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Bis(imidazolidine)pyridine-$NiCl_2$ Catalyst for Nitro-Mannich Reaction of Isatin-Derived *N*-Boc Ketimines: Asymmetric Synthesis of Chiral 3-Substituted 3-Amino-2-oxindoles

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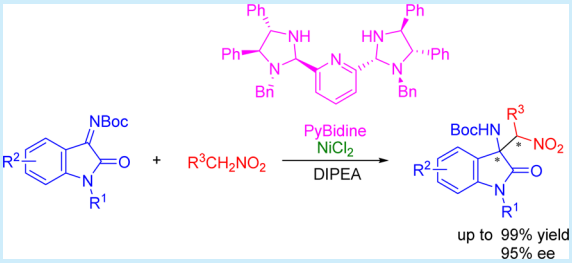
Supporting Information

ABSTRACT: An (*S*,*S*)-diphenyldiamine-derived bis(imidazolidine)-pyridine (PyBidine)-$NiCl_2$ complex catalyzed the nitro-Mannich reaction of isatin-derived *N*-Boc ketimines to construct a chiral quaternary aminocarbon center at the C3 position of oxindoles in yields of up to 99% with 95% ee.



Complex molecules containing an indole skeleton, which are widely found in nature, are promising candidates for drug development.[1]

For example, SSR-149415 was the first orally active nonpeptide vasopressin V_{1b} receptor antagonist,[2] and AG-041R, a gastrin/cholecystokinin type B receptor antagonist, is effective in repairing cartilage defects.[3] In a family of chiral spiro-oxindoles,[4−7] spirohydantoin compounds have been reported as being effective for the treatment of pain,[5] and as CRTH2 antagonists.[6] These molecules have a 3-subtituted 3-amino-2-oxindole as a common core structure (Figure 1).

For constructing a chiral quaternary aminocarbon center at the C3 position of oxindoles, catalytic asymmetric nucleophilic addition to isatin-derived ketimines is the most direct and rational approach.[8] In 2010, Zhou et al. reported the synthesis of 3-cyano-3-amino-2-oxindoles using a phosphoramide-catalyzed asymmetric Strecker reaction.[9] Subsequently, a Mannich reaction,[10] a Friedel−Crafts reaction,[11] a Pictet−Spengler reaction,[12] and a Povarov reaction[13] were also successfully utilized in the catalytic asymmetric synthesis of 3-subtituted 3-amino-2-oxindoles.[14] Because the Mannich reaction, in particular, can be examined using a wide range of nucleophiles, catalytic asymmetric Mannich reactions play a major role, although the catalytic asymmetric variation of the nitro-Mannich reaction (aza-Henry reaction)[15] using nitroalkanes has not been applied to isatin-derived ketimines to any great extent.[16] Here, we report a metal-catalyzed asymmetric nitro-Mannich reaction of isatin-derived *N*-Boc ketimines.[17]

For asymmetric Mannich-type reactions, we developed a chiral bis(imidazolidine)pyridine ligand, abbreviated as PyBidine, for metal catalysis.[18] A PyBidine-$Cu(OTf)_2$ complex catalyzed the reaction of *N*-tosyl aldimines with iminoesters.[19] The PyBidine-$CoCl_2$ variant efficiently catalyzed the asymmetric nitro-Mannich reaction of *N*-tosyl aldimines with nitromethane, while the PyBidine-$Ni(OAc)_2$ complex catalyzed the asymmetric nitro-Mannich reaction using *N*-Boc aldimines (Scheme 1).[20]

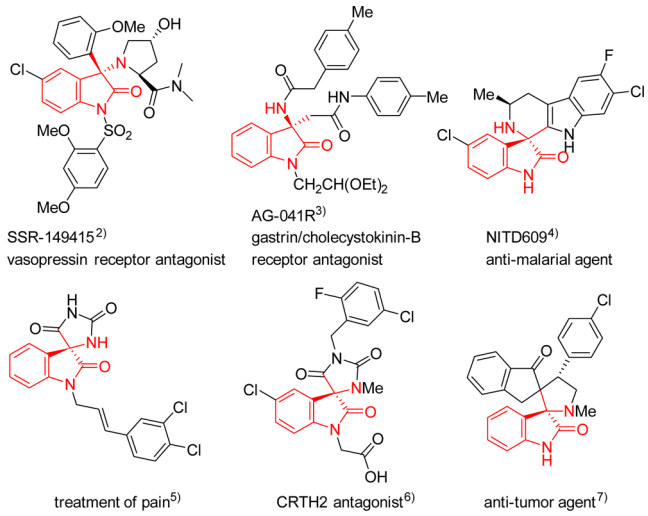


Figure 1. Examples of biologically important 3-subtituted 3-amino-2-oxindoles.

Our examination of asymmetric synthesis of 3-subtituted 3-amino-2-oxindoles in a nitro-Mannich reaction started with exploration of the appropriate PyBidine−metal salt complex for the isatin-derived *N*-Boc ketimine substrate (Table 1).

Using PyBidine-$Ni(OAc)_2$, which is shown in the nitro-Mannich reaction using *N*-Boc aldimines in Scheme 1b, the reaction proceeded smoothly to give the product in 84% yield,

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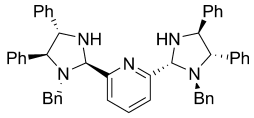
Scheme 1. Pilot Study of Nitro-Mannich Reaction Catalyzed by PyBidine−Metal Salts



Bis(imidazolidine)pyridine
PyBidine (**L1**)

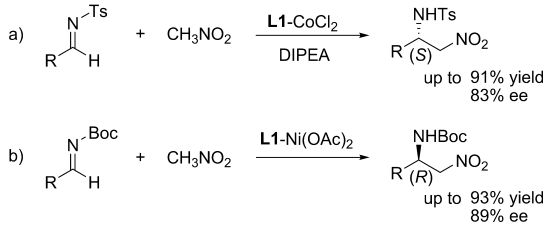
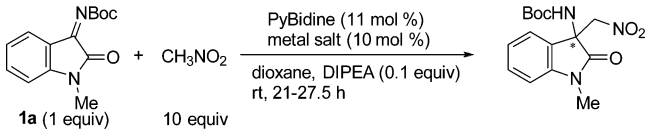
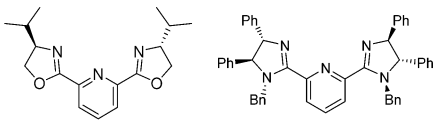


Table 1. Exploration of Efficient Asymmetric Nitro-Mannich Catalysis for Isatin-Derived *N*-Boc Ketimine (1a)



entry	ligand	metal salt	yield (%)	ee (%)
1	PyBidine	$Ni(OAc)_2$-$4H_2O$	84	21
2	PyBidine	$Cu(OTf)_2$	<99	−55
3	PyBidine	$CoCl_2$	78	87
4	PyBidine	$Co(ClO_4)_2$-$6H_2O$	54	70
5	PyBidine	$Co(OAc)_2$-$4H_2O$	53	67
6	PyBidine	$Co(acac)_3$	94	9
7	PyBidine	$FeCl_3$	<40	rac
8	PyBidine	$NiCl_2$	98	90
9	PyBidine	$CuCl_2$	<98	−17
10	PyBidine	$ZnCl_2$	75	35
11	PyBidine	$NiBr_2$	89	70
12	PyBidine	NiI_2	85	53
13	PyBidine	−	86	rac
14	pybox	$NiCl_2$	28	56
15	pybim	$NiCl_2$	99	−40

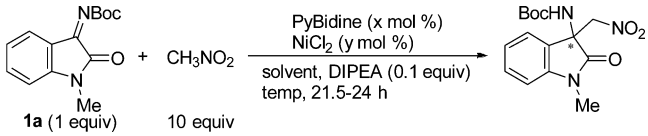


bis(oxazoline)pyridine (pybox) bis(imidazoline)pyridine (pybim)

but with only 21% ee (entry 1). The original PyBidine-$Cu(OTf)_2$ complex[18a,19] developed for the reaction of *N*-tosyl aldimines with iminoesters gave the product in excellent yield with 55% ee, with stereoselectivity opposite to that observed in the reaction shown in entry 1 (entry 2). Interestingly, PyBidine-$CoCl_2$, an approved catalyst for the nitro-Mannich reaction using *N*-Ts aldimines (Scheme 1a), gave the product in 78% yield with 87% ee (entry 3). Among the cobalt salts we examined, the $CoCl_2$-complex showed the best performance for asymmetric induction (entries 3−6). Among the chloride salts of the first-row transition metals (entries 7−10), PyBidine-$NiCl_2$ catalyzed the formation of the product with 98% yield and 90% ee (entry 8). When nickel bromide and nickel iodide salts were examined (entries 11−12), the PyBidine-$NiCl_2$ catalyst was found to be the best choice for the nitro-Mannich reaction of isatin-derived *N*-Boc ketimine. In the absence of metal salts, although PyBidine catalyzed the reaction by operating as an organocatalyst, the product was obtained in the racemic form (entry 13). Among other related ligands, bis(oxazoline)pyridine (pybox)[21]-$NiCl_2$ and bis(imidazolidine)-pyridine (pybim)[22]-$NiCl_2$ resulted in lower asymmetric induction (entries 14−15).

Next, the reaction conditions for the PyBidine-$NiCl_2$-catalyzed asymmetric nitro-Mannich reaction were optimized for the isatin-derived *N*-Boc ketimine **1a** (Table 2).

Table 2. Reaction Optimization for PyBidine-$NiCl_2$-Catalyzed Asymmetric Nitro-Mannich Reaction



entry	*x*	*y*	solvent	temp (°C)	yield (%)	ee (%)
1	11	10	dioxane	rt	98	90
2	11	10	THF	rt	89	92
3	11	10	toluene	rt	99	95
4	11	10	$CHCl_3$	rt	80	88
5	11	10	CH_3CN	rt	93	88
6	11	10	Et_2O	rt	>99	88
7[a]	11	10	toluene	rt	31	90
8	5.5	5	toluene	rt	87	95
9	11	10	toluene	0	83	95
10	11	10	toluene	30	99	95
11	11	10	toluene	40	98	93
12	5.5	5	toluene	30	99	94

[a]Without the use of DIPEA.

The nitro-Mannich reaction using PyBidine-$NiCl_2$ could be carried out in various organic solvents (entries 1−6), and the reaction in toluene gave the product in 99% yield with 95% ee (entry 3). Without use of DIPEA as a basic additive, the reaction became significantly slower (entry 7). (See the effects of the other basic additives in Supporting Information.) The reaction at 0 °C and/or with the amount of the catalyst reduced to 5 mol % resulted in low yields without any positive effect on the enantiomeric excess (entries 8−9). Finally, keeping the reaction temperature at 30 °C, catalysis at 5 mol % gave the product in 99% yield with 94% ee (entry 12).

The PyBidine-$NiCl_2$-catalyzed asymmetric nitro-Mannich reaction was examined under the optimized conditions, and the results are shown in Scheme 2. The absolute configurations were drawn by analogy with **2m**, confirmed by single-crystal X-ray analysis.

The isatin-derived *N*-Boc ketimines with alkyl substituents at R^1 (e.g., R^1 = Me, Bn, Allyl) were smoothly converted to the target products while maintaining high enantioselectivity, although the acetyl substituent significantly reduced the reactivity of the substrate. *N*-Methyl isatins containing not only electron-deficient substituents but also electron-donating substituents on the benzene ring reacted successfully to give the nitro-Mannich products **2** with ee values ranging from 78 to 95%. When the 5-bromo product **2g** was recrystallized from an Et_2O/*n*-hexane solvent system, racemic crystals were generated, while the **2g** remaining in the eluent had an ee of 93%. In an attempt at the diastereoselective variation, a reaction using nitroethane gave the product in a ratio of 80/20, with both diastereomers obtained in a highly enantioselective manner.

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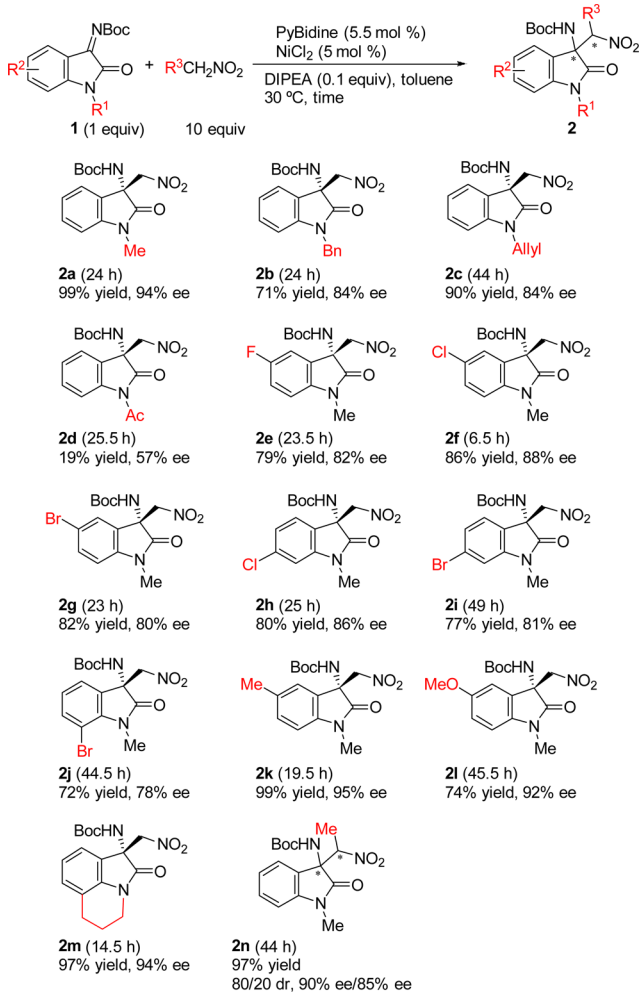
Scheme 2. PyBidine-$NiCl_2$-Catalyzed Asymmetric Nitro-Mannich Reaction



The absolute configuration of the nitro-Mannich product was determined for the tricyclic product **2m** (Figure 2).

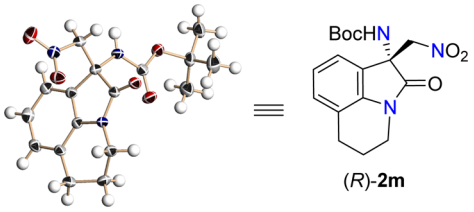


Figure 2. X-ray structure of (*R*)-**2m**.

The reason the (*S*,*S*)-diphenylethylene-derived PyBidine-$NiCl_2$ catalyst gave an (*R*)-enriched nitro-Mannich product is explained on the basis of the plausible reaction model depicted in Figure 3. It is suggested that because the PyBidine-$NiCl_2$-catalyzed asymmetric nitro-Mannich reaction requires the assistance of a base, a nucleophilic nitronate species is generated in the outer sphere of the asymmetric catalyst, and the PyBidine-$NiCl_2$ complex acts as a Lewis acid, activating the isatin-derived *N*-Boc ketimines.[20] Because of the affinity of nickel with nitrogen atoms, the isatin-derived *N*-Boc ketimines coordinate to the nickel center through the lone pair of the imine unit. The nitronate generated in the outer sphere attacks

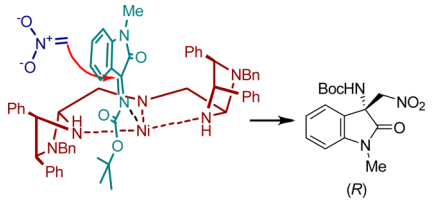
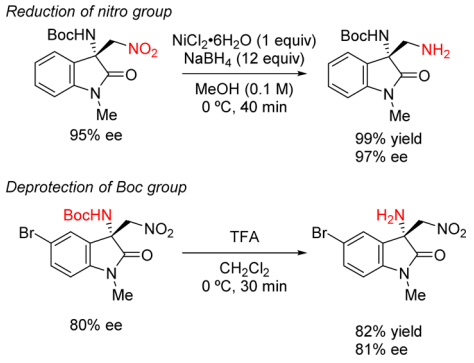


Figure 3. Plausible reaction mode of PyBidine-$NiCl_2$-catalyzed asymmetric nitro-Mannich reaction.

the isatin-derived *N*-Boc ketimines coordinating to the nickel center from the second quadrant. The fact that substrates with a variety of substituents at the R^1 position are successfully utilized in the asymmetric nitro-Mannich reaction, as examined in Scheme 2 (e.g., **2a**−**2c**, and **2m**), agrees with the coordination scenario for the (*R*)-enriched product.

Finally, simple transformations of the nitro-Mannich adducts are demonstrated in Scheme 3. Reduction of nitro group and

Scheme 3. PyBidine-$NiCl_2$-Catalyzed Asymmetric Nitro-Mannich Reaction



deprotection of Boc group were furnished with keeping the enantioselectivity. The protocol provides to exchange positions of primary amino-functionality in the synthesis of 3-amino-methyl-2-oxindoles and 3-amino-2-oxindoles.

In conclusion, the bis(imidazolidine)pyridine (PyBidine)-$NiCl_2$ catalyst enables a general asymmetric nitro-Mannich reaction of the isatin-derived *N*-Boc ketimines, which becomes a powerful synthetic methodology to give diverse chiral 3-substituted 3-amino-2-oxindoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, crystal data (CIF), and copies of ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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