

A Highly *anti*-Selective Asymmetric Henry Reaction Catalyzed by a Chiral Copper Complex: Applications to the Syntheses of (+)-Spisulosine and a Pyrroloisoquinoline Derivative

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Abstract: A highly *anti*-selective asymmetric Henry reaction has been developed, affording synthetically versatile β -nitroalcohols in a predominately *anti*-selective manner (mostly above 15:1) and excellent *ee* values (mostly above 95%). Moreover, the *anti*-selective Henry reaction was carried out in

the presence of water for the first time with up to 99% *ee*. The catalytic mechanism was proposed based on the de-

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tection of the intermediates by extractive electrospray ionization mass spectrometry (EESI-MS). Furthermore, the *anti* adducts have been successfully transformed into the biochemically important (+)-spisulosine and a pyrroloisoquinoline derivative.

Introduction

The catalytic asymmetric nitroaldol reaction provides a facile method to generate enantiomerically enriched β -amino alcohols by reduction of the nitro group, which is an important structural motif in natural and synthetically designed compounds with interesting biological properties.^[1] Since the Shibasaki group reported the first catalytic asymmetric nitroaldol reaction,^[2] tremendous efforts have been made to develop a catalytic asymmetric Henry reaction.^[3] Although there have been pioneering studies into *anti*-selective Henry reactions by the Ooi group,^[4] which involved the use of a chiral tetra-aminophosphonium salt, and by the Shibasaki group,^[5] which utilized heterobimetallic catalysts, we have found few examples of *anti*-selective asymmetric Henry reactions^[7] that overcome the simple chelation model

for *syn*-selectivity.^[5a,d,6] Because optically active *anti*-amino alcohols are versatile building blocks in many natural products,^[8] the development of more efficient catalytic systems for highly *anti*-selective Henry reactions with excellent enantioselectivity is still of great significance.

The design of ideal chiral catalysts that could catalyze the desired reactions with high yield and excellent enantiomeric excess is one of the primary goals for synthetic chemistry. Enzymes are good examples of this principle because they catalyze a wide range of chemical processes.^[9] With an aim to simulate nature by developing catalytic systems analogous to enzymatic processes, the concept of a combined catalytic system has been employed in catalyst design to enhance their reactivity and selectivity.^[10] However, asymmetric transformations have typically been carried out in organic solvents, despite the fact that many enzymatic processes take place in an aqueous environment.^[11] Herein we report a highly *anti*-selective nitroaldol reaction that occurs with excellent enantioselectivities, and, remarkably, the first example of an *anti*-selective Henry reaction in the presence of water. Furthermore, the synthetic utility of this methodology was illustrated in the syntheses of (+)-spisulosine and a pyrroloisoquinoline derivative.

Results and Discussion

Encouraged by the success of asymmetric Henry reactions in our group,^[12] we envisioned the possibility of employing more challenging nitroalkanes than nitromethane as nucleophiles to realize high diastereo- and enantioselectivities. Based on previous studies, the Lewis acidity of the Cu atom was considered to be crucial for the reactivity and selectivity,^[3c,6] and therefore, a trifluoromethyl group was added to

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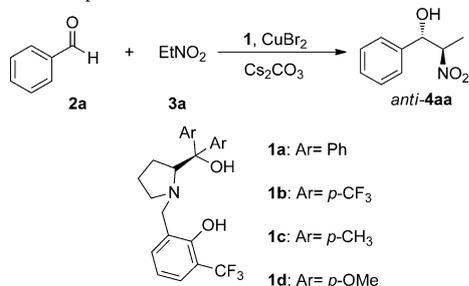
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the phenoxy functionality of ligand **1** to increase the acidity of the Lewis acid center.

The addition of benzaldehyde (**2a**) to nitroethane (**3a**) was used as a model reaction, and initial experiments were performed to optimize the ligand **1** (Table 1, entries 1–4).

Table 1. Selected optimization conditions.^[a]



Entry	Ligand	Temp. [°C]	Yield ^[b] [%]	d.r. ^[c] (<i>anti/syn</i>)	<i>ee</i> ^[d] [%]
1	1a	RT	71	6:1	90
2	1b	RT	73	7:1	75
3	1c	RT	71	2:1	87
4	1d	RT	65	4:1	85
5 ^[e]	1a	RT	67	11:1	92
6 ^[e]	1a	−15	49	22:1	95
7 ^[e,f]	1a	−15	81	20:1	95

[a] Reaction conditions: **2a** (0.5 mmol), **3a** (5 mmol), **1** (5 mol %), CuBr₂ (5 mol %), Cs₂CO₃ (5 mol %), THF (1 mL), RT, 12 h. [b] Isolated yield. [c] Determined by ¹H NMR analysis. [d] The *ee* value of *anti-4aa*. [e] Supernatant was used after centrifugation (ca. 1 × 10⁴ rpm). [f] 7.5 mol % of Cs₂CO₃ was used, 24 h.

Among the ligands examined, ligand **1a** was found to be ideal with regard to selectivities and chemical yield (Table 1, entry 1). Screening the other typical reaction parameters indicated that THF was the best solvent in combination with CuBr₂ as the Cu^{II} source (see the Supporting Information for details). A detailed inspection of the reaction progress showed that a heterogeneous reaction mixture was formed. When the precipitate was removed by centrifugation, the supernatant solution of the catalyst gave a better reaction result (Table 1, entry 5). Inductively coupled plasma mass spectrometry (ICP-MS) and X-ray photoelectron spectroscopy (XPS) analyses indicated that the precipitate was an inorganic salt instead of the chiral copper complex (the concentration ratio of Cs/Cu in the precipitate was 28:1; see the Supporting Information for details). The supernatant was then subjected to extractive electrospray ionization mass spectrometry (EESI-MS) analysis, and the results showed that the supernatant included the copper complex coordinated with the chiral ligand (see the mechanistic study for details). Additional studies suggested that better selectivities could be obtained by decreasing the reaction temperature (Table 1, entry 6). Because basic additives are known to accelerate the Henry reaction,^[31,6] a larger amount of Cs₂CO₃ was added to increase the reactivity of the reaction. It was found that the addition of 7.5 mol % of Cs₂CO₃ improved

Table 2. Diastereoselective Henry reaction catalyzed by a chiral copper complex in THF.^[a]

Entry	R ¹	R ²	Product	Time	Yield ^[b] [%]	d.r. ^[c] (<i>anti/syn</i>)	<i>ee</i> ^[d] [%]
1	C ₆ H ₅	Me	4aa	24	81	20:1	95
2 ^[e]	2-MeC ₆ H ₄	Me	4ba	72	61	39:1	99
3 ^[e]	2-MeOC ₆ H ₄	Me	4ca	72	74	39:1	97
4 ^[e]	2-ClC ₆ H ₄	Me	4da	84	62	22:1	99
5	2-BrC ₆ H ₄	Me	4ea	72	89	16:1	95
6	2-NO ₂ C ₆ H ₄	Me	4fa	72	85	23:1	95
7	3-MeC ₆ H ₄	Me	4ga	84	87	15:1	97
8	3-Cl-C ₆ H ₄	Me	4ha	72	91	39:1	96
9 ^[e]	4-MeC ₆ H ₄	Me	4ia	84	80	20:1	96
10 ^[e]	4-MeOC ₆ H ₄	Me	4ja	72	87	27:1	97
11	4-ClC ₆ H ₄	Me	4ka	72	79	25:1	96
12 ^[e]	4-BrC ₆ H ₄	Me	4la	72	82	26:1	96
13	4-NO ₂ C ₆ H ₄	Me	4ma	72	90	23:1	98
14	(<i>E</i>)-cinnamyl	Me	4na	84	83	20:1	91
15	2-furyl	Me	4oa	72	76	> 50:1	88
16	pentyl	Me	4pa	84	89	15:1	99
17	phenylethyl	Me	4qa	72	69	19:1	93
18	isobutyl	Me	4ra	84	81	15:1	92
19	cyclohexyl	Me	4sa	84	79	10:1	96
20	C ₆ H ₅	Et	4ab	96	67	18:1	95

[a] Reaction conditions: **2** (0.5 mmol), **3** (5 mmol), **1a** (5 mol %), CuBr₂ (5 mol %), Cs₂CO₃ (7.5 mol %). [b] Isolated yield. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] The *ee* value of *anti-4*. [e] The reaction was performed at −10 °C.

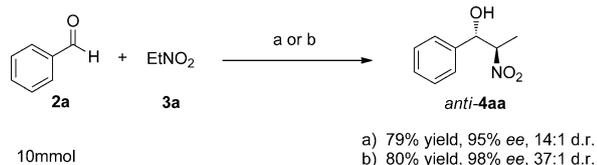
the yield to 81 %, with only a slight decrease in the diastereoselectivity (Table 1, entry 7).

With the optimized conditions in hand, the substrate scope was examined. As presented in Table 2, a variety of aldehydes, including challenging aliphatic aldehydes, were successfully used in the Henry reaction to provide the β-nitroalcohols in moderate yields and excellent selectivities. In most cases, the reactions were carried out at −15 °C. For some of the less active substrates, the temperature was raised to −10 °C to accelerate the reaction rate (Table 2, entries 2–4, 9, 10, and 12). To examine the electronic and steric effects of the substrate on the reaction, aromatic aldehydes with different substituents at the *ortho*, *meta*, and *para* positions were employed. The reaction tolerated the use of aromatic aldehydes with substituents at any position of the aromatic ring and both electron-donating and electron-withdrawing functionalities were compatible, affording the nitroaldol products in moderate yields and high selectivities (*anti/syn* mainly above 20:1, 95–99 % *ee* values; Table 1, entries 2–13). It should be noted that reactions of the aldehydes with a strong electronic effect, including the strongly electron-donating methoxy group (Table 2, entries 3 and 10) and the electron-withdrawing nitro group (Table 2, entries 6 and 13), also proceeded smoothly with good yields and excellent selectivities.

The α,β-unsaturated (*E*)-cinnamylaldehyde gave the nitroaldol product **4na** in 83 % yield with a diastereomeric ratio (d.r.) of 20:1 and 91 % *ee* (Table 2, entry 14). Although

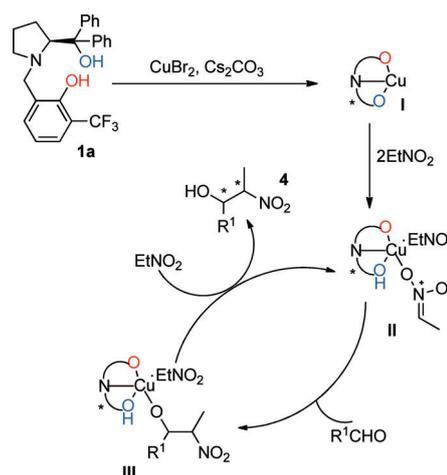
a slight decrease in the *ee* value resulted when the heteroaromatic 2-furylaldehyde was employed as a reaction substrate, the highest d.r. value (*antisyn* above 50:1) was obtained in this case (Table 2, entry 15). Aliphatic aldehydes have proven to be challenging substrates in previously reported examples; however, the simple aliphatic aldehydes were suitable electrophiles under these optimized conditions. In case of the linear aliphatic aldehydes, good diastereoselectivities and excellent enantioselectivities were achieved (Table 2, entries 16–18). When sterically hindered cyclohexanecarboxaldehyde was employed as the reaction substrate, the corresponding nitroaldol product **4sa** was obtained in 96% *ee* and a 10:1 d.r. (Table 2, entry 19). The use of the less reactive nitropropane as a nucleophile afforded the desired product **4ab** in 67% yield with 18:1 *antisyn* selectivity and 95% *ee*, although a longer reaction time was required (Table 2, entry 20).

Upon scaling up to gram quantities (10 mmol), the desired product **4aa** was obtained in good yield (79%) with excellent selectivities (95% *ee*, 14:1 d.r.) by using 5 mol% of the **1a**–Cu complex (Scheme 1). When the catalyst loading for this reaction was increased to 10 mol%, the corresponding product **4aa** was obtained in 80% yield and excellent selectivities (98% *ee* and 37:1 d.r., see the Supporting Information for details).



Scheme 1. The *anti*-selective Henry reaction on a gram scale. Reaction conditions: a) **2a** (10 mmol), **3a** (100 mmol), **1a** (5 mol%), CuBr₂ (5 mol%), Cs₂CO₃ (7.5 mol%), THF (20 mL), –15°C, 48 h; b) **2a** (10 mmol), **3a** (100 mmol), **1a** (10 mol%), CuBr₂ (10 mol%), Cs₂CO₃ (15 mol%), THF (20 mL), –15°C, 48 h.

A possible catalytic cycle that accounts for the complexation system of the reaction in THF is shown in Scheme 2. EESI-MS analysis^[13] provided reliable structural information about the intermediates shown in Scheme 2. When the ligand **1a** was reacted with CuBr₂ and Cs₂CO₃ in THF, the complex **I** was indicated by the ion peak at *m/z* 548 ([**I**+CH₃CN+H₂O+H]⁺; see Figures S2–S5 in the Supporting Information for details). After the addition of nitroethane, the copper–alkoxide moiety in intermediate **I** functioned as a Lewis base to deprotonate EtNO₂, generating the five-coordinate copper complex **II**, which was indicated by the ion peak at *m/z* 680 ([**II**+CH₃CN+H]⁺; see Figures S6–S9 in the Supporting Information for details). It is worth noting that copper(II) was bonded to one molecule of nitronate and coordinated with one molecule of EtNO₂ in the intermediate **II**. With the subsequent addition of the aldehyde, two contiguous stereocenters were formed simultaneously (intermediate **III**). With the participation of another prenucleophilic reagent (nitroethane), the nitroaldol adduct



Scheme 2. Proposed catalytic cycle for the *anti*-selective Henry reaction in THF.

4 was formed and the reactive metal–nitronate **II** was regenerated to undergo the next reaction cycle. Possible transition-state structures that account for the observed stereoselectivity are shown in the Supporting Information (see Figure S10 for details).

To enhance the applicability of the catalyst, the diastereoselective Henry reaction was studied in the presence of water. By using the addition of benzaldehyde (**2a**) to nitroethane (**3a**) as a model reaction, a library of phase-transfer catalysts (PTCs) and additives was examined (Table 3; see Tables S3–S5 in the Supporting Information for details). Initially, a series of PTCs were screened in the absence of any additives (Table 3, entries 1–9). Hexadecyltrimethylammoniumbromide (CTAB) was found to be the PTC of choice with regard to the chemical yield and selectivities (Table 3, entry 7). A series of weak acid additives were then added to the reaction mixture to improve the chemical yield (Table 3, entries 10–14). The best result was obtained with the use of *ortho*-chlorophenol as an additive (Table 3, entry 10).^[14] Lowering the reaction temperature to 0°C improved the diastereo- and enantioselectivities but slowed the reaction, thus prolonged reaction times were needed to obtain an acceptable yield (Table 3, entry 15). Increasing the amount of the nitroethane starting material improved the diastereo- and enantioselectivities slightly (Table 3, entry 16). The control experiments showed that the diastereoselective Henry reaction was not promoted by CTAB or *ortho*-chlorophenol in the absence of a copper complex. CTAB may play a key role in the migration of organic reactants into water and the achiral *ortho*-chlorophenol additive, a weak acid, may facilitate the proton transfer in the reaction process;^[14] however, these mechanisms are speculative and other possible mechanisms may exist. Further studies are required to firmly elucidate the roles of the PTC and the acid additive.

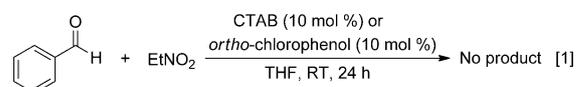
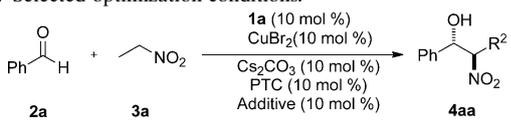


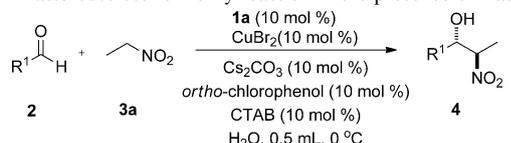
Table 3. Selected optimization conditions.^[a]



Entry	PTC	Additive	Yield ^[b] [%]	d.r. ^[c] (<i>anti/syn</i>)	<i>ee</i> ^[d] [%]
1	<i>n</i> Bu ₄ NBr	–	51	5.4:1	86
2	<i>n</i> Bu ₄ NF	–	44	6.7:1	92
3	<i>n</i> Et ₄ NBr	–	13	2.6:1	79
4	<i>n</i> Bu ₄ NPF ₆	–	31	4:1	88
5	<i>n</i> Bu ₄ NBF ₄	–	26	4:1	86
6	PVP	–	27	3.3:1	81
7	CTAB	–	64	5:1	87
8	SDS	–	25	3.6:1	83
9	SLS	–	27	2.6:1	76
10	CTAB	2-ClC ₆ H ₄ OH	77	5:1	86
11	CTAB	2-MeOC ₆ H ₄ OH	73	4:1	84
12	CTAB	2- <i>t</i> BuC ₆ H ₄ OH	69	3.8:1	86
13	CTAB	4- <i>t</i> BuC ₆ H ₄ OH	68	6:1	86
14	CTAB	HFIP	58	4.6:1	85
15 ^[e]	CTAB	2-ClC ₆ H ₄ OH	74	7.3:1	92
16 ^[f]	CTAB	2-ClC ₆ H ₄ OH	73	8.5:1	94

[a] Reaction conditions: **2a** (0.25 mmol), **3a** (2.5 mmol, 10 equiv), **1a** (10 mol %), CuBr₂ (10 mol %), Cs₂CO₃ (10 mol %), PTC (10 mol %), additive (10 mol %), H₂O (0.5 mL), 5 °C, 24 h. [b] Isolated yield. [c] Determined by ¹H NMR analysis. [d] The *ee* value of *anti*-**4aa**. [e] The reaction was performed at 0 °C for 72 h. [f] Reaction conditions: **2a** (0.25 mmol), **3a** (4 mmol), **1a** (10 mol %), CuBr₂ (10 mol %), Cs₂CO₃ (10 mol %), CTAB (10 mol %), *ortho*-chlorophenol (10 mol %), H₂O (0.5 mL), 0 °C, 72 h. PVP = polyvinyl pyrrolidone, SDS = sodium dodecylsulfate, SLS = sodium laurylsulfonate, HFIP = hexafluoroisopropanol.

Table 4. Diastereoselective Henry reaction in the presence of water.^[a]



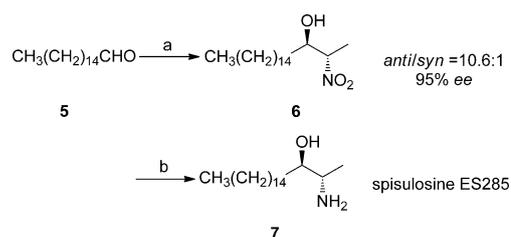
Entry	R ¹	Product	Yield ^[b] [%]	d.r. ^[c] (<i>anti/syn</i>)	<i>ee</i> ^[d] [%]
1	C ₆ H ₅	4aa	73	8.5:1	94
2	2-MeC ₆ H ₄	4ba	66	5.6:1	93
3	2-MeOC ₆ H ₄	4ca	61	5.7:1	90
4	2-NO ₂ C ₆ H ₄	4fa	76	9:1	97
5	3-ClC ₆ H ₄	4ha	74	8.3:1	93
6	4-MeC ₆ H ₄	4ia	69	7.8:1	92
7	4-MeOC ₆ H ₄	4ja	67	7.4:1	91
8	4-ClC ₆ H ₄	4ka	75	7.9:1	92
9	4-BrC ₆ H ₄	4la	76	8:1	93
10	4-NO ₂ C ₆ H ₄	4ma	84	10:1	99
11	PhCH=CH	4na	68	3:1	94
12	pentyl	4pa	62	1.1:1	83
13	PhCH ₂ CH ₂	4qa	64	1.4:1	85

[a] Reaction conditions: **2** (0.25 mmol), **3a** (4 mmol), **1a** (10 mol %), CuBr₂ (10 mol %), Cs₂CO₃ (10 mol %), *ortho*-chlorophenol (10 mol %), CTAB (10 mol %), H₂O (0.5 mL), 0 °C, 72 h. [b] Isolated yield. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] The *ee* value of *anti*-**4**.

The scope of the diastereoselective Henry reaction in the presence of water was then examined with a variety of aldehydes under the optimized conditions (Table 4). As shown

in Table 4, a series of aryl-substituted aldehydes efficiently underwent the Henry reaction to give the adducts **4aa–ma** in moderate to high yields with good enantioselectivities (90–99% *ee*) and moderate diastereoselectivities (*anti/syn* ratio up to 10:1; Table 4, entries 1–10). It was found that the nature of the substituents on the aryl groups had a slight influence on the diastereo- and enantioselectivities, whereas the chemical yield was largely influenced by the electronic effect. Generally, electron-deficient aldehydes gave better results than the electron-rich aldehydes. For instance, electron-deficient *para*-nitrobenzaldehyde gave the Henry adduct **4ma** in 84% yield with 99% *ee* and 10:1 d.r. (Table 4, entry 10), whereas the electron-rich *para*-methoxybenzaldehyde gave the corresponding adduct **4ja** in only 67% yield with 91% *ee* and 7.4:1 d.r. (Table 4, entry 7). When α,β -unsaturated (*E*)-cinnamaldehyde was employed as the electrophile, the adduct **4na** was obtained in moderate yield and selectivities (94% *ee*, 3:1 d.r.; Table 4, entry 11). However, aliphatic aldehydes were found to be poor substrates under the standard reaction conditions, providing the corresponding products in low yields and selectivities (Table 4, entries 12 and 13).

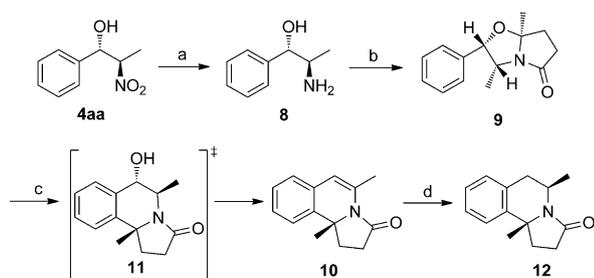
The utility of the reaction was further demonstrated in the syntheses of the biochemically important (+)-spisulosine **7** (Scheme 3) and a pyrroloisoquinoline derivative **12**



Scheme 3. Enantioselective synthesis of (+)-spisulosine. Reaction conditions: a) EtNO₂ (10 equiv), *ent*-**1a** (10 mol %), CuBr₂ (10 mol %), Cs₂CO₃ (15 mol %), THF, 0 °C, 72 h, 82% yield; b) 10% Pd/C (10 mol %), H₂, MeOH, RT, 12 h, 73% yield.

(Scheme 4). (+)-Spisulosine ES285 was isolated from *Spisula polynyma*, and has been shown to possess long-lasting antitumor cytotoxic activity on the nanomolar scale, both in vitro and in vivo.^[15] The pyrroloisoquinoline ring system forms the central skeleton of the erythrina alkaloid group.^[16] The treatment of *n*-hexadecanal **5** and nitroethane with 10 mol % of the *ent*-**1a**–Cu^I complex in THF at 0 °C for 72 h resulted in the formation of the *anti*-nitroalcohol **6** (*anti/syn* = 10.6:1) in 82% yield with 95% *ee*. Reduction of the nitro group by the Pd/C catalyst gave spisulosine **7**, which contains a long, saturated alkyl chain (C18) and a 1,2-aminoalcohol motif arranged in an *anti* manner. It should be mentioned that this is the shortest enantioselective synthesis of ES285 reported so far.^[8,17]

With the *anti*-nitroalcohol **4aa** in hand, aminoalcohol **8** could be obtained in 87% yield (Scheme 4). Then, the cyclocondensation process between aminoalcohol **8** and levulinic



Scheme 4. Enantioselective synthesis of a pyrroloisoquinoline derivative. Reaction conditions: a) 10% Pd/C (10 mol%), H₂, EtOH, RT, 10 h, 87% yield; b) levulinic acid (1 equiv), toluene, reflux, 24 h, 79% yield; c) TiCl₄ (3 equiv), dichloromethane, -78°C to 40°C, 30 h, 69% yield; d) 10% Pd/C (10 mol%), H₂, EtOH, RT, 10 h, 87% yield.

acid led to the formation of compound **9** in 79% yield. With the participation of TiCl₄, lactam **9** could be transformed into enamide **10** in 69% yield. During the reaction process, compound **11** was observed, which suggests that this intermediate (**11**) may be formed by a Pictet–Spengler-type reaction from lactam **9** and was then dehydrated to yield enamide **10**. The desired pyrroloisoquinoline derivative **12** was obtained in 87% yield by the catalytic hydrogenation of enamide **10** at room temperature (see the Supporting Information for details). The stereochemistry of the resulting compounds (compounds **9**, **11**, and **12**) was determined by NOESY experiments (see the Supporting Information for details).

Conclusion

An efficient catalytic system for highly anti-selective Henry reactions in organic media has been developed with excellent enantioselectivities. Moreover, the anti-selective Henry reaction in the presence of water was carried out for the first time with good diastereoselectivities and excellent enantioselectivities. The key intermediates in the catalytic cycle were structurally illustrated by EESI-MS analyses. Furthermore, the synthetically useful anti-nitroalcohol motif has been successfully transformed into the biochemically important (+)-spisulosine and a pyrroloisoquinoline derivative. Further studies to clearly understand the mechanism of the PTC and the role of the acidic additive are ongoing in our group.

Experimental Section

General procedure for the anti-selective Henry reaction in THF: Nitroalkane **3** (5 mmol) was added to a mixture of ligand **1a** (0.025 mmol), CuBr₂ (0.025 mmol), and Cs₂CO₃ (0.0375 mmol) in dry THF (1 mL). The mixture was allowed to stir at room temperature for 4 h and a white precipitate appeared. The tube was centrifuged for 5 min (ca. 1 × 10⁴ rpm) and the supernatant was transferred into a reactor (10 mL). After cooling to -15°C, compound **2** (0.5 mmol) was added to the reactor. The mixture was reacted for the time indicated in Table 2, quenched with dilute HCl

(0.5 mL, 1 M), and then extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried with Na₂SO₄ and evaporated under vacuum. Purification of the residue by flash column chromatography gave the desired β-nitroalcohol **4**. The anti/syn ratio was determined by ¹H NMR analysis of the crude mixture. The enantiomeric excess was determined by HPLC analysis.

General procedure for the anti-selective Henry reaction in water: Nitroethane (**3a**; 4 mmol) was added to a mixture of ligand **1a** (0.025 mmol), CuBr₂ (0.025 mmol), Cs₂CO₃ (0.025 mmol), ortho-chlorophenol (0.025 mmol), and CTAB (0.025 mmol) in H₂O (0.5 mL). The mixture was allowed to stir at room temperature for 1 h. After cooling to 0°C, compound **2** (0.25 mmol) was added to the reactor. The mixture was reacted for 72 h, quenched with dilute HCl (0.5 mL, 1 M), and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried with Na₂SO₄ and evaporated under vacuum. Purification of the residue by column chromatography gave the desired β-nitroalcohol **4**. The anti/syn ratio was determined by ¹H NMR analysis of the crude mixture. The enantiomeric excess was determined by HPLC analysis.

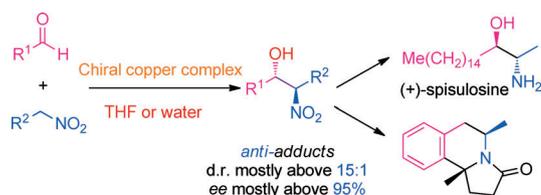
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Friendly water: An asymmetric Henry reaction that affords synthetically versatile β -nitroalcohols in an *anti*-selective manner and with excellent *ee* values has been developed (see scheme). The reaction was carried out

in water for the first time with up to 99% *ee*, and the *anti*-adducts were successfully transformed into the biochemically important (+)-spisulosine and a pyrroloisoquinoline derivative.

Asymmetric Synthesis

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A Highly *anti*-Selective Asymmetric Henry Reaction Catalyzed by a Chiral Copper Complex: Applications to the Syntheses of (+)-Spisulosine and a Pyrroloisoquinoline Derivative

