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A new procedure for the enantioselective vinylogous aldol reaction of Chan's diene

Rosaria Villano,* Maria Rosaria Acocella, Antonio Massa, Laura Palombi and Arrigo Scettri*

Dipartimento di Chimica, Università di Salerno, 84084 Fisciano (Salerno), Italy

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Abstract—Chiral δ-hydroxy-β-ketoesters are easily available through the enantioselective vinylogous aldol reaction of Chan's diene promoted by a $SiCl_4$/chiral phosphoramide catalytic system. The procedure is conveniently exploited for a very rapid approach to (+)-kavain, a natural bio-active α-pyrone compound.
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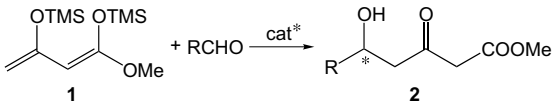
1. Introduction

Over the last few years, the nucleophilic properties of Chan's diene **1**,[1] a synthetic equivalent of acetoacetate dianion, have been widely exploited in a variety of procedures for C–C bond formation, leading to δ-hydroxy-β-ketoesters, γ-alkylidenebutenolides, 2-alkylidenetetrahydrofurans, functionalized cyclopent-2-en-1-ones, 6-methoxybicyclo [4.3.0]non-9-en-8-ones, methyl 2-hydroxybenzoate, tetraline derivatives, 4,5-benzotropones, oxabicyclo-[3.2.1]octan-3-ones, anthraquinones, etc.[2]

2. Results and discussion

Chiral aldols of type **2** (Scheme 1), key-intermediates in the synthesis of important bio-active natural and unnatural products,[3] proved to be easily accessible through a highly efficient and enantioselective modification of the original Sato's procedure, based on the use of Ti(O*i*Pr)$_4$/BINOL complexes, as catalysts.[4] Furthermore, the detection of positive nonlinear effects allowed the attainment of chiral aldols **2** in high yields and enantiomeric excesses (ees) by using enantioenriched Ti(O*i*Pr)$_4$/BINOL catalysts.[5]



Scheme 1.

More recently, our interest was focused on the reactivity of silyloxydiene **1** in the presence of non-metallic catalysts and $SiCl_4$, a very poor Lewis acid, which proved to be capable of promoting the conversion **1** → **2** in very satisfactory way, so that, for example, benzaldehyde, submitted to treatment with **1** for 10 min in the presence of $SiCl_4$ (1 equiv) in CH_2Cl_2 solution at −78 °C, afforded vinylogous aldol **2a** (R = –Ph) in >99% yield.[6]

Less nucleophilic reagents than silyloxydiene **1** (such as silyl ketene acetals, enolsilanes, dioxanone-derived silyl dienolate, amide-derived silyl enol ethers) have been conveniently employed by Denmark in an impressive series of procedures[7] for highly enantioselective C–C bond formation *previa* activation of $SiCl_4$ with suitable chiral ligands.

In particular, the $SiCl_4$/(*R*,*R*)-**3** system (Fig. 1) was recently found to promote the vinylogous aldol reaction of linear

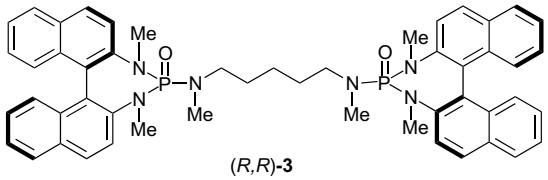


Figure 1.

* Corresponding authors. Tel.: +39 089969583; fax: +39 089969603; e-mail addresses: rvillano@unisa.it; scettri@unisa.it

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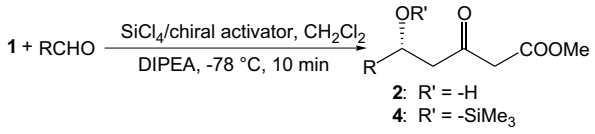
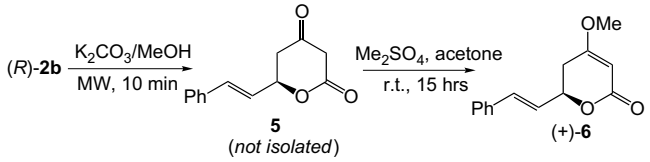


Scheme 2.



Scheme 3.

and cyclic silyloxydienes (deriving, respectively, from unsaturated esters, ketones, amides and 2,2,6-trimethyl-4*H*-[1,3-dioxin]-4-one)[7j,k,m] with complete γ-selectivity, high yields and moderate to high ees.

From a general point of view, the occurrence of a competing background reaction in a relevant way can represent a serious disadvantage for the achievement of an enantioselective process. Nevertheless, an investigation was devoted to verify the possibility of employment of $SiCl_4$/chiral activator systems, as catalysts in asymmetric reactions of type **1** → **2**.

Keeping in mind recent reports on related topics pointing out the capability of achiral and chiral sulfoxides to increase the catalytic properties of $SiCl_4$, the reactivity of a $SiCl_4$/(*R*)-*p*TolSOMe system was examined.

In the preliminary phase, benzaldehyde was chosen as the representative substrate and submitted to a reaction with **1** under the experimental conditions reported in Scheme 2 and Table 1. However, in spite of a rather satisfactory efficiency, the vinylogous aldol **2a** was isolated in racemic form (entry 1). The same result was obtained by using a reduced amount of $SiCl_4$ in the attempt to limit the occurrence of the competing background reaction (entry 2). Moreover, poor yields and ees were observed by performing the reaction in THF (entry 3).

More interesting results were afforded by the activation of $SiCl_4$ with the chiral bis-phosphoramide **3**: in fact, in the presence of only 0.01 equiv of **3** (with respect to aldehyde), the benzaldehyde was converted into a mixture of **2a** and *O*-trimethylsilyl protected aldol **4a** in very high overall yield (97%) and satisfactory ee, especially in consideration of the strongly competing background reaction. As already reported in a previous paper, the deprotection of **4a** to **2a** can be performed by acidic treatment with quantitative yield and no loss of enantiomeric excess.

Other aromatic, heteroaromatic and α,β-unsaturated aldehydes were submitted to the same treatment as benzaldehyde in entry 4 (entries 5 and 7–9) and moderate to high yields and ees were obtained. As shown in entry 6, an attempt to enhance the level of enantioselectivity by using greater amounts of chiral ligand (0.025 equiv) proved to be unsuccessful, since aldol **2b** was isolated in comparable yield, but in lower ee (69%) than in entry 5.

However, the result obtained in entry 5 was exploited for a new approach to (+)-kavain **6**,[10,11] a member of a family of natural products isolated from the Kava plant, known as kavalactones and characterized by anxiolitic and soporific properties.

Through a convenient modification of a known procedure,[11] involving in the first step (Scheme 3) a very rapid process of lactonization carried out under microwave (MW) irradiation, (*R*)-**2b** (75% ee) was converted into the easy enolizable ketolactone **5**. Next, the typical enol-etherification by Me_2SO_4 treatment on crude **5** afforded (+)-kavain **6** with an unchanged ee (75% ee) in 75% overall yield from (*R*)-**2b** and in only two steps from cinnamaldehyde.[12]

Table 1. Enantioselective vinylogous aldol addition realized via Scheme 2[8]

Entry	R	Activator	Product	Yield[a] (%)	ee[b] (%)
1[c]	Ph	(*R*)-*p*TolSOMe	**2a**	76 (−)	0
2[d]	Ph	(*R*)-*p*TolSOMe	**2a**	52 (−)	0
3[e]	Ph	(*R*)-*p*TolSOMe	**2a**	43 (−)	22
4	Ph	(*R*,*R*)-**3**	**2a**	67 (30)[f]	67
5	PhCH=CH	(*R*,*R*)-**3**	**2b**	60 (24)[f]	75
6	PhCH=CH	(*R*,*R*)-**3**	**2b**	62 (26)[f]	69
7	*p*-$MeOC_6H_4$	(*R*,*R*)-**3**	**2c**	61 (8)[f]	95
8	3-Furyl	(*R*,*R*)-**3**	**2d**	61 (−)	75
9	2-Furyl	(*R*,*R*)-**3**	**2e**	80 (−)	54

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by spectroscopic data. In all entries aldehyde/**1**/$SiCl_4$/chiral activator/DIPEA 1/1.2/1.1/0.01/1.1 ratios were used. The reaction was performed on 1 mmol of aldehyde.

[b] ees have been determined by chiral-phase HPLC analysis (CHIRALPAK AD, hexane/EtOH 95/5 + 0.1% TFA, 1 ml/min, $\lambda = 254$ nm). The (*R*)-configuration was assigned to all the aldols **2a**–**e** by comparing the signs of specific rotation with the ones reported in the literature.[4b,9]

[c] The experiment was performed by using 0.20 equiv of chiral sulfoxide.

[d] Reaction conditions: aldehyde/**1**/$SiCl_4$/chiral activator/DIPEA 1/1.2/0.2/0.2/0.2 ratios and 1 h/−78 °C.

[e] Reaction conditions: aldehyde/**1**/$SiCl_4$/chiral activator/DIPEA 1/1.2/0.2/0.4/0.2 ratios, THF and 3 h/−78 °C.

[f] Values in parentheses refer to the yields of trimethylsilyl-derivatives of type **4**.

3. Conclusion

In conclusion, in spite of the high reactivity of Chan's diene in aldol-type reactions promoted by $SiCl_4$, the appropriate combination of $SiCl_4$/chiral phosphoramide proved to be important for the achievement of an enantioselective approach to vinylogous aldols **2** in good yields and moderate to high ees.

By this procedure, a completely transition metal-free synthetic sequence allowed the rapid and convenient access to (+)-kavain, a bio-active natural product belonging to a family of α-pyrone derivatives.

Acknowledgement

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8. *General procedure for the preparation of compounds* **2** (Table 1): In a dry round bottom flask, a solution of ligand (*R*,*R*)-**3** (0.01 mmol) in CH_2Cl_2 (3 ml) was prepared. This solution was cooled at −78 °C and after 10 min DIPEA (1.1 mmol), aldehyde (1 mmol), $SiCl_4$ (1.1 mmol) and a solution of diene **1** (1.2 mmol) in CH_2Cl_2 (1 ml) were added dropwise. The resulting mixture was stirred for 10 min at −78 °C, then it was neutralized by the addition of saturated aq $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 and the combined organic phase dried over $MgSO_4$ and concentrated. The residue was purified by non-flash chromatography ($CHCl_3$/Et_2O 9/1) to give products **2**. The silylated aldol, when present, was subjected to deprotection by treatment with TFA at −78 °C according to Carreira's procedure.[13]
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12. *General procedure for the preparation of (+)-kavain:* Aldol (*R*)-**2b** (0.4 mmol, ee = 75%), K_2CO_3 (0.8 mmol) and MeOH (2 ml) were placed in an ACE pressure tube and submitted to MW-irradiation in a kitchen oven for 10 min. Then, the mixture was diluted with acetone (2 ml) and Me_2SO_4 (0.8 mmol) was added. The suspension was stirred overnight. The reaction mixture was neutralized by the addition of 1 M HCl and extracted with AcOEt. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by non-flash chromatography (petroleum ether/AcOEt 1/1) to give product (+)-**6** (whose structure was confirmed by spectroscopic data) with unchanged ee (75% ee) in 75% overall yield from (*R*)-**2b**.
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