Cycloaddition

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Catalytic Asymmetric *exo′*-Selective [3+2] Cycloaddition of Iminoesters with Nitroalkenes**

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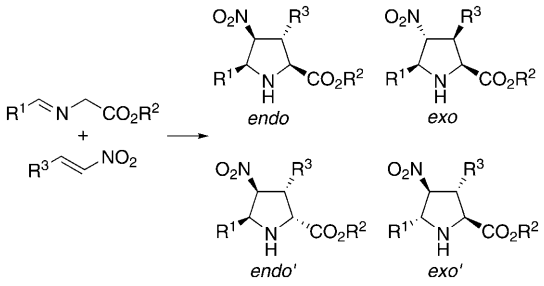
Highly functionalized complex molecules are key tools for promoting biochemical research and developing pharmaceutical compounds because the positions of the heteroatoms and the direction of lone pairs in the molecules are closely linked to their biological activities. Catalytic asymmetric synthesis is a fundamental technique to supply these complex compounds in a stereoselective manner. As a representative example, the catalytic asymmetric 1,3-dipolar cyclization reaction has been widely studied for the synthesis of multisubstituted pyrrolidines.[1] Azomethine ylides, generated from an iminoester and a nitroalkene, can be used to introduce an additional nitro functionality onto the pyrrolidine ring, thus affording four stereogenic centers and up to eight diastereomers. When a *trans* nitroalkene is used, the stereoconjunction between the 3- and 4-positions is fixed in a *trans* conformation, and four diastereomers are possible, classified as *endo*, *exo*, *endo′*, and *exo′* isomers (Scheme 1).

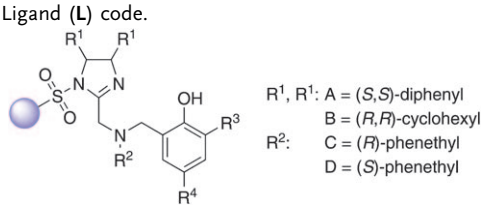


Scheme 1. Possible diastereomers generated in the pyrrolidine synthesis using an iminoester and a *trans* nitroalkene.

In 2005, Carretero and co-workers reported an example of *exo*-selective pyrrolidine ring construction,[2a,3] and Hou and co-workers succeeded in switching the *endo*/*exo* selectivity by tuning the electron density of the chiral ligand.[4,5] We have also recently succeeded in performing the *endo*-selective cyclization using a PyBidine/Cu(OTf)$_2$ catalyst.[6] Success in the *endo*-selective cyclization led us to undertake the additional challenge of obtaining the other diastereomers.[7]

Screening of the metal salts to investigate the *exo′* (and/or *endo′*) adduct ratio found that nickel salts facilitated the selective production of the *exo′* product.[8] As the basis for exploring efficient asymmetric catalysts, we prepared a library of solid-phase imidazoline–aminophenol/metal catalysts (Table 1)[9] and developed a new high-throughput screening

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



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	**L11**	B	C	H	H
L2	A	C	H	*t*Bu	**L12**	B	C	H	*t*Bu
L3	A	C	H	Br	**L13**	B	C	H	Br
L4	A	C	Br	Br	**L14**	B	C	Br	Br
L5	A	C	Br	NO_2	**L15**	B	C	Br	NO_2
L6	A	D	H	H	**L16**	B	D	H	H
L7	A	D	H	*t*Bu	**L17**	B	D	H	*t*Bu
L8	A	D	H	Br	**L18**	B	D	H	Br
L9	A	D	Br	Br	**L19**	B	D	Br	Br
L10	A	D	Br	NO_2	**L20**	B	D	Br	NO_2

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Screening of the metal salts to investigate the *exo′* (and/or *endo′*) adduct ratio found that nickel salts facilitated the selective production of the *exo′* product.[8] As the basis for exploring efficient asymmetric catalysts, we prepared a library of solid-phase imidazoline–aminophenol/metal catalysts (Table 1)[9] and developed a new high-throughput screening (HTS) method, in which the reaction mixtures were directly analyzed following the solid-phase catalysis by circular dichroism (CD) spectroscopy.[10] Using this "solid-phase catalysis/CD-HTS" system, appropriate catalysts for the *exo′*-selective synthesis were explored using the solid-phase imidazoline–aminophenol/Ni(OAc)$_2$ catalysts (Figure 1). The solid-phase **L9**/Ni(OAc)$_2$ and **L10**/Ni(OAc)$_2$ catalysts recorded the highest CD intensities among the 20 solid-phase catalysts tested. Specifically, the **L9**/Ni(OAc)$_2$ catalyst gave the *exo′* adduct in 32% yield and 70% *ee*, whilst **L10**/Ni(OAc)$_2$ gave the adduct in 23% yield and 76% *ee*. With this fascinating *exo′*-selective asymmetric catalysts in hand, the reaction conditions were re-examined in the solution phase (for optimization, see the Supporting Information).

Under the optimized condition, the **L21** (corresponding to **L9** without the solid support)/Ni(OAc)$_2$ catalysis reaction in K_2CO_3 gave the product in 99% yield in acetonitrile at −10 °C in a highly *exo′*-selective manner (*exo′*/*endo*/*exo*/*endo′* = 82:16:1:1), and the *exo′* adduct was obtained in up to

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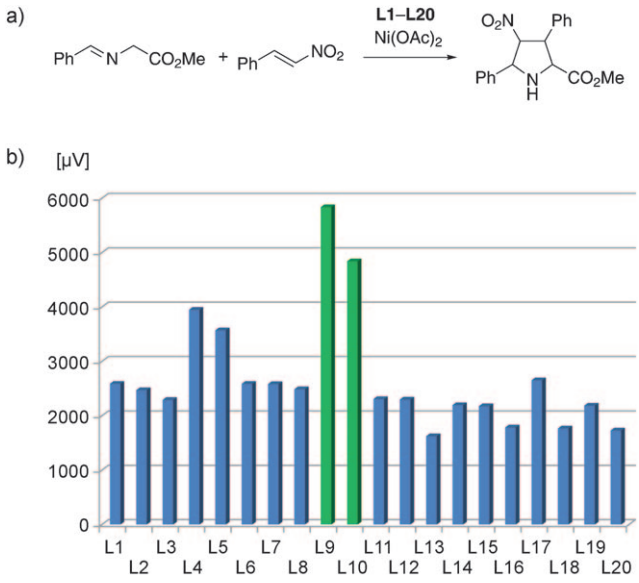


Figure 1. Solid-phase catalysis/CD-HTS.

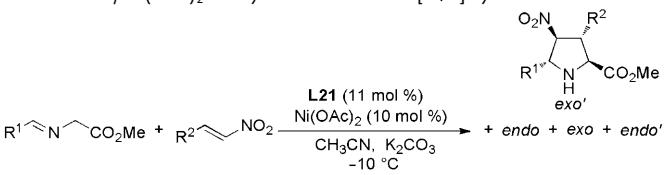
97% *ee*. For **L22** (corresponding to **L10** without the solid support)/$Ni(OAc)_2$, the reaction using Et_3N in dioxane at 10°C gave the product in a highly *exo*′-selective manner (*exo*′/*endo*/*exo*/*endo*′ = 90:8:0:2), though the *ee* of the *exo*′ adduct was 91%. The scope of the **L21**/$Ni(OAc)_2$-catalyzed *exo*′-selective synthesis of chiral pyrrolidines is summarized in Table 2.

exo′ Products were obtained from various aromatic substrates bearing electron-deficient or electron-rich substituents in good diastereoselectivities and high enantiomeric excesses (Table 2, entries 1–14). Aliphatic nitroalkenes were also converted into their corresponding *exo*′ products in the **L21**/$Ni(OAc)_2$ or **L22**/$Ni(OAc)_2$-catalyzed reactions (Table 2, entries 15 and 16).

The structures of the *exo*′ products were confirmed by an nOe experiment for the compound obtained in Table 2, entry 9 (for details, see the Supporting Information). The absolute configuration of the *exo*′ product obtained in Table 2, entry 2 was unequivocally determined by X-ray crystallographic analysis after oxidation of the product (Scheme 2). Because DDQ oxidation of the *exo*′ product gave the same compound as oxidation of *endo* product,[6] the stereochemistry of *exo*′ product was attributed to be the 5-epimer of the *endo* product.

This synthesis is the first general success in the catalytic asymmetric *exo*′-selective reaction of iminoesters and nitroalkenes.[11] A plausible mechanism for why the **L21**/$Ni(OAc)_2$ provides the adduct *exo*′-selectively is shown in Scheme 3.[12] The stereochemistry of the *exo*′ product suggests that the **L21**/$Ni(OAc)_2$-catalyzed reaction isn't a concerted 1,3-dipolar cyclization of the metal-bound azomethine ylide with the nitroalkene. We confirmed that no epimerization of the *endo* and *exo*′ adducts occurred under these reaction conditions. One plausible mechanism could involve an initial nickel-catalyzed Michael addition of the iminoester to the nitroalkene.[13] The nucleophilic addition at the C2 position of the

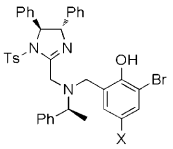
Table 2: **L21**/$Ni(OAc)_2$-catalyzed *exo*′-selective [3+2] cycloadditions.[a]



IE1: R^1=Ph
IE2: R^1=4-$MeOC_6H_4$
IE3: R^1=3-$MeOC_6H_4$
IE4: R^1=4-ClC_6H_4
IE5: R^1=3,4-(OCH_2O)-C_6H_3
IE6: R^1=1-naphthyl
IE7: R^1=2-naphthyl

NA1: R^2=Ph
NA2: R^2=4-$MeOC_6H_4$
NA3: R^2=4-BrC_6H_4
NA4: R^2=3-ClC_6H_4
NA5: R^2=2-BrC_6H_4

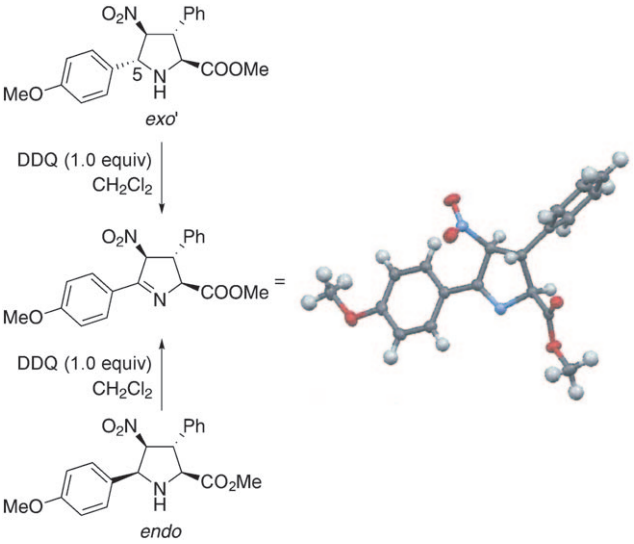
NA6: R^2=4-$NO_2C_6H_4$
NA7: R^2=3-$NO_2C_6H_4$
NA8: R^2=3,4-(OCH_2O)-C_6H_3
NA9: R^2=$CH_3(CH_2)_4$
NA10: R^2=$Ph(CH_2)_2$



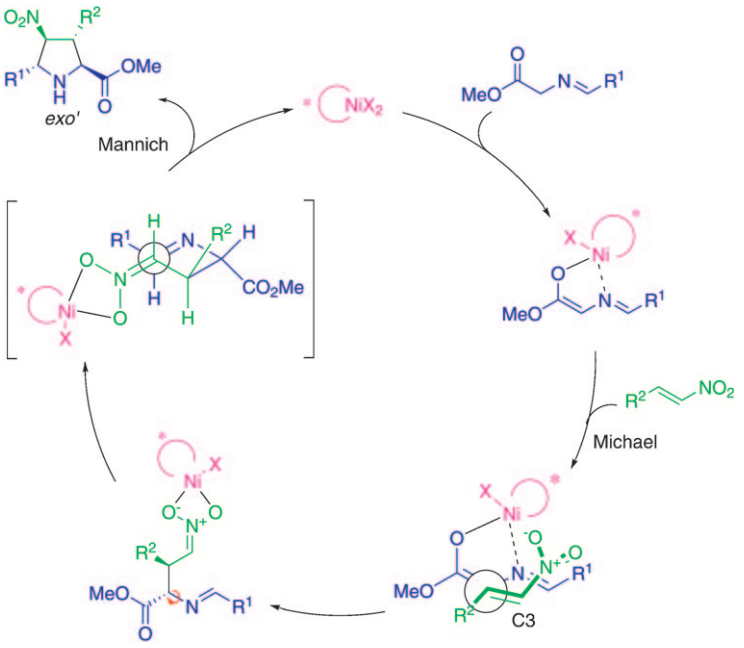
(**L21**: X=Br, **L22**: X=NO_2)

No.	Imino-ester	Nitro-alkene	*t* [h]	Yield [%]	*exo*′/*endo*/*exo*/*endo*′	*ee* of *exo*′ [%]
1	**IE1**	**NA1**	63	99	82:16:1:1	97
2	**IE2**	**NA1**	43	79	90:10:0:0	93
3	**IE3**	**NA1**	42	67	89:11:0:0	96
4	**IE4**	**NA1**	43	84	87:9:0:4	97
5	**IE5**	**NA1**	57	70	88:10:0:2	91
6	**IE6**	**NA1**	42	67	85:8:0:7	91
7	**IE7**	**NA1**	42	70	92:7:0:1	99
8	**IE1**	**NA2**	57	93	86:13:0:1	96
9	**IE1**	**NA3**	45	85	85:14:0:1	97
10	**IE1**	**NA4**	46	86	82:16:0:2	95
11	**IE1**	**NA5**	57	94	80:17:0:3	96
12	**IE1**	**NA6**	45	87	88:11:0:1	96
13	**IE1**	**NA7**	32	78	81:15:1:3	97
14	**IE1**	**NA8**	45	66	84:14:0:2	96
15	**IE1**	**NA9**	45	68	68:28:0:4	92
16	**IE1**	**NA10**	45	64	79:21:0:0	94

[a] The absolute configuration of the *exo*′ products was determined by analogy to the structure examined in entry 2.



Scheme 2. Structural determination of the [3+2] cycloadduct. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 3. Plausible reaction mechanism.

nitroalkene would be controlled by an interaction between the nitro functionality and the nickel center to direct the addition in *anti*-selective manner. However, after the *anti*-selective Michael addition, because the neutral nickel center cannot coordinate to both the nitro functionality and the iminoester at the same time, the nickel atom spontaneously flips 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. DFT calculations at the 6-31G/B3LYP level also suggest that the *exo′* adduct is the most stable among the four possible isomers depicted in Scheme 1. Finally, the **L21**/Ni(OAc)$_2$ catalysis would be controlled thermodynamically in the stepwise Michael/Mannich cyclization reactions.[14] In support of this mechanism, the groups of Chen, Takemoto, and Gong independently reported the organocatalytic asymmetric synthesis of pyrrolidine rings. Though the organocatalytic reaction could proceed in a stepwise manner, without chiral information at the 2-position, the *exo′* pathway could not be confirmed.[15]

In conclusion, we have reported the first successful catalytic asymmetric *exo′*-selective reaction of iminoesters and nitroalkenes using a **L21**/Ni(OAc)$_2$ catalytic system. A well-designed stepwise reaction would alleviate the limitations of the concerted reaction, which is restricted by the symmetry of the orbital interaction, and would supply more-flexible synthetic routes.

Experimental Section

The ligand (0.0165 mmol) and Ni(OAc)$_2$·4H$_2$O (0.015 mmol) were added to a two-necked round-bottomed flask containing a stirrer bar under an argon atmosphere. Acetonitrile (0.75 mL) was added to the flask and the mixture was stirred for 2 hours. To the resulting yellow solution, nitroalkene (0.15 mmol) and K_2CO_3 (0.015 mmol) were added successively at room temperature, and the imino ester (0.15 mmol) was added at −10 °C. After being stirred for the appropriate time (indicated in Table 2), the reaction mixture was quenched with water. The organic layer was extracted with ethyl acetate and dried over Na_2SO_4. After the solvent had been removed under reduced pressure, the diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. The crude mixture was purified by column chromatography on silica gel to afford the Michael/Mannich product. The enantiomeric excesses of the products were determined by HPLC on a chiral stationary phase using a Daicel Chiralcel OD–H, OJ–H, Chiralpak AD–H, or Chiralpak AS–H column.

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