Highly functionalised cyclohexa-1,3-dienes by sulfonyl Nazarov reagents

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ABSTRACT

The Hayashi–Jørgensen organocatalyst has made possible a sulfonyl Nazarov analogue reagent to give a Diels–Alder reaction at the double bond, without involving the activated methylene affording chiral highly functionalised cyclohexa-1,3-dienes.

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1. Introduction

The chemistry of Nazarov reagents has increased in the last years due to their versatility and possibility to be excellent starting materials for the synthesis of biologically active compounds.[1] The sulfone group, both as a powerful electron withdrawing group and as an easily removable substituent,[2] is ideal for the substitution of the carboethoxymethyl group in the Nazarov reagent. Sulfone and sulfoxide analogues of Nazarov reagents have been used as dienophiles in asymmetric Diels–Alder reactions with dienes and employing a chiral metallic Lewis acid as catalyst or in anionic polycyclisations.[3] In our group, the reactivity of Nazarov reagent **1** has been developed in a divergent manner for diversity oriented syntheses (Scheme 1).[4,5] The interest of a compound like **1** is, besides the fact that it can act as a Nazarov reagent, the extra functionality provided by the hydroxyl group, which can be further employed for the synthesis of diversity oriented compounds or as a linker in solid support chemistry.[6] It was observed that employing organocatalyst **I** and L-Proline in a tandem reaction different cyclohexenones **A** were obtained diastereoselectively.[4] On the other hand, using L-Proline or derivatives, MacMillan catalysts, thioureas or even chiral phosphoric acids in the reaction of **1** with
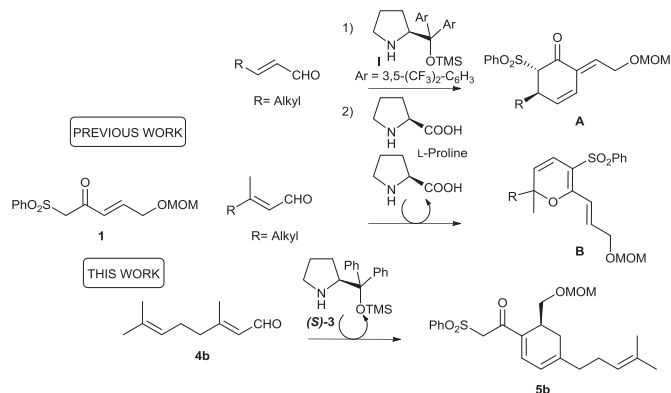
Scheme 1. Reactivity of Nazarov reagent **1** with unsaturated aldehydes and prenal derivatives.

β,β-disubstituted aldehydes, racemic pyrans **B** were obtained instead of the cyclohexenone ring (Scheme 1).[5]

Monosubstituted unsaturated aldehydes have been widely used in organocatalysis for the synthesis of very interesting compounds.[7] However, β-methyl-β-disubstituted unsaturated aldehydes have been much less used in organocatalysis. Prof. Serebryakov et al. have developed the asymmetric synthesis of cyclohexa-1,3-dienes from prenal and unsaturated esters or derivatives,[8] Watanabe et al., using Proline as organocatalyst, made citral to dimerise through a Diels–Alder reaction[9] and Christmann

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et al. reported an intramolecular Rauhut–Curier-type reaction via dienamine activation.[10] We realised that neither us, nor Prof. Serebryakov had employed the Hayashi–Jørgensen organocatalyst.[11] Thus, we decided to test the reactivity of sulfone **1** with citral **4b** using organocatalyst (*S*)-**3**. To our delight the reaction worked and surprisingly led to a new structure, namely cyclohexa-1,3-dienes, instead of cyclohexenones or pyran rings, constituting the first time that a Nazarov reagent acts as dienophile using organocatalysis (Scheme 1). This fact gives an idea that organocatalysis is still an undeveloped area and that a reaction can be diversely directed just by tuning the organocatalyst used.

2. Results and discussion

Cyclohexa-1,3-dienes and their derivatives are structurally important since they are versatile intermediates for the synthesis of natural products and biologically active compounds.[12] We started our study (Table 1) using commercially available 3-methyl-butenal **4a** and sulfone **2** since, as we previously demonstrated,[4,5] it behaves exactly the same as **1** but the tetrahydropyranyl (THP) protecting group is much more easily removable.

Table 1
Reaction of Nazarov reagent **2** with **4a**[a]
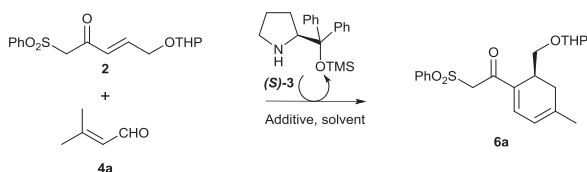
Entry	2/4a Ratio	Additive (20 mol %)	Solvent	Time[b]	Yield[c] (%)
1	2/1	—	2-Propanol	47 h	42
2	1/2	—	2-Propanol	44 h	49
3	2/1	B.A.	2-Propanol	47 h	50
4	2/1	BinapOH	2-Propanol	46 h	27
5	2/1	*p*-TsOH	2-Propanol	40 h	13
6	2/1	Na$_2$CO$_3$	2-Propanol	7 days	17
7	2/1	K$_2$CO$_3$	2-Propanol	6 days	31
8	2/1	CsCO$_3$	2-Propanol	2 days	60
9	2/1	LiOAc· H$_2$O	2-Propanol	3 days	65
10	2/1	NaOAc	2-Propanol	6 days	63
11	2/1	FeCl$_3$·6H$_2$O	2-Propanol	42 h	S.M.
12	2/1	ZnCl$_2$	2-Propanol	47 h	S.M.
13	2/1	—	Hexane	80 h	23
14	2/1	—	Toluene	79 h	66
15	2/1	—	CH$_2$Cl$_2$	74 h	67
16	2/1	—	CHCl$_3$	71 h	73
17	2/1	—	Et$_2$O	30 h	26
18	2/1	—	THF	46 h	32
19	2/1	—	MeOH	56 h	DEC
20	2/1	—	EtOH	49 h	75[d]
21	1/2	—	EtOH	24 h	40
22	1/1	—	EtOH	45 h	7
23	**2/1**	**B.A.**	**EtOH**	**48 h**	**79**[e]

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in the corresponding solvent at 0.18 M and 50 mol % (*S*)-**3**.
[b] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).
[c] Isolated yield after chromatography on silica gel.
[d] 89% ee determined by HPLC.
[e] 92% ee determined by HPLC. B.A.=benzoic acid. BinapOH=(*S*)-(+)-1,19-binaphthyl-2,29-diyl hydrogen phosphate. S.M.=Starting Material. DEC=decomposition.

A screening of different sulfone/aldehyde ratios, solvents and additives was carried out in order to test the importance of the β-substituent.

As shown in Table 1, the sulfone/aldehyde ratio did not change the reaction yield substantially, (entries 1 and 2). Use of acid additives (entries 3–5) decreased yields comparing to initial

conditions except for benzoic acid (entry 3). Brønsted bases had similar effect, and although lithium or sodium acetate made a good improvement, the reaction time increased (entries 6–10). Lewis acids did not produce any reaction (entries 11 and 12). Solvent screening (entries 13–20) proved EtOH to be the best solvent. After testing the sulfone/aldehyde ratio (entries 21 and 22) and the use of benzoic acid (entry 23) we found the best conditions were a sulfone/aldehyde ratio of 2/1 and 20% of benzoic acid in EtOH. The ee was measured for the best conditions (entries 20 and 23) observing that the use of benzoic acid slightly increased the yield and the enantiomeric excess (ee) as before. Finally we carried out a study of catalyst loading (Table 2), finding that a 50 mol % catalyst was the optimum amount needed for the best yield and ee. The absolute stereochemistry was determined by X-ray analysis of an analogue as shown later on.

Table 2
Catalyst load screening[a]

Entry	Catalyst (*S*)-**3** (mol %)	Yield[b] (%)	ee[c] (%)
1	5	S.M.	—
2	10	S.M.	—
3	20	39	89
4	**50**	**79**	**92**
5	100	75	90

Bold value signifies the best conditions with the best results found.
[a] All the reactions were carried out at rt, in EtOH at 0.18 M in 48 h, with a 2/1 ratio of **2**/**4a** and 20 mol % benzoic acid.
[b] Isolated yield of **6a** after chromatography on silica gel.
[c] ee determined by HPLC analysis, carried out on a CHIRALCEL IC column; *n*-hexane/2-propanol [60/40 (v/v)]; flow rate: 1.0 mL/min.

Once the best conditions were established for this reaction, several β,β-alkylsubstituted aldehydes **4a**–**f**, were tested with differently protected sulfones **1** and **2** (Table 3).

When sulfone **1** was used, yields were from moderate to good except for compounds **5c** and **5e** (entries 3 and 5) due to a possible oxo-Michael reaction.[13] The enantiomeric excess in all cases vary from good to excellent. Similar behaviour was observed when using sulfone **2**. In this case and in order to corroborate the obtained results, enantiomeric catalyst (*R*)-**3** was used (entries 7, 9 and 13) obtaining the corresponding enantiomers with similar ee, adding more versatility to this procedure.

It can be concluded that when both β-substituents are alkyl groups, cyclohexa-1,3-diene derivatives **5/6** are obtained from low to good yields (16–79%) and in good to excellent ee (75–92%).

Compounds **5/6** obtention can be understood through a Diels–Alder mechanism between dienamine **II** formed between the catalyst and the α,β-unsaturated aldehyde,[14] and the Nazarov reagent acting as dienophile similarly as in the cases of Prof. Serebryakov et al.[8] It is noteworthy that in this reaction the diene is established with the methyl group and not with the methylene group as in the case of the Rauhut–Curier-type reaction of Christmann et al. (Fig. 1).[10a] Intermediate **III** is demonstrated by NMR and HRMS experiments and observed its slowly transformation into the final products.

With these results in hand we decided to test the behaviour when one of the alkyl groups is changed to an aromatic ring. Using Nazarov reagent **2** with different aromatic aldehydes under the same conditions, cyclohexa-1,3-dienes **7** were formed instead of cyclohexa-1,3-dienes **6** (Table 4). The stereochemistry at the new chiral centre in **7** is proposed to come from a 1,5-*H* sigmatropic rearrangement, since the formation of the same intermediate **III** is observed with both aliphatic and aromatic substituents. As shown in Table 4, yields and enantiomeric excesses are good in all cases.

In order to see the value of this reaction, different compounds in a diversity oriented strategy were obtained. Compound **5a** was submitted to oxygen atmosphere and direct sunlight using Rose