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Synthesis of Chiral 1,3-Diamines Derived from *cis*-2-Benzamidocyclohexanecarboxylic Acid and Their Application in the Cu-Catalyzed Enantioselective Henry Reaction

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Abstract: In this study, 13 different chiral 1,3-diamines were synthesized from (−)-*cis*-2-benzamidocyclohexanecarboxylic acid. They were successfully applied as ligands in the Cu-catalyzed asymmetric Henry reaction between benzaldehyde and nitromethane. It was confirmed that the enantioselectivity of the product could be controlled by the substituents on the two amino groups. A time-course study revealed a decrease in product enantioselectivity caused by spontaneous retro-Henry reaction, which was suppressed by conducting the reaction at 0 °C. This versatile reaction afforded various β-nitroalcohols in excellent yields and enantioselectivities (up to 98% yield, 91% enantiomeric excess) under the optimized reaction conditions. The chiral induction mechanism was explained on the basis of a previously proposed transition-state model.

Keywords: asymmetric synthesis · chirality · copper · diamines · Henry reaction

Introduction

Due to the high demand and preference for the use of enantiopure compounds in the fields of pharmaceuticals, perfumes, food additives, etc., there has been a great interest in catalytic asymmetric synthesis as a tool for their efficient preparation. Although large numbers of chiral ligands and organocatalysts have been synthesized and applied for a variety of asymmetric reactions, most of them are derivatives and analogues of the "privileged chiral catalysts".[1] To further expand the potential of asymmetric synthesis, we aimed to develop novel chiral catalysts without privileged structures in a readily accessible manner.

We focused on *cis*-2-benzamidocyclohexanecarboxylic acid (**1**) as a starting material for the synthesis of chiral catalysts. Compound **1** is a very attractive chiral compound because, not only can it be readily synthesized from inexpensive starting materials, but it also has functional groups that can be easily transformed (i.e., hydroxy and amino groups). In addition, both enantiomers of **1** can be prepared by preferential resolution and, therefore, require no resolving agent as an external chiral source.[2] Thus, compound **1** can be easily and economically derivatized as a completely man-made chiral catalyst, that is, no naturally occurring enantiopure compound is used in the synthesis of the chiral catalysts.

Since the report revealing the preparation of enantiopure **1** by preferential crystallization, compound **1** and its derivatives have been applied as resolving agents,[3] for example, in the synthesis of β-peptides.[4] However, to the best of our knowledge, few reports about their application towards asymmetric synthesis have been published.[5] For example, Saigo reported the only example of their application to a catalytic asymmetric reaction and the enantiomeric excess (*ee*) values achieved in this reaction were very low (<10% *ee*).[6] These facts also motivated us to explore reactions in which derivatives of **1** can be applied as chiral catalysts.

Recently, our group reported the application of 1,3-aminoalcohols and 1,3-aminosulfonamide chiral ligands derived from (−)-**1** to the catalytic enantioselective addition of organozinc reagents to aldehydes.[7a–c] Also, chiral ionic liquids and 1,3-aminothioureas derived from (+)-**1** have been applied in asymmetric Michael addition reactions between aldehydes and β-nitroolefins.[7d–e] As an extension of our work, we designed and synthesized an array of enantiopure 1,3-diamines derived from (−)-**1** and investigated whether these 1,3-diamines would be applicable as chiral ligands for the Cu-catalyzed enantioselective Henry reaction.

The Henry reaction entails addition of a nitroalkane to the carbonyl group of an aldehyde or a ketone.[8] Since the first asymmetric version of this reaction was reported by Shibasaki,[9] various chiral metal-containing catalysts and organocatalysts have been developed. In particular, it has been determined that Cu complexes with chiral aza-containing ligands (e.g. aminoalcohols, Schiff bases, diamines) are highly efficient catalysts for the asymmetric Henry reac-

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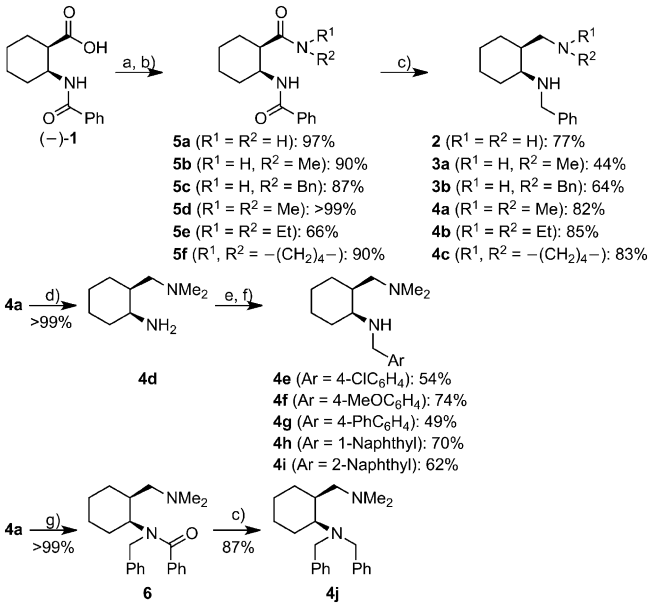
tion.[10] Chiral β-nitroalcohols, the products of this asymmetric transformation, are very important intermediates or building blocks in organic synthesis because they can be readily converted into β-aminoalcohols by reduction of the nitro group, α-hydroxycarboxylic acids by the Nef reaction, and so on.[11] Due to the practical importance of this reaction, it is a worthy challenge to develop an efficient and readily available catalyst for the asymmetric Henry reaction.

Herein, we report the synthesis of novel chiral 1,3-diamines from (−)-**1** by simple chemical transformations and their successful application as chiral ligands in the Cu-catalyzed enantioselective Henry reaction.

Results and Discussion

Synthesis of chiral 1,3-diamine ligands derived from (−)-1: We designed 1,3-diamines with two different amino groups: a cyclohexylmethylamino (^{prim}C-amino) group and a cyclohexylamino (^{sec}C-amino) group. The synthetic routes to three types of 1,3-diamines, namely, **2** (primary ^{prim}C-amine), **3a** and **3b** (secondary ^{prim}C-amines), and **4a–j** (tertiary ^{prim}C-amines), are shown in Scheme 1. All of the enantiopure 1,3-



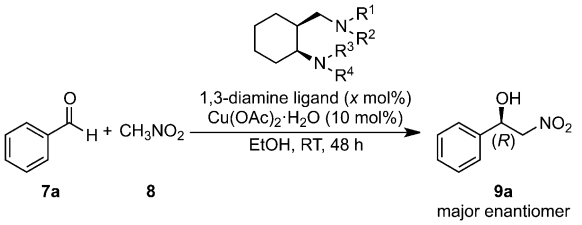
Scheme 1. Synthetic routes to the chiral 1,3-diamine ligands **2**–**4**. Reagents and conditions: a) $ClCO_2Et$, triethylamine (TEA), dry THF or dry CH_2Cl_2, 0 °C to RT; b) add R^1R^2NH, RT; c) $LiAlH_4$, dry THF or dry 1,4-dioxane, 0 °C to reflux temperature; d) H_2 (1 atm), cat. Pd/C, EtOH, 70 °C; e) **7**, 3 Å molecular sieves, dry CH_2Cl_2, RT or MeOH, reflux temperature; f) $NaBH_4$, EtOH or MeOH, RT; g) PhCOCl, TEA, dry THF, 0 °C to RT.

diamines were synthesized by simple methods in moderate to high yields. The synthesis and characterization of **2**, **4a–d**, **5a**, and **5d–f** were reported in a previous paper.[7c] Enantiopure (−)-**1** was prepared according to the literature procedure.[2] The reaction of (−)-**1** and ethyl chloroformate to form a mixed anhydride, followed by addition of the appropriate amine (or aqueous amine solution) furnished diamides **5a–f**. Subsequent reduction of the diamides with lithium aluminum hydride afforded the corresponding 1,3-diamines, **2**, **3a**, **3b**, and **4a–c**. Diamine **4a** was further converted to **4d** by hydrogenolysis of the *N*-benzyl group, catalyzed by Pd/C. The reductive amination of **4d** with a variety of aromatic aldehydes afforded diamines **4e–i**. Aminoamide **6** was formed by amidation of **4a** with benzoyl chloride, which was then reduced to yield **4j**.

Investigation of chiral 1,3-diamine ligands in the Cu-catalyzed enantioselective Henry reaction: With the enantiopure 1,3-diamine ligands **2**, **3a**, **3b**, and **4a–j** in hand, we examined their asymmetric induction abilities in the Cu-catalyzed enantioselective Henry reaction between benzaldehyde (**7a**) and nitromethane (**8**) in the presence of $Cu(OAc)_2{\cdot}H_2O$ in 99 % EtOH.[12]

The results are summarized in Table 1. When diamine **4a** was used as a chiral ligand, **9a** was obtained with a moder-

Table 1. Investigation of 1,3-diamine ligands in the catalytic enantioselective Henry reaction.



		1,3-Diamine ligand ([mol %])				Yield	*ee*
		R^1	R^2	R^3	R^4	[%][a]	[%][b,c]
1	**2** (12)	H	H	H	Bn	65	rac.[d]
2	**3a** (12)	H	Me	H	Bn	87	5
3	**3b** (12)	H	Bn	H	Bn	>99	rac.[d]
4	**4a** (12)	Me	Me	H	Bn	83	55
5	**4b** (12)	Et	Et	H	Bn	85	30
6	**4c** (12)	−(CH$_2$)$_4$−		H	Bn	>99	24
7	**4d** (12)	Me	Me	H	H	>99	19
8	**4e** (12)	Me	Me	H	4-ClC$_6$H$_4$CH$_2$	82	55
9	**4f** (12)	Me	Me	H	4-MeOC$_6$H$_4$CH$_2$	77	60
10	**4g** (12)	Me	Me	H	4-PhC$_6$H$_4$CH$_2$	77	53
11	**4h** (12)	Me	Me	H	1-naphthy−CH$_2$	73	63
12	**4i** (12)	Me	Me	H	2-naphthyl−CH$_2$	90	54
13	**4j** (12)	Me	Me	Bn	Bn	51	11
14	**4h** (10)	Me	Me	H	1-naphthyl−CH$_2$	66	69

[a] Yields based on **7a**. [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data. [d] Less than 5 % *ee*.

ate *ee* (Table 1, entry 4). In contrast, the product was obtained with negligible selectivity when ligands **2**, **3a**, or **3b** were used (Table 1, entries 1–3). Considering the relationship between the structures of these ligands and *ee* values of the obtained Henry adducts, it appears that a tertiary ^{prim}C-amino group in the chiral ligand results in improved enantioselectivity. Additionally, the use of **4d** and **4j** as chiral ligands afforded products with low *ee* values. Moreover, in

the case of **4j**, the yield of the product also decreased (Table 1, entries 7 and 13). Comparing these results with that reported in Table 1, entry 4, from the perspective of the chiral ligand structures and resultant enantioselectivities, it is evident that the ^{sec}C-amino group in the chiral ligands should be a secondary amino group to further increase the enantioselectivity of the reaction. The details of the relationships between the structures of the chiral ligands and the enantioselectivities are discussed later in terms the transition-state model (see below, Figure 1). A subsequent investigation of the substituents on the tertiary ^{prim}C-amino group (Table 1, entries 4–6) and secondary ^{sec}C-amino group (Table 1, entries 8–13) revealed that 1,3-diamine **4h** was the most effective chiral ligand for the enantioselective Cu-catalyzed Henry reaction (Table 1, entry 11). Reducing the loading amount of **4h** from 12 to 10 mol% improved the *ee* of the Henry adduct (Table 1, entry 14). This result is probably due to the suppression of a non-enantioselective reaction pathway catalyzed by an excess amount of free diamine **4h**. From these results, it was demonstrated that **4h**, which features (*N*,*N*-dimethylamino)methyl and *N*′-(1-naphthylmethyl)amino groups at the 1,2-*cis* positions of the cyclohexane ring, is the optimal chiral ligand for this reaction.

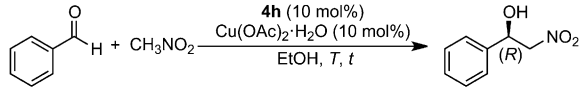
Verification and control of the retro-Henry reaction in the catalytic enantioselective Henry reaction: Although it was determined that 1,3-diamine **4h** is the optimal chiral ligand for the enantioselective Henry reaction, the enantioselectivity was still not very high. According to Nagasawa, the *ee* of the Henry adduct can gradually decrease as a result of a retro-Henry reaction.[13] To investigate the influence of the retro-Henry reaction under the above reaction conditions, time-course studies of the reaction were carried out at room temperature. The *ee* values of the Henry adduct remained constant until 12 h, however, they gradually decreased as the reaction continued (Table 2, entry 1). This result indicates that the retro-Henry reaction did proceed at RT and lowered the enantioselectivity of the reaction. Based on this result, we conducted the reaction at 50 °C to culminate the reaction within 12 h before the retro-Henry reaction begins. However, at 50 °C, the retro-Henry reaction was notably accelerated and the enantioselectivity decreased to 71% *ee* after only 1 h (Table 2, entry 2). Furthermore, the yield of the adduct also decreased as the reaction proceeded. This is because of the enhanced dehydration reaction of adduct **9a** at a higher temperature to afford β-nitrostyrene, which was confirmed by ^{1}H NMR spectroscopic analysis. Therefore, we conducted the reaction at 0 °C to prevent the retro-Henry reaction; it was found that the decrease in the *ee* of the adduct was suppressed until the reaction was finished and the selectivity was improved, although the reaction rate was drastically reduced (Table 2, entry 3).

Optimization of the reaction conditions: To improve the reaction rate without promoting the retro-Henry reaction, further optimization of the reaction conditions was carried out. First, the effects of an additional base were examined because the deprotonation of nitromethane to form the corresponding nitronate is a rate-determining step in the Henry reaction.[10] Triethylamine (TEA) was selected as a basic additive; the effect of loading amount was investigated and the results are summarized in Table 3. The addition of increasing amounts of TEA was found to drastically enhance the reaction, however, more than 5 mol% of TEA resulted in lower enantioselectivities (Table 3, entries 4–7) and an equimolar amount of TEA afforded the product with only 59% *ee* (Table 3, entry 7). This result is probably due to enhancement of the non-enantioselective reaction pathway mentioned above. The best result was obtained by the addition of TEA (2 mol%) as an external base (Table 3, entry 2).

Several organic bases were examined as additives and the results are shown in Table 4. Notably, weaker bases afforded the product in slightly higher enantioselectivities (Table 4, entries 5–7). Considering the pK_a value of nitromethane (10.2) and the pK_{aH} values of the corresponding conjugate acids, the bases with pK_{aH} values smaller than 10.2 afforded higher selectivities. This is because the weaker bases selectively deprotonate Cu-coordinated nitromethane, which is more acidic than free nitromethane, and suppression of the unselective reaction pathway results. The exceptionally lower yield of **9a** after the addition of pyridine is probably due to the higher coordination affinity of the latter for the copper ion (Table 4, entry 7). Judging from these results and the properties of the bases, DABCO was selected as the best external base to give **9a** in high yield and selectivity (Table 4, entry 5).

Finally, the solvent and the amount of the catalyst were optimized, as shown in Table 5. The *ee* values of the product **9a** were almost unchanged in the five solvents examined (Table 5, entries 1–5), however, ethanol resulted in a higher yield than any of the other solvents (Table 5, entry 1). This is probably because the lower solubility of $Cu(OAc)_2$ in the other solvents decreased the amount of avail-

Table 2. Verification and control of the retro-Henry reaction in the catalytic enantioselective Henry reaction (time-course studies at several reaction temperatures).

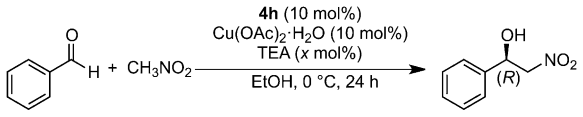


7a 8 9a major enantiomer

	T [°C]	Yield [%][a] (*ee* [%])[b,c] 1 h	3 h	6 h	12 h	24 h	48 h	72 h	96 h
1	RT	20 (84)	40 (85)	54 (84)	65 (83)	67 (76)	70 (71)	–	–
2	50	47 (71)	70 (50)	60 (42)	54 (42)	36 (40)	27 (23)	–	–
3	0	4 (83)	5 (89)	11 (89)	25 (90)	40 (88)	52 (90)	83 (90)	99 (90)

[a] Yields based on **7a**. [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data.

Table 3. Effect of TEA as an external base on the catalytic enantioselective Henry reaction.

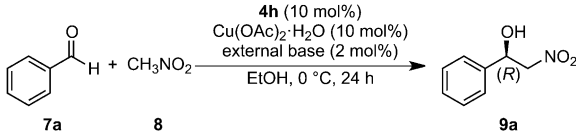


7a 8 9a major enantiomer

	TEA [mol%]	Yield [%][a]	*ee* [%][b,c]
1[d]	0	40	88
2	2	86	88
3	5	94	85
4	10	91	82
5	20	90	76
6	50	89	67
7	100	84	59

[a] Yields based on **7a**. [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data. [d] The result reported in Table 2, entry 3 at 24 h.

Table 4. Investigation of external bases in the catalytic enantioselective Henry reaction.



7a 8 9a major enantiomer

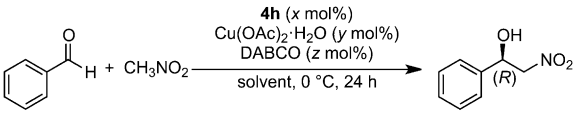
	External base	pK_{aH}[a]	Yield [%][b]	*ee* [%][c,d]
1	DBU	12.5	94	84
2	proton Sponge[e]	12.3	92	87
3	DIPEA	11.4	91	86
4	TEA	10.8	86	88
5	DABCO	8.8[f]	89	90
6	NMM	7.4	88	90
7	pyridine	5.2	53	90

[a] The pK_a value of the conjugate acid of the external base. [b] Yield based on **7a**. [c] Determined by chiral HPLC analysis. [d] Absolute configurations were determined by comparison of the HPLC elution order with the literature data. [e] 1,8-bis(dimethylamino)naphthalene. [f] The pK_a value of the monoprotonated species. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; DIPEA = *N*,*N*-diisopropylethylamine (Hünig's base); DABCO = 1,4-diazabicyclo[2.2.2]octane; NMM = *N*-methylmorpholine.

able active **4h**–[Cu(OAc)$_2$] complex. Next, the catalyst loading was investigated with ethanol as the solvent. When the amount of catalyst was decreased to 5 mol%, the yield of **9a** decreased but the selectivity remained high (Table 5, entries 6 and 7). On the other hand, increasing the amount of catalyst to 20 mol% afforded similar results to the initial conditions (Table 5, entries 8 and 9). In summary, from these investigations the optimized reaction conditions are: Cu(OAc)$_2$·H$_2$O (10 mol%), **4h** (10 mol%), DABCO (2 mol%), EtOH, 0 °C.

Proof of suppression of the retro-Henry reaction under the optimized conditions: To further confirm suppression of the retro-Henry reaction under the optimized conditions, the change in the enantiopurity of product **9a** was examined by

Table 5. Investigation of solvents and loading amount of pre-catalysts in the catalytic enantioselective Henry reaction.



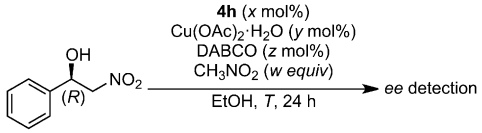
7a 8 9a major enantiomer

	Solvent	Cu(OAc)$_2$·H$_2$O/**4h**/DABCO [mol%]	Yield [%][a]	*ee* [%][b,c]
1	EtOH	10:10:2	89	90
2	MeOH	10:10:2	72	88
3	THF	10:10:2	56	87
4	toluene	10:10:2	21	87
5	CH_2Cl_2	10:10:2	17	86
6	EtOH	5:5:1	59	90
7	EtOH	5:5:2	65	90
8	EtOH	20:20:2	87	90
9	EtOH	20:20:4	92	90

[a] Yields based on **7a**. [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data.

exposing **9a** with a known enantiopurity (88% *ee*) to various conditions for 24 h (Table 6). Enantioenriched **9a** was dissolved in ethanol and the enantiopurity of recovered **9a** was unchanged, which revealed that no spontaneous retro-Henry reaction proceeded, even at room temperature (Table 6, entry 1). In the presence of Cu(OAc)$_2$·H$_2$O (10 mol%) or **4h** (10 mol%), the enantiopurity of recovered **9a** remained high, however, it was notably decreased in the presence of both Cu(OAc)$_2$·H$_2$O and **4h** (Table 6, entries 2–4). These results suggest that the retro-Henry reaction proceeded through interaction of **9a** with the Cu–diamine complex. The further addition of **8** (9 equiv) improved the enantiopurity of recovered **9a** to some extent (Table 6, entry 5). It is

Table 6. Verification of the suppression of the retro-Henry reaction under the optimized reaction conditions.[a]



9a major enantiomer

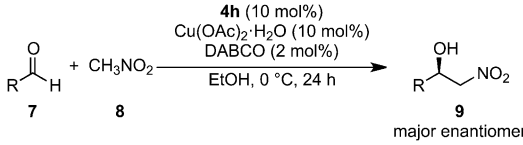
	Cu(OAc)$_2$·H$_2$O [mol%]	**4h** [mol%]	DABCO [mol%]	**8** [equiv]	*T* [°C]	*ee* of starting **9a** [%][b,c]	*ee* of recovered **9a** [%][b,c]
1	–	–	–	–	RT	88	87
2	10	–	–	–	RT	88	88
3	–	10	–	–	RT	88	85
4	10	10	–	–	RT	88	73
5	10	10	–	9	RT	88	80
6	10	10	–	9	0	88	87
7	10	10	2	9	0	88	87

[a] All reactions were performed on a 0.1 mmol scale in EtOH (0.3 mL). [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data.

plausible that coordination of an excess amount of CH_3NO_2 to the Cu–diamine complex prevents the interaction between **9a** and the Cu–diamine complex. Lowering the temperature to 0°C resulted in no change in the enantiopurity of recovered **9a** (Table 6, entry 6) and the inclusion of DABCO (2 mol%), which corresponds to the optimized conditions, afforded the same result (Table 6, entry 7). These experiments clearly show that racemization of **9a** through the retro-Henry reaction was successfully suppressed under the optimized conditions.

Scope and limitation of the substrates: A variety of aromatic and aliphatic aldehydes were tested as substrates under the optimized conditions to demonstrate the reaction versatility. The results are summarized in Table 7. The reactions of benzaldehydes substituted with electron-donating groups afforded the Henry adducts **9b**, **9c**, and **9g** in lower yields than **9a** (Table 7, entries 2, 3, and 7). Conversely, electron-withdrawing substituents made the yield higher (Table 7, entries 4–6). Although the electronic properties of the substituents on the aromatic ring affected the yield, they had little influence on the enantioselectivity. Next, the steric effect of the aldehydes was investigated with positional isomers of tolualdehyde (Table 7, entries 7–9). It was found that the further the methyl group was from the formyl group, the lower the chemical yield (i.e. *p*-tolualdehyde gave the lowest yield). In addition, a bulkier phenyl group at the *para* position of benzaldehyde lowered the yield further (Table 7, entry 10). All of the aldehydes showed comparable selectivities. The relationship between the yield and the position of the substituent is discussed later (see Scheme 4 and Figure 1 below). The reaction proceeded in a highly enantioselective fashion for other aromatic aldehydes (Table 7, entries 11–14) and an α,β-unsaturated aldehyde (Table 7, entry 15). Under the same conditions, the reactions of aliphatic aldehydes **7p–t** afforded **9p–t** in low yields (Table 7, entries 16–20). Such a drastic decrease in yield for the aliphatic aldehydes with an sp^3-hybridized α-carbon atom indicates that this reaction is very sensitive to the steric demand around the carbonyl carbon atom. The products from reaction of the α-branched aliphatic aldehydes, **9p** and **9q**, showed *ee* values as high as those of the aromatic analogues (Table 7, entries 16 and 17). On the other hand, the selectivities decreased for β-branched, γ-branched, and linear aliphatic substituents (Table 7, entries 18–20). Doubling the reaction time (48 h) for substrate **7s** gave **9s** in approximately double the yield (Table 7, entry 19) and no products other than **9s** were detected by analytical TLC during the reaction, which indicates that the low yields for the aliphatic aldehydes were not caused by undesirable side reactions but rather by their slower reaction rates. It was also revealed that, in all cases, the nucleophilic addition proceeded from the *Si* face of the aldehydes.

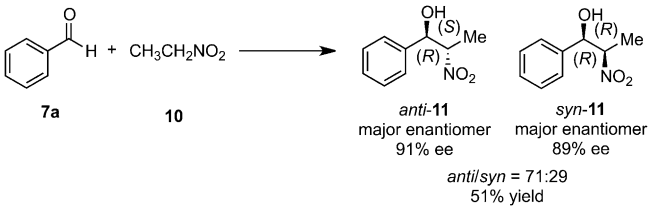
Table 7. Scope of aldehydes in the catalytic enantioselective Henry reaction.



	R	Aldehyde	Product	Yield [%][a]	*ee* [%][b]	Configuration[c]
1	Ph	**7a**	**9a**	89	90	*R*
2	4-$MeOC_6H_4$	**7b**	**9b**	61	91	*R*
3	3,4-$(MeO)_2C_6H_3$	**7c**	**9c**	60	88	*R*
4	4-ClC_6H_4	**7d**	**9d**	90	88	*R*
5	4-BrC_6H_4	**7e**	**9e**	97	87	*R*
6	4-$NO_2C_6H_4$	**7f**	**9f**	94	83	*R*
7	4-MeC_6H_4	**7g**	**9g**	67	91	*R*
8	3-MeC_6H_4	**7h**	**9h**	76	88	*R*
9	2-MeC_6H_4	**7i**	**9i**	85	87	*R*
10	4-PhC_6H_4	**7j**	**9j**	55	86	*R*
11	1-naphthyl	**7k**	**9k**	74	89	*R*
12	2-naphthyl	**7l**	**9l**	98	88	*R*
13	2-thienyl	**7m**	**9m**	63	84	*S*[d]
14	2-furyl	**7n**	**9n**	81	85	*S*[d]
15	(*E*)-PhCH=CH	**7o**	**9o**	71	84	*R*
16	Cy	**7p**	**9p**	26	86	*R*
17	*i*Pr	**7q**	**9q**	12	85	*R*
18	*i*Bu	**7r**	**9r**	32	71	*R*
19[e]	$PhCH_2CH_2$	**7s**	**9s**	18 (33)	79 (80)	*R*
20	Et	**7t**	**9t**	36	73	*R*

[a] Yields based on **7**. [b] Determined by chiral HPLC analysis. [c] Absolute configurations were determined by comparison of the HPLC elution order with the literature data. [d] Formal inversion of the stereodescriptor due to the Cahn–Ingold–Prelog notation. [e] The values in parentheses are the results after 48 h.

Catalytic diastereo- and enantioselective Henry reaction between nitroethane and benzaldehyde: The successful results obtained for the catalytic enantioselective Henry reaction promoted us to carry out a diastereo- and enantioselective Henry reaction between **7a** and nitroethane (**10**) under the optimized conditions (Scheme 2).[14]

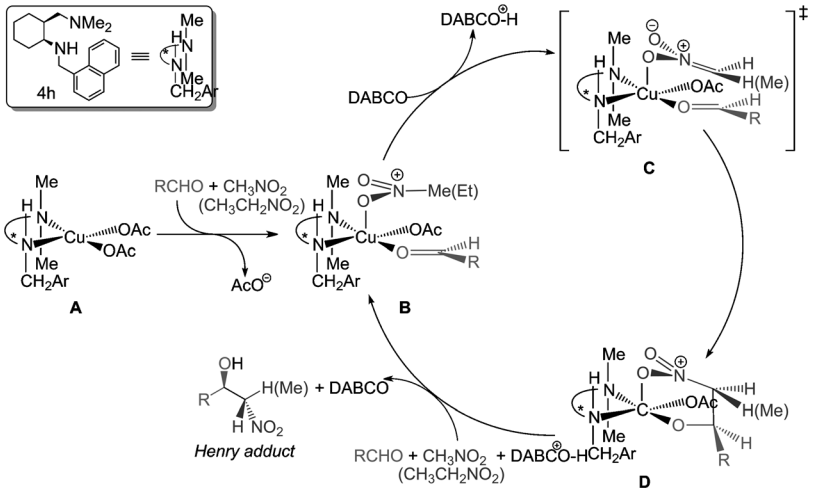


Scheme 2. Catalytic diastereo- and enantioselective Henry reaction between benzaldehyde and nitroethane. Reaction conditions: **4h** (10 mol%), $Cu(OAc)_2·H_2O$ (10 mol%), DABCO (2 mol%), EtOH, 0°C, 24 h.

The reaction gave the products **11** with moderate diastereoselectivity (*anti*/*syn* = 71:29) and high enantioselectivities (91 and 89% *ee* for the *anti*- and *syn*-isomers, respectively). The enantioselectivities were similar to the enantioselective reaction of **7a** with **8** to give (*R*)-**9a** (Table 7, entry 1) and the absolute configurations of the products were (1*R*,2*S*)-*anti*-**11** and (1*R*,2*R*)-*syn*-**11**; the 1*R* centers were commonly

produced by nucleophilic addition from the *Si* face of the carbonyl group of benzaldehyde. This result indicates that both reactions proceed through a similar transition state. The lower yield of **11** relative to **9a** can probably be attributed to the steric hindrance of **10** because its acidity is higher than that of **8** ($pK_a = 8.6$ and 10.2, respectively).

Catalytic cycle and the mechanism of the Henry reaction: Based on the above results and Jorgensen's report,[15] we proposed a catalytic cycle for this asymmetric Henry reaction (Scheme 3). First, complex **A** was formed from $Cu(OAc)_2$ and **4h**, followed by coordination of the nitroalkane and aldehyde to generate complex **B**. Deprotonation of the nitroalkane was promoted by DABCO and stereoselective bond formation was achieved through transition state **C** to give complex **D**. Finally, release of the adduct from complex **D** and coordination of another nitroalkane and aldehyde molecule regenerated complex **B** to complete the catalytic cycle.



Scheme 3. Proposed catalytic cycle for the Cu-catalyzed asymmetric Henry reaction.

To clarify the mechanism of the enantioselective Henry reaction, a detailed analysis of transition state **C** was carried out, based on the generally accepted model proposed by Evans (Figure 1a).[16] The octahedral Cu^{II} complex gives four strong coordination sites at the equatorial positions and two weak coordination sites at the apical positions, by Jahn–Teller distortion. The two highly coordinative nitrogen atoms of **4h** occupy two neighboring strong coordination sites. Both the aldehyde and nitroalkane reactants are efficiently activated by coordination to the equatorial and apical positions of the Cu complex, respectively. To explain the observed enantioselectivity, a schematic illustration of the transition state is represented in Figure 1b. The substituents on the two amino groups of **4h** sterically shield three sections around the reaction site (I, III, and IV) to leave only one space (II). The aldehyde molecule coordinates to the copper ion with the bulky R group oriented towards the

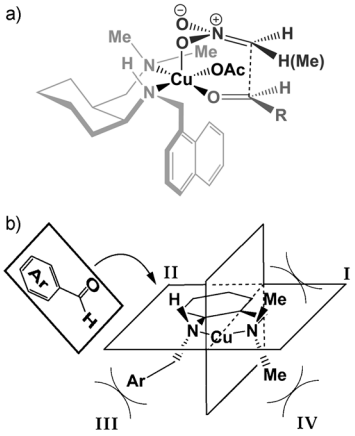


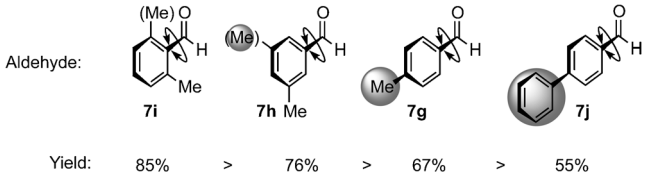
Figure 1. a) Proposed transition state for the catalytic asymmetric Henry reaction with **4h** as the diamine ligand. b) Schematic representation of the transition state. Nitronate and acetate are omitted for clarity.

less-crowded space II, whereas the corresponding nitroalkane approaches from the unoccupied upper side of the complex to permit nucleophilic attack from the *Si* face of the aldehyde. For the diastereoselective reaction, the *anti* isomer was obtained as the major product. This is probably because the terminal methyl group of coordinated **10** was oriented toward the vacant space II to avoid steric interactions. The moderate diastereoselectivity is probably attributed to the less control of the orientation of an approaching molecule of **10** because the methyl group is remote from the ligand and less sensitive to steric effects than **7a**, which results in moderate recognition between the terminal methyl group and hydrogen atom in coordinated **10**.

This model also explains the relationship between the structure of 1,3-diamines and their chiral induction ability. The 1,3-diamines with primary or secondary ^{prim}C-amino groups (**2**, **3a**, and **3b**) shield spaces I and IV less effectively, which reduces the control over the orientation of the aldehyde. The primary ^{sec}C-amino group (**4d**) shields spaces II and III less effectively, whereas the tertiary ^{sec}C-amino group (**4j**) shields both spaces II and III. In either case, it is difficult to control the direction of nitroalkane addition, which, in turn, results in lower enantioselectivities.

Finally, the difference in the product yields for the three positional isomers of tolualdehyde is discussed (Table 7, entries 7–9). As shown in Figure 1b, an aromatic aldehyde is positioned in space II to avoid steric repulsion between its aromatic ring and the Cu–diamine complex. The tilted alde-

hyde viewed from the upper side of Figure 1b is represented in Scheme 4. Considering the rotation of the aromatic ring around the C–C bond, the steric hindrance of the substitut-



Scheme 4. Relationship between the position of the benzaldehyde substituent and yield of the Henry adduct. The aldehydes are viewed from the upper side of space II in Figure 1b.

ed methyl group towards the approaching nitroalkane increases in the order *ortho* < *meta* < *para*. That is, the 4-methyl group always protrudes to the upper side of space II and, on the other hand, the 2-methyl group gives little steric hindrance regardless of the bond rotation. It appears that the 3-methyl group prevents the approach of the nitroalkane from the upper side, dependant on the rotation angle of the aromatic group. It is expected that 4-biphenylcarbaldehyde (**7j**) affords the largest steric demand. The decrease of the product yield reflects this steric effect, which prevents coordination of the nitroalkane to the metal ion.

Conclusion

We have developed structurally related enantiopure 1,3-diamines derived from (−)-*cis*-2-benzamidocyclohexanecarboxylic acid (**1**), and applied them as ligands for the catalytic enantioselective Henry reaction. It was found that the product enantioselectivity was controlled by the substituents on the two amino groups of the ligands. A gradual decrease in enantioselectivity caused by the retro-Henry reaction was successfully suppressed by conducting the reaction at 0 °C. Further optimization of the reaction conditions (external bases, solvents, and loading amounts of the precatalysts) improved the results and enantiomeric β-nitroalcohols were provided in high yields and enantioselectivities (up to 98% yield and 91% *ee*). It has been proven that high chiral induction was achieved by the enantiopure diamine ligand **4h** (derived from **1**) which is available without any external chiral source. The successful control of enantioselectivity by changing the substituents on the two amino groups will enable us to design other 1,3-functionalized chiral ligands derived from **1**. Their development and application to various catalytic asymmetric reactions are currently under investigation.

Experimental Section

General and materials: All ^{1}H and ^{13}C NMR (with complete proton decoupling) spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts (δ) of ^{1}H NMR spectra are given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard (δ = 0 ppm) in $CDCl_3$ solution and those of the ^{13}C NMR spectra are given in ppm relative to the residual solvent peak (δ = 77.16 ppm) in $CDCl_3$ solution. Multiplicity is described as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app. = apparent. The coupling constants (J) are given in hertz (Hz). IR spectra are reported in reciprocal centimeters (cm^{-1}). Mass spectra were recorded by using electrospray ionization mass spectrometry (ESI MS). Determination of the *ee* was conducted by means of chiral HPLC. Optical rotations were measured with a polarimeter. Melting points are uncorrected.

All commercially available substrates were used in reactions as received unless noted. Dry CH_2Cl_2 was prepared by distillation from CaH_2, and stored over 4 Å molecular sieves under N_2 atmosphere. Dry THF was freshly distilled from sodium and benzophenone (as a moisture indicator) under N_2 atmosphere. All liquid aldehydes were freshly distilled under reduced pressure and solid aldehydes were purified by silica gel column chromatography before use. (−)-*cis*-2-benzamidocyclohexanecarboxylic acid ((−)-**1**) was prepared according to the literature procedure.[2]

Analytical TLC was performed on precoated aluminum-backed silica gel 60 F_{254} plates and visualized by UV lamp (254 nm) and staining with phosphomolybdic acid or ninhydrin. Silica gel (B-5F, 45 μm) was used for preparative TLC (PTLC) and silica gel (Silica gel 60N, spherical, neutral, 100–210 μm) was used for column chromatography. The synthesis and characterization of compounds **2**, **4a–d**, **5a**, and **5d–f** have been reported in our previous paper.[7c]

Typical procedure A, for the synthesis of diamides 5a–f: At 0 °C, ethyl chloroformate (96.5 μL, 1.02 mmol) was added dropwise to a solution of (−)-**1** (251 mg, 1.01 mmol) and TEA (145 μL, 1.04 mmol) in dry CH_2Cl_2 (10 mL). After the addition was complete, the reaction mixture was allowed to warm to RT and stirred for 30 min. A 25% aqueous NH_3 solution (5.00 mL, 66.8 mmol) was added to the reaction mixture under vigorous stirring and stirring was continued for 15 h at RT. The reaction mixture was neutralized by addition of 6 M aqueous HCl solution and the solvents were removed under reduced pressure. The residue was diluted with EtOAc (20 mL) and the organic solution was washed with 1 M aqueous HCl solution (2 × 10 mL) and 1 M aqueous NaOH solution (2 × 10 mL), then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was dried in vacuo to give diamide **5a** (242 mg, 0.984 mmol, 97%) as a white powder. Diamide **5a** was used directly in the next reaction without further purification.

Compound 5b: Diamide **5b** (233 mg, 0.895 mmol, 90%) was obtained as a white powder by typical procedure A; (−)-**1** (247 mg, 1.00 mmol), TEA (140 μL, 1.01 mmol), ethyl chloroformate (95.0 μL, 1.00 mmol), 40% aqueous $MeNH_2$ solution (2.00 mL, 23.2 mmol). An analytical sample was prepared by silica gel PTLC (EtOAc/hexane = 1:1). M.p. 101–102 °C; $[\alpha]_D^{23} = -14.0$ (c = 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.78 (m, 2H), 7.62 (br d, J = 6.8 Hz, 1H), 7.50–7.46 (m, 1H), 7.44–7.40 (m, 1H), 6.20–6.00 (br, 1H), 4.26 (ddd, J_1 = 11.6 Hz, $J_2 = J_3$ = 4.8 Hz, 1H), 2.78 (d, J = 4.8 Hz, 3H), 2.70 (ddd, $J_1 = J_2 = J_3$ = 4.8 Hz, 1H), 2.16–2.10 (m, 1H), 1.95–1.90 (m, 1H), 1.80–1.74 (m, 1H), 1.69–1.67 (m, 2H), 1.55–1.47 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 166.9, 134.9, 131.4, 128.6, 127.1, 49.0, 44.7, 29.5, 27.6, 26.3, 23.4, 22.8 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3344, 3299, 2943, 2928, 2846, 1639, 1578, 1542, 1488, 1419, 1324, 1303, 1264, 1162, 691, 599 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{15}H_{20}N_2O_2Na$: 283.1417 $[C_{15}H_{20}N_2O_2+Na]^+$; found: 283.1424.

Compound 5c: Diamide **5c** (150 mg, 0.445 mmol, 87%) was obtained as a white powder by typical procedure A; (−)-**1** (127 mg, 0.513 mmol), TEA (71.5 μL, 0.514 mmol), ethyl chloroformate (49.0 μL, 0.517 mmol), $BnNH_2$ (56.0 μL, 0.514 mmol), dry THF. An analytical sample was prepared by silica gel PTLC (EtOAc/hexane = 1:1). M.p. 140–141 °C; $[\alpha]_D^{18}$ = +8.8 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.6 Hz, 1H), 7.46–7.40 (m, 3H), 6.40–6.20 (br, 1H), 4.47–4.37 (m, 2H), 4.34–4.28 (m, 1H), 2.78 (ddd, $J_1 = J_2 = J_3$ = 4.8 Hz, 1H), 2.21–2.15 (m, 1H), 1.97–1.93 (m, 1H), 1.84–1.80 (m, 1H), 1.79–1.69 (m, 2H), 1.60–1.49 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 166.9, 138.2, 134.8, 131.5, 128.8, 128.6, 127.7, 127.6, 127.1, 49.0, 44.8, 43.5, 29.4, 27.6, 23.5, 22.6 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3287, 2931, 1630,

1545, 1415, 1291, 729, 695 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{24}N_2O_2Na$: 359.1730 $[C_{21}H_{24}N_2O_2+Na]^+$; found: 359.1738.

Typical procedure B, for the synthesis of diamines 2, 3a, 3b, and 4a–c: At 0 °C under N_2 atmosphere, a solution of **5a** (235 mg, 0.956 mmol) in dry THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (181 mg, 4.78 mmol) in dry THF (5 mL). After the addition was complete, the reaction mixture was heated at reflux for 96 h. The reaction was quenched at 0 °C by addition of ion-exchanged water (180 μL), 15% aqueous NaOH solution (180 μL), and a second portion of ion-exchanged water (540 μL). The cloudy reaction mixture was filtered through Celite, the filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M aqueous HCl solution (20 mL). The aqueous solution was washed with EtOAc (2×10 mL) and basified (pH > 11) by addition of 6 M aqueous NaOH solution. The resulting cloudy aqueous solution was extracted with $CHCl_3$ (3×10 mL) and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford diamine **2** (160 mg, 0.733 mmol, 77%) as a white powder.

Compound 3a: Diamine **3a** (88.9 mg, 0.383 mmol, 44%) was obtained as a pale yellow oil by typical procedure B; **5b** (226 mg, 0.868 mmol), $LiAlH_4$ (166 mg, 4.18 mmol). $[\alpha]_D^{21} = +33.8$ ($c = 0.40$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.33$–7.27 (m, 4H), 7.23–7.20 (m, 1H), 3.82 (d, $J = 13.0$ Hz, 1H), 3.68 (d, $J = 13.0$ Hz, 1H), 2.77 (ddd, $J_1 = 6.5$ Hz, $J_2 = J_3 = 3.5$ Hz, 1H), 2.71 (dd, $J = 12.0$, 7.5 Hz, 1H), 2.42 (dd, $J = 12.0$, 6.5 Hz, 1H), 2.36 (s, 3H), 1.83–1.72 (m, 2H), 1.61–1.52 (m, 2H), 1.49–1.27 ppm (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 141.2$, 128.2, 128.0, 126.7, 55.1, 53.3, 51.2, 39.6, 36.8, 28.5, 26.7, 24.0, 22.1 ppm; IR (neat): $\tilde{\nu}_{max} = 3302$, 2926, 2852, 2791, 1495, 1453, 741, 699 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{15}H_{25}N_2$: 233.2012 $[C_{15}H_{24}N_2+H]^+$; found: 233.2015.

Compound 3b: Diamine **3b** (87.7 mg, 0.284 mmol, 64%) was obtained as a white solid by typical procedure B; **5c** (149 mg, 0.442 mmol), $LiAlH_4$ (85.1 mg, 2.24 mmol), dry 1,4-dioxane. M.p. 64–65 °C; $[\alpha]_D^{18} = +12.7$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.31$–7.20 (m, 10H), 3.82 (d, $J = 13.5$ Hz, 1H), 3.76 (d, $J = 13.5$ Hz, 1H), 3.73 (d, $J = 13.0$ Hz, 1H), 3.69 (d, $J = 13.0$ Hz, 1H), 2.84–2.79 (m, 2H), 2.52 (dd, $J = 11.5$, 6.0 Hz, 1H), 1.85–1.81 (m, 1H), 1.78–1.73 (m, 1H), 1.60–1.45 (m, 5H), 1.42–1.26 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 141.3$, 140.9, 128.4, 128.3, 128.2, 126.9, 55.4, 54.5, 51.5, 50.9, 39.9, 28.7, 27.0, 24.2, 22.2 ppm; IR (KBr): $\tilde{\nu}_{max} = 3270$, 2925, 2884, 2852, 1496, 1451, 1145, 1115, 1091, 746, 699 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{29}N_2$: 309.2325 $[C_{21}H_{28}N_2+H]^+$; found: 309.2328.

Typical procedure C for the synthesis of diamines 4e–i

*Method a (**4e**)*: *p*-Chlorobenzaldehyde (79.4 mg, 0.565 mmol) was added to a mixture of **4d** (79.5 mg, 0.509 mmol) and 3 Å molecular sieves (50 mg) in dry CH_2Cl_2 (5 mL) and the mixture was stirred for 24 h at RT. After completion of the reaction, the molecular sieves were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (5 mL), then $NaBH_4$ (53.6 mg, 1.42 mmol) was added to the solution under stirring. After stirring for 24 h, the reaction was quenched by addition of 1 M aqueous HCl solution (1 mL) and the solvents were removed under reduced pressure. The residue was dissolved in 1 M aqueous HCl solution (10 mL) and the aqueous solution was washed with EtOAc (2×10 mL) and basified (pH > 11) by addition of 6 M aqueous NaOH solution. The resulting cloudy aqueous solution was extracted with $CHCl_3$ (3×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to furnish diamine **4e** (76.6 mg, 0.273 mmol, 54%) as a pale yellow oil. $[\alpha]_D^{22} = +16.3$ ($c = 0.39$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 3.81 (d, $J = 13.4$ Hz, 1H), 3.69 (d, $J = 13.4$ Hz, 1H), 2.82 (ddd, $J_1 = 6.0$ Hz, $J_2 = J_3 = 3.2$ Hz, 1H), 2.38 (dd, $J = 12.4$, 7.2 Hz, 1H), 2.21–2.17 (m, 7H), 1.85–1.80 (m, 1H), 1.73–1.65 (m, 1H), 1.60–1.52 (m, 2H), 1.48–1.26 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.6$, 132.5, 129.6, 128.5, 61.0, 55.6, 50.7, 46.2, 37.4, 28.8, 26.9, 24.0, 22.3 ppm; IR (neat): $\tilde{\nu}_{max} = 2929$, 2854, 2816, 2765, 1491, 1458, 1091, 1032, 1015, 848, 813 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{26}ClN_2$: 281.1779 $[C_{16}H_{25}ClN_2+H]^+$; found: 281.1779.

*Method b (**4g**)*: *p*-Phenylbenzaldehyde (68.2 mg, 0.374 mmol) was added to a solution of **4d** (51.2 mg, 0.328 mmol) in MeOH (5 mL) and the reaction mixture was heated at reflux for 5 h. After completion of the reaction, the mixture was cooled to RT, then $NaBH_4$ (38.2 mg, 1.01 mmol) was added and the mixture was stirred for 24 h. Workup and purification were performed as described in method a to afford diamine **4g** (51.8 mg, 0.161 mmol, 49%) as a pale yellow oil. $[\alpha]_D^{23} = +11.9$ ($c = 0.49$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.6$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.44–7.40 (m, 4H), 7.32 (t, $J = 7.2$ Hz, 1H), 3.87 (d, $J = 13.2$ Hz, 1H), 3.76 (d, $J = 13.2$ Hz, 1H), 2.85 (ddd, $J_1 = 6.4$ Hz, $J_2 = J_3 = 3.2$ Hz, 1H), 2.36 (dd, $J = 12.2$, 6.4 Hz, 1H), 2.26–2.21 (m, 7H), 1.84–1.82 (m, 1H), 1.76–1.72 (m, 1H), 1.62–1.50 (m, 3H), 1.48–1.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.2$, 140.5, 140.5, 139.8, 128.8, 128.7, 127.2, 127.2, 60.9, 55.7, 51.3, 46.3, 37.7, 29.0, 26.8, 24.1, 22.4 ppm; IR (neat): $\tilde{\nu}_{max} = 3028$, 2927, 2853, 2815, 2763, 1488, 1457, 1032, 849, 761, 737, 698 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{22}H_{31}N_2$: 323.2482 $[C_{22}H_{30}N_2+H]^+$; found: 323.2485.

Compound 4f: Diamine **4f** (103 mg, 0.372 mmol, 74%) was obtained as a pale yellow oil by typical procedure C, method a; **4d** (78.9 mg, 0.505 mmol), *p*-methoxybenzaldehyde (134 mg, 0.986 mmol), $NaBH_4$ (170 mg, 4.49 mmol). $[\alpha]_D^{22} = +8.4$ ($c = 0.38$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 3.79 (s, 3H), 3.76 (d, $J = 12.8$ Hz, 1H), 3.65 (d, $J = 12.8$ Hz, 1H), 2.81 (ddd, $J_1 = 6.4$ Hz, $J_2 = J_3 = 3.2$ Hz, 1H), 2.33 (dd, $J = 12.2$, 6.6 Hz, 1H), 2.24–2.20 (m, 7H), 1.85–1.77 (m, 1H), 1.72–1.65 (m, 1H), 1.61–1.45 (m, 3H), 1.45–1.26 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.6$, 133.4, 129.3, 113.8, 60.8, 55.6, 55.4, 51.0, 46.3, 37.5, 29.0, 26.8, 24.0, 22.4 ppm; IR (neat): $\tilde{\nu}_{max} = 2930$, 2854, 2764, 1612, 1513, 1458, 1301, 1248, 1180, 1038, 823, 524 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{17}H_{29}N_2O$: 277.2274 $[C_{17}H_{28}N_2O+H]^+$; found: 277.2275.

Compound 4h: Diamine **4h** (66.2 mg, 0.223 mmol, 70%) was obtained as a pale yellow oil by typical procedure C, method b; **4d** (49.8 mg, 0.319 mmol), 1-naphthaldehyde (55.2 mg, 0.353 mmol), $NaBH_4$ (38.2 mg, 1.01 mmol). $[\alpha]_D^{23} = +17.2$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.52–7.38 (m, 4H), 4.25 (d, $J = 12.8$ Hz, 1H), 4.12 (d, $J = 12.8$ Hz, 1H), 2.96 (ddd, $J_1 = 6.0$ Hz, $J_2 = J_3 = 3.2$ Hz, 1H), 2.33 (dd, $J = 12.2$, 7.0 Hz, 1H), 2.17 (s, 6H), 2.13 (dd, $J = 12.4$, 7.6 Hz, 1H), 1.83–1.81 (m, 2H), 1.64–1.55 (m, 3H), 1.50–1.31 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.0$, 133.9, 132.2, 128.6, 127.7, 126.2, 125.9, 125.6, 125.5, 124.4, 61.1, 56.2, 50.0, 46.3, 38.1, 29.1, 26.7, 24.4, 22.2 ppm; IR (neat): $\tilde{\nu}_{max} = 3045$, 2927, 2853, 2815, 2763, 1457, 794, 777 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{29}N_2$: 297.2325 $[C_{20}H_{28}N_2+H]^+$; found: 297.2323.

Compound 4i: Diamine **4i** (58.6 mg, 0.198 mmol, 62%) was obtained as a pale yellow oil by typical procedure C, method b; **4d** (49.8 mg, 0.319 mmol), 2-naphthaldehyde (54.7 mg, 0.350 mmol), $NaBH_4$ (38.2 mg, 1.01 mmol). $[\alpha]_D^{23} = +13.7$ ($c = 0.73$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$–7.78 (m, 4H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.46–7.40 (m, 2H), 3.98 (d, $J = 13.4$ Hz, 1H), 3.87 (d, $J = 13.4$ Hz, 1H), 2.85 (ddd, $J_1 = 6.0$ Hz, $J_2 = J_3 = 3.0$ Hz, 1H), 2.36 (dd, $J = 12.2$, 6.6 Hz, 1H), 2.26–2.21 (m, 7H), 1.84–1.82 (m, 1H), 1.75–1.71 (m, 1H), 1.62–1.48 (m, 3H), 1.45–1.30 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.8$, 133.5, 132.7, 127.9, 127.7, 127.7, 126.9, 126.4, 126.0, 125.5, 60.9, 55.5, 51.6, 46.3, 37.5, 28.9, 26.8, 24.1, 22.3 ppm; IR (neat): $\tilde{\nu}_{max} = 3053$, 2928, 2854, 2816, 2765, 1458, 1032, 853, 818, 753 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{29}N_2$: 297.2325 $[C_{20}H_{28}N_2+H]^+$; found: 297.2328.

Compound 6: At 0 °C, benzoyl chloride (105 μL, 0.908 mmol) was added to a solution of **4a** (199 mg, 0.806 mmol) and TEA (125 μL, 0.898 mmol) in dry THF (5 mL). The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction was quenched by addition of ion-exchanged water (1 mL) and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and the organic solution was washed with 1 M aqueous NaOH solution (2×10 mL) and 1 M aqueous HCl solution (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel PTLC (EtOAc) to give aminoamide **6** (283 mg, 0.806 mmol, >99%) as a colorless viscous liquid. $[\alpha]_D^{23} = -137.7$ ($c = 0.42$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$–7.00 (m, 10H), 4.80–4.55

(m, 1H), 4.50–4.21 (m, 1H), 2.65–2.60 (m, 1H), 2.55–2.05 (m, 8H), 2.01–1.80 (m, 1H), 1.80–1.65 (m, 2H), 1.57–1.55 (m, 2H), 1.51–1.40 (m, 1H), 1.30–1.25 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 139.9, 137.9, 129.0, 128.6, 128.4, 126.8, 126.2, 125.9, 60.0, 57.6, 51.1, 46.4, 34.4, 28.0, 26.4, 25.3, 20.2 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 2937, 2857, 2764, 1631, 1450, 1409, 755, 699 cm^{-1}; HRMS (ESI$^+$): *m*/*z* calcd for $C_{23}H_{30}N_2ONa$: 373.2250 $[C_{23}H_{30}N_2O+Na]^+$; found: 373.2256.

Compound 4j: At 0 °C under N_2 atmosphere, a solution of **6** (237 mg, 0.675 mmol) in dry THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (76.9 mg, 2.03 mmol) in dry THF (5 mL). After the addition was complete, the reaction mixture was heated at reflux for 24 h. The reaction was quenched at 0 °C by addition of ion-exchanged water (77.0 μL), 15% aqueous NaOH solution (77.0 μL), and a second portion of ion-exchanged water (230 μL), then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in 1 M aqueous HCl solution (20 mL). The aqueous solution was washed with EtOAc (2 × 10 mL) and basified (pH > 11) by addition of 6 M aqueous NaOH solution. The resulting cloudy aqueous layer was extracted with $CHCl_3$ (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford diamine **4j** (198 mg, 0.587 mmol, 87%) as a pale yellow oil. $[\alpha]_D^{22} = -37.2$ (*c* = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.2 Hz, 4H), 7.27 (dd, $J_1 = J_2 = 7.4$ Hz, 4H), 7.18 (t, *J* = 7.2 Hz, 2H), 3.76 (d, *J* = 14.4 Hz, 2H), 3.63 (d, *J* = 14.4 Hz, 2H), 2.72 (ddd, $J_1 = 12.0$ Hz, $J_2 = J_3 = 3.8$ Hz, 1H), 2.62 (dd, $J_1 = J_2 = 11.6$ Hz, 1H), 2.41 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.24 (s, 6H), 1.90 (app. d, *J* = 12.8 Hz, 1H), 1.74–1.65 (m, 2H), 1.39–1.11 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 128.5, 128.2, 126.6, 61.9, 56.6, 55.6, 46.3, 35.5, 27.7, 26.5, 25.6, 20.6 ppm; IR (neat): $\tilde{\nu}_{max}$ = 3084, 3061, 3026, 2931, 2855, 2814, 2762, 1494, 1454, 1260, 1030, 975, 854, 745, 698 cm^{-1}; HRMS (ESI$^+$): *m*/*z* calcd for $C_{23}H_{33}N_2$: 337.2638 $[C_{23}H_{32}N_2+H]^+$; found: 337.2639.

Typical procedure D, for the enantioselective Henry reaction between aldehydes and nitromethane: $Cu(OAc)_2{\cdot}H_2O$ (9.98 mg, 0.05 mmol, 10 mol%) was added to a solution of **4h** (14.8 mg, 0.05 mmol, 10 mol%) in EtOH (1 mL, 99% solvent grade) and the mixture was stirred for 1 h at RT, during which time the color of the solution turned from green to blue. A solution of aldehyde **7** (0.5 mmol) and DABCO (1.12 mg, 0.01 mmol, 2 mol%) in EtOH (0.5 mL, 99% solvent grade) was added to the blue solution and the reaction mixture was cooled to 0 °C over 15 min. CH_3NO_2 (**8**; 270 μL, 5 mmol) was added and the mixture was stirred for 24 h at 0 °C. After 24 h, the mixture was filtered through a silica gel column (10 cm^3) with EtOAc (50 mL) to remove the catalyst. The resulting colorless filtrate was concentrated under reduced pressure at < 30 °C (to avoid the dehydration reaction) and the residue was purified by silica gel PTLC (EtOAc/hexane) to give the corresponding enantioenriched β-nitroalcohol **9**. The diastereo- and enantioselective Henry reaction was performed in the same way, with benzaldehyde (**7a**) and nitroethane (**10**). The *ee* value of the nitroalcohol was determined by chiral HPLC analysis.[12a,14b,17]

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