Organocatalysis

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An Achiral-Acid-Induced Switch in the Enantioselectivity of a Chiral *cis*-Diamine-Based Organocatalyst for Asymmetric Aldol and Mannich Reactions**

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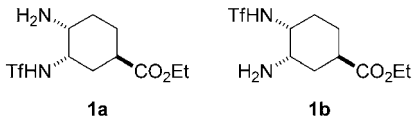
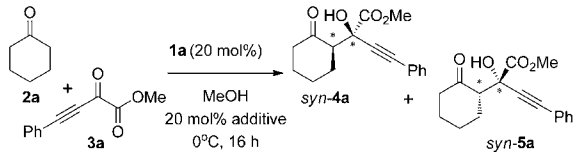
From a practical point of view, the development of a novel approach for the asymmetric synthesis of both enantiomeric products through catalytic asymmetric transformations with the same chiral catalyst would be very useful.[1] Various types of chiral metal complexes have already been introduced.[2] However, strictly speaking, many of these examples have employed a distinct three-dimensional association between a chiral ligand and different metals, or vice versa. In marked contrast, an initial effort for the synthetic application of chiral organocatalysts has appeared very recently, but has not been developed to a synthetically useful level.[3] In this context, we explored the capability of an additive to induce an unexpected inversion in catalyst selectivity for certain asymmetric transformations catalyzed by a single chiral organocatalyst. Herein we present the first practical example of such a system, employing achiral, organic acids as reliable additives in asymmetric, direct aldol reactions catalyzed by a chiral, *cis*-diamine-based, Tf-amido organocatalyst of type **1** (Tf = trifluoromethanesulfonyl Scheme 1).[4–7]



Scheme 1. Chiral *cis*-diamine-based regioisomeric organocatalysts. Tf = trifluoromethanesulfonyl.

Initally, the asymmetric direct aldol reaction of cyclohexanone and α-keto ester **3a** was carried out with organocatalyst **1a** to establish the optimum reaction conditions. The treatment of cyclohexanone **2a** and α-keto ester **3a** with 20 mol% of **1a** in methanol at 0°C gave the corresponding aldol products **4a** in moderate yields; the major isomer, *syn*-**4a**, was obtained with high enantioselectivity (Table 1, entry 1). We had previously observed a remarkable enhancement in enantioselectivity for the asymmetric conjugate addition of heterosubstituted aldehydes to vinyl sulfones by using bulky benzoic acid additives under the influence of a structurally rigid, *trans*-diamine-based, Tf-amide catalyst with a dihydroanthracene framework.[8] This finding prompted us to test a series of benzoic acid derivatives to probe their potential for the reversal of enantioselectivity in these products as well.

Table 1: Screening of reaction conditions for asymmetric aldol reactions.[a]



Entry	Additive[b]	Yield[c] [%]	d.r.[d] (*syn*/*anti*)	aldol	*ee*[e] [%]
1	none	63	8.1:1	**4a**	94
2	C_6F_5OH	78	5.0:1	**4a**	58
3	4-(NMe_2)-$C_6H_4CO_2H$	98	4.8:1	**4a**	88
4	$C_6H_5CO_2H$	95	5.2:1	**4a**	81
5	4-$FC_6H_4CO_2H$	94	5.2:1	**4a**	79
6	4-NO_2-$C_6H_4CO_2H$	90	5.6:1	**4a**	72
7	3,5-$F_2C_6H_3CO_2H$	87	6.2:1	**4a**	72
8	2,6-$F_2C_6H_3CO_2H$	75	7.3:1	**4a**	20
9	2,6-$(OH)_2C_6H_3CO_2H$	38	6.0:1	**5a**	45
10	2,6-$(NO_2)_2C_6H_3CO_2H$	72	5.9:1	**4a**	59
11	$C_6F_5CO_2H$	71	9.2:1	**5a**	42
12	$C_6F_5SO_3H$	29	3.7:1	**5a**	0
13	CF_3CO_2H	18	3.0:1	**5a**	5

[a] Unless otherwise specified, the asymmetric aldol reaction of cyclohexanone and α-keto ester **3a** was conducted in the presence of 20 mol% of catalyst **1a** and 20 mol% of acid additives for 16 h under the given conditions. [b] Order based on decreasing pK_a values (approximate). [c] Yield of isolated product. [d] Diastereoselectivity was determined by ^{1}H NMR spectroscopy. [e] Enantiopurity of aldols was determined by HPLC analysis on a chiral stationary phase with hexane/2-propanol as solvent (see the Supporting Information).

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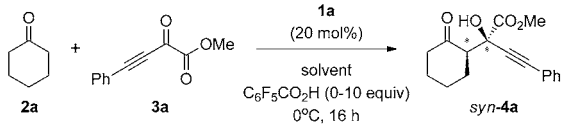
Initially, several *para*-substituted benzoic acids were tested to identify the correlation between acidity and the reaction outcomes. As shown in Table 1, the addition of benzoic acid derivatives lowered the overall enantioselectivities obtained in the reaction (entries 3–6 vs. entry 1). The acid strength seems to influence the reaction rate as well as the stereoselectivity. Although weaker acids resulted in higher yields, as acid strength increased, diastereoselectivity improved and a further reduction in enantioselectivity was observed (entries 2–6).

Inversion of catalyst selectivity (that is, generation of *syn*-**5a**) was observed with both 2,6-dihydroxybenzoic acid and pentafluorobenzoic acid (Table 1, entries 9 and 11). Changing the nature of the acids induced a drastic effect on the reaction outcome; a further increase in acidity resulted in a negative effect on the reaction rate (entries 12 and 13). As shown in Table 2, the acid stoichiometry also has a significant effect on

Table 2: Effect of additives in asymmetric aldol reactions.[a]



2a **3a** *syn*-**4a**

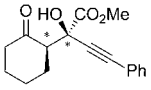
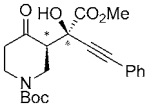
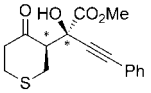
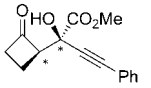
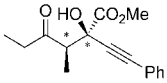
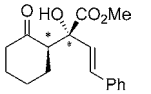
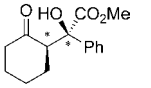
Entry	Solvent	Equivalents of additive	Yield[b] [%]	*syn*/*anti*[c]	*ee*[d] [%]
1	MeOH	0	63	8.1:1	94
2	MeOH	1	71	9.2:1	−42
3	MeOH	3	37	13:1	−58
4	MeOH	10	32	13:1	−60
5	MeCN	0	69	9:1	92
6	MeCN	1	65	9:1	−43
7	H_2O	0	47	6:1	−58
8	H_2O/MeOH[e]	1	68	8:1	−90
9	H_2O/MeCN[e]	1	74	8:1	−88

[a] Unless otherwise specified, the asymmetric aldol reaction of cyclohexanone and α-keto ester **3a** was conducted in the presence of 20 mol% of catalyst **1a** for 16 h under the given conditions. [b] Yield of isolated product. [c] Diastereoselectivity was determined by ^{1}H NMR spectroscopy. [d] Enantiopurity of aldols was determined by HPLC analysis on a chiral stationary phase with hexane/2-propanol as solvent (see the Supporting Information). [e] Volume ratio = 1:1.

the reaction outcome. As acid stoichiometry increases, regardless of their acid strengths, improved diastereoselctivities while diminishing enantioselectivity values (Table 2, entries 1–4; see also the Supporting Information). The use of acetonitrile did not alter reactivity or selectivity in this aldol reaction and can be employed as a solvent when the substrate shows poor solubility in methanol (entries 5 and 6). Interestingly, switching the solvent to water also resulted in a reversal in enantioselectivity (entry 7). Similarly, a large reversal effect was observed when aqueous methanol (or acetonitrile) was used along with one equivalent of pentafluorobenzoic acid (entries 8 and 9). However, the enantiomeric excess remained unchanged when 2,6-dihydroxybenzoic acid was employed in the aqueous methanol system.[9]

With the optimal reaction conditions in hand, we further investigated the generality of asymmetric, direct aldol reactions of various ketones and α-keto esters in the presence of catalyst **1a** (Table 3). The use of catalyst **1a** alone always gave *syn*-aldol products (*syn*-**4**) with one (2*R*,1′*R* for *syn*-**4a**) configuration, while use of pseudoenantiomeric catalyst **1b** afforded products (*syn*-**5**) with the opposite (2*S*,1′*S* for *syn*-**5a**) configuration (entry 1 vs. 3). The absolute structure of the aldol product was unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information). For reactions with an acid additive, an aqueous acetonitrile solvent system was employed instead of aqueous methanol owing to solubility issues with some of the α-keto esters in these experiments. Under these conditions, the reverse in enantioselectivity was higher than that of the reaction catalyzed by **1b** (entry 2 vs. 3). Both cyclic and acyclic ketones were tested for various α-keto esters, including alkenyl- and Phenyl-substituted α-keto esters (entries 1–15). In all cases, an efficient inversion of product configuration was observed. To our knowledge, such a high magnitude of

Table 3: Practical synthesis of both enantiomeric aldols in asymmetric direct aldol reactions catalyzed by **1a** with or without pentafluorobenzoic acid as additive.[a]

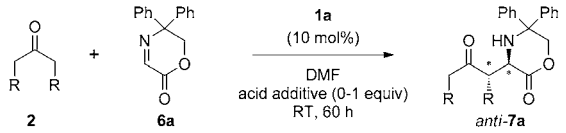
Entry	Product	Additive & solvent[b,c]	Yield[d] [%] (*syn*/*anti*)	*ee*[e] [%]
1		MeOH	93 (8:1)	94
2		$C_6F_5CO_2H/H_2O$/MeCN	>99 (8:1)	−88
3[f]		MeOH	96 (7.3:1)	−72
4		MeOH	83 (2.3:1)	89
5		$C_6F_5CO_2H/H_2O$/MeCN	98 (8:1)	−87
6		MeOH	87 (8:1)	90
7		$C_6F_5CO_2H/H_2O$/MeCN	91 (7:1)	−93
8		MeOH	62 (20:1)	95
9		$C_6F_5CO_2H$/brine	70 (20:1)	−94
10		neat	44 (15:1)	87
11		$C_6F_5CO_2H$/brine	57 (16:1)	−93
12		MeOH	88 (1:2.7)	93
13		$C_6F_5CO_2H/H_2O$/MeCN	98 (1:6.7)	−87
14		MeOH	57 (20:1)	95
15		$C_6F_5CO_2H/H_2O$/MeCN	41 (18:1)	−96

[a] Unless otherwise specified, asymmetric aldol reaction of cyclic ketone **2** and α-keto ester **3** was conducted in the presence of 20 mol% of catalyst **1a** for 40 h under the given conditions. [b] Volume ratio of H_2O/MeCN = 1:1. [c] Certain substrates do not dissolve in aqueous MeOH, and thus the use of aqueous MeCN is recommended instead. [d] Yield of isolated product. [e] Enantiopurity of major aldol isomers was determined by HPLC analysis on a chiral stationary phase with hexane/2-propanol as solvent (see the Supporting Information). [f] With catalyst **1b**.

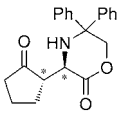
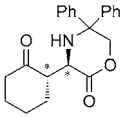
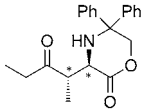
enantiomeric inversion using achiral additives has never been previously reported.

A similar reversal in catalyst selectivity was observable for the asymmetric, *anti*-selective Mannich reaction of a cyclic imino ester[10] (Table 4, entries 1–7). Optimum results were

Table 4: Practical synthesis of both enantiomeric Mannich products in asymmetric Mannich reactions catalyzed by **1a** with or without an acid additive.[a]



2 **6a** *anti*-**7a**

Entry	Product	Additive/solvent	Yield[b] [%] (*anti*/*syn*)	*ee*[c] [%]
1		none/DMF	90 (>20:1)	>99
2		2,6-$(NO_2)_2C_6H_3CO_2H$/DMF	93 (>20:1)	−88
3		$C_6F_5CO_2H$/DMF	86 (18:1)	90
4		none/DMF	98 (>20:1)	>99
5		2,6-$(NO_2)_2C_6H_3CO_2H$/DMF	93 (>20:1)	−83
6		none/DMF	70 (16:1)	98
7		2,6-$(NO_2)_2C_6H_3CO_2H$/DMF	74 (19:1)	−87

[a] Unless otherwise specified, asymmetric Mannich reaction of various ketones **2** and cyclic imine **6a** was conducted in the presence of 10 mol% of catalyst **1a** for 60 h under the given conditions. [b] Yield of isolated product. [c] Enantiopurity of major aldol isomers was determined by HPLC analysis on a chiral stationary phase.

obtained when the reactions were conducted in DMF using 10 mol% of catalyst **1a** in the absence of an acid additive (entries 1 and 4). In contrast to the aldol reaction described above, the use of pentafluorobenzoic acid did not reverse the enantioselectivity (entry 3). However, the use of 10 mol% 2,6-dinitrobenzoic acid did provide for an efficient inversion in product configuration (entries 2, 5, and 7). Unlike the aldol reaction with an α-keto ester, the addition of water did not improve this enantioselectivity reversing effect.[11]

Based on the above observations, we propose two possible transition state models (Figure 1a and b), which are optimized at the B3LYP/6-31G* level of approximation, to account for the observed absolute configuration of both aldol products. In the absence of acid additives, α-ketoesters are chelated and activated through the carbonyl group of the ketone by both the acidic Tf-amide hydrogen atom and the acidic enamine NH hydrogen atom. The enamine moiety would then attack from the back side, as shown in (Figure 1a) to furnish aldol product *syn*-**4**.

On the other hand, in the presence of acid additives and water, the two point chelation ability of α-keto esters plays an important role in the reversal of enantioselectivities.[12] The acidic Tf-amide hydrogen atom in catalyst **1a** activates the

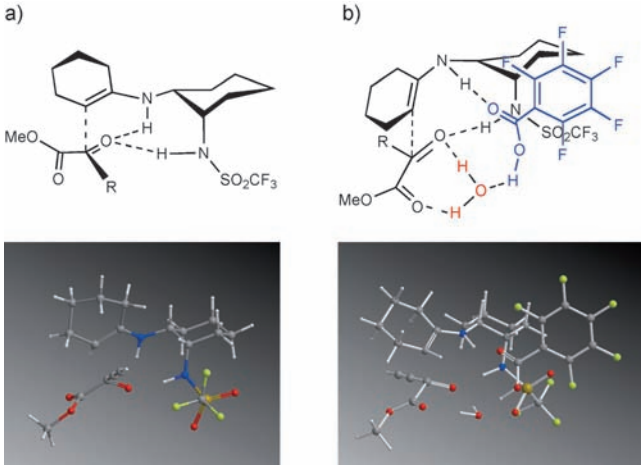


Figure 1. Possible transition-state structures optimized by B3LYP/6-31G*.[15,16]

ketone carbonyl group while the acidic enamine NH hydrogen atom is involved in the recruitment of the acid additive, coordinating onto the carbonyl oxygen of the acid through a hydrogen bond. From several scenarios that we tested, it appears that the involvement of one molecule of water is required for the observed inversion in catalyst enantioselectivity, as shown in Figure 1.[13] The water molecule, which might be generated by formation of imine from ketones, is involved in bridging the added acid to the α-keto ester, leading to the favorable formation of transition state (**B**) and thus furnishing the enantiomer *syn*-**5**.

In the absence of acid additives, a switch in solvent from methanol (or acetonitrile) to water also resulted in inversion of the enantiomeric configuration of the product (Table 2, entries 1 vs. 7). However, in direct aldol reactions between various ketones and benzaldehyde derivatives, we did not observe any major differences in enantioselectivity or diastereoselectivity when the solvent was changed from methanol to water. Therefore, it is less likely that the catalyst ring conformation changes, unlike those cases previously reported with peptide based catalysts.[14] More detailed mechanistic studies using DFT calculations are currently underway.

In summary, we have succeeded in obtaining both enantiomeric aldol and Mannich products by using a single chiral organocatalyst **1a** in the presence or absence of achiral acids as additives. In principle, this strategy is applicable to other keto and imino esters, as well as other catalytic systems. Further efforts towards this end, as well as more detailed mechanistic studies, are currently underway in our laboratory.

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[9] The use of 2,6-$(OH)_2C_6H_3CO_2H$ in H_2O/MeOH gave: 47% yield, d.r. (*syn*/*anti*) = 5.8:1, −44% *ee*.

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[11] In the case of 50% water in DMF without an acid additive, the *ee* value of *syn*-**4a** is identical (94% *ee*) to that in entry 1 of Table 4. In contrast, a racemic product was obtained when 20 mol% of 2,6-dinitrobenzoic acid was used along with a solvent system of 50% water in DMF.

[12] No enantiomeric inversion was observed in the direct aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in the presence of various organic acids and/or water.

[13] In aldol reactions without a water molecule present in the transition state, B3LYP/6-31G* calculations indicated the favorable formation of *syn*-**4a**. Furthermore, the calculation involving two molecules of water in the transition state by did not match with our observations.

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[16] Some of the substrate and the catalyst functionalities have been omitted to simplify the calculations. The role of the omitted ethyl ester moiety on the catalyst is to lock the Tf-amide group in the axial position and the enamine nitrogen in the equatorial position.

