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Amine-Catalyzed Asymmetric Cross-Aldol Reactions Using Heterofunctionalized Acetaldehydes as Nucleophiles

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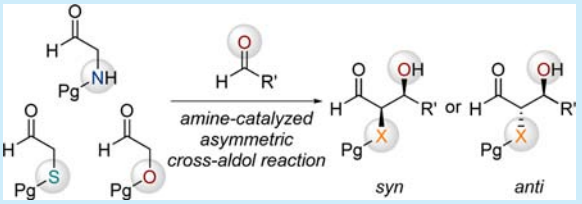
Supporting Information

ABSTRACT: Various heterofunctionalized acetaldehydes were successfully employed in an amine-catalyzed asymmetric cross-aldol reaction, affording a variety of synthetically useful 1,2-difunctionalized compounds such as 1,2-diols and 1,2-aminoalcohols. With this method, both *syn*- and *anti*-1,2-difunctionalized compounds were obtained from the same set of reactants by using the appropriate amine catalyst.



Amine-catalyzed asymmetric cross-aldol reactions between two different aldehydes provide an attractive approach toward the construction of useful chiral building blocks.[1,2] In such cross-aldol reactions, both *syn*- and *anti*-aldol adducts have become available from the same set of reactants by simply switching the amine catalyst.[3] In addition, heterofunctionalized acetaldehydes are also applicable as donor aldehydes to prepare synthetically important 1,2-difunctionalized compounds such as 1,2-diols[4] and 1,2-aminoalcohols.[5] Despite their synthetic potential and diversity, however, most cross-aldol reactions of heterofunctionalized acetaldehydes employ benzyloxyacetaldehyde or siloxyacetaldehydes and are limited to the preparation of *anti*-1,2-diol derivatives.[6−8] This prompted us to investigate both a *syn*- and *anti*-selective asymmetric cross-aldol reaction of various heterofunctionalized acetaldehydes **1** (Figure 1),[9,10] affording various densely functionalized compounds, and herein, we report our recent results.

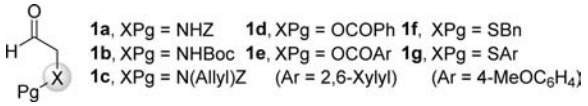
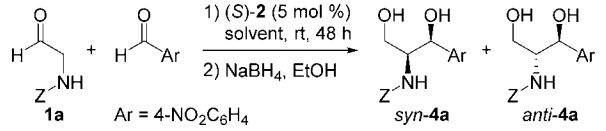


Figure 1. Heterofunctionalized acetaldehydes.

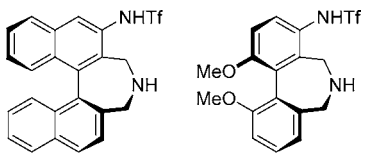
We have previously developed the axially chiral amino sulfonamide catalyst (*S*)-**2**,[11] which shows unusual *syn*-selectivity in the direct asymmetric cross-aldol reaction of aldehydes,[2a] in sharp contrast to the *anti*-selective reaction catalyzed by proline and the related catalysts. Accordingly, we first examined the *syn*-selective direct cross-aldol reaction between *N*-Z-protected aminoacetaldehyde **1a**[9] and 4-nitrobenzaldehyde in the presence of 5 mol % of (*S*)-**2** in various solvents (Table 1). The reaction in amide solvents NMP and DMF at room temperature afforded the desired *syn*-1,2-aminoalcohol **4a** in good yield with virtually perfect diastereo- and enantioselectivity (entries 1 and 2). Use of DMSO resulted in a slight decrease in yield (Table 1, entry 3). When other solvents, such as acetonitrile, THF, CH_2Cl_2, and toluene were used, a significant decrease in yield and stereoselectivity was observed (Table 1, entries 4−7). Consequently, NMP was found to be among the best in terms of both yield and stereoselectivity.

Table 1. *syn*-Selective Cross-Aldol Reaction between 1a and 4-Nitrobenzaldehyde Catalyzed by (*S*)-2[a]



entry	solvent	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	NMP	77	>20/1	99
2	DMF	69	>20/1	98
3	DMSO	55	>20/1	99
4	CH_3CN	70	4.6/1	94
5	THF	58	5.9/1	90
6	CH_2Cl_2	48	4.8/1	82
7	toluene	34	2.3/1	90

[a]The reaction of **1a** (0.125 mmol) with 4-nitrobenzaldehyde (0.250 mmol) was carried out in the presence of (*S*)-**2** (0.00625 mmol) in a solvent (125 μL). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]The ee of *syn*-**4a** was determined by HPLC using a chiral column.



With the optimized reaction conditions in hand, the *syn*-selective cross-aldol reactions of various heterofunctionalized acetaldehydes **1** with other acceptor aldehydes were examined, and the results are summarized in Scheme 1. In the presence of

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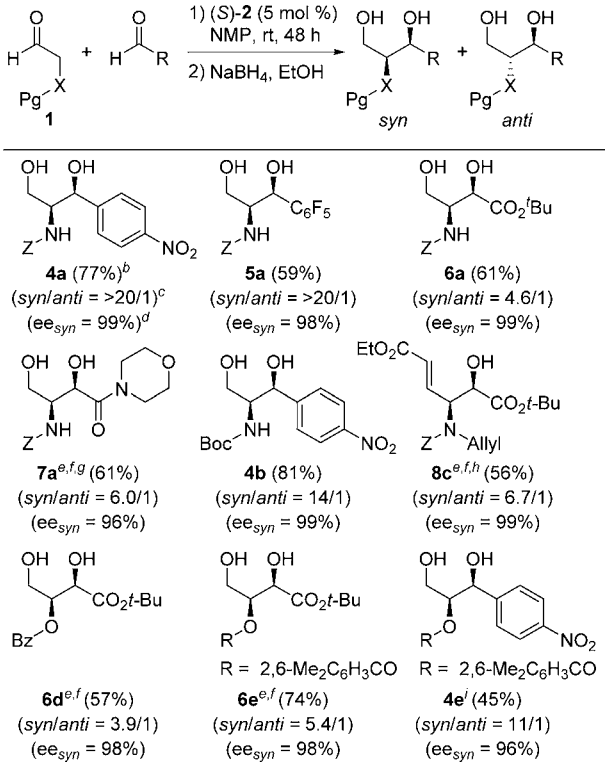
Scheme 1. *syn*-Selective Cross-Aldol Reaction of Heterofunctionalized Acetaldehyde 1 Catalyzed by (*S*)-2[a]

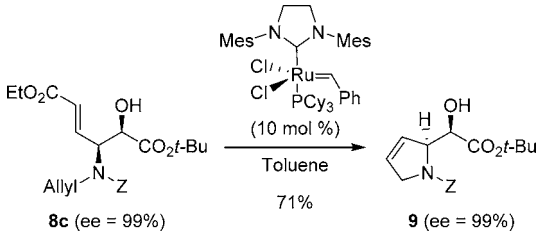


[a]The reaction of **1** (0.125 mmol) with an acceptor aldehyde (0.250 mmol) was carried out in the presence of (*S*)-**2** (0.00625 mmol) in NMP (125 μL) at room temperature for 48 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The ee of *syn*-product was determined by HPLC using a chiral column. [e] Use of **1** (0.250 mmol) and an acceptor aldehyde (0.125 mmol). [f] The reaction was performed for 24 h. [g] Use of acetonitrile (125 μL) as solvent. [h] Isolated after olefination with a Wittig reagent instead of reduction. [I] Use of (*S*)-**3** (0.00625 mmol).

5 mol % of (*S*)-**2**, the reaction of *N*-Z-protected aminoacetaldehyde **1a** with reactive acceptor aldehydes gave the desired *syn*-aldol adducts in moderate to good yields with high diastereo- and enantioselectivities (**4a**, **5a**, **6a**, and **7a**). Unfortunately, the reaction of **1a** or **1d** with a less reactive acceptor aldehyde such as benzaldehyde or pivalaldehyde gave only a trace amount of the desired product. In addition, *N*-Boc-protected aminoacetaldehyde **1b** and *N*-allyl-*N*-Z-aminoacetaldehyde (**1c**) were applicable to the present aldol reaction (**4b** and **8c**). The absolute configuration of **4b** was determined by comparing the optical rotation with the literature value.[12] The aldol adduct in the reaction using **1c** was converted to the corresponding *α*,*β*-unsaturated ester **8c** by treatment with a Wittig reagent. The following ring-closing metathesis of **8c** gave dihydropyrrole **9** without epimerization (Scheme 2).[13]

When benzoyloxyacetaldehyde (**1d**) was employed as a new entry of oxyacetaldehydes as a donor aldehyde, the *syn*-1,2-diol derivative was obtained as a major diastereomer in moderate yield with high enantioselectivity (**6d**). The benzoyl moiety of **1d** and **6d** was found to be slightly unstable under the reaction conditions and silica gel column chromatography. When 2,6-dimethylbenzoyloxyacetaldehyde (**1e**) was employed instead of **1d**, the improved yield and diastereoselectivity were obtained as expected (**6e**). We then attempted the aldol reaction between

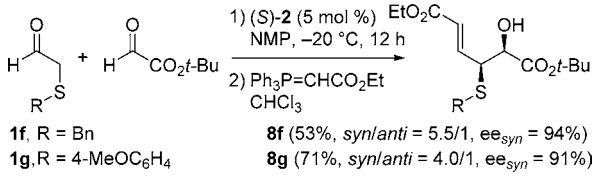
Scheme 2. Synthesis of Dihydropyrrole 9



1e and 4-nitrobenzaldehyde catalyzed by (*S*)-**2**; however, the desired product was obtained in only 19% yield, albeit with high stereoselectivity (*syn*/*anti* = 11/1, 97% ee (*syn*)). Use of the more nucleophilic catalyst (*S*)-**3** resulted in a higher yield with excellent stereoselectivity (**4e**).[3,14] These results represent the first example of utilization of the oxyacetaldehyde protected with acyl groups instead of commonly used protecting groups such as benzyl and silyl groups.

To further expand the scope of the cross-aldol reaction of heterofunctionalized acetaldehydes, we also examined the possibility of using *α*-thio acetaldehydes **1f** and **1g** as donor aldehydes.[6b,10,15] When the cross-aldol reactions of **1f** and **1g** with *tert*-butyl glyoxylate were performed in the presence of 5 mol % of (*S*)-**2** in NMP at −20 °C, the desired *syn*-aldol adducts were obtained as major diastereomers in good enantioselectivities (Scheme 3).[16] These aldol adducts were isolated after the conversion to the corresponding *α*,*β*-unsaturated ester **8f** and **8g** by treatment with a Wittig reagent.

Scheme 3. *syn*-Selective Cross-Aldol Reaction Using *α*-Thio Acetaldehydes



Although some examples of *anti*-selective cross-aldol reactions using heterofunctionalized acetaldehydes have been reported to date,[6,8] the diversity of the reaction is still unsatisfactory. Thus, we turned our attention to further explore the *anti*-selective cross-aldol reaction using heterofunctionalized acetaldehydes **1**. After the optimization of the reaction conditions (see Supporting Information), the proline-catalyzed *anti*-selective cross-aldol reaction of **1a** with several acceptor aldehydes was examined (Table 2). The reactions of **1a** with 4-nitrobenzaldehyde and pentafluorobenzaldehyde gave the desired *anti*-aldol adducts in high yield and stereoselectivity (Table 2, entries 1 and 2). On the other hand, the proline-catalyzed reaction with *tert*-butyl glyoxylate gave an unsatisfactory result in terms of both yield and stereoselectivity (Table 2, entry 3). Fortunately, use of a commercially available prolinol catalyst (*S*)-**10** instead of proline resulted in an improvement of yield, *anti*-selectivity, and enantioselectivity (Table 2, entry 4).[17]

Furthermore, the *anti*-selective aldol reaction of oxyacetaldehyde **1e** with *tert*-butyl glyoxylate was examined (Scheme 4). Use of proline as the catalyst gave only a trace amount of the desired product. On the other hand, the catalyst (*S*)-**10** was found to give the highly enantiomerically enriched product **12**

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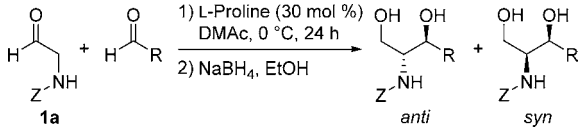
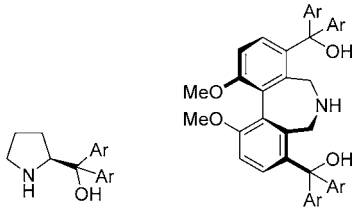
Table 2. *anti*-Selective Cross-Aldol Reaction between 1a and Acceptor Aldehydes[a]

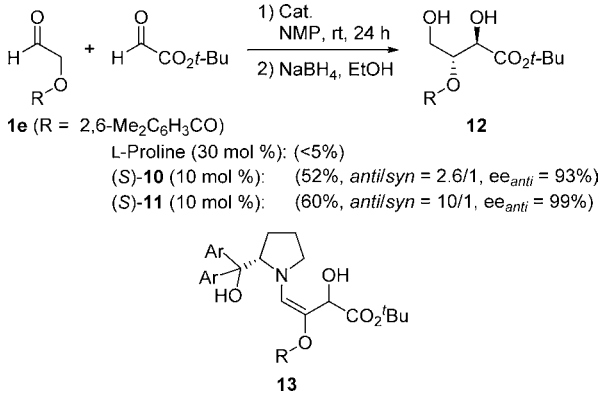


entry	R	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	4-$NO_2C_6H_4$	90	13/1	99
2	C_6F_5	90	20/1	99
3	CO_2t-Bu	41	2.1/1	88
4[e]	CO_2t-Bu	61	4.8/1	95

[a]The reaction of **1a** (0.125 mmol) with 4-nitrobenzaldehyde (0.250 mmol) was carried out in the presence of L-proline (0.0375 mmol) in DMAc (250 μL) at 0 °C for 24. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]The ee of *anti*-product was determined by HPLC using a chiral column. [e]The reaction of **1a** (0.250 mmol) and *tert*-butyl glyoxylate (0.125 mmol) catalyzed by (*S*)-**10** (0.0125 mmol) was performed in NMP (125 μL) at room temperature.



Scheme 4. *anti*-Selective Cross-Aldol Reaction Using 1e with *tert*-Butyl Glyoxylate Catalyzed by (*S*)-10 or (*S*)-11



in moderate yield albeit with low *anti*-selectivity. In this reaction, a side product **13** was observed by ^{1}H NMR analysis of the crude reaction mixture, and the consumption of both the catalyst and the product was indicated. When the biphenyl-based secondary amino diol catalyst (*S*)-**11** was employed,[18] the desired *anti*-product was obtained with high diastereo- and enantioselectivity.

In summary, we have successfully developed a *syn*- and *anti*-selective asymmetric cross-aldol reaction using a variety of heterofunctionalized acetaldehydes and demonstrated the utility of heterofunctionalized acetaldehydes as nucleophiles in enamine catalysis. This organocatalytic process can provide both *syn*- and *anti*-difunctionalized compounds from the same set of reactants by simply replacing the catalyst. Further investigations to expand the scope of this and related reactions are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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