Asymmetric Catalysis

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PyBidine–Cu(OTf)$_2$-Catalyzed Asymmetric [3+2] Cycloaddition with Imino Esters: Harmony of Cu–Lewis Acid and Imidazolidine-NH Hydrogen Bonding in Concerto Catalysis**

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Abstract: *A bis(imidazolidine)pyridine (PyBidine)–Cu(OTf)$_2$ complex catalyzing the endo-selective [3+2] cycloaddition of nitroalkenes with imino esters was applied to the reaction of methyleneindolinones with imino esters to afford spiro[pyrrolidin-3,3′-oxindole]s in up to 98% ee. X-ray crystallographic analysis of the PyBidine–Cu(OTf)$_2$ complex and DFT calculations suggested that an intermediate Cu enolate of the imino ester reacts with nitroalkenes or methyleneindolinones, which are activated by NH-hydrogen bonding with the PyBidine–Cu(OTf)$_2$ catalyst.*

Diverse optically active pyrrolidines are widely observed in biologically significant compounds. Since Grigg's pioneering work on Co catalysis,[1] efficient catalytic asymmetric [3+2] cycloaddition reactions have been widely investigated for the stereoselective construction of highly substituted pyrrolidine rings.[2] Among these, the reaction of imino esters with nitroalkenes is particularly important in the construction of fully functionalized pyrrolidine rings.[3] With regard to the significance of pyrrolidines in pharmaceutical research directed toward the development of drug candidates, some practical and useful [3+2] cycloaddition reactions have been applied to the synthesis of more complex molecules.[4] For example, in combination with the indole skeleton, several unique families of spiro[pyrrolidin-3,3′-oxindole] scaffolds have been conventionally constructed using the [3+2] cycloaddition of 2-oxoindolin-3-ylidene derivatives.[5] The first catalytic asymmetric route to spiro[pyrrolidin-3,3′-oxindole] was shown by Gong and co-workers in 2009, who employed a three-component [3+2] cycloaddition with a chiral Brønsted acid catalyst.[5a] Simultaneously, Waldmann and co-workers reported a Lewis acidic Cu^{I}-catalyzed [3+2] cycloaddition of methyleneindolinones and imino esters,[5b,c] and the group of Wang reported a Ag^{I}-catalyzed [3+2] cycloaddition.[5d] The pioneering work on these [3+2] cycloaddition reactions has been successfully applied not only to the synthesis of natural products, but also in the screening of a new generation of biologically active compounds in biology-oriented synthesis (BIOS).[4b]

In our efforts toward diversity-oriented asymmetric catalysis (DOAC),[6g,7g,8] we have developed the chiral imidazoline-aminophenol (IAP) ligand[6] and the bis(imidazolidine)pyridine (PyBidine) ligand[7] for the [3+2] cycloaddition of nitroalkenes with imino esters. The IAP–nickel catalyst provided the first general methodology for *exo*′-selective cycloaddition reactions (Figure 1 a).[6d,9,10]

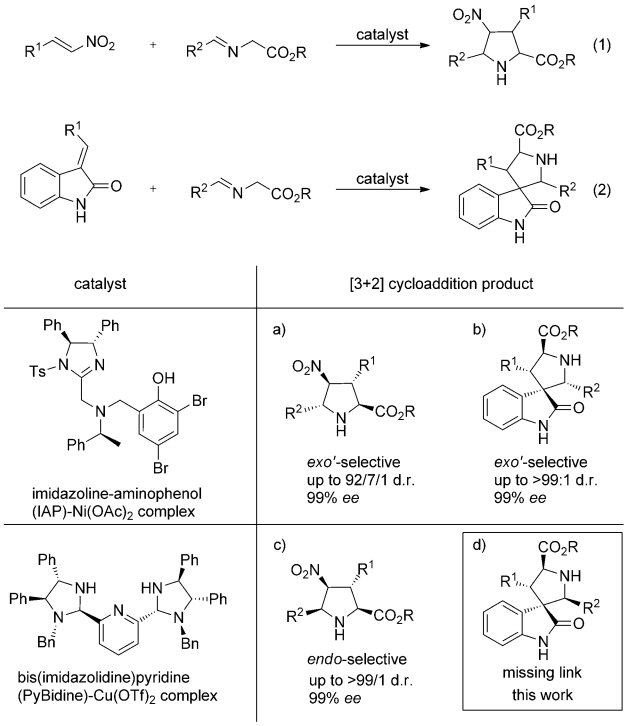

Figure 1. Classification of the stereochemical output of the [3+2] cycloaddition using the IAP–Ni(OAc)$_2$ catalyst and the PyBidine–Cu(OTf)$_2$ catalyst.

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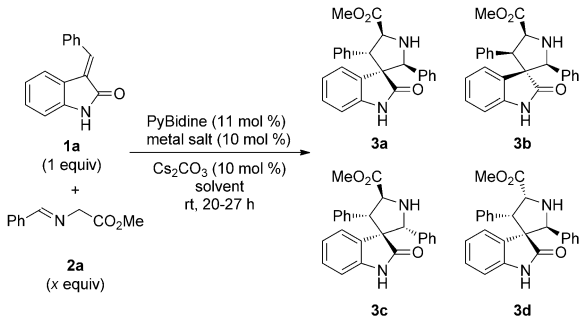
The IAP–nickel catalyst system has also been successfully applied to the [3+2] cycloaddition of imino esters with methyleneindolinones to construct novel diastereomers of spiro[pyrrolidin-3,3′-oxindole] with *exo*′-orientation (Figure 1b).[6e] In contrast, the bis(imidazolidine)pyridine (PyBidine)–$Cu(OTf)_2$ complex catalyzed an *endo*-selective [3+2] reaction of imino esters with nitroalkenes to give adducts in up to 99% *ee* (Figure 1c).[7a] The excellent *endo*-selectivity observed using the PyBidine–Cu-catalyzed [3+2] cycloaddition prompted us to apply the PyBidine–metal catalyst to the stereoselective construction of spiro[pyrrolidin-3,3′-oxindole] (Figure 1d). Herein, the role of the PyBidine–metal catalyst in controlling the stereoselective [3+2] cycloaddition reaction is also examined in detail using DFT calculations.

The study began with an exploration of the most appropriate PyBidine–metal system for the reaction of β-phenyl methyleneindolinone **1a** with imino ester **2a** (Table 1).

Table 1: Optimization of reaction conditions for the PyBidine–metal-catalyzed [3+2] cycloaddition of an imino ester with methyleneindolinone.



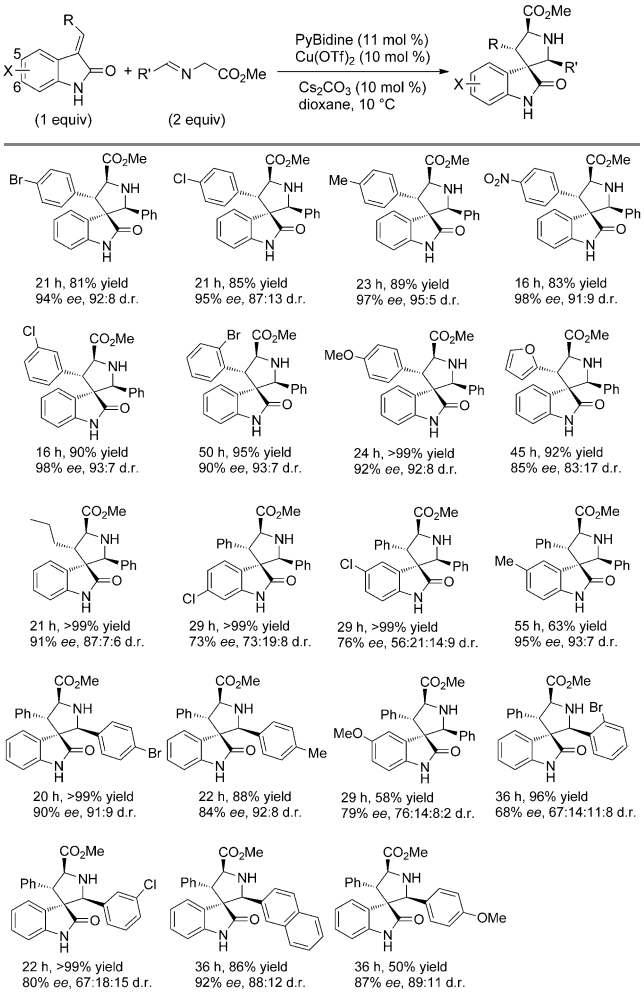
Entry	Metal salt	*x*	Yield [%]	d.r. **3a**/**3b**	*ee* of **3a** [%]
1	$Cu(OTf)_2$	1.1	49	87:13	97
2	$Ni(OAc)_2$	1.1	80	69:31	13
3	$NiCl_2$	1.1	55	61:39	44
4	$CoCl_2$	1.1	75	79:21	12
5	$Ni(OTf)_2$	1.1	54	73:27	44
6	$Zn(OTf)_2$	1.1	36	94:6	72
7	$Cu(OTf)_2$	2.0	78	89:11	91
8[a]	$Cu(OTf)_2$	2.0	86	94:6	96
9[a,b]	$Cu(OTf)_2$	2.0	91	90:10	93

[a] The reaction was performed at 10°C. [b] With 5 mol% $Cu(OTf)_2$ and 5.5 mol% PyBidine for 47 h.

When 10 mol% PyBidine–$Cu(OTf)_2$ catalyst was used in the reaction of **1a** with 1.1 equiv of **2a** under the reaction conditions optimized for the previous reaction using nitroalkenes,[7a] the spirooxindole compound **3** was obtained in 49% yield with 87:13 diastereoselectivity. The major isomer **3a** had an *ee* of 97% (entry 1). The PyBidine–metal-salt catalysts with $Ni(OAc)_2$, $NiCl_2$, and $CoCl_2$, which had previously been shown to be effective, gave the product in moderate to low enantiomeric excess (entries 2–4). Among the triflate salts of first-row transition metals that we examined, the PyBidine–$Cu(OTf)_2$ complex showed the best catalytic activity for this [3+2] cycloaddition reaction. For the reaction catalyzed by the PyBidine–$Cu(OTf)_2$ complex, the use of 2.0 equiv of imino ester improved the chemical yield, and the reaction at 10°C gave the product in 86% yield with a diastereoselectivity of up to 94:6 (entry 8).

Under the optimized reaction conditions (Table 1, entry 8), the generality of the PyBidine–$Cu(OTf)_2$-catalyzed asymmetric [3+2] cycloaddition of methyleneindolinones with various imino esters was examined (Table 2). For β-

Table 2: PyBidine–$Cu(OTf)_2$-catalyzed asymmetric [3+2] cycloaddition of methyleneindolinones with various imino esters.



aryl methyleneindolinones, both electron-deficient and electron-rich aryl groups were compatible, giving the product with high enantioselectivities ranging from 90–98% *ee*. 2-Furyl methyleneindolinone was converted to the product in 92% yield with 85% *ee* (83:17 d.r.). A β-alkyl methyleneindolinone, *n*-propyl methyleneindolinone, was quantitatively transformed to the product with 91% *ee* (87:7:6 d.r.).

The PyBidine–$Cu(OTf)_2$ was able to generate an array of variously functionalized spiro[pyrrolidin-3,3′-oxindole]s. For understanding the role of the catalyst PyBidine–$Cu(OTf)_2$, the following three points (1–3) are worth mentioning.

1) Enantioface selection mode: Using an (*S*,*S*)-diphenylethylene diamine-derived PyBidine–$Cu(OTf)_2$ catalyst, meth-

yl(2*S*,3*R*,4*S*,5*S*)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate, known as the *endo*-product, was obtained as the major product in the reaction of imino ester with nitrostyrene. In the reaction of imino ester with β-phenyl methyleneindolinone, the major product was methyl (2′*S*,3*R*,4′*S*,5′*S*)-2-oxo-2′,4′-diphenylspiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (**3a**). The mode of enantioface selection is the same for the *endo*-selective [3+2] cycloaddition using nitroalkenes (Figure 2).

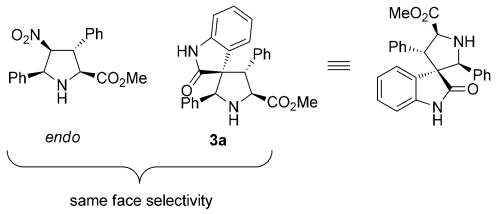
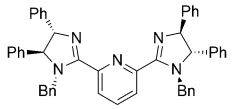


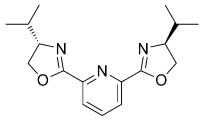
Figure 2. Enantioface selection mode of PyBidine–Cu(OTf)$_2$-catalyzed asymmetric [3+2] cycloaddition.

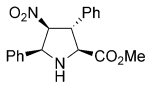
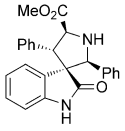
2) Comparison of catalyst activity: The catalytic activity of PyBidine–Cu(OTf)$_2$ was compared with those of the well-known pyridinebisimidazoline (pybim)[11] and pyridinebisoxazoline (pybox) complexes with Cu(OTf)$_2$,[12] and the results are shown in Table 3. In both reaction systems, the use of the Cu(OTf)$_2$ catalysts pybim and pybox resulted in only trace amounts of product under our conditions.

3) Structure of PyBidine–Cu(OTf)$_2$: The structure of PyBidine–Cu(OTf)$_2$ was determined by X-ray crystallographic analysis and is provided in Figure 3. In the first report on PyBidine, the X-ray structure was reported with omission of the counter anions and protons for clarity.[7a] However, two triflate anions occupy the apical positions,

Table 3: Comparison of the catalyst activity of PyBidine–Cu(OTf)$_2$ with pybim–Cu(OTf)$_2$ and pybox–Cu(OTf)$_2$.


pyridinebisimidazoline (pybim)


pyridinebisoxazoline (pybox)

Entry	Product	Ligand	Yield [%]	d.r.	*ee* [%]
1[a]		PyBidine	96	99:1	97
2[a]		pybim	trace	–	–
3[a]		pybox	trace	–	–
4[b]		PyBidine	86	94:6	96
5[b]		pybim	trace	–	–
6[b]		pybox	trace	–	–

[a] The reaction was performed using ligand (5.5 mol%) and Cu(OTf)$_2$ (5 mol%) with Cs_2CO_3 (10 mol%) in dioxane at rt for 21–24 h. [b] The reaction was performed using ligand (11 mol%) and Cu(OTf)$_2$ (10 mol%) with Cs_2CO_3 (10 mol%) in dioxane at 10°C for 27 h (entry 4) and 15 h (entries 5 and 6).

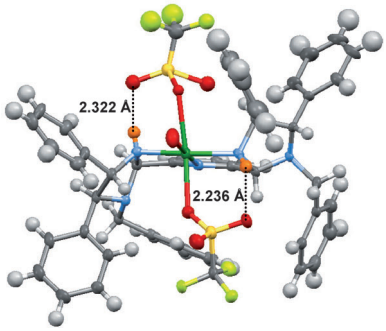


Figure 3. X-ray structure of PyBidine–Cu(OTf)$_2$–H$_2$O complex.

and the imidazolidines of PyBidine coordinate to the Cu, keeping the protons (marked in orange) at the nitrogen atoms. Apparently there are hydrogen bonds between one of the oxygen atoms in each triflate anion and the imidazolidine-NH atoms, with distances of 2.322 and 2.236 Å.

With considering these points, DFT calculations[13] were performed for the PyBidine–Cu(OTf)$_2$-catalyzed [3+2] cycloadditions shown in Eq. (1) and (2) (Figure 1).[14] There are two possibilities for the activation of substrates by Cu^{2+} and Brønsted acidic sites. One scenario is that a Cu-bound enolate of the imino ester nucleophilically attacks the electrophilically activated nitroalkene on the imidazolidine-NH moiety (**TS1**). The other possibility is that the enolate anion coordinates to the imidazolidine-NH moiety and the nitroalkene is electrophilically activated on the Lewis acidic Cu^{2+} center (**TS2**). Four transition states (TSs) corresponding to two activation modes (**TS1**, **TS2**) and two facial selectivities of the nitroalkene (***exo*-TS**, ***endo*-TS**) were compared (Figure 4).

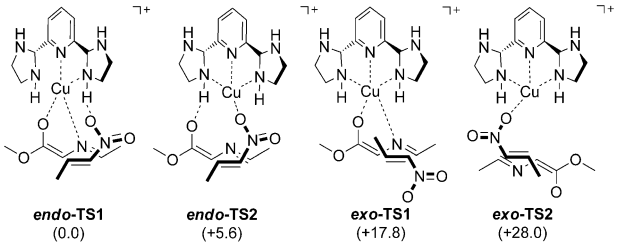


Figure 4. Two types of activation mode in *endo* and *exo* TSs. The relative energies are given in kcal mol^{-1}.

In both activation modes, the ***endo*-TS** is energetically more favored than the ***exo*-TS**. The lowest-energy TS is ***endo*-TS1**, in which a bidentate coordination of the imino ester enolate on the Cu^{2+} cation and hydrogen bonding interactions between the nitroalkene and the imidazolidine-NH distinctly define the positions of both substrates to provide a high level of stereocontrol (see details in the Supporting Information, SI).

Next, to elucidate the origin of the high enantioselectivities observed experimentally, the realistic diastereomeric TSs (**TSa** and **TSb**) were explored based on the ideal transition state model ***endo*-TS1**. In the [3+2] cycloaddition of the imino ester with the nitroalkene (**TS3**), ***endo*-TS3b** is 8.1 kcal mol^{-1} higher in energy than ***endo*-TS3a** (Figure 5).

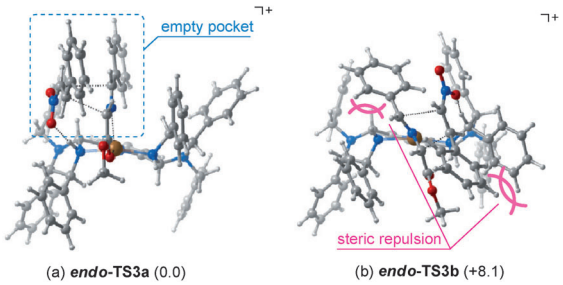


Figure 5. 3D structures of a) ***endo*-TS3a** and b) ***endo*-TS3b** for the [3+2] cycloaddition of imino ester with nitroalkene.

In the energetically favored ***endo*-TS3a**, both substrates are located in the empty chiral pocket and avoid steric repulsion (Figure 5a). The energetically disfavored ***endo*-TS3b** exhibits significant repulsive steric interactions with the imidazolidine ring (left purple curves in Figure 5b) and its Ph group (right purple curves in Figure 5b). Whereas the Ph group of the imino ester is deformed and twisted by the former steric interaction, a ring flip occurs in the imidazolidine ring (right) due to the latter interaction. These repulsive steric interactions destabilize ***endo*-TS3b**.

Similar structural features to **TS3** are found in the [3+2] cycloaddition of the imino ester with methyleneindolinone (**TS4**). Both substrates are appropriately oriented for the chiral reaction space in ***endo*-TS4a** (Figure 6a). In contrast,

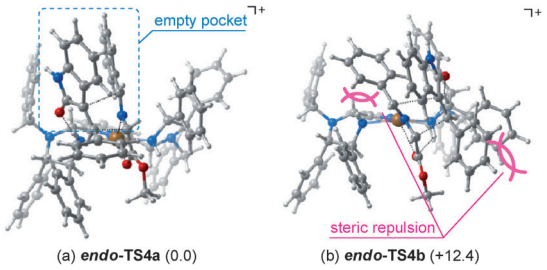


Figure 6. 3D structures of a) ***endo*-TS4a** and b) ***endo*-TS4b** for the [3+2] cycloaddition of imino ester with methyleneindolinone.

the sterically hindered imidazolidine rings exert undesired structural impact on ***endo*-TS4b** (Figure 6b). The ***endo*-TS4b** is 12.4 kcal mol^{-1} higher in energy than ***endo*-TS4a**. These computational results offer a rational explanation of the high enantioselectivities observed in the experiments.

The electronic and structural properties of PyBidine–Cu(OTf)$_2$ are summarized in the multiple interactions operating in concert and the deep asymmetric reaction space using imidazolidine as the "chiral fences". (In the PyBidine–Cu(OTf)$_2$ complex, two imidazolidine rings stand perpendicular (ca. 93°) to the equatorial terdentate coordination plane.) The synergistic action of the Cu^{2+} cation and the imidazolidine-NH not only activates both substrates but also controls their relative orientation.

In summary, PyBidine–Cu(OTf)$_2$ demonstrates that imidazolidine-NH can harmonize with the Cu^{2+} cation for constructing a new dual activation system.[15,16] This opens up the possibility to develop divergent metal catalysts using variably functionalized chiral secondary amine ligands.

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[16] The previously studied IAP–Ni$(OAc)_2$ complex catalyzed the reaction in *exo′* manner, after the *anti*-selective Michael addition, because the neutral Ni center cannot allow strong coordination of both, the nitro functionality and the imino ester, and the Ni atom would smoothly flip to the nitronate for opening the strained 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. See Ref. [6d].

