Organocatalysis

Synthesis of β-Hydroxyaldehydes with Stereogenic Quaternary Carbon Centers by Direct Organocatalytic Asymmetric Aldol Reactions**

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Asymmetric organocatalysis, especially with L-proline, is receiving renewed attention, although the foundations for this approach were laid over 30 years ago in studies with preformed L-proline-derived enamines[1] and shortly there-

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after in catalytic asymmetric intramolecular aldol reactions.[2] L-Proline and other chiral amines have recently been shown to be efficient catalysts of asymmetric intermolecular aldol reactions[3] and a variety of other imine- and enamine-based reactions.[4–7] Although impressive, the synthetic scope of L-proline is not sufficient to address all aspects of the aldol reaction.[3b] For example, the synthesis of compounds with quaternary carbon atoms is currently one of the most challenging topics in asymmetric organic chemistry that is not addressed efficiently with L-proline catalysis.[8,9] L-Proline-catalyzed aldol reactions have focused on the use of α-monoalkyl-substituted or α-heteroatom-substituted carbonyl compounds as donors. The use of α,α-dialkyl aldehyde donors should provide direct access to enantiomerically enriched products with a quaternary carbon atom. However, the application of this approach to reactions of α,α-dialkyl aldehyde donors has not provided satisfactory results.

Since an amine-catalyzed aldol reaction proceeds via an enamine intermediate, acceleration of the formation of the enamine intermediate can be key to improving the construction of α,α-dialkyl aldol products. Recently we demonstrated the utility of a fluorescence detection system[10] for monitoring the progress of C–C bond formation in the reaction of the maleimide **1** and acetone (**2**). This Michael-type reaction can then be used as a surrogate-reporter reaction for other enamine-based reactions. By monitoring the formation of the fluorescent product **3** (Figure 1), catalysts of enamine formation were evaluated, and an effective pyrrolidine/acetic acid bifunctional catalyst was identified for the use of α,α-dialkyl aldehydes as aldol donors.[11] This study provided us with the incentive to find asymmetric catalysts for this important class of aldol reactions. Herein we present the results of our investigation of direct asymmetric intermolecular aldol reactions of α,α-dialkyl aldehydes with aryl aldehydes through high-throughput fluorescence-based screening.

To evaluate the catalytic efficiency of the chiral amines **4**–**8** in the presence of various acid additives, such as Lewis, Brønsted, and organic acids, the reaction of **1** with acetone was performed in the presence of each of these catalysts, and the increase in fluorescence was monitored (Figure 1). The best results were observed in the reactions with the catalyst **8** and the acid additive trifluorosulfonic acid (run 74, RFU = 160.0 s^{-1}),[12] and with the catalyst **8** and the acid additive trifluoroacetic acid (run 78, RFU = 152.5 s^{-1}). The addition of these acids significantly improved the reaction rate relative to that with the catalyst **8** in the absence of an acid (run 65, RFU = 35.0 s^{-1}). The initial rate of reactions catalyzed by L-proline (**4**, run 1, RFU = 79.2 s^{-1}) and L-prolinol (**5**, run 17, RFU = 73.9 s^{-1}) were not increased by the addition of any of the acids. The reaction with the catalyst **6**, which has a bulky diphenylhydroxymethyl substituent, had a low rate in the absence of an acid (run 33, RFU = 1.6 s^{-1}), and the rates remained low even when acids were added. For the catalyst **7**, the rate was enhanced by the addition of acetic acid (RFU = 14.8 s^{-1} without acid, run 49 and RFU = 85.5 s^{-1} with acetic acid, run 63). The chiral-amine/acid combinations were also evaluated in different solvents, such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide, 1,4-dioxane, acetone, MeCN, THF, PhMe, *i*PrOH, and MeOH. DMSO was determined to be the most effective solvent.

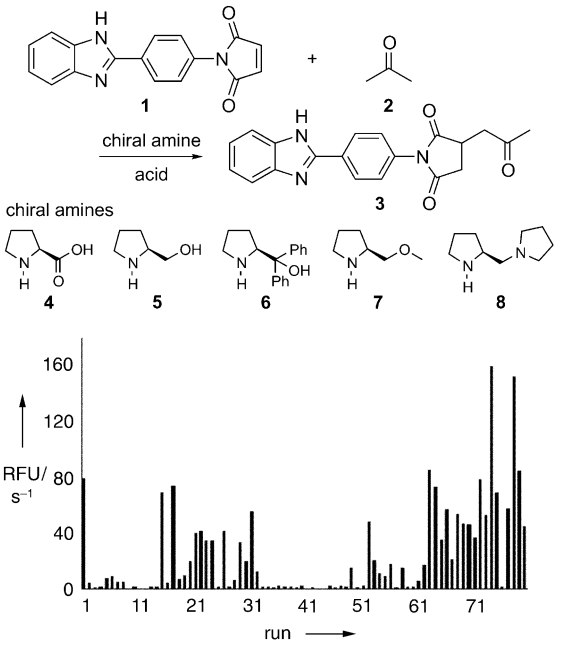
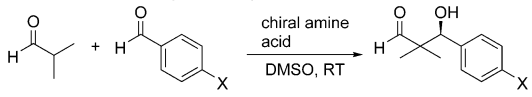


Figure 1. Initial rates of reactions of chiral-amine/acid combinations with the fluorogenic substrate **1** and acetone (**2**). Catalysts and runs: L-proline (**4**, runs 1–16), L-prolinol (**5**, runs 17–32), (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol (**6**, runs 33–48), (*S*)-(+)-2-(methoxymethyl)pyrrolidine (**7**, runs 49–64), and (*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine (**8**, runs 65–80). Each catalyst was evaluated with each of the following acid additives (from left for each catalyst): none, $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Y(OTf)_3$, $La(OTf)_3$, $Eu(OTf)_3$, $Yb(OTf)_3$, H_2SO_4, CF_3SO_3H, *p*-TsOH, D-(+)-10-camphorsulfonic acid, HNO_3, CF_3CO_2H, CH_3CO_2H, H_3PO_4. Reactions were carried out with the chiral amine (3 mM), acid (3 mM), and **1** (6 μM) in 20% acetone/80% DMSO, and the initial reaction rates were determined by monitoring the fluorescence (λ_{ex} = 315 nm, λ_{em} = 365 nm) over 20 min. DMSO = dimethyl sulfoxide, RFU = relative fluorescence unit, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

The utility of the chiral amine catalysts was evaluated in intermolecular aldol reactions between α,α-dialkyl aldehyde donors **9** and aryl aldehyde acceptors **10** (Table 1). The catalyst **8** and CF_3CO_2H (0.3 equiv; Table 1, entry 7) provided **11a** (X = NO_2) in excellent yield with 94% *ee*. A lower catalyst loading (0.05 equiv; Table 1, entry 9) also led to good results (92% yield, 96% *ee*). The addition of an acid, in an amount equimolar to the amine **8**, improved the reactivity (Table 1, entry 6 versus entry 7) as well as the enantioselectivity (Table 1, entry 6 versus entries 7–9). The data in Table 1 are consistent with the results of the fluorescence assay. The combination of **8** and CF_3SO_3H was also effective (Table 1, entry 10). However, the use of the catalysts L-proline (**4**; Table 1, entry 1), L-prolinol (**5**; Table 1, entry 2), and **6**/CH_3CO_2H (Table 1, entry 3) provided the aldol product **11a** in low yields. Although a reaction with the combination **7**/CH_3CO_2H (0.3 equiv) provided **11a** in better yield in much less time (Table 1, entry 5) compared to the reaction with **7** alone (Table 1, entry 4), both reactions proceeded with low enantioselectivities. The catalyst **8**/CF_3CO_2H was effective in

Table 1: Direct aldol reaction catalyzed by a chiral amine/acid for the synthesis of aldols with quaternary carbon centers.[a]



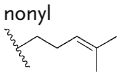
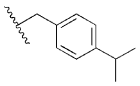
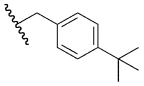
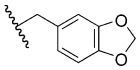
9a **10** **11**

Entry	X	Chiral amine (equiv)	Acid (equiv)	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	NO_2	**4** (0.3)	–	72	34	80
2	NO_2	**5** (0.3)	–	96	50[d]	50
3	NO_2	**6** (0.3)	CH_3CO_2H (1.5)	96	20[d]	33
4	NO_2	**7** (0.3)	–	5	85	34
5	NO_2	**7** (0.3)	CH_3CO_2H (0.3)	0.5	94	27
6	NO_2	**8** (0.3)	–	3	93	35
7	NO_2	**8** (0.3)	CF_3CO_2H (0.3)	2	95	94
8	NO_2	**8** (0.1)	CF_3CO_2H (0.1)	12	94	95
9	NO_2	**8** (0.05)	CF_3CO_2H (0.05)	24	92	96
10	NO_2	**8** (0.1)	CF_3SO_3H (0.1)	4	95	90
11	CN	**8** (0.1)	CF_3CO_2H (0.1)	12	95	92
12[e]	Br	**8** (0.1)	CF_3CO_2H (0.1)	72	80	95
13[e]	Cl	**8** (0.1)	CF_3CO_2H (0.1)	72	74[d]	92
14[e]	OMe	**8** (0.1)	CF_3CO_2H (0.1)	96	40[d]	93
15[e]	H	**8** (0.1)	CF_3CO_2H (0.1)	96	32[d]	96

[a] Typical procedure: The acid and the chiral amine were added in the molar ratios indicated to a solution of *p*-nitrobenzaldehyde (**10a**; 0.5 mmol) and isobutyraldehyde (**9a**; 1.0 mmol) in DMSO (0.5 mL). The reaction mixture was stirred at room temperature for the indicated time, then purified by flash column chromatography on silica gel, without a workup, to provide the aldol product **11a**. [b] Yield of isolated product after purification by column chromatography. [c] Determined by HPLC analysis on a chiral phase (CHIRALPAK AS-H). [d] The aryl aldehyde **10** was recovered in 42% (entry 2), 73% (entry 3), 22% (entry 13), 54% (entry 14), and 59% yield (entry 15). [e] Aldehyde **9a**: 10 equivalents. RT = room temperature.

Table 2: Direct aldol reaction catalyzed by **8**/CF_3CO_2H for the synthesis of aldol products with quaternary carbon centers.

9 **10a** **11**

Entry	R	Yield [%][a]	d.r.[b] (*anti*/*syn*)	*ee* [%][c] *anti*	*ee* [%][c] *syn*
1	Et	96	62:38	91	75
2	Pr	92	66:34	89	66
3	nonyl	93	69:31	91	68
4		96	65:35	89	52
5[d]		97	84:16	95	74
6[d]		91	85:15	96	68
7		91	77:23	90	53

[a] Yield of isolated product after purification by column chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral phase (CHIRALPAK AS-H and CHIRALCEL OJ-H). [d] Aldehyde **9**: 10 equivalents.

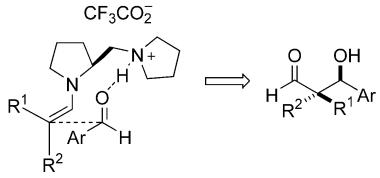


Figure 2. Proposed transition state.

reactions with various aryl aldehyde acceptors, even in the case of acceptors with low reactivity, such as *p*-anisaldehyde (Table 1, entry 14) and benzaldehyde (Table 1, entry 15). The expected aldol products **11** were produced in 92% *ee* or over (Table 1, entries 11–15). The *S* enantiomer of **11** was formed as the major enantiomer in the presence of all catalysts shown in Table 1.

Encouraged by these results, we further explored the scope of this class of aldol reactions with a series of α-alkyl α-methylaldehyde donors under the same reaction conditions. The expected aldol products **11** were obtained in at least 90% yield with high *ee* values (Table 2).

The aldol product **11a** was determined to have the *S* configuration by derivation as the Mosher ester.[13] Thus, **8**/CF_3CO_2H catalyzes a *Re*-face attack on the aryl aldehyde via an enamine intermediate (Figure 2). This result is in accordance with previously proposed L-proline-based aldol transition states.[14]

In summary, we have used a rapid fluorescence assay to optimize catalysts and reaction conditions for asymmetric intermolecular direct aldol reactions of α,α-dialkyl aldehydes with aryl aldehydes, thus underscoring the value of high-throughput assays for catalyst development. The diamine **8**/CF_3CO_2H bifunctional catalyst system developed demonstrates excellent reactivity and enantioselectivity in this class of aldol reaction. Further studies that focus on the full scope of this catalyst system are currently under investigation and will be reported in due course.

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Keywords: aldol reaction · asymmetric catalysis · enantioselectivity · high-throughput screening · organocatalysis

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