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Chiral Quaternary Ammonium Aryloxide/*N,O*-Bis(trimethylsilyl)acetamide Combination as Efficient Organocatalytic System for the Direct Vinylogous Aldol Reaction of (5*H*)-Furan-2-one Derivatives

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Abstract: A chiral quaternary ammonium amide was generated *in situ* from *N,O*-bis(trimethylsilyl)-acetamide (BSA) as non-nucleophilic Brønsted base precursor and the combination of chiral quaternary ammonium halide/sodium aryloxide as chiral Lewis base. This system was applied to an *anti*-selective organocatalytic direct vinylogous aldol (ODVA) reaction of (5*H*)-furan-2-one derivatives with aldehydes. Several 5-(1′-hydroxy)-γ-butenolides were obtained in good diastereomeric ratios (up to 95/5) and excellent enantioselectivities (up to 94%) with both aliphatic or (hetero)aromatic aldehydes, so providing a rare example of general and efficient conditions for the ODVA reaction.

Keywords: aldol reaction; asymmetric catalysis; ion pairs; organocatalysis

The γ-butenolide skeleton is largely widespread in biologically active natural compounds[1] and considerable efforts have been devoted in the last few decades to the functionalization of this relevant motif.[2] The most popular approach to prepare optically active γ-substituted butenolides has long been based on the functionalization of 2-silyloxyfuran derivatives. More recently, the direct addition of (5*H*)-furan-2-one derivatives to several electrophiles was extensively reported mainly by means of organocatalytic processes.[3,4] However, access to γ-substituted butenolides through organocatalytic direct vinylogous aldol (ODVA) reaction still remains rarely reported in the literature.[5] Furthermore, the substrate scope is mostly limited to aromatic aldehydes and only cyclohexanecarboxaldehyde was used as an aliphatic aldehyde,[5b,c] pointing out the need for developing more general methodologies. All the aforementioned ODVA approaches involve a chiral tertiary ammonium dienolate **I** as key intermediate (Figure 1, pathway a) resulting from the deprotonation of the (5*H*)-furan-2-one by bifunctional catalysts such as axially chiral guanidines,[5a] *Cinchona* alkaloid-thioureas[5b,c] and diamine-derived squaramides.[5c,d] Another attractive approach might be to consider asymmetric phase-transfer catalysis (PTC) to generate a chiral quaternary ammonium dienolate **II** as key intermediate. However, while asymmetric PTC has experienced significant advances these last years,[6] its use in aldol reactions remains sporadic[7] and no application to the

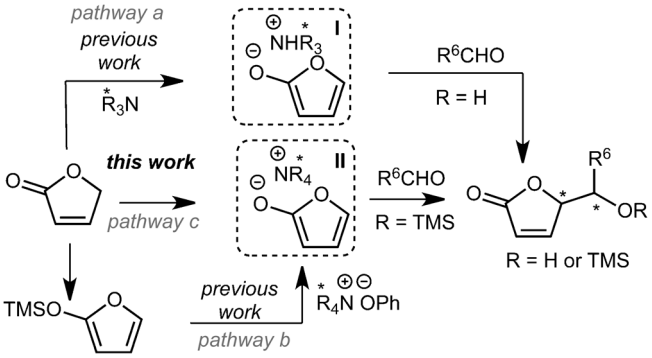


Figure 1. Organocatalytic vinylogous aldol processes by *in situ* generation of dienolate of (5*H*)-furan-2-one derivatives **I**–**II** bearing either chiral tertiary ammonium (pathway a) or chiral quaternary ammonium (pathway b, c) counter-ions.

ODVA reaction with (5*H*)-furan-2-one derivatives has yet been reported. The most plausible reason stems from the possible retro-aldol reaction occurring under the required stoichiometric harsh basic conditions.[7e]

An alternative way of producing *in situ* a chiral quaternary ammonium dienolate **II** was reported by Mukaiyama et al. from 2-trimethylsilyloxyfuran (TMSOF) in the presence of a quaternary ammonium phenoxide as chiral Lewis base (R_4*N^+,PhO^-) (Figure 1, pathway b).[8,9] Under these conditions, the trapping of the resulting aldol product as a silyl ether might prevent the putative retro-aldol reaction while regenerating the Lewis base catalyst (R_4*N^+,PhO^-). Although appealing, this approach suffers from the need to prepare in advance TMSOF from the parent (5*H)*-furan-2-one, not to mention its tricky purification and handling. Inspired by this work, we set out to develop a new ODVA process based on *in situ* formation of a chiral quaternary ammonium dienolate **II** from the parent (5*H)*-furan-2-one (Figure 1, pathway c).

For that purpose, we postulated that upon activation of a silylated base (B-TMS) by a chiral Lewis base (R_4*N^+,ArO^-), the resulting chiral Brønsted base (R_4*N^+,B^-) will be able subsequently to deprotonate the parent carbonyl compound to furnish the desired chiral quaternary ammonium dienolate **II** (Figure 2). This approach would represent an appealing alternative to the standard PTC conditions for the *in situ* generation of a chiral quaternary ammonium enolate under mild conditions. It would also provide a real added value to Mukaiyama's process in terms of efficiency and simplicity by developing this approach from the more available parent carbonyl compounds.

Therefore, with our basic idea in mind, we undertook the preparation of several chiral quaternary ammonium halides derived from the parent *Cinchona* alkaloids (i.e., quininium QN^+, quinidinium QD^+, cinchoninium CN^+ and cinchonidinium CD^+). The corresponding aryloxides were obtained *via* an ion metathesis process by means of ion exchange resins as previously reported (Figure 3).[10,11]

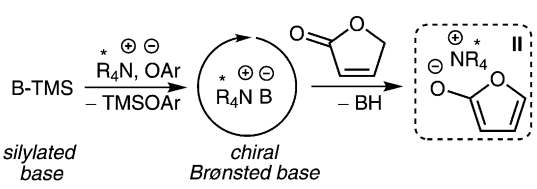


Figure 2. New approach for *in situ* generation of a chiral quaternary ammonium dienolate **II** derived from (5*H*)-furan-2-one derivatives by means of the ammonium aryloxide/*N,O*-bis(trimethylsilyl)acetamide combination.

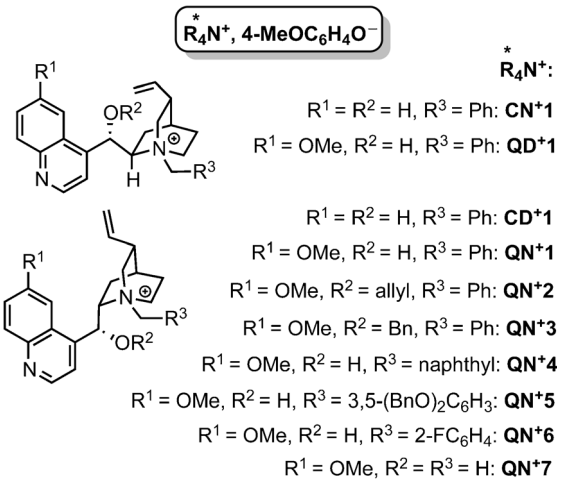
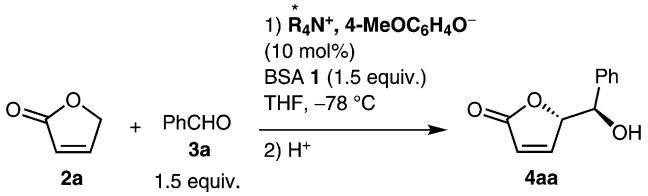


Figure 3. Structures of the chiral ammonium aryloxides **R_4*N^+,4-$MeOC_6H_4O^-$**.

First, we studied the addition of (5*H*)-furan-2-one **2a** to benzaldehyde **3a** as a model reaction in the presence of *N,O*-bis(trimethylsilyl)acetamide **1** (BSA)[12] (1.5 equiv.) and **QN^+1,4-$MeOC_6H_4O^-$** (10 mol%) at −78 °C. A good diastereomeric ratio (*dr*) of 88:12 along with an encouraging 63% *ee* measured on the major *anti* isomer were obtained at −78 °C.[13] At this stage, we decided to compare these reaction conditions with the more commonplace PTC conditions that are easier to implement. No conversion was observed when the reaction was conducted at −78 °C in the presence of **QN^+1,Cl^-** (10 mol%) and Cs_2CO_3 (10 mol%). Only a low conversion (< 20%) was obtained by raising the temperature to 0 °C. In a last attempt, the reaction was achieved in the presence of **QN^+1,Cl^-** (10 mol%) and 1.5 equiv. of Cs_2CO_3. The aldol product **4aa** was obtained in a modest 25% isolated yield and the major *anti* isomer was isolated in only 4% *ee*. Two main reasons may be put forward to account for the superiority of our process over standard PTC procedures: (i) the catalytically active chiral Brønsted base is generated *in situ* under mild conditions, avoiding any background reaction to occur, (ii) a retro-aldol reaction may be prevented by trapping the aldol product **4aa** as its silyl ether.

Having in hand these preliminary results, we decided to undertake a rapid screening of the new chiral ammonium aryloxides at our disposal (Table 1, entries 3–11). This screening revealed that catalysts in the QN^+ series furnished the best enantioselectivity (Table 1, entry 1) whereas those in the CN^+ and CD^+ series provided the higher diastereoselectivities (Table 1, entries 4 and 5). A pseudo-enantiomeric effect was observed in the QD^+ series affording *anti*-**4aa** with the opposite configuration (Table 1, entries 1 *vs.* 3). Further modifications at both C-9 position and

Table 1. Preliminary catalysts screening.

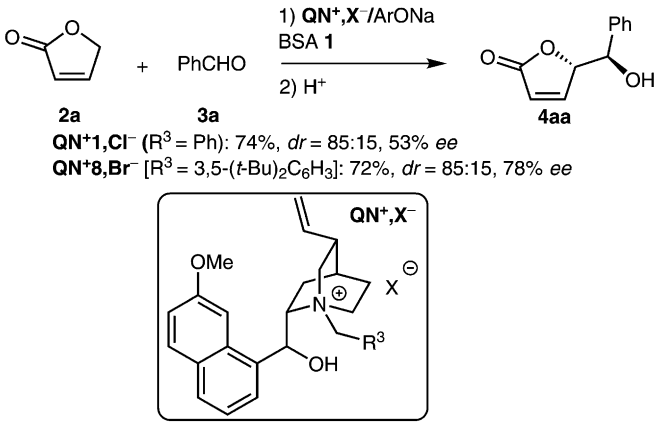


Entry	R_4*N^+	Yield	*dr* (*anti:syn*)[a]	*ee anti*[b]
1	**QN$^+$1**	81%	88:12	63%
2[c]		80%	81:19	34%
3	**QD$^+$1**	69%	82:18	−50%
4	**CD$^+$1**	61%	92:8	30%
5	**CN$^+$1**	67%	92:8	−10%
6	**QN$^+$2**	54%	91:9	−16%
7	**QN$^+$3**	67%	95:5	−11%
8	**QN$^+$4**	80%	76:24	62%
9	**QN$^+$5**	61%	85:15	58%
10	**QN$^+$6**	62%	86:14	54%
11	**QN$^+$7**	68%	90:10	0%

[a] Measured by ^{1}H NMR of the crude product.
[b] Measured by HPLC analysis using a chiral column (see the Supporting Information).
[c] Reaction performed at 0 °C.

nitrogen quinuclidine of the quinine backbone allowed us to highlight the main structural features responsible for the enantioselectivity observed (Table 1, entries 6–11). First, the substitution of the OH at C-9 position results in a dramatic drop of the enantiomeric excess along with an inversion of the sense of stereoinduction (Table 1, entries 6 and 7). Further structural modifications at the nitrogen quinuclidine by changing the nature of the aromatic group in R^3 (Table 1, entries 8–10) gave rise to slightly lower diastereo- and enantioselectivities. Nevertheless, the presence of an aromatic substituent in R^3 seems to be crucial to ensure a high level of enantioselection. Indeed, its substitution by a hydrogen atom (Table 1, entry 11) provides **4aa** with a good diastereomeric ratio. Unfortunately, the major isomer was obtained as a racemic mixture. Because many quaternary ammonium aryloxides proved to be tedious and tricky to isolate, we then turned our attention to the *in situ* generation of these species.[14] Thus, by adding both the chiral quaternary ammonium halide and 4-MeO-C_6H_5ONa in the reaction mixture, one could expect ion metathesis to take place to form the required quaternary ammonium aryloxide (Scheme 1).

First of all, we took pains to check that no background reaction occurs in the absence of any chiral quaternary ammonium halide. In contrast, when the reaction was conducted in the presence of both **QN$^+$1,Cl$^-$** and 4-$MeOC_6H_5ONa$,[16] we were pleased to find out that the formation of **4aa** occurred smoothly with almost the same level of stereoselectivity and comparable conversion as those obtained with the pre-formed catalyst (Table 1, entry 1). This new procedure not only makes the experimental conditions much easier to implement but also allowed us to test other chiral quaternary ammonium halides for which ion metathesis failed to provide the corresponding ammonium aryloxides. Among them,[11] the chiral quaternary ammonium halide **QN$^+$8,Br$^-$** bearing a 3,5-(*t*-Bu)$_2C_6H_3$ as R^3 group gave the best result in terms of enantioselectivity (78% *ee*).



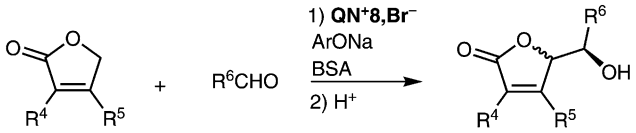
Scheme 1. *In siu* generation of the chiral ammonium aryloxides.[15]

The substrate scope of the reaction was further investigated under the optimized reaction conditions[15] with various (5*H*)-furan-2-ones **2a–c** and aldehydes **3a–q** (Table 2).

From a general viewpoint, higher enantiomeric excesses were obtained for the *anti* isomers. Regarding the influence of the substitution pattern of the furanone ring, the presence of a methyl group at C-3 or C-4 position resulted in a substantial increase of the enantioselectivity (Table 2, entries 1–3); 3-methyl (5*H*)-furan-2-one **2b** being superior from a reactivity viewpoint (Table 2, entry 2). Then, we examined the aldehyde scope of the reaction. Generally speaking, substitution at the phenyl ring was found to have a beneficial effect on the enantioselectivity (Table 2, entries 4–7), except when the *para* position bears an electron-donating group (Table 2, entries 8 and 9). Others aromatic aldehydes including 1- or 2-naphthaldehydes (Table 2, entries 11 and 12) and heteroaromatic aldehydes (Table 2, entries 13 and 14) were also well-tolerated.

Last but not least, this optimized protocol was also successfully expanded to aliphatic aldehydes **3m–q** (Table 2, entries 15–19), provided that the reaction is achieved at somewhat higher temperature (−60 °C to −40 °C) to ensure a complete conversion. Gratifyingly, an excellent 94% *ee* could be reached by using pivaldehyde **3o** (Table 2, entry 17). Lastly, it should be mentioned that easily enolizable aldehydes such as **3q**

Table 2. Scope of the reaction.[15,17]



2a: R^4 = H, R^5 = H
2b: R^4 = Me, R^5 = H
2c: R^4 = H, R^5 = Me

3a–q

4aa, ca, ba–bq

Entry	2	3	4: Yield [%]	*dr*[a]	*ee*[b] [%] *anti* (*syn*)
1	**2a**	R^6 = Ph, **3a**	**4aa**: 72	85:15	78 (*nd*)
2	**2b**		**4ba**: 77	95:5	89 (*nd*)
3	**2c**		**4ca**: 28	*nd*	83 (*nd*)
4	**2b**	R^6 = 4-BrC_6H_4, **3b**	**4bb**: 62	95:5	92 (57)
5		R^6 = 4ClC_6H_4, **3c**	**4bc**: 75	95:5	92 (78)
6		R^6 = 4-FC_6H_4, **3d**	**4bd**: 82	95:5	92 (*nd*)
7		R^6 = 2-ClC_6H_4, **3e**	**4be**: 65	90:10	91 (*nd*)
8		R^6 = 4-MeC_6H_4, **3f**	**4bf**: 73	83:17	79 (*nd*)
9		R^6 = 4-MeOC_6H_4, **3g**	**4bg**: 82	79:21	75 (*nd*)
10		R^6 = 3-MeOC_6H_4, **3h**	**4bh**: 73	95:5	86 (*nd*)
11		R^6 = α-naphthyl, **3i**	**4bi**: 87	95:5	87 (82)
12		R^6 = β-naphthyl, **3j**	**4bj**: 79	84:16	83 (*nd*)
13		R^6 = 2-thienyl, **3k**	**4bk**: 59	70:30	88 (*nd*)
14		R^6 = 3-furyl, **3l**	**4bl**: 72	85:15	82 (56)
15[c]		R^6 = *c*-C_6H_{11}, **3m**	**4bm**: 85	83:17	85 (63)
16[d]		R^6 = *c*-C_3H_5, **3n**	**4bn**: 84	71:29	66 (50)
17[d]		R^6 = *t*-Bu, **3o**	**4bo**: 77	90:10	94 (*nd*)
18[d]		R^6 = *i*-Pr, **3p**	**4bp**: 81	82:18	74 (74)
19[d,e]		R^6 = PhCH_2CH_2, **3q**	**4bq**: 83	66:34	74 (40)

[a] The *anti:syn* ratio was measured by ^{1}H NMR of the crude product.
[b] Measured by HPLC analysis using a chiral column (see the Supporting Information). *nd*: not determined.
[c] Reaction conducted at −60 °C for 24 h.
[d] Reaction conducted at −40 °C for 24 h.
[e] A solution of the aldehyde in THF was added dropwise over a period of 6 h.

gave rise to the aldol product **4bq** with a good yield along with a fairly good 74% *ee* provided the aldehyde was added dropwise (Table 2, entry 19).

In order to gain insight into the mechanism of the reaction, a control experiment was realized to determine whether or not the presence of BSA leads to the transient formation of trimethylsilyloxyfuran as key intermediate in the stereochemical outcome of the reaction. To address this issue, the vinylogous aldol reaction was performed with TMSOF and benzaldehyde **2a** in the presence of 10 mol% of catalyst **QN^+1,4-$MeOC_6H_4O^-$** in THF at −78 °C. Despite quantitative conversion and a good diastereomeric ratio of 84:16 (*anti:syn*), *anti*-**4aa** was obtained with only 8% *ee* (*vs.* 63% *ee* from **2a**, Table 1, entry 1). These results clearly rule out the involvement of the transient TMSOF in the enantiodetermining step,[18] but rather support a mechanism involving a chiral ammonium enolate as key intermediate.

In line with this assumption, a plausible mechanism depicted in Figure 4 would start with an ion metathesis providing the chiral ammonium aryloxide **A**. Activation of BSA mediated by **A** would lead to the chiral ammonium amide **B**,[19,20] basic enough to deprotonate the (5*H*)-furan-2-one **2**. The resulting chiral ammonium enolate **C**[21] would then afford alkoxide **D** by subsequent addition to aldehyde **3** which upon silylation by ArOTMS (pathway I) or BSA (pathway II) would furnish the silylated vinylogous aldol product along with the concomitent regeneration of either **A** or **B**, respectively.

In summary, we have reported an efficient and general ODVA reaction between (5*H*)-furan-2-one derivatives **2a–c** and aldehydes **3a–q** catalyzed by a chiral ammonium amide (generated *in situ* from chiral ammonium aryloxide and BSA). High diastereomeric ratios and excellent enantioselectivities were obtained with a large panel of (hetero)aromatic aldehydes and more importantly with the less studied aliphatic aldehydes providing a complementary approach for the synthesis of enantioenriched 5-(1′-hydroxy)-γ-butenolides **4**. The extension of this catalytic system is currently under evaluation within our laboratory.

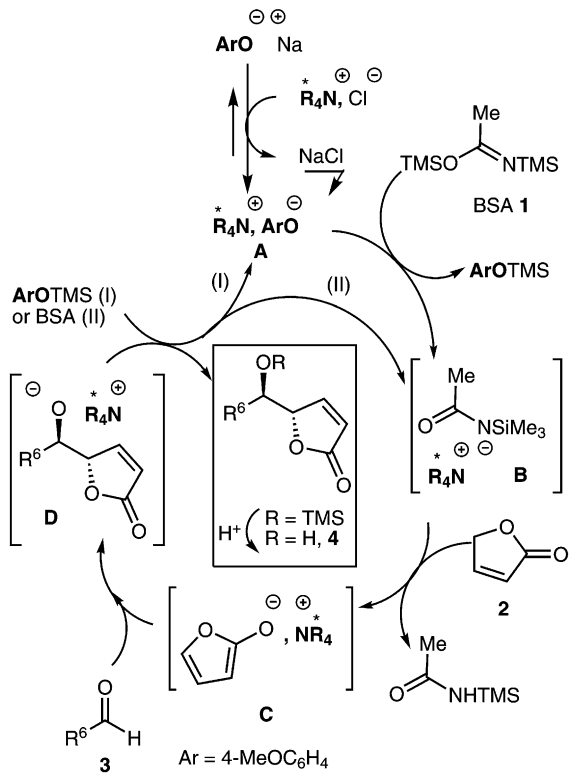


Figure 4. Mechanism proposal.

Experimental Section

General Procedure for the Organocatalytic Direct Vinylogous Aldol Reaction

To a solution of **QN$^+$8, Br$^-$** (0.05 mmol, 30.4 mg) in THF (3 mL) at room temperature was added sodium 4-methoxyphenoxide freshly prepared as a solution in THF (1 M, 0.04 mmol, 40 μL). The whole was stirred for 1 hour at this temperature, after which the (5*H*)-furan-2-one derivatives **2a–c** (0.5 mmol) was added. The resulting mixture was cooled to the required temperature and aldehyde (0.75 mmol) and BSA (0.75 mmol, 184 μL) were added and the solution was stirred at the same temperature for the specified time for each individual compound. An aqueous solution of HCl (10%, 0.5 mL) was added and the reaction flask was placed at 0 °C. The resulting mixture was stirred for 30 min at this temperature. Water was added (2 mL) and the mixture was extracted with AcOEt (2 × 4 mL). The aqueous phase was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt (5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel by using petroleum ether/AcOEt and subjected to HPLC analysis using chiral column.

Acknowledgements

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[11] See the Supporting Information for further details.

[12] Various silylated bases were tested such as *N,O*-bis(trimethylsilyl)acetamide **1** (BSA), *N*-(trimethylsilyl)acetamide, *N,O*-bis(trimethylsilyl)trifluoroacetamide, *N*-methyl-*N*-(trimethylsilyl)acetamide, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide or *N*-(trimethylsilyl)imidazole among which only BSA **1** has provided the addition product **4aa**.

[13] Relative and absolute configurations of **4aa** were determined by comparison with data in ref.[5b]

[14] For examples, see: a) H. Zhao, B. Qin, X. Liu, X. Feng, *Tetrahedron* **2007**, *63*, 6822–6826; b) L. Bernardi, E. Indrigo, S. Pollicino, A. Ricci, *Chem. Commun.* **2012**, *48*, 1428–1430.

[15] *General conditions:* 1) **2** (1 equiv.), **3** (1.5 equiv.), $\mathbf{QN^+,X^-}$ (10 mol%), ArONa (Ar = 4-$MeOC_6H_4$, 8 mol%), BSA **1** (1.5 equiv.), THF, −78 °C, 5 h. 2) HCl (10% aq.), 0 °C, 30 min.

[16] Other sodium or potassium aryloxides [PhONa, sodium or disodium (*R*)-binaphtolate, 4-$MeOC_6H_4OK$] or sodium ethanethiolate gave similar or lower enantiomeric excesses, see the Supporting Information.

[17] All attempts to separate both diastereoisomers have failed.

[18] An additional control experiment that sought to track the formation of TMSOF in our optimized conditions by GC-MS failed. Lastly, when the reaction was conducted in the absence of benzaldehyde, TMSOF still remains undetected.

[19] The characterization of 4-$MeOC_6H_4OTMS$ by GC-MS and the absence of reaction without BSA give strong support to the formation of a chiral ammonium amide as catalytically active species.

[20] During the preparation of this manuscript, Kondo et al. and Shibata et al. reported the *in situ* generation of racemic ammonium amide bases starting from Me_2NTMS/Me_4NF or BSA/Me_4NF combination respectively, see: a) K. Inamoto, H. Okawa, H. Taneda, M. Sato, Y. Hirono, M. Yonemoto, S. Kikkawa, Y. Kondo, *Chem. Commun.* **2012**, *48*, 9771–9773; b) G. Haufe, S. Suzuki, H. Yasui, C. Terada, T. Kitayama, M. Shiron, N. Shibata, *Angew. Chem.* **2012**, *124*, 12441–12445; *Angew. Chem. Int. Ed.* **2012**, *51*, 12275–12279.

[21] For a proposal of plausible transition states that account for the origin of asymmetric induction, see the Supporting Information.