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Synthesis of enantiomerically enriched secondary and tertiary phenylthio- and phenoxy-aldols

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Abstract

α-Phenoxy- and phenylthio-ketones have been explored as donors and acceptors in organocatalytic aldol reactions. Our studies have revealed effective methodologies for accessing structurally varied and enantiomerically enriched secondary and tertiary phenylthio- and phenoxy-aldols, expanding the scope and potential synthetic utility of organocatalytic direct aldol reactions.

Keywords: Organocatalyst; Asymmetric reaction; Aldol reaction; Proline

Enantiomerically enriched β-phenylthio- and phenoxy-substituted alcohols are particularly attractive synthetic intermediates since these have been used for a variety of organic transformations. β-Phenylthio alcohols are widely used as intermediates in the synthesis of oxiranes,[1] aziridines,[2] thiiranes,[3] tetrahydrofurans[1c,4] and β-hydroxy esters.[5] Moreover, these are easily oxidized to β-hydroxy sulfoxides[6] or sulfones[7] which are extremely useful chiral building blocks for the synthesis of a variety of chiral organic compounds, such as oxiranes,[8] allylic alcohols,[9] lactones,[10] and tetrahydrofurans.[11] Also their phenoxy analogues are very important chiral synthons[12] and are found as structural moieties[13] in a variety of natural products. For this reason many methods have been developed for their enantioselective synthesis using kinetic resolution,[14] baker's yeast,[12,15] enzyme[16] and chiral oxazaborolidine-catalyzed borane[17] mediated reduction of α-phenylthio- and phenoxy-ketones.

Among the different approaches that could be envisaged for their synthesis we were particularly interested in the organocatalyzed aldol reaction of phenylthio- and phenoxy-ketones, since one or two new stereogenic centres can be generated simultaneously in only one synthetic step.

Our synthetic plan reported in Figure 1 involved a double use of ketones **2** both as aldol donors and acceptors as we considered that both the reactivities were worth being examined mainly for the following two reasons.

First of all, despite recent advances in the area of asymmetric aldol reaction,[18] in most cases simple ketones are usually examined as aldol donors and few direct catalytic

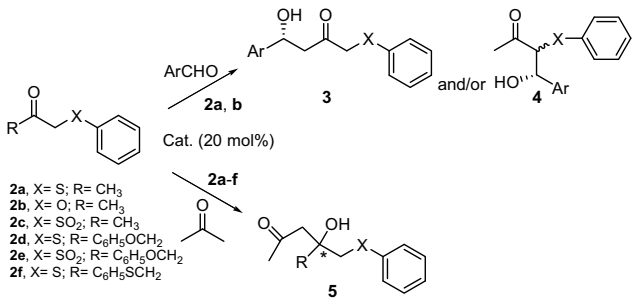

Fig. 1.

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aldol reactions with unsymmetric ketones α-substituted by heteroatoms such as oxygen,[19a] sulfur,[19b] chlorine[19c] and fluorine[19d] are reported.

Moreover, in nearly all the intermolecular organocatalyzed asymmetric aldol reactions, the substrates used as acceptors or electrophiles are mostly aldehydes,[18] and only rarely some very highly active non enolizable ketones[20] carrying an electron-withdrawing group adjacent to the carbonyl carbon are used in this role.

For what concerns the first part of the project, we found that the reaction between phenoxyacetone and several aromatic aldehydes proceeded with high regioselectivities and good enantioselectivities favouring the formation of products **4** resulting from the reaction at the position adjacent to the oxygen atom of the ketone when using catalysts **I** and **II**, while the use of **III** (Table 1, entry 3) gave a mixture of the two regioisomers **3** and **4**.

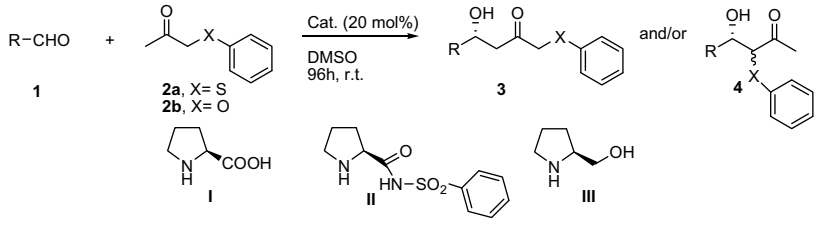
The product distribution observed for the reactions catalyzed by **I** and **II** (Table 1, entries 1, 2, and 4–6) was in accordance with the regiochemical outcome reported in the literature for the direct aldol reactions between α-hydroxy ketones and aldehydes catalyzed by L-proline.[18,19a,22]

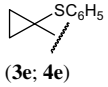
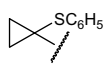
The aldol reaction of phenoxyacetone with an aliphatic aldehyde such as isobutyraldehyde did not proceed in the presence of either catalyst **I**, **II**, and **III** whilst 1-(phenylthio)cyclopropane carbaldehyde, that is an excellent electrophile for the aldol reaction,[1c] afforded the corresponding aldol products **3e** and **4e** in good yields and high enantioselectivity, albeit with no regioselectivity (Table 1, entry 7).

The reaction of phenylthioacetone **2a** with *p*-nitrobenzaldehyde in the presence of catalysts **I**, **II**, and **III** led always to variable yields of product **4f**, obtained as a racemic mixture and with low diastereoselection (Table 1, entries 8–10).

Interestingly, the aldol reaction with benzaldehyde in the presence of catalyst **III** afforded the corresponding aldol **4g** in excellent diastereoselectivity and ee (90%) but in low yield (20%) (Table 1, entry 11).

Table 1
Direct aldol reaction of aldehydes with phenylthio- and phenoxyacetone[21]



Entry	Product (R)	X	Cat.	Ratio **3**:**4**	Yield[a] (%)	ee **3**[b] (%)	ee **4**[b] (%)	dr **4**[c] *anti*:*syn*
1	*p*-NO_2–Ph (**4a**)	O	**I**	<1:99	65	—	71	>99:1
2	*p*-NO_2–Ph (**4a**)	O	**II**	<1:99	51	—	84	99:1
3	*p*-NO_2–Ph (**3a**; **4a**)	O	**III**	60:40	66	14	*syn* 22 *anti* 0	50:50
4	*p*-CN–Ph (**4b**)	O	**I**	<1:99	70	—	*syn* 64 *anti* 90	80:20
5	*p*-Cl–Ph (**4c**)	O	**I**	<1:99	70	—	*syn* 18 *anti* 99	75:25
6	Ph (**4d**)	O	**I**	<1:99	66	—	*syn* 22 *anti* 64	85:15
7	 (**3e**; **4e**)	O	**I**	50:50	70	96	*anti* 93	96:4
8	*p*-NO_2–Ph (**4f**)	S	**I**	<1:99	40	—	0	60:40
9	*p*-NO_2–Ph (**4f**)	S	**II**	<1:99	70	—	0	65:35
10	*p*-NO_2–Ph (**4f**)	S	**III**	<1:99	90	—	0	65:35
11	Ph (**4g**)	S	**III**	<1:99	20	—	90	99:1
12	Ph (**3g**)	S	**I**	99:<1	27	68	—	—
13	*p*-CN–Ph (**3h**; **4h**)	S	**I**	20:80	35	nd[d]	0	60:40
14	*p*-Cl–Ph (**3i**; **4i**)	S	**I**	50:50	40	78	0	50:50
15	 (**3j**; **4j**)	S	**I**	95:5	40	95	—	99:1

[a] Isolated yields.
[b] The ee values of the products were determined by HPLC analyses using Chiralcel OJ column or Chiralcel OD-H column.
[c] *syn*/*anti* Ratio was based on ^{1}H NMR. Stereochemistry was assigned on the basis of previous aldol reactions.[19a,e,d,20g]
[d] Not determined.

This result prompted us to examine the reactivity of phenylthioacetone with other aldehydes and the results were quite peculiar. When benzaldehyde was reacted with phenylthioacetone using **I** as a catalyst, the regioselectivity was inverted and regioisomer **3g** was obtained in moderate ee (Table 1, entry 12). The reactivity of **2a** in the presence of **I** is quite remarkable since it looks as the regio- and the stereocontrol were dependent on the electronic properties of the aromatic moiety.

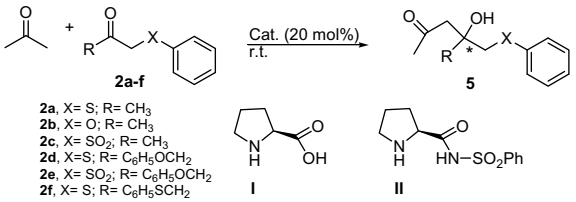
The reaction of phenylthioacetone with other different *p*-substituted aromatic aldehydes confirmed a strong effect of the electronic properties of the aromatic moiety on the stereo- and regioselectivity. As revealed in Table 1, an apparent correlation was observed between the reaction regioselectivity/enantiocontrol and the reactivity of aldehydes. More specifically, the presence of electron-withdrawing substituents at the *para* position tends to increase the formation of regioisomer **4**, ranging from <1% (benzaldehyde), 50% (4-chlorobenzaldehyde), 80% (4-cyanobenzaldehyde) to >99% (4-nitrobenzaldehyde) with moderate yields and no enantioselectivity. Regioisomer **3i** was obtained in good ee (78%) (Table 1, entry 14) whilst regioisomer **3j** was obtained from the reaction of 1-(phenylthio)cyclopropanecarbaldehyde with useful levels of enantiocontrol (95%) but with poor conversion (40%) (Table 1, entry 15). Anyway α-phenylthioacetone was a less good donor in comparison with phenoxyacetone. Nevertheless, these results are quite intriguing and these deserve deeper attention in the future.

The second part of this work was stimulated by the recently reported result that 2-dimethyl-1,3-dioxan-5-one was a good substrate for asymmetric self-aldol condensation reaction.[23] This unusual reactivity of dioxanones is due to the fact that the electron-poor carbonyl group forces these ketones to display a highly electrophilic character. On the basis of the above mentioned result, we reasoned that α-phenoxy- and phenylthio-ketones should be active enough as enamine acceptors (by field/inductive effects) but less reactive than acetone as nucleophiles (by steric effects) in the ketone–ketone cross aldol reaction.

The cross aldol reaction of **2a** with acetone, catalyzed by **I**, in DMSO at room temperature gave the aldol product **5a** in 50% of yield and with an ee value of 47%. Under the same reaction conditions, **2b** produced the corresponding aldol **5b** in 40% yield and ee 39%. An ee value of 80% but low yield (30%) was obtained for the cross aldol reaction of **2a** and acetone when **II** was used as the catalyst and the reaction was carried out in acetone.

The low yield could be explained by a competing formation of a very stable enamine[25] between the catalyst and the α-heteroatom substituted ketones. This conclusion is further substantiated by the fact that the reaction between phenylsulfonylacetone **2c** and acetone did not give the aldol product. In fact, here deprotonation at the α-carbon is facilitated by the enhanced acidity caused by the presence of a sulfone group and, consequently, the catalyst is probably all engaged in a parasitic enamine formation.

Table 2
Direct ketone–ketone cross aldol reaction[24]



Entry	Product (R)	X	Cat.	Solvent	Yield[a] (%)	ee **5**[b,c] (%)	*t* (h)
1	CH_3 (**5a**)	S	**I**	DMSO	50	47	96
2	CH_3 (**5b**)	O	**I**	DMSO	40	39	96
3	CH_3 (**5a**)	S	**II**	Acetone	30	80	96
4	CH_3 (**5b**)	O	**II**	Acetone	20	27	96
5	CH_3 (**5c**)	SO_2	**II**	Acetone	0	—	96
6	$C_6H_5OCH_2$ (**5d**)	S	**I**	DMSO	74	16	48
7	$C_6H_5OCH_2$ (**5d**)	S	**II**	Acetone	60	47	48
8	$C_6H_5OCH_2$ (**5d**)	S	**II**	DMSO	30	40	48
9	$C_6H_5OCH_2$ (**5d**)	S	**II**	CH_3CN	33	45	48
10	$C_6H_5OCH_2$ (**5d**)	S	**II**	$CHCl_3$	70	46	48
11	$C_6H_5OCH_2$ (**5e**)	SO_2	**II**	Acetone	60	70	96
12	$C_6H_5SCH_2$ (**5f**)	S	**II**	Acetone	60	—	96

[a] Isolated yields.
[b] The ee values of the products were determined by HPLC analyses using Chiralcel OJ column or Chiralcel OD-H column.
[c] The absolute configuration of these products is unknown.

Hoping to increase the reaction rate and yield, we selected **2d** as an acceptor with the expectation that it would be highly electrophilic and yet sterically more deactivated towards enamine formation than **2a** and **2b**. L-Proline **I** catalyzed the reaction of **2d** with acetone giving the aldol product **5d** in 74% of yield and 16% of ee, while using **II** as the catalyst, **5d** was obtained in 60% yield and in a 47% of ee. Attempts to increase the enantioselectivity performing the reaction in different solvents were unsuccessful (Table 2, entries 8–10). This result indicates that if this reaction follows the normal aldol mechanism,[26] the poor enantioselectivity is not surprising, since the energy difference between the two diastereomeric transition states, which leads to the two enantiomers, probably is not that much.

In a further effort to improve the enantioselectivity, we supposed that an increased steric demand of one of the two substitution groups on the carbonyl was expected to enforce the high levels of stereocontrol. Gratifyingly, the aldol reaction between **2e** and acetone using **II** as the catalyst afforded the desired compound **5e** in 60% of yield and 70% ee (Table 2, entry 11).

In summary, α-phenoxy- and phenylthio-ketones have been examined as donors and acceptors in organocatalytic aldol reactions. Our studies have revealed effective methodologies for accessing structurally varied and enantiomerically enriched secondary and tertiary phenylthio- and phenoxy- aldols, expanding the scope and potential

synthetic utility of organocatalytic direct aldol reactions. Further investigations into the mechanistic aspects and the use of new organocatalysts for this reaction are underway and will be reported in due course.

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Supplementary data

Supplementary data (Experimental procedures and analytical data for all new compounds) associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2008.03.066.

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21. A typical procedure for the reaction of aldehydes with phenylthio- and phenoxyacetone is as follows: To a mixture of anhydrous DMSO (20 mL) and ketone donor (5 mL) was added the corresponding aldehyde (4.4 mmol) followed by the catalyst (20 mol %) and the resulting mixture was stirred at room temperature for 96 h. The reaction mixture was poured into saturated ammonium chloride solution, the layers were separated and, the aqueous phase was extracted several times with diethyl ether. The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated to afford the crude aldol adducts. The residue was purified by flash chromatography (silica gel, light petroleum–diethyl ether 1:1). *4-Hydroxy-4-(4-nitrophenyl)-3-phenoxybutan-2-one* (**4a**): Orange oil. Yield 65%. IR (neat): 3500, 1720, 1517, 1347 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.22 (d, 1H, $J = 3.6$ Hz), 4.63 (d, 1H, $J = 6$ Hz), 5.25–5.27 (m, 1H), 6.75–6.79 (m, 2H), 6.99 (t, 1H), 7.21–7.33 (m, 2H), 7.61 (d, 2H), 8.20 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.5, 73.3, 85.4, 114.9, 122.4, 123.4, 127.6, 129.9, 146.1, 157.0, 208.7. MS: m/z (%) = 283 (M^+-18 (5)), 212 (3), 154 (4), 133 (8), 89 (12), 77 (48), 63 (16), 51 (28), 43 (100). $[\alpha]_D^{26}$ +2.7 (c 0.36, CH_2Cl_2), 84% ee. The ee was determined by HPLC on a Chiralcel OD-H column with hexane–*i*-PrOH (80:20) as the eluent, flow rate 1 mL/min, $\lambda = 254$ nm. t_R (major): 7.4 min, t_R (minor): 8.4 min. Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.7; H, 5.06; N, 4.69.
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24. A typical procedure for the direct ketone–ketone cross aldol reaction is as follows: To a suspension of catalyst (20 mol %) in anhydrous acetone 5 mL was added the corresponding α-phenoxy- or phenylthio ketone (0.4 mmol). The resulting mixture was stirred at room temperature for a certain time and the reaction progress was monitored by TLC. The reaction mixture was poured into saturated ammonium chloride solution, the layers were separated and, the aqueous phase was extracted several times with diethyl ether. The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated to afford the crude aldol adducts. The residue was purified by flash chromatography (silica gel, light petroleum–diethyl ether 1:1). *4-Hydroxy-5-phenoxy-4-((phenylsulfonyl)methyl)pentan-2-one* (**5e**): Orange oil. Yield 60%. IR (neat): 3400, 1720, 1340, 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 3.22 (ABq, 2H, $J = 17.7$ Hz, $J = 36$ Hz), 3.66 (ABq, 2H, $J = 14.4$ Hz, $J = 30.3$ Hz), 4.09 (d, 2H,

$J = 1.5$ Hz), 4.42 (br s, 1H), 6.85–7.91 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.5, 47.2, 59.7, 72.2, 72.4, 114.6, 121.4, 127.7, 129.2, 129.4, 133.8, 140.5, 158.0, 209.2. MS: m/z (%) = 290 (M^+-58 (3)), 197 (3), 141 (77), 107 (11), 91 (12), 77 (100), 51 (36). $[\alpha]_D^{20}$ +18.6 (c 0.43, $CHCl_3$), 70% ee. The ee was determined by HPLC on a Chiralcel OD-H column with hexane–*i*-PrOH (90:10) as the eluent, flow rate 1.2 mL/min, $\lambda = 254$ nm. t_R (major): 22.7 min, t_R (minor): 26.6 min. Anal. Calcd for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79; S, 9.2. Found: C, 62; H, 5.7; S, 9.34.

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