The organocatalytic addition of bis(arylsulfonyl)methane to α,β-unsaturated aldehydes and the synthesis of optically-enriched 3-methyl-alkanols†

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An indirect organocatalytic method for the β-methylation of α,β-unsaturated aldehydes that involves the addition of bis(arylsulfonyl)methane catalyzed by prolinol derivatives and further elimination of the chameleonic sulfonyl groups is presented.

In the last few years, organocatalysis has proved to be a powerful tool in the development of a large number of enantioselective reactions.[1] Among them, asymmetric 1,4-conjugate addition has emerged as a powerful strategy to easily obtain chiral organic compounds.[2] In this field, covalent strategies have mainly been used for the β-functionalization of α,β-unsaturated aldehydes.[3] These processes are usually based on the activation of the carbonyl group by the formation of iminium ions with chiral amines,[3] which react with doubly-activated methylenes such as β-ketoesters.[3b] Despite the large number of reactions describing the β-functionalization of α,β-unsaturated aldehydes, the introduction of simple alkyl groups has never been reported. The importance of the problem has a special significance in the case of methylation. 3-Methyl-alkanols, obtained by the β-methylation of α,β-unsaturated aldehydes and subsequent reduction, are themselves important pheromones,[4] building blocks[5] or are directly implicated in the synthesis of various different terpenoids in the fragrance industry.[6] These compounds are currently prepared from citronellal by various different synthetic sequences involving a large number of steps.[7]

Taking advantage of the chameleonic ability of sulfones to be transformed into different functionalities,[8] they have been used in enamine-type organocatalysis. Thus, starting in 2005, Alexakis *et al.* published the reaction of aldehydes with α,β-unsaturated bis-sulfones catalyzed by *N-i*-Pr-2,2′-bipyrrolidine.[9] Interestingly, in 2008–2009, the groups of Palomo,[10a] Alexakis[10b] and Lu[10c] independently published the addition of aldehydes to vinyl-bis-sulfones catalyzed by silyl-biaryl prolinol ethers[11] (Scheme 1), affording α-functionalized aldehydes in high enantiomeric excesses. In all of these cases, the electrophiles were activated by the sulfonyl group, which could be transformed (or simply removed) at the end of the sequence, converting the obtained compounds into alkyl derivatives (Scheme 1).

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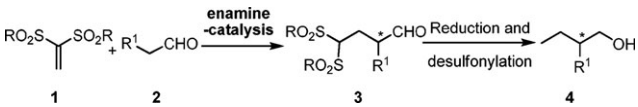
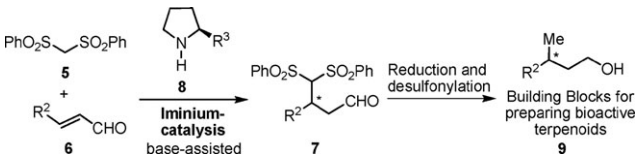
The same strategy could be used for introducing alkyl groups at the β-position of α,β-unsaturated aldehydes **6**. Surprisingly, the reactions of bis(arylsulfonyl)methanes **5** as nucleophiles with α,β-unsaturated aldehydes catalyzed by proline derivatives have never been reported. In this work, we present the first organocatalytic asymmetric addition of bis(phenylsulfonyl)methane to α,β-unsaturated aldehydes, and their subsequent reduction and desulfonylation to obtain 3-methyl-1-alkanoles (Scheme 2).



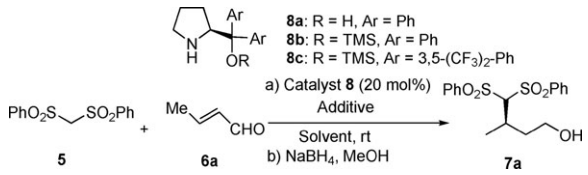
Scheme 1 The α-functionalization of aldehydes with α,β-unsaturated bis-sulfones.



Scheme 2 The organocatalytic enantioselective approach of this work.

When we tried the reaction of aldehyde **6a** with bis(phenylsulfonyl)methane (**5**) catalyzed by proline derivative **8a** (entry 1, Table 1), we did not observe any change in the reaction mixture. This would explain the absence of references concerning this topic. Taking into account the similar pK_a[12] value for **5** (12.2) and β-ketoesters (~14.2), the scarce reactivity of the bis(arylsulfonyl)methane was intriguing and we decided to investigate. The only reason to explain the different reactivity of β-ketoesters and bis-sulfones with α,β-unsaturated aldehydes must be related to the equilibration of the esters with their enolic forms, which are weak nucleophiles that are able to react with the iminium intermediates. A similar process is not possible with bis-sulfones, and a significant amount of α-sulfonyl carbanion must not be generated under standard iminium catalytic conditions (usually performed in the presence of weak acids such as $PhCO_2H$ or AcOH). These latter conditions were also unfruitful, as applied to the reaction of **5** with **6a** (entry 2, Table 1). This fact suggests that reactions could be possible in the presence of an appropriate base that is able to deprotonate the methylenic proton of **5** and be compatible with the organocatalytic reaction. Surprisingly, the addition of LiOAc[13] allowed us to detect the desired

Table 1 The screening of various reaction conditions[a]



Entry	Catalyst	Additive	Solvent	Yield (%)	er[b]
1	**8a**	—	CH_2Cl_2	nr	—
2	**8a**	$PhCO_2H$	CH_2Cl_2	nr	—
3	**8a**	—	CH_2Cl_2	5<	—
4	**8b**	—	CH_2Cl_2	nr[c]	—
5	**8b**	LiOAc	CH_2Cl_2	60	75 : 25
6	*ent*-**8b**	LiOAc	CH_2Cl_2	42	24 : 76
7	**8b**	LiOAc	Toluene	nr[c]	—
8	**8c**	LiOAc	CH_2Cl_2	50	85 : 15
9	**8c**	$PhCO_2H$	CH_2Cl_2	nr[c]	—
10	**8c**	AcOH	CH_2Cl_2	nr[c]	—
11	**8c**	LiOAc	$CHCl_3$	50	85 : 15
12	**8c**	LiOAc	EtOH	50	82 : 18
13	**8c**	LiOAc	CH_3CN	5<	nd[d]
14	**8c**	LiOAc	H_2O	nr[c]	—
15	**8c**	LiOAc	THF	68	85 : 15
16	**8c**	LiOAc	THF	95[e]	90 : 10

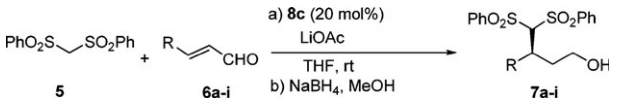
[a] Performed at room temperature with **5** (0.20 mmol), **6a** (0.40 mmol), catalyst **8** (20 mol%), additive (100 mol%) and solvent (0.2 mL) in each case. [b] Enantiomeric ratio determined by chiral stationary phase HPLC. [c] No reaction. [d] Not determined. [e] Reaction performed at 0 °C.

addition product in the crude mixture,[14] although the conversion was very low (entry 3, Table 1). The reaction with the catalyst's TMS derivative, **8b**, was also unfruitful in the absence of base (entry 4, Table 1), but the addition of LiOAc afforded **7a** in a 60% yield as a 75 : 25 mixture of enantiomers (entry 5, Table 1). Interestingly, a similar result was obtained when this reaction was catalyzed by *ent*-**8b**; the alkanol enantiomer (*ent*-**7a**) was obtained with a similar result (entry 6, Table 1). The reaction did not work by using toluene instead of CH_2Cl_2 as the solvent (entry 7, Table 1).

The best stereoselectivity was obtained by using the bulkier catalyst, **8c**,[11] in CH_2Cl_2 (50% yield and 85 : 15 er; entry 8, Table 1). With this catalyst, the addition of AcOH or $PhCO_2H$, which usually improves other catalytic processes *via* iminium ions, had a negative influence (entries 9 and 10, Table 1). The choice of solvent therefore seems to be very important. Thus, results in $CHCl_3$ or EtOH (entries 11 and 12, Table 1) were similar to those obtained in CH_2Cl_2, but the conversion was very poor in H_2O and CH_3CN (entries 13 and 14, Table 1). The best results were obtained in THF (entries 15 and 16, Table 1) with a 65% yield (85 : 15 er) at rt and a 95% yield (90 : 10 er) at 0 °C. Reaction times were longer (5 d) at 0 °C than at rt (3 d).

We then studied the reactions of alkyl aldehydes **6a–j** with **5** catalyzed by **8c**[11] under the optimized conditions of Table 1; the results are shown in Table 2. Starting from **6b**, the observed enantioselectivity at rt was substantially higher than that from **6a** (compare entries 1 and 2, Table 2). We also studied the reaction of **6b** at 0 °C (entry 2, Table 2), but the selectivity and yield remained unaltered (value in brackets of entry 2, Table 2), and the reaction time increased from 3 to 5 d.

Table 2 The scope of various unsaturated aldehydes[a]



Entry	R	Product	Yield (%)	ee (%)[b]
1	Me (**6a**)	**7a**	95	80[c]
2	Et (**6b**)	**7b**	92 (91)[c]	91 (91)[c]
3	Et (**6b**)	*ent*-**7b**	97	−90[d]
4	*n*-Pr (**6c**)	**7c**	96	90
5	*n*-Bu (**6d**)	**7d**	99	90
6	*n*-Pentyl (**6e**)	**7e**	83	96
7	*n*-Hexyl (**6f**)	**7f**	83	94
8	*n*-Nonyl (**6g**)	**7g**	73	96
9	*i*-Pr (**6h**)	**7h**	70	90
10	$PhCH_2CH_2$ (**6i**)	**7i**	63	90
11	Ph (**6j**)	**7j**	nr[e]	—

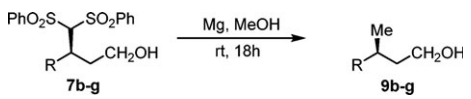
[a] Performed with **5** (0.20 mmol), **6** (0.40 mmol), LiOAc (100 mol%) and **8c** (20 mol%) as the catalyst in 0.2 mL of THF at rt. [b] Enantiomeric excess determined by chiral stationary phase HPLC. [c] Reaction performed at 0 °C. [d] *ent*-**8c** was used as the catalyst. [e] No reaction.

Consequently, we studied the behaviour of the rest of the aldehydes only at rt. When the size of the R group at the double bond of the aldehyde was larger, better enantioselectivities were observed (compare entry 1 with the other entries in Table 2). Interestingly, compound *ent*-**7b** (the enantiomer of **7b**) could be easily obtained by using catalyst *ent*-**8c** (entry 3, Table 2). Almost quantitative yields (91–99%) and high enantiomeric excesses (90–91%) were obtained from aldehydes **6b–d** (entries 2–5, Table 2), whereas the yield was slightly decreased (73–83%) and the stereoselectivity was increased in the reactions of **6e–6g** (94–96% ee; entries 6–8, Table 2). The results were analogously good for compounds with bulkier groups, such as **6h** (*i*-Pr; entry 9, Table 2) or **6i** ($PhCH_2CH_2$; entry 10, Table 2). Unfortunately, no reaction was observed for aromatic α,β-unsaturated aldehydes (entry 11, Table 2).

Elimination of the chameleonic sulfonyl group[8] in compounds **7** provides products corresponding to the β-methylation of the α,β-unsaturated aldehydes. In order to assign the configuration of compounds **7**, we transformed **7b** into 3-methylpentanol (**9b**) by a reaction with Mg/MeOH (entry 1, Table 3). The sign of the specific rotation of **9b** was the opposite of that reported for (*S*)-3-methylpentanol,[15] which supports the (*R*)-configuration of **9b** and therefore **7b**.[15] This configuration is the one expected by assuming the stereochemical models reported for the β-functionalization of α,β-unsaturated aldehydes catalyzed by **8**.[3,11]

The use of similar conditions should allow 3-methyl-1-alkanols to be obtained in high optical purity (the reaction conditions do not affect the chiral center). We have illustrated this possibility by preparing compounds that exhibit the most interesting features (entries 2–6, Table 3). Alkanol **9c** has been employed in the synthesis of the pheromone of the southern corn rootworm,[16] and was obtained in 40% yield. Interestingly, longer alkyl chains provided better yields (entries 3–6, Table 3). Thus, **9d** (R = *n*-Bu), used as a building block in the synthesis of HUN-7293[5c] and as intermediate in the

Table 3 Desulfonylation of various alcohols **7b–g**



Entry	R	Product	Yield (%)
1	Et (**7b**)	**9b**	51
2	*n*-Pr (**7c**)	**9c**	40
3	*n*-Bu (**7d**)	**9d**	92
4	*n*-Pentyl (**7e**)	**9e**	75
5	*n*-Hexyl (**7f**)	**9f**	87
6	*n*-Nonyl (**7g**)	**9g**	96

synthesis of different pheromones,[17] was obtained in 92% yield. An intermediate of the sex attractant of the yellow mealworm, **9e** (R = *n*-pentyl),[18] was obtained in 75% yield (entry 4, Table 3). Alcohol **9f** (R = *n*-hexyl), used as an intermediate in the synthesis of the sex pheromones of the western hemlock looper,[19a] of the red flour beetle[19b] and of some marine lipids,[19c] was obtained in 87% yield (entry 5, Table 3). Finally, **9g** (R = *n*-nonyl), which has been used in the synthesis of pheromones,[20] could be obtained in an almost quantitative yield (entry 6, Table 3). The present procedure for preparing all of these compounds involves two steps from commercially available materials, and therefore it is much more simple and efficient than those methods so far reported, usually requiring much longer synthetic sequences.

In conclusion, we report here the first organocatalytic additions of a bis(arylsulfonyl)methane, catalyzed by the diarylprolinol ether **8c** in the presence of LiOAc, to a wide-range of α,β-unsaturated aldehydes. The reactions take place with excellent yields and high enantioselectivities (up to 96% ee). Further *in situ* reduction and elimination of the sulfonyl groups provides an indirect method for the organocatalytic β-methylation of α,β-unsaturated aldehydes. This sequence allows the synthesis of highly important 3-methyl-1-alkanols in high optical purity from commercially available reagents.

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