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Asymmetric Henry Reactions Catalyzed by Metal Complexes of Chiral Boron-Bridged Bisoxazoline (borabox) Ligands

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Keywords: Henry reaction / Asymmetric catalysis / Borabox ligands / Copper complexes / Nitropropane

Metal complexes of boron-bridged bisoxazolines (borabox ligands) were evaluated as catalysts for the Henry reaction. Copper(II) complexes induced high enantio- and diastereoselectivity in reactions with nitroethane and nitropropane. The amount of base added had a strong influence on the formation of the chiral complex and the enantioselectivity. Comparison with the corresponding dimethylmethylene-bridged bisoxazoline and other privileged ligands showed that borabox was the most suitable ligand system for the enantio- and diastereoselective formation of nitroalcohols derived from nitropropane and aliphatic aldehydes.

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Introduction

Chiral C_2-symmetric bisoxazolines **1** (box) belong to the most versatile ligands for asymmetric catalysis (Figure 1).[1] The success of these ligands is explained by the short, efficient synthesis from readily available precursors, the ease of modifying the structure, and the ideal position of the stereogenic centers near the coordination sphere, which permits efficient, direct chirality transfer to a coordinated substrate.

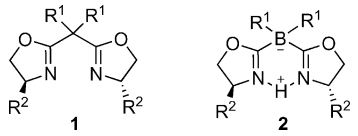

Figure 1. Box and borabox ligands.

We have recently introduced a new variant of this privileged ligand structure, anionic boron-bridged bisoxazolines **2** (borabox).[2] Like the box ligands the borabox analogs are readily synthesized from chiral amino alcohols. Comparative studies of the two ligand systems revealed that the reactivities and enantioselectivities of box- and borabox-derived metal catalysts often differed substantially. For example, in copper-catalyzed enantioselective acylations of *meso*-1,2-diols and kinetic resolution of chiral 1,2-diols and pyridyl alcohols, borabox ligands outperformed their box counterparts. The results obtained so far indicate that borabox ligands are a valuable addition to the known chiral bisoxazolines, as they may provide a useful alternative when standard box ligands fail.

In view of the successful application of chiral bisoxazolines in enantioselective copper-catalyzed nitroaldol (or Henry) reactions,[3,4] we decided to evaluate analogous borabox ligands in this respect. Here we report the results of this study, which demonstrate that copper(II)-borabox complexes are efficient catalysts for Henry reactions, and can induce high enantio- and diastereoselectivities, especially in reactions between nitroethane or nitropropane and aliphatic aldehydes.

Results and Discussion

Initial Screening

Initially the reactivity and selectivity of various borabox complexes for the Henry reaction were investigated. The reaction between benzaldehyde and nitromethane in the presence of 5 mol-% of metal source, 5.5 mol-% of borabox ligand and triethylamine was chosen as a model system. Zinc(II) and copper(II) triflate proved to be the most suitable metal sources as other metal salts such as zinc(II) chloride, copper(II) chloride and copper(II) acetate induced lower enantioselectivities. Table 1 summarizes the results of the screening experiments. The ratio of base to ligand was found to strongly influence both the reactivity and selectivity of the reaction (Table 1, Entries 1 to 3). Variation of the amount of base added after complexation of the ligand showed that in the presence of zinc(II) triflate and ligand **2a**, 10.5 mol-% of base gave the highest enantiomeric excess (70% yield, 24% *ee*, Entry 2). It was supposed that 5.5 mol-% of triethylamine was needed for the deprotonation of the

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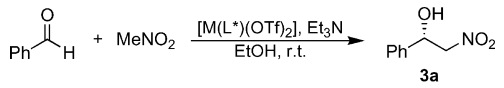
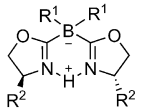
Table 1. Optimization of the catalytic enantioselective Henry reaction between benzaldehyde and nitromethane in the presence of triethylamine as base.[a]





2a R^1 = Ph; R^2 = *i*Pr
2b R^1 = Ph; R^2 = *t*Bu
2c R^1 = Et; R^2 = *t*Bu
2d R^1 = Et; R^2 = Bn
2e R^1 = Et; R^2 = *i*Bu
2f R^1 = Cy; R^2 = *t*Bu

Entry	Ligand	Metal salt	Et_3N [mol-%]	Yield [%][b]	*ee* [%][c]
1	**2a**	$Zn(OTf)_2$	5.5	59	2 (*R*)
2	**2a**	$Zn(OTf)_2$	10.5	70	24 (*S*)
3	**2a**	$Zn(OTf)_2$	15.5	75	22 (*S*)
4	**2a**	$Cu(OTf)_2$	10.5	90	1 (*R*)
5	**2b**	$Zn(OTf)_2$	10.5	86	3 (*R*)
6	**2b**	$Cu(OTf)_2$	10.5	85	35 (*S*)
7	**2b**	$Cu(OTf)_2$	10.5[d]	94	70 (*S*)
8	**2c**	$Zn(OTf)_2$	10.5[d]	50	25 (*R*)
9	**2c**	$Cu(OTf)_2$	10.5[d]	85	66 (*S*)
10	**2d**	$Zn(OTf)_2$	10.5[d]	81	3 (*R*)
11	**2d**	$Cu(OTf)_2$	10.5[d]	41	5 (*R*)
12	**2e**	$Zn(OTf)_2$	10.5[d]	50	6 (*R*)
13	**2e**	$Cu(OTf)_2$	10.5[d]	33	6 (*R*)
14	**2f**	$Zn(OTf)_2$	10.5[d]	56	17 (*R*)
15	**2f**	$Cu(OTf)_2$	10.5[d]	85	54 (*S*)

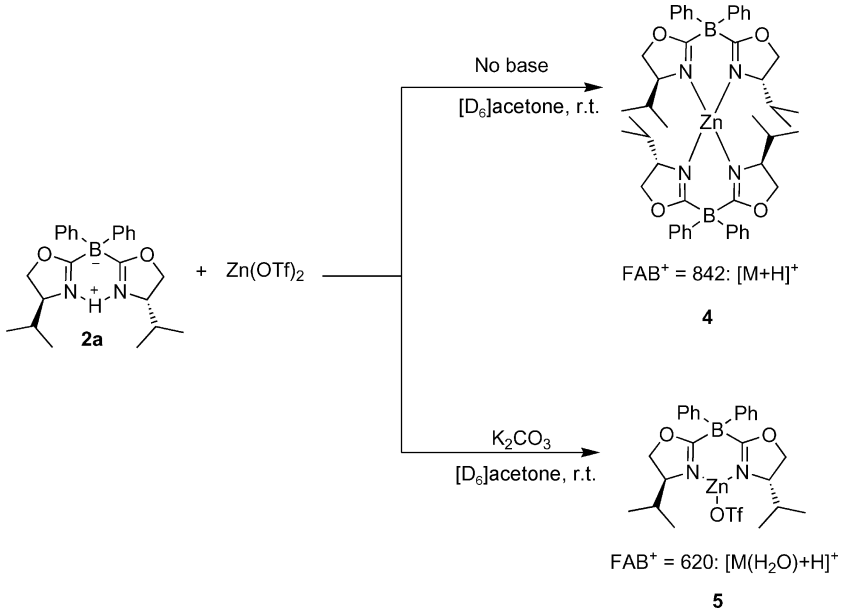
[a] Reactions were performed on a 0.5 mmol scale: $Cu(OTf)_2$ (5 mol-%) and ligand **2** (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, benzaldehyde (1 equiv.), nitromethane (10 equiv.) and triethylamine were added and the reaction mixture was stirred for 24 h. [b] After column chromatography. [c] Determined by chiral HPLC. The absolute configuration of **3a** was assigned by comparison with that reported in the literature.[4a] [d] 5.5 mol-% of triethylamine were added initially. After complexation for 3 to 5 hours at room temp. and the addition of benzaldehyde and nitromethane, 5 mol-% of triethylamine was added.

protonated borabox ligand in the complexation step and 5 mol-% for the deprotonation of nitromethane. Thus, instead of adding the base in one batch, first 5.5 mol-% of base was used to induce complexation, followed by a second portion when the reaction was started. For the catalyst system derived from copper(II) triflate and ligand **2b**, this procedure resulted in increased yield and product **3a** was formed with higher enantiomeric excess of 70% (Table 1, Entries 6 and 7).

To gain additional information on the complexation reaction, the formation of boraboxzinc(II) complexes was studied by NMR and mass spectrometry (Scheme 1). When equimolar amounts of the borabox **2a** and zinc(II) triflate were dissolved in [D_6]acetone without the addition of a base, the NMR and FAB-MS indicated quantitative formation of a bis(borabox) complex **4**. In contrast, in the presence of one equivalent of potassium carbonate, only the mono(borabox) zinc triflate complex **5** was observed. Thus, the addition of base suppresses the formation of a unreactive homoleptic bis(borabox) complex.

The results obtained with different borabox derivatives showed that ligands carrying a *tert*-butyl group at the stereogenic center were most effective (Table 1, Entries 8, 9, 14 and 15). The substituents at the boron atom had only a minor influence on the reactivity and enantioselectivity. Based on the data summarized in Table 1, copper(II) triflate and ligand **2b**, which gave the best results, were chosen for subsequent studies.

Screening of different reaction media showed that protic solvents generally gave the best results (EtOH, *i*PrOH, MeOH) followed by aprotic polar solvents (MeCN, acetone, $MeNO_2$), whereas aprotic apolar solvents (CH_2Cl_2, THF) were not suitable for this reaction. Other bases were also tested, including Hünig's base and potassium carbonate, but the enantioselectivities were lower than with triethylamine.



Scheme 1. Complexation studies with $Zn(OTf)_2$.

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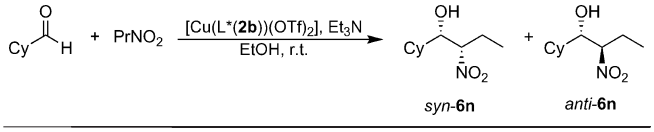
Influence of the Base

Subsequently, the influence of the amount of triethylamine on the reactivity and stereoselectivity was studied in greater detail. The quantity of base used for complex formation was kept constant at 5.5 mol-% (1 equiv. based on the borabox ligand), while the additional portion of triethylamine added after the complexation step was varied from 0 to 5.5 mol-% (Table 2).

Table 2. Influence of the amount of triethylamine in the Henry reaction between cyclohexanecarboxaldehyde and nitropropane.[a]



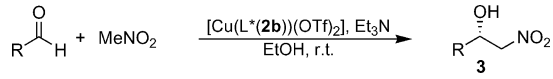
Entry	Et_3N [b] [mol-%]	Conversion [%][c]	*syn*/*anti*[c]	*ee* (*syn*) [%][d,e]	*ee* (*anti*) [%][d,f]
1	5.5	64	86:14	82 (1*S*,2*S*)	50 (1*S*,2*R*)
2	5	52	90:10	84 (1*S*,2*S*)	41 (1*S*,2*R*)
3	4.5	60	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
4	3.0	68	90:10	91 (1*S*,2*S*)	31 (1*S*,2*R*)
5	1.5	62	91:09	91 (1*S*,2*S*)	28 (1*S*,2*R*)
6	0	70	92:08	75 (1*S*,2*S*)	30 (1*S*,2*R*)

[a] Reactions were performed on a 0.5 mmol scale: $Cu(OTf)_2$ (5 mol-%), ligand **2b** (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, cyclohexanecarboxaldehyde (1 equiv.), nitropropane (10 equiv.) and triethylamine were added and the reaction mixture was stirred for 5 days. [b] Additional amount of triethylamine added after the complexation step. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC. [e] The absolute configuration of *syn*-**6n** was determined by comparison with published HPLC retention times.[5] [f] The absolute configuration of *anti*-**6n** was determined by analogy with the absolute configuration of compound *anti*-**7a**.[6]

Applying the optimal reaction conditions described in Table 1 (5 mol-% of additional triethylamine), the reaction between cyclohexanecarboxaldehyde and nitropropane afforded the corresponding nitro alcohol **6n** with encouraging diastereoselectivity and enantioselectivity [90:10 *syn*/*anti*, 84% *ee* (*syn*), Table 2, Entry 2]. With more base (5.5 mol-% of additional triethylamine) the conversion increased to 64% but the stereoselectivity decreased [86:14 *syn*/*anti*, 82% *ee* (*syn*), Entry 1]. When the amount of additional triethylamine was reduced to 4.5 mol-%, the diastereoselectivity and enantioselectivity as well as conversion increased [92:08 *syn*/*anti*, 91% *ee* (*syn*), Entry 3]. Essentially the same enantio- and diastereoselectivity were obtained with 3 and 1.5 mol-% of additional triethylamine (Entries 4 and 5). When no additional base was added, the diasteroselectivity remained high but the enantioselectivity dropped to 75% *ee* (Entry 6).

To see if reactions with other substrates showed the same base dependence, we carried out a series of Henry reactions with nitromethane and several aldehydes (Table 3). As found for the reaction of nitropropane with cyclohexanecarbaldehyde, reducing the amount of additional base from 5.5 to 5.0 mol-% had a beneficial effect on enantioselectivity and conversion for the aliphatic aldehydes tested (Table 3, compare Entries 1/2, 3/4, and 5/6). However, for aromatic aldehydes like *ortho*-methoxybenzaldehyde, the effect was negligible (Entries 7/8).

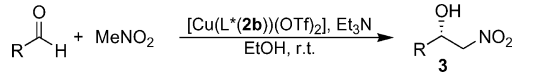
Table 3. Influence of the amount of triethylamine in Henry reactions of nitromethane.[a]



Entry	R	**3**	Et_3N[b] [mol-%]	Time [days]	Yield [%]	*ee* [%][d]
1	*i*Pr	**3n**	5	5	78[c]	38 (*S*)
2	*i*Pr	**3n**	4.5	5	83[c]	56 (*S*)
3	Et	**3o**	5	5	87[c]	38 (*S*)
4	Et	**3o**	4.5	5	90[c]	55 (*S*)
5	Cy	**3p**	5	5	85[c]	71 (*S*)
6	Cy	**3p**	4.5	5	93[c]	81 (*S*)
7	2-$MeOC_6H_4$	**3g**	5	1	82	65 (*S*)
8	2-$MeOC_6H_4$	**3g**	4.5	1	80	68 (*S*)

[a] Reactions were performed on a 0.5 mmol scale: $Cu(OTf)_2$ (5 mol-%), ligand **2b** (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, the aldehyde (1 equiv.), nitromethane (10 equiv.) and triethylamine were added and the reaction mixture was stirred for 1 to 5 days. [b] Additional amount of triethylamine added after the complexation step. [c] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC. The absolute configuration of nitroalcohol products were assigned by comparison with that reported in the literature.[4a]

Table 4. Henry reaction with nitromethane catalyzed by **2b**/$Cu(OTf)_2$.[a]



Entry	R	**3**	Time [days]	Yield [%]	*ee* [%][c]
1	Ph	**3a**	1	94	70 (*S*)
2	2-$NO_2C_6H_4$	**3b**	1	95	10 (*S*)
3	4-$NO_2C_6H_4$	**3c**	1	86	2 (*S*)
4	2-ClC_6H_4	**3d**	1	93	27 (*S*)
5	4-ClC_6H_4	**3e**	1	90	38 (*S*)
6	3-MeC_6H_4	**3f**	1	70	56 (*S*)
7	2-$MeOC_6H_4$	**3g**	1	80	68 (*S*)
8	4-$MeOC_6H_4$	**3h**	1	63	52 (*S*)
9	1-naphthyl	**3i**	1	95	46 (*S*)
10	4-PhC_6H_4	**3j**	1	89	53 (*S*)
11	*i*Bu	**3k**	5	92[b]	57 (*S*)
12	*n*Bu	**3l**	5	80[b]	60 (*S*)
13	*t*Bu	**3m**	5	89[b]	79 (*S*)
14	*i*Pr	**3n**	5	83[b]	56 (*S*)
15	Et	**3o**	5	90[b]	55 (*S*)
16	Cy	**3p**	5	93[b]	81 (*S*)

[a] Reactions were performed on a 0.5 mmol scale: $Cu(OTf)_2$ (5 mol-%), ligand **2b** (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, the aldehyde (1 equiv.), nitromethane (10 equiv.) and triethylamine (4.5 mol-%) were added and the reaction mixture was stirred for 1 to 5 days. [b] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC. The absolute configuration of nitroalcohol products **3** were assigned by comparison with that reported in the literature.[4a]

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Reactions with Nitromethane

With an optimized procedure in hand, the scope of the Henry reaction with nitromethane was further investigated (Table 4). Aromatic aldehydes in general gave only low to moderate enantioselectivities. The highest enantiomeric excesses were obtained with benzaldehyde and derivatives with electron-rich aryl groups (46–70% *ee*; Entries 1 and 6–10). Reactions with electron-deficient aromatic aldehydes gave very poor results: 2- and 4-nitrobenzaldehyde led to nearly racemic products, while 2- and 4-chlorobenzaldehyde reacted with 27 and 38% *ee*, respectively (Entries 2–5).

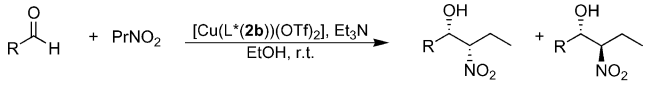
Aliphatic aldehydes, such as propionaldehyde, isobutyraldehyde, valeraldehyde, and isobutyraldehyde were converted into the corresponding nitro alcohols with moderate enantioselectivities of 55–60% *ee* (Entries 11, 12, 14, 15). Much better results were obtained with the more sterically hindered pivaldehyde and cyclohexanecarboxaldehyde: the Henry products **3m** and **3p** were formed with 79 and 81% *ee* and high conversion (Entries 13 and 16). Overall, the borabox ligands induced lower enantioselectivity in the Henry reaction with nitromethane than bisoxazoline ligands.[4a] However, the promising results obtained with aliphatic aldehydes prompted us to further evaluate the borabox ligand **2b** in the Henry reaction with nitropropane.

Reactions with Nitropropane

With the exception of 2- and 4-nitrobenzaldehyde, which again gave nearly racemic products, aromatic aldehydes reacted with moderate to good enantioselectivity (Table 5, Entries 1–8). The diastereoselectivities on the other hand were rather low. The highest *ee* values were recorded for 2-chlorobenzaldehyde (85%) and 4-methoxybenzaldehyde (82%). Interestingly, the corresponding 4-chloro and 2-methoxy derivatives afforded lower enantioselectivities, whereas in the reaction with nitromethane the opposite selectivity order was observed (4-Cl > 2-Cl; 2-MeO > 4-MeO).

Much higher *syn*/*anti* ratios were obtained in the aliphatic series with isobutyraldehyde, propionaldehyde and cyclohexanecarboxaldehyde (Entries 12–18). The best results were achieved with the latter two substrates: **6m**: *syn*/*anti* 85:15, 87% *ee* (*syn*); **6n:** 92:08, 91% *ee*. In order to increase the rate of reaction, the reactions with propionaldehyde and cyclohexanecarboxaldehyde were conducted at 35 °C (Entries 15 and 18). In the latter case, the diastereoselectivity dropped slightly to 85:15, but the enantiomeric excess of the major *syn* isomer remained at 91% while the conversion increased to 73% (Entry 18). For propionaldehyde, both the diastereoselectivity and enantioselectivity de-

Table 5. Henry reaction with nitropropane catalyzed by **2b**/Cu(OTf)$_2$.[a]



syn-**6** *anti*-**6**

Entry	R	**6**	Time [days]	Yield [%][b]	*syn*/*anti*[c]	*ee* (*syn*) [%][d,e]	*ee* (*anti*) [%][d,f]
1	Ph	**6a**	1	74	62:38	65 (1*S*,2*S*)	14 (1*S*,2*R*)
2	2-$NO_2C_6H_4$	**6b**	1	90	68:32	3 (1*S*,2*S*)	3 (1*S*,2*R*)
3	4-$NO_2C_6H_4$	**6c**	1	80	73:27	2 (1*S*,2*S*)	8 (1*S*,2*R*)
4	2-ClC_6H_4	**6d**	1	59	53:47	85 (1*S*,2*S*)	38 (1*S*,2*R*)
5	4-ClC_6H_4	**6e**	1	96	65:35	48 (1*S*,2*S*)	12 (1*S*,2*R*)
6	2-$MeOC_6H_4$	**6f**	1	83	61:39	50 (1*S*,2*S*)	10 (1*S*,2*R*)
7	4-$MeOC_6H_4$	**6g**	2	58	75:25	82 (1*S*,2*S*)	48 (1*S*,2*R*)
8	2-naphthyl	**6h**	1	70	63:37	54 (1*S*,2*S*)	2 (1*S*,2*R*)
9	$PhCH_2CH_2$	**6i**	2	45[g]	63:37	39 (1*S*,2*S*)	11 (1*S*,2*R*)
10	*i*Bu	**6j**	5	53[g]	66:34	63 (1*S*,2*S*)	21 (1*S*,2*R*)
11	*n*Bu	**6k**	4	64[g]	64:36	48 (1*S*,2*S*)	8 (1*S*,2*R*)
12	*i*Pr	**6l**	5	55[g]	87:13	75 (1*S*,2*S*)	19 (1*S*,2*R*)
13	Et	**6m**	4	62[g]	85:15	87 (1*S*,2*S*)	49 (1*S*,2*R*)
14	Et	**6m**	4	55[h]	82:18	89 (1*S*,2*S*)	58 (1*S*,2*R*)
15	Et	**6m**	5	97[g][i]	61:39	30 (1*S*,2*S*)	8 (1*S*,2*R*)
16	Cy	**6n**	5	60[g]	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
17	Cy	**6n**	5	53[h]	93:07	94 (1*S*,2*S*)	74 (1*S*,2*R*)
18	Cy	**6n**	5	73[g][i]	85:15	91 (1*S*,2*S*)	27 (1*S*,2*R*)

[a] Reactions were performed on a 0.5 mmol scale: Cu(OTf)$_2$ (5 mol-%), ligand **2b** (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, the aldehyde (1 equiv.), nitropropane (10 equiv.) and triethylamine (4.5 mol-%) were added and the reaction mixture was stirred for 1 to 5 days. [b] Combined yields of *syn* and *anti* isomers. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC. [e] The absolute configuration of nitroalcohol products *syn*-**6** were assigned by analogy with compound *syn*-**6n**. [f] The absolute configuration of nitroalcohol products *anti*-**6** were assigned by analogy with compound *anti*-**7a**. [g] Conversion determined by ^{1}H NMR spectroscopy of the crude product. [h] Reactions were performed on a 2.5 mmol scale. [i] Reactions were carried out at 35 °C.

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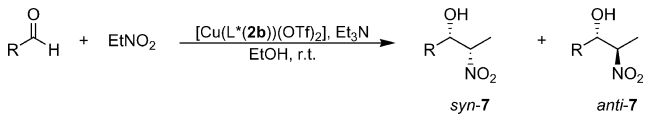
terioriated significantly at elevated temperature (Entry 15). Reactions with these two aldehydes were also carried out on a larger scale. Using 2.5 mmol of aldehyde, the enantioselectivities were improved in both cases (89 and 94% *ee* for the *syn* isomers **6m** and **6n**, Entries 14 and 17).

Reactions with Nitroethane

In addition, nitroethane was also briefly investigated as reactant (Table 6). Again the reaction with cyclohexanecarboxaldehyde was highly stereoselective [90:10 *syn*/*anti*, 90% *ee* (*syn*); Entry 2]. However, the Henry adducts **7a** and **7c** derived from benzaldehyde and propionaldehyde were formed with low diastereo- and enantioselectivity.

Table 6. Henry reaction with nitroethane catalyzed by 2**b**/Cu(OTf)$_2$.[a]



Entry	R	7	Time [days]	Yield [%][b]	*syn*/*anti*[c]	*ee* (*syn*) [%][d,e]	*ee* (*anti*) [%][d,f]
1	Ph	**7a**	1	80	62:38	21 (1*S*,2*S*)	15 (1*S*,2*R*)
2	Cy	**7b**	5	82[g]	90:10	90 (1*S*,2*S*)	47 (1*S*,2*R*)
3	Et	**7c**	5	80[g]	64:36	51 (1*S*,2*S*)	23 (1*S*,2*R*)

[a] Reactions were performed on a 0.5 mmol scale: Cu(OTf)$_2$ (5 mol-%), ligand **2b** (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, the aldehyde (1 equiv.), nitroethane (10 equiv.) and triethylamine (4.5 mol-%) were added and the reaction mixture was stirred for 1 to 5 days. [b] Combined yield of *syn* and *anti* isomers. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC. [e] The absolute configuration of nitroalcohol products *syn*-**7** were assigned by analogy with compound *syn*-**7a**.[6] [f] The absolute configuration of nitroalcohol products *anti*-**7** were assigned by analogy with compound *anti*-**7a**.[6] [g] Conversion determined by ^{1}H NMR spectroscopy of the crude product.

Comparison of Borabox 2b with Box and Other Ligands

In order to assess the efficiency of the borabox ligand **2b** in comparison to analogous bisoxazolines and other privileged ligands,[7] box **1a**, pybox **8**, phox derivatives **9a** and **9b**, and binap **10** were tested in the Henry reaction between cyclohexanecarboxaldehyde and nitropropane (Table 7). In general, the Cu^{II} complexes of these ligands were more reactive than the Cu-borabox catalyst. With ligands (*R*)- and (*S*)-**10** the reaction was complete after less than one day, however, enantioselectivities were very low (Entries 6 and 7). Phox and pybox ligands also performed poorly. Better results were obtained with the box derivative **1a**, but both the *syn*/*anti* ratio and the *ee* were significantly lower than with the borabox analog **2b**.

Conclusions

The results of this study show that boraboxcopper(II) complexes are active and stereoselective catalysts for asymmetric Henry reactions of nitroalkanes with aldehydes. The highest enantio- and diastereoselectivities were obtained in reactions between cyclohexanecarboxaldehyde and nitroethane or nitropropane. For reactions of this type, which build up two new sterogenic centers, borabox-Cu complexes rival the most selective catalysts known to date.[3] With *ee* values of up to 94% and *syn*/*anti* ratios of ≥ 90:10, the borabox ligand **2b** clearly outperformed the corresponding box derivative **1a** and other privileged ligands. On the other hand, for reactions with nitromethane the box ligand **1a** proved to be superior to borabox analogue **2b**. Overall, these findings are in line with previous studies, which have shown that the performance of borabox and box ligands can differ substantially despite their similarity.[2] Thus, replacement of box by borabox ligands may serve as a useful strategy for reactions that give unsatisfactory results with box complexes.

Experimental Section

General Procedure for the Copper-Catalyzed Nitroaldol Reaction: Ligand **2b** (11.5 mg, 0.027 mmol), Cu(OTf)$_2$ (9.00 mg, 0.025 mmol) and Et$_3$N (3.80 µL, 0.027 mmol) were added to a dry Young tube containing a magnetic stirring bar. Ethanol (0.75 mL) was added and the mixture was stirred at room temp. for 3 to 5 hours. To the resulting dark green solution the nitroalkane (5.00 mmol), the aldehyde (0.50 mmol) and Et$_3$N (3.00 µL, 0.022 mmol) were added. After stirring at room temperature for the indicated time (see Tables 2, 3, 4, and 5), the volatile compounds were removed under reduced pressure and the crude product was purified by column chromatography on silica gel [Chemie Uetikon (C-560 D, 0.040–0.063 mm) or Merck (silica gel 60, 0.040–0.063 mm)].

Nitroalcohol (*S*)-3f: The crude product was purified by column chromatography using 15% EtOAc/hexanes as eluent to give a colorless oil (63 mg, 70%, R_f = 0.33). $[\alpha]_D^{20}$ = +7.7 (*c* = 1.1, CHCl$_3$, 56% *ee*). ^{1}H NMR (400.1 MHz, CDCl$_3$, 295 K): δ = 7.29 (t, $^3J_{HH}$ = 7.6 Hz, 1 H, H$_{Ar}$), 7.22–7.20 (m, 1 H, H$_{Ar}$), 7.20–7.16 (m, 2 H, H$_{Ar}$), 5.42 (br. d, $^3J_{HH}$ = 9.6 Hz, 1 H, C*H*OH), 4.60 (dd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.6 Hz, 1 H, C*H*HNO$_2$), 4.50 (dd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 3.0 Hz, 1 H, CH*H*NO$_2$), 2.85 (s, 1 H, OH), 2.37 (s, 3 H, CH$_3$) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$, 295 K): δ = 139.3 (C$_{Ar}$), 138.5 (C$_{Ar}$), 130.1 (CH$_{Ar}$), 129.3 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 123.4 (CH$_{Ar}$), 81.7 (CHOH), 71.4 (CH$_2$NO$_2$), 21.8 (CH$_3$) ppm. IR (NaCl): $\tilde{\nu}$ = 3460 (m$_{br}$), 2984 (m), 2927 (m), 1735 (s), 1556 (s), 1423 (w), 1377 (s), 1247 (s), 1158 (w), 1046 (s), 918 (w), 889 (w), 848 (w), 790 (m), 707 (m) cm^{-1}. C$_9$H$_{11}$NO$_3$ (181.19 g/mol): calcd. C 59.66, H 6.12, N 7.73; found C 59.42, H 6.14, N 7.55. MS (EI, 70 eV): *m*/*z* (%) = 181 (4) [M$^+$], 134 (45), 121 (23), 120 (75), 119 (90), 117 (11), 93 (19), 92 (18), 91 (100), 77 (10), 65 (19), 61 (19), 43 (47). HPLC: OD-H, *n*-heptane/*i*PrOH (85:15), 0.8 mL/min, 20 °C, 220 nm, t_R = 10.7 min (*R*), 12.4 min (*S*).

The absolute configuration of **3f** was assigned based on the sign of optical rotation in comparison with the optical rotation of the corresponding product **3a** reported in the literature.[4a]

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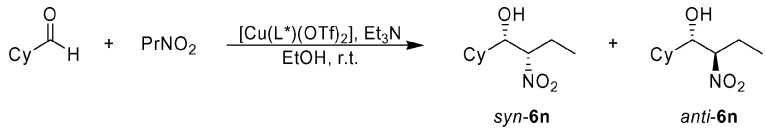
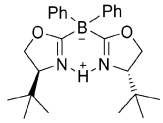
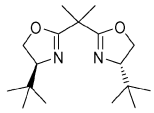
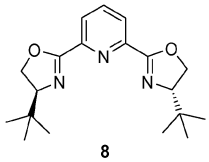
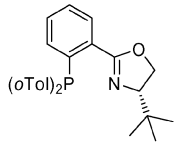
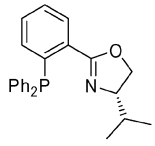
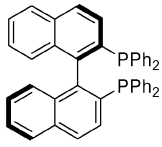
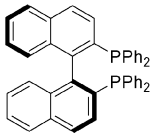
Table 7. Comparison of borabox **2b** with other ligands in the Henry reaction between cyclohexanecarboxaldehyde and nitropropane.[a]



Entry	Ligand	Time [days]	Conversion [%][b]	*syn*/*anti*[b]	*ee syn* [%][c]	*ee anti* [%][c]
1	 **2b**	5	60	92:08	91 (1*S*,2*S*)	33 (1*S*,2*R*)
2	 **1a**	2	65	79:21	66 (1*S*,2*S*)	16 (1*S*,2*R*)
3	 **8**	4	98	73:27	17 (1*S*,2*S*)	2 (1*R*,2*S*)
4	 **9a**	1	97	61:39	25 (1*R*,2*R*)	60 (1*R*,2*S*)
5	 **9b**	1	76	76:24	1 (1*S*,2*S*)	9 (1*S*, 2*R*)
6	 (*R*)-**10**	1	>99	63:37	7 (1*R*,2*R*)	13 (1*R*,2*S*)
7	 (*S*)-**10**	1	>99	64:36	13 (1*S*,2*S*)	15 (1*S*,2*R*)

[a] Reactions were performed on a 0.5 mmol scale: $Cu(OTf)_2$ (5 mol-%), ligand (5.5 mol-%) and triethylamine (5.5 mol-%) were stirred in ethanol (0.75 mL) under Ar at room temperature. After a stirring period of 3 to 5 hours, cyclohexanecarboxaldehyde (1 equiv.), nitropropane (10 equiv.) and triethylamine (4.5 mol-%) were added and the reaction mixture was stirred for 1 to 5 days. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by chiral HPLC.

Nitroalcohols *syn*-6n and *anti*-6n: The crude product was purified by column chromatography using 15% EtOAc/hexanes as eluent to give *syn*-**6n** (50 mg, 50%, R_f = 0.29) and *anti*-**6n** (6 mg, 3%, R_f = 0.19) as colorless oils. ***syn*-6n**: $[\alpha]_D^{20}$ = +2.0 (*c* = 0.73, $CHCl_3$, 94% *ee*). ^{1}H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.54 (ddd, $^3J_{HH}$ = 10.7, $^3J_{HH}$ = 6.4, $^3J_{HH}$ = 4.4 Hz, 1 H, $CHNO_2$), 3.63–3.58 (m, 1 H, C*H*OH), 2.20 (d, $^3J_{HH}$ = 6.9 Hz, 1 H, OH), 2.08–2.01 (m, 1 H, C*H*HCH_3), 1.88–1.82 (m, 1 H, CH*H*CH_3), 1.80–1.72 (m, 3 H, H_{Cy}), 1.67–1.63 (m, 2 H, H_{Cy}), 1.39–1.33 (m, 1 H, H_{Cy}), 1.26–1.10 (m, 5 H, H_{Cy}), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (125.0 MHz, $CDCl_3$, 295 K): δ = 91.9 ($CHNO_2$), 75.9 (CHOH), 40.3 (CH_{Cy}), 29.8 (CH_{2Cy}), 26.8 (CH_{2Cy}), 26.1 (CH_{2Cy}), 26.0 (CH_{2Cy}), 25.7 (CH_{2Cy}), 24.0 (CH_2), 10.2 (CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 3441 (s_{br}), 2929 (s), 2855 (s), 1550 (s), 1451 (m), 1378 (m), 1306 (w), 1109 (w), 1028 (w), 892 (w) cm^{-1}. $C_{10}H_{19}NO_3$ (201.26 g/mol): calcd. C 59.68, H 9.51, N 6.96; found C 59.88, H

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9.35, N 6.79, HPLC: AD-H, *n*-heptane/*i*PrOH (97:03), 0.8 mL/min, 20 °C, 215 nm, t_R = 18.9 min (1*S*,2*S*), 29.4 min (1*R*,2*R*).

***anti*-6n:** $[\alpha]_D^{20}$ = –1 (*c* = 0.12, $CHCl_3$, 74% *ee*). ^1H NMR (500.1 MHz, $CDCl_3$, 295 K): δ = 4.48 (ddd, $^3J_{HH}$ = 11.1, $^3J_{HH}$ = 4.7, $^3J_{HH}$ = 3.0 Hz, 1 H, $CHNO_2$), 3.76 (appt, $^3J_{HH}$ = 5.4 Hz, 1 H, C*H*OH), 2.46 (br. s, 1 H, OH), 2.14–2.08 (m, 1 H, C*H*HCH_3), 1.89–1.86 (m, 1 H, CH*H*CH_3), 1.79–1.71 (m, 3 H, H_{Cy}), 1.67–1.63 (m, 2 H, H_{Cy}), 1.53–1.48 (m, 1 H, H_{Cy}), 1.26–1.10 (m, 5 H, H_{Cy}), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$, 295 K): δ = 91.7 ($CHNO_2$), 76.4 (CHOH), 40.4 (CH_{Cy}), 29.4 (CH_{2Cy}), 28.1 (CH_{2Cy}), 26.1 (CH_{2Cy}), 25.8 (CH_{2Cy}), 25.5 (CH_{2Cy}), 24.2 (CH_2), 10.7 (CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 3448 (m_{br}), 2929 (s), 2855 (s), 1550 (s), 1451 (m), 1379 (m), 1306 (w), 1108 (m), 1058 (w), 893 (w) cm^{-1}. $C_{10}H_{19}NO_3$ (201.26 g/mol): calcd. C 59.68, H 9.51, N 6.96; found C 59.48, H 9.32, N 6.80, HPLC: AD-H, *n*-heptane/EtOH (97:03), 0.5 mL/min, 20 °C, 215 nm, t_R = 31.4 min (1*R*,2*S*), 38.2 min (1*S*,2*R*).

The relative configuration was assigned by comparison of the ^{13}C NMR spectra of **6n** with similar compounds reported in the literature.[8] The absolute configuration of *syn*-**6n** was determined by comparison with published HPLC retention times[5] and the absolute configuration of *anti*-**6n** was assigned by analogy with the absolute configuration of nitroalcohol *anti*-**7a**.[6]

Supporting Information (see also the footnote on the first page of this article): Characterization data including microanalytical analyses for compounds **6c**–**6h**, **6j**–**6m**, **7a** and **7c**.

Acknowledgments

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