Cooperative Catalysis

DOI: 10.1002/anie.201107785

Urea/Transition-Metal Cooperative Catalyst for *anti*-Selective Asymmetric Nitroaldol Reactions**

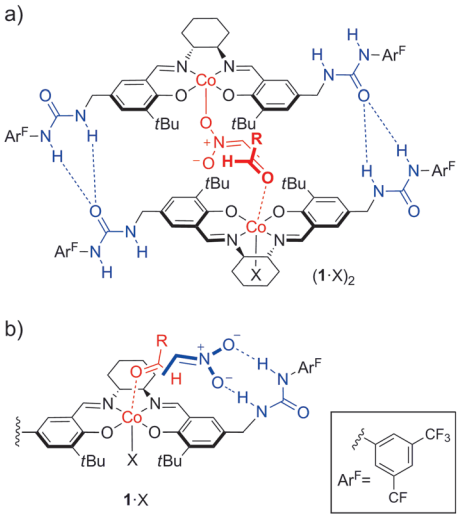
*Kai Lang, Jongwoo Park, and Sukwon Hong**

Dedicated to Professor Eun Lee on the occasion of his 65th birthday

Simultaneous activation of two reaction partners in a well-defined spatial arrangement is a common theme in enzyme catalysis. This nature-inspired concept of cooperative activation has emerged as a new trend in the design of highly efficient asymmetric catalysts.[1] A number of bimetallic catalysts,[2] bifunctional organocatalysts,[3] and bifunctional metal catalysts[4] that demonstrate excellent performance have been developed. Among them, bifunctional catalysts often feature an acidic site (Lewis acid or H-bond-donor unit), which is tethered to a base. Nonetheless, examples of an alternative design in which a Lewis acid and an H-bond donor are tethered are quite rare.[5]

Asymmetric nitroaldol (Henry) reactions[6–8,9a,b,10] have drawn much attention as important carbon–carbon bond-forming reactions. Several bimetallic and bifunctional catalysts exhibited high enantioselectivity in Henry reactions with nitromethane. However, asymmetric Henry reactions with nitroalkanes other than nitromethane proved to be more challenging,[7,8] and often suffered from slow reaction rates and poor diastereoselectivity. Particularly, *anti* diastereoselectivity is difficult to achieve,[8] which could be attributed to the fact that a metal-chelation transition state would favor a *syn* diastereomer.[8g] Thus, an open antiparallel transition state was strategically pursued for *anti*-selective Henry reactions.[8a–c] Recently, the research groups of Ooi and Shibasaki have independently reported highly *anti*-selective catalysts that enable an antiparallel transition geometry by double H-bonding[8d,e] and a heterobimetallic scaffold,[8f,g] respectively.

With the aim to design dual activation catalysts, we previously developed base-tethered copper catalysts[9a] and self-assembled dinuclear cobalt catalysts through aminopyridine/pyridone H-bonding interactions.[9b] Recently, we devised second-generation self-assembled catalysts that feature urea–urea H-bonding, and such [(bisurea–salen)Co] catalysts showed significant rate acceleration in bimetallic transformations.[9c] During the course of the study, we were intrigued by the possibility that the [(bisurea–salen)Co] catalyst might enable the antiparallel transition state for the Henry reaction,[10] either by bimetallic dual activation or by H-bond/metal bifunctional activation (Scheme 1). Herein we report highly enantio- and *anti*-diastereoselective Henry reactions that are catalyzed by the [(bisurea–salen)Co] catalysts **1**·X. The cooperative activation by H-bonds of urea and the Lewis acidic metal center is suggested by preliminary studies.



Scheme 1. a) Bimetallic (self-assembled) and b) monometallic (bifunctional) activation by [(bisurea–salen)Co] catalysts.

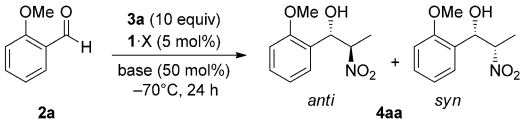
[(Bisurea–salen)Co] catalysts (**1**·X) were optimized with the diastereoselective Henry reaction with nitroethane (**3a**) at −70 °C (Table 1). The metal oxidation state proved to be pivotal, and a Co^{III}-based catalyst (X = OTs) significantly improved the reaction yield, the *anti*/*syn* diastereomeric ratio, and the enantioselectivity (Table 1, entry 1 versus entry 2). The reaction conditions were then further optimized with regard to solvent, base, and counterion. Higher *anti* selectivity was observed with methyl *tert*-butyl ether (MTBE) as solvent and *N*-ethylpiperidine (EtPip) as base. Although both toluene-*p*-sulfonate (OTs) and 3,5-bis(trifluoromethyl)benzoate (OBz^F) gave excellent stereoselectivity with **2a** (Table 1, entries 7 and 8), OBz^F was selected from further screening with 4-fluorobenzaldehyde (**2b**).[11] Note that an excellent *anti* diastereoselectivity (48:1) and enantioselectivity (96% *ee*) were achieved under the optimized conditions (Table 1, entry 8).

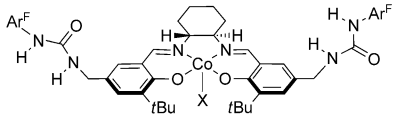
[*] K. Lang, J. Park, Prof. S. Hong
Department of Chemistry, University of Florida
Gainesville, FL 32611-7200 (USA)
E-mail: sukwon@ufl.edu

[**] This work was supported by the U.S. National Science Foundation (Grant CHE-0957643).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107785.

Table 1: Optimization of reaction conditions.[a]





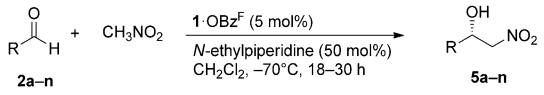
1·X (Ar^F=3,5-$(CF_3)_2C_6H_3$)

Entry	X^-	Base	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	–	DIPEA	CH_2Cl_2	49	4:1	53/18
2	OTs	DIPEA	CH_2Cl_2	71	8:1	92/59
3	OTs	DIPEA	MTBE	68	11:1	87/58
4	OTs	Et_3N	CH_2Cl_2	88	13:1	90/59
5	OTs	Et_3N	MTBE	82	18:1	93/73
6	OTs	EtPip	CH_2Cl_2	83	24:1	95/82
7	OTs	EtPip	MTBE	81	>50:1	93/n.d.
8	**OBz^F**	**EtPip**	**MTBE**	**84**	**48:1**	**96/n.d.**

[a] All reactions were performed on a 0.25 mmol scale of aldehyde with **1**·X (5 mol%) and nitroethane (10 equiv) in solvent (0.1 mL) at −70°C. [b] Yields of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] *ee* values of *anti*/*syn* diastereomers determined by HPLC analysis on a chiral stationary phase. DIPEA = *N*,*N*-diisopropylethylamine, n.d. = not determined. The entry in bold marks the optimized reaction conditions.

The optimized catalyst **1**·OBz^F was first applied to enantioselective Henry reactions with nitromethane (Table 2). Excellent enantioselectivities (94–97% *ee*) and good yields (82–99%) were observed with variously substituted benzaldehydes (Table 2, entries 1–11). Furthermore, high enantioselectivities (91–92% *ee*) and good yields (88–90%) were also observed with an α,β-unsaturated aldehyde (Table 2, entry 12) and linear aliphatic aldehydes (Table 2, entries 13 and 14).

Table 2: Enantioselective Henry reactions with nitromethane.[a]

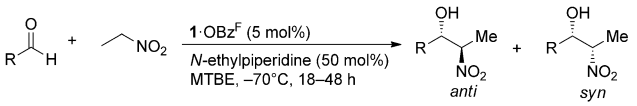


Entry	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	2-MeO-C_6H_4 (**2a**)	20	99	97
2	2-Cl-C_6H_4 (**2c**)	24	94	95
3	2-F-C_6H_4(**2d**)	24	99	96
4	1-naphthyl (**2e**)	24	99	97
5	3-F-C_6H_4 (**2f**)	24	88	95
6	4-F-C_6H_4 (**2b**)	24	85	94
7	4-Cl-C_6H_4 (**2g**)	24	87	95
8	4-Ph-C_6H_4 (**2h**)	18	95	96
9[d]	4-MeO-C_6H_4 (**2i**)	30	82	94
10	4-benzodioxole (**2j**)	24	86	95
11	C_6H_5(**2k**)	24	85	97
12	(*E*)-Ph-CH=CH (**2l**)	30	88	92
13	$BnOCH_2CH_2$(**2m**)	24	90	92
14[d]	$PhCH_2CH_2$ (**2n**)	18	89	91

[a] Reactions were performed on a 0.25 mmol scale of aldehyde with **1**·OBz^F (5 mol%) and nitromethane (10 equiv) in CH_2Cl_2 (0.3 mL) at −70°C. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction was run at −50°C. Bn = benzyl.

Catalyst **1**·OBz^F generally gave excellent enantioselectivities (90–98% *ee* for *anti* product) and good yields (80–94%) in the Henry reactions with nitroethane (**3a**; Table 3).

Table 3: Scope of diastereoselective Henry reactions.[a]



Entry	R	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	2-MeO-C_6H_4 (**2a**)	24	84	48:1	96/nd
2	2-BnO-C_6H_4(**2o**)	24	85	11:1	96/76
3	2-Cl-C_6H_4(**2c**)	20	89	10:1	90/74
4	2-F-C_6H_4 (**2d**)	24	90	8:1	94/82
5	3-F-C_6H_4 (**2f**)	24	82	1.8:1	95/85
6[e]	3-MeO-C_6H_4(**2p**)	24	95	2.0:1	99/87
7	4-F-C_6H_4 (**2b**)	18	87	2.5:1	98/85
8	4-Ph-C_6H_4 (**2h**)	24	86	2.4:1	97/86
9	C_6H_5 (**2k**)	48	94	1.6:1	97/82
10	$BnOCH_2CH_2$ (**2m**)	24	89	1.1:1	96/90
11	Me_2C=CH (**2q**)	30	80	9:1	98/65
12	(*E*)-Ph(Me)C=CH (**2r**)	36	82	4:1	97/90

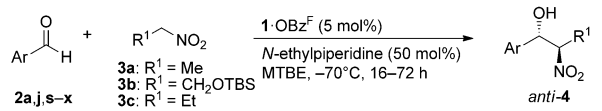
[a] Reactions were performed on a 0.25 mmol scale of aldehyde with **1**·OBz^F (5 mol%) and nitroethane (10 equiv) in MTBE (0.1 mL) at −70°C. [b] Yields of isolated products. [c] Ratio of *anti*:*syn* determined by ^{1}H NMR spectroscopy. [d] *ee* values of *anti*/*syn* diastereomers, determined by HPLC analysis on a chiral stationary phase. [e] Reaction was run at −50°C.

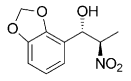
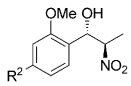
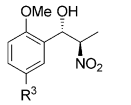
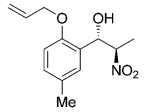
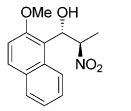
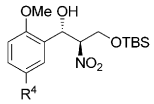
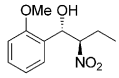
However, the *anti* diastereoselectivity varies with the substrate. While high *anti* selectivities were obtained with benzaldehydes with an ortho substituent (Table 3, entries 1–4), *anti* selectivity significantly decreased with benzaldehydes that lack *ortho* substitution (d.r. ≈ 2:1; Table 3, entries 5–9). Interestingly, a similar "*ortho* effect" was observed with non-aromatic aldehydes (Table 3, entries 11 and 12 versus entry 10).

High *anti* selectivities as well as excellent enantioselectivities were observed for di- or trisubstituted benzaldehydes that bear an *ortho*-alkoxy substituent (Table 4). Additional substitution at the C-3 (Table 4, entry 1), C-4 (entries 2 and 3), and C-5 positions (entries 4–7) seems to be well tolerated if an *ortho*-alkoxy group is present. Furthermore, it is possible to use other nitroalkanes, such as $TBSOCH_2CH_2NO_2$ (**3b**; Table 4, entries 8–10) and nitropropane (**3c**; entry 11). To the best of our knowledge, examples of highly *anti*-selective asymmetric nitroaldol reactions with such 2-alkoxy-containing benzaldehydes are very rare.[12]

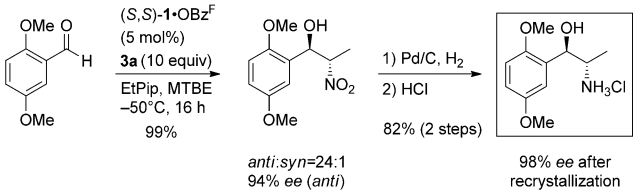
The synthetic utility of *anti*-selective nitroaldol reactions of 2-alkoxy-containing benzaldehydes is demonstrated by the short stereoselective synthesis of (1*R*,2*S*)-methoxamine hydrochloride, an α_1-adrenergic receptor agonist[13] (Scheme 2). While previous stereoselective syntheses of methoxamine·HCl typically involved diastereoselective reduction of a chiral α-aminoketone,[14] the current method allows the introduction of both stereocenters in a single step with

Table 4: Henry reactions of substituted benzaldehydes that bear an *ortho*-alkoxy group.[a]



Entry	Product		*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1		**4ja**	24	96	8:1	96/80
2		**4sa** (R^2 = Br)	24	94	15:1	95/96
3		**4ta** (R^2 = OMe)	72	81	>50:1	90/n.d.
4		**4ua** (R^3 = F)	24	92	26:1	96/86
5[e]		**4va** (R^3 = OMe)	16	99	24:1	96/76
6		**4wa**	24	96	9:1	94/n.d.
7[e]		**4xa**	36	95	17:1	97/n.d.
8[f]		**4ab** (R^4 = H)	48	88	>50:1	94/n.d.
9[f]		**4ub** (R^4 = F)	42	99	8:1	93/75
10[f]		**4vb** (R^4 = OMe)	60	97	7:1	91/76
11		**4ac**	36	67	6:1	85/88

[a] Reactions were performed on a 0.25 mmol scale of aldehyde with **1**·OBz^F (5 mol%) and nitroethane (10 equiv) in MTBE (0.1 mL) at −70°C. [b] Yields of isolated products. [c] Ratio of *anti*:*syn* determined by ^{1}H NMR spectroscopy. [d] *ee* values of *anti*/*syn* diastereomers, determined by HPLC analysis on a chiral stationary phase. [e] Reaction was run at −50°C. [f] Reaction was run at −50°C with **3b** (5 equiv) in MTBE (0.5 mL). TBS = *tert*-butyldimethylsilyl.

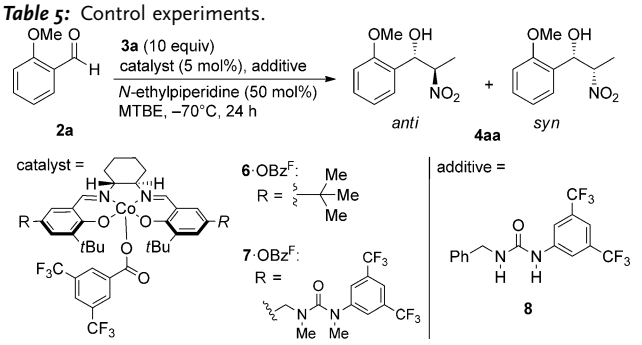


Scheme 2. Asymmetric synthesis of (1*R*,2*S*)-methoxamine·HCl.

excellent stereocontrol (*anti*:*syn* = 24:1, 94% *ee* for *anti*) by using 5 mol% of the antipode catalyst (*S*,*S*)-**1**·OBz^F.

To elucidate the mechanism of the [(bisurea–salen)Co] catalyzed reaction, a series of experimental studies were performed. Firstly, the NH moiety of urea proved to be crucial for both the reaction rate and stereoselectivity (Table 5). The unfunctionalized [(salen)Co^{III}] catalyst **6**·OBz^F and the *N*-methyl-functionalized catalyst **7**·OBz^F gave nitroaldol product **4aa** in much lower yield and stereoselectivity (Table 5, entries 1 and 5), compared to urea-functionalized catalyst **1**·OBz^F (Table 5, entry 6). Furthermore, control experiments with varying amounts of exogenous urea additive[15] **8** show that the reaction is significantly accelerated by the additive (Table 5, entries 1–3). Note that **8** alone (without the Co catalyst) can catalyze the diastereoselective Henry reaction to give the product in 85% yield and 3:1 d.r. (Table 5, entry 4), thus suggesting that urea **8** is capable to activate the reactants.[16]

Table 5: Control experiments.



Entry	Catalyst	Additive	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**6**·OBz^F	–	30	3:1	78/81
2	**6**·OBz^F	**8** (10 mol%)	75	5:1	62/65
3	**6**·OBz^F	**8** (50 mol%)	85	5:1	62/64
4[d]	–	**8** (10 mol%)	85	3:1	0/0
5	**7**·OBz^F	–	14	4:1	85/82
6	**1**·OBz^F	–	84	48:1	96/n.d.

[a] Yields of isolated products. [b] Ratio of *anti*/*syn* determined by ^{1}H NMR spectroscopy. [c] *ee* values of *anti*/*syn* diastereomers, determined by HPLC analysis on a chiral stationary phase. [d] The reaction does not proceed with *N*-ethylpiperidine alone at −70°C.

Secondly, when the relationship between the enantiomeric purity of the [(salen)Co] catalysts and that of the Henry reaction product **5a** was investigated, an interesting trend was observed (Figure 1). A positive nonlinear effect[17] was observed for both Co^{II} catalysts (**6** and **1**), thus suggesting a nonmonomeric active species (Figure 1a and c), whereas a linear relationship was observed for the corresponding Co^{III} catalysts (**6**·OBz^F and **1**·OBz^F; Figure 1b and d). Furthermore, while the rate of the reaction **2a**→**5a** was second order with respect to [catalyst] for the unfunctionalized Co^{II} catalyst **6** (rate = k[**6**]^2),[9b] the corresponding Co^{III} catalyst **6**·OBz^F showed first-order kinetics (rate = k[**6**·OBz^F]).[18,19] These results suggest that a monometallic pathway is favored in [(salen)Co^{III}]-catalyzed Henry reactions. Our initial attempts to determine the association constant between urea **8** and nitroalkane from ^{1}H NMR experiments were unsuccessful,[11] presumably because of the weak urea/nitroalkane interaction.[20] In sharp contrast, when the pregenerated 2-nitropropanate anion and urea **8** were used in the ^{1}H NMR titration experiment, a sufficiently high association constant (K_a = 510 M^{-1}) was observed in [D$_6$]-DMSO at 25°C, which is in good agreement with previous reports.[21] Note that the NMR titration results support the idea that the urea group can interact/activate anionic nitronate nucleophiles. All of

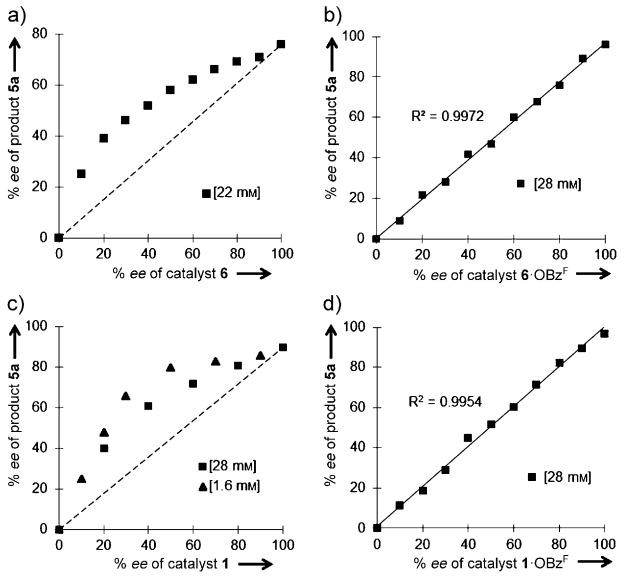


Figure 1. Studies on the (non)linear effect of the reaction of **2a** to **5a** with [(salen)Co] catalysts by varying the metal oxidation state and the presence of the bisurea functionality. Reactions with a) unfunctionalized Co^{II} catalyst, b) unfunctionalized Co^{III} catalyst, c) bisurea-functionalized Co^{II} catalyst, and d) bisurea-functionalized Co^{III} catalyst.

those observations collectively suggest that the monometallic, bifunctional mechanism is operative for the [(bisurea–salen)Co^{III}] catalyzed nitroaldol reactions in which the cooperative activation is provided by H-bonds of urea[22,23,24] and the Lewis acidic metal center (Scheme 1b).

In conclusion, a new type of cooperative catalyst that features urea H-bonding and a cobalt center has been developed for *anti*-selective asymmetric nitroaldol reactions. The urea H-bonds play a crucial role in the dramatic improvement in reaction yield, enantioselectivity, and *anti*-diastereoselectivity. The use of the urea–cobalt bifunctional catalyst successfully extends the substrate scope of *anti*-selective Henry reactions to previously unexplored aldehydes, and the synthetic utility is demonstrated by the concise asymmetric synthesis of (1*R*,2*S*)-methoxamine hydrochloride. Further application of this novel concept as well as more detailed mechanistic studies are currently under way in our research group.

Received: November 4, 2011
Published online: January 4, 2012

Keywords: asymmetric catalysis · cobalt · cooperative effects · hydrogen bonds · ureas

[1] Reviews: a) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566; b) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655; c) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117.

[2] For selected recent examples, see: a) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572; b) C. Mazet, E. N. Jacobsen, *Angew. Chem.* **2008**, *120*, 1786; *Angew. Chem. Int. Ed.* **2008**, *47*, 1762; c) S. Handa, V. Gnanadesikan, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 4925; d) K. Endo, M. Ogawa, T. Shibata, *Angew. Chem.* **2010**, *122*, 2460; *Angew. Chem. Int. Ed.* **2010**, *49*, 2410.

[3] For reviews on bifunctional organocatalysts, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; b) S. J. Connon, *Chem. Commun.* **2008**, 2499; c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632.

[4] For selected examples of bifunctional metal/tethered amine catalysts, see: a) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668; b) S. France, M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth, T. Lectka, *J. Am. Chem. Soc.* **2005**, *127*, 1206; c) Y.-M. Lin, J. Boucau, Z. Li, V. Casarotto, J. Lin, A. N. Nguyen, J. Ehrmantraut, *Org. Lett.* **2007**, *9*, 567; d) F. Yang, D. Zhao, J. Lan, P. Xi, L. Yang, S. Xiang, J. You, *Angew. Chem.* **2008**, *120*, 5728; *Angew. Chem. Int. Ed.* **2008**, *47*, 5646; e) T. Kull, J. Cabrera, R. Peters, *Chem. Eur. J.* **2010**, *16*, 9132.

[5] For a recent example of cooperative catalysis that comprises a Lewis acid and an amine–urea organocatalyst, see: T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140.

[6] For recent reviews, see: a) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561; for selected examples, see: b) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418; c) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875; d) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889; *Angew. Chem. Int. Ed.* **2002**, *41*, 861; e) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692; f) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem.* **2005**, *117*, 3949; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881.

[7] For *syn*-selective asymmetric Henry reactions, see: a) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388; b) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894; c) Y. Sohtome, Y. Kato, S. Handa, N. Aoyama, K. Nagawa, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2231; d) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761; e) T. Arai, R. Takashita, Y. Endo, M. Watanabe, A. Yanagisawa, *J. Org. Chem.* **2008**, *73*, 4903; f) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588.

[8] a) D. Seebach, A. K. Beck, F. Lehr, T. Weller, E. Colvin, *Angew. Chem.* **1981**, *93*, 422; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 397; for *anti*-selective asymmetric Henry reactions using silyl nitronates, see: b) T. Risgaard, K. V. Gothelf, K. A. Jørgensen, *Org. Biomol. Chem.* **2003**, *1*, 153; c) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054; for *anti*-selective Henry reactions using nitroalkanes directly, see: d) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392; e) D. Uraguchi, S. Nakamura, T. Ooi, *Angew. Chem.* **2010**, *122*, 7724; *Angew. Chem. Int. Ed.* **2010**, *49*, 7562; f) S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 3274; *Angew. Chem. Int. Ed.* **2008**, *47*, 3230; g) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860; h) G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725; i) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Org. Lett.* **2010**, *12*, 3058.

[9] a) K. Lang, J. Park, S. Hong, *J. Org. Chem.* **2010**, *75*, 6424; b) J. Park, K. Lang, K. A. Abboud, S. Hong, *J. Am. Chem. Soc.* **2008**, *130*, 16484; c) J. Park, K. Lang, K. A. Abboud, S. Hong, *Chem. Eur. J.* **2011**, *17*, 2236.

[10] For [(salen)metal]-catalyzed Henry reactions, see: a) Y. Kogami, T. Nakajima, T. Ikeno, T. Yamada, *Synthesis* **2004**, 1947; b) R. Kowalczyk, Ł. Sidorowicz, J. Skarżewski, *Tetrahedron: Asymmetry* **2007**, *18*, 2581; c) R. Kowalczyk, P. Kwiatkowski, J.

Skarżewski, J. Jurczak, *J. Org. Chem.* **2009**, *74*, 753; d) A. Zulauf, M. Mellah, E. Schulz, *J. Org. Chem.* **2009**, *74*, 2242; also see ref. [9b].
[11] See the Supporting Information for details.
[12] To the best of our knowledge, there is only one report that shows significant *anti* selectivity for 2-alkoxy-containing benzaldehydes. Pedro and co-workers reported the Cu-catalyzed *anti*-selective Henry reaction between **2a** and nitroethane (**3a**) to afford **4aa** in 95% yield, *anti*:*syn* = 82:18, and 95%/94% *ee* (*anti*/*syn*). See Ref. [8h].
[13] a) P. N. Patil, A. Tye, J. B. LaPidus, *J. Pharmacol. Exp. Ther.* **1967**, *156*, 445; b) R. Baltzly, N. B. Mehta, *J. Med. Chem.* **1968**, *11*, 833; c) R. M. DeMarinis, W. M. Bryan, D. H. Shah, J. P. Hieble, R. G. Pendleton, *J. Med. Chem.* **1981**, *24*, 1432; d) O. M. Jones, J. M. Thompson, A. F. Brading, N. J. M. Mortensen, *Br. J. Surg.* **2003**, *90*, 872.
[14] M. Fujita, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 5415.
[15] For a recent example showing the synergy between a chiral Co catalyst and a thiourea additive, see: H. Y. Kim, K. Oh, *Org. Lett.* **2011**, *13*, 1306.
[16] In contrast, urea additives decreased the rate of the [(salen)-Co^{III}]-catalyzed hydrolytic kinetic resolution of epoxides. See Ref. [9c].
[17] T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456.
[18] Increased Lewis acidity of Co^{III} versus Co^{II} might be a plausible reason for this mechanism change.
[19] First-order kinetics are observed for both bisurea-containing Co^{II} catalyst **1** and Co^{III} catalyst **1**·OBz^F (see the Supporting Information for details). However, first-order kinetics alone cannot distinguish between the two mechanisms (Scheme 1a versus b), as the first-order kinetics is expected from the covalently tethered bimetallic catalysts or strongly self-associating systems. For relevant discussions, see: a) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687; b) D. G. Blackmond, *Adv. Synth. Catal.* **2002**, *344*, 156; c) Ref [9c].
[20] The interaction between (thio)ureas and neutral nitro compounds is generally weak, see: a) T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072; b) J. Bu, N. D. Lilienthal, J. E. Woods, C. E. Nohrden, K. T. Hoang, D. Truong, D. K. Smith, *J. Am. Chem. Soc.* **2005**, *127*, 6423.
[21] Hamilton determined the K_a ($120\,M^{-1}$) between $Bu_4N^+NO_2CHCH_3^-$ and 1,3-dimethylthiourea in [D_6]-DMSO. It was found that the negative charge on the nitronate is crucial for a strong association with thiourea, see: B. R. Linton, M. S. Goodman, A. D. Hamilton, *Chem. Eur. J.* **2000**, *6*, 2449.
[22] For anion recognition by (thio)urea, see: C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520.
[23] For reviews on H-bond-donor catalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187.
[24] For reviews on catalysis involving (thio)urea/nitro(nate)interactions, see: a) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593; for selected examples, see: b) T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470; *Angew. Chem. Int. Ed.* **2005**, *44*, 466; c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; d) C. Rabalakos, W. D. Wulff, *J. Am. Chem. Soc.* **2008**, *130*, 13524; e) W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016.

