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Organocatalyzed direct aldol condensation using L-proline and BINAM-prolinamides: regio-, diastereo-, and enantioselective controlled synthesis of 1,2-diols

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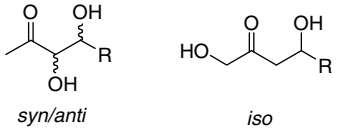
Abstract—Recoverable BINAM-prolinamide derivatives, as well as L-proline, give results complementary to antibodies when used as organocatalysts for aldol reactions between aldehydes and α-alkoxyacetones driving regioselectively to *anti*/*syn*-1,2-diols. The formation of the *iso*-regioisomer is suppressed using α-hydroxyacetone in DMSO at rt, achieving the corresponding *anti*-1,2-diol with ee's up to 85%. For α-alkoxyacetones (methoxy, benzyloxy, and *tert*-butyldimethylsilyloxy), the highest regio- and diastereoselectivity is achieved using α-methoxyacetone in DMF at 0 °C; the enantiomeric excess for the *anti*-1,2-isomer being up to 98%.

1. Introduction

A large variety of natural products and drugs of biological interest include polyoxygenated architectures. The synthesis of simple hydroxy ketone or diol units, occurring in these complex molecules, has attracted the attention of synthetic organic chemists.[1] The catalytic asymmetric aldol reaction is one of the most powerful and straightforward methods for preparing these units from two carbonyl compounds.[2] Over the last few years, the direct enantioselective aldol reaction has become a powerful and efficient methodology for the asymmetric synthesis of β-hydroxy carbonyl compounds avoiding protecting group strategies. There are two general approaches for this purpose: biocatalysts, using either aldolases[2e,3] or catalytic antibodies,[4] and chemical catalysis, using in this case either transition metal complexes[5] or small organic molecules.[6] An important challenge of the aldol reaction is the simultaneous control of the regio-, diastereo-, and enantioselectivity when unsymmetrical ketones are used. Especially interesting is the coupling of α-hydroxyacetone[7] as the aldol nucleophilic donor with aldehydes as the electrophilic counterpart yielding directly aldols bearing the 1,2-diol unit (Fig. 1).

When antibodies are used as catalysts, different regioselectivities were obtained depending on the chosen nucleophilic ketone. Thus, mixtures of the corresponding *syn*/*anti* diastereomers were obtained using α-hydroxyacetone,[8] whilst α-methoxyacetone gave the corresponding *iso*-isomer.[9]

On the other hand, under organocatalytic conditions, α-hydroxyacetone gave *anti*/*syn* diastereomers using L-proline, or 5,5-dimethylthiazolidinium-4-carboxylate (DMTC) as catalysts.[10] The obtained *anti*-1,2-diol unit has a complementary configuration to the *syn*-1,2-diol that can be achieved by the Sharpless AD of α,β-unsaturated carbonyl compounds. However, L-Pro-based small peptides catalyzed the formation of *iso*-regioisomeric compounds[11] for α-hydroxyacetone when aqueous THF was used as solvent. The choice of the appropriate α-alkoxy substituent in the ketone in order to prepare regio-, diastereo-, and enantioselectively the corresponding *anti*/*syn*-diols has not been studied.



syn/anti *iso*

Figure 1. Aldol products in the reaction of α-hydroxyacetone and aldehydes.

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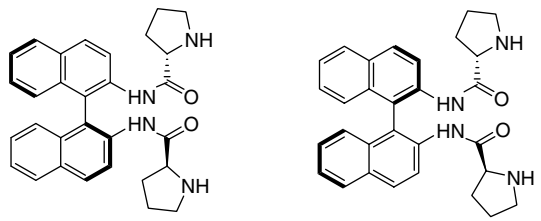


1a, (S_a)-BINAM-L-Pro **1b**, (R_a)-BINAM-L-Pro

Figure 2. BINAM-prolinamide catalysts.

Herein, we report adequate conditions for the direct aldol condensation of α-hydroxy- and α-alkoxyacetones with aldehydes in the presence of L-Pro or recoverable BINAM-prolinamides **1**[12] (Fig. 2) as catalysts, in order to prepare mainly *anti*-1,2-diols.

2. Results and discussion

Initial studies were performed with *p*-nitrobenzaldehyde because this was the acceptor used by Gouverneur et al.[9,13] for catalytic antibodies studies. L-Pro was tested in the aldol reaction between *p*-nitrobenzaldehyde and α-hydroxyacetone under different reaction conditions (Table 1 and Scheme 1). We have recently described that BINAM-prolinamide **1a** is a recoverable and reusable catalyst, which showed similar efficiency to L-Pro. For that reason, its catalytic activity was also studied in this coupling. The reaction carried out in DMSO as a solvent using catalyst **1a** at rt gave a mixture of *anti:syn*-diols **2aa** with a 3:1 dr and 82% and 35% ee, respectively (Table 1, entry 1). When the temperature was decreased to 0 °C, a ca. 2:1:1 mixture of the three possible isomers was obtained (Table 1, entry 2). The use of L-Pro as a catalysts in DMSO at rt gave similar results to using **1a** (Table 1, compare entries 1 and 3). Similar diastereoselectivity has been reported in the reaction between *p*-nitrobenzaldehyde and α-hydroxyacetone in aqueous DMSO using L-Ala-L-Ala as a catalyst giving *anti*-**2aa** with 75% ee.[14] However, when L-Pro was used as a catalyst in buffered aqueous media, a lower diastereoselectivity (dr 1:1) was achieved.[15]

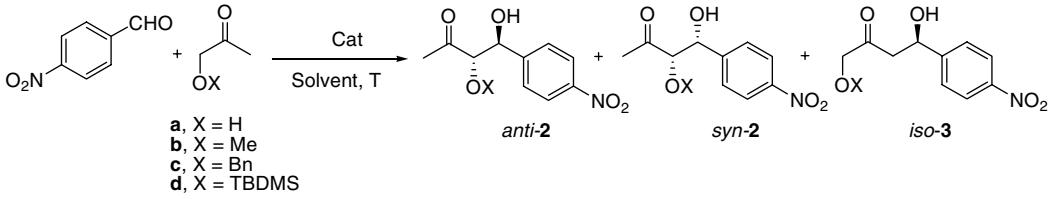
The effect of the axial stereoelement in the stereochemical outcome of the reaction was studied. Thus, when (R_a)-BINAM-L-Pro **1b** was used as catalyst, a 1:1 mixture of diastereomers was obtained, although in very low ee's and with an opposite configuration (Table 1, entry 4). This suggests that the stereochemical pathway of the reaction is controlled to some extent by the axial stereogenic element of the BINAM moiety, catalyst **1a** being the matched diastereomer for this transformation. As expected, the enantiomeric 1,2-diols **2aa** were obtained by changing the catalysts to (R_a)-BINAM-D-Pro *ent*-**1a**, although with a slightly lower dr (Table 1, compare entries 1 and 5).

When the reaction was carried out in DMF at rt, the regioselectivity achieved with **1a** as a catalyst was again superior to when L-Pro was used (Table 1, compare entries 6 and 8); however, *anti*-**2aa** was obtained in lower ee than in DMSO. Working at 0 °C in DMF, the reaction time increased to 4 d and dr was lower, the enantioselectivities being slightly higher than those obtained at rt (Table 1, compare entries 6 and 7). Recently, it has been reported that the addition of some amount of water to the solvent accelerated the reaction rate.[16] However, in our hands the presence of water in DMSO or DMF as organic solvents showed a negative effect in the enantioselectivity for the *anti*-isomer **2aa** (Table 1, entries 9–11). It has been reported that the use of aqueous THF media favors the synthesis of 1,4-isomeric diols.[11] However, a 1:1 diastereo-

Table 1. Reaction conditions studies of the direct aldol reaction of *p*-nitrobenzaldehyde with α-hydroxyacetone[a]

Entry	Catalyst	Solvent	T (°C)	t (d)	Yield[b] (%)	Isomer ratio[c]		ee[d] (%)		
						Regioselectivity (**2aa**/**3aa**)	dr (*anti*/*syn*)	*anti*-**2aa**	*syn*-**2aa**	*iso*-**3aa**[e]
1	**1a**	DMSO	25	1	86	>50:1	3:1	82	35	—
2	**1a**	DMSO	0	1	96	4:1	5:2	80	23	84
3	L-Pro	DMSO	25	1.5	79	>50:1	3:1	85	42	—
4	**1b**	DMSO	25	1	99	20:1	1:1	24[f]	4[f]	—
5	*ent*-**1a**	DMSO	25	1	99	>50:1	2:1	81[f]	8[f]	—
6	**1a**	DMF	25	1	99	>50:1	3:2	72	10	—
7	**1a**	DMF	0	4	98	>50:1	1:1	74	31	—
8	L-Pro	DMF	25	1	99	15:1	1:1	71	20	92
9	**1a**	DMSO/H_2O[g]	25	1	95	19:1	1:1	67	9	—
10	**1a**	DMF/H_2O[h]	25	1	98	>50:1	1:1	19	74	85
11	L-Pro	DMF/H_2O[h]	25	1	7	>50:1	1:1	24	1	—
12	**1a**	THF/H_2O[h]	25	2	80	>50:1	1:1	25	33	—
13	L-Pro	THF/H_2O[h]	25	2	10	>50:1	1:1	14	5	—

[a] 27.6 mmol of α-hydroxyacetone per mmol of aldehyde in 1 mL of solvent and 20 mol % of catalyst **1** or 40 mol % of L-proline at the temperature indicated were used.
[b] Of the isolated products after column chromatography.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC (Chiralpak AD, hexane/isopropanol: 96/4).
[e] (*R*)-Stereoisomer determined by comparison with the specific rotation.
[f] Opposite configuration.
[g] 10 equiv of water were added.
[h] 1/1.



Scheme 1. Aldol reaction between *p*-nitrobenzaldehyde and α-alkoxyketones.

meric mixture of *anti*/*syn*-**2aa** diols was obtained with low ee's for both diastereomers (Table 1, entries 12 and 13). It can be concluded that the use of DMSO as a solvent at rt is the best reaction condition with α-hydroxyacetone and *p*-nitrobenzaldehyde in order to achieve the highest regio-, diastereo-, and enantioselectivity.

We next studied the influence of the α-alkoxyacetone as nucleophilic donor in the selectivity of the reaction. First, we used α-methoxyacetone as the source of the nucleophile and *p*-nitrobenzaldehyde as the electrophile. To the best of our knowledge, it is the first time that this ketone has been used in the organocatalyzed direct aldol reaction, although it is a common nucleophile in antibodies catalyzed aldol reaction.[9,13] We looked for the best reaction conditions using **1a** and L-Pro as catalysts (Scheme 1 and Table 2). In all cases tested, the mixture of the three possible products was obtained with both catalysts, although in every case the *anti*-**2ba** product was the major isomer. When the reaction was carried out in DMSO at rt, the isomer mixture with both catalysts was almost similar, the enantioselectivity for the *anti*-**2ba** product being 79% and 98% using **1a** and L-Pro, respectively (Table 2, entries 1 and 2). In the case of using DMF as a solvent, the regioselectivity increased up to 7:1 with catalyst **1a** (Table 2, compare entries 1 and 3). As described previously, the use of **1b** as a catalyst gave poorer results with inverse enantioselectivities (Table 2, entry 4). When the temperature was decreased to 0 °C, both catalysts **1a** and L-Pro gave ca. 7:1 and 5:1 dr of *anti*/*syn*-**2ba** products, respectively (Table 2, entries 5 and 6). Under these reaction conditions, the *anti*-**2ba** isomer was obtained in 92% and 98% ee. Again, the use of aqueous DMF at 0 °C did not afford better results concerning regio-, diastereo-, and enantioselection (Table 2, entry 7).

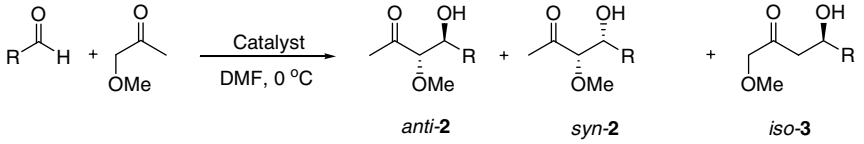
Attempts to recover catalyst **1a** from the aldol reactions performed in DMSO failed. However, BINAM-prolinamide **1a** could be recovered by extractive work-up when the reaction was performed in DMF, after quenching with 6 M HCl, the aldol products being extracted in the organic layer. The acidic aqueous layer was treated with NaOH until pH ~ 11 and extracted with AcOEt to recover the catalyst, which was recrystallized in $CHCl_3/Et_2O$. The recovered catalyst was re-used to give the same results as the freshly prepared catalyst (Table 2, entry 8). In summary, α-methoxyacetone gave higher dr and ee than α-hydroxyacetone when using DMF as a solvent at 0 °C, allowing the recovery of the BINAM-prolinamide.

The influence of other alkoxy substituents at the α-position in the acetone donor was studied. Thus, when α-benzyl-

Table 2. Direct aldol reaction of 4-nitrobenzaldehyde with α-alkoxyacetones[a]

Entry	Catalyst	Solvent	*X*	*T* (°C)	*t* (d)	Yield[b] (%)	Products	Isomer ratio[c]		ee[d] (%)		
								Regioselectivity (**2**/**3**)	dr (*anti*/*syn*)	*anti*-**2**	*syn*-**2**	*iso*-**3**[e]
1	**1a**	DMSO	Me	25	3	98	**ba**	4:1	3:1	79	1	45
2	L-Pro	DMSO	Me	25	2	98	**ba**	5:1	5:1	98	68	64
3	**1a**	DMF	Me	25	2	74	**ba**	7:1	10:3	80	15	50
4	**1b**	DMF	Me	25	3	75	**ba**	3:1	5:3	58[f]	38[f]	49[f]
5	**1a**	DMF	Me	0	4	88	**ba**	5:1	7:1	92	58	80
6	L-Pro	DMF	Me	0	1	82	**ba**	3:1	5:1	98	5	69
7	**1a**	DMF:H_2O[g]	Me	0	2	99	**ba**	7:3	6:1	84	55	83
8	**1a**[h]	DMF	Me	0	4	70	**ba**	9:1	7:2	93	63	83
9	**1a**	DMF	Bn	0	5.5	96	**ca**	2:3	1:2	19	88	60
10	L-Pro	DMF	Bn	0	3	96	**ca**	2:3	1:3	59	99	74
11	**1a**	DMF	TBDMS	0	6	98	**da**	9:2	5:1	22	69	64
12	L-Pro	DMF	TBDMS	0	5.5	98	**da**	9:2	2:1	60	4	75

[a] 27.6 mmol of α-alkoxyacetone per mmol of aldehyde in 1 mL of solvent and 10 mol % of catalyst **1a** or 20 mol % of L-proline at the temperature indicated were used.
[b] Of the isolated products after column chromatography.
[c] Determined by ^1H NMR.
[d] Determined by HPLC.
[e] *R*-Stereoisomer determined by comparison with the optical rotation.
[f] Opposite configuration.
[g] 1:1.
[h] Recovered catalyst.



Scheme 2. Aldol reaction between different aldehydes and α-methoxyacetone.

Table 3. Direct aldol reaction of aldehyde with α-methoxyacetone[a]

Entry	Catalyst	*R*	*t* (d)	Yield[b] (%)	Products	Isomer ratio[c]		ee[d] (%)		
						Regioselectivity (**2**/**3**)	dr (*anti*/*syn*)	*anti*-**2**	*syn*-**2**	*iso*-**3**
1	**1a**	4-$NO_2C_6H_4$	4	88	**ba**	5:1	7:1	92	58	80
2	L-Pro	4-$NO_2C_6H_4$	1	82	**ba**	3:1	5:1	98	5	69
3	**1a**	2-$NO_2C_6H_4$	3	98	**bb**	>50:1	7:1	97	>99	—
4	L-Pro	2-$NO_2C_6H_4$	2	80	**bb**	>50:1	7:1	98	>99	—
5	**1a**	3-$NO_2C_6H_4$	4	77	**bc**	9:2	5:1	90	24	1
6	L-Pro	3-$NO_2C_6H_4$	1	88	**bc**	10:1	5:1	91	27	39
7	**1a**	2-ClC_6H_4	4	99	**bd**	>50:1	2:1	73	67	—
8	L-Pro	2-ClC_6H_4	5.5	94	**bd**	>50:1	3:1	98	72	—

[a] 27.6 mmol of α-methoxyacetone per mmol of aldehyde in 1 mL of DMF at 0 °C and 10 mol % of catalyst **1a** or 20 mol % of L-proline were used.
[b] Of the isolated products after column chromatography.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.

oxyacetone was condensed with *p*-nitrobenzaldehyde in DMF at 0 °C and using **1a** and L-Pro as catalysts, the regio- and diastereoselectivity inverted, affording mainly the *iso*-regioisomer **3ca** and the *syn*-**2ca**, respectively (Table 2, entries 9 and 10). In this case, the *syn*-**2ca** diastereomer was obtained with the highest enantioselectivity (88% and 99% ee). In the case of the *O*-*tert*-butyldimethylsilyl protected α-hydroxyacetone, the aldol reaction has already been described using L-Pro as a catalyst.[17] However, in our hands the results obtained in the reported conditions were drastically different.[18] When the reaction was performed with either **1a** or L-Pro at 0 °C, the major regioisomer was again the *anti*/*syn* diol **2da**, but in lower ee than with α-methoxyacetone (Table 2, entries 11 and 12). Probably the longer O–Si bond makes the OTBDMS less bulky than the OBn group. It can be concluded that α-methoxyacetone is the best donor for the diastereo- and enantioselective synthesis of *anti*-diols **2**.

α-Methoxyacetone was used as the nucleophile in the reaction with different substituted aldehydes in DMF at 0 °C using **1a** and L-Pro as catalysts (Scheme 2 and Table 3). In all cases, *anti*/*syn* isomers were mainly obtained with high ee for the *anti*-**2** compounds independently of the employed catalyst. Remarkably, the best regio- (up to 50:1), diastereo- (up to 7:1) and enantioselectivities (up to 99%) were obtained when *o*-nitrobenzaldehyde was used as aldol donor (entries 3 and 4). However, *o*-chlorobenzaldehyde gave lower diastereoselectivities, dr 2:1 or 3:1 using **1a** or L-Pro, respectively, although with a 98% ee for *anti*-**2bd** when L-Pro was used as a catalyst (Table 3, entries 7 and 8).

3. Conclusion

In conclusion, (S_a)-BINAM-prolinamide **1a** and L-proline can been used as efficient catalysts for the aldol reaction between α-alkoxy substituted ketones and *p*-nitrobenzaldehyde. The results with **1a** are comparable, and sometimes better, than those obtained with L-proline, with the advantage that the prolinamide system could be recovered after the reaction when DMF was used as solvent. With respect to the structure of the α-alkoxy substituted ketones, the formation of the *iso*-regioisomer can be avoided using α-hydroxyacetone in DMSO, achieving up to 3:1 dr and 82% and 85% ee with **1a** and L-Pro, respectively. The highest enantiomeric excesses were obtained for the *anti*-1,2-isomer with α-methoxyacetone (98% ee for L-Pro, 92% ee for **1a**) in DMF, with a dr up to 5:1 when **1a** was used as catalyst, which can also be recovered.

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18. When we carried out the reaction in DMSO at 25 °C using L-Pro (30 mol %) as catalysts, we found an *anti*:*syn*:*iso* ratio of 37:35:28 with 56%, 42%, and 27% ee, respectively. The reported results[17] for the same reaction conditions being *anti:syn:iso* ratio of 90:7:3 with 90% and 15% ee for the *anti* and *syn* diastereomers, respectively.