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Chiral Primary−Tertiary Diamine−Brønsted Acid Salt Catalyzed Syn-Selective Cross-Aldol Reaction of Aldehydes

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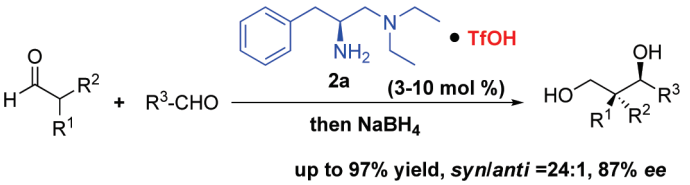

Highly syn-selective cross-aldol reaction of aldehydes has remained a challenging subject in the field of aminocatalysis. To achieve this end, chiral primary amines have been explored and the primary−tertiary diamine−Brønsted acid salts are found to promote the cross-aldol reactions of aldehydes with high activity and syn selectivity. Among various vicinal diamines screened, L-phenylalanine derived **2a**/TfOH conjugate is identified as the optimal catalyst, showing good catalytic activity (up to 97% yield) and high syn selectivities (syn/anti up to 24:1, 87% ee). The current catalysis works selectively with small aliphatic aldehydes donors such as propionaldehyde and isobutyraldehyde, but not with aliphatic aldehydes bearing larger β-substitute (> Me). In addition, the use of **2a**/TfOH conjugate has also enabled the first syn-selective cross-aldol reactions of glycoaldehyde donors.

Introduction

The aldol reaction, a fundamental C−C bond-forming reaction, undergoes constant rebirth echoing the advances in modern organic synthesis.[1] In the past decade, enamine-based organocatalysts, exemplified by the typical chiral pyrrolidines such as L-proline, have enabled a range of asymmetric direct aldol reactions.[2] In this area, cross-aldol reactions of aldehydes have been known to be difficult because of the various side products with enolizable aldehydes and the accompanying uncontrolled self-aldolization.[2f,3] With judicious selection of coupling partners and strict control of reaction conditions, chiral secondary amines such as L-proline and MacMillan's imidazoline catalyst have been shown to catalyze cross-aldol reactions of aldehdyes. In most of the secondary amine catalyses, the reactions mainly afford anti-diastereoselctive aldol products.[4] In contrast, syn-selective cross-aldol reactions of aldehdyes have been much less explored. The development of syn-selective cross-aldol reactions with a simple chiral catalyst is still highly desirable and has remained an elusive goal until recently.

Maruoka and co-workers recently reported the first example of syn-selective cross-aldol reaction of aldehydes by an axially chiral secondary aminocatalyst. Good syn-diastereoselectivity and enantioselectivity were obtained with cross coupling of aliphatic aldehydes and aromatic

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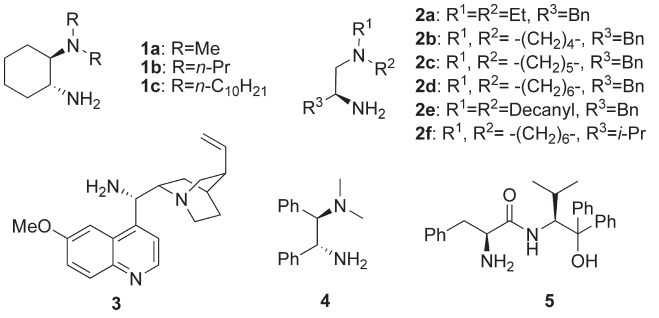


FIGURE 1. Chiral primary amines in this study.

aldehydes.[5] Previously, we and others have showed that primary amines could promote syn-selective aldol reactions of ketones via thermodynamically favored Z-type enamine intermediates.[6,7] Simple chiral primary−tertiary diamines such as **1** and **2** (Figure 1) have been successfully applied to catalyze a range of syn-selective aldol reactions of aliphatic ketones such as α-hydroxy ketones,[7d] dihydroxyacetone,[7b] pyruvic acetals,[7c] and acetoacetals.[7e] With the objective of developing an effective and simple chiral aminocatalyst for syn-selective cross-aldol reactions of aldehydes, we reasoned that the application of chiral primary amine should enable

SCHEME 1. Primary Amines for *syn*-Aldol Reaction

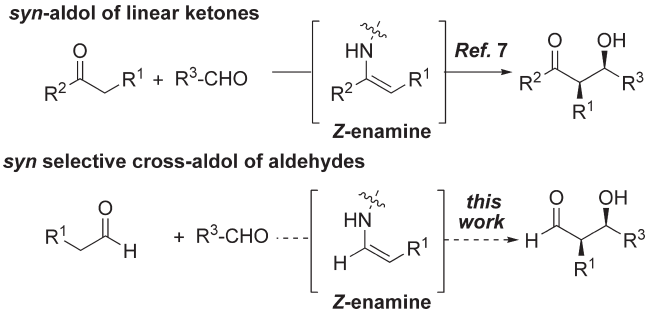
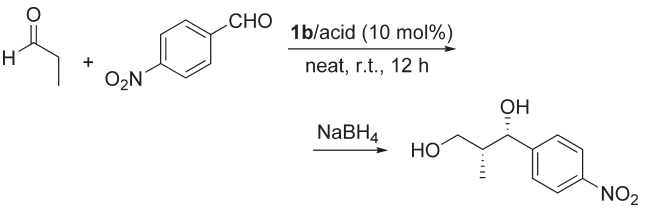


TABLE 1. Screening of Brønsted Acid in 1b Catalyzed Cross-Aldol Reaction



entry[a]	acid	yield[b]	syn:anti[c]	ee[d] (%)
1[e]		82	2:1	39
2	*m*-NO_2PhCOOH	89	3:1	59
3	salicylic acid	90	2:1	47
4	DBSA	89	3:1	58
5	TFA	88	5:1	57
6	PTSA	91	9:1	55
7	2,4-DNBS	92	5:1	54
8	phthalic acid	87	9:1	52
9	TfOH	90	10:1	58
10[f]	TfOH	< 20		

[a]Unless otherwise stated, the reaction was performed with 0.5 mmol of *p*-nitrobenzaldehyde and 0.5 mL of propionaldehyde for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]No acid was used. [f]Additional 10 mol % of *m*-NO_2PhCOOH was used. DBSA: dodecylsulfonic acid. PTSA: *p*-toluenesulfonic acid. DNBS: dinitrobenzenesulfonic acid.

syn-diastereoselectivity in this reaction via a *Z*-enamine (Scheme 1). A recent report by Mahrwald and co-workers has shown that chiral primary amine L-histidine was indeed a viable catalyst for cross-aldol reactions of aldehydes, encouragingly enolizable aldehydes, with good syn-diastereoselectivity and moderate to good enantioselectivity.[8] However, the reactions were limited to α-substituted aliphatic aldehyde donors. Herein, we report a simple chiral primary−tertiary diamine derived from L-phenylalanine as a highly effective syn-selective catalyst for cross-aldol reactions of both α-substituted and unsubstituted aldehyde donors.

Results and Discussion

Screening of Acidic Additives. We started with our previously developed primary amine catalyst **1b**/TfOH,[7a] and the reaction between propionaldehyde and *p*-nitrobenzaldehyde was selected as the model reaction. To our delight, **1b**/TfOH was found to be an effective catalyst for the reaction, showing good syn-diastereoselectivity (syn/anti 10:1, Table 1,

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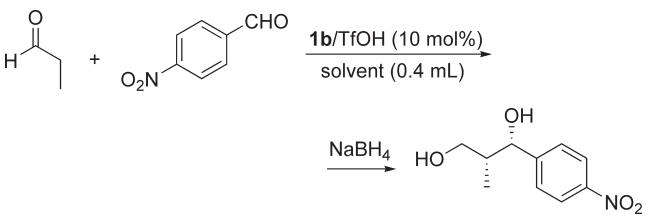
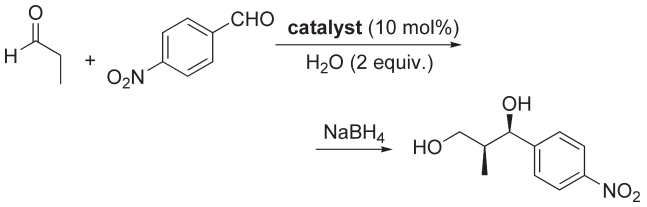
TABLE 2. Solvent Screening for 1b/TfOH-Catalyzed Cross-Aldol Reaction



entry[a]	solvent	yield[b] (%)	syn:anti[c]	ee[d] (%)
1	neat	90	10:1	58
2	*n*-hexane	33	6:1	49
3	CH_2Cl_2	36	3:1	37
4	DMF	14	5:1	11
5	THF	37	4:1	7
6	MeOH	16	6:1	29
7	toluene	13	16:1	38
8	NMP	67	3:1	17
9	[BIMB]BF_4	74	2:1	55
10[e]	H_2O (30 equiv)	75	5:1	55
11[e]	H_2O (10 equiv)	77	6:1	64
12[f]	H_2O (4 equiv)	80	8:1	68
13[f]	H_2O (2 equiv)	88	11:1	70
14[f]	H_2O (1 equiv)	77	6:1	64

[a]Unless otherwise stated, the reaction was performed with 0.5 mmol of *p*-nitrobenzaldehyde and 0.1 mL of propionaldehyde in 0.4 mL of solvent for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]0.3 mL of propionaldehyde was used. [f]0.5 mL of propionaldehyde was used.

TABLE 3. Catalyst Screening for the Cross-Aldol Reaction



entry[a]	catalyst	yield[b] (%)	syn/anti[c]	ee[d] (%)
1	L-Phe-OH	trace		
2	L-His-OH	14	2:1	12
3	**1a**/TfOH	88	11:1	70
4	**1b**/TfOH	90	5:1	73
5	**1c**/TfOH	92	9:1	70
6	**2a**/TfOH	93	6:1	87
7	**2b**/TfOH	90	8:1	84
8	**2c**/TfOH	91	7:1	85
9	**2d**/TfOH	90	7:1	86
10	**2e**/TfOH	86	4:1	81
11	**2f**/TfOH	94	7:1	73
12	**3**/TfOH	23	4:1	55
13	**4**/TfOH	35	4:1	41
14	**5**/TfOH	73	4:1	71
15[e]	**2a**/TfOH	94	7:1	87

[a]Unless otherwise stated, the reaction was performed with 0.5 mmol of *p*-nitrobenzaldehyde and 0.1 mL of propionaldehyde in 0.4 mL of solvent for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]The reaction was performed in the presence of 3 mol % of catalyst for 24 h at 4 °C.

entry 9) and moderate enantioselectivity (58% ee). Bearing in mind that acidic additives generally exhibit significant impact on both activity and stereoselectivity in the catalysis of **1b**,[7] we next screened different acidic additives in order to further improve the activity and stereoselectivity. Surprisingly, the reaction proceeded equally well in the absence of any acidic additives to give 82% yield, albeit with lower stereoselectivity (2:1 syn/anti, 39% ee, Table 1, entry 1), to note that similar aldol reaction of acetone barely occurred in the presence of only **1b** without any acidic additive.[7a] In a separate experiment with (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine as the catalyst, the reaction afforded only trace product (< 5% yield) with virtually no enantioselectivity (< 2% ee). These observations together with the obtained significant chiral induction in the catalysis of **1b** suggest that enol-based mechanism is insignificant in the latter reaction and the catalysis of **1b** would occur via enamine intermediate even in the absence of acids.[9]

A survey of a range of acidic additives has also been conducted. As shown in Table 1, both the product yields and enantioselectivities are generally improved in the presence of acidic additives but maintain at a similar level regardless of their varying acidity (Table 1, entries 2−9). On the other hand, the acidity of the added acids was shown to impact the diastereoselectivity considerably with more acidic additive generally offering better syn diastereoselectivity. Accordingly, the most acidic additive TfOH gave the optimal syn diastereoselectivity (syn/anti 10:1, Table 1, entry 9). Under this condition (**1b**/TfOH), the reaction gave 90% yield, 10:1 syn/anti, and 58% ee (Table 1, entry 9). The further addition of a second weak acid such as *m*-nitrobenzoic acid led to serious depletion of activity (Table 1, entry 10).

Screening of Solvents. With **1b**/TfOH conjugate as the catalyst, the reaction was next optimized by screening different solvents. Not quite unexpectedly, the reaction becomes sluggish in the dilute conditions in organic solvents, and to make it even worse, the stereoselectivity is also deteriorated under these conditions (Table 2, entries 2−8). Neither the use of ionic liquid nor that of the large quantity of water led to any improvements (Table 2, entries 9 and 10). Finally, it was delightful to find out that the addition of small amount of water results in marked improvements of enantioselectivity (Table 2, entries 11−14). A similar water effect has previously been observed in similar enamine-based aldol reactions.[10] The optimal quantity of water was then determined to be 2 equiv (Table 2, entries 11−14). In the presence of 2 equiv of water under neat conditions, the **1b**/TfOH (10 mol %)-catalyzed reaction afforded the optimal 70% ee and 11:1 syn/anti (Table 2, entry 13). These were then selected as the optimal conditions for the subsequent studies.

Screening of Chiral Primary Amines. Under the optimized conditions, a range of chiral primary amines were examined. The natural primary amino acids such as L-phenylalanine and L-histine are almost inactive for this reaction (Table 3, entries 1 and 2). Primary−tertiary vicinal diamines were again found to be the skeleton of choice for this cross-aldol

(9) The reason why acetone and propionaldehyde perform quite differently remains an intriguing problem. Presumably this may be rationalized by considering the readily enolizable nature of propionaldehyde.

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SCHEME 2

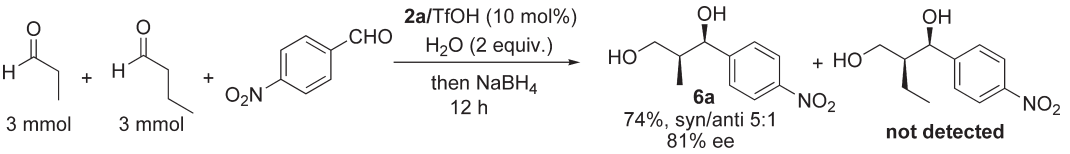
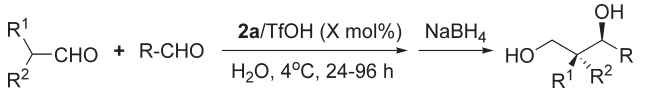


TABLE 4. *2a*/TfOH-Catalyzed Cross-Aldol Reaction of Aldehydes



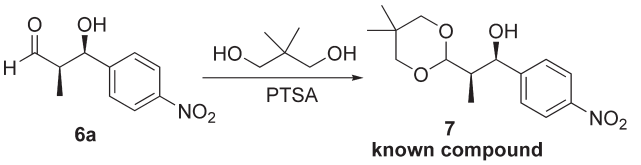
entry (X)[a]	R^1, R^2	R	yield[b] (%)	syn/anti[c]	ee[d] (%)
1 (3)	Me, H	4-NO_2Ph	94/**6a**	7:1	87
2 (3)	Me, H	3-NO_2Ph	94/**6b**	10:1	84
3 (3)	Me, H	2-NO_2Ph	93/**6c**	8:1	87
4 (3)	Me, H	4-CNPh	97/**6d**	13:1	84
5 (3)	Me, H	3-Py	87/**6e**	10:1	84
6 (3)[e]	Me, H	4-CF_3Ph	87/**6f**	6:1	82
7 (10)[e]	Me, H	2-ClPh	64/**6g**	6:1	87
8 (10)[e]	Me, H	4-ClPh	56/**6h**	6:1	81
9 (10)[e]	Me, H	2,4-Cl_2Ph	75/**6i**	7:1	87
10 (10)[e]	Me, H	4-PhPh	75/**6j**	2:1	83
11 (10)	H, H	4-NO_2Ph	*h*		
12 (10)	Et, H	4-NO_2Ph	*h*		
13 (10)	*i*-Pr, H	4-NO_2Ph	*h*		
14 (10)[f]	Me, Me	4-NO_2Ph	97/**6k**		76
15 (10)[f]	Me, Me	3-NO_2Ph	96/**6l**		75
16 (10)[f]	Me, Me	2-NO_2Ph	99/**6m**		78
17 (10)[f]	Me, Me	1-Naph	45/**6n**		69
18 (10)[f]	Me, Me	$BnOCH_2$	67/**6o**		40
19 (10)[g]	$-(CH_2)_5-$	4-NO_2Ph	42/**6p**		10

[a]Unless otherwise stated, the reaction was performed with 0.5 mmol of aromatic aldehyde and 0.5 mL of alkyl aldehyde in the presence of 1 mmol of H_2O. [b]Isolated yield. [c]Determined by ^1H NMR. [d]Determined by HPLC. [e]Datas for the acetylated 1,3-diol products after reduction with $NaBH_4$ by treatment with Ac_2O/pyridine. [f]4 equiv of isobutyraldehyde was used as donor in toluene in the presence of 10 mol % of **2d**/TFA without H_2O. [g]4 equiv of cyclohexanecarbaldehyde as aldol donor in toluene in presence of 10 mol % **2d**/TFA without H_2O, and the product was isolated directly without reduction with $NaBH_4$. [h]No desired cross-aldol products were isolated.

reaction (Table 3, entries 3−5 and 7−13). Among different vicinal diamines (**3**−**5**) screened, the L-phenylalanine-derived **2a** was found to be the optimal catalyst in terms of both activity and stereoselectivity (Table 3, entry 6). In the presence of **2a**/TfOH (10 mol %), the reactions gave 93% yield, 6:1 syn/anti, and 87% ee. Primary amine amide catalyst with multihydrogen bonding **5** was also tested, showing inferior activity and stereoselectivity. Further study indicated that the catalyst loading amount could be reduced to 3 mol % with still high yield and maintained selectivities in 24 h (Table 3, entry 15).

Substrate Scope. Under the optimal conditions, other substrates including various aldehyde donors and acceptors were next examined. The reactions between electron-poor aromatic aldehydes including heteroaromatic aldehyde such as nicotinaldehyde and propionaldehyde proceeded smoothly to give the desired aldol products with up to 97% yield, 13:1 syn/anti, and 87% ee (Table 4, entries 1−10). In all these cases, only trace self-aldol product of propionaldehyde was detected. In addition, no further aldolization of the cross-aldol products was observed. The reactions of electron-rich aromatic aldehydes or aliphatic aldehyde have also been

SCHEME 3. Determination of the Absolute Configuration



Literature report, $[\alpha]^{20}_D$ -8.4° ($CHCl_3$, c=1.0)
Determined $[\alpha]^{20}_D$ -8.9° ($CHCl_3$, c=1.0)

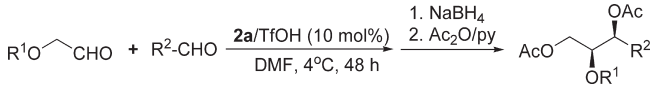
attempted but without success, probably due to the low reactivity of these acceptors.

With respect to other aldehyde donors, branched aldehyde such as isobutyraldehyde[4o] was also applicable in the catalysis of **2d**/TFA with moderate to excellent yields and moderate enantioselectivity (Table 4, entries 14−18). Under the present conditions, the reaction of acetaldehyde afforded unfortunately no desired cross-aldol product (Table 4, entry 11) with aldehyde donors larger than propionaldehyde such as *n*-butyraldehyde and isovaleraldehyde in the catalysis of **2a**/TfOH (Table 4, entries 12 and 13). These results, which on one hand clearly define the limitations of the current reactions, may on the other hand set the basis for further developing syn-selective cross-aldol reactions as the primary amine catalyst demonstrates considerable differentiation between enolizable aldehydes. In a competitive experiment, the reaction was conducted in the presence of equal amounts of propionaldehyde and *n*-butyraldehyde (Scheme 2). Only cross-aldol adduct **6a** derived from propionaldehyde was isolated with slightly lower stereoselectivity and yield (unreacted aldehyde recovered), and no obvious aldol product of *n*-butyraldehyde was detected in the reaction mixture (Scheme 2), highlighting the differentiation power of the catalysis of **2a**/TfOH. Concurrently, the origin of this differentiating effect remains unclear, and a rough analysis suggests that a larger β-substitute in the putative *Z*-enamine (R^1 > Me, Figure 1; see also Scheme 3) would be unfavored for the subsequent aldol coupling probably due to steric hindrance of β-substitute. Further studies to rationalize this phenomena are clearly warranted.

Glycol aldehyde and its derivatives are versatile building blocks in chemical and enzymatic synthesis of carbohydrates.[4h,k,m,11] Though the parent glycol aldehyde was totally inactive in the current catalysis (Table 5, entry 1), 2-benzyloxyacetaldehyde, a protected glycol aldehyde, could react with *p*-nitrobenzaldehyde smoothly to afford the desired syn-selective cross-aldol products with DMF as the optimal solvent (Table 5, entries 2−5). Other aromatic

(11) For selected examples on direct aldol reaction of glycol aldehyde, see: (a) Garrabou, X.; Castillo, J. A.; Guérard-Hélaine, C.; Parella, T.; Joglar, J.; Lemaire, M.; Clapés, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5521–5525. (b) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151. (c) Kofoed, J.; Machuqueiro, M.; Reymond, J. L.; Barbre, T. *Chem. Commun.* **2004**, 1540–1541.

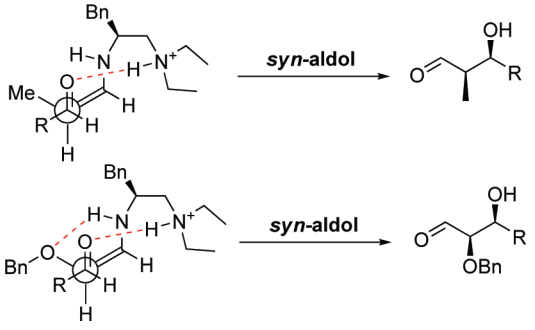
TABLE 5. 2a/TfOH-Catalyzed Cross-Aldol Reaction of 2-Benzyloxyacetaldehyde



entry[a]	R^1	R^2	solvent	yield[b] (%)	syn/anti[c]	ee[d] (%)
1	H	4-NO_2Ph	DMF	trace		
2[e]	Bn	4-NO_2Ph	DMF	71/**6q**	13:1	80
3[e]	Bn	4-NO2Ph	NMP	70/**6q**	13:1	77
4[e]	Bn	4-NO_2Ph	CH_2Cl_2	20/**6q**	16:1	70
5	Bn	4-NO_2Ph	DMF	90/**6q**	16:1	79
6	Bn	3-NO2Ph	DMF	83/**6r**	24:1	80
7	Bn	2-NO_2Ph	DMF	87/**6s**	24:1	78
8	Bn	4-CNPh	DMF	74/**6t**	7:1	85
9[f]	Bn	BnOCH_2−	DMF	65/**6u**	2:1[d]	46

[a]Unless otherwise stated, the reaction was performed with 0.25 mmol of aromatic aldehyde and 1 mmol of 2-benzyloxyacetaldehyde in the presence of 0.5 mmol of H_2O in 0.2 mL of solvent. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]No H_2O was added. [f]The reaction was performed with 1.0 mmol of 2-benzyloxyacetaldehyde and 0.1 mmol of **2a**/TfOH in 0.2 mL of DMF in the presence of 1 mmol of H_2O, and the product was isolated directly without acetylation after reduction with $NaBH_4$.

SCHEME 4. Proposed Transition States of *syn*-Aldol Reactions



aldehydes with strong electron-withdrawn groups could also react with 2-benzyloxyacetaldehyde to afford *syn*-aldol products in high yield and good stereoselectivities (Table 5, entries 6−8). However, less active aldehydes as acceptors gave complicated product mixtures because 2-benzyloxyacetaldehyde itself acted as an acceptor[4h] in the primary amine catalysis to afford moderate stereoselectivities (Table 5, entry 9).

Proposed Transition State. The absolute configurations of the *syn*-aldol products were determined by comparison of the optical rotation value with the known compounds and determined as (1*R*,2*S*) for the reduced 1,3-diol products (Scheme 4).[5] Consistent with previous reports, the high syn selectivity could be reasoned by a *Z*-enamine transition state. Following this model, the N−H·O hydrogen bond was assumed to play a critical role for stabilizing the *Z*-enamine in the cases of 2-(benzyloxy)acetaldehyde to achieve high distereocontrol (Scheme 4).

Conclusions

To conclude, the simple primary amine catalysts such as **2a**/TfOH could catalyze syn-selective cross-aldol reaction of aldehydes to afford the desired products with up to 97% yield, 24:1 syn/anti, and 87% ee for a range of substrates. In particular, the catalysis of **2a**/TfOH has enabled the first syn-selective aldol reactions of glycoaldehyde donors. Though the substrate scope is still limited, this study presents a simple catalyst for the syn-selective cross-aldol reactions of aldehydes and sets the basis for future development along this line.

Experimental Section

General Information. Commercial reagents were used as received, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz instruments, as noted, and are internally referenced to the residual protic solvent signals. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not easily interpreted are designated as multiplet (m) or broad (br). HPLC analysis was performed using Chiralcel columns purchased. Absolute configurations were determined by correlation to literature reported results.[5]

General Procedure for the Cross-Aldol Reaction between Propionaldehyde and *p*-Nitrobenzaldehyde. Catalyst **2a**/TfOH (5.4 mg, 0.015 mmol), H_2O (18 mg, 1 mmol), propionaldehyde (0.5 mL), and *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) were mixed together and stirred at 4 °C for 24 h. Then the mixture was concentrated and diluted with 20 mL of CH_2Cl_2/MeOH (5:1, v/v) mixed solvent. $NaBH_4$ (76 mg, 2 mmol) was added and reacted for 10 min, followed by the addition of 20 mL of 3% $NaHCO_3$ aqueous solution. After 15 min, the organic phase was separated, and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The organics was combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was directly purified by flash column chromatography carefully to afford the aldol adducts **6a** (99 mg, yield 94%).[12] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80−0.83 (3 H, d, J = 7.2 Hz), 2.07 (1 H, m), 2.19 (1 H, br), 3.35 (1 H, br), 3.72 (1 H, m), 3.85 (1 H, m), 5.14 (1 H, d, J = 2.7 Hz), 7.51−7.54 (2 H, d, J = 8.7 Hz), 8.18−8.22 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9, 41.2, 66.4, 75.4, 123.4, 126.8, 147.1, 150.6. HRMS for $C_{10}H_{13}NO_4$ (M): calcd 211.0845, found 211.0843. The enantiomeric excess was determined by HPLC (AD-H column, 254 nm, 2-propanol/*n*-hexane = 1:9 as eluent, 25 °C, 1.0 mL/min), t_R = 13.9 min (major syn isomer), t_R = 15.0 min (minor syn isomer), 87% ee (1*R*,2*S*). Aldol products **6a**,[5a] the anti isomers of **6b**−**d**,**f**−**j** had been previously reported,[4g] and **6e** is a new compound.

Cross-aldol products of isobutyraldehydes **6k**−**n**,[4o] **6o**,[13] and **6p**[4r] were known compounds.

(1*R*,2*S*)-2-Methyl-1-(3-nitrophenyl)propane-1,3-diol (6b). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73 (3 H, d, J = 7.2 Hz), 1.99 (1 H, m), 2.95 (2 H, br), 3.60−3.75 (2 H, m), 5.04 (1 H, d, J = 3.6 Hz), 7.42 (1 H, m), 7.60 (1 H, d, J = 7.8 Hz), 8.03 (1 H, d, J = 8.1 Hz), 8.13 (1 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9, 41.2, 66.3, 75.0, 121.0, 122.1, 129.0, 132.2, 145.3, 148.2. HRMS for $C_{10}H_{13}NO_4$ (M): calcd 211.0845, found 211.0843.

(1*R*,2*S*)-2-Methyl-1-(2-nitrophenyl)propane-1,3-diol (6c). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (3 H, d, J = 6.7 Hz), 2.09 (1 H, m), 2.64 (2 H, br), 3.72−3.94 (2 H, m), 5.69 (1 H, d, J = 2.7 Hz), 7.42 (1 H, m), 7.64 (1 H, m), 7.87−7.96 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.3, 39.8, 67.4, 70.9, 124.6, 127.8, 129.0,

(12) In several cases, the reduced aldol products were acetylated for purification.

(13) Matsuno, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739–6750.

133.0, 138.7, 147.4. HRMS for $C_{10}H_{13}NO_4$ (M): calcd 211.0845, found 211.0844.

(1*R*,2*S*)-2-Methyl-1-(4-cyanophenyl)propane-1,3-diol (6d). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72 (3 H, d, J = 7.4 Hz), 1.96 (1 H, m), 2.63 (2 H, br), 3.59−3.75 (2 H, m), 5.00 (1 H, d, J = 2.9 Hz), 7.39 (2 H, d, J = 8.4 Hz), 7.55−7.58 (2 H, d, 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9, 41.2, 66.5, 75.5, 110.8, 118.9, 126.8, 132.0, 148.6. HRMS for $C_{11}H_{13}NO_2$ (M): calcd 191.0946, found 191.0945.

(1*R*,2*S*)-2-Methyl-1-(pyridin-3-yl)propane-1,3-diol (6e). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.87 (3 H, s), 3.79 (1 H, br), 4.21 (2 H, s), 6.51 (1 H, s), 7.25 (1 H, m), 7.58 (1 H, m), 8.40 (1 H, dd, J = 4.8 Hz, 1.5 Hz), 8.49 (1 H, d, J = 1.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.2, 67.9, 120.4, 123.2, 133.7, 136.0, 141.0, 147.0, 149.7. HRMS for $C_9H_{13}NO_2$ (M): calcd 167.0946, found 167.0942.

(1*R*,2*S*)-2-Methyl-1-(4-trifluoromethylphenyl)propane-1,3-diol (6f). The acetylated product was obtained by treated of the 1,3-diols after reduction with Ac_2O and pyridine. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (3 H, d, J = 6.9 Hz), 2.03 (3 H, s), 2.12 (3 H, s), 2.32 (1 H, m), 3.79−4.07 (2 H, m), 5.84 (1 H, d, J = 5.7 Hz), 7.38 (2 H, d, J = 8.1 Hz), 7.60 (2 H, d, 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.9, 20.7, 20.9, 38.3, 65.4, 75.3, 122.2, 125.3, 125.5, 125.8, 127.4, 129.9, 130.2, 143.2, 169.9, 170.8. HRMS for $C_{15}H_{17}F_3O_4$ (M): calcd 318.1079, found 318.1080.

(1*R*,2*S*)-2-Methyl-1-(2-chlorophenyl)propane-1,3-diol (6g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81−0.87 (3 H, m), 1.94 (3 H, s), 2.05 (3 H, s), 2.35 (1 H, m), 3.93 (2 H, m), 6.11 (1 H, d, J = 4.2 Hz), 7.02−7.08 (1 H, m), 7.18−7.23 (2 H, m), 7.44 (1 H, d, 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.8, 20.8, 36.4, 65.7, 74.0, 122.0, 127.3, 127.8, 129.1, 133.1, 138.6, 169.6, 170.9. HRMS for $C_{14}H_{17}ClO_4$ (M): calcd 284.0815, found 284.0814.

(1*R*,2*S*)-2-Methyl-1-(4-chlorophenyl)propane-1,3-diol (6h). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.97 (3 H, d, J = 0.9 Hz), 2.00−2.10 (6 H, m), 2.33 (1 H, m), 3.76−4.12 (2 H, m), 5.75 (1 H, d, J = 6.0 Hz), 7.19−7.32 (4 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.2, 20.7, 38.3, 65.6, 75.4, 127.8, 128.6, 133.7, 137.6, 169.9, 170.8. HRMS for $C_{14}H_{17}ClO_4$ (M): calcd 284.0815, found 284.0813.

(1*R*,2*S*)-2-Methyl-1-(2,4-dichlorophenyl)propane-1,3-diol (6i). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (3 H, m), 1.95 (3 H, s), 2.03 (3 H, s), 2.29 (1 H, m), 3.90−3.93 (2 H, m), 6.10 (1 H, d, J = 4.4 Hz), 7.18 (2 H, m), 7.30 (1 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.0, 20.7, 20.8, 65.5, 71.7, 127.1, 128.4, 129.6, 132.8, 134.0, 135.8, 169.6, 170.9. HRMS for $C_{14}H_{16}Cl_2O_4$ (M): calcd 318.0426, found 318.0423.

(1*R*,2*S*)-2-Methyl-1-(4-phenylphenyl)propane-1,3-diol (6j). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86−1.02 (3 H, m), 2.02−2.11 (6 H, m), 2.31−2.37 (1 H, m), 3.80−4.15 (2 H, m), 5.69−5.85 (1 H, m), 7.24−7.57 (9 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4, 13.6, 20.8, 21.1, 65.5, 65.8, 76.0, 76.6, 126.9, 127.1, 127.2, 127.4, 127.8, 128.9, 137.7, 138.0, 140.7, 140.9, 141.0, 170.1, 171.0. HRMS for $C_{20}H_{22}O_4$ (M): calcd 326.1518, found 326.1516.

(*S*)-2,2-Dimethyl-1-(naphthalen-1-yl)propane-1,3-diol (6n). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (3 H, s), 0.86 (3 H, s), 3.33−3.40 (2 H, m), 3.55−3.67 (2 H, m), 5.64 (1 H, s), 7.42−7.52 (3 H, m), 7.70−7.86 (3 H, m), 8.06 (1 H, d, J = 2.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 23.3, 40.3, 72.4, 123.7, 125.1, 125.3, 125.7, 128.1, 128.9, 131.7, 133.4, 137.9. HRMS for $C_{15}H_{18}O_2$ (M): calcd 230.1307, found 230.1309.

(*R*)-4-(Benzyloxy)-2,2-dimethylbutane-1,3-diol (6o). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (3 H, s), 0.91 (3 H, s), 3.00 (1 H, br), 3.12 (1 H, t), 3.44−3.51 (3 H, m), 3.59−3.63 (1 H, m), 3.73−3.76 (1 H, d, J = 8.4 Hz), 4.56 (2 H, s), 7.30−7.36 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.4, 22.5, 37.4, 71.2, 71.7, 73.5, 76.6, 127.8, 127.9, 128.5, 137.7. HRMS for $C_{13}H_{20}O_3$ (M): calcd 224.1412, found 224.1415.

(*S*)-(1-(Bydroxymethyl)cyclohexyl)(4-nitrophenyl)methanol (6p). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11−1.19 (1 H, m), 1.24−1.30 (3 H, m), 1.48−1.58 (5 H, m), 1.66−1.79 (1 H, m), 3.62−3.65 (2 H, m), 4.01−4.03 (1 H, d, J = 5.7 Hz), 4.76−4.77 (1 H, d, J = 5.4 Hz), 7.51−7.53 (2 H, d, J = 8.7 Hz), 8.18−8.20 (2 H, d, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 21.4, 26.0, 28.7, 30.3, 41.0, 66.0, 81.7, 122.9, 128.6, 147.3, 149.0. HRMS for $C_{14}H_{19}NO_4$ (M): calcd 265.1314, found 265.1315.

General Procedure for the Cross-Aldol Reaction of 2-Benzyloxyacetaldehyde. Catalyst **2a**/TfOH (9 mg, 0.025 mmol), H_2O (9 mg, 0.5 mmol), 2-benzyloxyacetaldehyde (150 mg, 1 mmol), and *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) were mixed together and stirred at 4 °C for 24 h. Then the mixture was diluted with 10 mL of CH_2Cl_2/MeOH (5:1, v/v) mixed solvent. $NaBH_4$ (76 mg, 2 mmol) was added and reacted for 10 min, followed by the addition of 10 mL of 3% $NaHCO_3$ aqueous solution. After 15 min, the organic phase was separated, and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The organics were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in 1 mL of CH_2Cl_2. To the solution were added Ac_2O (0.2 mL) and pyridine (0.5 mL). After 24 h of stirring, the reaction was quenched with 1 M HCl and extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel to afford (1*S*,2*S*)-2-(benzyloxy)-1-(4-nitrophenyl)propane-1,3-diyl diacetate (**6q**, 87 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (3 H, s), 2.15 (3 H, s), 3.90−3.95 (2 H, m), 4.24−4.26 (1 H, m), 4.46−4.62 (2 H, m), 5.98 (1 H, d, J = 2.1 Hz), 7.15 (2 H, m), 7.24 (3 H, m), 7.49 (2 H, d, J = 8.7 Hz), 8.16 (2 H, dd, J = 6.9 Hz, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.9, 62.6, 73.4, 76.7, 123.5, 127.8, 128.1, 128.3, 128.4, 137.1, 144.3, 147.8, 169.7, 170.5. HRMS for $C_{20}H_{21}NO_7$ (M): calcd 387.1318, found 387.1316. The enantiomeric excess was determined by HPLC (OJ-H column, 254 nm, 2-propanol/-zhexane =15:85 as eluent, 25 °C, 1.0 mL/min), t_R = 40.7 min (minor syn isomer), t_R = 47.2 min (major syn isomer), 79% ee (1*S*, 2*S*). Aldol products **6q**−**t** were all new compounds, and the anti isomer of **6u** was a known compound.[4h]

(1*S*,2*S*)-2-(Benzyloxy)-1-(3-nitrophenyl)propane-1,3-diyl Diacetate (6r). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.03−2.15 (6 H, m), 3.87−3.98 (2 H, m), 4.22−4.27 (1 H, m), 4.47−4.64 (2 H, m), 5.99 (1 H, d, J = 4.5 Hz), 7.15−7.18 (2 H, m), 7.28−7.31 (3 H, m), 7.47−7.52 (1 H, m), 7.65−7.67 (1 H, d, J = 7.8 Hz), 8.14−8.17 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.9, 62.5, 73.4, 73.6, 77.8, 122.0, 123.2, 128.1, 128.4, 129.4, 133.0, 137.0, 139.3, 148.3, 169.7, 170.5. HRMS for $C_{20}H_{21}NO_7$ (M): calcd 387.1318, found 387.1316.

(1*S*,2*S*)-2-(Benzyloxy)-1-(2-nitrophenyl)propane-1,3-diyl Diacetate (6s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.99 (3 H, s), 2.04 (3 H, s), 4.07−4.13 (2 H, m), 4.16−4.25 (2 H, m), 4.37−4.40 (1 H, m), 6.39 (1 H, d, J = 2.4 Hz), 6.96−6.99 (2 H, m), 7.11−7.18 (3 H, m), 7.37−7.39 (1 H, m), 7.50−7.55 (1 H, m), 7.60−7.63 (1 H, m), 7.86−7.88 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 20.9, 62.5, 70.1, 73.8, 76.6, 124.7, 127.9, 128.2, 128.3, 128.7, 129.7, 133.1, 133.4, 137.0, 147.7, 169.7, 170.7. HRMS for $C_{20}H_{21}NO_7$ (M): calcd 387.1318, found 387.1317.

(1*S*,2*S*)-2-(Benzyloxy)-1-(4-cyanophenyl)propane-1,3-diyl diacetate (6t). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (3 H, S), 2.14 (3 H, s), 3.86−3.94 (2 H, m), 4.20−4.24 (1 H, m), 4.45−4.61 (2 H, m), 5.93 (1 H, d, J = 4.2 Hz), 7.14−7.18 (2 H, m), 7.27−7.31 (3 H, m), 7.44 (2 H, d, J = 8.4 Hz), 7.62 (2 H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 20.9, 62.6, 73.4, 73.9, 77.8, 112.1, 118.5, 127.6, 128.0, 128.4, 132.2, 137.1, 142.3, 160.7, 170.5, 193.2. HRMS for $C_{21}H_{21}NO_5$ (M): calcd 367.1420, found 367.1421.

(2*S*,3*S*)-2,4-Bis(benzyloxy)butane-1,3-diol (6u). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43 (1 H, br), 2.74 (1 H, br), 3.51−3.67 (3 H, m), 3.63−3.67 (2 H, m), 3.94−3.97 (1 H, m), 4.48−4.70 (4 H, m), 7.27−7.37 (10 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 61.5, 70.8, 70.9, 72.3, 73.5, 76.6, 127.9, 128.0, 128.1, 128.5, 128.6,

137.7, 137.9. HRMS for $C_{18}H_{23}O_4$ (M + H): calcd 303.1596, found 303.1592.

Typical Procedure for Determining the Absolute Configuration. After the reaction between propional and *p*-nitrobenzaldehyde (0.5 mmol) catalyzed by **2a**/TfOH was finished, the mixture was diluted with 5 mL of aqueous NaCl solution (2 M) and extracted with CH_2Cl_2 (3 mL) three times. The organics were combined and dried with anhydrous Na_2SO_4. After concentration in vacuo, the residue was dissolved in 2 mL of CH_2Cl_2. To the solution were added 2,2-dimethyl-1,3-propanediol (62 mg, 0.6 mmol), triethyl orthoformate (0.091 mL, 0.55 mmol), and *p*-toluenesulfonic acid (9 mg, 0.05 mmol) sequentially at room temperature. After 4 h of stirring, the reaction was quenched with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel to afford (1*R*,2*R*)-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-nitrophenyl)propan-1-ol (**7**, 93 mg, 63% yield). $[\alpha]^{25}_D$ −8.9 ($CHCl_3$, *c* = 1.0). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.77 (3 H, s), 0.82−0.84 (3 H, d, *J* = 7.2 Hz), 1.24 (3 H, s), 2.00−2.04 (1 H, m), 3.44−3.53 (2 H, m), 3.67−3.73 (3 H, m), 4.59 (1 H, d, *J* = 2.4 Hz), 5.40 (1 H, s), 7.52−7.55 (2 H, d, *J* = 8.4 Hz), 8.18−8.20 (2 H, d, *J* = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 7.1, 21.0, 21.8, 30.3, 43.8, 71.8, 77.2, 77.8, 104.0, 123.1, 126.5, 146.3, 150.7. HRMS for $C_{15}H_{21}NO_5$ (M): calcd 295.1420, found 295.1422. The absolute configuration of **7** was determined as (1*R*,2*R*), and the reduced cross-aldol product **6a** was thus determined as (1*R*,2*S*).

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Supporting Information Available: NMR spectra and HPLC traces for aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.