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Direct, pyrrolidine sulfonamide promoted enantioselective aldol reactions of α,α-dialkyl aldehydes: synthesis of quaternary carbon-containing β-hydroxy carbonyl compounds

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Abstract—A procedure has been developed for direct, asymmetric aldol reactions of α,α-dialkyl aldehydes with aromatic aldehydes, which produces quaternary carbon-containing β-hydroxy carbonyl compounds. The processes, promoted by the organocatalyst (*S*) pyrrolidine sulfonamide, take place in high yields with exceptionally high levels of enantioselectivities.

The aldol reaction is one of the most powerful methods to form C–C bonds in complex organic substances. Consequently numerous procedures to perform asymmetric aldol reactions have been uncovered.[1,2] Direct aldolization processes are atom economic, and thus they serve as attractive approaches for the synthesis of versatile polyoxygenated compounds. Recently, a great effort has been made to the development of chiral organocatalysts for the asymmetric version of this process. Most studies have focused on reactions that produce either β-hydroxy carbonyls or α-alkyl-β-hydroxy carbonyls.[3–11] However, organocatalyst promoted asymmetric synthesis of α,α-dialkyl-β-hydroxyl carbonyl compounds remains a challenge since low reaction yields and poor enantioselectivities are typically observed. The major reason for this is the general inaccessibility of either starting α,α-disubstituted aldehydes or their stereochemically defined enolates. The only method that can be used for this purpose was uncovered by Barbas and co-workers and it relies on the use of a chiral diamine as the organocatalyst.[6a,12]

In this letter, we report a new, direct pyrrolidine sulfonamide promoted asymmetric aldol reaction that occurs with sterically hindered α,α-dialkyl aldehydes to provide quaternary carbon-containing β-hydroxycarbonyl compounds with exceptionally high levels of enantioselectivity. To our knowledge, this is the first example in which a bifunctional organocatalyst is employed without the need for acid additives.

The motivation for this investigation came from our recent study in exploring the utility of pyrrolidine sulfonamide **I** to catalyze highly efficient Michael addition reactions of α,α-dialkyl aldehydes with β-nitrostyrenes (Fig. 1, Eq. 1).[13] In the process, **I** effectively catalyzes enolization of an α,α-dialkyl aldehyde to form an electron-rich enamine, which then adds to the nitroolefin electrophile. Intrigued by the possibility that this mechanistic scenario might be expanded to encompass other electrophilic forms such as aldehydes, we postulated that organocatalyst **I** promoted aldol reactions of α,α-dialkyl aldehydes as donors with aldehyde acceptors, would generate products containing quaternary carbon centers (Fig. 1, Eq. 2).[14] The results of this effort on exploring this proposal have demonstrated that the asymmetric aldol reactions using 20 mol % of (*S*) pyrrolidine sulfonamide **I** take place to form β-hydroxyaldehydes in high yields (81–97%) and excellent enantioselectivities (91–97% ee).

Initial studies, testing the feasibility of this catalytic process, focused on the reaction of *iso*-butyraldehyde **1a** as an aldol donor and *p*-nitrobenzaldehyde **2a** as an acceptor in the presence of 20 mol % **I** in DMSO at room temperature. The reaction took place smoothly

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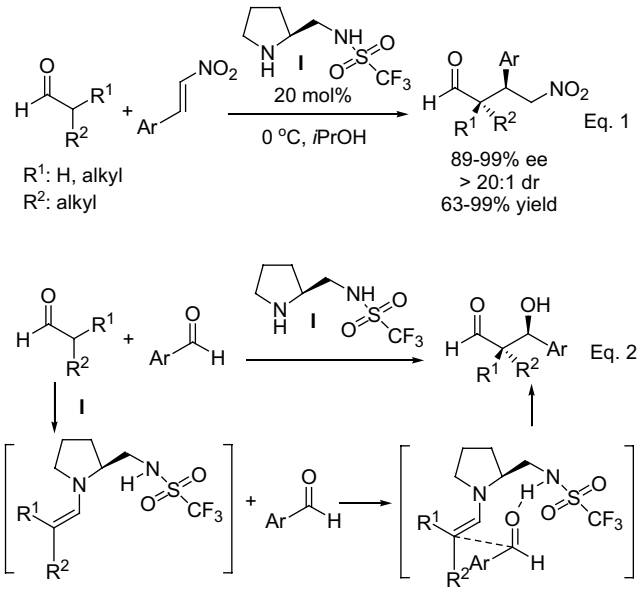
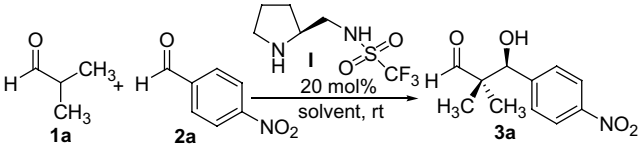


Figure 1. Pyrrolidine sulfonamide **I** catalyzed enolization of α,α-dialkyl aldehydes.

and afforded the aldol adduct **3a** in a good yield (83%) and a high enantioselectivity (91% ee) (Table 1, entry 1). The absolute configuration at the chiral center in aldol product **3a** was determined to be *S* configuration by comparison of the ^{1}H NMR and optical rotation data for **3a** with those of the known compound.[6a,15] A poor reaction rate, yield, and enantioselectivity was observed when other solvents were used for this process (Table 1, entries 2–6). Thus, DMSO was selected as a reaction medium for reactions probing the scope of the asymmetric aldol processes.

A number of aldol reactions were carried out under the reaction conditions described above in the presence of 20 mol % **I** in DMSO. Examination of the results reveals that the (*S*) pyrrolidine sulfonamide **I** promoted aldol processes are generally applicable to variously functionalized aldehyde acceptors (Table 2, entries 1–10). In all cases, high levels of enantioselectivities (91–97%) and high reaction yields (81–97%) were observed. Interestingly, only one of the aldehyde groups in terephthalaldehyde participated in the reaction with *iso*-butyraldehyde **1a** to give the *mono*-aldol addition product exclusively in excellent yield (97%) and enantioselectivity (97% ee),

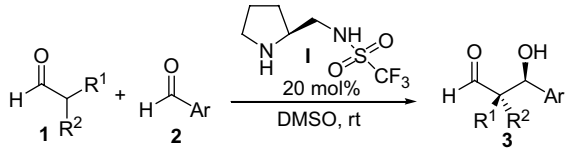
Table 1. Effect of the solvents on the asymmetric aldol reaction of *iso*-butyraldehyde **1a** with *p*-nitrobenzaldehyde **2a** by pyrrolidine sulfonamide **I**[a]

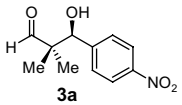
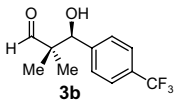
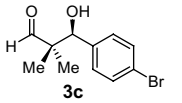
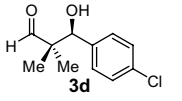
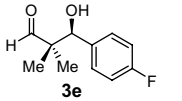
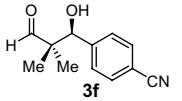
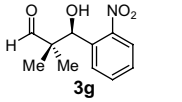
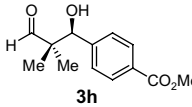
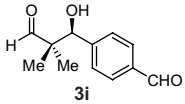
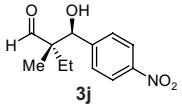


Entry	Solvent	*t* (h)	Yield (%)[b]	ee (%)[c]
1	DMSO	43	83	91
2	DMF	72	77	81
3	1,4-Dioxane	72	41	80
4	CH_3CN	72	63	48
5	THF	72	68	79
6	MeOH	72	37	18

[a] Unless otherwise specified, the reaction was carried out using **1a** (4.0 mmol) and **2a** (0.4 mmol) in the presence of 20 mol % **I** in 1.0 mL of solvent at room temperature.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

Table 2. Synthesis of aldol products by forming quaternary carbon centers catalyzed by pyrrolidine sulfonamide **I**[a]



Entry	Product **3**	*t* (h)	Yield (%)[b]	ee (%)[c]
1	 **3a**	43	83	91
2	 **3b**	24	83	95
3	 **3c**	84	94	94
4	 **3d**	96	96	94
5	 **3e**	96	81	93
6	 **3f**	72	95	95
7	 **3g**	72	81	93
8[d]	 **3h**	144	93	94
9	 **3i**	72	97	97
10[e]	 **3j**	168	85	93

[a] See footnote a in Table 1.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H or Chialcel OJ-H).
[d] The reaction was run at 0 °C in DMF.
[e] dr determined by ^{1}H NMR with a ratio of 6/1 *anti*/*syn*.

even when an excess of **1a** (10 equiv) was used (Table 2, entry 9). Moreover, two stereogenic centers were formed simultaneously in a high diastereo-controlled manner (93% ee, 6/1 *anti*/*syn*) when unsymmetric dialkyl aldehyde α-ethyl-β-methyl aldehyde was used (Table 2, entry 10).

In conclusion, we have observed that the bifunctional (*S*) pyrrolidine trifluoromethanesulfonamide **I** is an effective organocatalyst for promoting direct, asymmetric aldol reactions of α,α-dialkyl aldehydes. These processes, which lead to formation of quaternary carbon centers, take place in high yields and exceptionally high enantioselectivities. Further studies are underway to investigate the full scope of the reaction and to explore its applications in synthesis of biologically active targets.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.067.

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15. In Ref. 6a, the authors did not give the data of the optical rotation for compound **3a**. We used the chiral diamine as a catalyst to produce compound **3a** in 95% ee and then determined its optical value: $[\alpha]_D^{25}$ +35.7 (*c* 1.0, $CHCl_3$); the data obtained by using pyrrolidine sulfonamide **I** is: $[\alpha]_D^{25}$ +31.6 (*c* 1.0, $CHCl_3$).