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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

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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 detection 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.

Keywords: amino alcohols · asymmetric catalysis · copper · enantioselectivity · Henry reaction

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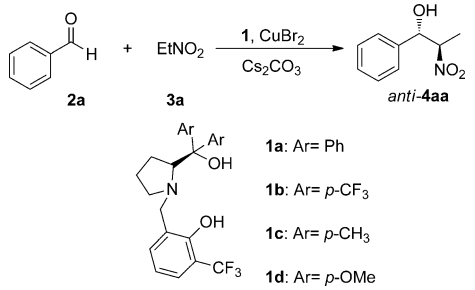
the phenoxy functionality of ligand **1** to increase the acidity of the Lewis acid center.

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]

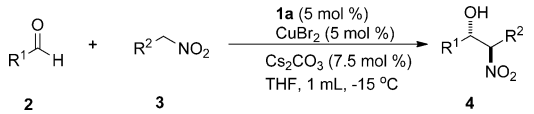


Entry	Ligand	Temp. [°C]	Yield[b] [%]	d.r.[c] (*anti*/*syn*)	*ee*[d] [%]
1	**1a**	RT	71	6:1	90
2	**1b**	RT	73	7:1	75
3	**1c**	RT	71	2:1	87
4	**1d**	RT	65	4:1	85
5[e]	**1a**	RT	67	11:1	92
6[e]	**1a**	−15	49	22:1	95
7[e,f]	**1a**	−15	81	20:1	95

[a] Reaction conditions: **2a** (0.5 mmol), **3a** (5 mmol), **1** (5 mol%), $CuBr_2$ (5 mol%), Cs_2CO_3 (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. 1×10^4 rpm). [f] 7.5 mol% of Cs_2CO_3 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 $CuBr_2$ 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,[3i,6] a larger amount of Cs_2CO_3 was added to increase the reactivity of the reaction. It was found that the addition of 7.5 mol% of Cs_2CO_3 improved the yield to 81%, with only a slight decrease in the diastereoselectivity (Table 1, entry 7).

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] (*anti*/*syn*)	*ee*[d] [%]
1	C_6H_5	Me	**4aa**	24	81	20:1	95
2[e]	2-MeC_6H_4	Me	**4ba**	72	61	39:1	99
3[e]	2-MeOC_6H_4	Me	**4ca**	72	74	39:1	97
4[e]	2-ClC_6H_4	Me	**4da**	84	62	22:1	99
5	2-BrC_6H_4	Me	**4ea**	72	89	16:1	95
6	2-$NO_2C_6H_4$	Me	**4fa**	72	85	23:1	95
7	3-MeC_6H_4	Me	**4ga**	84	87	15:1	97
8	3-Cl-C_6H_4	Me	**4ha**	72	91	39:1	96
9[e]	4-MeC_6H_4	Me	**4ia**	84	80	20:1	96
10[e]	4-MeOC_6H_4	Me	**4ja**	72	87	27:1	97
11	4-ClC_6H_4	Me	**4ka**	72	79	25:1	96
12[e]	4-BrC_6H_4	Me	**4la**	72	82	26:1	96
13	4-$NO_2C_6H_4$	Me	**4ma**	72	90	23:1	98
14	(*E*)-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_6H_5	Et	**4ab**	96	67	18:1	95

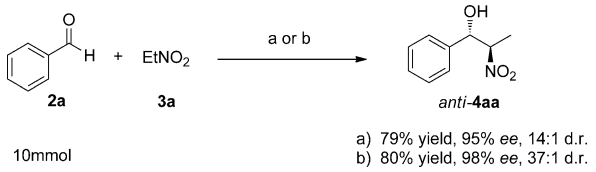
[a] Reaction conditions: **2** (0.5 mmol), **3** (5 mmol), **1a** (5 mol%), $CuBr_2$ (5 mol%), Cs_2CO_3 (7.5 mol%). [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] The *ee* value of *anti*-**4**. [e] The reaction was performed at −10°C.

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

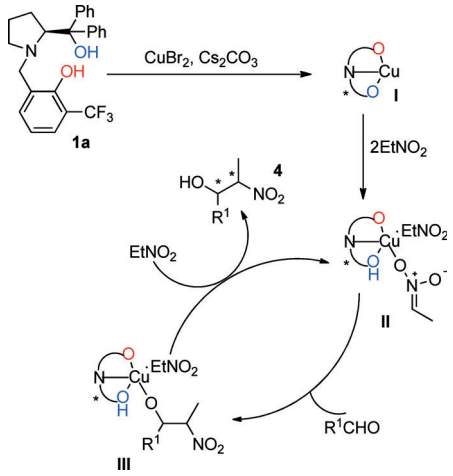
a slight decrease in the *ee* value resulted when the heteroaromatic 2-furylaldehyde was employed as a reaction substrate, the highest d.r. value (*anti*/*syn* above 50:1) was obtained in this case (Table 2, entry 15). Aliphatic aldehydes have proven to be challenging substrates in previously reported 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 *anti*/*syn* 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%), $CuBr_2$ (5 mol%), Cs_2CO_3 (7.5 mol%), THF (20 mL), −15°C, 48 h; b) **2a** (10 mmol), **3a** (100 mmol), **1a** (10 mol%), $CuBr_2$ (10 mol%), Cs_2CO_3 (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 $CuBr_2$ and Cs_2CO_3 in THF, the complex **I** was indicated by the ion peak at *m*/*z* 548 ($[\mathbf{I}+CH_3CN+H_2O+H]^+$; 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 $EtNO_2$, generating the five-coordinate copper complex **II**, which was indicated by the ion peak at *m*/*z* 680 ($[\mathbf{II}+CH_3CN+H]^+$; 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 $EtNO_2$ in the intermediate **II**. With the subsequent addition of the aldehyde, two contiguous stereocenters were formed simultaneously (intermediate **III**). With the participation of another prenucleophlic reagent (nitroethane), the nitroaldol adduct



Scheme 2. Proposed catalytic cyclic 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.

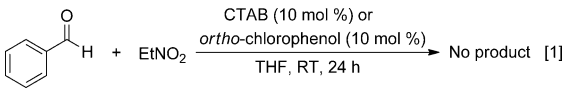
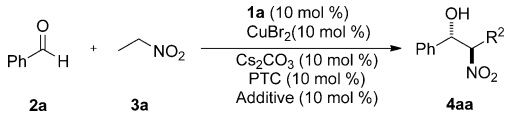


Table 3. Selected optimization conditions.[a]

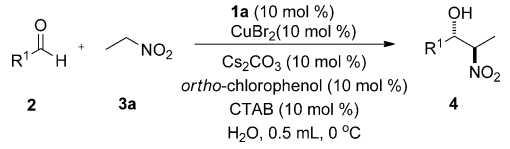


2a 3a 4aa

Entry	PTC	Additive	Yield[b] [%]	d.r.[c] (*anti*/*syn*)	*ee*[d] [%]
1	nBu$_4$NBr	–	51	5.4:1	86
2	nBu$_4$NF	–	44	6.7:1	92
3	nEt$_4$NBr	–	13	2.6:1	79
4	nBu$_4$NPF$_6$	–	31	4:1	88
5	nBu$_4$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-tBuC$_6$H$_4$OH	69	3.8:1	86
13	CTAB	4-tBuC$_6$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 %), $CuBr_2$ (10 mol %), Cs_2CO_3 (10 mol %), PTC (10 mol %), additive (10 mol %), H_2O (0.5 mL), 5 °C, 24 h. [b] Isolated yield. [c] Determined by ^{1}H 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 %), $CuBr_2$ (10 mol %), Cs_2CO_3 (10 mol %), CTAB (10 mol %), *ortho*-chlorophenol (10 mol %), H_2O (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]



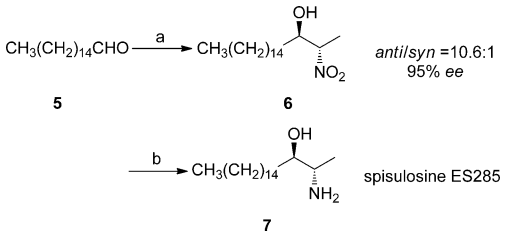
2 3a 4

Entry	R^1	Product	Yield[b] [%]	d.r.[c] (*anti*/*syn*)	*ee*[d] [%]
1	C_6H_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 %), $CuBr_2$ (10 mol %), Cs_2CO_3 (10 mol %), *ortho*-chlorophenol (10 mol %), CTAB (10 mol %), H_2O (0.5 mL), 0 °C, 72 h. [b] Isolated yield. [c] Determined by ^{1}H 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).

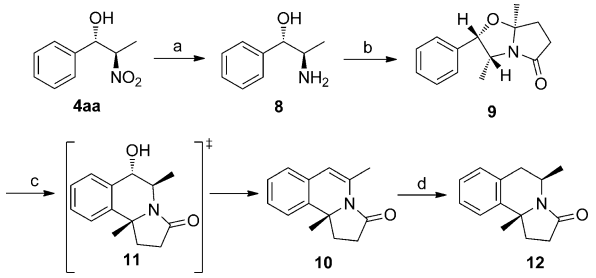
The utility of the reaction was further demonstrated in the syntheses of the biochemically important (+)-spisulosine **7** (Scheme 3) and a pyrroloisoquinoline derivative **12**



Scheme 3. Enantioselective synthesis of (+)-spisulosine. Reaction conditions: a) $EtNO_2$ (10 equiv), *ent*-**1a** (10 mol %), $CuBr_2$ (10 mol %), Cs_2CO_3 (15 mol %), THF, 0 °C, 72 h, 82 % yield; b) 10 % Pd/C (10 mol %), H_2, 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^{II} 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%), H_2, EtOH, RT, 10 h, 87% yield; b) levulinic acid (1 equiv), toluene, reflux, 24 h, 79% yield; c) $TiCl_4$ (3 equiv), dichloromethane, −78°C to 40°C, 30 h, 69% yield; d) 10% Pd/C (10 mol%), H_2, EtOH, RT, 10 h, 87% yield.

acid led to the formation of compound **9** in 79% yield. With the participation of $TiCl_4$, 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), $CuBr_2$ (0.025 mmol), and Cs_2CO_3 (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. 1×10^4 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 Na_2SO_4 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 ^{1}H 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), $CuBr_2$ (0.025 mmol), Cs_2CO_3 (0.025 mmol), *ortho*-chlorophenol (0.025 mmol), and CTAB (0.025 mmol) in H_2O (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 Na_2SO_4 and evaporated under vacuum. Purification of the residue by column chromatography gave the desired β-nitroalcohol **4**. The *anti*/*syn* ratio was determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric excess was determined by HPLC analysis.

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