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PII: S0040-4020(18)31370-X

DOI: https://doi.org/10.1016/j.tet.2018.11.030

Reference: TET 29941

To appear in: *Tetrahedron*

Received Date: 13 August 2018

Revised Date: 8 November 2018

Accepted Date: 14 November 2018

Please cite this article as: Prause F, Wagner S, Breuning M, Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.11.030.

Graphical Abstract

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Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives

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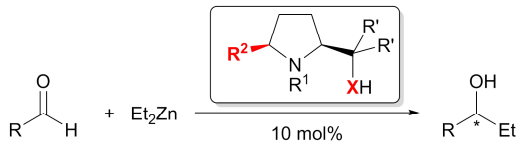

R^1 = Me; R^2 = Ph; R' = Ph; X = O: up to **99% ee** (***S***)
R^1 = Me; R^2 = *c*Pent; R' = H; X = NMe: up to **98% ee** (***R***)
R^1 = Me; R^2 = Ph; R' = H; X = NSO_2CF_3: up to **78% ee** (***S***)

Tetrahedron
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Enantioselective catalysis
Chiral ligands
Pyrrolidine
Diethylzinc
Asymmetric addition

ABSTRACT

5-*Cis*-substituted prolinols, prolinamines, and prolinamine sulfonamides proved to be efficient ligands for the enantioselective addition of diethylzinc to aldehydes, providing up to 99% ee. The sense of asymmetric induction can be controlled by the nature of the exocyclic functional group (CPh_2OH vs. CH_2NHR vs. CH_2NHSO_3R). The additional 5-*cis* substituent exerts a strong beneficial effect on the chirality transfer since it rigidifies the catalyst structure. The stereochemical outcome of the reactions is discussed in detail on the respective transition states.

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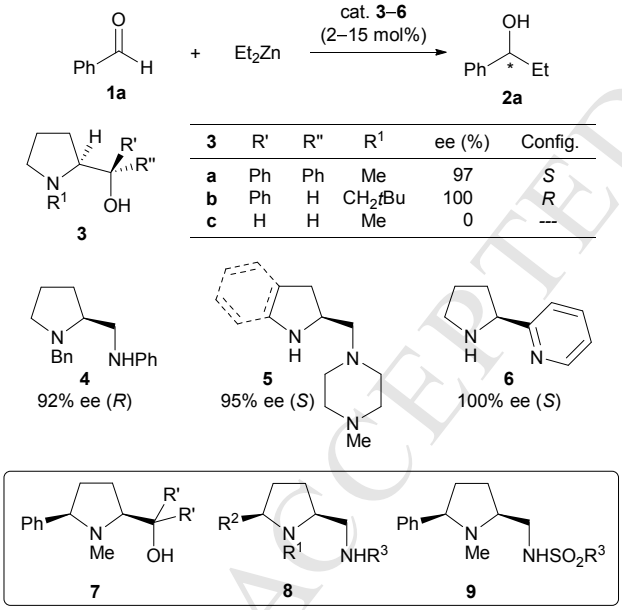
1. Introduction

The catalytic enantioselective addition of diorgano zinc reagents to aldehydes nowadays belongs to the standard repertoire of synthetic organic chemists.[1] Since the initial discovery by Oguni and Omi in 1984,[2] a plethora of chiral ligands permitting good to excellent enantioselectivities has been developed.[3] Among them are some proline derivatives, of which α,α-diphenyl-*N*-methyl-2-pyrrolidinemethanol (DPMPM, **3a**, Scheme 1), introduced by Soai and coworkers in 1987,[4] received particular attention.[5] Structure–enantioselectivity studies[4,6] on the addition of diethylzinc to benzaldehyde (**1a**) revealed that the geminal α,α-diphenyl group in **3a** is crucial for high asymmetric induction (97% ee) in favor of the *S*-configured product (*S*)-**2a**. Enantio-complementary (*R*)-**2a** can be obtained with virtually perfect stereocontrol (100% ee) in the presence of **3b**, which solely possesses an *erythro* phenyl group R' and the bulkier neopentyl group R^1 at the pyrrolidine nitrogen atom. The α-unsubstituted prolinol **3c** failed to transfer any stereo information (0% ee). More recently, it was discovered that the structurally closely related prolinamines **4**–**6** also permit good to excellent enantioselectivities (92–100% ee, *R* or *S*), even without an α-substituent.[7] The different sense of asymmetric induction is governed by the substituents at the nitrogen atoms and backbone, since all proline derivatives **3**–**6** possess the same *S*-configuration at the stereocenter in the pyrrolidine.

Recently, we had shown that bidentate, 2,5-*cis*-disubstituted pyrrolidines provide good to excellent asymmetric inductions when used as the chiral ligands in Cu-catalyzed Henry reactions and oxidative biaryl couplings or as the skeleton of tricyclic oxazaborolidines in the borane reduction of ketones.[8] In



3	R'	R''	R^1	ee (%)	Config.
a	Ph	Ph	Me	97	*S*
b	Ph	H	CH_2tBu	100	*R*
c	H	H	Me	0	---

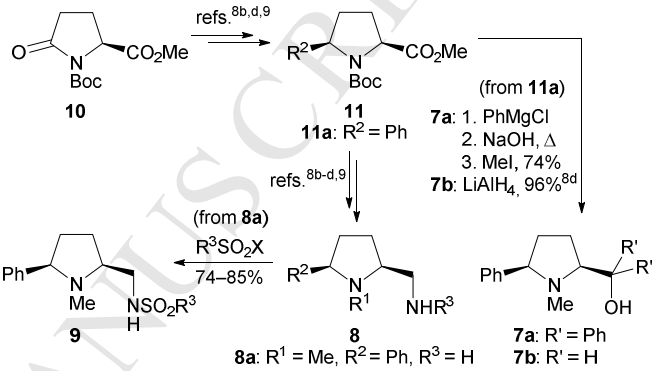
Scheme 1. Soai's prolinols **3**[4] and the prolinamines **4**–**6**,[7] all successfully used in the enantioselective addition of Et_2Zn to aldehydes (ee values refer to **1a** as the substrate), and the new 5-*cis*-substituted proline derivatives **7**–**9**.

continuation of these studies we decided to evaluate the prolinols **7** and prolinamines **8** and **9** in the enantioselective addition of Et_2Zn to aldehydes. We anticipated that the additional 5-*cis* substituent R^2 will be beneficial for the stereotransfer, which was confirmed by structure selectivity studies. A rationale for the observed trends and the reversals in the sense of asymmetric induction is given.

2. Results and discussion

2.1. Synthesis of the 5-*cis*-substituted proline derivatives

The proline derivatives **7**–**9** were prepared from methyl Boc-L-pyroglutamate (**10**) following procedures developed by us[9] and others[10,11] (Scheme 2). The 5-*cis* substituent R^2 was introduced by Grignard addition and subsequent reductive recyclization, which provided the esters **11** with good to high diastereoselectivities. Simple reduction of **11a** (R^2 = Ph) afforded the prolinol **7b** (96%),[8d] while the α,α-diphenyl derivative **7a** was synthesized by phenyl addition, *N*-deprotection, and *N*-methylation (74%). The known[8b–d,9] prolinamines **8** were accessed from **11** by Boc/R^1 exchange and conversion of the ester function into an amine. Finally, treatment of **8a** (R^1 = Me, R^2 = Ph, R^3 = H) with R^3SO_2Cl or $(R^3SO_2)_2O$ provided the new sulfonamides **9** in good 74–85% yield.



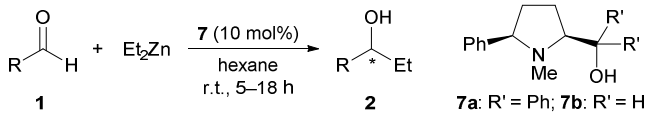
Scheme 2. Synthesis of the 5-*cis*-substituted proline derivatives **7**–**9**.[8b–d,9]

2.2. Enantioselective additions of diethylzinc to aldehydes

All enantioselective additions of Et_2Zn were carried out under standard conditions, by addition of the respective aldehyde to a mixture of the chiral ligand (2–10 mol%) and Et_2Zn (2 equiv.).

In a first set of experiments we wanted to demonstrate that the additional 5-*cis* substituent exerts a beneficial effect on the chirality transfer. Since Lüdtke and Correia[12] had recently shown that prolinol **7a**, which possesses the skeleton of **3a** plus a 5-*cis* phenyl group, permits excellent 95% ee in the arylation of *p*-tolualdehyde with phenylboronic acid, we decided to test **7a** as the chiral ligand (10 mol%) in the addition of Et_2Zn to aldehydes (Table 1). Good to excellent asymmetric inductions were reached with the model substrates benzaldehyde (**1a**), cyclohexyl carbaldehyde (**1b**), and hydrocinnamic aldehyde (**1c**). For **1a**, the amount of ligand **7a** was lowered to 2 mol% without any loss in chemical and optical yield. In terms of stereoselectivity, prolinol **7a** exceeded **3a** for **1a** (**7a**: 99% ee vs. **3a**: 97% ee[4]) and, significantly, for **1b** (**7a**: 96% ee vs. **3a**: 38% ee[4]), while **3a** was slightly better with **1c** (**7a**: 85% ee vs. **3a**: 92% ee[4]). Thus, there is indeed a beneficial effect of the additional 5-*cis* substituent, at least for **1a** and **1b**. The sense of asymmetric induction (*S*) with **7a** was identical to that of **3a**. Interestingly, the α,α-unsubstituted prolinol **7b** provided in the reaction with **1a** the enantio-complementary product (*R*)-**2a**, albeit with low 25% ee. The apparently slight *R*-preference inherent to the basic skeleton **7b** must have been fully overwritten in **7a** by the stereochemical steering of the α,α-diphenyl unit.

Table 1. Addition of Et_2Zn to aldehydes **1** in the presence of the prolinols **7**.[a]



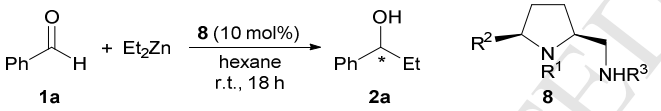
1 **2** **7a**: R' = Ph; **7b**: R' = H

Entry	Ligand	**1**, **2**	R	Yield (%)[b]	ee (%), Config.[b]
1	**7a**	**a**	Ph	98	99 (*S*)
2[c]	**7a**	**a**	Ph	99	99 (*S*)
3	**7a**	**b**	Cy	67	96 (*S*)
4	**7a**	**c**	$Ph(CH_2)_2$	90	85 (*S*)
5	**7b**	**a**	Ph	78	25 (*R*)

[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinol **7** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL).
[b] Isolated yield; ee and configuration determined by HPLC on chiral phase.
[c] Reaction with 2 mol% of catalyst **7a** in toluene/hexane (1:1) at 0 °C.

Next we put our focus on the prolinamines **8**, which are devoid of any α-substituent, but offer the advantage of another modifiable substituent R^3 at the exocyclic amino function. In search of the optimum ligand, this substituent R^3 as well as R^1 at the pyrrolidine nitrogen atom and the 5-*cis* substituent R^2 were varied. The addition of Et_2Zn to benzaldehyde (**1a**) in the presence of **8** (10 mol%) was used as the test reaction (Table 2). Prolinamine **8a** (R^1 = Me; R^2 = Ph, R^3 = H) carrying a primary exocyclic amino function provided the *R*-configured product (*R*)-**2a**, albeit with poor 12% ee. Significantly improved enantiocontrol (71% ee) was observed with diamine **8b** (R^3 = Me), which had been the ligand of choice in asymmetric Henry reactions done earlier.[8b,d] Further increase of the steric demand of R^3 (**8c**,**d**: R^3 = Et, *i*Pr) or variation

Table 2. Addition of Et_2Zn to benzaldehyde (**1a**) in the presence of the prolinamines **8**: Catalyst optimization.[a]



1a **2a** **8**

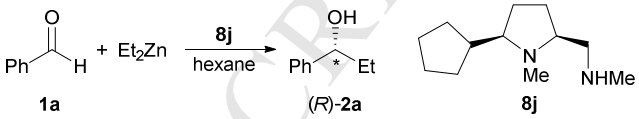
Entry	**8**	R^1	R^2	R^3	Yield (%)[b]	ee (%), Config.[b]
1	**a**	Me	Ph	H	69	12 (*R*)
2	**b**	Me	Ph	Me	81	71 (*R*)
3	**c**	Me	Ph	Et	91	4 (*R*)
4	**d**	Me	Ph	*i*Pr	91	20 (*S*)
5	**e**	H	Ph	Me	63	11 (*R*)
6	**f**	Et	Ph	Me	59	12 (*R*)
7	**g**	*i*Pr	Ph	Me	31	0 (–)
8	**h**	Bn	Ph	Me	35	4 (*S*)
9	**i**	Me	H	Me	68	45 (*R*)
10	**j**	Me	*c*Pent	Me	88	84 (*R*)
11	**k**	Me	Cy	Me	82	77 (*R*)
12	**l**	Me	Bn	Me	75	70 (*R*)
13	**m**	Me	3,5-Me_2Ph	Me	76	61 (*R*)

[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinamine **8** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL).
[b] Isolated yield; ee and configuration determined by HPLC on chiral phase.

of R^1 as in **8e–h** (R^1 = H, Et, *i*Pr, Bn) caused a drastic loss in stereoselectivity. Altering the 5-*cis* substituent R^2 (derivatives **8i–m**) revealed that a cyclopentyl group is most suited; prolinamine **8j** as the catalyst delivered (*R*)-**2a** in 88% yield and improved 84% ee. The necessity of a 5-*cis* substituent is obvious from the unsubstituted derivative **8i** (R^2 = H), which gave just low 45% ee. Finally, it must be noted that the sense of asymmetric induction switched from *R* to *S* when, as in **8d** and **8h**, a bulky substituent R^1 or R^3 was introduced.

The reaction conditions were optimized using prolinamine **8j** (Table 3). It was found that hexane as the solvent is slightly superior to toluene/hexane mixtures and that 20 °C are a good compromise between asymmetric induction and reaction rate. Lowering the catalyst loading from 10 to 5 or 2 mol% resulted in a loss of stereocontrol. The best yield (90%) and enantioselection (90% ee, *R*) was reached when the reaction was conducted at a concentration of *c*(**1a**) = 0.125 M.

Table 3. Optimization of the reaction conditions in the presence of **8j**.[a]



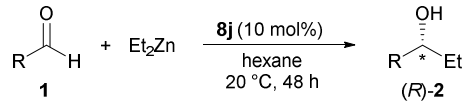
1a (*R*)-**2a** **8j**

Entry	T (°C)	**8j** (mol%)	t (h)	Yield (%)[b]	ee (%)[b]
1[c]	r.t.	10	16	91	82
2	r.t	10	18	88	84
3	30	10	21	82	84
4	20	10	16	85	88
5	10	10	16	73	88
6	0	10	72	65	90
7	20	5	72	82	87
8	20	2	72	84	82
9[d]	20	10	17	85	84
10[e]	20	10	17	90	90

[a] The aldehyde (500 µmol) was added to a solution of the prolinamine **8j** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL).
[b] Isolated yield; ee and configuration (*R*) determined by HPLC on chiral phase.
[c] Reaction in toluene/hexane (1:1, 2.0 mL).
[d] Reaction at double concentration.
[e] Reaction at half concentration.

The scope of prolinamine **8j** is shown in Table 4. Aromatic aldehydes with electron-withdrawing (**1d**) or -donating (**1e**) groups, with *meta* (**1g**) or *para* (**1d–f**) substituents, 2-naphthyl carbaldehyde (**1i**), and hetarylic 2-thienyl carbaldehyde (**1k**) provided the *R*-configured product in >80% yield and with good 83–90% ee. *Ortho* substituents such as methyl in **1h** or an *ortho*, *meta*-annelated ring as in 1-naphthyl carbaldehyde (**1j**) reduce the level of chirality transfer (80% and 60% ee, respectively). Insufficient stereocontrol was observed for vinylic cinnamic (**1l**: 17% ee) and aliphatic hydrocinnamic (**1c**: 62% ee) aldehyde. The presence of an α-branched alkyl group permitted high enantioselectivities, as obvious from the excellent 98% ee reached with cyclohexyl carbaldehyde (**1b**).

Table 4. Substrate scope of the prolinamine **8j**.[a]

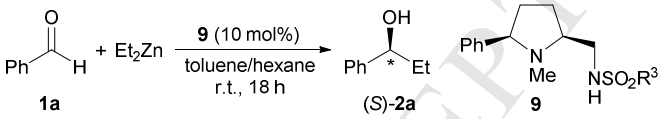


Entry	**1**, **2**	R	Yield (%)[b]	ee (%)[b]
1	**a**	Ph	90	90
2	**d**	4-ClPh	84	88
3	**e**	4-MeOPh	88	84
4	**f**	4-MePh	81	90
5	**g**	3-MePh	85	90
6	**h**	2-MePh	96	80
7	**i**	2-Naph	88	86
8	**j**	1-Naph	81	60
9	**k**	2-Thienyl	86	83
10	**l**	(*E*)-Ph-CH=CH	73	17
11	**c**	$Ph(CH_2)_2$	34	62
12	**b**	Cy	91	98

[a] The aldehyde (500 µmol) was added at 20 °C to a solution of the prolinamine **8j** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (4.0 mL).
[b] Isolated yield; ee and configuration (*R*) determined by HPLC on chiral phase.

Finally, the sulfonamides **9**, in which the electron-donating character of the exocyclic nitrogen atom is strongly reduced, were evaluated in the addition of Et_2Zn to benzaldehyde (**1a**, Table 5).[13] The highest asymmetric induction (78% ee) was reached when the reaction was conducted in toluene/hexane 1:1 in the presence of the triflate **9b** (10 mol%) that carries the small and strongly electron-withdrawing CF_3 group. Larger substituents R^3 again caused an, in part, significant loss in stereocontrol. Surprisingly, the sense of the chirality transfer with **9** (*S*) is opposite to that of **8j** (*R*).

Table 5. Additions to **1a** in the presence of the prolinamine sulfonamides **9**.[a]



Entry	**9**	R^3	Yield (%)[b]	ee (%)[b]
1[c]	**a**	Me	70	60
2	**a**	Me	95	68
3	**b**	CF_3	84	78
4	**c**	4-MePh	90	64
5	**d**	Bn	63	72
6	**e**	2,4,6-Me_3Ph	87	17

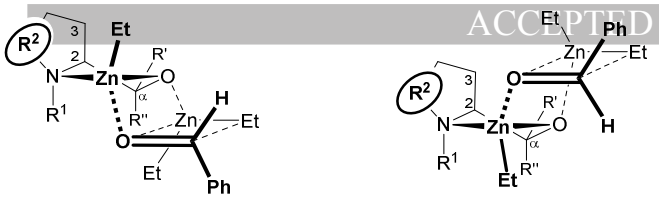
[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinamine sulfonamide **9** (50 µmol) and Et_2Zn (1.0 mmol) in hexane/toluene 1:1 (2.0 mL).
[b] Isolated yield; ee and configuration (*S*) determined by HPLC on chiral phase.
[c] Reaction in hexane (2 mL) as the solvent.

2.3. Stereochemical considerations

The stereo transfer with the proline-derived ligands **7**–**9**, including the observed switches in the sense of asymmetric induction, can be explained by inspection of the respective transition states. The following argumentation is based on quantumchemical calculations on Soai's prolinols **3**[14] and related amino alcohols,[15] which had revealed that eight transition states have to be taken into consideration. They differ in the orientation of the bicyclic catalyst core relative to the transient, inner 4-membered ring [*exo* (**12A**, **12C**) vs. *endo* (**12B**, **12D**), Figure 1, illustrated on the addition of Et_2Zn to benzaldehyde (**1a**) in the presence of the prolinols **3** and **7**] and to the outer 4-membered ring [*anti* (**12A**, **12B**) vs. *syn* (**12C**, **12D**)], and in the orientation of the aldehyde [coordination via the *trans* lone pair (**12A**–**D**) or the *cis* one (not shown)]. The latter *cis* arrangements were calculated to be, at least for aromatic aldehydes, of significantly higher energy and are, therefore, neglected in the following discussion. The same accounts for the *endo*-*syn* transition state **12D**, because of the strong repulsion between the coordinated reactants and the bicyclic catalyst backbone. The remaining three arrangements **12A**–**C** can be close in energy, although **12C** (*exo*-*syn*) is normally disfavored due to higher steric crowding. For high levels of stereotransfer, the substituents attached to the chiral ligand have to induce a sufficient difference in energy between **12A** (*exo*-*anti*; *R*-selective) and **12B**/**12C** (*endo*-*anti*/*exo*-*syn*; both *S*-selective).

The most simple prolinol, **3c** (R^1 = Me; R^2, R', R" = H), had been shown earlier[4] not to exert any asymmetric induction at all. Apparently, there is no transition state favored by the basic prolinol skeleton, presumably due to too much conformational flexibility, despite of the bicyclic backbone. The situation changes with an additional 5-*cis* substituent R^2 such as phenyl in ligand **7b**. The phenyl group most likely occupies a pseudo-equatorial position (minimizes 1,2-repulsion), which, like an anchor, rigidifies the bicyclic catalyst backbone, forcing it into the conformation shown in Figure 1. The resulting pseudo-axial orientation of the C2–C3 bond and the increased steric hindrance in the northwestern quadrant now disfavor the *endo*-binding mode **12B**, which results in the preferred formation of the *R*-configured product via **12A**. The stereocontrol, however, is low with **7b** (25% ee) since the stereo-deteriorating *exo*-*syn* transition state **12C** is not sufficiently suppressed. It should be noted that the same configurational 'freeze' was achieved by Soai[4] with the α-positioned *endo* phenyl group in prolinol **3b**. The bulky neopentyl group R^1 at the pyrrolidine nitrogen atom additionally disfavors **12C**, which explains the virtually perfect asymmetric induction (100% ee) reached.

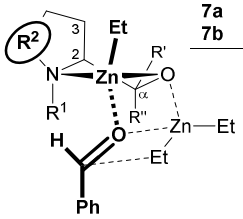
The α,α-diphenyl group in the prolinols **3a** and **7a** (R', R" = Ph) induces a reversal in the sense of asymmetric induction. The pseudo-equatorial orientation of R' (avoids severe 1,2-repulsion with the C2–C3 bond) forces R" into a pseudo-axial position, which efficiently shields the *exo* hemisphere and virtually excludes the arrangements **12A** and **12C**. Consequently, the reaction proceeds via transition state **12B**, leading to the *S*-configured product with excellent stereocontrol (97% ee). The additional 5-*cis* phenyl group in **7a** (R^2 = Ph) also supports this conformation (vide supra) and, therefore, augments the pseudo-axial orientation of R", which further destabilizes stereo-deteriorating **12A**. Thus, **12B** gets even more favored, despite an increased steric hindrance in the *endo* hemisphere due to R^2, leading to an improved asymmetric induction as compared to **3a**.



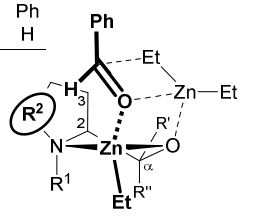
12A (*exo-anti*) [→ (*R*)-**2a**]
(slightly favored for **7b**,
strongly favored for **3b**)

12B (*endo-anti*) [→ (*S*)-**2a**]
(strongly favored for **3a**, **7a**)

3	R^1	R^2	R'	R''
3a	Me	H	Ph	Ph
3b	CH_2tBu	H	Ph	H
3c	Me	H	H	H
7a	Me	Ph	Ph	Ph
7b	Me	Ph	H	H



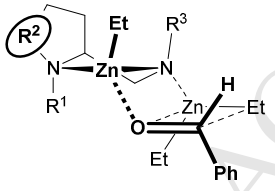
12C (*exo-syn*) [→ (*S*)-**2a**]



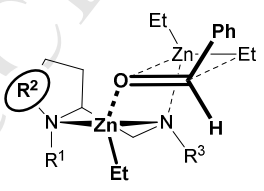
12D (*endo-syn*) [→ (*R*)-**2a**]
(generally disfavored)

Figure 1. Possible transition states **12A**–**12D** for the ethylation of **1a** in the presence of the prolinols **3** and **7**. The disfavored transition states with *cis* coordination of the aldehyde are not shown.

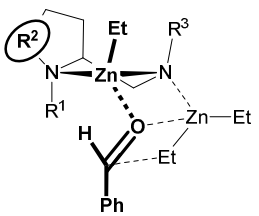
The prolinamines **8** can principally react via the transition states **13A**–**13D** (Figure 2).[16] Their relative stabilities basically follow the order discussed above for **7b**: **13D** (*endo-syn*) << **13B** (*endo-anti*) < **13C** (*exo-syn*) < **13A** (*exo-anti*). The formal exchange of the oxygen atom in **7b** for the secondary amino group in **8** introduces a new substituent R^3, which destabilizes the majorly stereo-deteriorating arrangement **13C** because it increases the 1,2-*syn* repulsion R^3/Et (of Et_2Zn) in the central four-membered ring. This permitted higher levels of chirality transfer of up to a maximum of 90% ee (*R*) in the case of **8j** (R^1, R^3 = Me, R^2 = *c*Pent).[17] However, the preference for **13A** over **13B** and **13C** and, thus, the enantioselection, is based on a fragile and delicate balance between the crowding in the *exo* and *endo* hemisphere and, thus, between the steric demands of the substituents R^1–R^3. Just slightly larger ethyl groups for R^1 (**8f**) and R^3 (**8c**) cause drastic losses in asymmetric induction (≤12% ee),[18,19] while bulkier substituents such as R^1 = Bn (**8h**) or R^3 = *i*Pr (**8d**) even disfavor **13A** to the point that **13B** or **13C** become favorable, leading to the enantio-complementary product (*S*)-**2a** in up to 20% ee. The



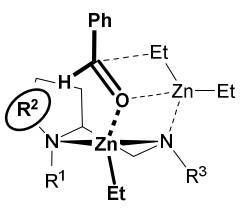
13A (*exo-anti*) [→ (*R*)-**2a**]
(favored for **8j**)



13B (*endo-anti*) [→ (*S*)-**2a**]



13C (*exo-syn*) [→ (*S*)-**2a**]

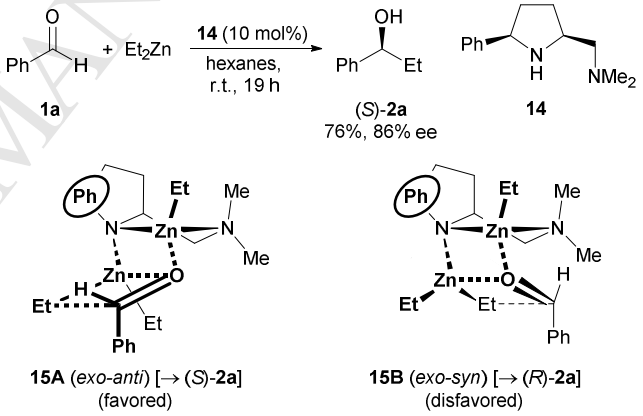


13D (*endo-syn*) [→ (*R*)-**2a**]
(generally disfavored)

Figure 2. Possible transition states **13A**–**13D** for the ethylation of **1a** in the presence of the prolinamines **8**. The disfavored transition states with *cis* coordination of the aldehyde are not shown.

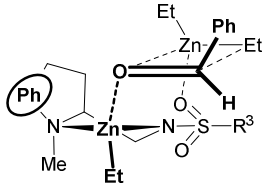
substituent R^2 is necessary to destabilize **13B**, as obvious from the low 45% ee reached with **8i** (R^2 = H). Although there is more steric tolerance at this position (**8j**–**m**: R^2 = *c*Pent, Cy, Bn, 3,5-Me_2Ph: 90–61% ee), larger groups diminish the stereocontrol, probably since steric crowding begins to destabilize the *exo* arrangements **13A** and **13C**.

In order to find out, which of the two stereo-deteriorating transition states, **13B** (*endo-anti*) or **13C** (*exo-syn*), is primarily responsible for the non-perfect chirality transfer even with the best ligand **8j**, benzaldehyde (**1a**) was ethylated in the presence of the prolinamine **14**. This diamine, which possesses a secondary pyrrolidine nitrogen atom and a tertiary exocyclic amino function, afforded (*S*)-**2a** in good 86% ee (Scheme 3). The reversed sense of the asymmetric induction is a consequence of the activation of Et_2Zn by the pyrrolidine nitrogen atom in **14** (and not, as for the prolinamines **8**, by the exocyclic amine), which directs the attack to the opposite face of the coordinated benzaldehyde. Since geometric restrictions exclude *endo*-type alignments with **14**, (*S*)-**2a** must have been formed via the *exo-anti* transition state **15A** and the unwanted minor enantiomer, (*R*)-**2a**, by a competing pathway via the *exo-syn* transition state **15B**. This makes it very likely that the minor enantiomer (*S*)-**2a** of the reaction catalyzed by **8j** is formed via the corresponding *exo-syn* alignment **13C**.



Scheme 3. Addition of Et_2Zn to **1a** in the presence of prolinamine **14** and the proposed transition states **15A** and **15B**.

The exocyclic nitrogen atom in **9** is part of a sulfonamide group, which strongly reduces its ability to pre-coordinate and activate the Et_2Zn. We postulate that one of the two Lewis-basic oxygen atoms of the sulfonamide group takes this function.[20] The observed *S*-selectivity in the ethylation of **1a** can be explained, for example, by the *endo-anti* transition state **16A** (Figure 3), but other arrangements are also possible, because the larger, six-membered central ring offers more conformational freedom. The flattening of the [1,3,2]-diazazincolidine, caused by the sp^2-hybridization of the sulfonamide nitrogen atom, might be a reason for the lower asymmetric inductions reached with **9** (up to 78% ee).



16A (*endo-anti*) [→ (*S*)-**2a**]

Figure 3. Proposed preferred transition state **16A** for the ethylation of **1a** in the presence of the sulfonamides **9**.

3. Conclusion

5-*Cis*-substituted prolinols **7**, prolinamines **8**, and prolinamine sulfonamides **9**, which are accessible from commercially available methyl Boc-L-pyroglutamate (**10**), were evaluated as the chiral ligands in the addition of Et_2Zn to aldehydes. The additional 5-*cis* substituent R^2 was found to significantly improve the chirality transfer (e.g. **8i** (R^2 = H): 45% ee vs. **8j** (R^2 = *c*Pent): 84% ee). The sense of asymmetric induction depended on the existence of α-substituents and the nature of the exocyclic functionality: While up to 99% ee in favor of the *S*-configured products were reached with the 5-*cis*,α,α-triphenyl prolinol **7a**, the enantio-complementary, *R*-configured products were obtained with the α,α-unsubstituted prolinamines **8** (up to 98% ee for **8j**). The prolinamine sulfonamides **9** again preferentially provided the *S*-enantiomers (up to 78% ee for **9b**). Structure-selectivity studies on the prolinamines **8** revealed that even minor changes in the substituents R^1 at the pyrrolidine nitrogen atom and R^3 at the exocyclic amino function cause drastic losses in enantiocontrol. The stereochemical behavior of the ligands **7**–**9** can be explained by the respective transition states. The 5-*cis* substituent exerts a beneficial effect since it locks the catalyst structure in a favorable conformation. Of the energetically relevant transition states that differ in the relative orientation of the two transient four-membered rings formed during ethyl transfer, the *endo-anti* alignment **12B** is favored for **7a** because the α,α-diphenyl group shields the *exo* hemisphere. The prolinamines **8** react preferentially via the *exo-anti* transition state **13A**, thus avoiding steric crowding in the *endo* hemisphere. The activation of Et_2Zn in the sulfonamides **9** is proposed to occur by one of the oxygen atoms of the sulfone, leading to a six-membered inner ring during C,C-bond formation.

4. Experimental section

4.1. General

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[21] 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 $KMnO_4$ or vanillin. 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 made 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 on a ThermoFisher Scientific Q-Exactive (Orbitrap) mass spectrometer using ESI (electronspray ionization). The enantiomeric excess of the alcohols **2** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak AD-H or Daicel Chiralcel OD-3).

Prolinamines **8a–h**,**j**,**k**,**m**, **14** and sulfonamide **9a** were prepared according to literature procedures.[8b–d,9] Diamine **8i** is commercially available.

*4.2. ((2S,5R)-1-Methyl-5-phenylpyrrolidin-2-yl)diphenylmethanol (**7a**)*

PhMgCl (20.9 mL, 2.0 M in THF, 41.7 mmol) was added at 0 °C to a solution of the ester **11a**[8d] (4.25 g, 13.9 mmol) in anhydrous THF (42 mL). After 1 d at r.t., the reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) and the organic layer was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was suspended in EtOH (140 mL) and freshly ground NaOH (5.56 g, 139 mmol) was added at r.t. The reaction mixture was refluxed for 2 d and concentrated under reduced pressure. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL). The combined organic layers were washed with brine (90 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, hexanes:EtOAc 14:1–9:1) provided known[10a] ((2*S*,5*R*)-5-phenylpyrrolidin-2-yl)diphenylmethanol (3.95 g, 12.0 mmol, 86%) as a slightly yellow solid.

The amino alcohol prepared above (880 mg, 2.67 mmol) was dissolved in DMF (11 mL) and MeI (351 µL, 796 mg, 5.61 mmol) and K_2CO_3 (812 mg, 5.87 mmol) were added at r.t. H_2O (20 mL) was added after 4 h and the mixture was extracted with Et_2O (5 × 30 mL). The combined organic layers where dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, hexanes:EtOAc 29:1–9:1) and trituration with Et_2O (6 mL) afforded known[12] prolinol **7a** (789 mg, 2.30 mmol, 86%) as a colorless solid.

*4.3. (2R,5S)-2-Benzyl-1-methyl-5-((methylamino)methyl)pyrrolidine (**8l**)*

MsCl (86.6 µL, 129 mg, 1.12 mmol) and NEt_3 (216 µL, 157 mg, 1.55 mmol) were added at 0 °C to a solution of (2*R*,5*S*)-2-benzyl-5-(hydroxymethyl)-1-methylpyrrolidine[9] (177 mg, 862 µmol) in anhydrous CH_2Cl_2 (1.7 mL). After 1 d at r.t., H_2NMe (2.35 mL, 40 wt% in H_2O, 25.9 mmol), NEt_3 (72.1 µL, 52.3 mg, 517 µmol), and MeOH (4 mL) were added. The reaction mixture was stirred 17 h and the solvent evaporated. Column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 95:4.5:0.5–93:6.3:0.7) provided prolinamine **8l** (137 mg, 627 µmol, 73%) as an orange oil.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 90:9:1) 0.30; $[\alpha]_D^{30}$ +34.1 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 2972, 2935, 2770, 1453, 1433, 1358, 1125, 1087, 1049, 1037, 813, 757, 748, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.26 (2H, m, Ph-H), 7.18 (3H, m, Ph-H), 3.00 (1H, dd, *J* 12.2, 3.0 Hz, 2-C*H*H), 2.66 (1H, dd, *J* 11.3, 3.8 Hz, 5-C*H*H), 2.54 (1H, dd, *J* 11.2, 6.3 Hz, 5-CH*H*), 2.48 (2H, m, 2-H, 5-H), 2.44 (3H, s, $NHCH_3$), 2.43 (1H, m, 2-CH*H*), 2.38 (3H, s, 1-CH_3), 1.77 (1H, m, 4-*H*H), 1.64 (1H, m, 3-*H*H), 1.57 (1H, m, 4-H*H*), 1.45 (1H, m, 3-H*H*), 1.36–1.08 (1H, br s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.1 (C_q-Ph), 129.4, 128.3, 126.0 (CH-Ph), 69.2 (C-2), 66.7 (C-5), 55.9 (5-CH_2), 41.2 (2-CH_2), 40.0 (1-CH_3), 37.3 ($NHCH_3$), 29.8 (C-3), 27.4 (C-4) ppm; HRMS (ESI, pos.): MH^+, found 219.1850. $C_{14}H_{23}N_2^+$ requires 219.1856.

*4.4. Synthesis of the N-sulfonylated prolinamines **9***

4.4.1. General procedure

NEt_3 (1.1 equiv) and the sulfonyl chloride or anhydride (1.1 equiv) were added at r.t. to a solution of the prolinamine **8a** in anhydrous CH_2Cl_2 (1 mL/100 µmol **8a**). After 2–3 h, MeOH (260 µL/100 µmol **8a**) was added. Removal of the solvent and column chromatography provided the *N*-sulfonylated prolinamine **9**.

4.4.2. (2R,5S)-1-Methyl-2-phenyl-5-((trifluoromethylsulfonamido)methyl)pyrrolidine (9b)

According to the GP, the prolinamine **8a** (73.7 mg, 387 µmol) was sulfonylated with trifluoromethanesulfonic anhydride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9b** (92.0 mg, 285 µmol, 74%) as a brownish wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.56; $[\alpha]_D^{23}$ +24.9 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3298 (br), 2952, 1389, 1367, 1230, 1185, 1146, 1032, 948, 755, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.34 (2H, m, Ph-H), 7.27 (3H, m, Ph-H), 5.22–4.00 (1H, br s, NH), 3.47 (1H, dd, *J* 12.5, 3.5 Hz, 5-C*H*H), 3.38 (2H, m, 2-H, 5-CH*H*), 2.77 (1H, m, 5-H), 2.15 (3H, s, 1-CH_3), 2.12 (1H, m, 3-*H*H), 2.03 (1H, m, 4-*H*H), 1.87 (1H, m, 4-H*H*), 1.71 (1H, m, 3-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.3 (C_q-Ph), 128.8, 127.7, 127.3 (CH-Ph), 120.0 (q, *J* 321.3 Hz, CF_3), 72.1 (C-2), 63.6 (C-5), 44.5 (5-CH_2), 38.2 (1-CH_3), 33.9 (C-3), 26.4 (C-4) ppm; HRMS (ESI, pos.): MH^+, found 323.1028. $C_{13}H_{18}F_3N_2O_2S^+$ requires 323.1036.

4.4.3. (2S,5R)-1-Methyl-2-((4-methylphenylsulfonamido)methyl)-5-phenylpyrrolidine (9c)

According to the GP, the prolinamine **8a** (70.5 mg, 371 µmol) was sulfonylated with 4-toluenesulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9c** (105 mg, 305 µmol, 82%) as a yellowish wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.43; $[\alpha]_D^{26}$ +49.4 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3295 (br), 2951, 1598, 1493, 1454, 1427, 1323, 1152, 1069, 813, 697, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.78 (2H, d, *J* 8.3 Hz, Ar-H), 7.29 (7H, m, Ar-H), 5.10 (1H, d, *J* 8.0 Hz, NH), 3.28 (1H, dd, *J* 9.9, 6.8 Hz, 5-H), 3.09 (1H, m, 2-C*H*H), 2.99 (1H, ddd, *J* 11.8, 3.9, 1.2 Hz, 2-CH*H*), 2.62 (1H, m, 2-H), 2.42 (3H, s, Ar-CH_3), 2.04 (1H, m, 4-*H*H), 1.92 (3H, s, 1-CH_3), 1.85 (2H, m, 3-H_2), 1.64 (1H, m, 4-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.4, 142.9, 136.8 (C_q-Ar), 129.8, 128.6, 127.5, 127.33, 127.29 (CH-Ar), 72.2 (C-5), 63.9 (C-2), 43.7 (2-CH_2), 38.2 (1-CH_3), 34.0 (C-4), 26.6 (C-3), 21.7 (Ar-CH_3) ppm; HRMS (ESI, pos.): MH^+, found 345.1623. $C_{19}H_{25}N_2O_2S^+$ requires 345.1631.

4.4.4. (2S,5R)-1-Methyl-2-((benzylsulfonamido)methyl)-5-phenylpyrrolidine (9d)

According to the GP, the prolinamine **8a** (73.0 mg, 384 µmol) was sulfonylated with benzylsulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9d** (112 mg, 325 µmol, 85%) as a colorless oil.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.29; $[\alpha]_D^{27}$ +25.3 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3291 (br), 2949, 1455, 1327, 1151, 1125, 909, 730, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.46 (2H, m, Ph-H), 7.40 (3H, m, Ph-H), 7.27 (3H, m, Ph-H), 7.20 (2H, m, Ph-H), 4.85 (1H, d, *J* 6.5 Hz, NH), 4.33 (2H, s, CH_2Ph), 3.30 (1H, dd, *J* 9.9, 6.6 Hz, 5-H), 3.12 (1H, dd, *J* 12.0, 3.9 Hz, 2-C*H*H), 3.04 (1H, m, 2-CH*H*), 2.64 (1H, m, 2-H), 2.07 (3H, s, 1-CH_3), 2.04 (1H, m, 4-*H*H), 1.89 (2H, m, 3-H_2), 1.61 (1H, m, 4-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.8 (C_q-Ph), 130.7 (CH-Ph), 129.7 (C_q-Ph), 129.0, 128.9, 128.5, 127.4, 127.3 (CH-Ar), 72.2 (C-5), 64.2 (C-2), 58.9 (CH_2Ph), 44.4 (2-CH_2), 38.5 (1-CH_3), 34.2 (C-4), 26.5 (C-3) ppm; HRMS (ESI, pos.): MH^+, found 345.1623. $C_{19}H_{25}N_2O_2S^+$ requires 345.1631.

4.4.5. (2R,5S)-1-Methyl-2-phenyl-5-((2,4,6-trimethylphenylsulfonamido)methyl)pyrrolidine (9e)

According to the GP, the prolinamine **8a** (69.4 mg, 365 µmol) was sulfonylated with 2,4,6-trimethylbenzenesulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9e** (107 mg, 287 µmol, 79%) as a colorless wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.43; $[\alpha]_D^{29}$ +54.9 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3301 (br), 2972, 2850, 1607, 1456, 1419, 1379, 1330, 1152, 1038, 865, 758, 705, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.33 (2H, m, Ar-H), 7.27 (3H, m, Ar-H), 6.95 (2H, s, Ar-H), 5.33 (1H, d, *J* 8.7 Hz, NH), 3.29 (1H, dd, *J* 10.0, 6.7 Hz, 2-H), 3.03 (1H, ddd, 11.5, 9.0, 2.0 Hz, 5-C*H*H), 2.91 (1H, ddd, *J* 11.5, 3.9, 1.5 Hz, 5-CH*H*), 2.67 (6H, s, Ar-CH_3), 2.63 (1H, m, 5-H), 2.29 (3H, s, Ar-CH_3), 2.05 (1H, m, 3-*H*H), 1.92 (3H, s, 1-CH_3), 1.86 (2H, m, 4-H_2), 1.67 (1H, m, 3-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.8, 142.2, 139.2, 133.3 (C_q-Ar), 132.0, 128.6, 127.5, 127.3 (CH-Ar), 72.2 (C-2), 63.6 (C-5), 43.1 (5-CH_2), 38.1 (1-CH_3), 34.1 (C-3), 26.6 (C-4), 23.0, 21.1 (Ar-CH_3) ppm; HRMS (ESI, pos.): MH^+, found 373.1936. $C_{21}H_{29}N_2O_2S^+$ requires 373.1944.

4.5. General procedure for the addition of diethylzinc to aldehydes in the presence of 8j

Et_2Zn (1.0 mL, 1.0 M in hexane, 1.00 mmol) was added to a solution of prolinamine **8j** (9.82 mg, 50.0 µmol) in hexane (3 mL). After 20 min at r.t., freshly distilled aldehyde **1** (500 µmol) was added at 20 °C and stirring was continued for 2 d. EtOAc (5 mL) and HCl (5 mL, 1.0 M in H_2O) were added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (hexanes:EtOAc) provided the enantiomerically enriched alcohols **2**.

Acknowledgments

Financial support by the DFG (German research foundation) is gratefully acknowledged.

Supplementary data

Supplementary data (copies of NMR spectra and HPLC chromatograms) associated with this article can be found, in the online version, at "http://XXX..."

References and notes

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16. Prolinamine **8e**, which possesses a secondary pyrrolidine nitrogen atom, might also adopt transition states of type **15** (with NHMe instead of NMe_2).
17. The low enantioselectivities obtained with the linear aliphatic and vinylic aldehydes **1c** and **1l** (17% and 62% ee, respectively, see Table 4) are most likely not caused by a diminished preference of **13A** over **13B**–**D**, but the consequence of an interfering coordination mode of these aldehydes via their *cis* lone pair, which gives the enantiomeric product.
18. We assume that the pseudo-equatorial orientation of the 5-*cis* substituent locks the pictured envelope conformation of the central diazazincolidine in **13A**–**D**, thus creating the rigid backbone required for high asymmetric inductions (see Figure 1 and discussion). It might be possible that larger substituents R^1 and R^3, which would have to occupy pseudo-equatorial positions in the 'locked conformation' of **13**, destabilize that conformation, resulting in a conformationally flexible backbone and different transition states with low stereocontrol.
19. A comparable drastic loss in enantioselectivity was also observed in Cu-catalyzed oxidative biaryl couplings.[8c]
20. Coordination of Et_2Zn to a sulfonamide group was proposed to occur via the nitrogen atom[13a] and via an oxygen atom.[13d]
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