Design and Synthesis of Chiral Imidazolidine-Pyridine Ligands

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Received 3 September 2009

Abstract: Condensation of chiral diamines and aldehydes gave a series of chiral imidazolidine-pyridine compounds with high diastereoselectivities. The ability of these compounds to act as chiral ligands was examined in the catalytic Henry reaction.

Key words : asymmetric catalysis, ligands, imidazolidine, copper, Henry reaction

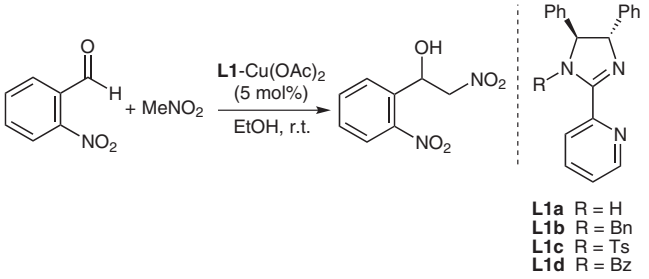
The synthesis of chiral molecules in a catalytic asymmetric manner is essential for supplying fundamentally valuable organic compounds.[1] Because the creation of a well-organized reaction sphere using highly functionalized chiral ligands is the key to controlling stereoselective metal catalysis, the design and development of new chiral ligands is at the forefront of research on catalytic asymmetric synthesis. In this communication, the quick and efficient stereoselective synthesis of imidazolidine compounds is reported, and their ability to act as chiral ligands is examined in the $Cu(OAc)_2$-catalyzed Henry reaction.[2,3]

As part of our research program for exploring efficient asymmetric catalysts, we have succeeded in developing imidazoline-containing chiral ligands for metal-catalyzed reactions.[4,5] For example, imidazoline-aminophenol (**L0**)-Cu complexes have been realized as efficient catalysts for the Henry reaction,[4d] the Friedel–Crafts reaction,[4d,e] and the tandem Friedel–Crafts–Henry reaction.[4f]

Although the unique asymmetric reaction sphere produced by the imidazoline-aminophenol (**L0**)-metal complex has potential for successful application to other various asymmetric reactions, the simple imidazoline-pyridine analogues (**L1**) were not effective for the $Cu(OAc)_2$-catalyzed Henry reaction (Table 1, entries 2–5). We assumed that the relatively flat structure around the Cu center in the square-planar **L1**-Cu(II) complex was not sufficient to promote the stereoselective reactions [see Figure 1, **L1** and Figure 4, **L1b**-$Cu(OAc)_2$]. 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 [Figure 1, **L2** and Figure 4, **L2a**-$Cu(OAc)_2$].

Relatives of the imidazolidines, chiral imidazolidinones are widely employed as organocatalysts for asymmetric reactions, as pioneered by MacMillan.[6] Furthermore, Uozumi reported elegant work on the stereoselective synthesis of an imidazoindole ligand for asymmetric palladium catalyses.[7] Despite the prevailing applications as organocatalysts,[8] however, the challenges on the ligand for the metal catalysts are rather limited.[9,10]

Table 1 Henry Reaction Catalyzed by Imidazoline-pyridine (**L1**)-$Cu(OAc)_2$



Entry	Ligand	Time (h)	Yield (%)	ee (%)
1	**L0**	40	98	94
2	**L1a**	24	57	26
3	**L1b**	24	55	14
4	**L1c**	24	97	44
5	**L1d**	24	49	19

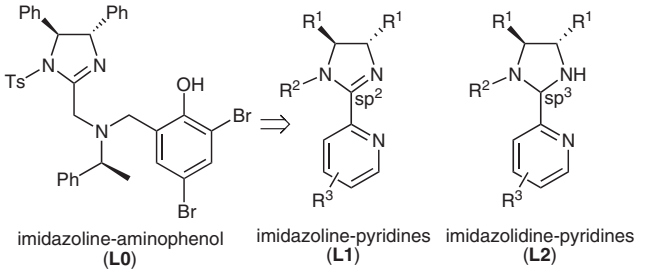


Figure 1 Structurally simplified analogues (**L1** and **L2**) of **L0**

Although the newly formed sp^3-carbon is a stereogenic center, we envisioned that the configuration of the product would be controlled by the steric repulsion relayed from the substituents of the chiral diamine. A DFT calculation at the level of B3LYP/6-31G* suggested that **L2** depicted in Figure 2 is more stable than the epimer at the newly formed asymmetric sp^3-carbon by 5.7 kcal/mol.

The synthesis of imidazolidine-pyridine ligands was readily achieved by a simple condensation of monoalkyl chiral diamines and aldehydes using acetic acid

SYNLETT 2009, No. 19, pp 3167–3170
Advanced online publication: 23.10.2009
DOI: 10.1055/s-0029-1218311; Art ID: U08909ST

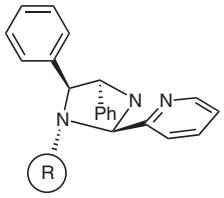
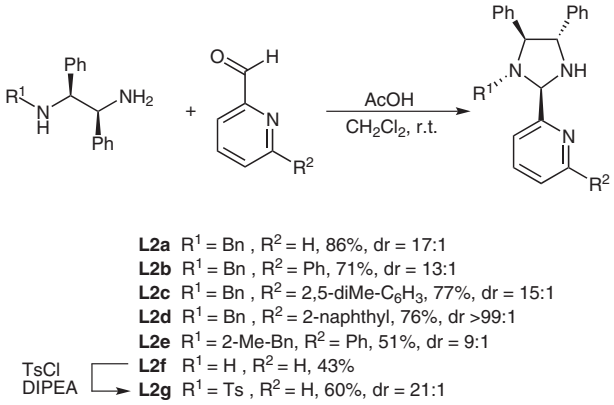


Figure 2 Stable isomer of imidazolidine-pyridines (**L2**)



L2a R^1 = Bn , R^2 = H, 86%, dr = 17:1
L2b R^1 = Bn , R^2 = Ph, 71%, dr = 13:1
L2c R^1 = Bn , R^2 = 2,5-diMe-C_6H_3, 77%, dr = 15:1
L2d R^1 = Bn , R^2 = 2-naphthyl, 76%, dr >99:1
L2e R^1 = 2-Me-Bn, R^2 = Ph, 51%, dr = 9:1
L2f R^1 = H , R^2 = H, 43%
L2g R^1 = Ts , R^2 = H, 60%, dr = 21:1

Scheme 1 Synthesis of imidazolidine-pyridine ligands (**L2**)

(Scheme 1). The tosyl-imidazoline analogue (**L2g**) was prepared by tosylation after forming the imidazolidine (**L2f**).

The highly diastereoselective construction of the imidazolidine-pyridines was confirmed by ^{1}H NMR analysis. Moreover, the X-ray crystallographic analysis of a single crystal of **L2b** revealed an all-*trans* stereochemical outcome (Figure 3).[11]

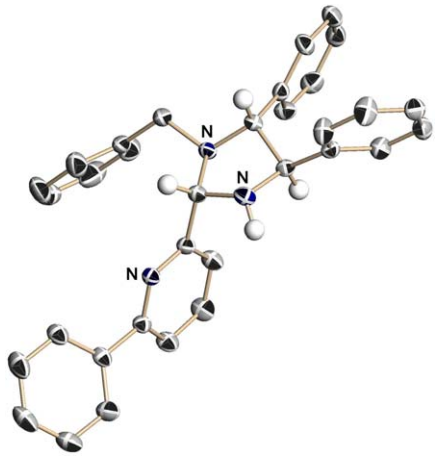


Figure 3 All-*trans* imidazolidine-pyridine (**L2b**)

The newly obtained imidazolidine-pyridine ligands are stable to moisture at ambient temperature, and can be kept under air. When **L2** was added to $Cu(OAc)_2$ in EtOH, the solution immediately turned a green color. The formation of the **L2b**-Cu(II) complex was strongly suggested by ESI-TOF mass spectrometry by the observation of an ion peak at *m/z* = 589.11 corresponding to [**L2b** + $Cu(OAc)]^+$.[12] The DFT calculation at the level of B3LYP/6-31G* suggested a slightly twisted square-planar Cu(II) complex with **L2**, though the **L1**-$Cu(OAc)_2$ complex is square-planar (Figure 4).

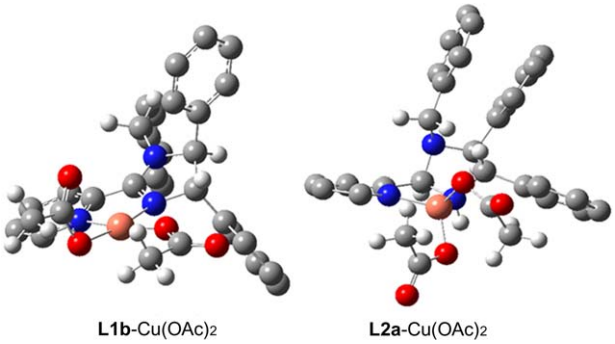
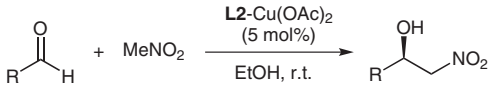


Figure 4 **L1b**-$Cu(OAc)_2$ complex and **L2a**-$Cu(OAc)_2$ complex (Cu: orange; N: blue; O: red; C: gray; H: white)

The three-dimensional structure of the imidazoline-pyridine ligand (**L2**) would have an obvious advantage over **L1** in constructing the reaction sphere to promote the asymmetric reaction.

The ability of the imidazolidine-pyridines to act as chiral ligands was examined and the results are shown in Table 2. The Henry reaction of *o*-nitrobenzaldehyde with nitromethane was smoothly catalyzed by the imidazolidine-pyridine (**L2a**)-$Cu(OAc)_2$ complex to give the adduct in 98% yield with 59% ee. For cyclohexanecarboxaldehyde, imidazolidine-phenylpyridine **L2b** showed better selectivity to provide the adduct with 71% ee (entry 4).

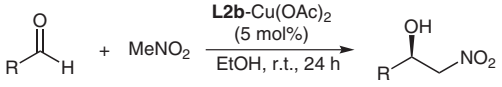
Table 2 **L2**-$Cu(OAc)_2$-Catalyzed Asymmetric Henry Reaction



Entry	Ligand	R	Yield (%)	ee (%)
1	**L2a**	2-$O_2NC_6H_4$	98	59
2	**L2a**	cyclohexyl	75	46
3	**L2b**	2-$O_2NC_6H_4$	>99	53
4	**L2b**	cyclohexyl	84	71
5	**L2c**	cyclohexyl	16	30
6	**L2d**	cyclohexyl	61	65
7	**L2e**	cyclohexyl	81	70
8	**L2f**	cyclohexyl	76	2
9	**L2g**	cyclohexyl	31	30

The generality of the enantioselective Henry reaction using **L2b**-$Cu(OAc)_2$ was next examined and the results are shown in Table 3.

Table 3 Asymmetric Henry Reaction Catalyzed by **L2b**-$Cu(OAc)_2$



Entry	R	Yield (%)	ee (%)
1	Ph	93	53
3	4-$O_2NC_6H_4$	92	47
4	2-ClC_6H_4	99	64
5	2-$MeOC_6H_4$	>99	76
6	$Me(CH_2)_3$	>99	72
7	$Me(CH_2)_4$	91	70
8	Me_2CHCH_2	>99	75
9	Me_2CH	98	76
11	$PhCH_2CH_2$	>99	74

Various aldehydes were smoothly converted to Henry adducts at room temperature, and in all cases, the *R*-enriched products were obtained using the (*S*,*S*)-diphenylethylenediamine-derived ligand **L2b**. The simplest aromatic aldehyde, benzaldehyde, was converted to the Henry adduct in 93% yield with 53% ee. Typically, the use of aliphatic aldehydes provided the corresponding adducts with higher enantioselectivities than those obtained using aromatic aldehydes. In particular, α-branched aliphatic aldehydes such as pivalaldehyde and cyclohexanecarboxaldehyde gave the adducts with good enantioselectivity (up to 76% ee) without a significant decrease in reaction rate.

In summary, we have succeeded in developing a concise method for the synthesis of chiral imidazolidine-pyridine ligands. The newly synthesized imidazolidine-pyridine (**L2b**)-$Cu(OAc)_2$ complex smoothly catalyzed the Henry reaction, and the desired products were obtained in high chemical yields with moderate to good enantiomeric excesses. Due to this fascinating, short synthetic route, further study on the development of diverse imidazolidine-containing ligands and their application to asymmetric catalysis are in progress.

Synthesis of Imidazolidine-Pyridine Compounds

A solution of the appropriate aldehyde (1.0 mmol) and diamine (0.7 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C, and then AcOH (40 μL, 0.7 mmol) was added to the mixture. The resulting solution was allowed to warm to r.t. and stirred overnight. Sat. $NaHCO_3$ was added to the reaction mixture to make the solution alkaline. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give the corresponding imidazolidine-pyridine (**L2**). Recrystallization of **L2** from CH_2Cl_2–EtOH (1:5) is effective to remove the minor diastereomer.

Spectral Data of L2b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (d, *J* = 13.7 Hz, 1 H), 3.88 (d, *J* = 8.2 Hz, 1 H), 3.90 (d, *J* = 13.7 Hz, 1 H), 4.42 (d, *J* = 8.2 Hz, 1 H), 5.11 (s, 1 H), 7.03–7.10 (m, 5 H, arom.), 7.22–7.61 (m, 17 H, arom.), 8.03–8.06 (m, 1 H, arom.). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4, 69.4, 82.2, 119.3, 120.8, 126.6, 126.9, 127.1, 127.2, 127.5, 127.7, 128.2, 128.26, 128.30, 128.6, 128.8, 129.5, 136.8, 137.5, 139.5, 140.1, 141.6, 143.0, 156.3, 161.7. FT-IR: 3315, 2985, 2902, 1572, 1493, 1450, 1406, 1394, 1070, 758, 698 cm^{-1}. $[\alpha]_D^{20}$ +118.7 (*c* 1.38, $CHCl_3$, dr = 17:1). HRMS (FAB$^+$): *m/z* calcd for $C_{33}H_{30}N_3$ [M^+ + H]: 468.2440; found: 468.2400.

Catalytic Asymmetric Henry Reaction

The catalyst was prepared by the complex formation of **L2** (0.011 mmol) with $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) in anhyd CH_2Cl_2 (1.0 mL) under Ar. After stirring overnight at r.t., the solvent was removed under reduced pressure. Next, the residue was dissolved in EtOH (400 μL). To the resulting clear green solution was added nitromethane (432 μL, 8.0 mmol) and aldehyde (0.20 mmol) under Ar. After stirring for a further 24 h at r.t., the solution was directly purified by silica gel column chromatography to afford the adduct. The ee of the product was determined by HPLC analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 19028007, 'Chemistry of Concerto Catalysis') from the Ministry of Education, Science, Sports, Culture and Technology of Japan. We thank Mr. Naota Yokoyama for his kind technical support and helpful discussions.

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(11) **Crystal Data**
Orthorhombic, space group: *P*2 (1)2 (1)2 (1), a = 6.3601 (3), b = 8.1108 (4), c = 50.351 (3), V = 2597.4 (2), Z = 4, MoKα radiation, R_1 = 0.0456, wR_2 = 0.1458.

(12) The MS value of m/z = 997.29 was also detected for [(**L2b**)$_2$ – Cu]$^+$. Although the mixing ratio of **L2b** and Cu(OAc)$_2$ was reexamined to superior formation of the 1:1 complex, the ee of the Henry adduct was not improved.