Enantioselective Reaction Using Palladium Pincer Complexes with C_2 -Symmetric Chiral Bis(imidazoline)s

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Abstract: The development of novel chiral catalysts is one of the most challenging areas in organic chemistry. This account summarizes our recent studies on chiral bis(imidazoline)-palladium pincer type catalysts (phebim-Pd). The catalysts can be used in the enantioselective reaction of a wide variety of nitrile compounds with imines giving products in high yields with good stereoselectivities. This process offers a simple and efficient route for the synthesis of functionalized β -aminonitriles and their derivatives. We also examine the enantioselective allylation of ketimines derived from isatins using chiral phebim-Pd complexes to afford products in high yields with good enantioselectivities.

1. Introduction

Recently, the development of mild, catalytic and enantioselective versions of C-C bond-forming processes is a topic of paramount importance in modern organic chemistry. From this point of view, the development of novel asymmetric catalysts has been extensively studied. One of the most privileged chiral catalysts is bis(oxazoline) catalyst, which was constructed by two *N,O*-containing five-membered rings and a metal cation.¹ However, it is difficult to fine tune the electron density and steric bulkiness of the oxazoline ring. The highly tunable structure of bis(imidazoline) ligands provides the possibility of overcoming these limitations of bis(oxazoline)s (Figure 1).

Figure 1. Bis(oxazoline)s and bis(imidazoline)s.

In 2001, Dupont and co-workers reported the first enantioselective reaction using chiral bis(imidazoline) catalyst in the asymmetric arylation of norbornene.² After this pioneering work, many papers focusing on asymmetric reactions using bis(imidazoline) catalysts have been reported.³ We started to explore bis(imidazoline) catalysts and their application to asymmetric reactions from 2002. In 2008, we reported phenylene-linked bis(imidazoline) ligands "phebim" having various substituents, and their application to the enantioselective Friedel-Crafts alkylation of indole derivatives with ethyl 3,3,3-trifluoropyruvate using phebim-Cu(II) catalysts.⁴ The reaction using chiral Lewis acid catalysts prepared from Cu(OTf)₂ and phebim **A** having a tosyl group on nitrogen afforded the (*R*)-isomer of products with high enantioselectivity. In addition, the reaction using *N*-*p*-nitrobenzoyl-substituted phebim **B** and Cu(NTf₂)₂ in toluene afforded the opposite enantiomer of products than obtained from the reac-

Scheme 1. Enantioselective Friedel-Crafts alkylation of indole derivatives with ethyl 3,3,3-trifluoropyruvate using phebim-Cu(II) catalysts.

tion using phebim **A** and Cu(OTf)₂ (Scheme 1).

These results clearly showed that the substituent on imidazoline can control the enantioselectivity and stereochemistry of products. On the other hand, Gong and Song reported the synthesis of palladium and platinum pincer-type complexes with chiral bis(imidazoline) ligands, which activated the Friedel-Crafts reaction of indole with β -nitrostyrene to afford a product with 55% ee.⁵ Although that was a pioneering study for bis(imidazoline)-metal pincer-type complexes, it is highly desired to expand the scope of catalytic enantioselective reactions using pincer-type catalysts. Therefore, our research interest was expanded to use the bis(imidazoline)-metal pincer-type complex.⁶ This account summarizes our recent studies on the chiral phenylene-bis(imidazoline)-palladium pincer type catalysts (phebim-Pd(II)) and their application to asymmetric reactions.

2. Bis(imidazoline)-Pd(II) Complexes

At first, we prepared a series of phebim-Pd complexes having various substituents on imidazolines (Figure 2).

The structures of the obtained palladium pincer-type complexes **1a-c**, **e** were confirmed by X-ray crystal analysis (Figure 3). All bis(imidazoline) ligands were coordinated to the Pd(II) center via two nitrogens in imidazoline and one carbon in the aryl group in a tridentate manner. The complexes

Figure 2. Various phehim-Pd complexes.

Figure 3. X-ray crystal structures of phehim-Pd complexes **1a-c, e**. H atoms were omitted for clarity.

have a nearly square planar Pd(II) center, in which the five rings include two imidazolines, two palladacycles and benzene, which are approximately coplanar. The sum of the angles about the palladium atom is *ca.* 360°. Therefore, the palladium pincer complexes possess an approximate *C*₂-symmetry. As expected, the detailed structures of bis(imidazoline)s were different, such as dihedral angles between carbonyl groups, between the sulfonyl group and the imidazoline ring, or between two aryl groups on imidazoline. Therefore, there is a possibility that these structural differences affect the stereoselectivity of the reaction. Encouraged by these results, we next investigated asymmetric reactions using phehim-Pd catalysts.

3. Enantioselective Reactions of Nitrile Compounds with Imines

With these phehim-Pd complexes in hand, we first examined the enantioselective synthesis of optically active β -aminonitriles, which are important intermediates for the synthesis of biologically active compounds, such as idasanutlin,⁷ ruxolitinib,⁸ isoindoline derivatives⁹ and alkynitrile quinolines (Figure 4)¹⁰.

Furthermore, these compounds are easily converted to β -

Figure 4. Biologically active chiral β -aminonitriles.

aminocarboxylic acids¹¹ and 1,3-diamino compounds.¹² Therefore, the catalytic enantioselective synthesis of chiral β -aminonitriles has received considerable attention. One of the most efficient methods for the preparation of chiral β -aminonitriles is the stereoselective addition of alkynitriles as nucleophiles with imines.^{13,14} However, the generation of α -cyano carbanions is not an easy task due to the low acidity of α -protons for alkynitriles (*pK_a* 21–33 in DMSO).¹⁵ Therefore, *in situ* generation of α -cyano carbanions from nitrile compounds generally requires strong bases, such as LDA and phosphazenes, which may trigger undesired side reactions, such as an elimination reaction or epimerization of the product (Figure 5).

Figure 5. Side reaction of nitriles with imines using a strong base.

An attractive approach for the generation for α -cyano carbanions under mild reaction conditions is to enhance the acidity of alkynitriles by coordinating of transition metal catalysts, such as soft Lewis acid catalysts, to cyanide groups. However, there were only a few reports on catalytic enantioselective reactions of alkynitriles with imines using this strategy when we started our research. In 2008, Shibasaki and co-workers reported the enantioselective reaction of allylnitriles with ketimines using a chiral bisphosphine-Cu(I) catalyst giving β -aminonitriles with high enantioselectivity.^{13a} In the same year, Szabó and co-workers reported the enantioselective reaction of benzylnitriles with imines using chiral bisphosphine-Pd(II) catalysts to afford products with moderate enantioselectivity (up to 71% ee).^{13b} Despite the impressive progress achieved in enantioselective reactions of α -carbanion for alkynitriles with imines using chiral catalysts, expanding the scope of novel catalyst systems with acceptable catalytic activity and stereoselectivity still remain a major challenge. We expected that bis(imidazoline)-palladium pincer complexes would enhance the acidity of the α -proton in alkynitriles to afford palladium ketenimides, which would then react with imines to give products under mild reaction conditions

Figure 6. Enantioselective reaction of alkynitriles with imines using chiral palladium complexes.

(Figure 6).

3.1 Enantioselective Reaction of Alkyl nitriles with Imines^{16,17,18}

To prove this hypothesis, we first examined the enantioselective reaction of benzylnitrile with *N*-(*p*-toluenesulfonyl)-imine as a benchmark reaction of phehim-Pd catalyst. The results are shown in Table 1. The reaction using 5 mol% of **1a** and AgOAc gave product in good yield but with a low diastereomer ratio and a moderate enantiomer ratio, although the reaction without using AgOAc did not afford any product (entries 1 and 2). As expected, the enantioselectivity of the product depended on the substituents on the nitrogen atoms in the imidazoline. When acetylated catalyst **1b**, *p*-toluenesulfonylated catalyst **1c**, or methanesulfonylated catalyst **1d** were used as a catalyst, lower enantioselectivities were obtained compared with the reaction using catalyst **1a** (entries 3–5). The reaction using catalyst **1e** having 2,4,6-trimethylphenyl groups afforded a product with good diastereo- and enantioselectivity but in low yield (entry 6). The addition of molecular sieves 5A and K₂CO₃ as the base improved the reactivity and yield of the reaction (entry 7). Finally, the best enantioselectivity was obtained by the reaction using **1e**, AgOAc, K₂CO₃, and molecular sieves 5A at –20 °C in THF (entry 8).

Table 1. Enantioselective reaction of benzylnitrile with imine using phehim-Pd catalysts.

$\text{Ph}-\text{CH}=\text{N}-\text{Ts} + \text{Ph}-\text{CH}_2-\text{CN} \xrightarrow[\text{THF, 0}^\circ\text{C}]{\text{catalyst (5 mol\%), AgOAc (5 mol\%), base (1.0 equiv.)}} \text{Ph}-\text{CH}(\text{NHTs})-\text{CH}(\text{CN})-\text{Ph}$						
Entry	Cat.	Base	Time (h)	Yield (%)	Dr ^a	Er ^b
1	1a	–	60	65	58:42	84:16
2 ^c	1a	–	60	–	–	–
3	1b	–	60	53	55:45	80:20
4	1c	–	60	74	62:38	67:33
5	1d	–	60	56	56:44	66:34
6	1e	–	60	51	90:10	93:7
7 ^d	1e	K ₂ CO ₃	48	99	91:9	93:7
8 ^{d,e}	1e	K ₂ CO ₃	96	97	93:7	95:5

^aDiastereomer ratio was determined by ¹H NMR. ^bEnantiomer ratio for a major diastereomer was determined by HPLC analysis using a chiral column. ^cWithout AgOAc. ^dBenzylnitrile (1.25 equiv) was used, and MS5A was added. ^eAt –20 °C.

With these optimized conditions, we next examined the reaction of benzylnitrile with various imines using **1e** and AgOAc (Table 2). The reaction with imines bearing an electron-donating group, such as methyl and methoxy groups, gave products with high stereoselectivity but with low reactivity (entries 2 and 3). The reaction with electron-withdrawing imines afforded products in high yield and enantioselectivity (entries 4–8), although the reaction with *ortho*-substituted imine showed low enantioselectivity (entry 6). Naphthyl- and heteroatom-containing imines gave products in good yield with good stereoselectivity (entries 9–11).

The reaction of various nitrile compounds with *N*-tosylimine using **1e**, AgOAc and K₂CO₃ was also examined (Table 3). Benzylnitriles carrying either electron-donating or -withdrawing substituents gave products in high yield with high enantioselectivity (entries 1–8). The reaction of naphthylme-

Table 2. Enantioselective reaction of benzylnitrile with various imines.

$\text{Ar}-\text{CH}=\text{N}-\text{Ts} + \text{Ph}-\text{CH}_2-\text{CN} \xrightarrow[\text{THF, MS5A, -20}^\circ\text{C}]{\text{1e (5 mol\%), AgOAc (5 mol\%), K}_2\text{CO}_3 \text{ (1.0 equiv.)}} \text{Ar}-\text{CH}(\text{NHTs})-\text{CH}(\text{CN})-\text{Ph}$					
Entry	Imine (Ar)	Time (h)	Yield (%)	Dr	Er
1	Ph	96	97	93:7	95:5
2 ^a	4-CH ₃ C ₆ H ₄	144	87	89:11	95:5
3 ^a	4-CH ₃ OC ₆ H ₄	120	79	82:18	94:6
4	4-FC ₆ H ₄	96	94	89:11	92:8
5	4-ClC ₆ H ₄	72	86	80:20	92:8
6	2-ClC ₆ H ₄	96	87	77:23	78:22
7	3-ClC ₆ H ₄	120	93	85:15	88:12
8	4-BrC ₆ H ₄	72	62	85:15	91:9
9	1-Naphthyl	96	89	91:9	94:6
10	2-Naphthyl	144	85	88:12	93:7
11	2-Thienyl	168	85	83:17	88:12

^aAt –10 °C.

Table 3. Reaction of various benzylnitriles with an imine.

$\text{Ph}-\text{CH}=\text{N}-\text{Ts} + \text{Ar}-\text{CH}_2-\text{CN} \xrightarrow[\text{THF, MS5A, -20}^\circ\text{C}]{\text{1e (5 mol\%), AgOAc (5 mol\%), K}_2\text{CO}_3 \text{ (1.0 equiv.)}} \text{Ph}-\text{CH}(\text{NHTs})-\text{CH}(\text{CN})-\text{Ar}$					
Entry	Nitrile (Ar)	Time (h)	Yield (%)	Dr	Er
1	Ph	96	97	93:7	95:5
2 ^a	4-CH ₃ C ₆ H ₄	216	90	86:14	90:10
3 ^a	4-CH ₃ OC ₆ H ₄	240	87	87:13	95:5
4	4-FC ₆ H ₄	120	95	93:7	95:5
5 ^b	4-ClC ₆ H ₄	72	99	89:11	96:4
6 ^b	3-ClC ₆ H ₄	72	89	76:24	92:8
7 ^b	4-BrC ₆ H ₄	72	99	92:8	96:4
8 ^b	4-IC ₆ H ₄	66	99	91:9	95:5
9	2-Naphthyl	72	92	90:10	95:5
10	2-Thienyl	72	83	85:15	93:7

^aAt 0 °C. ^bAt –30 °C.

thyl nitrile and heteroarylmethylnitrile also afforded products with high enantioselectivity (entries 9–10).

The obtained α -aryl- β -aminonitriles can be readily converted to important chiral building blocks. Reduction of the cyano group of the product was carried out using NiCl₂·6H₂O, NaBH₄ and (Boc)₂O to give a chiral *N*-Boc amide (Scheme 2). In addition, hydrolysis of the product using Pd(OAc)₂, PPh₃, and acetaldoxime in refluxing aqueous EtOH afforded α -aryl- β -aminoamide in good yield without the loss of enantiopurity.

Scheme 2. Transformation of α -aryl- β -aminonitriles.

The assumed catalytic cycle for the reaction of benzylnitriles with imines is shown in Figure 7. The exchange reaction of bromide in **1e** to acetate was carried out by the addition of AgOAc to phebim-PdBr catalyst (complex **A**). The ligand exchange reaction of acetate in complex **A** to benzylnitrile affords cationic complex **B**, which can be easily deprotonated by acetate. The obtained palladium ketenimide (complex **C**) reacts with *N*-tosylimines to afford complex **D**, which subsequently proceeds protonation and decomplexation to give a product and regenerated complex **A**.

Figure 7. Proposed catalytic cycle for the reaction of benzylnitrile with imine using **1e**.

In order to clarify the reaction mechanism, we examined the MO calculation of complex **C** using a Gaussian 09 B3LYP/LANL2DZ level (Figure 8). The ketenimide of benzylnitrile coordinated to palladium avoiding the steric repulsion between the phenyl group in benzylnitrile and the bulky 2,4,6-trimethylphenyl groups in **1e**. Based on the absolute configuration of products, Figure 8 also shows a proposed transition state for the enantioselective reaction of palladium ketenimide with *N*-tosylimine. Bulky 2,4,6-trimethylphenyl groups on bis(imidazoline)s shielded the *Si*-face of the carbanionic center of palladium ketenimide. Therefore, imine approaches the *Re*-face of palladium ketenimide. Avoiding steric repulsion between the toluenesulfonyl group in *N*-tosylimine and the aryl group in palladium ketenimide, the *Re*-face of the imine reacts with palladium ketenimide to give the (1*S*,2*R*)-isomer.

Figure 8. MO calculation of complex **C** using Gaussian 09 B3LYP/LANL2DZ and assumed transition state.

Recently, we also examined the enantioselective reaction of α -thioacetoneitrile or α -aminoacetoneitrile with imine using the same strategy. The reaction of α -thioacetoneitrile or α -aminoacetoneitrile with various imines using catalyst **1e** and silver acetylacetonate afforded products in high yield with high enantioselectivity (Scheme 3).

Scheme 3. Reaction of α -thioacetoneitrile or α -aminoacetoneitrile with various imines.

3.2 Enantioselective Decarboxylative C–C Bond Formation Reaction of α -Cyanoacetic Acid¹⁹

We next examined the decarboxylative C–C bond formation reaction of α -cyanoacetic acids with imines. There is only one report on the enantioselective decarboxylative C–C bond formation reaction of α -cyanoalkanoic acids with imines.²⁰ Shibasaki and Kanai reported remarkable work on the highly enantioselective decarboxylative C–C bond formation reaction of activated benzylic α -cyano carbanions to imines using chiral bisphosphine–CuOAc catalyst. This reaction gave β -amino nitriles having a quaternary stereocenter with high enantioselectivity.^{13c,d} Although the impressive progress was achieved in catalytic enantioselective decarboxylative C–C bond formation reaction of benzylic α -cyano carbanions with imines, there remains room for development of the enantioselective reaction of simple alkyl nitriles. Therefore, we investigated an enantioselective decarboxylative C–C bond formation reaction of α -cyanoacetic acids, which is an attractive candidate for the generation of ketenimide for nitriles under a mild reaction condition, with imines using phebim–Pd catalysts (Table 4).

The reaction of *N*-tosylimine **1a** with cyanoacetic acid using 5 mol% of **1a** and AgOTf afforded product in high yield with moderate enantioselectivity (entry 1). The reactivity was improved by the reaction using *N*-(2-pyridinesulfonyl)imine (entry 2).²¹ In order to improve the enantioselectivity, we next examined the optimization of the catalyst structures (entries 3–5). We found that phebim–Pd catalyst **1b** having an acetyl group (R^1) and phenyl groups (Ar) was an efficient catalyst. The enantioselectivity improved slightly in the reaction performed at 0 °C (entry 6). The addition of KOTf also improved the enantioselectivity of the product (entry 7). Having established optimized condition for decarboxylative C–C bond formation reaction, we next tried the reaction of cyanoacetic acid with various imines having both electron-donating and -withdrawing group. The reaction with imines using 5 mol% of **1b** and AgOTf gave products in good yield with good enantioselectivity (entries 9–15). Furthermore, the reaction of 2-cyanopropionic acid with imine also gave product in moderate

Table 4. Enantioselective reaction of cyanoacetic acid with various imines using phehim-Pd catalysts.

$\text{R}^2\text{-CH=N-SO}_2\text{R}^1 + \text{HO}_2\text{C-CH}_2\text{CN} \xrightarrow[\text{THF, MS4A, r.t.}]{\text{catalyst (5 mol\%), AgOTf (5 mol\%)}} \text{R}^2\text{-CH(SO}_2\text{R}^1\text{)-CH}_2\text{CN}$ (3.0 equiv)						
Entry	R ¹	R ²	Cat.	Time (h)	Yield (%)	Er
1	4-Tol	Ph	1a	168	69	83:17
2	2-Py	Ph	1a	48	81	86:14
3	2-Py	Ph	1b	24	81	87:13
4	2-Py	Ph	1d	48	76	84:16
5	2-Py	Ph	1f	168	37	65:35
6 ^a	2-Py	Ph	1b	96	82	91: 9
7 ^{a,b}	2-Py	Ph	1b	96	82	94: 6
8 ^a	2-Py	3-ClC ₆ H ₄	1b	36	82	93: 7
9 ^{a,b}	2-Py	3-BrC ₆ H ₄	1b	36	79	94: 6
10 ^a	2-Py	3-FC ₆ H ₄	1b	36	70	90:10
11 ^a	2-Py	3-MeOC ₆ H ₄	1b	168	83	92: 8
12 ^{a,b}	2-Py	1-Naphthyl	1b	90	73	92: 8
13 ^a	2-Py	3-Furyl	1b	168	60	90:10
14 ^a	2-Py	2-Thienyl	1b	168	62	95: 5
15 ^a	2-Py	3-Thienyl	1b	168	78	95: 5

^aAt 0 °C using 2.0 equiv of cyanoacetic acid. ^bKOTf (10 mol%) was added.

Scheme 4. Reaction with 2-cyanopropionic acid using **1b** and AgOTf.

yield with high enantioselectivity but with low diastereoselectivity (Scheme 4).

Next, we synthesized key intermediates for optically active PDE-4 inhibitor (Scheme 5). Removal of the pyridinesulfonyl group in the product using magnesium/methanol gave β -aminonitrile, which was treated with 3-nitrophthalic anhydride to give the key intermediate for PDE-4 inhibitor without a loss of enantiopurity.

Scheme 5. Transformation to key intermediate for PDE4 inhibitor.

Two different reaction pathways are possible in the decarboxylative C–C bond formation reaction of cyanoacetic acid with imines: a) a decarboxylation–nucleophilic addition path-

way, in which cyanoacetic acid undergoes decarboxylation to form a palladium–ketenimide intermediate, which reacts with imines; b) deprotonation–nucleophilic reaction–decarboxylation pathway, in which the α -proton of the cyano group of cyanoacetic acid is deprotonated; subsequently the nucleophilic reaction of ketenimides to imines and decarboxylation affords the product (Figure 9).

In order to clarify the reaction pathway, we investigated APCI–Mass spectroscopic analysis of the reaction mixture of *N*-(pyridinesulfonyl)imine and cyanoacetic acid in THF. The APCI–Mass spectra showed the α -cyano- β -aminopropionic acid (intermediate **E**: cation mode, calcd for C₁₅H₁₄N₃O₄S: 332.1, found: 332.2). This species clearly showed that the first reaction is a nucleophilic reaction of the α -cyano carbanion of cyanoacetic acid to the imine (Figure 9, path b).

Figure 9. Two possible reaction pathways for the decarboxylative C–C bond formation reaction.

The proposed catalytic cycle for the reaction of cyanoacetic acid with imines is shown in Figure 10a. The reaction of AgOTf with phehim–PdBr affords the phehim–PdOTf complex (complex **F**). The triflate in complex **F** is exchanged to cyanoacetic acid giving complex **G**. The formation of complex **G** was confirmed by APCI–Mass spectroscopic analysis of this reaction mixture (cation mode, calcd for C₄₃H₃₆N₅O₄Pd as complex **G**+H⁺: 792.2, found: 792.2). Complex **G** can be deprotonated by a weak base to give palladium ketenimide (complex **H**). The nucleophilic reaction of complex **H** with imines gives complex **I**. In order to check the catalytic cycle for this reaction, we attempted the reaction of imine with malonic acid half-ester (HOOCCH₂CO₂Et) using phehim–Pd and AgOTf catalyst. However, the reaction did not afford the product. This result shows the importance of the coordination between the palladium complex and the nitrile group in complexes **G** and **H**.²²

We also conducted the MO calculation of complex **H** using a Gaussian 09 B3LYP/LANL2DZ level. The calculation showed that the carboxy group in cyanoacetic acid coordinated to palladium at the equatorial position, and that the cyano group in cyanoacetic acid also coordinated to palladium (Figure 5, SP-5 structure). The stabilization energy for the interaction between the CN group in ketenimide and the palladium cation in complex **H** was estimated to be 6.1 kcal/mol by NBO analysis. Based on the absolute configuration of products, imine approaches from the *Re*-face of the imine to react with palladium ketenimide (Figure 10b).

3.3 Aza–MBH Reaction of Acrylonitrile with Imines²³

We next examined the enantioselective aza–Morita–Baylis–Hillman reaction (aza–MBH reaction) of α,β -unsaturated nitriles with imines. This reaction is a powerful tool for the preparation of synthetically useful chiral α -methylidene- β -aminonitrile compounds. However, only limited attention has

Figure 10. Plausible catalytic cycle for the decarboxylative C-C bond formation reaction, MO calculation of complex H, and assumed transition state.

been paid to the catalytic enantioselective aza-MBH-reaction of acrylonitrile to imines,²⁴ although there are many reports on the enantioselective aza-MBH reaction for α,β -unsaturated carbonyl compounds.²⁵ Therefore, a more efficient catalytic system to synthesize these compounds with good reactivity and selectivity is still highly desirable. We hypothesized that the phebim-Pd catalyst can be applicable to the aza-MBH reaction of acrylonitrile with imines, in which phebim-Pd complexes activate the electrophilicity of acrylonitrile, then an achiral Lewis base attacks the β -position of acrylonitrile. The generated palladium ketenimide reacts with imines to give chiral α -methylene- β -amino nitriles (Figure 11).

Figure 11. Palladium pincer complexes catalyzed the aza-MBH reaction.

The enantioselective reaction of acrylonitrile with *N*-tosylimine was carried out by using 5 mol% of phebim-Pd catalysts **1**, 5 mol% of AgOAc, and DABCO (Table 5). After optimization of the structure for chiral catalysts, we found that catalyst

1f having an acetyl group (R^1) and 2,4,6-trimethylphenyl groups (Ar) or **1g** having an acetyl group (R^1) and 1-naphthyl groups (Ar) are suitable catalysts for the aza-MBH reaction (entries 1–5). The reaction at -10°C allowed for even more rigorous enantiofacial control (entry 7). Even 2.5 mol% of **1g** and DABCO showed the same enantioselectivity and reactivity (entry 8).

Table 5. Optimization of reaction conditions of the aza-MBH reaction.

$\text{Ph}-\text{CH}=\text{N}-\text{Ts} + \text{CH}_2=\text{CH}-\text{CN} \xrightarrow[\text{DABCO (X mol\%)}]{\text{catalyst (5 mol\%) AgOAc (5 mol\%)}} \text{Ph}-\text{CH}(\text{CN})-\text{CH}_2-\text{N}-\text{Ts}$ <p style="text-align: center;">(3.0 equiv)</p>					
Entry	Cat.	DABCO (X mol%)	Temp ($^\circ\text{C}$)	Yield (%)	Er
1	1a	20	r.t.	92	87:13
2	1b	20	r.t.	91	89:11
3	1c	20	r.t.	87	86:14
4	1f	20	r.t.	92	93:7
5	1g	20	r.t.	91	94:6
6	1g	5	r.t.	99	96:4
7 ^a	1g	5	-10	93	97:3
8 ^b	1g	2.5	r.t.	97	96:4

^aFor 48 h. ^b**1g** (2.5 mol%) and AgOAc was used.

The reaction of a series of imines using **1g**, AgOAc, and DABCO gave products in high yield with high enantioselectivity (Table 6, entries 1–14), although the reaction of *para*-substituted imines needed to use 2,4,6-trimethylphenyl-substituted phebim-Pd complex **1f** instead of **1g** (entries 2, 6, 10).

Table 6. Aza-MBH reaction of acrylonitrile with various imines.

$\text{Ar}-\text{CH}=\text{N}-\text{Ts} + \text{CH}_2=\text{CH}-\text{CN} \xrightarrow[\text{DABCO (5 mol\%)}]{\text{1g (5 mol\%) AgOAc (5 mol\%)}} \text{Ar}-\text{CH}(\text{CN})-\text{CH}_2-\text{N}-\text{Ts}$ <p style="text-align: center;">(3.0 equiv)</p>				
Entry	Ar	Time (h)	Yield (%)	Er
1	Ph	48	93	97:3
2 ^a	4-FC ₆ H ₄	72	84	96:4
3	3-FC ₆ H ₄	24	97	97:3
4	2-FC ₆ H ₄	24	89	88:12
5	3,5-F ₂ C ₆ H ₃	24	87	95:5
6 ^a	4-ClC ₆ H ₄	96	97	95:5
7	3-ClC ₆ H ₄	36	98	98:2
8	3-MeOC ₆ H ₄	84	96	97:3
9	1-Naphthyl	72	89	99:1
10 ^a	2-Naphthyl	72	98	96:4
11	2-Furyl	72	88	97:3
12	3-Furyl	72	87	98:2
13	2-Thienyl	96	93	95:5
14	2-Thienyl	72	88	99:1

^aThe reaction was carried out using 5 mol% of **1f** and 20 mol% DABCO at -20°C .

Next, the transformation of product to tetrahydroisoin-doline and pyrroline derivatives was carried out (Scheme 6). The reaction of the aza-MBH product with (*E*)-5-bromo-penta-1,3-diene and K₂CO₃ gave the *N*-alkylated product,

which was treated with BCl_3 to afford the corresponding 1-aryl-substituted tetrahydroisindoline derivative through an intramolecular Diels–Alder reaction without the loss of enantiopurity. Furthermore, the reaction of the aza-MBH product with allyl bromide using K_2CO_3 gave an *N*-allylated product. Then, the ring-closing metathesis of an *N*-allylated product using Grubbs-type II catalyst afforded pyrroline in high yield.

Scheme 6. Transformation of α -methylidene- β -aminonitrile to cyclic compounds.

In order to clarify the selective activation of nitrile compounds by phehim-Pd catalysts, the reactions of mixtures of acrylonitrile and ethyl acrylate to imine with or without **1g** and AgOAc were examined (Scheme 7). The reaction without **1g** and AgOAc afforded almost the same amount of products derived from acrylonitrile and ethyl acetate. On the other hand, the aza-MBH reaction of acrylonitrile using **1g** and AgOAc preferably afforded product than that using ethyl acrylate. The rate of the reaction with acrylonitrile using catalyst **1g** was at least 10 times faster than that for the reaction with ethyl acrylate. These results showed that the reactivity of acrylonitrile is effectively enhanced by selective coordination of phehim-Pd catalysts to the cyano group.

Scheme 7. Aza-MBH reactions of acrylonitrile and ethyl acrylate.

4. Allylation of Ketimines Using Phehim-Pd Catalysts²⁶

We next examined the enantioselective allylation of ketimines using phehim-Pd catalysts. The development of enantioselective allylation of ketimines is important for organic synthesis, as it provides efficient access to chiral tetra-substituted homoallylic amines. However, the enantioselective allylation of ketimines is not an easy task due to their low reactivity and difficulties associated with their enantiofacial control.²⁷ There are only two reports for the catalytic enantioselective allylation of ketimines. The first enantioselective allylation of ketimines was reported by Shibasaki and co-workers, in which the reaction of various acyclic ketimines with allylboronate using bisphosphine-CuF catalyst gave products with high enantio-

selectivity.^{27a} Lam and co-workers recently reported the catalytic enantioselective allylation of cyclic ketimines using chiral rhodium complexes.^{27b} On the other hand, the enantioselective nucleophilic addition to ketimines derived from isatins has attracted much attention, because the reaction affords a chiral 3-substituted 3-amino-2-oxindole structure, which is an important structural motif in biologically active compounds, such as HIV-1 protease²⁸ or medicinally relevant compounds (Figure 12).²⁹

Figure 12. Biologically active 3-substituted 3-amino-2-oxindoles.

However, there are no reports on the catalytic enantioselective allylation of ketimines derived from isatins. Therefore, our research interest was extended to the enantioselective allylation of ketimines derived from isatins using phehim-Pd complexes. We examined the reaction of isatin ketimine with allyltrimethoxysilane in the presence of 5 mol% of a series of phehim-Pd catalysts and silver fluoride (Table 7).

Table 7. Enantioselective allylation of ketimines derived from isatins using phehim-Pd **1**.

Entry	R	Cat.	Time (h)	Yield (%)	Er
1	$\text{C}_6\text{H}_5\text{CH}_2$	1a	36	91	86:14
2	$\text{C}_6\text{H}_5\text{CH}_2$	1c	24	90	21:79
3	$\text{C}_6\text{H}_5\text{CH}_2$	1d	36	92	19:81
4	$\text{C}_6\text{H}_5\text{CH}_2$	1h	24	93	89:11
5	$\text{C}_6\text{H}_5\text{CH}_2$	1i	24	92	93:7
6	$(\text{C}_6\text{H}_5)_3\text{C}$	1i	24	91	96:4
7 ^a	$(\text{C}_6\text{H}_5)_3\text{C}$	1i	36	92	97:3
8 ^b	$(\text{C}_6\text{H}_5)_3\text{C}$	1i	54	93	95:5

^aAt $-30\text{ }^\circ\text{C}$. ^b**1i** (1 mol%) was used.

The reaction of ketimine derived from *N*-benzylisatin with allyltrimethoxysilane using *N*-benzoylated phehim-Pd **1a** afforded product in high yield with moderate enantioselectivity (entry 1). On the other hand, the reaction using sulfonated phehim-Pd **1c, d** afforded product having opposite stereochemistry to the product of the reaction using **1a** (entries 2 and 3). The reaction using catalyst **1h** having electron-donating groups on the benzoyl group also afforded product with high enantioselectivity (entry 4). When catalyst **1i**, having a *tert*-butyl group on the phenylene linker, was used, good enantioselectivity was obtained (entry 5). The reaction with isatin ketimine having a triphenylmethyl group (trityl group: Tr) gave the product with higher enantioselectivity than that from the reaction of *N*-benzyl ketimine (entry 7). A lower reaction temperature ($-30\text{ }^\circ\text{C}$) can improve the enantioselectivity of the product (entry 8). Decreasing the catalyst loading to 1 mol% had little

effect on reactivity and enantioselectivity (entry 9).

We next examined the allylation of a series of ketimines using **1i** and AgF (Table 8). Both electron-donating and-withdrawing ketimines gave products in high yield with high enantioselectivity (entries 2–11). The reaction with 2-substituted allyltrimethoxysilane also afforded product in high yield with good enantioselectivity (entry 12). These results were the first example of enantioselective allylation of isatin ketimines.

Table 8. Enantioselective allylation of various ketimines using **1i**.

Entry	R ¹	R ²	Time (h)	Yield (%)	Er
1 ^a	H	H	72	92	98: 2
2	5-Me	H	36	91	97: 3
3	5-MeO	H	48	92	95: 5
4	5-F	H	60	92	96: 4
5	5-Cl	H	48	96	93: 7
6	5-Br	H	72	84	91: 9
7 ^a	4-Br	H	24	94	93: 7
8	6-Br	H	48	93	97: 3
9	6-Cl	H	36	93	97: 3
10	7-F	H	48	95	97: 3
11	4,6-Me	H	48	90	94: 6
12 ^b	H	Me	60	93	93: 7

^aAt -40 °C. ^cAt -25 °C.

We next examined the deprotection of both the Boc group and the trityl group in *N*-Boc-*N'*-trityl amide using trifluoroacetic acid to afford homoallylic amine in high yield without the loss of enantiopurity (Scheme 8). We also synthesized a spirocyclic compound from the product. The treatment of product using allylbromide, sodium hydride, and tetrabutylammonium bromide (TBAB) afforded *N*-allyl-*N*-Boc amine in high yield. The ring-closure metathesis of *N*-allyl-*N*-Boc amine using a second generation of Grubbs catalyst gave spirocyclic amine in high yield without the loss of enantioselectivity.

Scheme 8. Transformation of products to chiral homoallylic amines or spiroamine.

The proposed catalytic cycle for the allylation of isatin ketimines is shown in Figure 13. The ligand exchange reaction of bromide to fluoride gives complex **J**. Allylsilane is activated by the fluoride ion to afford an η^1 -allyl coordinated palladium pincer species (complex **K**). In order to clarify the assumed

catalytic cycle, we examined using ESI-Mass spectroscopic analysis, the mixture of **3b**, AgF, and allyltrimethoxysilane in a 1:1:1 ratio in THF. The analysis showed complex **K** (cation mode, calcd for C₄₃H₃₆N₃O₂Pd: 760.19, found: 760.19). Therefore, the nucleophilic reaction of allyl-palladium species with ketimines gives complex **L**, which subsequently undergoes transmetalation with silver fluoride to give product.

Figure 13. Proposed catalytic cycle for the allylation of ketimines.

The structure of allylpalladium complex **K** was optimized by using Gaussian 09 B3LYP/LANL2DZ level (Figure 14). The allyl group coordinates to palladium avoiding steric repulsion with the bulky phenyl groups in **1i**. The proposed transition state for the enantioselective allylation of imine using **1** is shown in Figure 14. The η^1 -allyl group on palladium attacks imines at the γ -position of the allyl moiety without coordination to ketimines. Ketimine approaches from the opposite side of the Pd-C bond. Avoiding steric repulsion of the trityl group in ketimines with the phenyl group in chiral bis(imidazoline), the *Re*-face of ketimine reacts with allylpalladium to give the (*S*)-isomer.

Figure 14. The optimized structure of complex **K** and the assumed transition state for the allylation of ketimines derived from isatins.

5. Conclusion

We have developed palladium pincer-type complexes of

1,3-bis(imidazolin-2-yl)benzene and applied them to several asymmetric syntheses. The enantioselective reactions of various nitriles with *N*-sulfonylimines using phebim-Pd catalysts gave products with good diastereo- and enantioselectivity. A range of nitrile compounds can be tolerated in enantioselective processes. These processes offer a simple and efficient way to synthesize of functionalized β -aminonitriles and their derivatives. We also developed an enantioselective allylation of ketimines derived from isatins using chiral palladium-pincer complexes. Further experiments are in progress to study the scope of this process and the potential application of imidazoline catalysts to other reactions.³⁰

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PROFILE

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