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Proline-catalyzed asymmetric aldol reactions of tetrahydro-4*H*-thiopyran-4-one with aldehydes

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Abstract—Proline-catalyzed enantioselective direct intermolecular aldol reactions of tetrahydro-4*H*-thiopyran-4-one with various aldehydes give *anti* adducts with high diastereo- and enantioselectivities in moderate to excellent yields. With the aromatic aldehydes best results were obtained in wet DMF whereas dry DMSO generally was superior with the aliphatic aldehydes. Desulfurization of the adducts with Raney Ni provides products equivalent to aldols from 3-pentanone with potential applications in polypropionate synthesis.

The 'directed' aldol reaction[1] of preformed enol(ate) derivatives with aldehydes is among the most powerful methods for stereocontrolled carbon–carbon bond formation[2] as evidenced by numerous applications[3] in natural product syntheses. The development of methods to achieve stereoselective 'direct' aldol reactions of unmodified ketones and(or) aldehydes is an important objective in the evolution of modern aldol chemistry.[4] A number of strategies have been investigated and methods based on enzyme-, antibody-, organometallic-, and organocatalysis have been reported recently.[4] In this regard, the use of proline and its derivatives to catalyze enantioselective direct intermolecular aldol reactions has attracted considerable attention since the initial report[5] by List, Lerner, and Barbas.[6,7] Although the results achieved to date are impressive, one of the major limitations of the proline-catalyzed direct aldol reaction is the rather narrow substrate scope.[6] For example, good to excellent stereoselectivity has been realized in certain cross-aldol reactions and generally in reactions of acetone and hydroxyacetone with various aryl and alkyl aldehydes.[6,7] However, reactions of cyclic ketones often proceed with modest diastereoselectivity and other simple ketones such as acetophenone and pentanone are unreactive.[6] In this letter we report that aldol reactions of tetrahydro-4*H*-thiopyranone (**1**) with various aldehydes are effectively catalyzed by proline in wet DMF or DMSO to give the *anti* adducts in good yield with good to excellent enantioselectivity. Desulfurization of these adducts gives products with applications in polypropionate synthesis and equivalent to those that would be derived from the unreactive 3-pentanone.

We have been investigating sequential two-directional aldol reactions of **1**[8] in the context of a thiopyran-based synthetic route to polypropionates.[9] In the course of these studies we noted higher reactivity[9d] and diastereoselectivity[9a,c,f] in aldol reactions **1** compared to those of cyclohexanone. Thus, despite the relatively mediocre results reported for cyclohexanone in proline-catalyzed enantioselective direct aldol reactions,[6] we were prompted to study the reaction of **1** with benzaldehyde (**2a**) in the presence of proline (Scheme 1, Table 1).[10]

Adapting the conditions reported for the reaction of **2a** with cyclohexanone,[11] reaction of **2a** (0.15 M in DMSO) with **1** (3 equiv) in the presence of proline (0.5 equiv) at room temperature for an arbitrary reaction time of 3 days furnished a 2:1 mixture of aldols **3a** (*anti*) and **4a** (*syn*),[9a,d] respectively, in low yield (entry 1). Several solvents were screened but only DMF was promising (entry 4).[12] Optimization of these conditions clearly showed increased yields at higher concentrations and superior stereoselectivity in DMF. Conversions were not improved with additional proline (cf. entries 5 and 6)[13] or with prolonged reaction times (cf. entries 8 and 9). Both the ratio of **3a**:**4a** and the ee of **3a** decreased with increased reaction times presumably due to the

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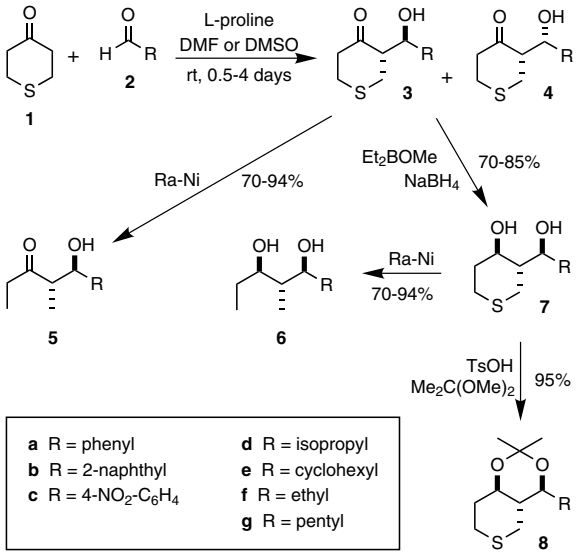

Scheme 1.

Table 1. Proline-catalyzed aldol reactions of **1** with **2a**[a]

Entry	[**2a**] (M)	Solvent	H_2O (equiv)	Time (d)	%Yield[b]	dr[c]	%ee[d]
1	0.15	DMSO	0	3	15	2	
2	1	DMSO	0	3	34	3	78
3	2	DMSO	0	3	33	3.5	83
4	0.15	DMF	0	3	10	10	
5	1	DMF	0	3	44	10	>98
6	1[e]	DMF	0	3	43	10	97
7	2	DMF	0	3	46	14	87
8	1	DMF	0	4	55	10	93
9	1	DMF	0	8	52	5	87
10	1	DMF	1	2	51	14	95
11	1	DMF	2	2	53	11	92
12	1	DMF	4	2	52	8	93
13	1	DMF	8	2	60	3	98
14	1	DMF	1	4	70	7	92
15	**2**	DMF	**1**	**4**	**92**	**14**	**96**

[a] Reactions at room temperature with **2a** (ca. 0.6 mmol), **1** (3 equiv), L-proline (0.5 equiv).
[b] Isolated yield of **3a** after chromatography; see Supplementary data for spectroscopic data.
[c] Ratio of **3a**:**4a** by ^{1}H NMR of the crude reaction mixture.
[d] ee of **3a** Determined by ^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral solvating agent. The absolute configuration of the major enantiomer is as shown.
[e] With 1 equiv of L-proline.

reversibility of the reaction (retroaldol) and/or isomerization of **3a** and **4a** via enolization. Although in many examples of proline-catalyzed direct aldol reactions the adducts were shown or assumed to be stable to the conditions,[6] both retroaldol[14] and isomerization[15] by enolization have been observed. We have previously shown the aldols derived from **1** are particularly susceptible to *syn–anti* isomerization via enolization.[9d] The reaction was substantially improved in the presence of water (entries 10–15) giving much higher yields while maintaining excellent stereoselectivity. Lower stereoselectivity was observed with greater water content (entries 10–13) and with longer reaction times (cf. entries 10 and 14); however, excellent results were obtained under optimized conditions (entry 15). Several authors have reported on the effects of water in proline-catalyzed direct aldol reactions. Although reactions typically proceed with low enantioselectivity in aqueous media,[16] small amounts of water are often tolerated[11b,17] and are sometimes beneficial.[18] In the present case, the origins of the positive effects from added water are uncertain but presumably relate to improved catalyst turnover and suppression of parasitic equilibria.[19]

To ascertain the scope of the process we investigated reactions of **1** with aldehydes **2b–g** (Table 2). Using the conditions optimized for **2a**, reaction of **2b** gave **3b** in good yield and with excellent stereoselectivity. Similar reaction with the more reactive **2c** gave **3c** with poor diastereoselectivity; however, selectivity commensurate with that observed for **3b** was obtained simply by reducing the reaction time to 12 h. In contrast to the aromatic aldehydes **2a–c**, reactions of the aliphatic aldehydes **2d–g** did not benefit from the presence of water and most gave superior results in DMSO compared to DMF. Nonetheless, with minor adjustments in conditions, the *anti* aldols **3d–g** were generally obtained with high stereoselectivity. In keeping with previous reports,[20] reactions with the α-unsubstituted aldehydes **2f** and **2g** gave lower stereoselectivities and yields than reactions with the α-branched aldehydes **2d** and **2e**. The stereoselectivities (particularly the diastereoselectivities) and yields obtained in proline-catalyzed aldol reactions of **1** are generally higher than those reported for similar reactions of cyclohexanone.[11,16a–c,20,21]

The *anti* relative configurations for aldols **3a–g** was suggested by the characteristic[22] large $^3J_{HH}$ observed for O=CC*HCHO*H (7–10 Hz) previously shown to be diagnostic for *anti* aldols of **1**.[9c,d] This assignment was confirmed for **3a**,**d**, and **3e** by diastereoselective reductions to the corresponding diols **7a**,**d**, and **7e**, respectively (Scheme 1); ^{1}H and ^{13}C NMR analysis (as detailed earlier)[9a,b] of the derived acetonides **8a**,**d**, and **8e** fully corroborated the illustrated relative configurations. The absolute configuration for **3b** was established by X-ray crystallographic analysis† and is consistent with that expected from previous studies[6] and from the proposed mechanistic model for proline-catalyzed aldol reactions.[23] The absolute configurations for **3a** and **3c–g** are assigned by analogy.

Desulfurizations of the enantioenriched aldols **3a**,**b**,**d**, and **3e** were achieved using Raney Ni (W-2) in EtOH/THF in the presence of acetate buffer (pH = 5.2) and sodium hypophosphite (10 equiv)[24] to give **5a**,[25] **5b**,[26] **5d**,[27] and **5e**,[28] respectively, in good yields (Scheme 1, Table 3). Despite the mildness of the conditions, the products

† Crystallographic data (excluding structure factors) for (+)-**3b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 247160. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 2. Proline-catalyzed aldol reactions of **1** with **2b–g**[a]

Entry	RCHO	Solvent[b]	Time (d)	Product	%Yield[c]	dr[d]	%ee[e]
1	**2b**	DMF/H_2O	4	**3b**	80	>20	>98[f]
2	**2c**	DMF/H_2O	4	**3c** + **4c**	72	2	96(82)[f]
3		DMF/H_2O	0.5	**3c**	97	>20	95[f]
4	**2d**	DMF/H_2O	4	**3d**	39		
5		DMF[g]	3		62	9	
6		DMSO/H_2O	4		53	11	
7		DMSO[g]	3		96	>20	>98[h]
8	**2e**	DMSO/H_2O	4	**3e** + **4e**	93	10	76[i]
9		DMSO	4		68	>20	92[i]
10	**2f**	DMF/H_2O	4	**3f**	20	5	
11		DMF[g]	3		47	16	80[i]
12		DMSO[g]	3		<5		
13	**2g**	DMSO/H_2O	4	**3g**	38	>20	90[j]
14		DMSO	4		28	14	93[j]

[a] Reactions at room temperature: [RCHO] = 2 M (ca. 0.6 mmol), **1** (3 equiv), L-proline (0.5 equiv).
[b] Containing 1 equiv of H_2O where indicated.
[c] Isolated yield of indicated product after chromatography; see Supplementary data for spectroscopic data.
[d] Ratio of **3**:**4** by ^{1}H NMR of the crude reaction mixture.
[e] ee of **3** (ee of **4** in parentheses).
[f] Determined by ^{1}H NMR in the presence of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE).
[g] [RCHO] = 1 M.
[h] Determined by ^{1}H NMR of the bis Mosher's ester of the derived diol **7e**.
[i] Determined by ^{1}H NMR of the derived Mosher's ester.
[j] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$.

Table 3. Desulfurizations of **3** and **7**[a]

Entry	Substrate	Temperature (°C)	Time (h)	Product	%Yield[b]
1	**3a**	25	1	**5a**[c]	94
2	**3b**	25	9	**5b**[c]	76
3	**3d**	25	9	**5d**[c]	70
4	**3e**	75	1.5	**5e**[c]	94
5	**7a**	25	1.5	**6a**	93
6	**7d**	75	3	**6d**	70
7	**7e**	75	1.5	**6e**	80

[a] Raney Ni (W-2) in EtOH/THF with acetate buffer (pH = 5.2) and NaH_2PO_2 (10 equiv).
[b] Isolated yield of indicated product after chromatography; see Supplementary data for spectroscopic data.
[c] A 10–15:1 mixture of **5** and the corresponding *syn* diastereomer.

5 were contaminated with up to 10% of the *syn* diastereomer presumably originating from *syn–anti* isomerization of **3** via enolization.[9d] Isomerization could be completely avoided by desulfurization of the diols **7a**,**d**, and **7e** to give **6a**,[29] **6d**,[30] and **6e**, respectively (Table 3).

In summary, enantioselective direct aldol reactions of tetrahydro-4*H*-thiopyran-4-one with aldehydes is effectively catalyzed by proline. Desulfurization of the aldol adducts or the derived diols gives products equivalent to those that would be obtained from 3-pentanone, a ketone that does is unreactive in these reactions. The aldols and their derivatives are useful in polypropionate synthesis and the details of our applications in this context will be communicated in due course.[31]

Acknowledgements

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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.2004.09.061.

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31. Note added in proof: During the review of this paper a related study was published on the accelerating effect of added water in proline-catalyzed direct aldol reactions including some examples with **1**: Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891–1896. Our results are qualitatively in agreement with those reported by Pihko et al.