Research Article

Exploration and Design of Novel Asymmetric Catalysts: Development of Imidazoline-aminophenol (IAP) and Bis(imidazolidine)pyridine (PyBidine)

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1. Introduction

As symbolized by awarding of the 2001 Nobel Prize in chemistry to K. B. Sharpless, R. Noyori, and W. S. Knowles, the catalytic synthesis of chiral molecules is of crucial importance in fine chemistry in order to ensure the supply of useful and valuable organic compounds. The importance of this research topic has stimulated chemists worldwide to develop numerous methods of asymmetric catalysis, although the process of developing new catalysts involves tedious effort even when modern methods are used. One way to overcome the time-consuming aspect of the process may be to use the technology of combinatorial chemistry for the discovery and optimization of catalysts. For efficient exploration of novel asymmetric catalysts using the combinatorial approach, a convenient technology of high-throughput screening (HTS) is required for analyzing both catalytic activity (chemical yield) and enantiomeric excess. Although recent remarkable work has resulted in some useful HTS systems, a more powerful analytical system is required in pursuit of wide application, easy handling, and practical use in broad asymmetric catalysis.

We have succeeded in the development of new HTS system by coupling circular dichroism (CD) detection and solid phase reaction. Here we wish to demonstrate the use of "Solid-phase Catalysis/CD-HTS" for the combinatorial development of a novel chiral imidazoline-aminophenol (**IAP**) ligand in asymmetric metal catalysis.

Furthermore, the chemistry of imidazoline-consisting ligand was extended to the imidazolidine-consisting ligand, which promoted us a design and development of Bis(imidazolidine)-pyridine (**PyBidine**) ligand.

Using **IAP** and **PyBidine** as the new type of chiral ligands, unique metal-catalyzed asymmetric reactions are conducted to provide novel highly functionalized chiral compounds having multiple stereogenic centers.

2. Solid-phase Catalysis/CD-HTS

A new HTS system has been developed by coupling circular dichroism (CD) detection and solid phase reaction (Figure 1). In this system, the origin of chirality is restricted

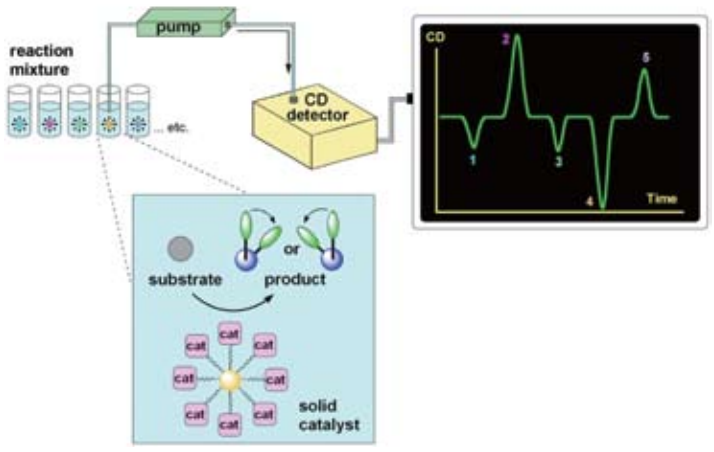


Figure 1. Solid-phase catalysis/CD HTS.

by the solid support. When the catalytic asymmetric reaction is examined using an achiral substrate in solution, no asymmetric induction occurs; therefore, when the solution is analyzed using CD, no significant signal should be detected. Because any two enantiomers have exactly opposite CD values at each wavelength, the CD detector could analyze a single appropriate wavelength and record a positive or negative signal corresponding to the amount of excess enantiomer.

Regarding the use of CD in the HTS, Mikami *et al.* reported pioneering works on the screening of solution-phase asymmetric catalysts.[2] In their system, the chiral catalyst and ligand are separated using achiral column, and the efficiency was examined using "g-factor". Although our system (Figure 1) isn't possible to use the g-factor due to the UV adsorption of co-existing substrate and/or undesired products, the introduction of reaction mixture to the CD detector without purification provides a "direct monitoring system of reaction mixture".

3. A Library of Chiral Imidazoline-Aminophenols: Discovering an Efficient Reaction Sphere

The reason why we have interested in the imidazoline-consisting chiral ligand is summarized in Figure 2. A representative example of the chiral ligand chemistry can be seen in the famous bis(oxazoline) ligands, in which the nitrogen atom of a *N*,*O*-containing five-membered ring of the oxazoline coordinates to the metal cation to form the complex. The bis(oxazoline)-metal complexes have been utilized in numerous asymmetric reactions. However, even in the beautiful success of bis(oxazoline) ligands in asymmetric catalysis, regulating the electron density of the oxazoline ring has been remained an unsolved problem. One way to overcome the limitation of electronic variation on the oxazoline ring would be by a rational design of a chemical analog (e.g. imidazoline) of oxazoline. Imidazoline, the *N*,*N*-analog of *N*,*O*-consisting oxazoline,

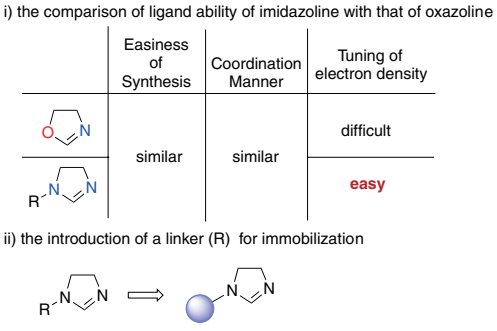
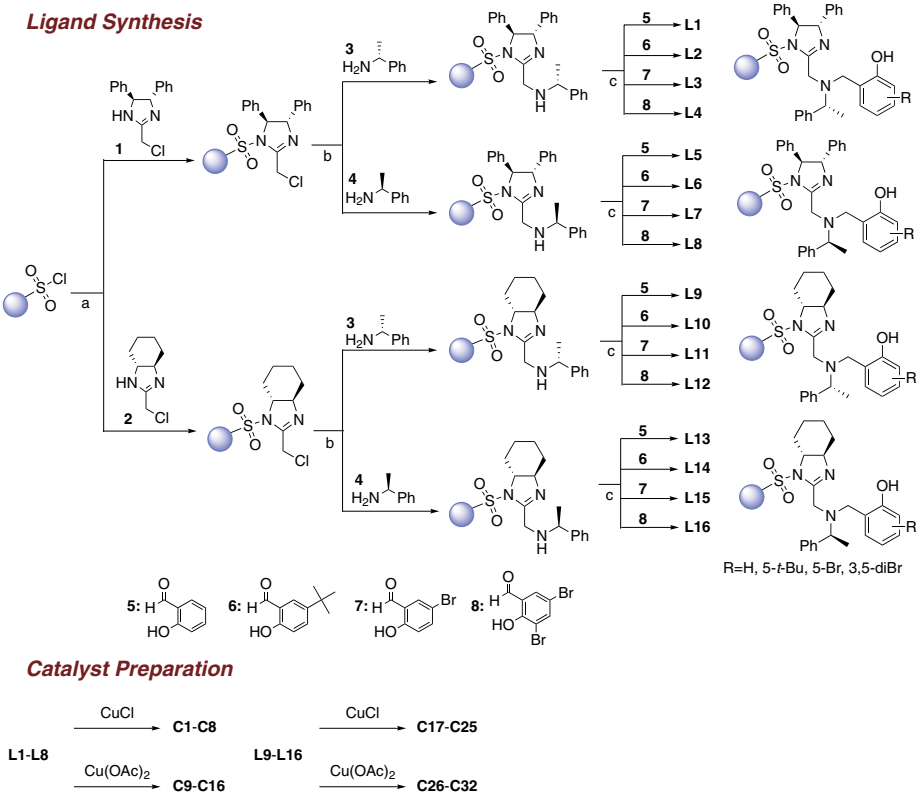


Figure 2. Imidazoline as a ligand.



Scheme 1. Library of imidazoline-aminophenol ligands (**L1-L16**) and the Cu catalysts (**C1-C32**): a) chloromethylated imidazoline, triethylamine, CH_2Cl_2; b) corresponding amine, KI, MeCN; c) corresponding salicylaldehyde; then $NaBH_3CN$, MeOH.

would be reasonably considered to sufficiently meet such an electronically tunable demand (Figure 2-i). Since the oxazoline oxygen atom is replaced by a NR group in the imidazoline, the basicity of the ligating nitrogen could be accurately adjusted with a selection of either electron-withdrawing or -donating substituent (R). Moreover, in a planning of the library synthesis of imidazoline-consisting ligands on a solid support, the substituent (R) at the nitrogen atom in the imidazoline would be fascinating for the introduction of the linker for the immobilization (Figure 2-ii).

Using an imidazoline, an amine, and a salicylaldehyde as the building blocks, the synthesis of the imidazoline-aminophenol library was formulated as shown in Scheme 1. After immobilization of the two types of chiral chloromethylated imidazolines (**1**, **2**) onto the polystyryl-sulfonyl chloride, a nucleophilic substitution using (*R*)- or (*S*)-phenylethylamine (**3**, **4**) provided the four combinations of polymer-supported imidazoline-amines. Further reductive alkylation using salicylaldehydes (**5-8**) provided a series of imidazoline-aminophenol ligands (**L1-L16**).

After classification of the library by the types of chiral imidazoline, the metal catalysts (**C1-C32**) were prepared by reaction with CuCl or $Cu(OAc)_2$. In all cases, the polystyrene beads turned to green, which suggested the formation of Cu complexes.

With the total of 32 polymer supported chiral catalysts (**C1-C32**) in hand, the Cu-catalyzed Henry reaction was examined to evaluate the efficiency of the reaction sphere.[3,4] After carrying out the asymmetric Henry reaction of nitromethane and *o*-nitrobenzaldehyde for 48 h, each reaction mixture was analyzed by continuous injection into a solid-phase catalysis/CD-HTS system, giving the profile shown in Figure 3.

Continuous injection of 32 reaction mixtures in each period of 2 min interval makes the conduction of CD-HTS within around 1 hour. Obviously, among the 32 reactions, the **C16** (i.e. **L8**-$Cu(OAc)_2$) catalyst shows a maximum CD intensity, which means the **C16** should be the most efficient asymmetric catalyst in the combination of chemical yield and enantiomeric excesses (Figure 3). The positive-intensity of CD signal at 254 nm suggests the (*S*)-selective formation of nitroaldol product.

A reaction with a good yield but with low enantiomeric excess should result in a CD signal of low intensity. In the same manner, when catalytic activity is low, resulting in a low yield, the intensity of CD signal is low even with high enantiomeric excess. The CD signal is of maximum intensity only when both chemical yield and enantiomeric excess are best. A precise expression of CD signal intensity is represented by Eq. 1, in which the square root of the chemical yield multiplied by the enantiomeric excess is defined as the asymmetric conversion yield (ACY).

The most efficient asymmetric catalyst should give the target product in good yield with high enantiomeric excess. This is a principle of fundamental importance, although it has not so far been clearly stated. Our HTS system allows us to determine the catalysts that meet the criterion of this new definition of ACY.

Based on the solid-phase catalysis/CD-HTS, the well-defined imidazoline-aminophenol ligand (**IAP1**) was prepared by solution phase synthesis (Scheme 2), and applied to the asymmetric Henry reaction. As a result, the **IAP1**-$Cu(OAc)_2$

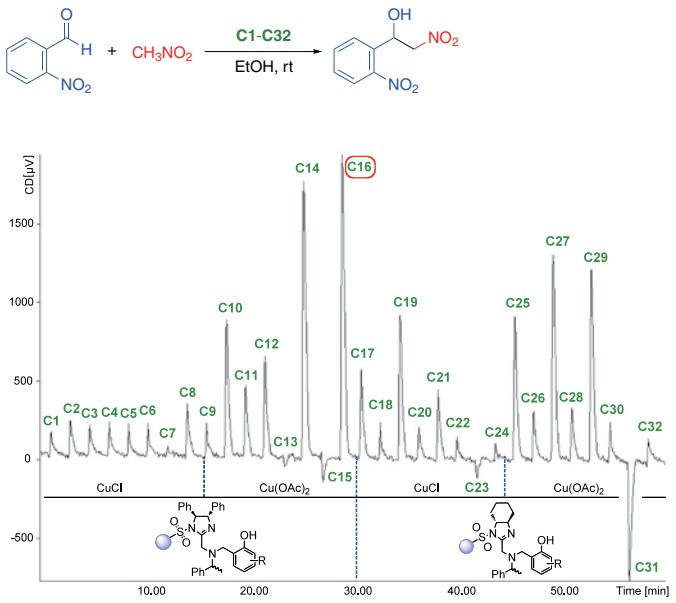


Figure 3. Solid-phase catalysis/CD-HTS of Cu-catalyzed Henry reaction.

$$\mathrm{ACY}(\%) = \sqrt{yield(\%) \times ee(\%)} \quad \ldots (\mathrm{eq.1})$$

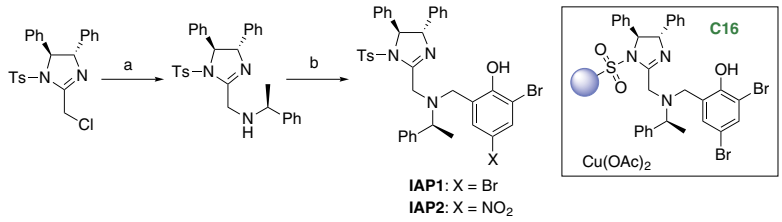
catalyst provide the Henry adduct in good yield with up to 95% ee (Scheme3-a).[5)]

When a new and unique chiral ligand is successfully explored, we can examine the utility in various asymmetric reactions. For the example, a catalytic asymmetric Friedel-Crafts alkylation[5)] of indole with nitroalkene was catalyzed by **IAP1**-CuOTf complex to give the product with highly enantioselective manner (Scheme 3-b).[6)] This catalyst system was also extensively applied to the catalytic asymmetric Friedel-Crafts reaction of nitroalkenes with pyrrole, which is less reactive substrate than the indole. For the less reactive pyrrole, newly synthesized nitro-substituted imidazoline-aminophenol (**IAP2**) is effective to increase the Lewis acidity of Cu catalyst to furnishing the smooth catalytic asymmetric Friedel-Crafts reaction with up to 92% ee (Scheme 3-c).[7)] In some reactions, the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is effective for improving both chemical yields and enantiomeric excesses.

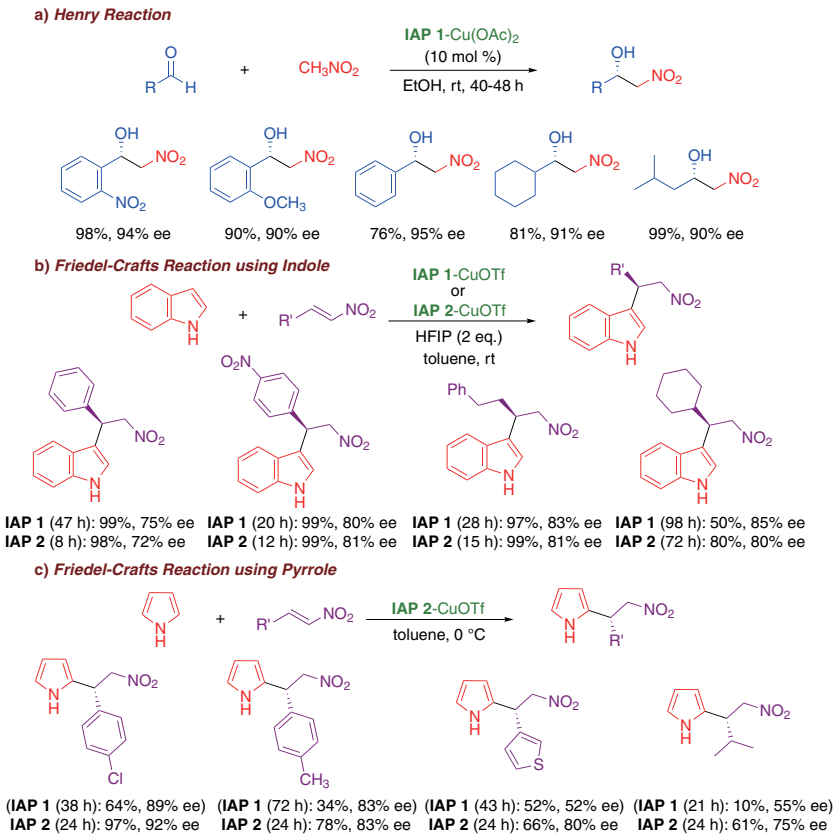
4. IAP-Cu Catalyzed Asymmetric Friedel-Crafts/ Henry(FCH) Reaction and Friedel-Crafts/ Protonation(FCP) Reaction

After the success on the exploration of novel **IAP**-metal catalyst, the next research project is the development of new asymmetric reactions. We have interested in tandem multi component coupling reaction for providing complex molecules. The obtained compounds having multiple stereogenic centers would provide a fascinating scaffold for facilitating diversity-oriented synthesis, and for reducing the number of chemical steps in target-oriented synthesis.

When the **IAP**-Cu(OTf)$_2$ complex acts as a Lewis-acid catalyst in the Friedel-Crafts reaction of indole with nitroalkene, the nucreophilic attack of indole to the Cu-activated nitroalkene will generate the Cu-nitronate as the coupled intermediate (Scheme 4). Typically the Cu-nitronate is protonated to give the Friedel-Crafts adduct. However, this coupled intermediate is an



Scheme 2. Synthesis of imidazoline-aminophenols (**IAP1** and **IAP2**): a) (*S*)-phenylethylamine, KI, DMF; b) 3,5-dibromosalicyl aldehyde (for **IAP1**) or 3-bromo-5-nitrosalicyl aldehyde (for **IAP2**), NaBH$_3$CN, MeOH.



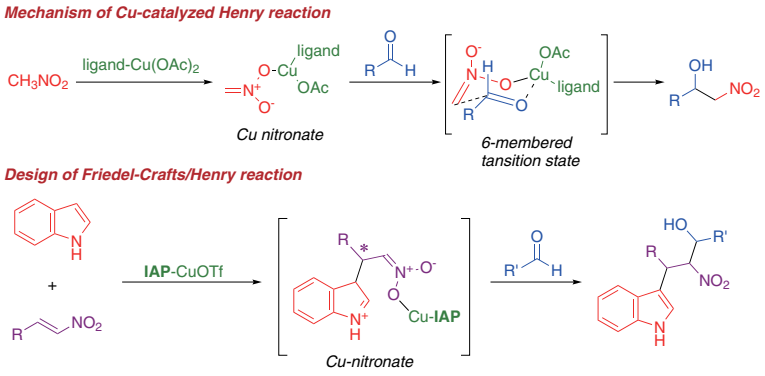
Scheme 3. IAP-Cu catalyzed asymmetric reactions.

equivalent of the Cu-nitronate for the Henry reaction. According to the reaction mechanism proposed by Evans, the Cu complex bearing moderately basic charged counter anion (e.g. OAc^-) would work for generation of a nitronate species.[4)]

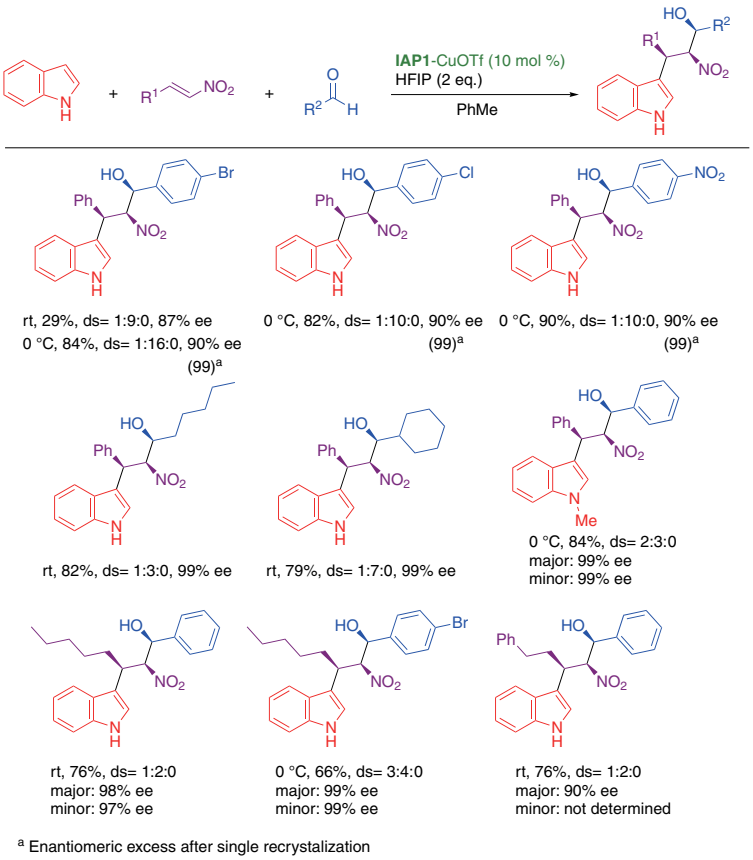
Because the Friedel-Crafts reaction of indole with aldehyde was relatively slow, we planed the tandem Friedel-Crafts/Henry (FCH) reaction of indole, nitroalkene, and aldehyde using the **IAP**-Cu catalyst.

When 1 eq. of benzaldehyde was added to the conventional Friedel-Crafts reaction mixture of indole with nitrostyrene (1:1), the desired three-component coupling FCH product was obtained. The addition of HFIP was effective in enhancing the catalytic reaction, and to perform the reaction with highly diastereoselective manner. Using the optimized conditions, the first catalytic asymmetric FCH reaction was established as shown in Scheme 5.[8)]

Scheme 6 shows a plausible reaction mechanism of the FCH reaction. At the first step, the nitroalkene is activated by the Lewis acid **IAP**-Cu catalyst to start the enantioselective Friedel-Crafts reaction. Then, the diastereoselective Henry reaction would be promoted through the Cu nitronate as planned. We confirmed that the reaction of the isolated Friedel-Crafts product and the aldehyde did not occur under the reaction conditions. The enantiomeric excess of FCH product was greatly improved to 99% from ca. 80% ee of the Friedel-Crafts adduct (Scheme 3b). Thus, the Henry reaction is considered to



Scheme 4. Design of new tandem Friedel-Crafts/Henry reaction.



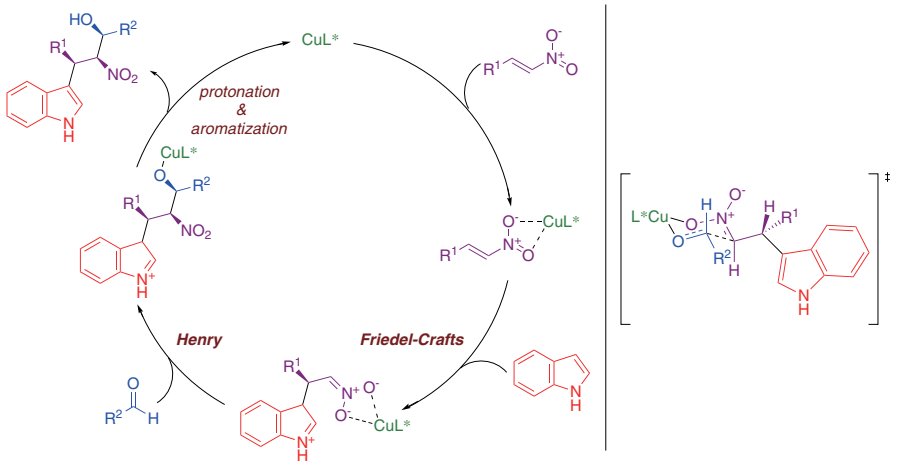
[a] Enantiomeric excess after single recrystalization

Scheme 5. Catalytic asymmetric Friedel-Crafts/Henry(FCH) reaction.

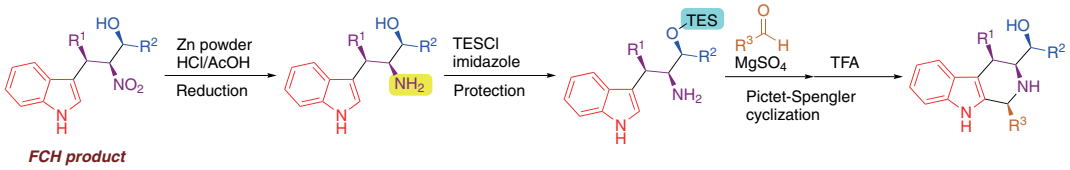
progress directly from the intermediary generated Cu-nitronate accompanying with the kinetic resolution of the nitronate. The absolute configuration of the major FCH product was determined by X-ray diffraction analysis as (1*R*,2*S*,3*S*)-form, which indicated the diastereoselective Henry reaction proceeded in a *syn*-selective manner. This *syn*-selectivity would be well explained by considering a Cu-containing 6-membered ring (right figure in Scheme 6). The relatively strong Lewis acidity of the CuOTf catalyst would enforce the diastereoselective Henry reaction via the cyclic transition state. Finally, protonation of the Cu-alkoxide and further aromatization furnishes the desired FCH product and regenerates the **IAP**-Cu catalyst.

Starting from the (1*R*,2*S*,3*S*)-FCH adduct, the (1*S*,3*S*,4*R*)-tetrahydro-β-Carbolines were eadily synthesized in a three-step operation including reduction of the nitro-functionality and Pictet-Spengler cyclization (Scheme 7).[9)]

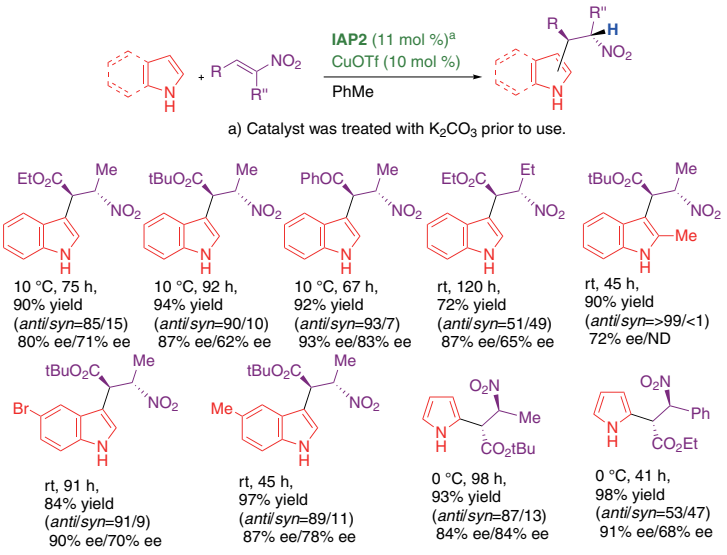
Furthermore, the **IAP2**-CuOTf complex furnished the catalytic asymmetric Friedel-Crafts/protonation(FCP) of indoles and pyrroles with α-substituted nitroalkenes to give the α-substituted β-heteroaryl-nitro adducts in a highly *anti*-selective manner. Because the nitro functionality of FCP adducts is easily reduced to amine using nickel boride with keeping the diastereo- and enantioselectivities, this became the first report on the diastereoselective construction of the chiral acyclic α-substituted β-indolyl-alkylamines (Scheme 8).[10)]



Scheme 6. Plausible reaction mechanism of FCH reaction and cyclic transition state for the *syn*-selective Henry reaction.



Scheme 7. Easy access to fully functionalized chiral tetrahydro-β-carboline alkaloids.



Scheme 8. Catalytic asymmetric Friedel-Crafts/protonation(FCP) of indole with α-methyl nitroalkenes.

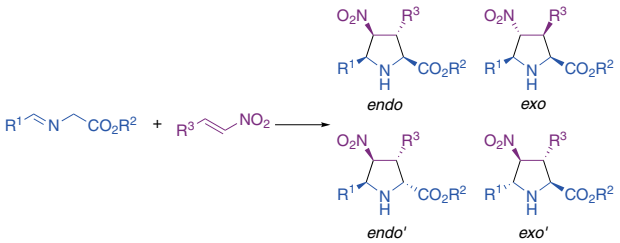
5. [3+2] Cycloaddition of Iminoesters with Nitroalkenes for Constructing Novel Chiral pyrrolidines

After the success of the control of three contiguous strereogenic centers using FCH reaction, the project moved on the control of four contiguous strereogenic centers on the cyclic compounds. Pyrrolidines, 5-membered *N*-heterocycles, are widely observed in biologically significant compounds. Due to the importance of pyrrolidines in pharmaceutical research, catalytic asymmetric 1,3-dipolar cyclization has been successfully utilized for the stereoselective construction of the pyrrolidine ring. The reaction of the azomethine ylide generated from an iminoester and a nitroalkene is a fascinating reaction system, in which an additional nitro functionality can be introduced on the pyrrolidine ring. In this particular reaction, the combination of four stereogenic centers can provide up to eight diastereomers. When a *trans*-nitroalkene is utilized, the stereoconjunction between the 3- and 4-positions is fixed, and four diastereomers are possible, classified as *endo*, *exo*, *endo'*, and *exo'* isomers (Scheme 9).[11]

There are many outstanding works on the catalytic asymmetric *endo*- and *exo*-selective pyrrolidine ring construction. However, before starting our research, there are no reports on *exo'*-product formation even in the *racemic* form.

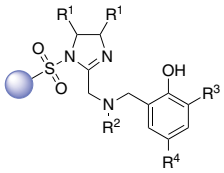
The study was stated from the screening of the appropriate metal salt for giving the *exo'*-adduct selectively, and we found that $Ni(OAc)_2$ facilitated the production of the *exo'*-product. The isolated *exo'*-product showed small, but unique CD signal at 280 nm. Based on these preliminary information, the "Solid-phase catalysis/CD-HTS" using the solid-phase imidazoline-aminophenol-$Ni(OAc)_2$ catalysts was re-examined for exploring the appropriate catalysts for the asymmetric *exo'*-selective 1,3-dipolar cyclization.

With including the *p*-nitro phenol derivatives, 20 solid-phase catalysts were prepared as coded in Table 1, and the CD-HTS were conducted in Figure 4. By monitoring the CD signals at 280 nm, the solid-phase **L8**-$Ni(OAc)_2$ and **L18**-$Ni(OAc)_2$ catalysts recorded superior CD intensities among the 20 solid-phase catalysts.



Scheme 9. Possible diastereomers generated in the pyrrolidine synthesis using an iminoester and a *trans*-nitroalkene.

Table 1. Ligand (**L**) code.



R^1, R^1: **A** = (*S*,*S*)-diphenyl
B = (*R*,*R*)-cyclohexyl
R^2: **C** = (*R*)-phenetyl
D = (*S*)-phenetyl

L	R^1,R^1	R^2	R^3	R^4	L	R^1,R^1	R^2	R^3	R^4
L1	A	C	H	H	**L9**	B	C	H	H
L2	A	C	H	*t*Bu	**L10**	B	C	H	*t*Bu
L3	A	C	H	Br	**L11**	B	C	H	Br
L4	A	C	Br	Br	**L12**	B	C	Br	Br
L17	A	C	Br	NO_2	**L19**	B	C	Br	NO_2
L5	A	D	H	H	**L13**	B	D	H	H
L6	A	D	H	*t*Bu	**L14**	B	D	H	*t*Bu
L7	A	D	H	Br	**L15**	B	D	H	Br
L8	A	D	Br	Br	**L16**	B	D	Br	Br
L18	A	D	Br	NO_2	**L20**	B	D	Br	NO_2

Although **L8** (corresponding to **IAP1**) and **L18** (corresponding to **IAP2**) showed the best performance again, the use of solid-phase catalysis/CD-HTS was apparent advantage on the rapid screening, because the analyses of 20 reactions using the conventional method should require much efforts.

The reaction condition for **IAP1**-Ni(OAc)$_2$ catalysis was optimized in solution phase reaction to give the results in Scheme 10. This is the first general success in the catalytic asymmetric *exo'*-selective reaction of iminoesters and nitroalkenes.[12)]

A plausible mechanism for why the **IAP1**-Ni(OAc)$_2$ provides the adduct *exo'*-selectively is explained in Scheme 11. Apparently, the stereochemistry of *exo'*-product suggests that the **IAP1**-Ni(OAc)$_2$ catalyzed reaction isn't the concerted 1,3- dipolar cyclization of the metal-bound azomethine ylide with nitroalkene. We confirmed that no epimerization of the *endo*- and *exo'*-adducts occurred under the reaction conditions. One plausible mechanism would be explained by the reaction started from the Ni-catalyzed Michael addition of iminoester to the nitroalkene. The nucleophilic addition at C2 of the

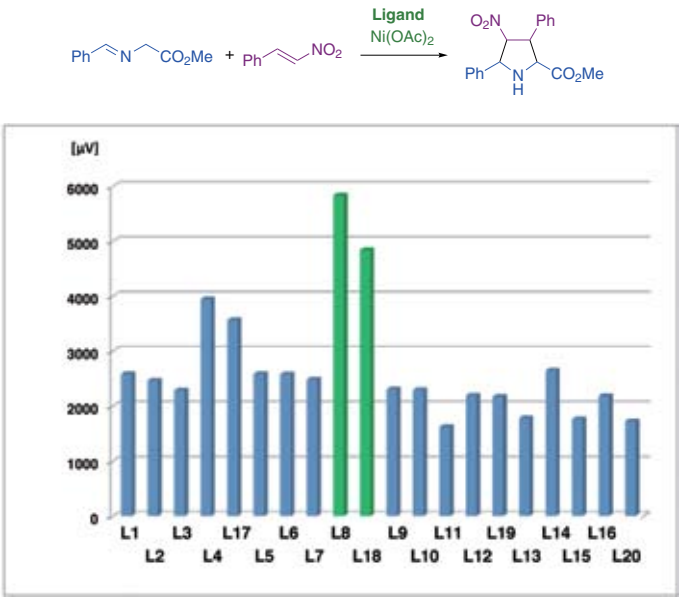
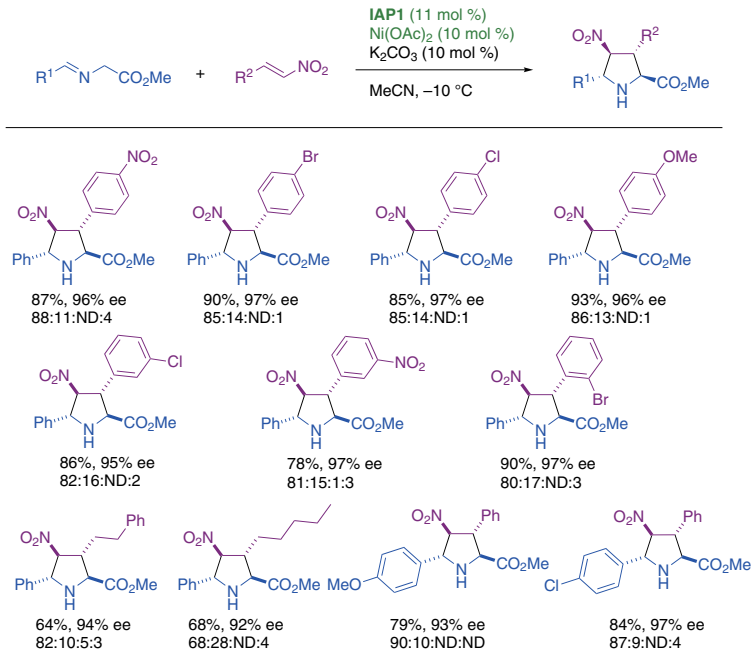


Figure 4. Solid-phase catalysis/CD-HTS of solid-phase imidazoline-aminophenol-Ni(OAc)$_2$ catalysts for *exo'*-selective cycloaddition.

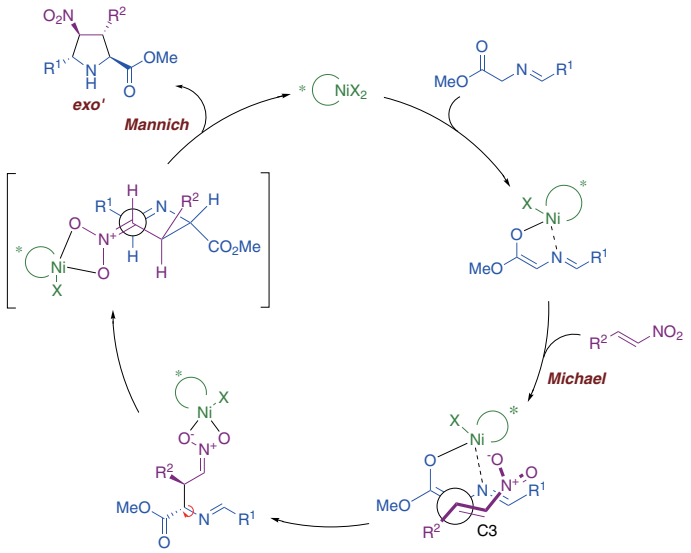


Scheme 10. IAP1-Ni(OAc)$_2$ catalyzed *exo'*-selective [3+2] cycloaddition of iminoesters with nitroalkenes.

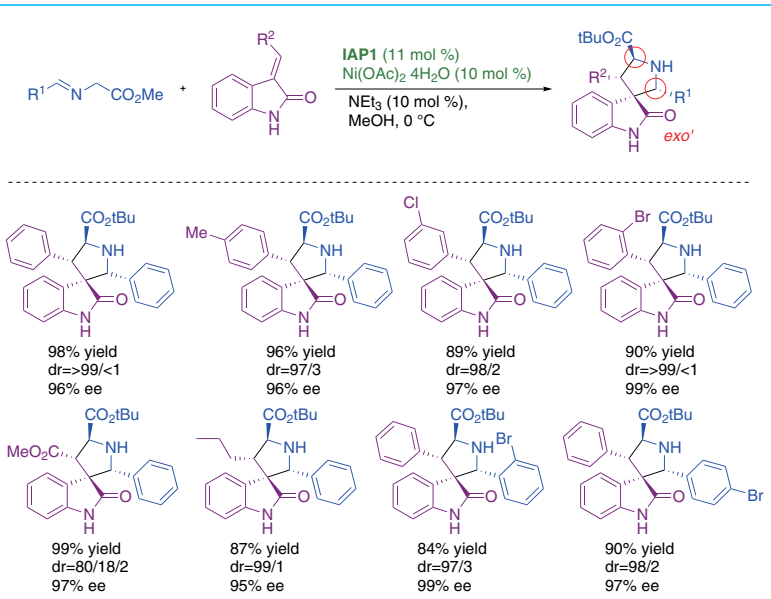
nitroalkene would be managed by an interaction between the nitro functionality and Ni center for controlling the nucleophilic reaction in *anti*-selective manner. However, after the *anti*-selective Michael addition, because the neutral Ni center cannot coordinate to both the nitro functionality and the iminoester, the Ni atom would spontaneously flip to the nitronate for opening the cyclic intermediate. Before the subsequent Mannich reaction, the C-N single bond must rotate to give the *exo'*-isomer via the most stable transition state. DFT calculations at the level of 6-31G/B3LYP also suggest that the *exo'*-adduct is the most stable among the four possible isomers depicted in Scheme 9.

Recently, the **IAP1**-Ni(OAc)$_2$ enabled the catalytic asymmetric *exo'*-selective [3+2] cycloaddition for constructing stereochemically diversified spiro[pyrrolidin-3,3'-oxindole]s (Scheme 12).[13)]

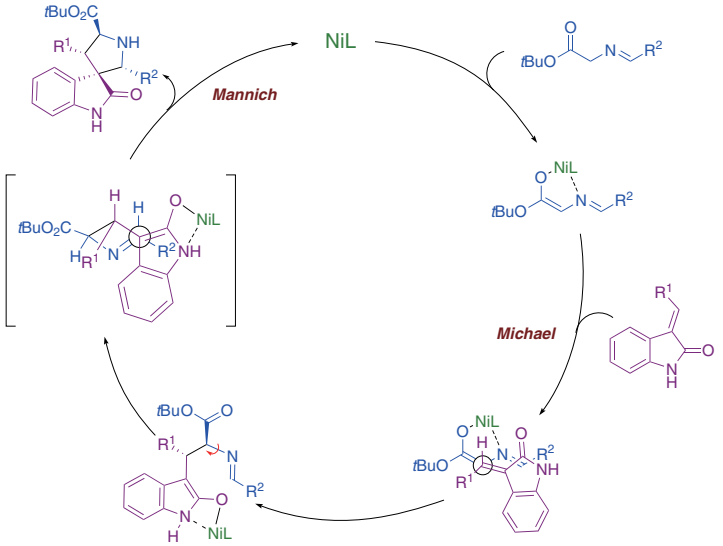
Using the **IAP1**-Ni(OAc)$_2$, the reaction proceeds in a similar stepwise Michael-Mannich reaction to provide the *exo'*-adducts as the stable isomers. The reaction would proceed by replacing the counter-substrate of nitroalkene in the previous study[13)] with the alkenyl amide part of methyleneindolinone to give (3*R*,4'*S*)-product as shown in Scheme 13.



Scheme 11. Plausible reaction mechanism on *exo'*-selective [3+2]-cycloaddition.



Scheme 12. Catalytic asymmetric synthesis of *exo'*- spiro[pyrrolidin-3,3'-oxindole]s.



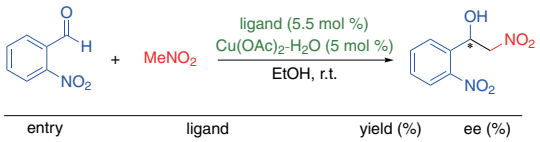
Scheme 13. Proposedreactionmechanism.

6. From Imidazoline to Imidazolidine

Although the unique asymmetric reaction sphere produced by the **IAP**-metal complex has potential for successful application to other various asymmetric reactions, the realization of the ligand-role in the asymmetric catalyst is difficult due to the structural complexity. The simple imidazoline-pyridine analog (**L21**) was not effective for the $Cu(OAc)_2$-catalyzed Henry reaction. We assumed that the relatively flat structure around the Cu-center in the square-planar **L21**-Cu(II) complex was not sufficient to promote the stereoselective reactions. To produce more stereochemical complexity, we focused on the imidazolidine ring, in which the sp^2 carbon of the imidazoline ring is replaced by a sp^3 carbon.

Although the newly formed sp^3 carbon is a stereogenic center, we envisioned that the configuration of the imidazolidine would be controlled by the steric repulsion relayed from the substituents of the chiral diamine.

The synthesis of imidazolidine-pyridine ligand (**L22**) was readily achieved by a simple condensation of monoalkyl chiral diamine and aldehyde using acetic acid. The highly diastereoselective construction of the imidazolidine-pyridine **L22** was confirmed by ^{1}H-NMR analysis. Moreover, the X-ray crystallographic analysis of a single crystal of **L22** revealed an all-*trans* stereochemical outcome as predicted. The ability of the imidazolidine-pyridine **L22** to act as chiral ligands was examined in Henry reaction (Figure 5). The Henry reaction of *o*-nitrobenzaldehyde with nitromethane was smoothly catalyzed by the imidazolidine-pyridine (**L22**)-$Cu(OAc)_2$ complex to give the adduct in 99% yield with improved stereoselectivity of 66% ee.



entry	ligand	yield (%)	ee (%)
1	imidazoline-pyridine (R = Bn) **L21**	99	6
2	imidazolidine-pyridine (R = Bn) **L22**	99	**66**

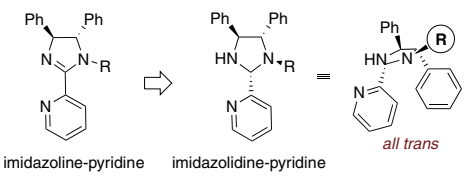


Figure 5. Ligand design of imidazolidine from imidazoline.

7. Development of Bis(imidazolidine)pyridine (PyBidine)

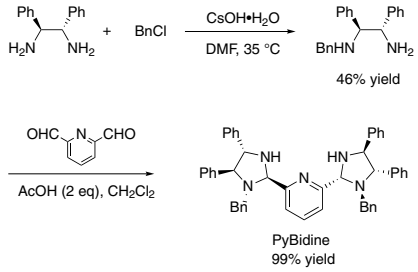
With employing imidazolidine, the new C_2-symmetric bis(imidazolidine)pyridine ligand (**PyBidine**) was designed and easily synthesized in a single condensation of 2,6-pyridyl aldehyde and optically active (*S*,*S*)-diphenylethylene diamine (Scheme 14).

The newly developed **PyBidine** ligand readily provided the metal complex with various metal salts. The structure of **PyBidine**-Cu(OTf)$_2$ complex was determined by X-ray crystallographic analysis of a single crystal as an aqua complex (Figure 6). Two triflate anions occupy the apical positions, and the imidazolidines of **PyBidine** coordinate to the Cu with keeping the proton at the nitrogen atoms.

The terdentate-coordination feature of **PyBidine** was compared with the famous C_2-symmetrical bis(oxazolinylpyridine) ligand (i.e., pybox) in Figure 7.[15, 16] In the pybox-metal complex, pyridine and oxazoline rings lie sprawled on the equatorial plane in coordination with the metal center, and two alkyl groups at the stereogenic center of the oxazoline are arranged as "chiral fences." In the current **PyBidine**-Cu(OTf)$_2$ complex, two imidazolidine rings stand perpendicular to the equatorial terdentate coordination plane. Thus, the imidazolidine rings themselves act as the "chiral fences" in the C_2-symmetric **PyBidine**-Cu(OTf)$_2$ to shield the first and third quadrants (Figure 7).

The catalytic activity was demonstrated in the [3+2] cycloaddition of iminoesters with nitroalkenes. Using **PyBidine**-Cu(OTf)$_2$ catalyst, the highly *endo*-selective reaction of iminoesters and nitroalkenes was achieved to give the adducts in up to 99% ee (Scheme 15).[17]

Based on the selective formation of (2*S*,3*R*,4*S*,5*S*)-pyrrolidine using (*S*,*S*,*S*,*S*)-**PyBidine**-Cu(OTf)$_2$ catalyst, the enantioface selection in the [3+2] cycloaddition is explained as follows. The Cu-catalyst would form the Cu-bound iminoester (or Cu-azomethine ylide). When the iminoester coordinates to the Cu using the equatorial and the upper apical site, the nitroalkene approaches from the second quadrant (Figure 7). In this reaction sphere, for giving the (2*S*,3*R*,4*S*,5*S*)-pyrrolidine, the nitrogen atom of the iminoester should stand at the upper apical site of Cu to react with nitroalkene using *re*-face of imine. The following access of the nitroalkene to the activated iminoester with avoiding the steric interaction is appropriate to give the product in *endo*-selective manner. (Concerted mechanism is also possible to be considered.)



Scheme 14. Synthesis of bis(imidazolidine)pyridine ligand (**PyBidine**).

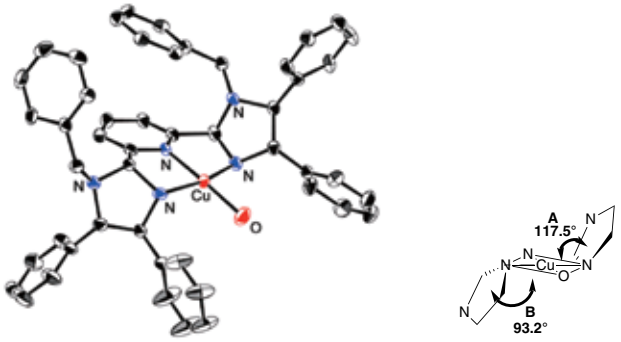


Figure 6. X-ray structure of **PyBidine**-Cu(OTf)$_2$-H$_2$O complex. Counteranions and protons are omitted for clarity.

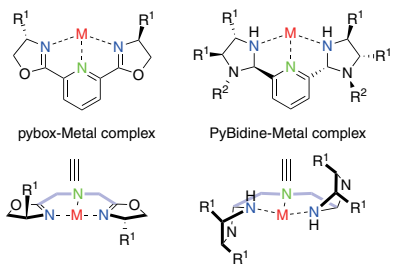
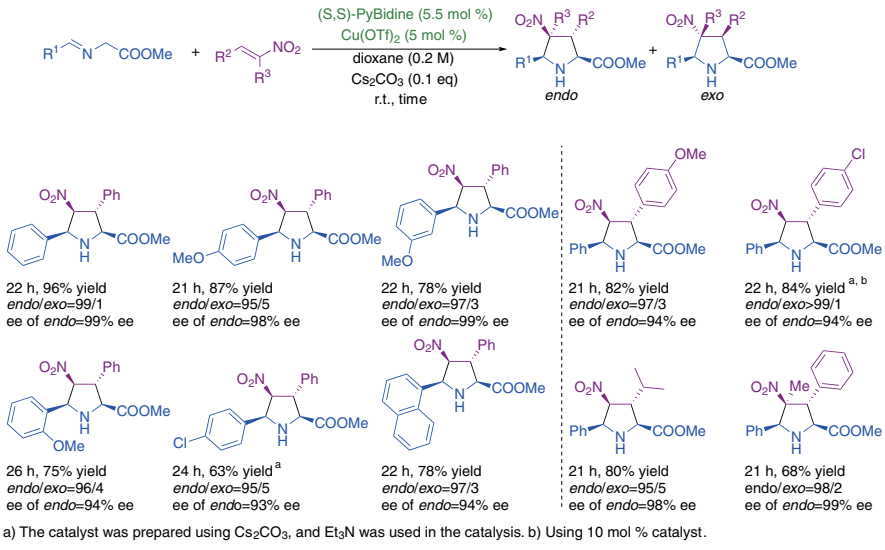


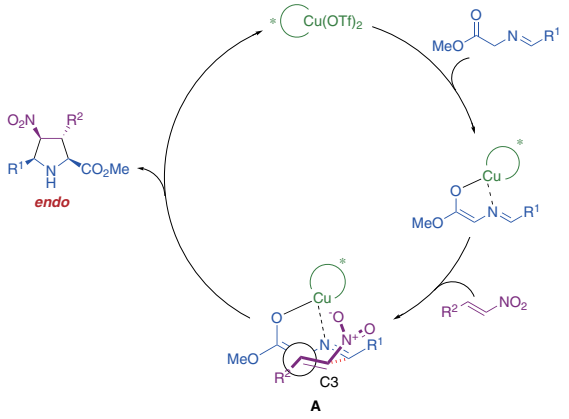
Figure 7. Structural comparison of **PyBidine**-metal complex to pybox-metal complex.

Noteworthy, the pybox-Cu(OTf)$_2$ complex[15] and the pybim-Cu(OTf)$_2$ complex[16] gave a trace amount of the adduct under the similar conditions (Figure 8). Although the highly selective reaction is reasonably explained by using the well-organized reaction sphere having **PyBidine**-Cu complex, it is hard to explain the high catalyst activity. The NH functionality in the **PyBidine** would play a significant role for activating the substrates in catalysis.

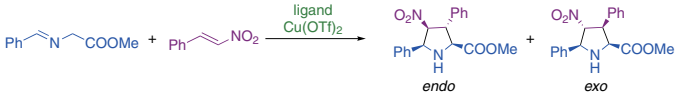


a) The catalyst was prepared using Cs_2CO_3, and Et_3N was used in the catalysis. b) Using 10 mol % catalyst.

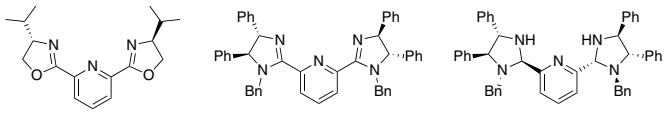
Scheme 15. PyBidine-Cu(OTf)$_2$ catalyzed *endo*-selective [3+2] cycloaddition of iminoesters with nitroalkenes.



Scheme 16. Plausible reaction mechanism for *endo*-selective [3+2]-cycloaddition.



entry	ligand	yield (%)	*endo*:*exo*	ee (%) (*endo*)
1	pybox	trace	—	—
2	pybim	trace	—	—
3	PyBidine	96	99:1	99



pybox
Nishiyama, H. *et al.*[15]

pybim
Beller, M. *et al.*[16]

PyBidine

Figure 8. Remarkable ligand-acceleration effect of **PyBidine**.

8. Conclusion

A library-based study using imidazoline-aminophenol ligands succeeded in the creation of a unique reaction sphere. Clearly, predicting the actual catalyst activity of **IAP1** and **IAP2** simply from its molecular structure is still quite hard even in modern chemistry, and the result reported herein is difficult to achieve without the use of combinatorial technology. Using **IAP**-Cu catalyst, a novel Friedel-Crafts/Henry (FCH) reaction was successfully conducted for generating three contiguous stereogenic centers. The first *exo'*-[3+2] cycloaddition of iminoesters with nitroalkenes was achieved by **IAP**-Ni catalyst.

As a designer chiral ligand, new bis(imidazolidine) pyridine (**PyBidine**) was also introduced for the Cu-catalyzed highly endo-selective [3+2]-cycloaddition of iminoesters with nitroalkenes.

The newly provided highly functionalized molecules in this research will be fascinating toward the development of biologically significant compounds for promoting pharmaceutical and medicinal science.

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This work has been conducted with my students in the laboratory of organic synthetic chemistry, Chiba University. I show my sincere thanks to their hard work. Especially, main players of the current paper are Dr. Naota Yokoyama, Ms. Atsuko Awata, Ms. Makiko Wasai, Mr. Masakiko Watanabe, Ms. Asami Mishiro, and Ms. Kuniko Suzuki.

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Prof. Dr. Takayoshi Arai accomplished his master degree from the University of Tokyo in 1994, and went on to the doctoral course. In 1995, he was appointed as an assistant professor of Prof. Shibasaki's group at the University of Tokyo, and received his Ph.D. degree in 1998 from the University of Tokyo. In 1997, he moved to the Institute of Scientific and Industrial Research, Osaka University. After carrying out a postdoc in Prof. S. L. Schreiber's group at the Harvard University in USA, he moved to Chiba University as an associate professor in 2003, and became a full professor in 2010. He received the Incentive Award in Synthetic Organic Chemistry, Japan in 2008.
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