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Asymmetric *Syn*-Selective Henry Reaction Catalyzed by the Sulfonyldiamine−CuCl−Pyridine System

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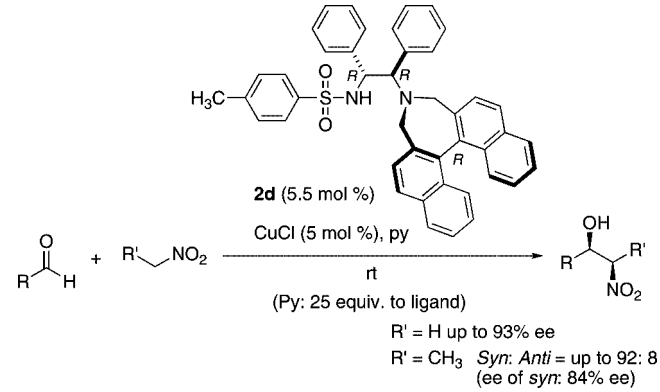

A catalytic asymmetric Henry reaction has been developed with use of a sulfonyldiamine−CuCl complex as a catalyst. A series of new binaphthyl-containing sulfonyldiamine ligands (**2a**−**h**) were readily synthesized in two steps starting from commercially available chiral 1,2-diamines. The (*R*,*R*)-diamine-(*R*)-binaphthyl ligand (**2d**)−CuCl complex smoothly catalyzed the enantioselective Henry reaction with the assistance of pyridine to give the corresponding adduct with high enantiomeric excess (up to 93%). Moreover, the **2d**−CuCl−pyridine system promotes the diastereoselective Henry reaction in *syn*-selective manner to give the adduct in up to 99% yield with 92:8 *syn*/*anti* selectivity. The enantiomeric excess of the *syn*-adduct was 84% ee.

Introduction

The Henry (nitroaldol) reaction is a powerful and atom-economical carbon−carbon bond-forming reaction that can be used to create a new stereogenic center at the β-position of a nitro functionality.[1] Because the resulting β-nitro alcohol adducts can be transformed to various biologically important building blocks such as β-amino alcohols and α-hydroxy ketones, recent research has focused on the catalytic asymmetric version of the Henry reaction.[2] Since the original pioneering work on hetero-bimetallic multifunctional catalysts containing lanthanoid elements,[3] various types of chiral metal catalysts (containing metals such as Zn,[4] Co,[5] Cu,[6] Mg,[7] and Cr[8]) and organocatalysts[9] have been developed. Among these, a Cu-based asymmetric catalyst, examined at room temperature, is particularly promising due to its high catalytic activity and excellent enantioselectivity. Following on from the ground-breaking work of Jørgensen and Evans,[6a,b] we succeeded in developing a C_2-symmetric diamine (**1**)−CuCl-catalyzed Henry reaction.[10] However, little research has been carried out into Cu-catalyzed diastereoselective Henry reactions.[11] We report herein the development of a *syn*-selective asymmetric Henry reaction using newly developed sulfonyl-

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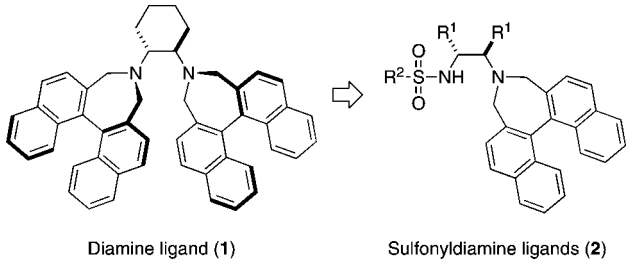


FIGURE 1. Sulfonyldiamine ligands.

diamine (**2**)−CuCl catalysts.[12] Remarkable acceleration effects due to pyridine are also presented.

Results and Discussion

As proposed by Evans et al., the Lewis acidity of the Cu atom is important for activating the aldehyde.[6b] This realization led us to design a new asymmetric ligand in which one of the nitrogen atoms of the 1,2-diamine group was sulfonylated to increase the acidity of the metal complex (Figure 1).

The binaphthyl-containing sulfonyldiamines were readily synthesized in two steps starting from commercially available 1,2-diamines.[13] Sulfonylation of the appropriate 1,2-diamine, followed by alkylation with chiral 2,2′-dibromomethyl-1,1′-binaphthalene, provided a series of new sulfonyldiamine ligands, as shown in Scheme 1. (See details in the Experimental Section.)

Before examining the diastereoselective Henry reaction, the potential of the newly developed sulfonyldiamine ligands **2** was examined in an enantioselective reaction by using *o*-nitrobenzaldehyde (**3a**), which have been utilized as a test substrate.[10] However, it was soon revealed that the reaction of **3a** with nitromethane was not smoothly promoted by **2**−CuCl. When

SCHEME 1. Synthesis of Sulfonyldiamine Ligands (2)

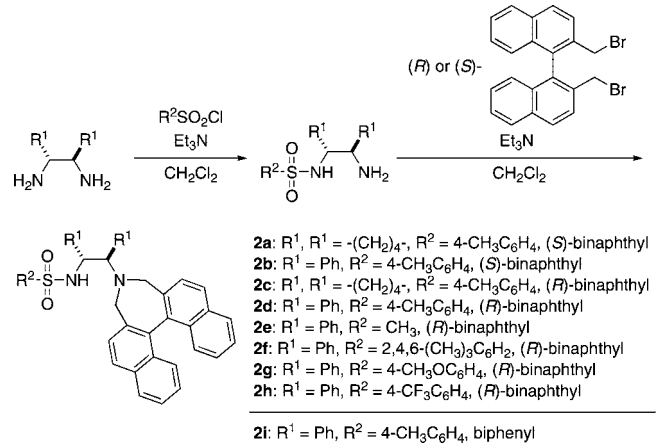
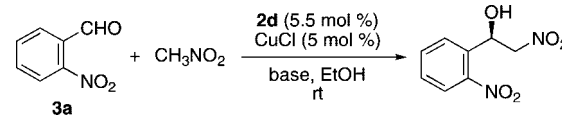


TABLE 1. Effects of Basic Additives on the 2d−CuCl-Catalyzed Enantioselective Henry Reaction



entry	base	amount of base[a]	time (h)	yield (%)	ee (%)
1			23	68	31
2	DBU	1	21	96	<1
3	DIPEA	1	21	92	27
4	Et_3N	1	23	84	15
5	2,6-lutidine	10	23	90	31
6	DMAP	50	17	84	<1
7	Py	10	18	83	57
8	Py	20	16	85	63
9	Py	25	18	97	67
10	Py	30	16	94	55

[a] Equivalent based on ligand.

we examined straightforward analogues of **1** (**2a** or **2b**), containing an (*R*,*R*)-diamine group and an (*S*)-binaphthyl skeleton, the reaction with **2a** provided only trace amounts of the adduct (rt, 45 h); **2b**−CuCl gave the adduct in 22% yield with only 1% ee (rt, 40 h). However, the use of the (*R*,*R*)-diamine-(*R*)-binaphthyl ligand **2d**, an epimer of **2b**, unexpectedly gave the (*R*)-enriched product in 68% yield with 31% ee (rt, 23 h); **2c**−CuCl gave only trace amounts of the adduct.

Because the Henry reaction is thought to employ basicity to generate the nitronate, the effects of various basic additives in promoting the reaction were examined.

As expected, the addition of basic amines enhanced the **2d**-catalyzed Henry reaction, although the enantiomeric excesses were diminished (entries 2−6, Table 1). Surprisingly, the addition of pyridine, a weak base, improved the chemical yield while increasing the enantiomeric excess to 57% (entry 7). When the amount of pyridine was increased to 25 equiv to ligand, the adduct was obtained in 97% yield with 67% ee (entry 9); the use of 30 equiv of pyridine resulted in a reduction in enantioselectivity to 55% ee (entry 10). These remarkable acceleration effects with improvement of enantioselectivity were also examined in the Henry reaction by using the other sulfonyldiamine ligands (**2**); the results are summarized in Table 2. The use of the cyclohexyldiamine analogue **2c** gave the adduct almost racemically (entry 3, Table 2). Ligand **2b**, the diastereomer of **2d**, was also unsuitable for the enantioselective Henry reaction (entry 2).

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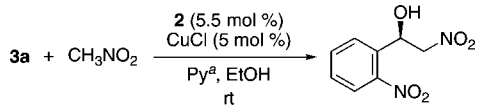
TABLE 2. Enantioselective Henry Reaction Catalyzed by 2−CuCl−Pyridine



entry	sulfonyldiamine	time (h)	Yield (%)	ee (%)
1	**2a**	40	53	<1
2	**2b**	16	86	3
3	**2c**	40	98	1
4	**2d**	18	97	67
5	**2e**	23	86	27
6	**2f**	17	92	<1
7	**2g**	20	99	35
8	**2h**	20	90	63
9	**2i**	27	73	46

[a] 25 equiv of py to ligand.

Regarding the efficient reaction sphere of **2d** produced by the combination of (*R*,*R*)-diphenylethylenediamine and (*R*)-binaphthyl moiety, an analogue of tosyl-(*R*,*R*)-diphenylethylenediamine−biphenyl ligand (**2i**) was prepared, and applied to the enantioselective Henry reaction of **3a**. Under similar conditions with 25 equiv of py to **2i**, the reaction was smoothly catalyzed to give the adduct in 73% yield with 46% ee, which is superior to the results with **2b** (86% yield, 3% ee in entry 2, Table 2). This suggests the **2i**−CuCl-catalyzed reaction would have a similar transition state to that of **2d**−CuCl catalysis, and the appropriate transition state of **2d**−CuCl catalysis would be more stable than that of **2b**−CuCl. The formation of the **2d**−CuCl complex was strongly suggested by ESI mass spectrometry by the observation of an ion peak [**2d** + CuCl + H]$^+$ at *m*/*z* 742.

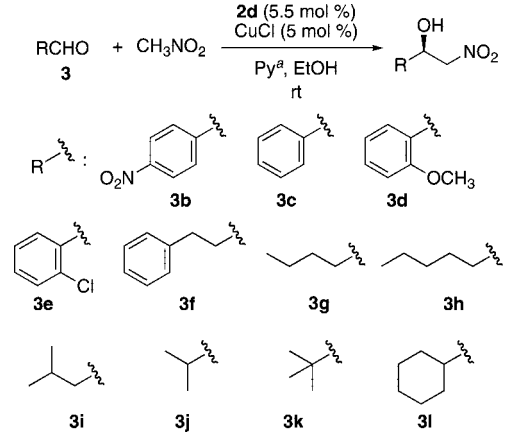
The nature of the R^2 group substituted at the sulfonyl group had a strong effect on the asymmetric induction ability, and the **2d**−CuCl−pyridine system gave the best overall result, with high chemical yield and enantiomeric excess. The scope and limitations of the **2d**−CuCl−pyridine catalyst system were examined, and the results are summarized in Table 3.

Various aldehydes were smoothly converted to Henry adducts at room temperature, and in all cases, the (*R*)-enriched products were obtained by using the tosyl-(*R*,*R*)-diphenylethylenediamine−(*R*)-binaphthyl ligand **2d**. The simplest aromatic aldehyde, benzaldehyde (**3c**), was converted to the Henry adduct in 94% yield with 83% ee. Typically, the use of aliphatic aldehydes provided the corresponding adducts with higher enantioselectivities than those obtained with aromatic aldehydes. In particular, α-branched aliphatic aldehydes such as pivalaldehyde (**3k**) and cyclohexanecarboxaldehyde (***3l***) gave the adducts with excellent enantioselectivity—up to 93% ee—without a significant decrease in reaction rate. Although the role of pyridine is unclear at present, its effect in accelerating the Henry reaction would suggest that it enforces nucleophilic addition of nitronate to the Cu Lewis acid-activated aldehyde in a cooperative manner.[3b]

Finally, the optimized catalyst system was applied to the diastereoselective Henry reaction; the results are shown in Table 4.

Although the reaction with nitroethane was slow, the reaction of **3f** without the use of ethanol as a solvent provided the adduct with moderate *syn*-selectivity. This *syn*-selectivity was in contrast with the results of Jørgensen's bis(oxazoline)−$Cu(OTf)_2$−catalyzed *anti*-selective Henry reaction with silyl nitronate.[11] Diastereoselectivity was also dramatically improved

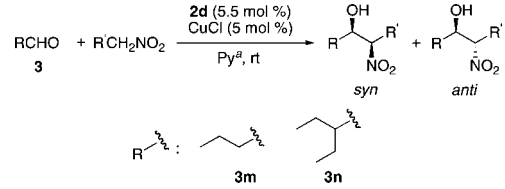
TABLE 3. 2d−CuCl-Catalyzed Enantioselective Henry Reaction



entry	aldehyde	time (h)	yield (%)	ee (%)
1	**3a**	18	97	67
2	**3b**	23	89	70
3	**3c**	23	94	83
4	**3d**	18	94	60
5	**3e**	15	99	59
6	**3f**	22	72	83
7	**3g**	18	96	87
8	**3h**	17	97	80
9	**3i**	18	95	85
10	**3j**	21	98	92
11	**3k**	20	79	93
12	***3l***	16	90	93

[a] 25 equiv of py to ligand.

TABLE 4. 2d−CuCl-Catalyzed Diastereoselective Henry Reaction[a]



entry	aldehyde	R′	time (h)	yield (%)	*syn*/*anti*	ee [%] *syn*/*anti*
1	**3f**	Me	16	55	80/20	66/22
2	**3i**	Me	43	70	73/27	64/27
3	**3j**	Me	94	89	85/15	82/30
4	***3l***	Me	41	99	92/8	84/43
5	***3l***	Et	42	63	91/9	81/55
6	**3m**	Me	66	90	76/24	80/22
7	**3m**	Et	96	92	74/26	68/23
8	**3n**	Me	14	81	90/10	81/32

[a] 25 equiv of py to ligand.

when α-branched aliphatic aldehydes were used; for example, the reaction of ***3l*** with nitroethane gave the product in 99% yield with 92:8 *syn*/*anti* selectivity. The enantiomeric excess of the *syn*-adduct was 84% (entry 4).[14]

To explain the *syn*-selectivity of the reaction, a plausible transition state is shown in Scheme 2. The formation of this Cu-containing cyclic transition state species would result in *syn*-selectivity due to steric hindrance.[15] In the Newman projections, the structure **S1**, which leads to the *syn*-adduct, is the most favorable.

(14) **2i**−CuCl-catalyzed diastereoselective Henry reaction of ***3l*** with nitroethane gave the adduct in 58% yield with 82:18 *syn*/*anti* selectivity. The enantiomeric excess of the *syn*-adduct was 60%.

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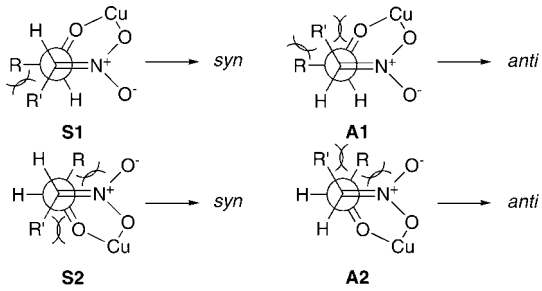
SCHEME 2. Plausible Transition Structure for the *Syn*-Selective Henry Reaction



Conclusion

In conclusion, we have succeeded in developing a new chiral sulfonyldiamine ligand as part of a catalyst system for diastereo- and enantioselective Henry reactions. With the assistance of pyridine, the reactions proceeded smoothly to provide the corresponding adducts with high *syn*-selectivity and high enantiomeric excess. Further detailed elucidation of the reaction mechanism is currently in progress.

Experimental Section

Preparation of (1*R*,2*R*)-*N*-(*R*)-Binaphtyl-*N*′-tosyl-1,2-diphenylethanediamine (2d). A solution of (1*R*,2*R*)-1,2-diphenylethanediamine (212 mg, 1.0 mmol), *p*-toluenesulfonyl chloride (191 mg, 1.0 mmol), and triethylamine (154 μl, 1.1 mmol) in dichloromethane (5.0 mL) was stirred at room temperature for 28 h under Ar. The reaction was quenched by the addition of distilled water, and the aqueous layer was extracted with dichloromethane. The organic phase was washed with brine, and then dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (using neutral silica gel, *n*-hexane/ethyl acetate = 1:1) to give (1*R*,2*R*)- *N*-tosyl-1,2-diphenylethanediamine (265 mg, 72% yield, as a white solid).

A solution of (1*R*,2*R*)-*N*-tosyl-1,2-diphenylethanediamine (160 mg, 0.437 mmol), (*R*)-2,2′-dibromomethyl-1,1′-binaphthalene (211 mg, 0.481 mmol), and triethylamine (134 μL, 0.960 mmol) in dichloromethane (2.2 mL) was stirred at room temperature. After being stirred for 67 h under Ar, the reaction was quenched by the addition of distilled water, and the aqueous layer was extracted with dichloromethane. The organic phase was washed with brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (using neutral silica gel, *n*-hexane/ethyl acetate = 5:1) to give **2d** (280 mg, 99% yield, as a pale yellow solid).

Spectral data for 2d:. $[\alpha]^{20}_{D}$ +28.6 (*c* 0.95, $CHCl_3$). IR (ATR) 3263, 3035, 2339, 1508, 1456, 1317, 1157, 1066, 928, 812, 752, 696, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.58 (d, J = 12.1 Hz, 2H), 3.85 (d, J = 12.3 Hz, 2H), 3.96 (d, J = 10.6 Hz, 1H), 4.92 (d, J = 10.6 Hz, 1H), 6.80−7.03 (m, 12H), 7.16−7.22 (m, 2H), 7.31−7.43 (m, 8H), 7.73 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 52.1, 58.4, 74.9, 125.3, 125.5, 126.8, 126.9, 127.2, 127.3, 127.48, 127.53, 127.6, 127.7, 127.8, 128.0, 128.15, 128.20, 128.4, 128.8, 129.2, 130.9, 132.8, 133.2, 134.6, 135.4, 137.7, 137.8, 142.6. HRMS (FAB+) calcd for $C_{43}H_{37}N_2O_2S$ (M^+ + H) 645.2576, found 645.2527.

General Procedure of the 2d−CuCl-Catalyzed Enantioselective Henry Reaction. The catalyst was prepared by a complex formation of ligand **2d** (12.9 mg, 0.02 mmol) with CuCl (1.8 mg, 0.018 mmol) in anhydrous dichloromethane (1.0 mL) under Ar. After the solution was stirred overnight at room temperature, solvent was removed under reduced pressure. Then, the residue was dissolved in EtOH (0.72 mL). To the resulting clear green solution were added nitromethane (196 μL, 3.64 mmol), pyridine (40 μL, 0.5 mmol), and cyclohexanecarboxaldehyde (44 μL, 0.364 mmol) under Ar. After the reaction was stirred for 16 h at room temperature, the volatile components were removed under reduced pressure and the residue was purified by column chromatography (using neutral silica gel, *n*-hexane/ethyl acetate = 4:1) to afford the adduct (56.6 mg, 90% yield). The enantiomeric excess was determined by HPLC analysis.

2d−CuCl-Catalyzed Diastereoselective Henry Reaction (Entry 4, Table 4). The catalyst was prepared by a complex formation of ligand **2d** (12.9 mg, 0.02 mmol) with CuCl (1.8 mg, 0.018 mmol) in anhydrous dichloromethane (1.0 mL) under Ar. After the reaction was stirred an overnight at room temperature, solvent was removed under reduced pressure. To the residue were added nitroethane (261 μL, 3.64 mmol), pyridine (40 μL, 0.5 mmol), and cyclohexanecarboxaldehyde (44 μL, 0.364 mmol) under Ar. After the reaction was stirred for 41 h at room temperature, the volatile components were removed under reduced pressure and the residue was purified by column chromatography (using neutral silica gel, *n*-hexane/ethyl acetate = 6:1) to afford the adduct (67.8 mg, 99% yield). Diastereoselectivity was determined by ^1H NMR spectroscopy and the enantiomeric excess was determined by HPLC analysis.

Acknowledgment. This work was supported by the Industrial Technology Research Grant Program (2006) from the New Energy and Industrial Technology Development Organization (NEDO) of Japan, a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science. We thank Prof. K. Nagasawa at the Tokyo University of Agriculture and Technology for providing the analytical data for the diastereoselective Henry reactions. We thank Mr. Y. Taneda and Ms. K. Suzuki for technical support.

Supporting Information Available: HPLC conditions for analyzing Henry adducts and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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