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Organocatalytic Asymmetric Nitroaldol Reaction: Cooperative Effects of Guanidine and Thiourea Functional Groups

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday

Abstract: Catalytic enantio- and diastereoselective nitroaldol reactions were explored by using designed guanidine–thiourea bifunctional organocatalysts under mild and operationally simple biphasic conditions. These catalytic asymmetric reactions have a broad substrate generality with respect to the variety of aldehydes and nitroalkanes. Based on this catalytic nitroaldol process, straightforward syntheses of cytoxazone and 4-*epi*-cytoxazone were achieved. These catalytic nitroaldol reactions require KI as an additive for highly asymmetric induction; it operates by inhibiting the retro mode of the reaction. On the basis of studies of structure and catalytic-activity relationships, a plausible guanidine–thiourea cooperative mechanism and a transition state of the catalytic reactions are proposed. Drastic substituent effects on the catalytic properties of this catalyst may lead to the development of new chiral surfactants.

Keywords: chemoselectivity · guanidine · nitroaldol reaction · organocatalysis · surfactants

Introduction

Catalytic asymmetric synthesis provides potentially atom-economical[1] and environmentally benign processes to generate optically active compounds from prochiral substrates.[2] The development of asymmetric bifunctional catalysts, which can activate both nucleophilic and electrophilic substrates, has received much attention, because the synergistic effect of the two active sites in the bifunctional catalyst is believed to activate the reaction substrates and to control the relative positions of the reacting components. Since the general design concept of bifunctional catalysts was proposed by Shibasaki and co-workers,[3] various metal-based bifunctional catalysts have been explored.[4] By tuning the combination of metals and/or chiral ligands, these catalysts can be applied to a wide range of asymmetric reactions. On the other hand, metal-free bifunctional organocatalysts, which have two active sites linked by a covalent bond through a chiral backbone, have recently been developed.[5] Their inertness to moisture and oxygen makes the reaction simple and practical. Despite rapid progress in this field, most bifunctional organocatalysts have "privileged" structures,[6] such as proline,[7] cinchona alkaloid,[8] 1,1′-bi-2,2′-naphthol (BINOL),[9] and tartaric acid.[10] The rational structure development of organocatalysts remains a challenging issue.

During our studies to develop new classes of organocatalysts,[11] we focused on specific molecular recognition involving guanidine[12] and thiourea[13–16] functional groups. These selective molecular recognitions,[17] that is, guanidinium cation/nucleophilic anions and thiourea group/carbonyl compounds, led us to develop a new class of asymmetric heterobifunctional organocatalysts that contain both guanidine and thiourea groups. Our concept for the design of these catalysts is shown in Scheme 1. We hypothesized that 1) catalysts that bear guanidinium and thiourea functional groups linked by a suitable chiral spacer might simultaneously activate a nucleophile and an electrophile in asymmetric proximity,

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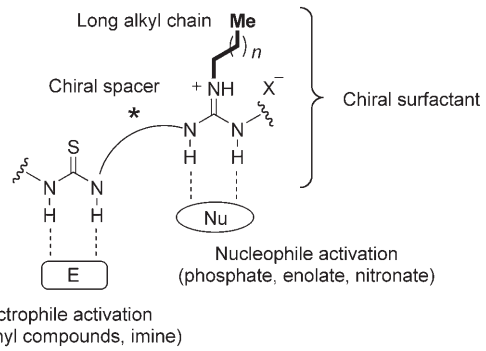


Scheme 1. Concept for the design of guanidine–thiourea heterobifunctional organocatalysts.

and 2) the introduction of a long alkyl chain on the guanidinium group of the catalyst might regulate self-aggregation of the catalyst in water-containing biphasic systems to form a chiral surfactant, thereby controlling the reactivity and selectivity of the catalytic reaction.

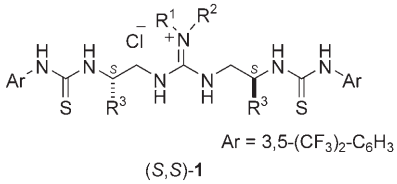
To evaluate this concept, we investigated catalytic asymmetric nitroaldol reactions by utilizing a guanidine–thiourea heterobifunctional organocatalyst. The nitroaldol reaction is a fundamental carbon–carbon bond-forming reaction that proceeds under mild basic conditions.[18,19] Despite the versatility of the substrates and ease of transformation into synthetically useful chiral building blocks, only a few highly selective asymmetric versions of this reaction with organocatalysts have been reported.[20–22] Furthermore, only one successful approach for a highly diastereo- and enantioselective nitroaldol reaction with prochiral nitroalkanes has been reported.[21] Herein we present details of our guanidine–thiourea heterobifunctional organocatalyst for a series of asymmetric nitroaldol reactions. The mechanism of the bifunctional catalytic reaction and the synthetic utility of this catalyst for stereoselective synthesis of biologically active compounds are also described.

Abstract in Japanese:
グアニジン/チオウレアヘテロ多官能基型触媒を用いて、アルデヒドとニトロアルカンを基質とする触媒的不斉ニトロアルドール反応を開発した。本反応は高い基質一般性を有しており、エナンチオ選択的反応、ジアステレオー エナンチオ選択的反応、ジアステレオ選択的反応を実現することができた。レトロニトロアルドール反応による選択性の低下を抑制するために、水/トルエン二相系条件、KIの添加が必須であった。また、触媒グアニジン上の長鎖アルキル鎖、キラルスペーサー上のベンジル基が、二相系溶媒界面における触媒の自己集合、即ち、不斉反応場の構築に寄与していることを見出した。更に触媒的不斉ニトロアルドール反応を活用し、効率的なcytoxazone 類の合成法を開発した。

Results and Discussion

Asymmetric Nitroaldol Reactions with Prochiral Aldehydes: Development of a Practical Process Free from the Retro-Nitroaldol Reaction[23]

On the basis of our concept, we designed and synthesized C_2-symmetric guanidine–thiourea catalysts **1** (Scheme 2) as a



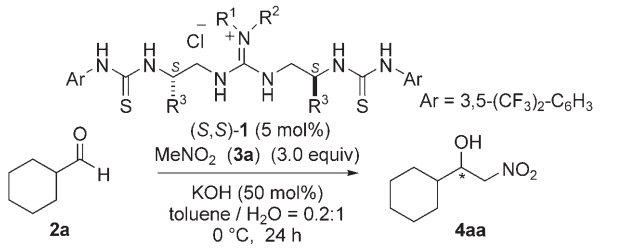
Scheme 2. Structure of guanidine–thiourea bifunctional organocatalyst (*S*,*S*)-**1**.

new class of bifunctional organocatalysts.[11f] These catalysts can be easily synthesized from optically active amino acids, one of the cheapest and most plentiful chiral sources, to give various chiral spacers (R^3), and the substituents on the guanidine group (R^1, R^2) can be easily modified as required.

In the catalytic asymmetric Henry reaction, retroreaction should be suppressed to obtain high asymmetric induction.[24] Considering the highly hydrophobic nature of **1** with a long alkyl chain in R^1, we planned to use **1** under biphasic conditions[25] to inhibit the retro-nitroaldol reaction.[26] We anticipated that if the C–C bond-forming process takes place at the interfacial layer through the expected dual-activation mode, the nitroaldol product should be transferred to the organic layer after hydrolysis of the initially formed nitroalcohol–catalyst complex, thus resulting in inhibition of the retro mode of the reaction. Based on this hypothesis, the enantioselective nitroaldol reaction of **2a** was examined in the presence of **1** (5 mol%) under toluene/aqueous potassium hydroxide biphasic conditions at 0°C (Table 1). Our initial catalyst screening revealed that **1a**, which has an octadecyl substituent at R^1 and a benzyl group at R^3 as a chiral spacer, was the most effective catalyst in terms of both reactivity and enantioselectivity (Table 1, entry 1).[27]

To clarify the occurrence of the retro-nitroaldol process under these reaction conditions, time-course studies were done with the catalyst **1a** (Table 2). As shown in Table 2, entry 1, the enantiomeric excess of the nitroaldol product **4aa** gradually decreased under the biphasic conditions as the reaction time was prolonged, which indicates that the retro-nitroaldol process occurred. After various conditions, such as the organic solvent used, the ratio of organic solvent to water, and the amount of KOH and additives used, were screened, we found that the addition of inorganic salts was effective for inhibiting the retro-mode reaction and for improving the enantioselectivity. Addition of a harder counteranion did not give good results, although it was reported to improve the selectivity in the case of chiral quaternary ammonium catalysts (Table 2, entries 2 and 3).[28] On the other hand, the addition of a softer anionic species improved the

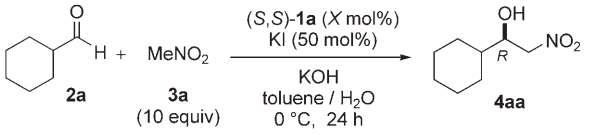
Table 1. Enantioselective nitroaldol reaction with (*S*,*S*)-**1a**[a]



Entry	Cat.	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**1a**	$C_{18}H_{37}$	H	Bn	91	43	*R*
2	**1b**	C_8H_{17}	H	Bn	34	8	*R*
3	**1c**	C_4H_9	H	Bn	37	33	*R*
4	**1d**	C_4H_9	C_4H_9	Bn	24	18	*S*
5	**1e**	$C_{18}H_{37}$	H	Me	80	14	*R*
6	**1f**	$C_{18}H_{37}$	H	*i*Pr	89	36	*R*
7	**1g**	$C_{18}H_{37}$	H	*t*Bu	55	9	*S*

[a] Reactions were carried out on the 0.1-mmol scale in 0.2 mL toluene and 1.0 mL H_2O. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute stereochemistry of **4aa** was determined based on the retention time reported by Trost and Yeh[20b] and Evans et al.[20c] Bn = benzyl.

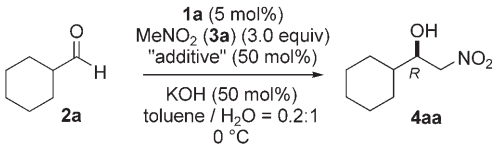
Table 3. Optimization of catalytic enantioselective nitroaldol reaction of **2a** with **3a**.[a]



Entry	Cat. [mol%]	Toluene/H_2O	KOH [mol%]	Yield [%][b]	*ee* [%][c]
1	10	0:1	50	99	32
2	10	0.2:1	50	99	52
3	10	0.5:1	50	99	67
4	10	1:1	50	99	69
5	10	2:1	50	99	68
6	10	1:2	50	99	52
7	10	1:1	30	99	87
8	10	1:1	10	94	90
9	10	1:1	5	91	92
10	5	1:1	5	99	95
11	3	1:1	5	80	89

[a] All reactions were carried out on the 0.1-mmol scale in 1.0 mL H_2O. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

Table 2. Time-course studies in the presence of various inorganic salts (screening conditions).



Time		1 h		3 h		12 h		24 h	
Entry	Additive	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1	–	52	52	71	50	90	47	91	43
2	KBF_4	55	61	60	59	75	47	77	47
3	$NaBF_4$	60	53	63	48	67	42	64	38
4	KBr	58	72	62	70	63	63	76	57
5	NaBr	57	70	60	68	65	60	65	60
6	LiI	60	72	62	70	65	68	65	66
7	NaI	46	75	57	76	64	68	64	67
8	KI	66	75	74	75	88	74	88	74

initial enantioselection (Table 2, entries 4–7, 1 h). We were delighted to find that KI inhibited the retro-mode reaction, and the nitroaldol product **4aa** was obtained in 88% yield and with 74% *ee* after 24 h without loss of the initial enantiomeric excess (Table 2, entry 8). The catalyst **1a**, when its counteranion was changed to iodide,[29] also catalyzed the reaction to give **4aa** in 85% yield and with 72% *ee*. This result indicates that the chloride counteranion of **1a** may be changed to iodide in situ under these reaction conditions in the presence of KI.

As suitable conditions for suppressing the retro-nitroaldol reaction were established, we next focused on improving the enantiomeric excess of the nitroaldol product **4aa** (Table 3). The toluene/H_2O ratio affected the enantioselectivity of **4aa** (Table 3, entries 1–6), and the best result (99% yield, 69% *ee*) was obtained with a toluene/H_2O ratio of 1:1 (Table 3, entry 4). Decreasing the amount of KOH improved the *ee* values (Table 3, entries 7–9).[30,31] We found that the selectivity was improved to as much as 95% *ee* when 5 mol% of KOH was used as a base (Table 3, entry 10). As shown in Table 3, entry 11, the reaction also proceeded with as little as 3 mol% of **1a** to give **4aa** in good yield and with good *ee*.

Next, to gain insight into the inhibition mechanism of the retro-nitroaldol reaction in this catalytic system, enantioenriched (*R*)-**4aa** (92% *ee*) was subjected to various reaction conditions.[32] Nitromethane (**3a**) and KI were found to be indispensable for inhibiting the retro-nitroaldol reaction in the presence of (*S*,*S*)-**1a** (Table 4). As shown in Table 4, entry 1, in the absence of catalyst, the *ee* value did not change even under basic conditions with 30 mol% KOH as an external base. The observation that the *ee* value was decreased only when (*S*,*S*)-**1a** was added in the absence of **3a** indicates that interactions of (*S*,*S*)-**1a** and (*R*)-nitroalcohol **4aa** promote the retro-mode reaction at the interfacial layer between toluene and basic aqueous solution (Table 4, entries 1–3). The retro reaction process was suppressed by the addition of **3a** (Table 4, entry 5 vs. 3).[24] Moreover, it was inhibited almost completely in the presence of **3a** and KI (Table 4, entries 6 and 7). Thus, we speculate that KI and nitronate, generated in situ,

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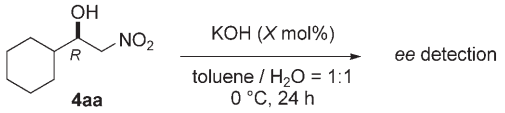
Table 4. Retro-nitroaldol reaction of **4aa**.[a]



Entry	Cat. (5 mol%)	Additive (50 mol%)	$MeNO_2$ **3a** [equiv]	KOH [mol%]	Starting **4aa**: *ee* [%]	Recovered **4aa**: *ee* [%]
1	–	–	–	30	92	92
2	(*R*,*R*)-**1a**	–	–	30	92	88
3	(*S*,*S*)-**1a**	–	–	30	92	47
4	(*S*,*S*)-**1a**	–	5	30	92	60
5	(*S*,*S*)-**1a**	–	10	30	92	80
6	(*S*,*S*)-**1a**	KI	10	30	92	92
7	(*S*,*S*)-**1a**	KI	10	5	92	91

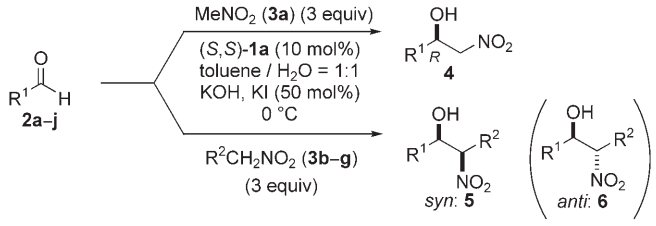
[a] All reactions were carried out on the 0.1-mmol scale in 1.0 mL toluene and 1.0 mL H_2O.

cooperatively cause **4aa** to dissociate from the catalyst, thereby achieving kinetic stereocontrol under these biphasic reaction conditions.

With the optimized conditions in hand, the scope of the **1a**-catalyzed enantioselective nitroaldol reaction was explored by using a variety of aldehydes and nitroalkanes (Table 5). For convenience, all reactions were performed with 10 mol% of **1a**. In the case of the cyclic aldehyde, the corresponding nitroalcohol **4ba** was obtained in good yield with good *ee* (Table 5, entry 1). Linear aliphatic aldehydes also served as substrates (Table 5, entries 2–5). α-Branched aldehydes afforded the nitroaldol products with high stereoselectivity (Table 5, entries 2–4), although the unbranched aldehyde gave only moderate *ee* (Table 5, entry 5).[33] These results stimulated us to apply **1a** to catalytic diastereo- and enantioselective nitroaldol reactions with prochiral nitroalkanes to examine the generality and synthetic utility of the substrate. Since Shibasaki and co-workers first reported catalytic direct diastereo- and enantioselective nitroaldol reactions in 1995,[21] no alternative methodology has been available to control 1) the retro-mode reaction, 2) epimerization at the α position of the nitro group, and 3) the facial selectivity of prochiral nitroalkanes,[34] until our method was developed.[11h] Thus, our reaction system was applied to the diastereo- and enantioselective nitroaldol reaction with prochiral nitroalkanes (Table 5, entries 6–21). In all cases examined, the *syn*-nitroaldol products **5** were obtained with high diastereo- and enantioselectivity.[35] Cyclic, α-branched, and β-branched aldehydes afforded the corresponding *syn* adducts with excellent diastereoselectivity and high enantioselectivity (Table 5, entries 6–9; *syn*/*anti* 93:7–99:1, 91–99% *ee*). Unbranched and heteroatom-substituted aldehydes also served as substrates and gave comparable results (Table 5, entries 10–13; *syn*/*anti* 86:14–90:10, 83–98% *ee*). Other alkyl-substituted nitroalkanes were also applicable in **1a**-catalyzed nitroaldol reactions (Table 5, entries 14–21). Notably, the reactions of **2a** with **3c**–**g** gave excellent diastereo- and enantioselectivities (Table 5, entries 14–17; *syn*/*anti* > 99:1, 90–95% *ee*).[36]

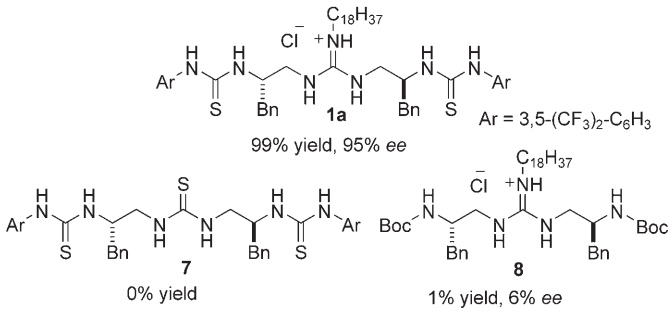
The crucial roles of the guanidine and thiourea functional groups in **1a** for dual activation of substrates are evident from a comparison of the reactivity of **1a** and its structural variants **7** and **8** under the optimized conditions (Scheme 3). Replacement of the guanidinium moiety with a thiourea group (**7**) to prevent activation of nitronate or removal of the thiourea group (**8**) to block activation of aldehyde drastically suppressed the catalytic activity. These results strongly support the role of cooperative effects of the guanidine and thio-

Table 5. Catalytic asymmetric nitroaldol reaction of various aldehydes **2** and nitroalkanes **3**.[a]



Entry	Aldehyde **2**	Nitroalkane **3**	KOH [mol%]	*t* [h]	Product	Yield [%][b]	*ee* [%][c]	*syn*/*anti*[c,d]
1	*c*-C_5H_9CHO (**2b**)	**3a**	40	5	**4ba**	76	82	–
2[e]	$(CH_3)_3CHO$ (**2c**)	**3a**	5	45	**4ca**	85	88	–
3[e]	$(CH_3)_2CHCHO$ (**2d**)	**3a**	10	19	**4da**	88	83	–
4	Et_2CHCHO (**2e**)	**3a**	10	36	**4ea**	70	88	–
5	$PhCH_2CH_2CHO$ (**2f**)	**3a**	5	18	**4fa**	79	55	–
6[e]	**2a**	$EtNO_2$ (**3b**)	8	24	**5ab**	77	93	99:1
7[e]	**2d**	**3b**	8	24	**5db**	50	90	97:3
8[e]	**2e**	**3b**	20	24	**5eb**	52	91	99:1
9[e]	$(CH_3)_2CHCH_2CHO$ (**2g**)	**3b**	5	24	**5gb**	58	99	97:3
10[e]	**2f**	**3b**	10	24	**5fb**	76	83	90:10
11[e]	$CH_3CH_2CH_2CHO$ (**2h**)	**3b**	20	24	**5hb**	91	84	87:13
12[e]	$TBSOCH_2CHO$ (**2i**)	**3b**	6	48	**5ib**	63	98	86:14
13[e]	$TBSOCH_2CH_2CHO$ (**2j**)	**3b**	8	24	**5jb**	50	92	90:10
14[e]	**2a**	*n*-$PrNO_2$ (**3c**)	5	40	**5ac**	61	95	99:1
15	**2a**	$TBSOCH_2CH_2NO_2$ (**3d**)	7	48	**5ad**	63	90	99:1
16	**2a**	$TIPSOCH_2CH_2NO_2$ (**3f**)	6	48	**5af**	60	90	99:1
17	**2a**	$PhCH_2NO_2$ (**3g**)	7	48	**5ag**	67	95	99:1
18[e]	**2h**	**3c**	5	48	**5hc**	63	85	99:1
19	**2h**	**3d**	3	48	**5hd**	51	87	93:7
20	**2h**	**3f**	3	24	**5hf**	58	87	92:8
21	**2h**	**3g**	10	24	**5hg**	70	87	91:9

[a] All reactions were carried out on the 0.1-mmol scale in toluene/H_2O = 1:1 (both 1.0 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The relative stereochemistry was determined from the ^1H NMR chemical shifts. [e] Determined by chiral HPLC analysis. [e] 10 equivalents of **3** was used. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

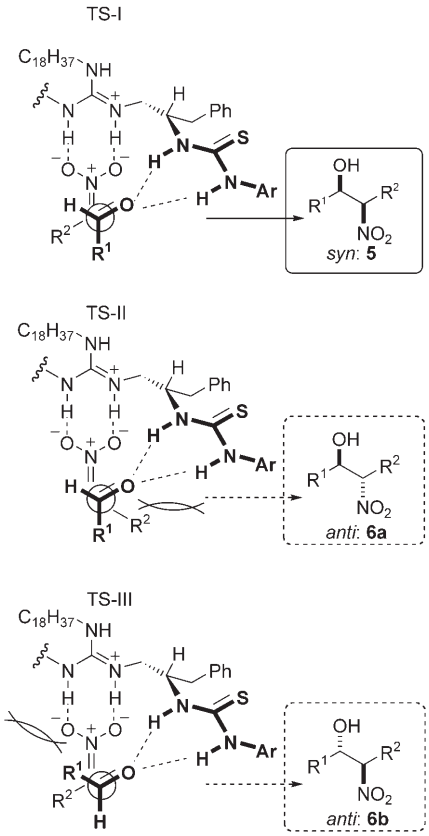


Scheme 3. Structures of **1a**, **7**, and **8**. Reaction of **2a** with **3a** was carried out in the presence of **1a**, **7**, and **8** under the conditions for Table 3, entry 10. Boc = *tert*-butoxycarbonyl.

urea functional groups in **1a** in the asymmetric catalytic nitroaldol reaction.

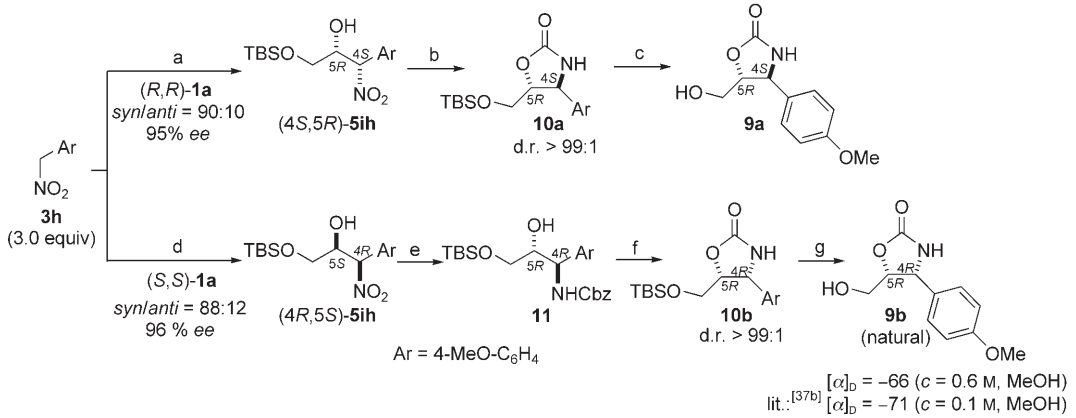
We assumed that chemoselective coordination of the catalysts and the substrates[17] would lead to a stereodiscrimination process. The transition state proposed in Scheme 4 provides an explanation for the stereoselectivity of the reaction catalyzed by **1a**. In this model, the guanidinium cation and thiourea group selectively coordinate to nitronate and the carbonyl group of the aldehyde, respectively, and substituents in both aldehyde (R^1) and nitroalkane (R^2) favor an *anti* relationship to avoid steric repulsion (TS-I: *anti*,*anti* conformation). Thus, the nitroaldol reactions of prochiral aldehydes proceed in a highly enantio- and *syn*-selective manner. The observation that the *ee* values of the products with prochiral nitroalkanes are much higher than those with nitromethane (**3a**, R^2 = H) (e.g., Table 5, entry 6 vs. 11) is consistent with this proposed transition state (TS-I) of the reaction, in which the facial selectivity of aldehydes is considered to be strictly controlled by the R^2 group in prochiral nitroalkanes.

We applied this efficient catalytic process to the asymmetric synthesis of 4-*epi*-cytoxazone (**9a**) and cytoxazone (**9b**),



Scheme 4. Plausible transition-state model of enantioselective nitroaldol reaction in the presence of **1a**. TS-I: *anti*,*anti* conformation; TS-II: gauche-*anti* conformation; TS-III: gauche-*anti* conformation.

a type-2 cytokine-selective modulator (Scheme 5).[37] Nitroaldol reaction of **2i** with **3h** in the presence of **1a** afforded the corresponding nitroaldol **5ih** with high diastereo- and enantioselectivity ((*R*,*R*)-**1a**: *syn*/*anti* 90:10, 95% *ee*; (*S*,*S*)-**1a**: *syn*/*anti* 88:12, 96% *ee*). 4-*epi*-Cytoxazone (**9a**) was con-



Scheme 5. Synthesis of 4-*epi*-cytoxazone (**9a**) and cytoxazone (**9b**). Reagents and conditions: a) **2j**, (*R*,*R*)-**1a** (10 mol%), toluene/H_2O = 1:1, 0°C, 76%. b) 1) $NiCl_2$, $NaBH_4$, MeOH, 0°C; 2) CDI, CH_3CN, 80°C. c) HF·py, CH_3CN, 0°C, 43% (3 steps). d) **2j**, (*S*,*S*)-**1a** (10 mol%), toluene/H_2O = 1:1, 0°C, 78%. e) 1) $NiCl_2$, $NaBH_4$, MeOH, 0°C; 2) CbzCl, K_2CO_3, $CHCl_3/H_2O$, room temperature, 83% (2 steps); 3) DMP, CH_2Cl_2, 0°C; 4) $NaBH_4$, EtOH, −78°C, 85% (2 steps), 93% *ee*, d.r. = 96:4. f) 1) H_2, Pd/C (1 atm); 2) CDI, CH_3CN, 80°C, 84% (2 steps); 3) recrystallization from hexane/methanol, 70%, 96% *ee*, d.r. > 99:1. g) HF·py, CH_3CN, 0°C, 93%. Cbz = benzyloxycarbonyl, CDI = *N*,*N*-carbonyldiimidazole, DMP = Dess–Martin periodinane, py = pyridine.

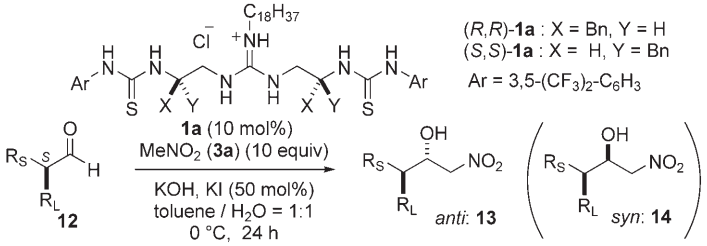
cisely synthesized by reduction of (4*S*,5*R*)-**5ih** with $NiCl_2$/$NaBH_4$, followed by cyclization with CDI[38] and deprotection of the TBS ether with HF/pyridine.[11h] (−)-Cytoxazone (**9b**) was similarly synthesized from (4*R*,5*S*)-**5ih**. After conversion of the nitro group of (4*R*,5*S*)-**5ih** to Cbz carbamate, the stereochemistry of the alcohol at C5 was inverted by oxidation–reduction, that is, Dess–Martin oxidation of the secondary alcohol and reduction of the resulting ketone with $NaBH_4$, to afford **11** with high diastereoselectivity (d.r. = 96:4).[39,40] Deprotection of the Cbz group and oxazolidinone formation with CDI gave **10b**. After a single recrystallization of **10b** (96% *ee*), removal of the TBS group gave **9b**. Further structural development of cytoxazones based on this diversity-oriented catalytic process, aimed at exploring structurally analogous molecular probes, is in progress.

Diastereoselective Nitroaldol Reaction with α-Chiral Aldehydes[41]

α-Branched aldehydes appeared to give rather higher asymmetric induction in the **1a**-catalyzed enantioselective nitroaldol reaction. This prompted us to extend this strategy to a diastereoselective version of the reaction by using α-chiral aldehydes,[22] and the results are summarized in Table 6.

After a study to optimize the reaction conditions,[11g] we found that excellent *anti* selectivity was obtained by utilizing (*R*,*R*)-**1a** with *N*,*N*′-dibenzyl-protected *S* amino aldehydes **12** (Table 6, entries 1 and 3–7; *anti*/*syn* 99:1).[42,43] Silyl ether substituted aldehydes also served as substrates and gave comparable results (Table 6, entries 8 and 9). Epimerization of chiral aldehydes was not observed in most cases examined. The reactivity and diastereoselectivity in the case of (*S*,*S*)-**1a** were greatly reduced, which indicates that the matched combination of (*R*,*R*)-**1a** and *S* aldehydes is crucial for the diastereoselective reactions (Table 6, entry 2).

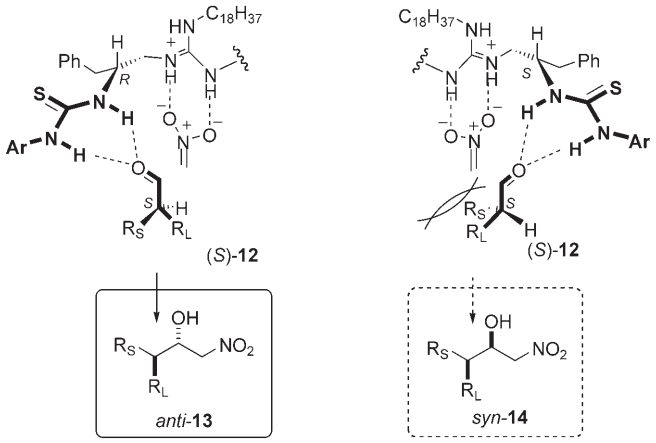
Table 6. Diastereoselecive nitroaldol reaction with α-chiral aldehydes **12**.



Entry	R_S	R_L	**1a**	KOH [mol%]	Product	Yield [%][a]	*anti*/*syn*[b]	*ee* [%][c]
1	Bn	NBn_2 (**12a**)	(*R*,*R*)	8	**13a**	75	95:5	99
2	Bn	NBn_2 (**12a**)	(*S*,*S*)	8	**13a**	8	64:36	80
3	CH_3	NBn_2 (**12b**)	(*R*,*R*)	20	**13b**	70	99:1	99
4	$(CH_3)_2CHCH_2$	NBn_2 (**12c**)	(*R*,*R*)	6	**13c**	70	99:1	95
5	$(CH_3)_2CH$	NBn_2 (**12d**)	(*R*,*R*)	10	**13d**	33	99:1	99
6	$TBSO(CH_2)_2$	NBn_2 (**12e**)	(*R*,*R*)	10	**13e**	70	99:1	95
7	$Bn_2N(CH_2)_4$	NBn_2 (**12f**)	(*R*,*R*)	10	**13f**	62	99:1	99
8	Ph	NBn_2 (**12g**)	(*R*,*R*)	5	**13g**	82	86:14	99
9	Me	NBn_2 (**12h**)	(*R*,*R*)	2	**13h**	80	84:16	99

[a] Yield of isolated product. [b] The relative stereochemistry was determined from the ^1H NMR chemical shift. [c] Determined by chiral HPLC analysis.

The match/mismatch relationships between catalyst **1a** and substrate **12** can be explained in terms of the Cram rule (Scheme 6). In our proposed transition-state model, the substituent on aldehyde would be located in an *anti* relationship to nitronate. As the largest substituent (R_L) should be in an *anti* position to the carbonyl group in **12**, the combination of (*R*,*R*)-**1a** and (*S*)-**12** (TS-I) is favored rather than that of (*S*,*S*)-**1a** and (*S*)-**12** (TS-II) due to the steric repulsion between R_S (the smallest substituent) and nitronate.



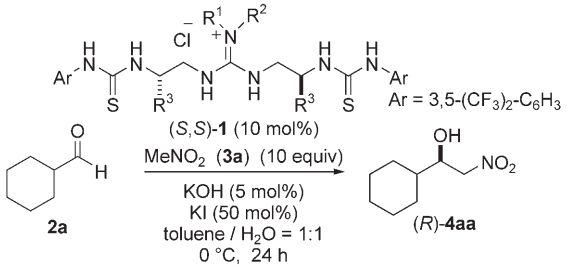
Scheme 6. Plausible transition state in the diastereoselective nitroaldol reaction.

A New Aspect of the Guanidine–Thiourea Bifunctional Catalyst as a Chiral Surfactant

We have developed efficient direct asymmetric nitroaldol reactions with high enantio- and/or diastereocontrol by utilizing the catalyst **1a**, which contains a long alkyl chain on the guanidine group and a flexible-chain chiral spacer. Attracted by the unique structural characteristics, we reevaluated the substituent effects (R^1–R^3) of **1** to gain insight into the hypothetical functionality of these molecules as chiral surfactants.[44] To clarify the substituent and catalytic-activity relationships under optimized conditions,[45] we investigated the enantioselective nitroaldol reactions of **2a** with **3a** by utilizing guanidine/thiourea compounds **1** with various substituents (Table 7).[46]

The substituent on the guanidine moiety was found to have a major influence on the catalytic reactivity (Table 7, entries 1–5).[47] In the case of alkyl chains shorter than 12 carbon atoms, the reaction rate

Table 7. Substituent effects of guanidine–thiourea catalyst **1** under optimized reaction conditions.[a]



Entry	Cat.	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
0	**1a**	$C_{18}H_{37}$	H	Bn	91	92
1	**1h**	$C_{22}H_{45}$	H	Bn	98	89
2	**1i**	$C_{15}H_{31}$	H	Bn	91	90
3	**1j**	$C_{12}H_{25}$	H	Bn	9	87
4	**1b**	C_8H_{17}	H	Bn	8	86
5	**1c**	C_4H_9	H	Bn	8	87
6[d]	**1d**	C_4H_9	C_4H_9	Bn	28	33
7	**1k**	(4-OMe)-Ph-C_3H_6	H	Bn	82	97
8	**1l**	(4-CF_3)-Ph-C_3H_6	H	Bn	88	82
9	**1m**	(1-Naph)-C_3H_6	H	Bn	67	88
10	**1n**	(2-Naph)-C_3H_6	H	Bn	47	89
11	**1e**	$C_{18}H_{37}$	H	Me	3	76
12	**1f**	$C_{18}H_{37}$	H	*i*Pr	1	32
13	**1g**	$C_{18}H_{37}$	H	*t*Bu	6	6
14[e]	**1a**	$C_{18}H_{37}$	H	Bn	0	–
15[f]	**1a**	$C_{18}H_{37}$	H	Bn	0	–
16[g]	**1a**	$C_{18}H_{37}$	H	Bn	1	56
17[d,h]	**1a**	$C_{18}H_{37}$	H	Bn	53	80
18[i]	**1a**	$C_{18}H_{37}$	H	Bn	0	–

[a] Reactions were carried out on the 0.1-mmol scale in 1.0 mL toluene and 1.0 mL H_2O. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] (*S*)-**4aa** was obtained. [e] 0.2 equivalents of SDS was added. [f] 0.2 equivalents of AOT was added. [g] 0.2 equivalents of Triton X-100 was added. [h] 0.2 equivalents of CTAB was added. [i] 0.5 equivalents of CTAB was added. AOT = sodium di-(2-ethylhexyl) sulfosuccinate, CTAB = cetyltrimethylammonium bromide, Naph = naphthyl, SDS = sodium dodecyl sulfate.

was remarkably suppressed, regardless of solubility in toluene (Table 7, entries 3–5).[48] When disubstituted **1d** was used as a catalyst, a reversal in the sense of asymmetric induction was observed (Table 7, entry 6). Notably, the introduction of an aromatic group at the end of a short alkyl chain led to a significant enhancement in reaction rate (Table 7, entries 7–10). The electronic effect of this aromatic moiety, which is far from the catalytic active site, affects the enantioselectivity (Table 7, entry 7 vs. 8). The benzyl group at R^3 on the chiral spacer was found to be critical for both reactivity and selectivity. The *ee* values decreased as the bulk of the R^3 group was increased (Table 7, entries 11–13). Catalytic activity was drastically decreased by addition of various surfactants (20 mol%; Table 7, entries 14–18). SDS (anionic), AOT (anionic), and Triton X-100 (nonionic) completely inhibited the **1a**-catalyzed nitroaldol reaction (Table 7, entries 14–16).[49] On the other hand, when 20 mol% of CTAB (cationic surfactant) was added, the catalytic activity of **1a** was lowered to give the corresponding product **4aa** in 53% yield with 80% *ee* (Table 7, entry 17). The **1a**-catalyzed nitroaldol reaction was suppressed by increasing the amount of CTAB to 50 mol% (Table 7, entry 18). As the cationic surface properties under biphasic conditions are important for the both reactivity and selectivity of the nitroaldol reaction, the catalytic activity of **1a** is suggested to be controlled by the mode of self-organized assembly.[50] Thus, the alkyl chain on the guanidine moiety would contribute to reactivity by controlling the proximity of the reactants based on hydrophobic interactions, and the benzyl group on the chiral spacer would fix the high-order asymmetric structure through its intermolecular π–π stacking interactions.

A positive nonlinear effect was observed between the enantiomeric excess of **1a** and that of the product **4aa**, which supports the hypothetical self-aggregation of **1a** (Figure 1).[51]

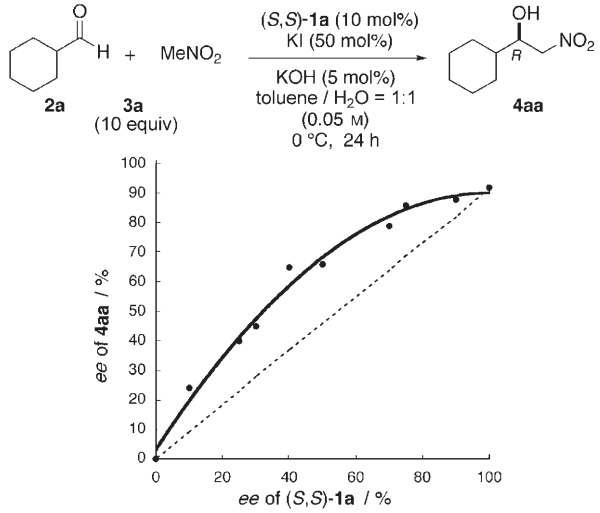


Figure 1. (+)-Nonlinear effects in enantioselective nitroaldol reactions with (*S*,*S*)-**1a**.

Conclusions

In summary, we have developed general and highly stereoselective organocatalyzed nitroaldol reactions by utilizing the newly designed guanidine–thiourea organocatalyst **1a**. Addition of KI is crucial for inhibiting the retro-nitroaldol reaction and achieving high asymmetric induction in toluene/water biphasic conditions. Evidence for the hypothetical guanidine–thiourea cooperative reaction mode was obtained by using structural variants of **1a**. Drastic substituent effects on the guanidinium and chiral spacer moiety suggest a role of **1a** as a chiral surfactant. Notably, highly stereoselective nitroaldol reactions proceeded with multiple functionalities in **1a**, including chemoselective activation sites for substrates through noncovalent bonding and hydrophobic interaction for self-aggregation of **1a**. Further mechanistic studies based on spectroscopic analysis are in progress.

CHEMISTRY
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Experimental Section

General

Flash chromatography was performed by using silica gel 60 (spherical, particle size 0.040–0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured on a JASCO DIP 370 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX300, ECA/ECX400, and ALPHA500 instruments. Mass spectra were recorded on JEOL JMS-T100LC and JMA-HX110 spectrometers. NMR chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the residual protons in the solvent.

Syntheses

Typical procedure for asymmetric nitroaldol reaction (Table 5, entry 6): Cyclohexanecarboxaldehyde (**2a**; 12.1 μL, 0.1 mmol) was added to a mixture of (*S,S*)-**1a** (11.6 mg, 0.01 mmol), KI (8.3 mg, 0.05 mmol), and nitroethane (**3b**; 71.5 μL, 1.0 mmol) in toluene (1.0 mL)/aqueous KOH (8 mM, 1.0 mL) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 24 h. Saturated aqueous NH_4Cl was then added, and the organic layer was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1, 10:1, 0:1) to give **5ab** (14.4 mg, 77 %). (*S,S*)-**1a** was recovered (11.5 mg, 99 %). The relative stereochemistry and diastereoselectivity (s*yn*/*anti* 99:1) of **5ab** were determined based on the reported ^{1}H NMR spectral data. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (dq, J = 6.8, 6.8 Hz, 1H), 3.65 (dd, J = 6.8, 4.9 Hz, 1H), 2.13 (br s, 1H), 1.78–1.65 (m, 4H), 1.53 (d, J = 6.7 Hz, 3H), 1.48–0.94 ppm (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.5, 77.2, 39.9, 30.0, 26.3, 26.2, 26.1, 25.9, 16.6 ppm. The enantiomeric excess of **5ab** (93 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 97:3, 1.0 mL min^{-1}, minor: 16.8 min, major: 25.3 min).

Typical procedure for diastereoselective nitroaldol reaction (Table 6, entry 1): Aqueous KOH (8 mM, 1.0 mL) was added to a mixture of (*R,R*)-**1a** (11.6 mg, 0.01 mmol), KI (8.3 mg, 0.05 mmol), **12a** (32.9 mg, 0.1 mmol), and **3a** (54.0 μL, 1.0 mmol) in toluene (1.0 mL) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 24 h. Saturated aqueous NH_4Cl was then added, and the organic later was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1, 10:1, 5:1, 0:1) to give **13a** (28.9 mg, 75 %). (*R,R*)-**1a** was recovered (11.5 mg, 99 %). The relative stereochemistry and diastereoselectivity of **13a** (95:5) was determined based on the ^{1}H NMR spectra reported by Corey and Zhang.[22b] The enantiomeric excess of **13a** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel OJ-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 90:10, 1.0 mL min^{-1}, minor: 28.8 min, major: 31.3 min).

Spectral Data

13b: $[\alpha]_D^{28}$ = +18.0° (c = 1.1 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3537, 3086, 3062, 3028, 2966, 2926, 1602, 1550, 1495, 1453, 1382, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 10H), 4.97 (dd, J = 13.7, 2.2 Hz, 1H), 4.28–4.23 (m, 1H), 4.02 (dd, J = 13.7, 9.5 Hz, 1H), 3.76 (d, J = 13.4 Hz, 2H), 3.39 (d, J = 13.4 Hz, 2H), 2.76–2.68 (m, 1H), 2.49 (br s, 1H), 1.23 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 128.8, 128.5, 127.3, 79.6 (br), 71.0, 55.3, 54.5, 29.8, 8.4 ppm; HRMS (FAB): m/z calcd for $C_{18}H_{23}N_2O_3$: 315.1709 $[M+H]^+$; found: 315.1751. The enantiomeric excess of **13b** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel OJ-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 95:5, 1.0 mL min^{-1}, minor: 28.5 min, major: 34.7 min).

13c: $[\alpha]_D^{28}$ = −2.2° (c = 1.0 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3470, 3061, 3028, 2954, 2926, 2867, 1603, 1551, 1494, 1453, 1382 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 10H), 4.71 (dd, J = 13.2, 2.2 Hz, 1H), 4.42–4.39 (m, 1H), 4.15 (dd, J = 13.2, 9.8 Hz, 1H), 3.68 (d, J = 13.4 Hz, 2H), 3.57 (d, J = 13.7 Hz, 2H), 2.75–2.70 (m, 1H), 2.67 (br s, 1H), 1.93–1.83 (m, 1H), 1.73–1.66 (m, 1H), 1.41–1.36 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.88 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 128.9, 128.5, 127.3, 79.9, 70.2, 57.1, 54.8, 35.8, 25.7, 23.2, 22.9 ppm; HRMS (FAB): m/z calcd for $C_{21}H_{29}N_2O_3$: 357.2178 $[M+H]^+$; found: 357.2176. The enantiomeric excess of **13c** (95 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel OJ-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 95:5, 1.0 mL min^{-1}, minor: 28.5 min, major: 34.7 min).

13d: $[\alpha]_D^{25}$ = −3.7° (c = 0.4 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3584, 2922, 2850, 1670, 1551, 1495, 1455, 1380, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 10H), 4.71 (dd, J = 12.9, 2.1 Hz, 1H), 4.57–4.51 (m, 1H), 4.20 (dd, J = 12.9, 10.0 Hz, 1H), 3.74 (d, J = 13.6 Hz, 2H), 3.61 (d, J = 13.4 Hz, 2H),2.80 (br s, 1H), 2.60 (dd, J = 7.2, 6.1 Hz, 1H), 2.30–2.17 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 1.10 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 128.9, 127.5, 80.0, 68.3, 64.2, 55.3, 26.4, 23.7, 19.8 ppm; HRMS (FAB): m/z calcd for $C_{20}H_{27}N_2O_3$: 343.2022 $[M+H]^+$; found: 343.2014. The enantiomeric excess of **13d** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel OJ-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 95:5, 1.0 mL min^{-1}, minor: 15.6 min, major: 26.5 min).

13e: $[\alpha]_D^{23}$ = +4.1° (c = 0.5 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3354, 3028, 2959, 2927, 2855, 1552, 1495, 1454, 1379, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 10H), 4.87 (dd, J = 12.5, 2.4 Hz, 1H), 4.42–4.38 (m, 1H), 4.02 (dd, J = 12.5, 9.5 Hz, 1H), 3.95–3.91 (m, 1H), 3.80 (d, J = 13.4 Hz, 2H), 3.59 (ddd, J = 10.1, 3.1 Hz, 2H), 3.37 (d, J = 13.4, 2H), 2.68–2.64 (m, 1H), 2.17–2.13 (m, 1H), 1.92–1.85 (m, 1H), 0.86 (s, 9H), 0.07 (s, 7H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 128.9, 128.6, 127.5, 80.6, 70.3, 62.8, 59.3, 54.6, 28.0, 25.8, 18.2, −5.5, −5.6 ppm; HRMS (FAB): m/z calcd for $C_{25}H_{39}N_2O_4Si$: 459.2679 $[M+H]^+$; found: 459.2725. The enantiomeric excess of **13e** (95 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 97:3, 1.0 mL min^{-1}, minor: 8.7 min, major: 9.2 min).

13f: $[\alpha]_D^{25}$ = +7.20° (c = 1.2 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3436, 3084, 3061, 3027, 2925, 2852, 2799, 1656, 1602, 1550, 1494, 1453, 1378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 20H), 4.68 (dd, J = 13.0, 2.2 Hz, 1H), 4.30 (ddd, J = 9.8, 7.8, 2.2 Hz, 1H), 4.01 (dd, J = 13.0, 9.8 Hz, 1H), 3.65 (d, J = 10.7 Hz, 2H), 3.62 (d, J = 10.7 Hz, 2H), 3.50 (d, J = 5.4 Hz, 2H), 3.47 (d, J = 5.4 Hz, 2H), 2.57–2.48 (m, 1H), 2.45–2.39 (m, 1H), 1.71–1.27 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 139.0, 128.9, 128.5, 128.1, 127.3, 126.8, 79.9 (br), 70.2, 59.2 (br), 58.5, 54.8, 52.3, 27.1, 25.7, 25.6 ppm; HRMS (FAB): m/z calcd for $C_{35}H_{42}N_3O_3$: 552.3226 $[M+H]^+$; found: 552.3221. The enantiomeric excess of **13f** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 90:10, 1.0 mL min^{-1}, minor: 7.7 min, major: 9.4 min).

13g: $[\alpha]_D^{28}$ = +51.8° (c = 1.3 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3584, 3064, 3022, 2955, 2929, 2857, 1556, 1471, 1383, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 5H), 4.50–4.26 (m, 3H), 2.47 (d, J = 5.9 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 3H), −0.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 128.7, 126.4, 77.1, 76.2, 73.6, 25.7, 18.1, −4.7, −5.2 ppm; HRMS (FAB): m/z calcd for $C_{15}H_{26}NO_4Si$: 312.1631 $[M+H]^+$; found: 312.1663. The enantiomeric excess of **13g** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 99:1, 1.0 mL min^{-1}, minor: 17.7 min, major: 22.4 min).

13h: $[\alpha]_D^{28}$ = +25.8° (c = 1.4 M, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3466, 2957, 2929, 2857, 1556, 1464, 1423, 1381, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (dd, J = 13.1, 2.7 Hz, 1H), 4.46 (dd, J = 13.1, 8.8 Hz, 1H), 4.16–4.10 (m, 1H), 3.93–3.87 (m, 1H), 2.65 (d, J = 6.3 Hz, 1H), 1.21 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 2H), 0.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.5, 73.1, 69.7, 25.8, 19.7, 18.0, −4.2, −4.9 ppm; HRMS (FAB): m/z calcd for $C_{10}H_{24}NO_4Si$: 250.1475 $[M+H]^+$; found: 250.1507. The enantiomeric excess of **13h** (99 % *ee*) was determined by means of chiral HPLC analysis (Chiralcel AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 99.9:0.1, 1.0 mL min^{-1}, minor: 29.1 min, major: 36.1 min).

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[29] a) The iodide salt of the catalyst was prepared by using Amberlist A-26 (OH) eluted with an excess of a solution of HI in methanol. We utilized KI as an additive from the viewpoint of atom economy. b) The catalyst–iodide anion complex gave broad ^{1}H NMR signals.

[30] In the absence of KOH, the reaction did not proceed at all. Furthermore, no reaction occurred after pretreatment of **1a** with an excess of KOH (10 equiv with respect to **1a**). KOH might deprotonate nitroalkane in this catalytic system.

[31] a) Toluene is the best organic solvent in this biphasic system. b) The tendency toward increased enantiocontrol as the polarity of the organic solvent is decreased is also consistent with our proposed mechanism based on hydrogen-bonding interactions. The solvent effects under the same conditions as in Table 3, entry 9 were: benzene: 62%, 82% *ee*; xylene: 12%, 78% *ee*; CH_2Cl_2: 16%, 76% *ee*; hexane: 21%, 69% *ee*; *n*-decane: 12%, 80% *ee*; Et_2O: 6%, 17% *ee*.

[32] Enantioenriched (*R*)-**4aa** was prepared by using the optimized conditions in Table 3, entry 9.

[33] After our publication,[11f] Hiemstra and Deng and their co-workers independently reported organocatalytic enantioselective nitroaldol reactions with cinchona derivatives.[20i,o]

[34] Even in the diastereoselective version of the nitroaldol reaction of chiral aldehydes with prochiral nitroalkanes, catalytic control of the chirality at the α position of the nitro group was problematic; see reference [22d].

[35] In this article we defined compound **5** as *syn* and compound **6** as *anti*.

[36] In all cases examined, the enantiomeric excess of the *anti* adducts **6** was low (14–40% *ee*). These results indicate that *anti* adducts were not generated by epimerization of **5**.

[37] For isolation and structure determination of **9b**, see: a) H. Kakeya, M. Morishita, K. Kobinata, M. Osono, M. Ishizuka, H. Osada, *J. Antibiot.* **1998**, *51*, 1126; b) H. Kakeya, M. Morishita, H. Koshino, T. Morita, K. Kobayashi, H. Osada, *J. Org. Chem.* **1999**, *64*, 1052; for

the first synthesis **9a** and **9b**, see: c) Y. Sakamoto, A. Shiraishi, J. Seonhee, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 4203; due to the potent bioactivity of this compound, several approaches aimed at synthesizing both diastereomers have been developed: d) M. Seki, K. Mori, *Eur. J. Org. Chem.* **1999**, 2965; e) P. H. Carter, J. R. LaPorte, P. A. Scherle, C. P. Decicco, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237; f) S. Milicevic, R. Matovic, R. N. Saicic, *Tetrahedron Lett.* **2004**, *45*, 955; g) S. Sugiyama, S. Arai, K. Ishii, *Tetrahedron: Asymmetry* **2004**, *15*, 3149; h) S. G. Davies, D. G. Hughes, R. L. Nicholson, A. D. Smith, A. J. Wright, *Org. Biomol. Chem.* **2004**, *2*, 1549; i) I. S. Kim, J. D. Kim, C. B. Ryu, O. P. Zee, Y. H. Jung, *Tetrahedron* **2006**, *62*, 9349; j) R. K. Mishra, C. M. Coates, K. D. Revell, E. Turos, *Org. Lett.* **2007**, *9*, 575; other synthetic studies of (4*R*,5*R*)-cytoxazone (**9b**) are cited in reference [37i].

[38] Compound **10a** was isolated as a single isomer by column chromatography on silica gel.

[39] Our attempts at catalytic *anti*-selective nitroaldol reactions with **1** failed. The design and synthesis of new catalysts are in progress.

[40] For catalytic *anti*-selective nitroaldol reactions with silyl nitronate, see: a) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054; for an enzymatic approach, see: b) T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew. Chem.* **2006**, *118*, 3532; *Angew. Chem. Int. Ed.* **2006**, *45*, 3454.

[41] Portions of this work were reported previously as a communication; see reference [11g].

[42] M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121.

[43] We defined compound **13** as *anti* in this article.

[44] For recent reviews, see: a) T. Dwars, E. Paetzold, G. Oehme, *Angew. Chem.* **2005**, *117*, 7338; *Angew. Chem. Int. Ed.* **2005**, *44*, 7174; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209.

[45] Preliminary catalyst screening (Table 1) suggests that the catalyst structure might control the interface of the self-aggregates, although retro-reaction and background reaction proceeded under the screening conditions.

[46] The differences in reactivity and selectivity cannot be attributed the three-dimensional structure of **1**, because the NMR spectra are quite similar.

[47] For a discussion about the effects of longer alkyl chains on a quaternary ammonium ion, see: a) M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2005**, *117*, 1573; *Angew. Chem. Int. Ed.* **2005**, *44*, 1549; for a combined proline–surfactant organocatalyst, see: b) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734; c) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527; for recent approaches to asymmetric reactions that utilize an excess of chiral surfactant, see: d) A. Dasgupta, R. N. Mitra, S. Roy, P. K. Das, *Chem. Asian J.* **2006**, *1*, 780, and references therein.

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