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Highly enantioselective vinylogous addition of 2-trimethylsilyloxyfuran to aldehydes promoted by the $SiCl_4$/chiral Lewis base system

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Abstract—This paper reports the regio-, diastereo- and highly enantioselective vinylogous aldol reaction of 2-trimethylsilyloxyfuran (TMSOF) promoted by the $SiCl_4$/Lewis base catalytic system. Several electron-pair donors proved to be effective as $SiCl_4$ activators versus the TMSOF γ-selective addition to aldehydes giving rise to different diastereoisomeric ratios, while Denmark's chiral bis-phosphoramide (*R*,*R*)-**7** gave the highest enantioselectivity for both the *anti*- and *syn*-diastereoisomers. Furthermore, by using ambident electrophiles such as α,β-unsaturated aldehydes, the $SiCl_4$/Lewis base-promoted process leads exclusively to the 1,2-addition products.

1. Introduction

Within the domain of C–C bond-forming processes, the vinylogous aldol reactions of silyloxy dienes have emerged as a powerful tool to gain access to highly functionalized aldol architectures.[1] In particular, the γ-addition of silyloxyfuran nucleophiles to carbonyl compounds provides directly δ-hydroxy butenolide structures, subunits found in many naturally occurring products. As well as the regiochemical issue, the synthesis of δ-hydroxy butenolides also poses a stereochemical challenge, due to the generation of two adjacent stereogenic centres at the C(4) of the ring and at the C–OH positions. Among diastereoselective synthetic methods starting from silyloxy furan derivatives,[2–6] Lewis acid-catalysis certainly arises as the most relevant one; nevertheless, little attention has been paid so far to enantioselective variants. Thus, many efforts are currently devoted to designing asymmetric strategies, encompassing both the diastereo- and the enantiocontrol of the reaction. The recent Ti(IV)-BINOL and Cr(III)-salen mediated processes, reported, respectively, by Figadère et al.[7] and Katsuki et al.[8] represent the pioneering works on this subject; no further papers have appeared in the literature to date. However, in the last few years, Denmark et al. have proposed a conceptually innovative strategy for aldol reactions, which does not involve transition metal-catalysts. Thanks to the ability of chiral phosphoramides to enhance the electrophilic character of the weak Lewis acid $SiCl_4$, some chiral non-metallic catalytic species have been originated and a number of stereoselective $SiCl_4$-promoted procedures, including vinylogous aldol additions, have been developed.[9–13]

In connection with our previous investigations on related aldol-type reactions,[14] we herein report a study on the catalytic ability of $SiCl_4$/chiral Lewis base systems to promote the vinylogous aldol addition of 2-trimethylsiloxyfuran to aldehydes targeted at the regio- diastereo- and enantioselective synthesis of δ-hydroxy butenolides.

2. Results and discussion

In a previous report[15] we showed the catalytic ability of $SiCl_4$/Lewis base systems to promote the vinylogous aldol addition of various synthetically useful dienes. During these studies, different organocatalysts (*NCOs*),[16] such as phosphoramides, sulfoxides, formamides and N-oxides, were found to be efficient $SiCl_4$ promoters for the vinylogous aldol addition of TMSOF to aldehydes. By using

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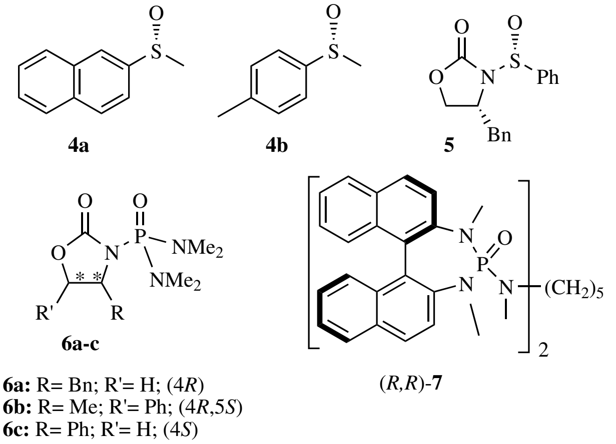
the $SiCl_4$/*NCO* system we were able to directly obtain the free aldol thus avoiding the usually required desilylation procedure. Furthermore, we always saw a diastereoselectivity trend opposite to the one observed when using titanium-[17] or tin based-catalysis,[4] (which led to *syn* as the prevailing diastereoisomer). However, as confirmed by a control experiment, in the absence of organocatalysts the reaction proved to be almost completely suppressed.

Thus, keeping in mind the inherent $SiCl_4$ inactivity, we envisaged the possibility of designing an enantioselective version of the reaction. To this end, we examined several enantiopure *NCOs* (Fig. 1) as $SiCl_4$ promoters, in the reaction of **1** with the representative electrophile **2a** under the conditions reported in Scheme 1 and Table 1.

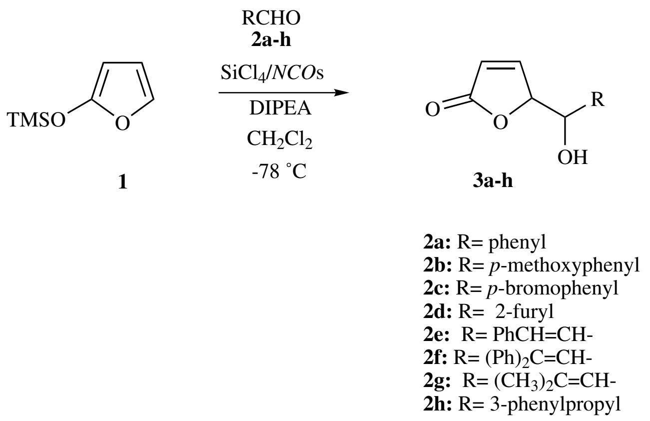
The use of chiral aryl methyl sulfoxides **4a** and **4b**[18] afforded butenolide **3a** in moderate yields and drs, but very low ees. Moreover, in spite of the presence of two enantiopure stereogenic centres, similar ees and even lower chemical yield were observed by using sulfonamide **5**[19] as a $SiCl_4$ promoter.

As a consequence of these poor results, we decided to test the chiral induction of phosphoramides **6** and **7**. With respect to sulfonamide **5**, chiral oxazolidin-2-one phosphoramide derivatives **6a–c** showed a remarkable reactivity increase and a slightly improved enantioselectivity (up to 30% ee for the *syn* isomer by using **6c**). No yield or enantioselectivity improvements were obtained when increasing (1 equiv) or reducing (3%) the amount of the organocatalysts.



6a: R= Bn; R'= H; (4*R*)
6b: R= Me; R'= Ph; (4*R*,5*S*)
6c: R= Ph; R'= H; (4*S*)

Figure 1.



2a: R= phenyl
2b: R= *p*-methoxyphenyl
2c: R= *p*-bromophenyl
2d: R= 2-furyl
2e: R= PhCH=CH-
2f: R= $(Ph)_2C$=CH-
2g: R= $(CH_3)_2C$=CH-
2h: R= 3-phenylpropyl

Scheme 1.

Table 1. $SiCl_4$/chiral *NCO* promoted enantioselective aldol reaction of **1** with **2a**

Entry	*NCO* (mol %)	Time (h)	% Yield[a]	*anti*/*syn*[b]	% ee (*anti*)[c]	% ee (*syn*)[c]
1	**4a** (10%)	2	48	57/43	2	0
2	**4b** (10%)	2	50	60/40	6	4
3	**5** (10%)	2	21	52/48	4	4
4	**6a** (10%)	2	42	58/42	4	4
5	**6b** (10%)	2	43	60/40	11	4
6	**6c** (10%)	1.5	53	57/43	17	30
7	(*R*,*R*)-**7** (10%)	0.7	54	74/26	96	>99
8	(*R*,*R*)-**7** (3%)	1	67	69/31	93	94
9	(*R*,*R*)-**7** (1%)	2	NR	—	—	—

[a] Yields refer to isolated products, after chromatographic purification. NR: no reaction.
[b] Calculated by ^1H NMR analysis, according to Refs. 7b and 8.
[c] Determined by HPLC analysis using CHIRALPAK AD column.

The enantioselectivity goal was achieved with the bidentate Denmark's chiral ligand (*R*,*R*)-**7**, which led to **3a** again with a moderate yield, but a good diastereoselectivity and an excellent enantioselectivity both for *anti*- (96% ee) and *syn*- (>99% ee) isomers. Although a lower catalyst loading (from 10 to 3 mol %) involved a slight stereoselectivity decrease, a higher chemical yield was achieved (entry 8). On the contrary, no catalytic activity was observed by the reduction of (*R*,*R*)-**7** loading to 1 mol % (entry 9).

Thus, the scope of the asymmetric (*R*,*R*)-**7**-catalyzed process was further investigated, as summarized in Table 2.

As shown, in the presence of 3 mol % of (*R*,*R*)-**7**, the vinylogous addition of TMSOF took place in a very satisfactory way with almost all the aldehydes examined, yielding compounds **3** with a good efficiency and diastereoselectivity and good to excellent ees. Rather interestingly, α,β-unsaturated aldehydes **2e–f** generally showed the best results, with

Table 2. $SiCl_4$/(*R*,*R*)-**7** promoted enantioselective aldol reaction of **1**

Entry	**2**	(*R*,*R*)-7 (mol %)	Reaction time (h)	% Yield[a]	*anti*/*syn*[b]	% ee (*anti*)[c]	% ee (*syn*)[c]
1	**2b**	3	1	80	80/20	>99	>99
2	**2c**	3	0.75	64	65/35	>99	>99
3	**2d**	3	0.75	60	80/20	50[d]	50
4	**2e**	3	0.50	63	84/16	>95[d]	42
5	**2f**	3	2	88	87/13	>95[d]	39
6	**2g**	3	18	NR	—	—	—
7	**2h**	3	18	NR	—	—	—

[a] Yields refer to isolated products, after chromatographic purification. NR: no reaction.
[b] Calculated by ^1H NMR analysis, according to Refs. 7b and 8.
[c] Determined by HPLC analysis using CHIRALPAK AD column, unless otherwise indicated.
[d] Determined by ^1H NMR using $Eu(hfc)_3$ chiral shift reagent.

regards to the starting material conversion, reaction time and diastereoselectivity. In fact, despite the ambident character of these electrophiles, no Mukaiyama–Michael addition products[20] were detected by ^{1}H NMR analyses of the crude mixtures.

Conversely, very poor efficiency was observed for α,β-unsaturated aldehyde **2g** and aliphatic aldehyde **2h**, which was found to be completely unreactive under a variety of experimental conditions. It should be noted that, in view of the *anti*-diastereoselectivity, this procedure can be considered complementary to the ones reported by Figadère et al.[7a] and Katsuki et al.,[8] which are both characterized by *syn*-diastereoselectivity. More conveniently, the organocatalyst could be quantitatively recovered for recycling after a simple silica gel chromatography.

3. Conclusion

In conclusion, δ-hydroxy butenolides, well-known key intermediates in the syntheses of a variety of natural compounds, proved to be accessible in a regio- diastereo- and enantioselective vinylogous aldol addition of TMSOF promoted by $SiCl_4$/(*R*,*R*)-**7** catalyst. With respect to the classical Ti(IV) or Sn(IV)-based Lewis acid-catalysis, the reported methodology involved an opposite diastereoselectivity, leading to *anti*-**3** as the prevalent isomer. This methodology represents the first non-metallic highly enantioselective version of the reaction.

4. Experimental

4.1. General

All the reactions were performed in a flame-dried glassware under an argon atmosphere. All the solvents were of reagent grade and were dried and distilled immediately before use (CH_2Cl_2 from calcium hydride). Purifications of **3a**–**i** and **6a**–**c** were performed by flash chromatography column (silica gel Merck). Chiral phosphoramide (*R*-*R*)-**7** were purchased from Obiter Research, LLC; starting materials and all the other reagents, unless otherwise indicated, were purchased from Aldrich or Fluka and used without further purification. The NMR spectra (Bruker DRX 400 (^{1}H 400 MHz; ^{13}C 100 MHz)) were performed in $CDCl_3$ solution and referenced to residual $CHCl_3$ (7.26 ppm (^{1}H); 77.23 ppm (^{13}C)). Chemical shifts are reported in parts per million, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in hertz. HPLC analyses of **3a**–**c** were performed with Waters Associates equipment (Waters 2487 Dual λ absorbance Detector), using CHIRALPAK AD column with hexane/propan-2-ol 95/5, flow rate 0.6 ml/min.

4.2. General procedure for the enantioselective vinylogous addition of TMSOF to aldehydes 2a–h

To a flame-dried two-neck round-bottomed flask, were added dry CH_2Cl_2 (2 ml), DIPEA (1.2 mmol) and the *NCOs* (**4a**, **4b**, **5**, **6a**–**c** or (*R*,*R*)-**7** (0.1 or 0.03 mmol). The solution was cooled at −78 °C whereupon $SiCl_4$ (1 mmol), the aldehyde (1 mmol) and TMSOF (1 mmol) were added. The mixture was stirred at −78 °C for the time indicated in Tables 1 and 2. The reaction was then quenched with $NaHCO_3$ saturated solution (2 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The combined organic phases were washed with brine (5 ml), dried over Na_2SO_4 and concentrated *in vacuum*. The crude mixture was than purified by flash chromatography, to yield products **3** as diastereoisomeric mixtures.

4.3. General procedure for the synthesis of phosphoramides 6a–c

To a solution of 3 mmol of chiral oxazolidin-2-one in 6 ml of dry THF under argon at 0 °C was added dropwise 129 μl (2.5 M in hexane, 3.2 mmol) of *n*-butyllithium over a 10-min period. The resultant suspension was stirred at 0 °C for 10 min and then *N*,*N*,*N*′,*N*′-tetra methylphosphorodiamidic chloride was added dropwise over a period of 5 min. The reaction mixture was stirred at 20 °C overnight, quenched by the addition of 8 ml of saturated aqueous NH_4Cl and extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuum*. The crude mixture was then purified by flash chromatography, yielding, respectively, 700 mg **6a**, 534 mg **6b** and 712 mg **6c** of a white solid.

Compound **6a**: Anal. Calcd for: $C_{14}H_{22}N_3O_3P$: C, 54.01; H, 7.12; N, 13.50; P, 9.95. Found: C, 54.12; H, 7.09; N, 13.47; P, 9.90. $[\alpha]_D = -44.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.34–7.25 (m, 5H); 4.48–4.44 (m, 1H); 4.18–4.10 (m, 2H); 3.49–3.45 (dd, 1H, $J_1 = 3.4$ Hz; $J_2 = 12.8$ Hz); 2.82 (s, 3H); 2.80 (s, 3H); 2.79 (s, 3H); 2.76 (s, 3H); 2.68–2.64 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 156.4; 135.9; 129.4 (2C); 128.8 (2C); 127.0; 67.1; 58.3; 40.3; 36.5 (4C).

Compound **6b**: Anal. Calcd for: $C_{14}H_{22}N_3O_3P$: C, 54.01; H, 7.12; N, 13.50; P, 9.95. Found: C, 54.10; H, 7.16; N, 13.42, P, 9.89. $[\alpha]_D = +0.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.49–7.31 (m, 5H); 5.06 (d, 1H, $J = 3.2$ Hz); 4.25–4.24 (m, 1H); 2.78 (s, 3H); 2.75 (s, 3H); 2.64 (s, 3H), 2.62 (s, 3H); 1.58 (d, 3H, $J = 6.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 156.0; 138; 128.9 (2C); 128.8; 125.0 (2C); 82.5; 60.6; 36.5 (2C); 36.4 (2C); 21.6.

Compound **6c**: Anal. Calcd for: $C_{13}H_{20}N_3O_3P$: C, 52.52; H, 6.78; N, 14.13; P, 10.42. Found: C. 52.58; H, 6.76; N, 14.16; P, 10.39. $[\alpha]_D = +11.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.45–7.33 (m, 5H); 5.20 (dd, 1H, $J_1 = 2.3$ Hz; $J_2 = 8.8$ Hz); 4.66 (t, 1H, $J = 8.8$ Hz); 4.38 (dd, 1H, $J_1 = 2.3$ Hz; $J_2 = 8.8$ Hz); 2.68 (s, 3H); 2.65 (s, 3H); 2.24 (s, 3H); 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 156.3; 140.7; 128.9 (2C); 128.7; 127.0 (2C); 70.5; 60.2; 36.3; 36.2; 35.9; 35.8.

Compound **3a**–**f**: Gave spectral and analytical data according to the literature.[15]

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