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Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

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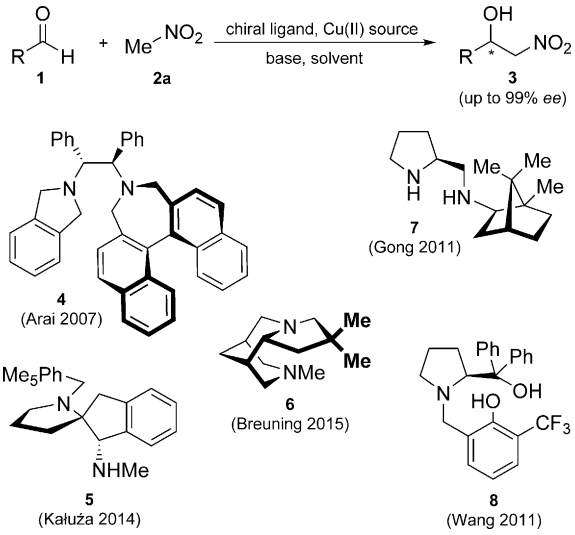
Dedicated to Prof. Dr. Dr. h.c. mult. Gerhard Bringmann on the occasion of his 65th birthday.

The development of a new catalytic system for enantioselective Henry reactions, which permits superb 99% *ee* with a broad variety of aldehydes, is presented. In-depth structure–selectivity investigations with 33 5-*cis*-substituted prolinamines, prepared from methyl Boc-L-pyroglutamate, revealed that an aromatic or sterically demanding aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while bulkier substituents at the nitrogen atoms diminish both, enantioselectivities and reaction rates. The scope of the prime catalyst was expanded to gram-scale and diastereomeric Henry reactions (up to 84:16 *dr*, 99% *ee*). In the course of mechanistic studies, it was proven that the resulting β-nitro alcohols are configurationally stable under the reaction conditions. In addition, competition experiments were used to determine the relative reaction rates of some of the prolinamine-modified catalysts.

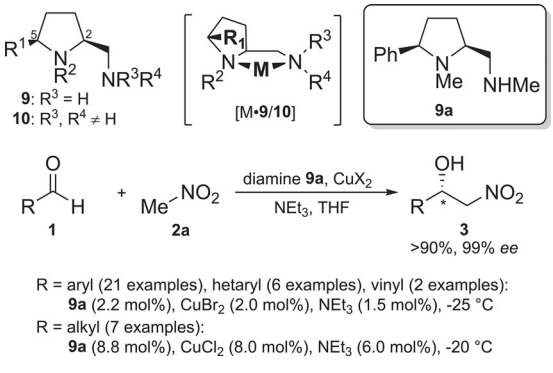
Introduction

The enantioselective Henry (nitro aldol) reaction[1] has drawn much attention as an asymmetric carbon–carbon bond forming reaction,[2] which triggered the development of many efficient catalytic systems based on heterobimetal[3] and transition-metal[4–6] complexes.[7] Chirally modified copper complexes received particular interest because of the wide structural variability of successful ligands, among them diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, and salen-type ligands.[5,6,8,9] Examples of diamines (**4**–**7**)[5a,j,p,8a] and ligands containing the proline motif (**7**, **8**)[5j,m] that permit 99% *ee* in the addition of nitromethane (**2a**) to at least one aldehyde substrate **1** are shown in Scheme 1. Notably, Gong's ligand **7**,[5j] which belongs to the most potent ones for this reaction, combines both structural features.

As part of our ongoing work on conformationally rigid diamines[8,10] and encouraged by the stereodiscriminating power of **7**, we became interested in prolinamines of general type **9** and **10** (Scheme 2),[11] which possess, as compared to other proline-derived ligands, an additional substituent R^1 in 5-*cis* position. Upon chelation of a metal M, a bicyclic complex [M·**9**/**10**] will be formed with the substituent R^1 shielding the upper left face, which might permit enhanced levels of stereocontrol in asymmetric transformations. This assumption was recently corroborated by copper-catalyzed, enantioselective Henry reac-



Scheme 1. The enantioselective, copper-catalyzed Henry reaction and a selection of diamine (**4**–**7**)[5a,j,p,8a] and proline-derived (**7**,**8**)[5j,m] ligands that give 99% *ee* with at least one aldehyde substrate.



Scheme 2. The proline-derived diamines **9** and **10**, their metal complexes [M·**9**/**10**], and enantioselective, copper-catalyzed Henry reactions in the presence of the chiral diamine **9a**.[9]

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tions of nitromethane (**2a**) with a series of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes **1**.[9,12] The $CuCl_2$ and $CuBr_2$ complexes of the simple prolinamine **9a** (R^1 = Ph; R^2, R^4 = Me; R^3 = H) provided the corresponding β-nitro alcohols **3** with superb, as yet unrivalled 99% *ee* in all cases (36 examples). Herein we present the development of the catalytic system CuX_2·**9a**, whose optimization included in-depth structure-enantioselectivity investigations with more than 30 diamines of types **9** and **10**. In addition, further studies on the substrate scope, some mechanistic investigations on the origin of the excellent enantioselectivities reached, and the preparation of the new diamines used in this study are described.

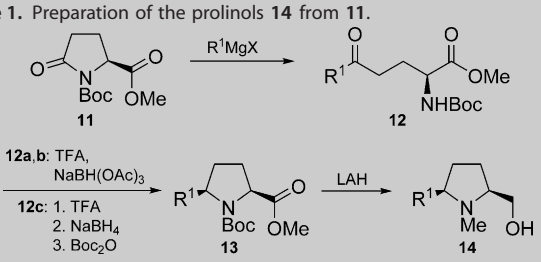
Results and Discussion

Synthesis of the prolinamines

A fast and variable access to prolinamines of type **9** and **10** was essential for the extensive ligand screening planned. We recently developed several routes to this class of diamines that all start from commercially available methyl Boc-L-pyroglutamate (**11**), but differ in the order of introduction of the substituents R^1–R^4, thus permitting a maximum of flexibility.[11] The new prolinamines used in this study were prepared with focus on a late-stage installation of the exocyclic amino function NR^3R^4, which is most easily achieved by hydroxy–amine exchange on the stage of the prolinol precursors **14**.

The substituent R^1 in 5-*cis* position was attached by chemoselective Grignard addition to the pyrrolidine carbonyl group in **11** and reductive cyclization of the resulting β-amino ketones **12** (Table 1). In accordance with earlier results,[11] the yield of the initial addition step strongly depended on the steric hindrance of the Grignard reagent. Good 78% were reached with 3,5-Me_2PhMgBr, whereas just mediocre 37% and 31% were obtained with the more bulky secondary alkyl Grignards *c*PentMgBr and *c*HexMgCl, respectively. The aliphatic β-amino ketones **12a** and **12b** were directly cyclized to the corresponding prolines **13a** and **13b** by using $NaBH(OAc)_3$ as the reductant, whereas ring closure of the aromatic derivative **12c** required a deprotection–reductive cyclization–reprotection sequence.[11] The *cis* diastereoselectivity was high in cyclizations (*dr* > 90:10). Final exhaustive reduction with LAH in refluxing THF afforded the prolinol intermediates **14a–c** in 91–95% yield.

Table 1. Preparation of the prolinols **14** from **11**.

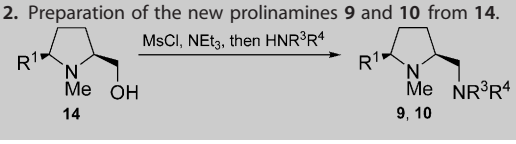


Entry	R^1	Yield of **12**[a] [%]	Yield of **13**[a] [%]	Yield of **14**[a] [%]
1	*c*Pent	37 (**12a**)	90 (**13a**)	92 (**14a**)
2	*c*Hex	31 (**12b**)	70 (**13b**)	95 (**14b**)
3	3,5-Me_2Ph	78 (**12c**)	59 (**13c**)[b]	91 (**14c**)

[a] Isolated yield. [b] 93:7 mixture of **13c** and its C5-epimer.

The alcohols **14a–c** thus prepared and the known derivatives **14d** (R^1 = Me)[11] and **14e** (R^1 = Ph)[9] were converted into the prolinamines **9** and **10** by mesylation of the hydroxy function and subsequent amination with an excess of the respective amine HNR^3R^4 (Table 2). The conversions of these reactions were good,[13] but the high polarity of the resulting diamines led to, in part, significant losses during column chromatographic purification, thus lowering the isolated yields to 50–76%.

Table 2. Preparation of the new prolinamines **9** and **10** from **14**.



Entry	**14**	R^1	**9**, **10**	NR^3R^4	Yield [%][a]
1	**a**	*c*Pent	**9b**	NHMe	54
2	**b**	*c*Hex	**9c**	NHMe	56
3	**c**	3,5-Me_2Ph	**9d**	NHMe	76
4[b]	**d**	Me	**9e**	NHMe	52[c]
5[d]	**e**	Ph	**9f**	NHAc	78[c]
6[d]	**e**	Ph	**9g**	NHMs	80[c]
7	**e**	Ph	**9h**	$NH(CH_2)_2OH$	50
8	**e**	Ph	**9i**	$NH(CH_2)_2OMe$	73
9	**a**	*c*Pent	**10a**	NMe_2	57
10	**b**	*c*Hex	**10b**	NMe_2	57
11	**c**	3,5-Me_2Ph	**10c**	NMe_2	73

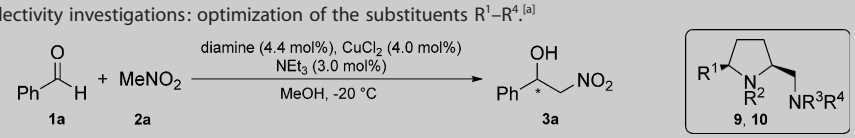
[a] Isolated yield. [b] Two-step sequence: 1. MsCl, NEt_3, then HN(Me)Bn; 2. H_2, $Pd(OH)_2$/C. [c] Yield over two steps. [d] Two-step sequence: 1. MsCl, NEt_3, then NH_3-MeOH (85%)[11] 2. for **9f**: Ac_2O, NEt_3; for **9g**: MsCl, NEt_3.

Notably, the direct preparation of **9e** (R^1 = Me, NR^3R^4 = NHMe, Table 2 entry 4) from **14d** by using the standard procedure, mesylation and amination with methylamine, failed. The pronounced volatility of the product made a removal of a higher boiling solvent such as MeOH, which was required as co-eluent in the chromatography of **9e**, practically impossible. We circumvented this problem by amination of **14d** with benzylmethylamine, giving the less polar and less volatile *N*-benzyl derivative of **9e**, which could be purified. Hydrogenolytic debenzylation under acidic conditions, basic extraction into Et_2O, and careful evaporation delivered **9e** in high purity and acceptable 52% yield over two steps. Finally, the amides **9f** and **9g** were synthesized by a two-step sequence (entries 5 and 6). Amination of **14e** with ammonia afforded the corresponding primary amine,[11] which was converted into **9f** and **9g** by N-acetylation and N-mesylation, respectively.

Optimization of the catalytic system

All enantioselective Henry reactions were performed under an argon atmosphere in a well-tempered cooling bath. In the case

Table 3. First structure–selectivity investigations: optimization of the substituents R^1–R^4.[a]



Entry	Diamine	R^1	R^2	NR^3R^4	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration[d]
1	**10d**	H	Me	NMe_2	24	99	71	*R*
2	**10e**	Me	Me	NMe_2	18	93	23	*S*
3	**10f**	Bn	Me	NMe_2	24	99	13	*S*
4	**10g**	*i*Pr	Me	NMe_2	40	99	84	*S*
5	**10a**	*c*Pent	Me	NMe_2	18	95	87	*S*
6	**10b**	*c*Hex	Me	NMe_2	18	93	88	*S*
7	**10h**	Ph	Me	NMe_2	20	95	84	*S*
8	**10i**	4-MeOPh	Me	NMe_2	24	99	83	*S*
9	**10j**	3,5-$(CF_3)_2$Ph	Me	NMe_2	24	93	88	*S*
10	**10c**	3,5-Me_2Ph	Me	NMe_2	18	92	90	*S*
11	**10k**	1-naphthyl	Me	NMe_2	24	72	87	*S*
12	**10l**	Ph	Me	N(Me)*t*Bu	48	0	–	–
13	**10m**	Ph	Me	pyrrolidinyl	40	99	94	*S*
14	**9a**	Ph	Me	NHMe	19	99	98	*S*
15	**9j**	Ph	Me	NHEt	48	70	98	*S*
16	**9k**	Ph	Me	NH*i*Pr	48	50	85	*S*
17	**9l**	Ph	Me	NH*t*Bu	48	25	30	*S*
18	**9m**	Ph	Me	NHPh	48	0	–	–
19	**9f**	Ph	Me	NHAc	24	0	–	–
20	**9g**	Ph	Me	NHMs	24	0	–	–
21	**9h**	Ph	Me	$NH(CH_2)_2OH$	40	35	84	*S*
22	**9i**	Ph	Me	$NH(CH_2)_2OMe$	40	34	95	*S*
23	**9n**	Ph	Me	NH_2	48	28	93	*S*
24	**9o**	Ph	H	NHMe	113	23	77	*S*
25	**9p**	Ph	Et	NHMe	40	99	98	*S*
26	**9q**	Ph	Bn	NHMe	40	32	90	*S*
27	**9r**	Ph	*i*Pr	NHMe	24	0	–	–

[a] Performed on a 1 mmol scale in MeOH (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase and rounded off to whole numbers. [d] Assigned by comparison with literature data.

of an important or unexpected result, the reaction was repeated at least twice. The enantiomeric excess of the products **3** was determined by HPLC on chiral phase with an accuracy of up to ±0.1 percentage points.

Ligand structure (I)

The initial ligand screening was done on the addition of nitromethane (**2a**) to benzaldehyde (**1a**) as the model reaction (Table 3), by using the following protocol: The chiral catalyst (4 mol%), prepared prior to use from $CuCl_2$ (4.0 mol%) and a slight excess of the chiral diamine **9** or **10** (4.4 mol%), and the aldehyde **1a** were dissolved in a 1:1 mixture of $MeNO_2$ (≈11 equivalents with respect to **1a**) and MeOH. After cooling to −20 °C, the reaction was started by addition of the ancillary base NEt_3 (3.0 mol%) and stirred for 18–113 h. Under these conditions, the most simple diamine, the 5-*cis*-unsubstituted prolinamine **10d** (R^1 = H), which furthermore possesses a pyrrolidine *N*-methyl and an exocyclic dimethylamino group (R^{2-4} = Me), provided the *R*-configured β-nitro alcohol (*R*)-**3a** in acceptable 71% *ee* and excellent 99% yield after 24 h (Table 3, entry 1). The level of enantioselection reached was quite remarkable, taking the low steric differentiation around the copper atom in the catalyst into account (see complex [M·**9**/**10**] in Scheme 2, with R^1 = H, R^{2-4} = Me).

In a first set of experiments we kept the methyl groups for R^{2-4} and varied the 5-*cis* substituent R^1 (entries 2–11), which was assumed to exert a strong effect on the chirality transfer. And indeed, its impact is clearly seen on the sense of the asymmetric induction. Compared to the reaction with **10d** (R^1 = H), the enantiomeric product, (*S*)-**3a**, was preferentially formed with all prolinamines carrying such a substituent ($R^1 \neq$ H). The level of stereoinduction rose with an increasing steric demand of R^1. Good enantioselectivities of 83–90% *ee* were reached with all diamines that possess an α-branched aliphatic or an aromatic substituent R^1 as in **10a–c,g–k** (entries 4–11). The good chirality transfers with the aliphatic diamines also exclude a decisive role of a π–π-stacking between R^1 and the aromatic substrate benzaldehyde (**1a**). Among the promising prolinamines, we chose to continue the ligand optimization with derivatives possessing a phenyl group as R^1, since these compounds are most easily accessible (for a reinvestigation on R^1 under optimized conditions, see Table 7).

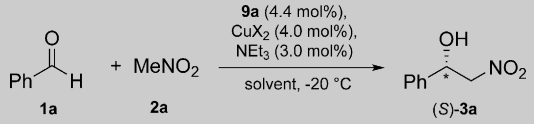
The influence of the substituents R^3 and R^4 at the exocyclic aminomethyl group was investigated next (Table 3, entries 12–23). Increasing the size of one of these substituents as in **10l** (NR^3R^4 = N(Me)*t*Bu) caused a complete breakdown in reactivity.

With pyrrolidinyl instead of NMe_2, improved 94% *ee* were reached. Another gain in stereocontrol was observed upon switching to the prolinamines **9**, which carry secondary aminomethyl groups NHR^4 (entries 14–22). Excellent 98% *ee* were reached with the diamines **9a** (NHMe) and **9j** (NHEt), whereas bulkier substituents R^4 as in **9k**,**l** (NH*i*Pr, NH*t*Bu) resulted in diminished asymmetric inductions. As a general trend, the catalytic activity significantly dropped with increasing steric demand of R^4, which is clear from the falling yields in the row **9a**, **9j**, **9k** to **9l**, even at prolonged reactions times. No product formation was observed with the anilinyl derivative **9m** (NHPh) and the amides **9f** (NHAc) and **9g** (NHMs). The potentially tridendate diamines **9h** ($NH(CH_2)_2OH$) and **9i** ($NH(CH_2)_2OMe$) and the primary diamine **9n** (NH_2) provided (*S*)-**3a** in acceptable 84–95% *ee*, but low 28–35% yield.

After having identified the NHMe group as the optimal NR^3R^4 function, we finally turned our attention to the substituent R^2 at the pyrrolidine nitrogen atom (entries 24–27). The same trend as with the NR^3R^4 group was observed: Excellent asymmetric inductions of 98% *ee* were achieved with small R^2 as in **9a** and **9p** (R^2 = Me, Et), while larger substituents R^2 as in **9q** and **9r** (R^2 = Bn, *i*Pr) or an NH function as in **9o** drastically reduced the activity of the catalyst.

In summary, the best result (98% *ee*, 99% yield) was achieved with the prolinamine **9a** possessing a phenyl substituent in 5-*cis* position, a pyrrolidine *N*-methyl group, and a 2-(methylaminomethyl) side chain. All further experiments were therefore performed with this diamine.

Table 4. Variation of the copper salt, solvent, and the solvent–$MeNO_2$ ratio.[a]



Entry	Cu Salt	Solvent	Solvent:$MeNO_2$	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	$CuCl_2$	MeOH	1:1	19	99	97.7
2	$CuCl_2$	EtOH	1:1	20	99	98.2
3	$CuCl_2$	THF	1:1	18	99	98.3
4	$CuCl_2$	$MeNO_2$	0:2	21	99	98.3
5	$CuBr_2$	MeOH	1:1	22	90	98.7
6	$CuBr_2$	EtOH	1:1	21	99	98.9
7	$CuBr_2$	THF	1:1	18	99	99.0
8	$CuBr_2$	$MeNO_2$	0:2	22	99	98.0
9[e]	$Cu(OAc)_2$[f]	MeOH	1:1	70	7	98.2
10[e]	$Cu(OAc)_2$[f]	EtOH	1:1	70	12	99.0
11[e]	$Cu(OAc)_2$[f]	THF	1:1	70	30	98.7
12[e]	$Cu(OAc)_2$[f]	$MeNO_2$	0:2	70	20	97.8
13	$Cu(OAc)_2$[f]	THF	1:1	17	88	90.8
14	$Cu(OAc)_2$[f]	MeOH	1:1	15	97	91.2
15	$CuBr_2$	THF	3:1	16	99	99.1
16	$CuBr_2$	THF	1:3	16	99	98.6
17[g]	$CuBr_2$	THF	1:1	16	99	99.0
18[h]	$CuBr_2$	THF	1:1	16	99	99.1

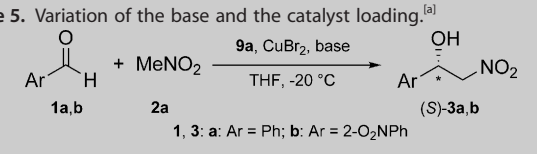
[a] Performed on a 1 mmol scale in the respective solvent–$MeNO_2$ mixture (1200 μL total, c(**1a**) = 0.83 M). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 3, entry 14. [e] No NEt_3 added. [f] Dihydrate. [g] Reaction in 600 μL solvent, c(**1a**) = 1.66 M. [h] Reaction in 2400 μL solvent, c(**1a**) = 0.42 M.

Reaction conditions

The copper source ($CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$) and the solvent (MeOH, EtOH, THF, and $MeNO_2$) were varied first (Table 4, entries 1–12). The influence of both parameters on the chirality transfer was marginal, which is clear from the excellent 97.7–99.0% *ee* obtained in all cases. A distinct difference in reactivity and, thus, in the yields, was observed between the copper halide and the copper acetate complexes. In the latter Henry reactions, no NEt_3 was added since the acetate freed from the catalyst upon coordination of the substrates can act as the base.[14] The low 7–30% yield obtained after 70 h are presumably a consequence of the weaker basicity of acetate, which slows down the deprotonation of nitromethane. Addition of NEt_3 (3 mol%, entries 13 and 14) accelerated the reaction (≥88% yield after 17 h), but resulted in lower stereocontrol (91% *ee*). A closer inspection of the enantioselectivities achieved with the $CuCl_2$ and $CuBr_2$ complexes revealed the latter ones as slightly superior (98.0–99.0% *ee* vs. 97.7–98.3% *ee*). All solvents examined permitted similar levels of chirality transfer, but the reaction with $CuBr_2$ in THF seemed to proceed somewhat faster. Since this will be beneficial for lower-temperature reactions (see Table 6), we decided to continue with this combination. Changes in the solvent–$MeNO_2$ ratio from 1:1 to 3:1 and 1:3 (entries 15 and 16) as well as in the concentration from 0.83 M to 1.66 M and 0.42 M (entries 17 and 18) had no noticeable effect on yield and enantioselectivity.

A short base screening (Table 5, entries 1–3) revealed that the steric demand of the base is not of importance, which is clear from the excellent 99% yield and 99.0% *ee* reached with both, NEt_3 and $EtNiPr_2$. A sufficient basicity, however, was re-

Table 5. Variation of the base and the catalyst loading.[a]



Entry	**1**, **3**	$CuBr_2$:**9a** : Base [mol%/mol%]	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	4.0:3.0	NEt_3	18	99	99.0
2	**a**	4.0:3.0	$EtNiPr_2$	20	99	99.0
3	**a**	4.0:3.0	pyridine	20	traces	–
4	**a**	4.0:3.0	–	16	0	–
5	**a**	4.0:6.0	NEt_3	21	99	98.9
6	**a**	4.0:1.0	NEt_3	16	13	99.0
7	**a**	2.0:1.5	NEt_3	18	99	99.1
8	**a**	1.0:0.75	NEt_3	17	48	99.2
9	**a**	0.50:0.375	NEt_3	41	7	98.5
10	**b**	4.0:3.0	NEt_3	17	99	99.0
11	**b**	2.0:1.5	NEt_3	17	99	98.9
12	**b**	1.0:0.75	NEt_3	17	64	99.0
13	**b**	0.50:0.375	NEt_3	42	13	94.4

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL), **9a** : $CuBr_2$ = 1.1:1. [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 4, entry 7.

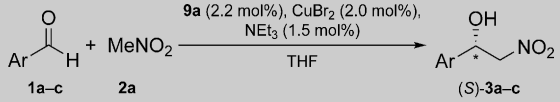
quired, because only traces of product were formed in the presence of pyridine. This observation is in good agreement with the slow reaction rates observed for the $Cu(OAc)_2$ complexes in which acetate served as the base (see Table 4, entries 9–12). As expected, there was no reaction without a base (Table 5, entry 4).

Changing the ratio catalyst–NEt_3 from standard 4:3 to 4:6 or 4:1 had little to no effect on the enantioselectivity (Table 5, entries 5 and 6). The yield, however, dropped to mere 13% if just 1 mol% of NEt_3 was used. The catalyst loading can be reduced to 2 mol% without any loss in yield and stereocontrol, if the catalyst–NEt_3 ratio is kept constant at 4:3 (entry 7). With just 1 mol% of catalyst and 0.75 mol% of base, the hitherto best enantioselection of 99.2% *ee* was achieved (entry 8). Although the 48% yield reached are just mediocre, the level of conversion is quite surprising as compared to the reaction with 4 mol% $CuBr_2$·**9a** and 1 mol% NEt_3 (see entry 6), which provided just 13% product within the same time frame, despite of the higher amounts of base and catalyst. Further lowering of the catalyst loading to 0.5 mol% resulted in a slight loss of asymmetric induction (98.5% *ee*), but a drastically reduced yield (7% after 41 h, entry 9).

At this point we checked that our optimization was not too substrate specific. As electron-deficient aldehydes might more readily undergo the uncatalyzed background reaction (vide infra), and, thus, require higher catalyst loadings, the latter experiments were repeated with 2-nitrobenzaldehyde (**1b**, entries 10–13). In the presence of 2 mol% catalyst, also this substrate provided the corresponding β-nitro alcohol (*S*)-**3b** in excellent 98.9% *ee* and 99% yield. Further reduction of the amount of catalyst to 0.5%, however, led to a significantly stronger depletion in enantioselectivity (94.4% *ee*), as compared to the analogous reaction with benzaldehyde (**1a**, see entry 9).

The last parameter, the temperature, was optimized with benzaldehyde (**1a**), 2-nitrobenzaldehyde (**1b**), and 2-methoxybenzaldehyde (**1c**) as the model substrates (Table 6). As expected, an increase in stereocontrol was observed by lowering the temperature to −30 °C, giving the β-nitro alcohols (*S*)-**3a–c** in excellent 99.1–99.5% *ee*. The reaction rates, however, markedly dropped below −25 °C, which is clear from the prolonged reaction times required and the incomplete conversion of the least reactive aldehyde **1c**. We therefore choose −25 °C as a good compromise between yield and chirality transfer.

Table 6. Optimization of the temperature.[a]



1, 3: **a**: Ar = Ph; **b**: Ar = 2-O_2NPh; **c**: Ar= 2-MeOPh

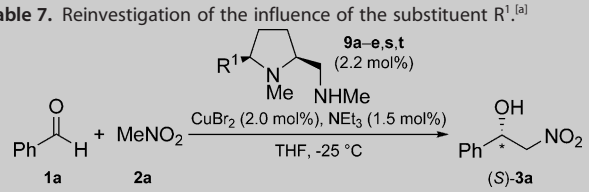
Entry	1, 3	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	−20	18	99	99.1
2[e]	**a**	−25	24	92	99.3
3	**a**	−30	66	99	99.5
4[f]	**b**	−20	17	99	98.9
5[e]	**b**	−25	20	97	99.0
6	**b**	−30	66	99	99.1
7	**c**	−20	40	99	99.2
8[e]	**c**	−25	42	97	99.5
9	**c**	−30	67	55	99.5

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 5, entry 7. [e] Data taken from Ref. [9]. [f] See Table 5, entry 11.

Ligand structure (II)

At this final stage we decided to reinvestigate the influence of the 5-*cis* substituent R^1, because there had been no clear preference for a particular group in the initial screening (see Table 3, entries 1–11). The re-evaluation was performed under the optimized reaction conditions with the secondary prolinamines **9b–e,s,t** carrying the better stereo-differentiating exocyclic NHMe group. As seen in Table 7, all derivatives of **9** with an aliphatic or aromatic substituent R^1 provided the β-nitro alcohol (*S*)-**3a** with high stereocontrol (≥96.0% *ee*), even the diamine **9e**, which possesses the small methyl group. The best stereoselection (99.3% *ee*) was achieved with the phenyl-substituted prolinamine **9a** (Table 7, entry 6), maybe as a result of the optimization process done on this compound. The surprising reversal in the sense of enantioselection, as it had been found with the tertiary diamine **10d** missing the substituent R^1 (see Table 3, entry 1), was not observed for the secondary prolinamine **9s**, which also afforded the *S*-configured product (*S*)-**3a**, albeit in low 25% *ee*.

Table 7. Reinvestigation of the influence of the substituent R^1.[a]



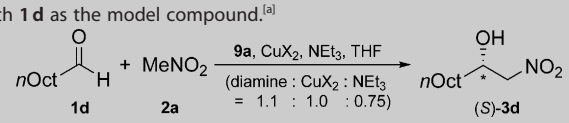
Entry	9	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**s**	H	18	95	25.2
2	**e**	Me	18	95	96.0
3	**t**	*i*Pr	18	99	96.9
4	**b**	*c*Pent	19	99	97.0
5	**c**	*c*Hex	18	99	97.7
6[d]	**a**	Ph	24	92	99.3
7	**d**	3,5-Me_2Ph	41	99	98.2

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 6, entry 2.

Aliphatic aldehydes

When applying the optimized conditions to the Henry reaction of the aliphatic aldehyde nonanal (**1d**), the β-nitro alcohol (*S*)-**3d** was produced in disappointing 53% yield and 94.5% *ee* (Table 8, entry 1). The yield and the level of enantioselection,

Table 8. Optimization of the reaction conditions for aliphatic aldehydes with **1 d** as the model compound.[a]



1d 2a (S)-3d

Entry	Cu Salt ([mol%])	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	$CuBr_2$ (2)	−25	40	53	94.5
2	$CuBr_2$ (4)	−25	60	75	96.2
3	$CuBr_2$ (8)	−25	24	90	97.0
4	$CuCl_2$ (8)	−25	21	87	98.2
5[d]	$CuCl_2$ (8)	−20	60	97	98.6
6	$CuCl_2$ (8)	−10	16	77	97.1

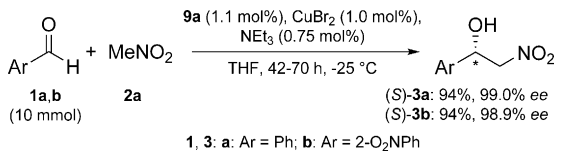
[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Data taken from ref. [9].

however, were raised by increasing the amount of catalyst to 8 mol% and the temperature to −20 °C, and by changing the copper source to $CuCl_2$. Under these conditions, the product (*S*)-**3 d** was obtained in excellent 97% yield and high 98.6% *ee*. One observation made in this context is noteworthy: The enantioselectivity of the reaction at −25 °C with $CuCl_2$·**9 a** as the catalyst was slightly lower than the one at −20 °C (entry 4 vs. 5). This unexpected result might have its origin in a beginning aggregation of the catalyst at −25 °C, as judged from the increasing turbidity of the reaction mixture, which would reduce the amount of active catalyst and, thus, favor the non-stereoselective background reaction. A similar effect was not observed for the complex $CuBr_2$·**9 a** in the reaction with aromatic aldehydes (see Table 6).

Under the optimized conditions for aromatic aldehydes [$CuBr_2$ (2 mol%), **9 a** (2.2 mol%), NEt_3 (1.5 mol%), THF/$MeNO_2$ = 1:1, −25 °C] and aliphatic aldehydes [$CuCl_2$ (8 mol%), **9 a** (8.8 mol%), NEt_3 (6.0 mol%), THF/$MeNO_2$ = 1:1, −20 °C], enantioselective Henry reactions with a broad variety of substrates were performed, providing the excellent results reported earlier.[9]

Gram-scale reactions

Finally, we decided to prove the practicability of our new catalytic system in gram-scale reactions (10 mmol aldehyde) with benzaldehyde (**1 a**) and 2-nitrobenzaldehyde (**1 b**) as the model substrates (Scheme 3). To further demonstrate its effectiveness, we cut, compared to the optimized procedure above, the amount of catalyst $CuBr_2$·**9 a** in half (1 mol%), which was the minimum amount required to preserve the excellent stereocontrol (see Table 5, entries 8 and 12). Even under these enforced conditions, the Henry products (*S*)-**3 a** and (*S*)-**3 b** were formed in high 94% yield each. The enantiomeric excess (99.0% and 98.9% *ee*, respectively) was as good as in the small-scale reactions.

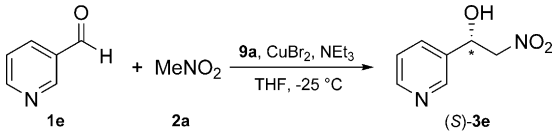


1a,b (10 mmol) 2a

Scheme 3. Gram-scale Henry reactions of **1 a** and **1 b**.

Extending the substrate scope

The good performance of the prolinamine **9 a** in Henry reactions prompted us to further study its scope and limitations. A tempting substrate is nicotinaldehyde (**1 e**, Scheme 4) because of its basic and nucleophilic pyridine moiety, which might promote the uncatalyzed background reaction[15] and, in addition, might competitively coordinate to the catalyst, thus reducing the amount of catalytically active species. And indeed, the Henry reaction of **1 e** in the presence of the catalyst $CuBr_2$·**9 a** (2 mol%) proceeded sluggishly and delivered (*S*)-**3 e** in unsatisfying 43% yield after 10 d and with low 82% *ee*. To accelerate the catalyzed reaction, we raised the amount of $CuBr_2$·**9 a** to 15 mol%. Under these conditions, (*S*)-**3 e** was obtained in improved 81% yield and acceptable 90% *ee* after 5 days.



1e 2a (S)-3e

9a (2.2 mol%), $CuBr_2$ (2.0 mol%), NEt_3 (1.5 mol%): 10 d, 43%, 82% *ee*
9a (16.5 mol%), $CuBr_2$ (15 mol%), NEt_3 (12 mol%): 5 d, 81%, 90% *ee*

Scheme 4. Henry reactions with basic nicotinaldehyde (**1 e**).

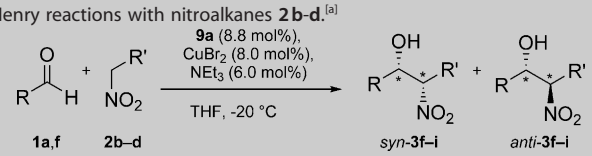
Diastereo- and enantioselective Henry reactions[16] with nitroalkanes **2** (R′ ≠ H) were first studied using benzaldehyde (**1 a**) as the substrate (Table 9). Owing to the lower reactivity of the nitroalkanes **2 b–d** (R′ = Me, Et, CH_2OTBS), the following reactions were performed at −20 °C and with 8 mol% catalyst $CuBr_2$·**9 a**. Whereas the *syn–anti* ratio in the nitroethane (**2 b**) derived product **3 f** was meager (60:40), acceptable ratios of 78:22 were obtained in **3 g** and **3 h** prepared from nitropropane (**2 c**) and sterically more demanding 2-TBSO-nitroethane (**2 d**), respectively. The enantioselectivities were always excellent (≥98% *ee*) in the major *syn* products and acceptable to good (82–93% *ee*) in the minor *anti* products. A further gain in selectivity was reached with the combination cyclohexanecarbaldehyde (**1 f**)-nitropropane (**2 c**), which provided the product **3 i** in a good 84:16 *syn-anti* ratio and with 99% *ee* in both diastereomers. Thus, the catalyst $CuBr_2$·**9 a** is also well suited for enantio- and diastereoselective Henry reactions.

Mechanistic investigations

Origin of enantioselection

Next we put our focus on the origin of the enantioselection. We wanted to prove that the high levels of stereocontrol solely arise from a kinetic differentiation in the *C,C*-coupling step and that processes involving product species, as, for example, an additional resolution on the stage of the primarily

Table 9. Enantio- and diastereoselective Henry reactions with nitroalkanes **2b-d**.[a]

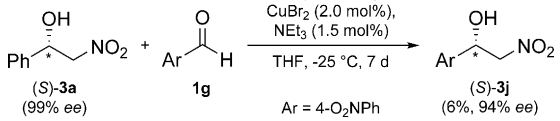


Entry	1	R	2	R′	*t* [d]	3	Yield [%][b]	*syn*:*anti*[c]	ee_{syn} [%][d]	ee_{anti} [%][d]
1	**a**	Ph	**b**	Me	4	**f**	99	60:40	99	93
2	**a**	Ph	**c**	Et	4	**g**	99	78:22	98	82
3	**a**	Ph	**d**	CH_2OTBS	7	**h**	98	78:22	99	93
4	**f**	cHex	**c**	Et	7	**i**	84	84:16	99	99

[a] Performed on a 1 mmol scale in THF (600 μL) and nitroalkane **2** (8 equiv). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC on chiral phase.

resulting, diastereomeric product–catalyst complexes, do not contribute.

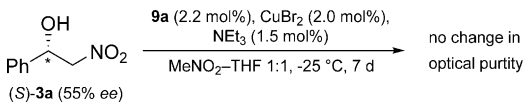
A necessary precondition for any dynamic process that influences the stereochemical outcome on the stage of the products is an equilibrium between the product species and the starting materials. The existence of such an equilibrium, although more or less fully shifted towards the products, was demonstrated by treatment of the β-nitro alcohol (*S*)-**3a** with 4-nitrobenzaldehyde (**1g**) under standard conditions (Scheme 5). The cross product **3j** observed in this reaction



Scheme 5. The formation of the cross product (*S*)-**3j** from (*S*)-**3a** and **1g** proves the reversibility of the Henry reaction under the standard reaction conditions.

must have been formed via a retro-Henry–Henry sequence. The rate of the back reaction, however, is pretty slow, which is clear from the low 6% yield obtained after 7 d. The good 94% *ee* indicates that at least the formation of (*S*)-**3j** must have been catalyzed by $CuBr_2$·**9a**.

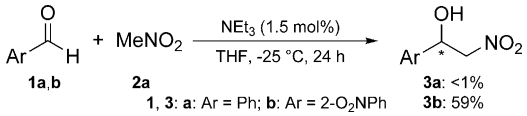
With the existence of the back reaction proven, the question remained whether this process induces any changes in the enantiopurity of the product. This cannot be the case because stirring of the scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) under standard conditions for 7 d did not noticeably alter its optical purity (Scheme 6). Thus, any scenario that affects the overall stereochemical outcome and involves product species can be safely excluded. The excellent stereodifferentiation observed must have its origin exclusively in the C,C-coupling step.



Scheme 6. The scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) is configurationally stable under standard Henry conditions.

Uncatalyzed background reaction

From the ≥98.9% *ee* reached with **1a** and **1b** in the presence of just 1 mol% of $CuBr_2$·**9a** (see Scheme 3) it follows that the catalyzed reaction must proceed at least 99 times faster than the non-stereoselective background reaction.[17] This is in good agreement with the observation that the latter one is virtually non-existing for benzaldehyde (**1a**: <1% conversion within 24 h, Scheme 7). In contrast to that, the rate of the background



Scheme 7. Uncatalyzed background reactions of **1a** and **1b**.

reaction is surprisingly high for the more electrophilic 2-nitrobenzaldehyde (**1b**, 59% conversion within 24 h). Although this does not noticeably affect the enantioselectivity of the catalyzed reaction with 1 mol% of $CuBr_2$·**9a**, it is most likely the main reason for the more pronounced loss in stereocontrol in the reaction of **1b** with 0.5 mol% catalyst, as compared to the analogous reaction of **1a** (98.5% vs. 94.4% *ee*, see Table 5, entry 9 vs. 13).

Relative reactivities of the catalysts derived from 9a and 10h

In parallel to the significantly enhanced stereocontrol reached with prolinamines of type **9** (secondary exocyclic amino group), as compared to those of type **10** (tertiary exocyclic amino group), we also observed a gain in reactivity. We therefore decided to measure the relative rates of reactions in the presence of our prime catalyst CuX_2·**9a** in comparison to those with CuX_2·**10h** (**10h**: dimethyl analogue of **9a**) under different conditions. Competition experiments, in which equimolar amounts of two chiral catalysts are used that deliver enantiomeric products, offer an experimentally simple method to do this, without the necessity of extensive kinetic studies. The relative rate constant k_{rel} can be calculated from the enantiomeric ratios of the single-catalyst and competition experiments using Equation (1):[18]

$$k_{rel} = \frac{k_{cat1}}{k_{cat2}} = \frac{(er_1 + 1)(er_{cp} - er_2)}{(er_2 + 1)(er_1 - er_{cp})} \quad (1)$$

er_1 = S/R ratio with catalyst 1
er_2 = S/R ratio with catalyst 2
er_{cp} = S/R ratio reached in the 1:1-competition experiment

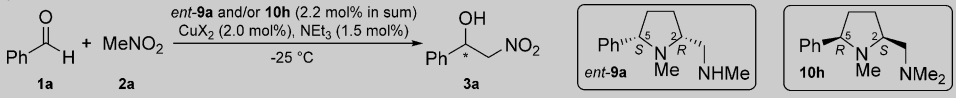
The required pseudo-enantiomeric catalyst *ent*-**9a** was prepared in analogy to **9a**, but starting from methyl Boc-D-pyroglutamate (*ent*-**11**).[9,11] The single-catalyst and competition experiments were done with the $CuBr_2$ and $CuCl_2$ catalysts derived from **10h** (2*S*,5*R*-configuration) and *ent*-**9a** (2*R*,5*S*-configuration) in THF and MeOH at −25 °C (Table 10). In THF and with $CuBr_2$·*ent*-**9a**, the product (*R*)-**3a** was obtained after 18 h in good 92% yield and excellent 99% *ee*, while the analogous reaction with $CuBr_2$·**10h** proceeded more slowly (58% yield after 43 h) and delivered the enantiomer (*S*)-**3a** with significantly lower stereocontrol (84% *ee*). The competition experiment (Table 10, entry 3) with equimolar amounts of both catalysts provided (*R*)-**3a** in 50% *ee*, clearly proving the higher catalytic activity of $CuBr_2$·*ent*-**9a**. By using Equation (1), a relative rate factor k_{rel} ($= k_{ent-9a} k_{10h}^{-1}$) of 2.73 in favor of $CuBr_2$·*ent*-**9a** was calculated. A similar k_{rel} value of 3.54 was observed for the corresponding chloro complexes $CuCl_2$·*ent*-**9a** and $CuCl_2$·**10h** (entries 4–6). MeOH as the solvent (entries 7–9) causes a general decrease in reactivity, which is clear from the prolonged reaction times required, which might be an effect of its better coordination abilities favoring a deactivation of intermediate catalyst species. In addition, the ratio k_{rel} of the reaction rates is higher: The catalytic system $CuCl_2$·*ent*-**9a** reacted 7.32 times faster than $CuCl_2$·**10h**. This furthermore underlines the existence of direct solvent-catalyst interactions—if this were not the case, the same k_{rel} values in THF and MeOH would be expected.

In the transition states of the Henry reactions with the secondary prolinamines **9**, there is the possibility of an additional hydrogen bridge between the NH function of the chiral ligand and the nitronate bound to the copper atom, which would further rigidify the system and, thus, explain the better stereocontrol observed.[9] This interaction should reduce the nucleophilicity of the nitronate and, in consequence, lower the activities of the catalysts CuX_2·**9**, as compared to CuX_2·**10**. Since the opposite effect was observed in the competition experiments, the existence of such a hydrogen bridge seems unlikely.[19] The higher enantioselectivities reached with secondary prolinamines **9** presumably originate from steric and conformational factors.

Conclusions

Several new, 5-*cis*-substituted prolinamines of type **9** and **10** were synthesized in 4–6 steps from methyl Boc-L-pyroglutamate (**11**). Their potential as the chiral ligands in enantioselective, copper-catalyzed Henry reactions was evaluated. In-depth structure–selectivity investigations with more than 30 diamines **9** and **10** revealed that an aromatic or sufficiently bulky aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while larger groups at the pyrrolidine nitrogen atom or at the exocyclic aminomethyl group cause an, in part, drastic loss in reactivity and enantioselectivity. The prolinamine **9a** (R^1 = Ph; R^2 = Me; NR^3R^4 = NHMe) was found to be the chiral ligand of choice. Optimization of other reaction parameters, such as temperature, solvent, concentration and catalyst loading, led to two highly efficient catalytic systems, $CuBr_2$·**9a** for aromatic aldehydes and $CuCl_2$·**9a** for aliphatic ones. With just 2 mol% of catalyst (8 mol% in the case of aliphatic aldehydes), the superb results reported earlier (99% *ee* with 36 aldehydes) were achieved.[9] In further studies we extended the scope of $CuBr_2$·**9a** to gram-scale and diastereoselective Henry reactions (up to 84:16 *dr*, 99% *ee*). It was also proven that the stereodifferentiation originates solely from the C,C-coupling step and that the product is configurationally stable under the reaction conditions. The uncatalyzed background reaction is virtually non-existing for benzaldehyde (**1a**), but remarkably high for the more electrophilic 2-nitrobenzaldehyde (**1b**). The relative reactivity of the catalysts derived from the prolinamines **9a** and **10h** was studied by competition experiments. The complexes with **9a** reacted up to 7.32 times faster, depending on the reaction conditions. This, however, does not explain the significant increase in enantioselectivity observed

Table 10. Single-catalyst and competition experiments with *ent*-**9a** and **10h** as the chiral diamines.[a]



Entry	Diamine	Cu Salt	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration	$k_{rel} = k_{ent-9a} k_{10h}^{-1}$[d]
1	*ent*-**9a**	$CuBr_2$	THF	18	92	99	*R*	
2	**10h**	$CuBr_2$	THF	43	58	84	*S*	
3	*ent*-**9a**/**10h** 1:1[e]	$CuBr_2$	THF	19	87	50	*R*	2.73
4	*ent*-**9a**	$CuCl_2$	THF	18	99	99	*R*	
5	**10h**	$CuCl_2$	THF	39	81	87	*S*	
6	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	THF	19	77	58	*R*	3.54
7	*ent*-**9a**	$CuCl_2$	MeOH	40	82	98	*R*	
8	**10h**	$CuCl_2$	MeOH	39	47	85	*S*	
9	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	MeOH	41	78	76	*R*	7.32

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Calculated using Equation (**1**). [e] The catalysts derived from *ent*-**9a** and **10h** were prepared separately and mixed shortly before use.

with **9a** (NR^3R^4 = NHMe), as compared to its dimethyl analogue **10h** (NR^3R^4 = NMe_2).

Experimental Section

All reactions with moisture-sensitive reagents were performed under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[20] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey–Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey–Nagel, particle size 40–63 μm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high-resolution mass spectra were recorded on a ThermoFisher Scientific Q-Exactive (Orbitrap) or a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess and the configuration of the β-nitro alcohols **3** were determined by HPLC analysis on chiral phase; the diastereomeric ratios were measured by ^{1}H NMR (for details see Supporting Information). Prolinols **14d**[11] and **14e**[9] and prolinamines **9a**,[9] **9j–m**,[12] **9n–r,t**,[11] **10e–k,m**[11] and **10l**[12] were prepared according to literature procedures. Diamines **10d** and **9s** are commercially available. The synthesis of the prolinamine **9b** and general procedures for the asymmetric Henry reactions are described here. For the preparation of all other new compounds, see Supporting information.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-cyclopentyl-5-oxopentanoate (12a)

A solution of the pyroglutamate **11** (10.0 g, 41.1 mmol) in anhydrous THF (120 mL) was treated at −40 °C with *c*PentMgBr, prepared from bromocyclopentane (5.95 mL, 8.27 g, 55.5 mmol) and Mg (1.49 mg, 61.1 mmol) in anhydrous THF (50 mL). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (20 mL) was added and THF was evaporated in vacuo. The resulting aqueous suspension was partitioned between sat. aq. NH_4Cl (200 mL) and CH_2Cl_2 (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 5:1) afforded amino ketone **12a** (4.75 g, 15.2 mmol, 37%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{31} = -18.6$ (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3375, 2952, 2871, 1745, 1706, 1513, 1366, 1146 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 1.56 (m, 2H, *c*Pent-H), 1.59–1.75 (m, 4H, *c*Pent-H), 1.79 (m, 2H, *c*Pent-H), 1.89 (m, 1H, 3-*H*H), 2.10 (m, 1H, 3-H*H*), 2.55 (m, 2H, 4-H_2), 2.84 (quint., J = 7.9 Hz, 1H, *c*Pent-H), 3.72 (s, 3H, OCH_3), 4.26 (m, 1H, 2-H), 5.09 ppm (d, J = 8.0 Hz, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1 (C-*c*Pent), 26.6 (C-3), 28.4 ($C(CH_3)_3$), 29.0, 29.1 (C-*c*Pent), 37.7 (C-4), 51.5 (C-*c*Pent), 52.5 (OCH_3), 53.1 (C-2), 80.1 ($C(CH_3)_3$), 155.6 (NCO_2), 173.1 (C-1), 212.2 ppm (C-5); HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{27}NO_5$ $[M+H]^+$ 314.19620, found 314.19637.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-cyclopentylpyrrolidine-1,2-dicarboxylate (13a)

$NaBH(OAc)_3$ (5.53 g, 26.1 mmol) was added at 0 °C to a solution of the amino ketone **12a** (4.20 g, 13.4 mmol) in EtOAc (60 mL). After 10 min, TFA (6.66 mL, 9.85 g, 86.4 mmol) was added dropwise and the reaction mixture was stirred overnight at RT. Sat. aq. $NaHCO_3$ (200 mL) was added and the reaction mixture was extracted with EtOAc (3×200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 15:1–4:1) provided diastereomerically pure **13a** (3.59 g, 12.1 mmol, 90%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{32} = -26.5$ (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2948, 2869, 1756, 1694, 1455, 1387, 1365, 1167, 1139, 1108 cm^{-1}; ^{1}H NMR* (500 MHz, $CDCl_3$): δ = 1.12 (m, 1H, *c*Pent-H), 1.36 (s, 5.4H, $C(CH_3)_3$), 1.42 (s, 3.6H, $C(CH_3)_3$), 1.49 (m, 3H, *c*Pent-H), 1.62 (m, 3H, *c*Pent-H), 1.78 (m, 3H, 4-H_2, *c*Pent-H), 1.86–2.13 (m, 2H, 3-*H*H, *c*Pent-H), 2.20 (m, 1H, 3-H*H*), 3.69 (s, 3H, OCH_3), 3.74 (m, 0.4H, 5-H), 3.86 (t, J = 7.9 Hz, 0.6H, 5-H), 4.17 (t, J = 8.6 Hz, 0.6H, 2-H), 4.29 ppm (t, J = 8.3 Hz, 0.4H, 2-H); ^{13}C NMR* (125 MHz, $CDCl_3$): δ = 25.0, 25.1, 25.3, 27.9 (C-*c*Pent), 28.3, 28.5 ($C(CH_3)_3$), 28.8, 28.9 (C-3, C-4), 29.5, 29.7, 30.3, 30.5, 44.6, 44.8 (C-*c*Pent), 51.9, 52.1 (OCH_3), 59.6, 60.1 (C-2), 62.4, 62.7 (C-5), 79.7, 80.0 ($C(CH_3)_3$), 154.4, 155.0 (1-CO_2), 174.1, 174.3 ppm (2-CO_2); HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{27}NO_4$ $[M+H]^+$ 298.20128, found 298.20134. * 60:40 mixture of rotamers.

(2*R*,5*S*)-2-Cyclopentyl-5-(hydroxymethyl)-1-methylpyrrolidine (14a)

$LiAlH_4$ (732 mg, 19.3 mmol) was added at 0 °C to a solution of the pyrrolidine ester **13a** (822 mg, 2.76 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 26 h. The resulting suspension was treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of Celite and the filter cake was rinsed with CH_2Cl_2-MeOH (9:1, 200 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2-MeOH-NH_3 (aq., 25%), 90:9:1) provided amino alcohol **14a** (467 mg, 2.55 mmol, 92%) as a colorless oil. R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); $[\alpha]_D^{31}$ = +22.5 (c = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3312, 2948, 2866, 2782, 1771, 1455, 1240, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (m, 2H, *c*Pent-H), 1.43–1.67 (m, 6H, 3-*H*H, 4-*H*H, cPent-H), 1.76 (m, 4H, 3-H*H*, 4-H*H*, *c*Pent-H), 2.02 (m, 1H, *c*Pent-H), 2.32 (s, 3H, 1-CH_3), 2.51 (dd, J = 13.6, 6.6 Hz, 1H, 2-H), 2.58 (m, 1H, 5-H), 2.80–3.25 (br s, 1H, OH), 3.36 (d, J = 10.6 Hz, 1H, 5-C*H*H), 3.63 ppm (dd, J = 10.6, 3.5 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4 (C-*c*Pent), 25.9, 26.3 (C-3, C-4), 26.9, 27.5, 30.7 (C-*c*Pent), 39.9 (1-CH_3), 43.5 (C-*c*Pent), 61.0 (5-CH_2), 67.6 (C-5), 70.7 ppm (C-2); HRMS (ESI, pos.) *m/z* calcd for $C_{11}H_{21}NO$ $[M + H]^+$ 184.16959, found 184.16908.

(2*R*,5*S*)-2-Cyclopentyl-1-methyl-5-((methylamino)methyl)pyrrolidine (9b)

MsCl (27.8 μL, 41.1 mg, 360 μmol) and NEt_3 (136 μL, 99.4 mg, 982 μmol) were added at 0 °C to a solution of the prolinol **14a** (60.0 mg, 327 μmol) in anhydrous CH_2Cl_2 (4 mL). After 3 d at RT, an excess of methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) was added and stirring was continued for 3 d. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3–95:4.5:0.5) delivered prolinamine **9b** (34.6 mg, 176 μmol, 54%) as a yellowish oil. R_f = 0.31 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1); $[\alpha]_D^{32}$ = +4.9 (c = 0.20 in

MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2951, 2865, 2780, 1450, 1209, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.30 (m, 2H, *c*Pent-H), 1.41–1.68 (m, 8H, 3-*H*H, 4-*H*H, *c*Pent-H, NH), 1.68–1.87 (m, 3H, 3-H*H*, 4-H*H*, *c*Pent-H), 1.97 (m, 1H, *c*Pent-H), 2.31 (s, 3H, 1-CH_3), 2.33 (m, 1H, 2-H), 2.45 (s, 3H, $NHCH_3$), 2.47 (m, 1H, 5-H), 2.53 (dd, *J* = 11.2, 6.0 Hz, 1H, 5-C*H*H), 2.64 ppm (dd, *J* = 11.2, 3.9 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.0 (C-*c*Pent), 27.0 (C-3), 27.92 (C-4), 27.93, 30.9 (C-*c*Pent), 37.2 ($NHCH_3$), 40.9 (1-CH_3), 43.8 (C-*c*Pent), 55.7 (5-CH_2), 67.0 (C-5), 71.3 ppm (C-2); HRMS (ESI, pos.) *m/z* calcd for $C_{12}H_{24}N_2$ $[M+H]^+$ 197.20123, found 197.20218.

General procedure for the enantioselective Henry reactions of aromatic aldehydes under optimized conditions

A solution of anhydrous $CuBr_2$ (66.7 mM in MeOH, 300 μL, 4.47 mg, 20.0 μmol, 2.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (36.7 mM in anhydrous THF, 600 μL, 4.49 mg, 22.0 μmol, 2.2 mol%), $MeNO_2$ (**2a**, 600 μL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution, which was cooled to −25 °C. NEt_3 (1.50 M in THF, 10.0 μL, 1.52 mg, 15.0 μmol, 1.5 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, hexanes–EtOAc 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

General procedure for the enantioselective Henry reactions of aliphatic aldehydes under optimized conditions

A solution of anhydrous $CuCl_2$ (267 mM in MeOH, 300 μL, 10.8 mg, 80.0 μmol, 8.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (147 mM in anhydrous THF, 600 μL, 18.0 mg, 88.0 μmol, 8.8 mol%), $MeNO_2$ (**2a**, 600 μL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to −20 °C. NEt_3 (1.50 M in THF, 40 μL, 6.08 mg, 60.0 μmol, 6.0 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, pentane–Et_2O 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

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Keywords: aldol reactions · amines · asymmetric catalysis · copper · ligand design

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[13] Rearrangements of **14** to β-amino piperidines (via the sequence mesylation-aziridinium formation-nucleophilic attack at C-2 under ring enlargement) did not occur to a significant degree.

[14] Enantioselective Henry reactions in the presence of chiral, $Cu(OAc)_2$-derived catalysts, a) without an ancillary base: Ref. 5 e,h,k,l,n–q; 6 d,h–k; 16 b,c,e,h; b) with an ancillary base: Ref. 5 a,c,g; 6 a,b; 16 d,i.

[15] Catalytic amounts of pyridine do only weakly promote the Henry reaction (see Table 5, entry 3). In the case of nicotinaldehyde (**1 e**), however, the pyridyl moiety is part of the substrate and, thus, present in a 50-fold excess with respect to the amount of catalyst (2 mol%).

[16] Selected recent examples of diastereo- and enantioselective Cu-catalyzed Henry reactions: a) H. Mei, X. Xiao, X. Zhao, B. Fang, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2015**, *80*, 2272 – 2280; b) T. Arai, A. Joko, K. Sato, *Synlett* **2015**, *26*, 209 – 214; c) A. Das, M. K. Choudhary, R. I. Kureshy, T. Roy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ChemPlusChem* **2014**, *79*, 1138 – 1146; d) L. Zhang, H. Wu, Z. Yang, X. Xu, H. Zhao, Y. Huang, Y. Wang, *Tetrahedron* **2013**, *69*, 10644 – 10652; e) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2013**, *19*, 16541 – 16544; f) J. D. White, S. Shaw, *Org. Lett.* **2012**, *14*, 6270 – 6273; g) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 12357 – 12362; h) R. Boobalan, G.-H. Lee, C. Chen, *Adv. Synth. Catal.* **2012**, *354*, 2511 – 2520; i) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger, W.-D. Woggon, *Adv. Synth. Catal.* **2011**, *353*, 1797 – 1806; j) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761 – 6765; k) T. Arai, Y. Taneda, Y. Endo, *Chem. Commun.* **2010**, *46*, 7936 – 7938; l) Ref. 5 d,f,g,i–k,n,p; 8 a,b.

[17] From $er_{obs} = (S_{cat} + S_{bg})/(R_{cat} + R_{bg}) \geq 99.5{:}0.5$ and under the assumption of a perfect catalyst ($S_{cat}/R_{cat} = 100{:}0$) follows $v_{cat}/v_{bg} \geq 99{:}1$. In the case of a nonperfect catalyst ($S_{cat}/R_{cat} < 100{:}0$), the ratio v_{cat}/v_{bg} would be even higher. obs = observed, cat = catalyzed reaction, bg = background reaction.

[18] This formula (deduction see Supporting Information) can be used under the following assumptions, which are—most probably—fulfilled by our reactions: (i) the rate laws for the for the two catalytic cycles are identical ($v_{cat1}/v_{cat2} \approx$ constant) and do not change in the course of the reaction, (ii) there is no interaction between the catalysts that unproportionally reduces the concentration of one catalyst (as, for example, the formation of a 2:1 oligomer), and (iii) the uncatalyzed background reaction is slow (here: 1% at maximum because of the excellent 99% *ee* reached) and, thus, does not measurably lower the enantiomeric excess.

[19] The existence of a hydrogen bridge cannot be fully ruled out, because the lower steric hindrance in **9** might induce an acceleration that overcompensates any deceleration induced by the hydrogen bounding.

[20] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals, 4th ed.*, Butterworth-Heinemann, Oxford, **2000**.

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