-free) hydroaminomethylation procedures. [5] Very recently, Beller's group has developed rhodium catalysts based on Iphos and Xantphos ligands for *n*-selective hydroaminomethylation of terminal and internal olefins (Scheme 3-1-2).[6] Their pioneer work showed that high reactivity and regioselectivity can be achieved by properly choosing the phosphine ligands and reaction conditions.

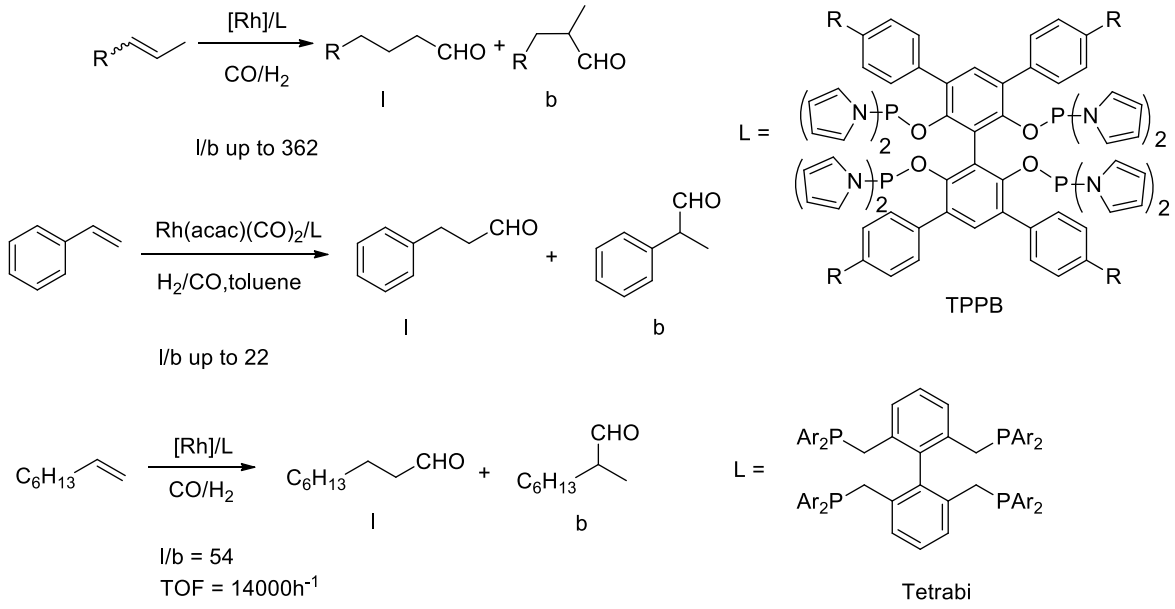


Scheme 3-1-2. Beller's results for hydroaminomethylation.

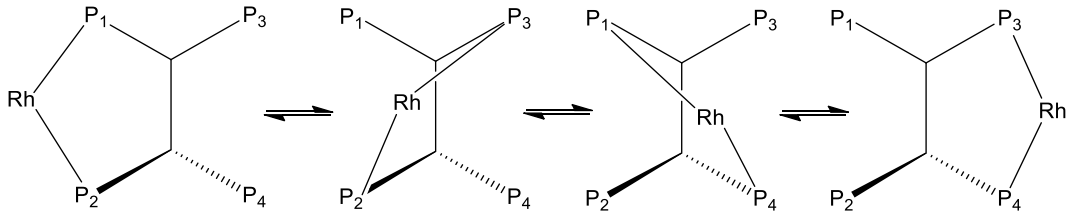
Some challenges still remain for catalytic regioselective hydroaminomethylation. First, the catalyst used in hydroaminomethylation must be active and selective in both the hydroformylation and the hydrogenation step. Moreover, the amine product can act as σ-donor ligand and thus compete with the original ligand. Also, given high reaction temperature, loss of regioselectivity is usually observed due to the dissociation of phosphorus ligands from the metal center. Carbonyl monoxide is a strong π acid that competes to bind to the rhodium center with the phosphorus ligand. The exchange between the ligands is also accelerated at high temperature

Our group have recently developed two systems of tetraphosphorous ligands, TPPB and Tetrabi,[7] which are based on a biphenyl backbone and can be successfully applied in the highly regioselective hydroformylation of terminal olefins and internal olefins (Scheme 3-1-3)(TPPB =

2,2',6,6'-tetrakis((di(1H-pyrrol-1-yl)phosphino)oxy)-1,1'-biphenyl,Tetrabi=2,2',6,6'-tetrakis((diphenylphosphino)methyl)-1,1'-biphenyl).



Scheme 3-1-3. TPPB and Tetrabi ligands for hydroformylation.



Scheme 3-1-4. Enhanced chelating ability of tetraphosphorous lignad through multiple chelating modes and increased local phosphorus concentration.

Our ligand design is based on the following reasons: 1) tetraphosphorus ligand has a higher concentration of the selective catalytic species due to the presence of multiple chelating modes: a rhodium metal center can form four possible equivalent bidentate complexes. 2) When ligand coordinates to the metal to form a bidentate system, the nearby intramolecular free phosphorus

atoms can effectively increase the local phosphorus concentration around the metal center and enhance the chelating ability. When a phosphane moiety in the bidentate ligand dissociates from the metal, two intermediates are formed by recoordination of another two phosphane moieties to the Rh center to reform the bidentate system (Scheme 3-1-4). Such "enhanced multidentarity" has been demonstrated to improve the ligand ability to stabilize catalytic systems and promote their longevity in transition-metal-catalyzed coupling reactions.[8] Thus, tetraphosphorus ligands TPPB and Tetrabi ligands should be tested in the hydroaminomethylation reactions.

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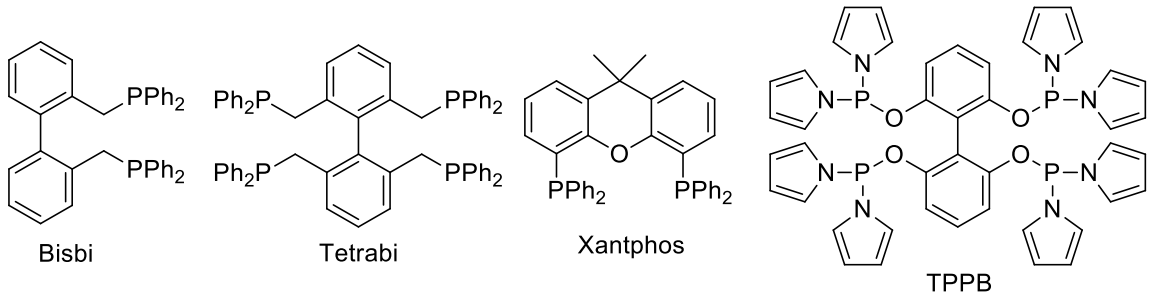
3.2 Highly regioselective hydroaminomethylation of terminal olefins to linear amines

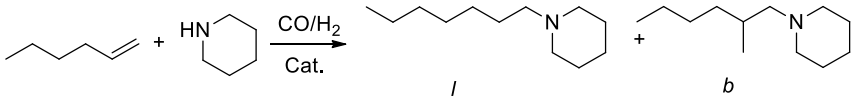
Results and discussion



Scheme 3-2-1. Structures of applied ligands.

We use Tetrabi and TPPB as ligands for the hydroaminomethylation of 1-hexene and piperidine with three different Rh precursors. Xantphos and Bisbi are used as "standard ligand" to compare the results (Scheme 3-2-1). As shown in Table 3-2-1, all entries have 99% conversions.. Xantphos has achieved 100 *l/b* ratio and 95.3% linear amine yield with $[Rh(cod)_2]BF_4$ (Table 3-2-1, Entry 8), which is consistent with the published result. Bisbi can give very high regioselectivity (l/b up to 146). However, the *n*-amine yield is only 78.6% (Table 3-2-1, Entry 10). To our delight, Tetrabi can afford up to 198 *l/b* ratio and 90.8% *n*-amine yield by using $Rh(acac)(CO)_2$ as the precursor (Table 3-2-1, Entry 1), which indicates that the tetraphosphorus ligands does improve the results from their biphosphine analogs. However, TPPB unfortunately only give morderate regioselectivity (*l/b*=19) (Table 3-2-1, Entry 4).

Table 3-2-1. Hydroaminomethylation of 1-hexene with piperidine using different Rh precursors and ligands.[a]



Entry	Ligand [1µmol]	Rh Precursor [4µmol]	Conv. [%]	*n*-Amine yield [%]	Amine selectivity [%][b]	*N*-formyl-piperidine [%][c]	*l/b*
1	Tetrabi	$Rh(acac)(CO)_2$	99	90.8	92.2	7.8	198
2	Tetrabi	$[Rh(cod)_2]BF_4$	99	90.8	92.4	7.6	126
3	Tetrabi	$[Rh(cod)Cl]_2$	99	81.4	84.1	7.1	45
4	BTPP	$Rh(acac)(CO)_2$	99	77.6	81.7	-	19
5	BTPP	$[Rh(cod)_2]BF_4$	99	78.2	84.7	-	12
6	BTPP	$[Rh(cod)Cl]_2$	99	81.0	91.1	-	8
7	Xantphos	$Rh(acac)(CO)_2$	99	88.8	90.6	4.3	99
8	Xantphos	$[Rh(cod)_2]BF_4$	99	95.3	97.2	2.8	100
9	Xantphos	$[Rh(cod)Cl]_2$	99	90.3	95.8	2.2	20
10	Bisbi	$Rh(acac)(CO)_2$	99	78.6	79.9	6.9	146
11	Bisbi	$[Rh(cod)_2]BF_4$	99	87.7	90.1	6.4	60
12	Bisbi	$[Rh(cod)Cl]_2$	99	76.8	82.8	5.3	15

[a] Reaction condition: S/Rh=1000, L/Rh = 4:1, [Rh] =1 µmol , 1 mmol 1-hexene, 1 mmol piperidine, 125˚C, 4h, CO/H_2 = 7/35 bar. 3 ml methanol/toluene=1:1. [b] Selectivity and yield was determined by GC analysis using 2-methoxyethyl ether (0.1ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] Other by products were aldol product and *N*-methylpiperidine.

Compared to Xantphos, best and reproducible result of the *l/b* ratio was obtained by using Tetrabi and $Rh(acac)(CO)_2$ as catalyst. But we do notice more formation of *N*-formylpiperidine as side-product probably due to its high formylation activity. Hence, Tetrabi and $Rh(acac)(CO)_2$ was chosen as the catalyst system for further studies. Different solvents were introduced for the suppression of *N*-formylpiperidine (Table 3-2-2, Entries 1-7). The survey showed that full conversion of 1-hexene can be obtained in ethanol with 61 *l/b* ratio and 4% of *N*-formylpiperidine (Table 3-2-2, Entry 2). The formation of *N*-formylpiperidine can be suppressed to lowest 0.5% with 65% conversion in toluene (Table 3-2-2, Entry 7). The best *l/b* ratio is 150,

which is obtained in 2-propanol with 85% conversion and 0.5% *N*-formylpiperidine. However, more enamine product was observed (Table 3-2-2, Entry 3). Then we consider using combination of ethanol and toluene or 2-propanol to improve the conversion and *l/b* ratio as well as to suppress the formation of *N*-formylpiperidine. As showed in the Entries 9-15, a l/b ratio of 215 with 92.7% linear amine yield was achieved in 2:1 mixture of ethanol and toluene (Table 3-2-2, Entry 10). l/b ratio of 134 and 96.8% linear amine yield were obtained by applying a 2:1 mixture of 2-propanol and ethanol with (Table 3-2-2, entry 14). As time increased, the conversion extends to more than 99% with 6 hours (*l/b*= 168) (Table 3-2-2, entry 17). Variation of L/Rh ratio and H_2/CO pressure and other reaction conditions were also tested (Table 3-2-2, entry 18-26).

Table 3-2-2. Optimization of reaction conditions for the hydroaminomethylation of 1-hexene with piperidine using Rh(acac)$(CO)_2$ and Tetrabi ligand.[a]

Entry	Solvent	PCO/PH_2 [bar]	T [°C]	*t* [h]	L/Rh	Conv. [%]	*n*-Amine yield [%]	Selectivity [%][b]				*l/b*
								Amine	Enamine	*N*-formyl-piperidine	Aldol product	
1	MeOH	7/35	125	8	4	>99	86.5	89.3	–	9.4	1.3	46
2	EtOH	7/35	125	**8**	**4**	>99	91.2	93.6	–	4	2.4	61
3	2-PrOH	7/35	125	8	4	85	77.5	91.8	2.8	0.5	4.9	150
4	EtOAc	7/35	125	8	4	65	4.6	7.1	56.2	1.2	35.5	-
5	Dioxane	7/35	125	8	4	75	3.5	4.7	80.5	0.9	13.9	-
6	THF	7/35	125	8	4	70	7.4	10.5	73.3	1.3	14.9	-
7	Toluene	7/35	125	8	4	65	3.3	5.1	60.2	0.5	34.2[c]	-
8	MeOH/Toluene=1:1	7/35	125	8	4	>99	90.8	92.2	–	6.4	1.4	198
9	EtOH/Toluene=1:1	7/35	125	8	4	>99	42.1	42.6	53.2	0.9	3.3	355
10	EtOH/Toluene=2:1	7/35	125	8	4	>99	92.7	94.1	1.5	2.0	2.4	215
11	EtOH/Toluene=5:1	7/35	125	8	4	>99	94.2	96.0	–	2.6	1.4	110

12	2-PrOH/EtOH=11:1	7/35	125	8	4	>99	91.8	93.3	1.4	0.5	4.8	152
13	2-PrOH/EtOH=5:1	7/35	125	8	4	>99	94.2	95.8	1.1	0.5	2..6	140
14	2-PrOH/EtOH=2:1	7/35	125	8	4	>99	96.8	98.5	–	0.8	0.7	134
15	2-PrOH/EtOH=1:1	7/35	125	8	4	>99	96.2	98.2	–	1.0	0.8	60
16	2-PrOH/EtOH=2:1	7/35	125	4	4	90	73.5	81.7	–	0.8	17.5[c]	192
17	2-PrOH/EtOH=2:1	7/35	125	6	4	>99	97.4	99.0	–	0.5	0.5	168
18	2-PrOH/EtOH=2:1	7/35	125	12	4	>99	95.1	97.3	–	1.5	1.2	78
19	2-PrOH/EtOH=2:1	7/35	125	6	2	95	92.8	98.4	–	0.9	0.7	135
20	2-PrOH/EtOH=2:1	7/35	125	6	1	90	88.0	98.8	–	0.8	0.5	94
21	2-PrOH/EtOH=2:1	5/25	125	6	4	95	90.5	95.9	–	0.8	3.3	145
22	2-PrOH/EtOH=2:1	10/50	125	6	4	>99	94.1	96.4	–	3.2	0.4	71
23	2-PrOH/EtOH=2:1	7/35	115	6	4	80	76.9	97.2	–	0.7	2.1	93
24	2-PrOH/EtOH=2:1	7/35	120	6	4	90	86.3	96.6	–	1.6	1.8	143
25	2-PrOH/EtOH=2:1	7/35	130	6	4	>99	94.7	96.4	–	2.1	1.5	121
26	2-PrOH/EtOH=2:1	7/35	135	6	4	>99	94.0	96.1	–	2.7	1.2	85

[a] Reaction condition: 1 μmol $Rh(acac)(CO)_2$, ligand = Tetrabi, 1mmol 1-hexene, 1mmol piperidine, 3ml solvent. Selectivity and yield was determined by GC analysis using 2-methoxyethyl ether (0.1ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] Major other by-products were aldehydes.

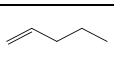
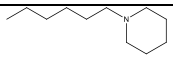
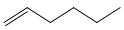
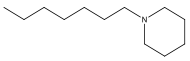
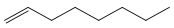
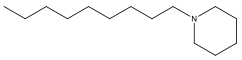
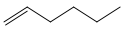
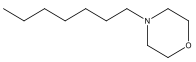
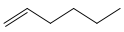
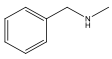
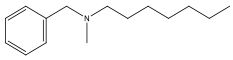
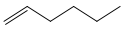
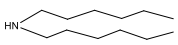
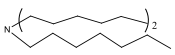
Then we tested the reactivity of the catalyst. When substrate/Rh ratio was increased from 1000 to 10000, longer time was needed for complete conversion of 1-hexene. With a Substrate/Rh ratio of 2500, 0.2% branched enamine was produced and the *l/b* ratio of amine was 525 with full conversion of 1-hexene (Table 3-2-3, Entry 2). With the ratio of 5000, 8000 and 10000, the linear amine is actually quantitative (100% of amine product as enamine was the only by-product). However, the conversion of 1-hexene drops from 99% to 70% (Table 3-2-3, Entries 3-5). The reason for the existence of the branched enamine should be the lower hydrogenation activity of Tetrabi catalyst system for branched enamine in such lower concentration. Thus, the *l/b* ratio of amine must be >525 at 5000 to 10000 S/Rh ratio with less than 1% branched enamine. To the best of our knowledge, such clean linear amine selectivity has never been achieved before.

Table 3-2-3. Turn over number test of Tetrabi with $Rh(acac)(CO)_2$ for hydroaminomethylation.[a]

Entry	S/Rh	*t* [h]	Conv. [%]	*n*-Amine yield [%]	Selectivity [%] [b]			TON[d]	l/b[e]
					Amine	Iso-Enamine	By-product [c]		
1	1000	6	99	97.5	99.1	–	0.9	981	156
2	2500	12	99	97.4	99.0	0.2	0.8	2450	525
3	5000	24	95	94.6	99.6	0.4	–	4731	>525[e]
4	8000	30	85	84.7	99.7	0.3	–	6780	>525[e]
5	**10000**	**36**	70	69.3	99.0	1.0	–	6930	>525[e]

[a] Reaction condition: Tetrabi / $Rh(acac)(CO)_2$ = 4:1, 1mmol 1-hexene, 1mmol piperidine, 125˚C, CO/H_2 = 7/35 bar, 3ml 2-propanol/ethanol=2:1. [b] Selectivity and yield was determined by GC analysis using 2-methoxyethyl ether (0.1ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] Major by-product is *N*-formylpiperidine. [d] Turnover number was determined on the basis of GC, error is estimated at <200. [e] No branched amine observed by GC.

Table 3-2-4. Hydroaminomethylation of various olefins and amines.[a]

Entry	Olefin	Amine	Major product	Conversion [%]	Amine [b] selectivity [%]	Amine yield[b] [%]	l/b
1				>99	99	>98	208
2				>99	99	>98	183
3[c]				>99	99	>98	121
4				>99	99	>98	167
5[c]				>99	99	>98	140
6				>99	99	>98	250

[a] Reaction condition: 1 μmol $Rh(acac)(CO)_2$, 4μmol Tetrabi, 1mmol olefin, 1mmol amine, 125˚C, 6h, CO/H_2 = 7/35 bar. 3ml 2-propanol/ethanol=2:1. [b] Selectivity and yield was determined by GC analysis using 2- methoxyethyl ether (0.1ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] 125 ˚C, 12h.

Finally, several different terminal olefins and secondary amines were tested to learn the compatibility of our catalyst. In all cases, the reaction proceeds with an extremely high degree of chemoselectivity (99%) and amine yield (>98%) towards the linear amines. We were pleased to find that other aliphatic olefins react well with piperidine to give the linear amine products with excellent selectivity (up to 208). We have to mention that olefins such as 1-octene needs longer time to get full conversion (121 *l/b* ratio) (Table 3-2-4, Entries1-3). *N*-methylbenzylamine and other aliphatic secondary amines (morpholine, dihexylamine) also react well with 1-hexene to give the corresponding amines in high yield and selectivity and the highest *l/b* ratio was 250 obtained with dihexylamine (Table 3-2-4, Entries 4–6).

Conclusion

Our Tetrabi ligand was first successfully applied in the hydroaminomethylation reaction. l/b up to 525 was achieved with 99% amine selectivity using 1-hexene and piperidine as model reactant. The TON can reach to 6930 at 10000 S/Rh ratio. Different terminal olefins and secondary amines have been applied successfully for the compatibility of this method.

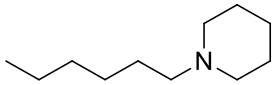
Experiment section

General procedure for the regioselective hydroaminomethylation

All hydroaminomethylation experiments were performed in the nitrogen-filled glove box. In a typical experiment, a 10-ml long neck vial with a magnetic stirring bar was charged with Tetrabi (4 μmol, 3.8 mg) and Rh (acac)$(CO)_2$ (1 μmol, 0.1 ml of 10 mmol solution in toluene). The mixture was stirred for 10 min; 1-hexene (1 mmol, 0.125 ml) and piperidine (1 mmol, 0.098 ml) was then added, followed by 2-methoxyethyl ether (0.1 ml) as internal standard, 2-propanol (2

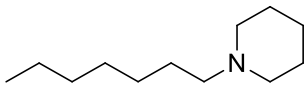
ml) and ethanol (1 ml). The reaction mixture was transferred to an autoclave, vial covered with a simple lid. The autoclave was purged with H_2 three times and subsequently charged with CO (7 bar) and H_2 (35 bar). The reaction was carried out at 125℃ for 6 h. After 6h, the autoclave was then cooled to room temperature and depressurized carefully in a well-ventilated hood. The reaction mixture was immediately analyzed by GC to determine the conversion and regio-selectivity.

1-hexylpiperidine



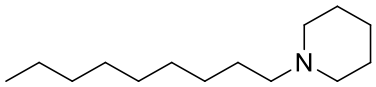
The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1, yield 98% by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.29 (s, br, 4H), 2.20 (t, J = 7.90 Hz, 2H), 1.51 (quintet, J = 4.05 Hz, 4H), 1.31-1.47 (m, 4H), 1.21 (s, 6H), 0.81 (t, J = 6.72 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.73, 53.68, 30.85, 26.48, 25.96, 25.02, 23.54, 21.62, 13.03.

1-heptylpiperidine



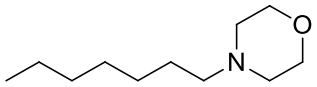
The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1, yield 98% by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.29 (s, br, 4H), 2.19 (t, J = 7.92 Hz, 2H), 1.51(quintet, J = 5.63 Hz, 4H), 1.30-1.48 (m, 4H), 1.20 (s, 8H), 0.81 (t, J = 6.90 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 58.73, 53.69, 30.82, 28.29, 26.76, 26.00, 24.98, 23.55, 21.62, 13.06.

1-nonylpiperidine



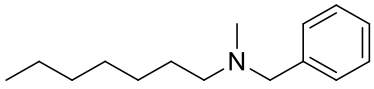
The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1, yield 98% by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.36 (s, br, 4H), 2.26 (t, J = 7.82 Hz, 2H), 1.58 (quintet, J = 5.22 Hz, 4H), 1.38-1.54 (m, 4H), 1.27 (s, 12H), 0.88 (t, J = 6.22 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 59.78, 54.92, 31.94, 29.68, 29.62, 29.34, 27.84, 27.02, 26.05, 24.57, 22.71, 14.11.

4-heptylmorpholine



The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1, yield 98 % by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 3.65 (t, J = 4.68 Hz, 4H), 2.36 (t, J = 4.16 Hz, 4H), 2.24 (t, J = 7.74 Hz, 2H), 1.41 (quintet, J = 7.26 Hz, 2H), 1.22 (m, 8H), 0.81 (t, J = 6.82 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 67.03, 59.26, 53.82, 31.78, 29.22, 27.49, 26.58, 22.59, 14.04.

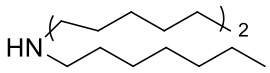
***N*-benzyl-*N*-methylheptan-1-amine**



The crude product was purified by flash chromatography (n-hexane/EtOAc, 20:1, yield 98% by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.15-7.23 (m, 5H), 3.39 (s, 2H), 2.27 (t, J = 7.50 Hz, 2H), 2.10 (s, 3H), 1.42(quintet, J = 4.89 Hz, 2H), 1.20 (s, 8H), 0.81 (t, J = 6.84 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ = 138.36, 128.02, 127.11, 125.78, 61.35, 56.63, 41.24, 30.86, 28.26, 26.43, 21.62, 13.06.

***N, N*-dihexylheptan-1-amine**

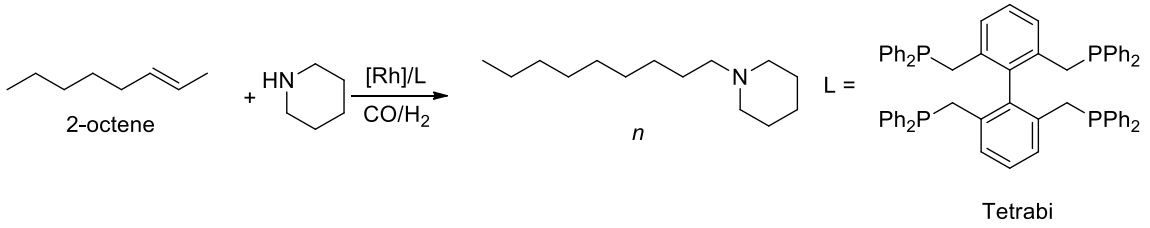


The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1, yield 98% by GC), clear liquid. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.30 (t, J = 7.60 Hz, 6H), 1.35(quintet, J = 7.27 Hz 6H), 1.21 (m, 20H), 0.81 (t, J = 6.84 Hz, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.32, 30.89, 28.32, 26.65, 26.37, 26.06, 21.68, 21.64, 13.06, 13.04. HRMS Calculated for $C_{19}H_{41}N$ [M+] 284.3317. Found 284.3313.

3.3 Highly regioselective isomerization-hydroaminomethylation of internal olefins

The success of Tetrabi in the regioselective hydroaminomethylation of of terminal olefins prompted us to try hydroaminomethylation of internal olefins. Internal olefin 2-octene was choosen as the standard substrate for the reaction with piperidine. Our initial studies showed that the H_2/CO pressure was critical for this reaction. Only 5/5 bar H_2/CO pressure provided high conversion and linear amine selectivity as higher H_2 or CO pressure led to lower regioselectivity or amine selectivity. This was probably resulted from the pressure dependency of the catalytic system to the reaction step of isomerization-hydroformylation.

Table 3-3-1. Hydroaminomethylation of 2-octene and piperidine under different reaction conditions with Tetrabi ligand and $Rh(acac)(CO)_2$.[a]



Entry	Solvent	T (°C)	*t* (h)	L/Rh	Con. (%)	Amine Sel.[b]	Linear Sel.[b]		TON[d]
							l/b	*n*-Amine (%)[c]	
1	Pr/Et=2:1	125	28	4	99	91.1	16.5	94.3	850
2	Et/To=2:1	125	28	4	90	84.1	16.6	94.3	714
3	Me/To=1:1	125	28	4	99	81.6	28.8	96.6	780
4	Pr/Me=2:1	125	28	4	99	94.6	12.1	92.4	865
5	Pr/Me=1:1	125	28	4	99	92.2	13.4	93.1	850
6	Pr/Me=1:2	125	28	4	99	89.3	12.6	92.6	819
7	EtOH	125	28	4	99	90.2	11.7	92.1	822
8	2-PrOH	125	28	4	99	91.4	27.2	96.5	873
9	2-PrOH	125	28	2	99	90.7	25.9	96.3	856
10	2-PrOH	125	28	6	99	91.8	27.8	96.5	877
11	2-PrOH	130	28	4	99	93.6	29.2	96.7	896
12	2-PrOH	130	36	4	99	95.3	36.2	97.3	918
13	2-PrOH	135	36	4	99	95.1	28.2	96.6	909

[a] Reaction conditions: 1 μmol $Rh(acac)(CO)_2$, ligand = Tetrabi, 1 mmol 2-octene, 1 mmol piperidine, 3 ml solvent, CO/H_2 = 5/5 bar. Me = methanol, Et = ethanol, Pr = 2-propanol, To = toluene. [b] Selectivity and *l/b* ratio were determined by GC analysis using 2-methoxyethyl ether (0.1 ml) as an internal standard, the average value of 3

repeated runs and 2 injections per run. [c] Percentage of linear amine in all amines. [d] Turnover number was determined on the basis of GC, error was estimated at <20.

Solvent screeening results were showed in Table 3-3-1. We applied different solvent combaniations such as 2-propanol and ethanol, ethanol and toluene, methanol and toluene, all of which supported excellent *l/b* ratio for terminal olefin hydroaminomethylation (See Chapter 3.2). Although full conversions were obtained, the amine selectivity and *l/b* ratio were not very high with these solvents (Table 3-3-1, Entries 1-3). Methanol was used to replace ethanol for the mixture of 2-propanol and ethanol to obtain higher amine selectivity. Unfortunately, the *l/b* ratio of amine could not be improved at all (Table 3-3-1, Entries 4-6). In this way, single polar solvents ethanol and 2-propanol were employed and the results showed that 2-propanol gave 91.4% amine selectivity and 27.2 *l/b* ratio at the same time (Table 3-3-1, Entry 8), which was the best solvent observed. Different Rh complex loading was also investigated. Although there was no much effect on catalytic activity, the regioselectivity was improved to some extent (*l/b* = 27.8) while the L/Rh ratio was changed from 2 to 6 (Table 3-1-1, Entries 8-10). An increase of the temperature to 130 °C led to better activity and regioselectivity (93.6% amine selectivity, *l/b* = 29.2) (Table 3-1-1, Entry 11). Increasing reaction time to 36 h at 130°C gave apparent improvement of amine selectivity (95.3%) and *l/b* ratio (36.2) (Table 3-3-1, Entry 12). Further increase the temperature to 135 ^{o}C caused slight decrease of the amine selectivity and *l/b* ratio (Table 3-3-1, Entry 13). Hence, the optimized reaction conditions were: H_2/CO = 5/5 bar, 2-propanol, S/L/Rh = 1000/4/1, 130 °C and 36 h. The highest turnover number of linear amine was achieved 918 with 95.3% amine selectivity and 36.2 *l/b* ratio at these conditions.

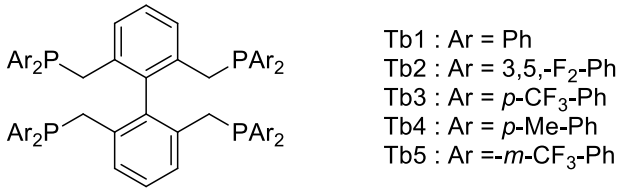
Table 3-3-2. Turnover number and ligand loading test of Tetrabi [a]

Entry	S/Rh	L/Rh	*t* (h)	Con. (%)	Amine Sel.[b]	Linear Sel.[b]		TON[d]
						l/b	*n*-Amine (%)[c]	
1	1000	4	60	99	95.2	32.3	97.0	914
2	2000	4	60	99	92.1	52.8	98.1	1789
3	5000	4	60	70	83.6	56.4	98.3	2876
4	8000	4	60	60	73.3	48.7	98.0	3448
5	10000	4	60	55	67.2	39.8	97.5	3604
6	5000	8	60	85	85.5	56.8	98.3	3572
7	5000	12	60	95	89.4	60.1	98.4	4179
8	8000	8	60	80	80.3	40.6	97.6	5016
9	8000	12	60	90	86.7	43.7	97.8	6105
10	10000	8	60	75	74.8	38.4	97.5	5470
11	10000	12	60	85	82.5	39.1	97.5	6837

[a] Reaction conditions: 1 mmol 2-octene, 1 mmol piperidine, 3 ml 2-propanol, CO/H_2 = 5/5 bar, 130°C. [b] Selectivity and *l/b* ratio were determined by GC analysis using 2-methoxyethyl ether (0.1 ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] Percentage of linear amine in all amines. [d] Turnover number was determined on the basis of GC, error was estimated at <200.

Based on the optimized reaction conditions, we studied reactivity of the catalyst based on Tetrabi ligand for 2-octene. The S/Rh ratio was increased from 1000 to 10000 while the L/Rh ratio was kept as 4. Longer reaction time was needed for completed conversion of 2-octene. Although the *l/b* ratio of amine was increased, the conversion was decreased subsequently to 55% and the enamines could not be hydrogenated smoothly at 10000 S/Rh ratio (Table 3-3-2, Entry 5). At 2000 S/Rh ratio, *l/b* ratio of amine was increased to 52.8 with 92.1% amine selectivity (Table 3-3-2, Entry 2). At the ratio of 5000, 8000 and 10000, *l/b* ratio of amine was kept in a high level while the branched and linear enamines remained as main byproducts (Table 3-3-2, Entry 3-5). The reason for the existence of the enamines might be the lower hydrogenation activity of

Tetrabi catalyst system for enamines in such low ligand loading, which also happened in the aminomethylation of terminal olefins. To obtain excellent conversion of enamines, the L/Rh ratio was increased to 8 and 12 at the S/Rh ratio of 5000, 8000 and 10000. As expected, the conversion of 2-octene was improved significantly while the amine selectivity was enhanced comparatively with higher *l/b* ratio (Table 3-3-2, Entries 7, 9, 11). Therefore, the best TON of linear amine was achieved with S/L/Rh ratio of 10000/12/1 and it was 6837 according to $Rh(acac)(CO)_2$ with 82.5% amine selectivity (*l/b* = 39.1) (Table 3-3-2, Entry 11). To the best of our knowledge, such high TON of linear amine has never been achieved for long chain internal olefin 2-octene.



Sheme 3-3-1. Structures of applied Tetrabi-type ligands.

Table 3-3-3. Hydroaminomethylation of different internal olefins with tetrabi-type phosphorus ligands.[a]

Entry	Internal Olefin	Ligand	Con. (%)	Amine Sel.[b]	Linear Sel.[b]		TON[d]
					l/b	*n*-Amine (%)[c]	
1	2-pentene	Tb1	99	97.5	48.5	98.0	946
2	2-pentene	Tb2	99	50.3	197.8	99.5	495
3	2-pentene	Tb3	99	26.6	123.9	99.2	259
4	2-pentene	Tb4	99	>99	28.5	96.6	950
5	2-pentene	Tb5	99	99.2	95.6	99.0	972
6	2-hexene	Tb1	99	96.1	42.3	97.7	930
7	2-hexene	Tb2	99	61.8	168.4	99.4	608
8	2-hexene	Tb3	99	46.7	110.6	99.1	458
9	2-hexene	Tb4	99	>99	19.8	95.2	933
10	2-hexene	Tb5	99	98.8	89.7	98.9	967
11	2-octene	Tb1	99	94.9	33.8	97.1	912
12	2-octene	Tb2	99	66.6	146.8	99.3	655
13	2-octene	Tb3	99	52.9	92.4	99.0	518
14	2-octene	Tb4	99	>99	14.8	93.7	918
15	2-octene	Tb5	99	98.2	86.8	98.9	961

[a] Reaction conditions: 1 μmol $Rh(acac)(CO)_2$, 4 μmol ligand, 1 mmol internal olefin, 1 mmol piperidine, 3 ml 2-propanol, CO/H_2 = 5/5 bar, 130°C, 36 h. [b] Selectivity and *l/b* ratio were determined by GC analysis using 2-methoxyethyl ether (0.1 ml) as an internal standard, the average value of 3 repeated runs and 2 injections per run. [c] Percentage of linear amine in all amines. [d] Turnover number was determined on the basis of GC, error is estimated at <20.

We later focused on the isomerization-hydroaminomethylation of different internal olefins (2-pentene, 2-hexene and 2-octene) . The Tetrabi ligand family was applied so that we can study the ligand effect for this reaction. It was supposed that the introduction of substituents at the diphenylphosphane moiety of Tb1 affected both the regioselectivity of the amines and the activity of the catalytic system. In all cases, the catalytic system with ligands contained electron-

withdrawing substituents showed higher regioselectivity (Tb2, Tb3 and Tb5). However, Methyl substituted ligand Tb4 seemed to give better conversion and amine selectivity. When 2-pentene used as substrate, the catalyst with Tb4 as ligand gave the best conversion (>99%) and amine selectivity (>99 %) albeit with *l/b* ratio of 28.5 (Table 3-3-3, Entry 4). Ligand Tb2 afforded the best *l/b* ratio (197.8) for 2-pentene although the conversion and amine selectivity were lower (Table 3-3-3, Entry 2). The position of the substituent also exerted some influence on the chemoselectivity of amine. Ligand Tb5, which contained a CF_3 substituent at the *meta*-position of the diphenylphosphane moiety, gave a higher amine selectivity for 2-pentene than the corresponding ligand Tb3 with the same substituent at the *para*-position (Table 3-3-3, Entries 3, 5). In consideration of conversion, amine selectivity and linear selectivity, ligand Tb5 was found to be the best ligand of these applied Tetrabi-type phosphorus ligands with 99.2% amine selectivity and 95.6 *l/b* ratio for 2-pentene (Table 3-3-3, Entriy 5), 98.8% amine selectivity and 89.7 *l/b* ratio for 2-hexene (Table 3-3-3, Entriy 10), 98.2% amine selectivity and 86.8 *l/b* ratio for 2-octene (Table 3-3-3, Entriy 15). Promisingly, this ligand could be applied in the further study on the isomerization-hydroaminomethylation of other functional olefins.

Conclusion

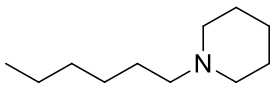
Our Tetrabi-type phosphorus ligands were successfully applied in the one-pot synthesis of amines by isomerization-hydroaminomethylation of internal olefins. 95.3% amine and 36.2 *l/b* ratio were obtained for 2-octene and piperidine with Tetrabi ligand at S/L/Rh ratio of 1000/4/1, and the TON could reach 6837 with 82.5% amine selectivity and 39.1 *l/b* ratio at S/L/Rh ratio of 10000/12/1. The *meta*-CF_3-Ph substituted modified Tetrabi ligand was found to be the best ligand at hand with up to 99.2% amine selectivity and 95.6 *l/b* ratio for 2-pentene.

Experiment section

General procedure for the regioselective hydroaminomethylation

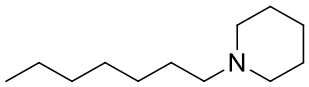
All hydroaminomethylation experiments were performed in the nitrogen-filled glove box. In a typical experiment, a 10-ml long neck vial with a magnetic stirring bar was charged with Tetrabi (4 μmol, 3.8 mg) and Rh (acac)$(CO)_2$ (1 μmol, 0.1 mL of 10 mmol solution in toluene). The mixture was stirred for 10 min; 2-octene (1 mmol, 0.158mL) and piperidine (1 mmol, 0.098 mL) 2 were then added, followed by 2-methoxyethyl ether (0.1 mL) as internal standard, 2-propanol (3mL). The reaction mixture was transferred to an autoclave, vial covered with a simple lid. The autoclave was purged with H_2 three times and subsequently charged with H_2 (5 bar) and CO (5 bar). The reaction was carried out at 130 ℃ for 36 h. After 36 h, the autoclave was then cooled to room temperature and depressurized carefully in a well-ventilated hood. The reaction mixture was immediately analyzed by GC to determine the conversion and regioselectivity.

1-hexylpiperidine (a)



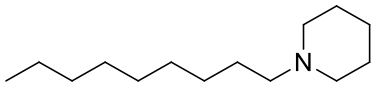
The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1), clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, br, 4H), 2.20 (t, *J* = 7.90 Hz, 2H), 1.51 (quintet, *J* = 4.05 Hz, 4H), 1.31-1.47 (m, 4H), 1.21 (s, 6H), 0.81 (t, *J* = 6.72 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =58.73, 53.68, 30.85, 26.48, 25.96, 25.02, 23.54, 21.62, 13.03.

1-heptylpiperidine (b)



The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1), clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, br, 4H), 2.19 (t, *J* = 7.92 Hz, 2H), 1.51 (quintet, *J* = 5.63 Hz, 4H), 1.30-1.48 (m, 4H), 1.20 (s, 8H), 0.81 (t, *J* = 6.90 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =58.73, 53.69, 30.82, 28.29, 26.76, 26.00, 24.98, 23.55, 21.62, 13.06.

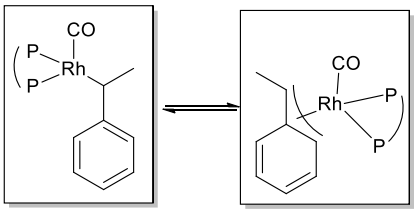
1-nonylpiperidine (c)



The crude product was purified by flash chromatography (n-hexane/EtOAc, 30:1), clear liquid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.36 (s, br, 4H), 2.26 (t, *J* = 7.82 Hz, 2H), 1.58 (quintet, *J* = 5.22 Hz, 4H), 1.38-1.54 (m, 4H), 1.27 (s, 12H), 0.88 (t, *J* = 6.22 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =59.78, 54.92, 31.94, 29.68, 29.62, 29.34, 27.84, 27.02, 26.05, 24.57, 22.71, 14.11.

3.4 Highly regioselective hydroaminomethylation of styrenes

Linear-selective hydroaminomethylation of styrenes is very challenging among the different alkenes. During the hydroformylation step, it has the intrinsic trend to form branched amines caused by the formation of η^3-Rh-complex (Scheme 3-4-1). Without any phosphine ligand, Rh can catalyze the hydroamino-methylation of styrenes to offer branched products with good electivity (b/l up to 16).[1] Selective hydroaminomethylation of styrene to linear amine (l/b = 82/18) in the presence of Xantphos as a ligand was previously reported by Beller's group.[2] however, there is no systematical study on the highly linear selective hydroaminomethylation of styrenes to produce 3-arylpropylamines.We believe that the choose of phosphine ligands is the key to implementing the highly linear selective hydroaminomethylation of styrenes. Styrene has been hydroformylated to the linear aldehyde with surprisingly high linear selectivity (l/b=22 for styrene, l/b up to >99:1 for its derivatives) with our Tetrabi and TBBP ligangs.[3] The high linear regioselectivity prompted us to assess our ligands further in the hydroaminomethylation of styrenes, since the selectivity in hydroaminomethylation is mainly provided by the initial hydroformylation step.



η^1-Rh-complex η^3-Rh-complex

Scheme 3-4-1.

Results and discussion

Initially, combinations of $[Rh(nbd)_2BF_4]$ with different tetraphosphorus ligands (Figure 3-4-1) were tested in the model reaction of styrene with piperidine. Some representative results regarding the influence of ligands and solvents are shown in Table 3-4-1.

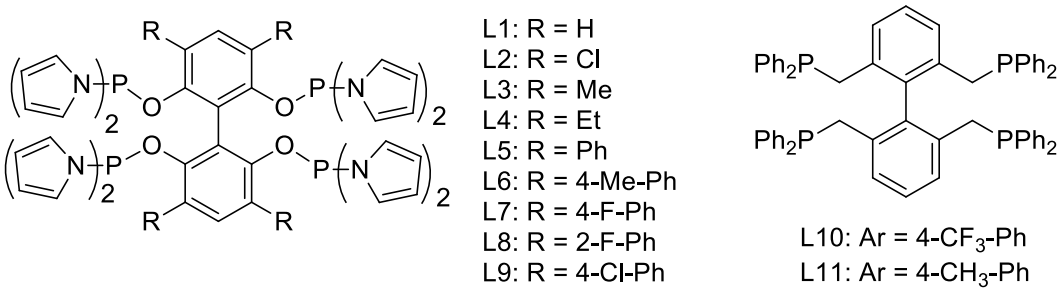
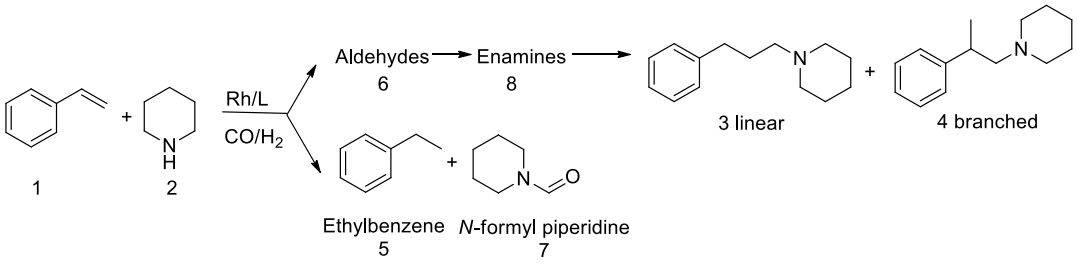


Figure 3-4-1. Structures of the tested ligands.

Table 3-4-1. Hydroaminomethylation of styrene with different ligands and solvents.



			product distribution (%)[b]					
entry	L	Conv.(%)	6	7	8	3+4	3[c]	l/b [d]
1	L1	97	4.8	3.1	59.9	32.2	60.0	1.5
2	L2	92	7.8	5.6	56.1	30.4	58.3	1.4
3	L3	100	1.5	1.9	40.2	56.3	82.1	4.6
4	L4	100	3.1	1.9	39.8	55.2	80.4	4.1
5	L5	100	3.9	16.0	41.6	38.1	62.9	1.7
6	L6	100	3.9	13.5	42.7	39.8	64.3	1.8
7	L7	98	5.1	24.1	32.7	38.0	54.5	1.2
8	L8	100	6.1	9.4	57.7	26.8	50.0	1.0
9	L9	100	8.5	10.7	57.4	23.4	47.4	0.9

10	L10	98	5.1	4.5	52.3	34.8	47.4	0.9
11	L11	82	1.7	6.7	21.2	66.3	23.1	0.3
12	L3	100	5.8	2.2	41.4	50.6	77.8	3.5
13	L3	100	0.7	2.3	0	97	11.5	0.13
14	L3	100	0.2	1.4	0	98.4	14.5	0.17
15	L3	100	0.5	1.2	0	98.3	16.0	0.19
16	L3	98	1.9	0.3	51.3	46.5	90.5	9.5
17	L3	99	0.4	2.4	18.0	79.2	52.4	1.1

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(nbd)_2]BF_4$/ligand/substrate ratio of 1:4:500, under syngas of CO/H_2 (30 bar/10 bar) at 125 ^oC for 8 h. Ethylbenzene accounts for the product balance. Solvents used: entries 1-11 (toluene), 12 (xylene), 13 (methanol), 14 (ethanol), 15 (isopropanol), 16 (tert-amylalcohol), 17 (tert-amyl alcohol/ methanol=1:1). [b] Determined by GC analysis using bis(methoxyethyl) ether as an internal standard. [c] Percentage of linear amine in all amines. [d] The linear/branched ratio was determined on the basis of GC analysis and repeated three times; error is estimated to be <0.2. nbd=2,5-norbornadiene.

The result showed that most of the Rh catalysts used give high conversions. It should be noted that compared with pyrrole-based tetraphosphorus ligands (L1- L9), Tetrabi ligands produced more ethylbenzene as byproduct through direct hydrogenation (Table 3-4-1, entries 10 and 11). Moreover, the linear selectivity of Tetrabi ligands is very poor with the branched amines as major products. Although the amines selectivity is not satisfactory, the linear selectivity is promising with the pyrrole-based TBBP ligands. Compared with ligand L1, the attachment of methyl and ethyl groups at the 3,3',5,5'-positions of the biphenyl backbone results in higher amines selectivity with yields of 56.3% and 55.2% and linear selectivity with an l/b ratio of 4.6 and 4.1, respectively (Table 3-4-1, entries 3 and 4). The linear selectivity is improved when replaced by a phenyl group (Table 3-4-1, entry 5). The effect of the substituents of the phenyl moiety on selectivity is also remarkable (Table 3-4-1, entries 5-9). Among the tested ligands, L3 appeared to be the optimal ligand giving good regioselectivity (l/b = 4.52). In the survey of solvent effects on the regioselectivity, aromatic solvent xylene was first tested to give both low

yield and linear selectivity, although full conversion was achieved (Table 3-4-1, entry 12). The reaction proceeds smoothly in more polar solvents (Table 3-4-1, entries 13-15) and the yields of amines are excellent. However, the regioselectivity of this reaction was converted to a branched amine. The linear selectivity increased following the trend MeOH< EtOH< iPrOH. It motivated us to test alcohol with more bulky groups. The regioselectivity improved dramatically in *tert*-amyl alcohol with l/b = 9.5. To improve the l/b ratio, other Rh sources with different counterions were screened with L3 in tert-amyl alcohol. A positive impact on regioselectivity was observed when the BF_4^- counterion was replaced by SbF_6^- (Table 3-4-2, entry 5, l/b=15.5).

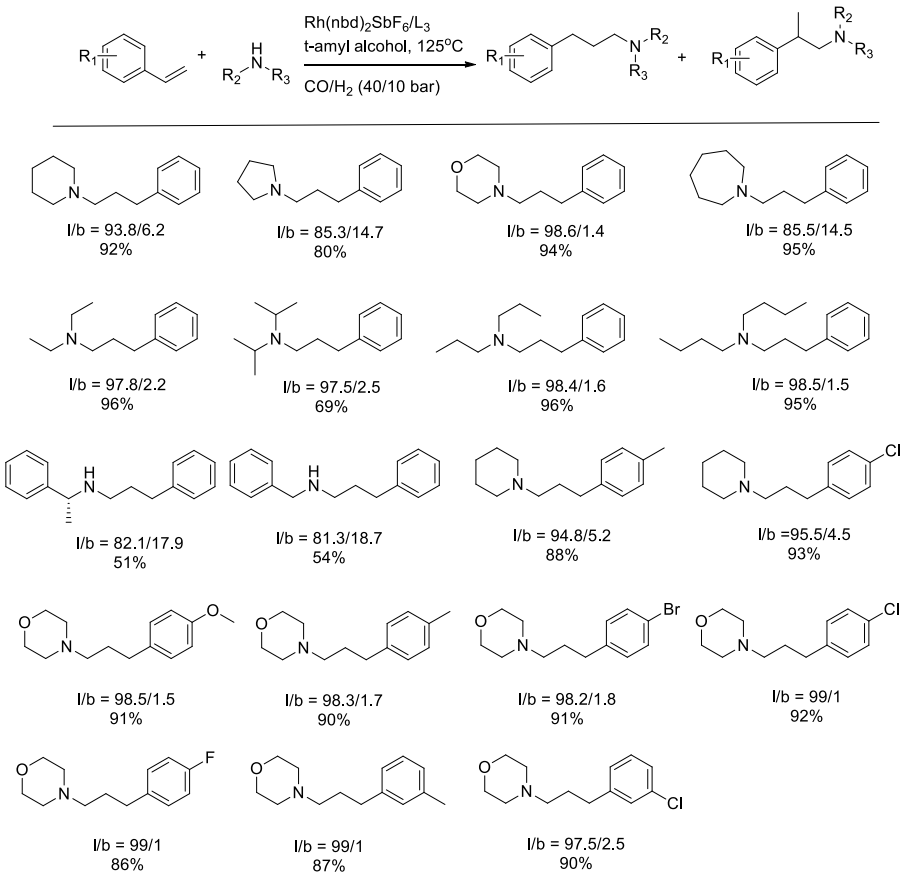
Table 3-4-2. Hydroaminomethylation of styrene with piperidine with different metal sources and pressures. [a]

			product distribution (%) [b]			
Entry	L/Rh	CO/H_2	8	3+4	3[c]	l/b [d]
1	4	30/10	33.6	62.4	87.2	6.8
2	4	30/10	44.8	48.9	91.1	10.2
3	4	30/10	32.9	61.1	91.9	11.4
4	4	30/10	34.4	60.3	92.8	12.8
5[e]	4	30/10	50.3	44.2	93.9	15.5
6[e]	4	20/10	53.7	42.3	93.4	14.1
7[e]	4	20/20	44.2	46.3	93.2	13.6
8[e]	4	10/30	42.1	50.6	91.8	11.2
9[f]	4	40/10	-	92.2	93.5	14.4
10[f]	2	40/10	-	92.4	93.8	15.1
11[f]	1	40/10	7.1	91.1	92.8	12.9
12[f,g]	2	40/10	45.4	54.4	91.4	10.6

[a] Rh/substrate=1:500, styrene/piperidine=1:1, *tert*-amyl alcohol, 125 ^oC, 8 h. Full conversion was achieved based on piperidine. Ethylbenzene and aldehydes account for the product balance. Entry 1 ($[Rh(cod)Cl]_2$), 2 ($Rh(cod)_2BF_4$), 3 ($Rh(acac)(CO)_2$), 4 ($Rh(acac)(C_2H_4)_2$), entries 5-12 ($Rh(nbd)_2SbF_6$). [b] Determined by GC analysis using bis(methoxyethyl) ether as an internal standard. [c] Percentage of linear amine in all amines. [d] The linear/branched ratio was determined on the basis of GC analysis and repeated three times [e] Trace of N-formylpiperidine was detected. [f] Styrene/piperidine=2, 16 h. [g] Rh/substrate=1:1000. cod=1, 5-cyclooctadiene, acac=acetyl acetonate, nbd=2,5-norbornadiene.

Further optimizations demonstrated that increasing the partial pressure of CO and doubling the reaction time raised the proportion of amines up to 92.4% and suppressed the formation of enamine thoroughly when one more equivalent of styrene was added (Table 3-4-2, entry 10). The ligand/Rh ratio can be reduced from 4 to 1 without obvious decline in conversion and the yields of amines (Table 3-4-2, entry 11). Thus, the consumption of ligands decreased compared with the available bisphosphorus and monophosphorus ligands in the hydroaminomethylation. Both the conversion and amine selectivity decreased when the catalyst loading was <0.2% (Table 3-4-2, entry 12). The optimized conditions were set as styrene/amine = 2:1, 0.2% Rh (L/Rh = 2), CO/H_2 (40 bar/10 bar), at 125 ^oC for 16 h.

Table 3-4-3. Hydroaminomethylation of styrenes and amines [a]



[a] Conditions: $Rh(nbd)_2SbF_6$/L3/styrenes/amine = 0.2:0.4:200:100,CO/H_2 (40 bar/10 bar), 125 ^oC,16 h. Full conversion was achieved based on the amines. Yields (data in parentheses) of the total amines were determined by

GC analysis using bis(methoxyethyl) ether as an internal standard. l/b = linear amine (%)/branched amine (%), determined on the basis of GC analysis and repeated three times; error is estimated to be <0.2.

The compatibility of our protocol in the hydroaminomethylation of styrenes with various amines was tested. As shown in Table 3-4-3. Styrene was hydroaminomethylated smoothly with a series of aliphatic secondary amines in full conversion, including both cyclic amines (3a-3d) and chain amines (3e-3h). Compared with cyclic amines without a heteroatom, the chain amines produced better regioselectivity with l/b> 95:5 and the linear selectivity followed the trend Ethyl < n-Propyl < n-Butyl (3e, 3g, 3h). Compared with piperidine (3a), azepane afforded a higher yield of amine (95%, 3d), albeit with lower linear selectivity. The erosion of both amine yield and regioselectivity was detected in the hydroaminomethylation of pyrrolidine (yield of 80%, l/b = 85.3/14.7, 3b), in which trace aldol product was also detected. The hydroaminomethylation of styrene with morpholine proceeded with excellent regioselectivity (l/b = 98.6/1.4) to give 94% of the desired amines (3c). Primary amines were also investigated in this reaction (3i and 3j), although the yield and selectivity were not satisfactory (bishydroaminomethylation and carbonylation of amines were detected. Ammonia was also tested without any promising results. Hydroaminomethylation of para-substituted styrenes with piperidine gave higher linear selectivities, regardless of the electronic effects of the substituents (3k and 3l). Both high yield of amines and good linear selectivity were obtained from the reaction of substituted styrenes with morpholine (3m-3s), among which p-chloro, p-fluoro, and m-methyl styrenes furnished excellent linear selectivity with l/b up to 99/1 (3p-3r).

Conclusion

A highly regioselective hydroaminomethylation of styrene and its derivatives to linear amines using $Rh(nbd)_2SbF_6$ with pyrrole-based TBBP ligands was disclosed. The highest linear selectivity was reported for the hydroaminomethylation of styrene and its derivatives. The

performance of the present system can be accounted for by the electron-withdrawing property of the pyrrole moiety and the steric interactions between the more bulky TPPB ligands and the substrates. This creates an obstacle for the formation of η^3-Rh-complexes that favors the branched product.

Experiment section

Typical procedure for hydroaminomethylation In the optimization of hydroaminomethylation of styrene and piperidine: For the ligands (L1~L9), all manipulations before being charged with CO/H_2 were performed and exposed to air. For the ligands (L10 and L11), all corresponding manipulations were carried out in a nitrogen-filled glovebox or using standard Schlenk techniques.

Typical optimized regioselective hydroaminomethylation A 5mL glass vial with a magnetic stirring bar was charged with $[Rh(nbd)_2]SbF_6$ (0.002mmol) with tetraphosphorus ligand L3 (0.004 mmol) in 1mL t-Amyl alcohol. The mixture was stirred for 15 min. Styrene (2 mmol) and piperidine (1 mmol) was then added, followed by the addition of 2-methoxyethyl ether (1mmol) as internal standard, 3 additional t-Amyl alcohol was added to bring the total reaction volume to 2 mL. The reaction mixture was transferred to an autoclave. The autoclave was purged with hydrogen three times and subsequently charged with H_2 (10 bar) and CO (40 bar). The autoclave was then immersed in a preheated oil bath (125℃) and well stirred. After desired time, the autoclave was cooled in icy water, and the pressure was carefully released in a well-ventilated hood. The reaction mixture was immediately analyzed by GC to determine conversion and regioselectivity prior to the further purification on column chromatography.

1-(3-phenylpropyl)piperidine (3a) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5%

Et_3N). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.43 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.58 (m, 4H, $N(CH_2CH_2)_2CH_2$), 1.82 (m, 2H, Ph-CH_2CH_2), 2.30~2.36 (m, 6H, CH_2N $(CH_2CH_2)_2CH_2$), 2.61 (t, *J* = 7.6 Hz, 2H, Ph-CH_2), 7.14~7.18 (m, 3H, aromatic *H*), 7.24~7.27 (m, 2H, aromatic *H*); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 24.5(CH_2), 26.2(2×CH_2), 28.7(CH_2), 33.9(CH_2), 54.6(2×CH_2) , 58.9(CH_2), 125.7(*CH*), 128.3(2×*CH*) 128.4(2×*CH*), 142.3 (*C*). ESI-MS, Calcd for [M+H] 204.18, found 204.21.

1-(2-phenylpropyl)piperidine (4a) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ:1.26 (d, *J* = 7.2 Hz , 3H, Ph-$CHCH_3$), 1.39~1.42 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.51~1.58(m, 4H, $N(CH_2CH_2)_2CH_2$), 2.30(m, 2H, Ph-$CH(CH_3)CH_2N$), 2.37-2.45(m, 4H, $N(CH_2CH_2)_2CH_2$), 2.95(m, 1H, Ph-C*H*(CH_3) CH_2N), 7.16~7.22 (m, 3H, aromatic *H*), 7.25~7.31 (m, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.1(CH_3), 24.5(2×CH_2), 26.0(2×CH_2), 37.5(*CH*), 54.9(CH_2), 67.1(CH_2), 126.0(*CH*) , 127.2(2×*CH*), 128.3(2×*CH*), 146.6(*C*). ESI-MS, Calcd for [M+H] 204.18, found 204.22.

1-(3-phenylpropyl)pyrrolidine (3b) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N).^{1}H-NMR ($CDCl_3$, 400 MHz) δ:1.71 (m, 4H, $N(CH_2CH_2)_2$), 1.81(m, 2H, Ph-CH_2CH_2), 2.39~2.46(m, 6H, $CH_2N(CH_2CH_2)_2$), 2.59(t, *J* = 8.0 Hz, 2H, Ph-CH_2). 7.09~7.13 (m, 3H, aromatic *H*), 7.19~7.23(m, 2H, 7aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 23.4 (2×CH_2), 30.6 (CH_2), 33.9 (CH_2), 54.2 (2×CH_2), 56.1(CH_2) , 125.7(*CH*), 128.3(2×*CH*), 128.4(2×*CH*), 142.2(*C*).ESI-MS, Calcd for[M+H] 190.16, found 190.17.

1-(2-phenylpropyl)pyrrolidine (4b) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ:1.29 (d, *J* = 7.2 Hz, 3H, Ph-$CHCH_3$), 1.71~1.74(m, 4H, $N(CH_2CH_2)_2$), 2.41~2.52(m, 5H, Ph-$CH(CH_3)$ CH_2-$N(CH_2CH_2)_2$), 2.69 (dd, *J* = 8.4 Hz, 12 Hz, 1H, Ph-$CH(CH_3)$ CH_2), 2.92(m, 1H, Ph-C*H*(CH_3)), 7.17~7.23(m, 3H, aromatic *H*),7.27~7.30(m, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.3(*CH_3*), 23.5(2×*CH_2*), 39.6(*CH*), 54.5(2×*CH_2*), 64.5(*CH_2*), 126.0(*CH*), 127.1(2×*CH*), 128.3(2×*CH*), 146.6(*C*). ESI-MS, Calcd for[M+H] 190.16, found 190.18.

4-(3-phenylpropyl)morpholine (3c) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.82(m, 2H, Ph-CH_2*CH_2*), 2.35(t, *J* = 8.0 Hz, 2H, Ph-CH_2CH_2*CH_2*), 2.43(t, *J* =4.4Hz, 4H, $N(CH_2CH_2)_2O$), 2.64(t, *J* = 7.6Hz, 2H, Ph-CH_2), 3.71(t, *J* = 4.4Hz, 4H, $N(CH_2CH_2)_2O$), 7.16~7.19 (m, 3H, aromatic *H*), 7.25~7.29 (m, 2H, aromatic *H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.2(*CH_2*), 33.6(*CH_2*), 53.7(2×*CH_2*), 58.4(*CH_2*), 67.0(2×*CH_2*), 125.9(*CH*), 128.3(2×*CH*), 128.4(2× *CH*), 142.1(*C*). ESI-MS, Calcd for[M+H] 206.15, found 206.17.

1-(3-phenylpropyl)azepane (3d) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N).^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.59~1.63(m, 8H, $N(CH_2CH_2$ $CH_2)_2$), 1.78(m, 2H, Ph-CH_2CH_2*CH_2*), 2.49(t, *J* = 7.2Hz, 2H, Ph-$CH_2CH_2CH_2$), 2.61(t, *J* = 8.4Hz, 2H, Ph-CH_2), 2.60~2.64(m, 4H, $N(CH_2CH_2$ $CH_2)_2$), 7.14~7.19(m, 3H, aromatic *H*), 7.25~7.28 (m, 2H, aromatic *H*); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 27.0(2× *CH_2*), 28.1(2 ×*CH_2*), 29.4(*CH_2*),

33.8(*CH*$_2$), 55.5(2 ×*CH*$_2$), 57.7(*CH*$_2$), 125.6(*CH*), 128.3(2 ×*CH*), 128.4(2×*CH*), 142.5(*C*). ESI-MS, Calcd for[M+H] 218.19, found 218.20.

N,N-diethyl-3-phenylpropan-1-amine (3e) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N).^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.94(t, *J* = 7.2Hz, 6H, $N(CH_2CH_3)_2$), 1.72(m, 2H, Ph-CH_2CH_2*CH*$_2$), 2.38~2.49(m, 6H, $CH_2N(CH_2CH_3)_2$), 2.54(t, *J* = 7.2Hz, 2H, Ph-CH_2), 7.08~7.13(m, 3H, aromatic *H*), 7.18~7.22 (m, 2H, aromatic *H*); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 11.6(2×*CH*$_3$), 28.6(*CH*$_2$), 33.9(*CH*$_2$), 46.9(2×*CH*$_2$), 52.4(*CH*$_2$), 125.7(*CH*), 128.3(2×*CH*), 128.4(2×*CH*),142.4(*C*).ESI-MS, Calcd for [M+H] 192.18, found 192.19.

***N,N*-diisopropyl-3-phenylpropan-1-amine (3f)** Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N).^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.02(d, *J* = 6.8Hz, 12H, 4×CH_3), 1.80(m, 2H, Ph-$CH_2CH_2CH_2$), 2.49(t, *J* = 7.6Hz, 2H, Ph-$CH_2CH_2CH_2$), 2.60(t, *J* = 7.6Hz, 2H, Ph-CH_2), 3.10(m, 2H, Ph- N(C*H*)$_2$), 7.14~7.19(m, 3H, aromatic *H*), 7.22~7.28 (m, 2H, aromatic *H*);^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.1(4 ×*CH*$_3$), 31.8(*CH*$_2$), 33.7(*CH*$_2$), 45.2(*CH*$_2$),49.5(2×*CH*), 125.7(*CH*),128.3(2×*CH*),128.4(2×*CH*), 142.2(*C*). ESIMS, Calcd for[M+H] 220.21, found 220.20.

3-phenyl-N,N-dipropylpropan-1-amine (3g) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.86(t, *J* = 7.6Hz, 6H, 2×CH_3), 1.43(m, 4H, $N(CH_2CH_2CH_3)_2$), 1.77(m, 2H, Ph-$CH_2CH_2CH_2$), 2.38(t, *J* = 7.6Hz, 4H, $N(CH_2CH_2CH_3)_2$), 2.46(t, *J* = 7.2Hz, 2H, Ph-$CH_2CH_2CH_2$N), 2.61(t, *J* = 7.6Hz, 2H, Ph-CH_2), 7.14~7.19(m, 3H, aromatic *H*), 7.25~7.28 (m, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ:11.9(2×*CH*$_3$),

20.0(2×*CH*$_2$), 28.7(*CH*$_2$), 33.8(*CH*$_2$), 53.7(*CH*$_2$), 6.1(2×*CH*$_2$), 125.7(*CH*), 128.3(2×*CH*), 128.4(2×*CH*), 142.4(*C*). ESI-MS, Calcd for[M+H] 220.21, found 220.18.

N-butyl-N-(3-phenylpropyl)butan-1-amine (3h) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 0.90(t, *J* = 7.2Hz, 6H, 2×CH_3), 1.29~1.43(m, 8H, N($CH_2CH_2CH_2CH_3$)$_2$), 1.76 (m, 2H, Ph-$CH_2CH_2CH_2$), 2.40(t, *J* = 7.2Hz, 4H, N($CH_2CH_2CH_2CH_3$)$_2$), 2.45(t, *J* = 7.6Hz, 2H, Ph-$CH_2CH_2CH_2N$), 2.61(t, *J* = 8.0Hz, 2H, Ph-CH_2), 7.15~7.20(m, 3H, aromatic *H*), 7.25~7.29 (m, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ:14.1(2×*CH*$_3$), 20.8(2×*CH*$_2$), 28.9(*CH*$_2$), 29.3(2×*CH*$_2$), 33.9(*CH*$_2$), 53.7(*CH*$_2$), 53.9(2×*CH*$_2$), 125.6(*CH*), 128.3(2×*CH*), 128.4(2×*CH*), 142.6(*C*). ESI-MS, Calcd for[M+H] 248.24, found 248.21.

(*R*)-3-phenyl-N-(1-phenylethyl)propan-1-amine (3i) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 10% MeOH in Ethyl acetate with 1% Et_3N). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.33(d, *J* = 7.2 Hz, 3H, Ph-CH*CH*$_3$), 1.48(s, br, 1H, NH), 1.78(m, 2H, Ph-CH_2*CH*$_2$), 2.44~2.67(m, 4H, Ph-$CH_2CH_2CH_2NH$), 3.74(q, *J* = 6.4 Hz, 1H,Ph-C*H*), 7.13~7.17(m, 3H, aromatic *H*), 7.20~7.28(m, 3H, aromatic *H*), 7.29~7.33(m, 4H, aromatic *H*); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 24.3(*CH*$_3$), 31.9(*CH*$_2$), 33.7(*CH*$_2$), 47.4(*CH*$_2$), 58.3(*CH*), 125.7(*CH*), 126.6(2×*CH*), 126.8(*CH*), 128.3(2×*CH*), 128.4(2×*CH*), 128.5(2×*CH*), 142.3(*C*), 145.9(*C*). ESI-MS, Calcd for[M+H] 240.18, found 240.20.

N-benzyl-3-phenylpropan-1-amine (3j) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 10% MeOH in Ethyl acetate

with 1% Et_3N). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.49(s, br, 1H, *NH*), 1.81(dd, *J*1=*J*2=8Hz, 2H, Ph-CH_2*CH_2*), 2.61~2.66 (m, 4H, Ph-CH_2CH_2 CH_2NH), 3.74(s, 2H,Ph-CH_2), 7.14~7.30(m, 10H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 31.7(*CH_2*), 33.7(*CH_2*), 48.9(*CH_2*), 54.0(*CH_2*), 125.8(*CH*), 126.9(*CH*), 127.8(2×*CH*), 28.2(2×*CH*), 128.4(2×*CH*), 128.5(2×*CH*), 140.4(*C*), 142.2(*C*). ESI-MS, Calcd for[M+H] 226.16, found 226.24.

1-(3-(p-tolyl)propyl)piperidine (3k) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.43 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.56 (m, 4H, $N(CH_2CH_2)_2CH_2$), 1.81 (m, 2H, Ph-CH_2*CH_2*), 2.25~2.35 (m, 6H, CH_2N $(CH_2CH_2)_2CH_2$), 2.31 (s, 3H, Ph-*CH_3*), 2.57 (t, *J* = 7.6 Hz, 2H, Ph-*CH_2*), 7.01~7.13 (m, 4H, aromatic *H*); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.9(*CH_3*), 24.5(*CH_2*), 26.1(2×*CH_2*), 28.8(*CH_2*), 33.5(*CH_2*), 54.6(2×*CH_2*), 59.1(*CH_2*), 128.3(2×*CH*), 128.9(2×*CH*), 135.1 (*C*), 139.2(*C*). ESI-MS, Calcd for[M+H] 218.19, found 218.21.

1-(3-(4-chlorophenyl)propyl)piperidine (3l) Light yellow oil, (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N, didn't get pure linear amine product because of similar physical properties of the linear and branched isomers). ESI-MS(mixture of 3l and 4l), Calcd for [M+H] 238.14, found 238.16.

1-(2-(4-chlorophenyl)propyl)piperidine (4l) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.15 (d, *J* = 7.2 Hz, 3H, Ph-CH*CH_3*), 1.31 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.45(m, 4H, $N(CH_2CH_2)_2CH_2$), 2.23~2.32(m, 6H, $CH_2N(CH_2CH_2)_2CH_2$), 2.85(m, 1H, Ph-C*H*), 7.05(dd, *J* = 1.6 Hz, 7.2 Hz, 2H, aromatic *H*), 7.17(dd, *J* = 1.6 Hz, 7.2 Hz,

2H, aromatic *H*) ; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ:20.1(*CH_3*), 24.4(*CH_2*), 26.0(2×*CH_2*), 37.0(*CH*), 54.9(2×*CH_2*), 66.8(*CH_2*), 128.3(2×*CH*), 128.6(2×*CH*), 131.5(*C*), 145.1(*C*). ESI-MS, Calcd for[M+H] 238.14, found 218.16.

4-(3-(4-methoxyphenyl)propyl)morpholine (3m) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.78 (m, 2H, Ph-CH_2*CH_2*), 2.34 (t, *J* = 7.6 Hz, 2H, Ph- CH_2CH_2*CH_2*), 2.42 (m, 4H, N(CH_2CH_2)$_2$O),. 2.58 (t, *J* = 7.6Hz, 2H, Ph-CH_2), 3.71 (t, *J* = 4.8Hz, 4H, N(CH_2CH_2)$_2$O), 3.78 (s, 3H, Ph-O*CH_3*), 6.82 (d, *J* = 8.4Hz, 2H, aromatic *H*), 7.08 (d, *J* = 8.4Hz, 2H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.5 (*CH_2*), 32.7 (*CH_2*), 53.8 (2×*CH_2*), 55.2 (O*CH_3*), 58.4 (*CH_2*), 67.0 (2×*CH_2*), 113.7 (2×*CH*), 129.3 (2×*CH*), 134.1 (*C*), 157.8 (*C*). ESI-MS, Calcd for M+H] 236.17, found 236.46.

4-(2-(4-methoxyphenyl)propyl)morpholine (4m) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.24 (d, *J* = 7.2 Hz, 3H, Ph-CH*CH_3*), 2.36~2.48 (m, 6H, CH_2N(CH_2CH_2)$_2$O), 2.89 (m, 1H, Ph-C*H*), 3.67 (t, *J* = 5.6Hz, 4H, N(CH_2CH_2)$_2$O), 3.77 (s, 3H, Ph-O*CH_3*), 6.84 (d, *J* = 8.4Hz, 2H, aromatic *H*), 7.12 (d, *J* = 8.4Hz, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.1 (*CH_3*), 36.2 (*CH*), 54.0 (2×*CH_2*), 55.2 (O*CH_3*), 66.8 (*CH_2*), 67.1 (2×*CH_2*), 113.7 (2×*CH*), 128.0 (2×*CH*), 138.1(*C*), 157.9 (*C*). ESI-MS, Calcd for [M+H] 236.17, found 236.25.

4-(3-(p-tolyl)propyl)morpholine (3n) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.78(m, 2H, Ph-CH_2*CH_2*), 2.31(s, 3H, Ph-*CH_3*), 2.37(t, *J* = 7.6 Hz, 2H, Ph- CH_2CH_2*CH_2*), 2.42(t, *J* = 4.4Hz, 4H, N(CH_2CH_2)$_2$O), 2.60(t, *J* = 7.6Hz, 2H, Ph-

CH_2), 3.71(t, *J* = 4.4Hz, 4H, N(CH_2CH_2)$_2$O), 7.05~7.10(m, 4H, aromatic *H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.1(*CH_3*), 28.4(*CH_2*), 33.2(*CH_2*), 53.8(2×*CH_2*), 58.4(*CH_2*), 67.0(2×*CH_2*), 128.3(2×*CH*), 129.0(2×*CH*), 135.2(*C*), 138.9(*C*). ESI-MS, Calcd for[M+H] 220.17, found 220.17.

4-(3-(4-bromophenyl)propyl)morpholine (3o) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.78 (m, 2H, Ph-CH_2*CH_2*), 2.31 (t, *J* = 4.4 Hz, 2H, Ph-CH_2CH_2*CH_2*), 2.37 (m,4H, N(CH_2CH_2)$_2$O), 2.61 (t, *J* = 7.2Hz, 2H, Ph-CH_2), 3.70 (t, *J* = 4.4Hz, 4H, N(CH_2CH_2)$_2$O), 7.05 (dd, *J*= 2.8 Hz, 8.4Hz, 2H, aromatic *H*), 7.38 (m, 2H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.1 (*CH_2*), 32.9 (*CH_2*), 53.7 (2×*CH_2*), 58.1 (*CH_2*), 67.0 (2×*CH_2*), 119.5 (*C*), 130.2 (2×*CH*), 131.4 (2×*CH*), 141.0 (*C*). ESI-MS, Calcd for[M+H] 284.07, found 284.58.

4-(2-(4-bromophenyl)propyl)morpholine (4o) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.23 (d, *J* = 6.8 Hz, 3H, Ph-CH*CH_3*), 2.37~2.44 (m, 6H, CH_2N(CH_2CH_2)$_2$O),2.92 (m, 1H, Ph-C*H*), 3.65 (t, *J* = 4.4Hz, 4H, N(CH_2CH_2)$_2$O), 7.07 (d, *J* = 7.6 Hz, 2H, aromatic *H*), 7.40(d, *J* = 7.6 Hz, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 19.9 (*CH_3*), 36.6(*CH*), 53.9 (2×*CH_2*), 66.2 (*CH_2*), 67.0 (2×*CH_2*), 119.7 (*C*), 128.9 (2×*CH*), 131.4 (2×*CH*), 145.0 (*C*). Calcd for[M+H] 284.07, found 284.38.

4-(3-(4-chlorophenyl)propyl)morpholine (3p) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.77(m, 2H, Ph-CH_2*CH_2*), 2.32(t, *J* = 7.2 Hz, 2H, Ph-CH_2CH_2*CH_2*), 2.41(t, *J* = 4.4Hz, 4H, N(CH_2CH_2)$_2$O), 2.60(t, *J* = 7.6Hz, 2H, Ph-CH_2),

3.69(t, *J* = 4.4Hz, 4H, $N(CH_2CH_2)_2O$), 7.09(d, *J* = 7.2Hz, 2H, aromatic *H*), 7.22(dd, *J* = 1.6 Hz ,7.2Hz, 2H, aromatic *H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:28.1(*CH_2*), 32.8(*CH_2*), 53.7(2×*CH_2*), 58.0(*CH_2*), 66.9(2×*CH_2*), 128.4(2×*CH*), 129.7(2×*CH*), 131.5(*C*), 140.5(*C*). ESI-MS, Calcd for[M+H] 240.12, found 240.11.

4-(2-(4-chlorophenyl)propyl)morpholine (4p) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.26(d, *J* = 7.2 Hz, 3H, Ph-CH*CH_3*), 2.38~2.47(m, 6H, $CH_2N(CH_2CH_2)_2O$), 2.94(m, 1H, Ph-C*H*), 3.67(t, *J* = 4.8Hz, 4H, $N(CH_2CH_2)_2O$), 7.15(d, *J* = 8.4 Hz, 2H, aromatic *H*), 7.26 (d, *J* = 8.4 Hz, 2H, aromatic *H*). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ:19.9 (*CH_3*), 36.6 (*CH*), 54.0 (2×*CH_2*), 66.3 (*CH_2*), 66.9 (2×*CH_2*), 128.4 (2×*CH*), 128.5(2×*CH*), 131.7(*C*), 144.5(*C*). ESI-MS, Calcd for[M+H] 240.12, found 240.08.

4-(3-(4-fluorophenyl)propyl)morpholine (3q) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.79 (m, 2H, Ph-CH_2*CH_2*), 2.34 (t, *J* = 7.6 Hz, 2H, Ph-CH_2CH_2*CH_2*), 2.37 (m, 4H, $N(CH_2CH_2)_2O$), 2.61 (t, *J* = 7.6 Hz, 2H, Ph-CH_2), 3.72 (t, *J* = 4.8Hz, 4H, $N(CH_2CH_2)_2O$), 6.96 (m, 2H, aromatic *H*), 7.14 (m, 2H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.4 (*CH_2*), 32.7(*CH_2*), 53.7(2×*CH_2*), 58.2 (*CH_2*), 67.0 (2×*CH_2*), 115.1 (d, *JCF* = 20 Hz, 2×*CH*), 129.7 (d, *JCF* = 8 Hz, 2×*CH*), 137.6 (d, *JCF* = 3 Hz, *C*), 161.2(d, *JCF* = 242 Hz, *C*). ESI-MS, Calcd for [M+H] 224.15, found 224.41.

4-(3-(m-tolyl)propyl)morpholine (3r) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.81(m, 2H, Ph-CH_2*CH_2*), 2.31 (s, 3H, Ph-*CH_3*), 2.34 (t, *J*

= 7.6 Hz, 2H, Ph- $CH_2CH_2CH_2$), 2.40~2.41 (m, 4H, $N(CH_2CH_2)_2O$), 2.59(t, *J* = 7.6Hz, 2H, Ph-CH_2), 3.69(t, *J* = 4.8Hz, 4H, $N(CH_2CH_2)_2O$), 6.96~6.99 (m, 3H, aromatic *H*), 7.15(dd, *J*1 = *J*2=7.6 Hz, 1H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.4(*CH*$_3$), 28.3(*CH*$_2$), 33.6(*CH*$_2$), 53.8(2 ×*CH*$_2$), 58.5(*CH*$_2$), 67.1(2 ×*CH*$_2$), 125.4(*CH*), 126.6(*CH*), 128.3(*CH*), 129.3(*CH*), 137.8(*C*), 142.1(*C*). ESI-MS, Calcd for[M+H] 220.17, found 220.11.

4-(2-(m-tolyl)propyl)morpholine (4r) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (d, *J* = 6.8 Hz, 3H, Ph-CH*CH*$_3$), 2.32 (s, 3H, Ph-*CH*$_3$), 2.37(m, 2H, Ph-CH*CH*$_2$), 2.41~2.45 (m, 4H, $N(CH_2CH_2)_2O$), 2.89 (m, 1H, Ph-*CH*CH_2), 3.63~3.71(m, 4H, $N(CH_2CH_2)_2O$), 6.98~7.01 (m, 3H, aromatic *H*), 7.14~7.19 (m, 1H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.9(*CH*$_3$), 21.6(*CH*$_3$), 37.1(*CH*), 54.1(2 × *CH*$_2$), 66.7(*CH*$_2$), 67.1(2 × *CH*$_2$), 124.2(*CH*), 126.9(*CH*), 128.1(*CH*), 128.3(*CH*), 137.8(*C*), 146.1(*C*). ESI-MS, Calcd for[M+H] 220.17, found 220.19.

4-(3-(3-chlorophenyl)propyl)morpholine (3s) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.79 (m, 2H, Ph-CH_2*CH*$_2$), 2.31 (t, *J* = 8.0 Hz, 2H, Ph-CH_2CH_2*CH*$_2$), 2.35~2.41 (m, 4H, $N(CH_2CH_2)_2O$), 2.61(t, *J* = 8.4Hz, 2H, Ph-CH_2), 3.71(t, *J* = 3.2Hz, 4H, $N(CH_2CH_2)_2O$), 7.04~7.06(m, 1H, aromatic *H*), 7.14~7.19 (m, 3H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9(*CH*$_2$), 33.2(*CH*$_2$), 53.7(2 × *CH*$_2$), 58.1(*CH*$_2$), 66.9(2 × *CH*$_2$), 125.9(*CH*), 126.6(*CH*), 128.6(*CH*), 129.5(*CH*), 134.1(*C*), 144.1(*C*). ESI-MS, Calcd for[M+H] 240.12, found 240.18.

4-(2-(3-chlorophenyl)propyl)morpholine (4s) Light yellow oil, purified on chromatography by gradient elution (Hexane/ Ethyl acetate= 1:1, Ethyl acetate, then 2% MeOH in Ethyl acetate with 0.5% Et_3N). ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 1.25 (d, *J* = 6.8 Hz, 3H, Ph-CH*CH*$_3$), 2.36~2.44 (m, 6H, $CH_2N(CH_2CH_2)_2O$), 2.91(m, 1H, Ph-*CH*CH_2), 3.66(t, *J* = 4.8 Hz , 4H, $N(CH_2CH_2)_2O$), 7.06~7.13 (m, 1H, aromatic *H*), 7.16~7.23 (m, 3H, aromatic *H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.8(*CH*$_3$), 36.9(*CH*), 53.9(2×*CH*$_2$), 66.2(*CH*$_2$), 67.1(2×*CH*$_2$), 125.5(*CH*), 126.3(*CH*), 127.4(*CH*), 129.6(*CH*), 134.1(*C*), 148.1(*C*). ESI-MS,Calcd for [M+H] 240.12, found 240.15.

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3

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