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, cisdiamine-based, Tf-amido organocatalyst of type 1 (Tf = trifluoromethanesulfonyl Scheme 1).^[4–7]



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

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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]

reactions. ^(a)						
0 J		Оно ∦ ∗ У	CO ₂ Me			
	0 1a (20 mol	%)	Ph [рно со	₂ Me	
2 a Pl	a + OMe MeOH 20 mol% a h 3a 0 0°C 16	H <i>syn-</i> 4a dditive Sh	+	svn-5	Ph	
Entry	Additive ^(b)	Yield ^[c] [%]	d.r. ^[d] (syn/anti)	aldol	ee ^[e] [%]	
1	none	63	8.1:1	4a	94	
2	C ₆ F ₅ OH	78	5.0:1	4 a	58	
3	4-(NMe ₂)-C ₆ H ₄ CO ₂ H	98	4.8:1	4a	88	
4	C ₆ H ₅ CO ₂ H	95	5.2:1	4 a	81	
5	4-FC ₆ H ₄ CO ₂ H	94	5.2:1	4 a	79	
6	4-NO ₂ -C ₆ H ₄ CO ₂ H	90	5.6:1	4 a	72	
7	3,5-F ₂ C ₆ H ₃ CO ₂ H	87	6.2:1	4 a	72	
8	2,6-F ₂ C ₆ H ₃ CO ₂ H	75	7.3:1	4 a	20	
9	2,6-(OH) ₂ C ₆ H ₃ CO ₂ H	38	6.0:1	5 a	45	
10	2,6-(NO ₂) ₂ C ₆ H ₃ CO ₂ H	72	5.9:1	4 a	59	
11	$C_6F_5CO_2H$	71	9.2:1	5 a	42	
12	$C_6F_5SO_3H$	29	3.7:1	5 a	0	
13	CF_3CO_2H	18	3.0:1	5 a	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 ¹H NMR spectroscopy. [e] Enantiopurity of aldols was determined by HPLC analysis on a chiral stationary phase with hexane/2propanol 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

1a

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

	0 + Ph 2a 3a	$ \begin{array}{c} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\$	1a 20 mol%) solvent 0 ₂ H (0-10 equiv) 0°C, 16 h	O HO CO2	Me Ph
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 ₂ O	0	47	6:1	-58
8	H ₂ O/MeOH ^[e]	1	68	8:1	-90
9	H ₂ O/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 ¹H 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 reac-

tions 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 (2R,1'R for syn-4a)

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

Entry	Product	Additive & sol- vent ^[b,c]	Yield ^[d] [%] (syn/anti)	ee ^[e] [%]
1 2	O HO CO ₂ Me	MeOH C ₆ F ₅ CO ₂ H/H ₂ O/ MeCN	93 (8:1) >99 (8:1)	94 88
3 ^[f]	\checkmark	MeOH	96 (7.3:1)	-72
4 5	O HO CO ₂ Me	MeOH C ₆ F ₅ CO ₂ H/H ₂ O/ MeCN	83 (2.3:1) 98 (8:1)	89 87
6 7	O HO CO ₂ Me	MeOH C ₆ F ₅ CO ₂ H/H ₂ O/ MeCN	87 (8:1) 91 (7:1)	90 93
8 9	HO CO ₂ Me	MeOH C ₆ F₅CO₂H/brine	62 (20:1) 70 (20:1)	95 94
10 11	O HO CO2Me	neat C ₆ F ₅ CO ₂ H/brine	44 (15:1) 57 (16:1)	87 93
12 13	O HO CO ₂ Me	MeOH C ₆ F ₅ CO ₂ H/H ₂ O/ MeCN	88 (1:2.7) 98 (1:6.7)	93 87
14 15	O HO CO ₂ Me	MeOH C ₆ F ₅ CO ₂ H/H ₂ O/ MeCN	57 (20:1) 41 (18:1)	95 —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 1 a 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/2propanol as solvent (see the Supporting Information). [f] With catalyst 1Ь.

configuration, while use of pseudoenantiomeric catalyst 1b afforded products (syn-5) with the opposite (2S,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 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]

∫ R	$ \begin{array}{cccc} & & & & Ph \\ & & & & N \\ & & & & R \\ & & & & R \\ & & & & R \\ & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & & & & & 0 \\ & & $	Ph 1a (10 mol%) O DMF acid additive (0-1 equiv) RT, 60 h	Ph O HN R R O anti- 7a	∑Ph ∑O
Entry	Product	Additive/solvent	Yield ^[b] [%] (anti/syn)	ee ^[c] [%]
1 2 3	Ph Ph O HN O HN O O	none/DMF 2,6-(NO ₂) ₂ C ₆ H ₃ CO ₂ H/ DMF C ₆ F ₅ CO ₂ H/DMF	90 (>20:1) 93 (>20:1) 86 (18:1)	>99 -88 90
4 5	Ph Ph HN ** 0	none/DMF 2,6-(NO ₂) ₂ C ₆ H ₃ CO ₂ H/ DMF	98 (>20:1) 93 (>20:1)	>99 -83
6 7	O HN +++O O O HN	none/DMF 2,6-(NO ₂) ₂ C ₆ H ₃ CO ₂ H/ DMF	70 (16:1) 74 (19:1)	98 —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 diaste-reoselectivity 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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