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Formal Highly Enantioselective Organocatalytic Addition of Alkyl Anions to α,β-Unsaturated Aldehydes: Application to the Synthesis of Isotope-Enantiomers

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Dedicated to Professor Andrew E. Greene on occasion of his retirement

During the last decade, chemists have devoted much effort to the development of new asymmetric methodologies to build complex scaffolds in a highly enantioselective fashion.[1] Among the strategies employed, organocatalysis[2] has received widespread attention due to its unique properties such as metal-free environment, easy predictability of stereoselectivity, use of inexpensive catalysts, and simplicity of reaction conditions.

Since the work on proline catalysis by List, Lerner, and Barbas III in 2000[3] and that on iminium catalysis by MacMillan soon after,[4] organocatalysis has grown exponentially both by improving catalysts and by the discovery of new reactions. However, there are still a number of challenges and issues that lie ahead. One notable challenge is the use of "naked" methyl or alkyl synthons as suitable nucleophiles. The catalytic enantioselective conjugate addition of non-functionalized hydrocarbon fragments to α,β-unsaturated aldehydes is an unsolved problem in organic synthesis. Whereas in the past few years major breakthroughs have been realized in the metal-catalyzed enantioselective conjugate addition of Grignard reagents[5] and of other organometallic reagents[6] to α,β-unsaturated ketones, esters, or amides, only recently Bräse and co-workers reported on the asymmetric conjugate addition of diethylzinc to cinnamaldehyde, by using *N*,*O*-planar chiral [2.2]paracyclophane-derived ligands.[7]

In the field of organocatalysis there are several carbon nucleophiles that can be used to form C–C bonds with unsaturated aldehydes. For example, Jorgensen and co-workers developed the addition of malonate to unsaturated aldehydes in excellent yields and enantioselectivities.[8] Soon after, several research groups developed similar routes to furnish a wide range of interesting scaffolds.[9] Among them, we can highlight useful asymmetric additions of ketoesters,[10] nitroalkanes,[11] *N*-nucleophiles,[12] *S*-nucleophiles, and *O*-nucleophiles[13] to unsaturated aldehydes. In spite of the fact that the addition of new functionalities in a molecule can be advantageous, the removal of these functional groups can be difficult and sometimes demands a protection–deprotection approach to render the desired "naked" product.

To circumvent these disadvantages, we aimed to develop an easy method to add "naked" methyl or alkyl chains to unsaturated aldehydes. Bis(phenylsulfonyl)methane has been extensively used in organic chemistry. For example, in 1997 Trost and co-workers used bis(phenylsulfonyl)methane as a nucleophile in the palladium-catalyzed addition to alkenyl epoxides.[14] A recent application of this compound is its use as a fluoromethyl anion equivalent: bis(phenylsulfonyl)methane is easily fluorinated by treatment with NaH and Selectfluor, which furnishes fluorobis(phenylsulfonyl)-methane that can be used as a nucleophile in a broad range of reactions.[15] However, there are few examples of the use of bis(phenylsulfonyl)methane derivatives with unsaturated aldehydes. Moreover, it is worth noting that for α,β-unsaturated aldehydes, such as cinnamaldehyde, only 1,2-addition products have been obtained. Only very recently, in our research group we studied the addition of fluorobis(phenylsulfonyl)methane to α,β-unsaturated aldehydes, and obtained the Michael adducts with excellent yields and enantioselectivities.[16]

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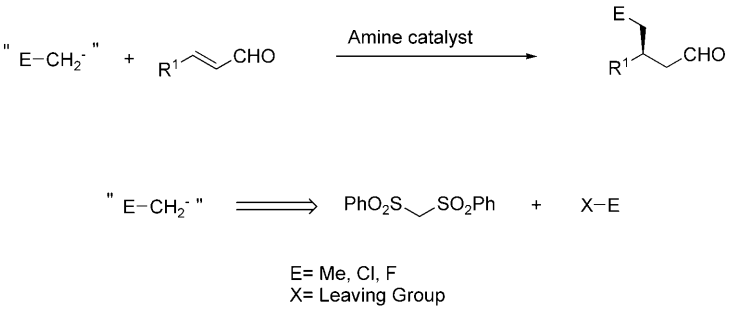
Spurred by these recent results, and taking into account the facile removal of the phenylsulfonyl moiety that makes this reactant a perfect choice to carry out the future conversion of the resulting compounds into attractive and interesting products for building blocks in medicinal chemistry, we decided to examine the use of bis(phenylsulfonyl)methane as a suitable nucleophile in the Michael addition to α,β-unsaturated aldehydes under asymmetric iminium catalysis (Scheme 1).

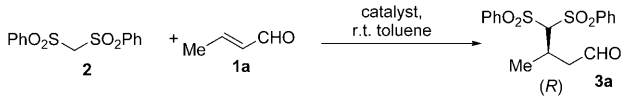


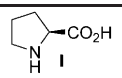
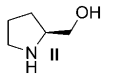
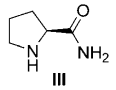
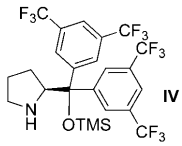
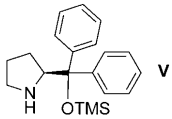
Scheme 1. General output of the reaction.

To our delight, this unprecedented reaction was efficiently catalyzed by chiral secondary amines, thus affording the corresponding Michael adducts in excellent conversions (Table 1). When crotonaldehyde (**1a**) was treated with bis(phenylsulfonyl)methane using proline (**I**) as a catalyst, the reaction led to the formation of the target Michael adduct **3a** with 7% conversion in 14 h (Table 1, entry 1). Moreover, when (+)-prolinol **II** was used as catalyst, the reaction rendered the Michael adduct in 93% conversion after 14 h and, more interestingly, with 54% *ee* (Table 1, entry 2). The best enantioselectivities were obtained when diphenyl prolinol derivatives were used. Catalyst **IV** afforded compound **3a** with 32% conversion and 70% *ee* after 14 h (Table 1, entry 3). The best catalyst was the trimethylsilyl(TMS)-protected (+)-diphenylprolinol **V** that showed full conversion after 14 h and produced **3a** with good enantioselectivity (85% *ee*, Table 1, entry 5).

Further optimization of temperature, solvent, and additives was performed, allowing us to conclude that the best conditions from the point of view of enantioselectivity were toluene as a solvent at −20°C as shown in Table 2.

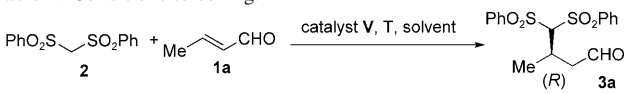
Table 1. Catalyst screening.[a]



Entry	Catalyst	Conversion (14 h) [%][b]	*ee* [%][c]
1	 **I**	7	n.d.
2	 **II**	93	−54
3	 **III**	traces	n.d.
4	 **IV**	traces	n.d.
5	 **V**	100	85

[a] In all cases, bis(phenylsulfonyl)methane (**2**) (1 equiv) was added to a solution of **1a** (1.5 equiv) and catalyst **I**–**V** (0.2 equiv) in toluene at room temperature; n.d. = not determined. [b] Determined by NMR spectroscopy. [c] Determined by chiral HPLC analysis.

Table 2. Conditions screening.[a]



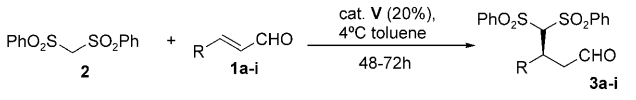
Entry	Solvent	Temperature	Additive	Conversion (14 h) [%][b]	*ee* [%][c]
1	toluene	RT	–	96	85
2	CH_2Cl_2	RT	–	97	50
3	AcOEt	RT	–	91	70
4	MeOH	RT	–	traces	n.d.
5	toluene	RT	Et_3N (1 equiv)	100	64
6	toluene	RT	PhCOOH (20 mol%)	100	77
7	toluene	4°C	–	100	88
8	toluene	−20°C	–	40	93

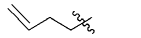
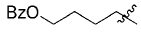
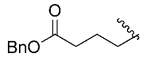
[a] In all cases, bis(phenylsulfonyl)methane (**2**) (1 equiv) was added to a mixture of **1d** (1.5 equiv) and catalyst (**V**) in the conditions specified in Table 2; RT = room temperature. [b] Determined by NMR spectroscopy. [c] Determined by chiral HPLC analysis.

With these optimized conditions in hand, we decided to examine the scope of this valuable methodology. The reaction took place in good yields and enantioselectivities when aliphatic unsaturated aldehydes were used (Table 3). For example, when 2-pentenal (**1b**) or 2-hexenal (**1c**) were treated with bis(phenylsulfonyl)methane (**2**) in toluene at 4°C and with 0.2 equivalents of catalyst **V**, the corresponding Michael adducts **3b** and **3c** were isolated in 74% and 81% yields, respectively, and more importantly, both in 99% *ee* (Table 3, entries 2 and 3). The scope of the reaction was further expanded by using different functionalities in the unsaturated aldehydes, rendering the Michael adducts in good yields and enantioselectivities (Table 3, entries 5, 6, 7, and 8). On the other hand, when cinnamaldehyde derivatives were used the reaction did not work, affording only, when more drastic conditions were used, the undesired 1,2-addition product (see the Supporting Information for details).

Once we had defined the scope of the reaction, and with a range of enantiomerically enriched β-(bisphenylsulfonylmethyl)aldehydes in our hands, we were in position to inves-

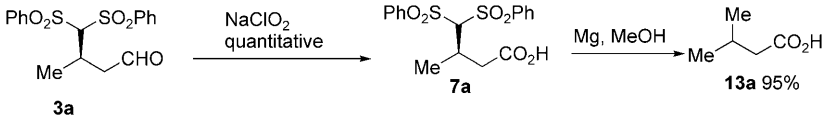
Table 3. Aldehyde scope.[a]



Entry	R	Compound	Yield [%][b]	*ee* [%][c] (Conf)
1[d]	Me	**3a**	90	93 (*R*)
2	Et	**3b**	74	99 (*R*)
3	*n*Pr	**3c**	77	99 (*R*)
4	*n*Bu	**3d**	79	90 (*R*)
5	CO_2Et	**3e**	74	94 (*R*)
6		**3f**	91	94 (*R*)
7		**3g**	72	97 (*R*)
8[e]		**3i**	61	91 (*R*)

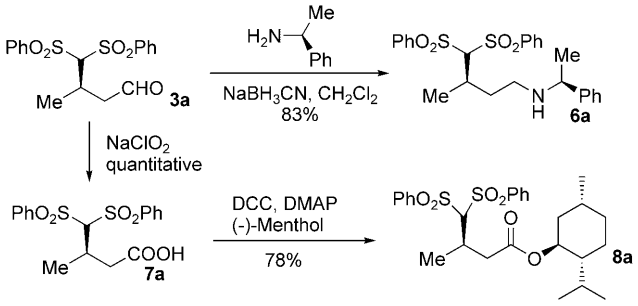
[a] In all cases, bis(phenylsulfonyl)methane (**2**) (1 equiv) was added to a mixture of **1a–i** (1.5 equiv) and catalyst **V** (0.2 equiv) in toluene at room temperature. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction performed at −20 °C. [e] determined by Mosher ester analysis.

tigate the reductive desulfonylation of compounds **3** to complete the sequence of enantioselective monomethylation. To show the viability of this sequence, we chose compound **3a**; the aldehyde was oxidized to the corresponding acid **7a**, which was subsequently treated with activated magnesium in methanol for the reductive removal of the sulfonyl groups. We obtained isoamylic acid **13a** in almost quantitative yield from the starting aldehyde **3a** (Scheme 2).



Scheme 2. Deprotection of addition products.

Furthermore, we synthesized different derivatives from **3a** to showcase the versatility of our method. We obtained amine **6a**, acid **7a**, and ester **8a** in excellent yields and in highly enantiopure form (Scheme 3).



Scheme 3. Synthetic transformations of product **3a**.

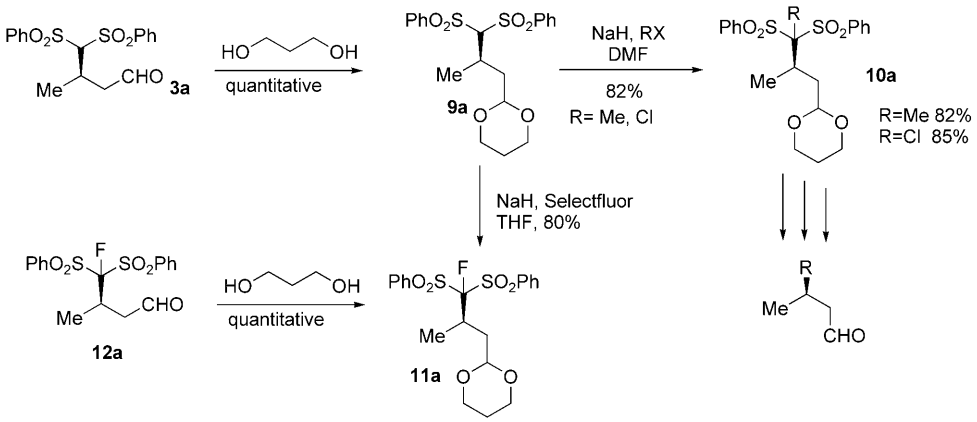
This methodology can be also regarded as an organocatalytic version of previous metal-based conjugate addition methodologies. As shown in Scheme 4, compound **3a** can be easily protected as the cyclic acetal **9a**; this compound can be deprotonated and subsequently reacted with an electrophile to afford a wide range of products (Scheme 4). This makes this methodology an efficient short-cut to highly enantiopure conjugate addition products that avoids the use of transition metals and chiral auxiliaries or ligands.

The absolute configuration of the obtained adducts was ascertained by chemical correlation (Scheme 4). Thus, compound **9a** was fluorinated by treatment with NaH and then with Selectfluor. Comparison of the optical rotation data of **11a** ($[\alpha]_D^{25}=+16.3$ ($c=1.2$, $CHCl_3$) with those obtained for material derived from the known compound **12a** ($[\alpha]_D^{25}=+15.6$ ($c=1.0$, $CHCl_3$)[16] revealed that the absolute configuration of this aldehyde **3a** was (3*R*). The absolute configuration of the remaining adducts **3b–i** was assigned by analogy.

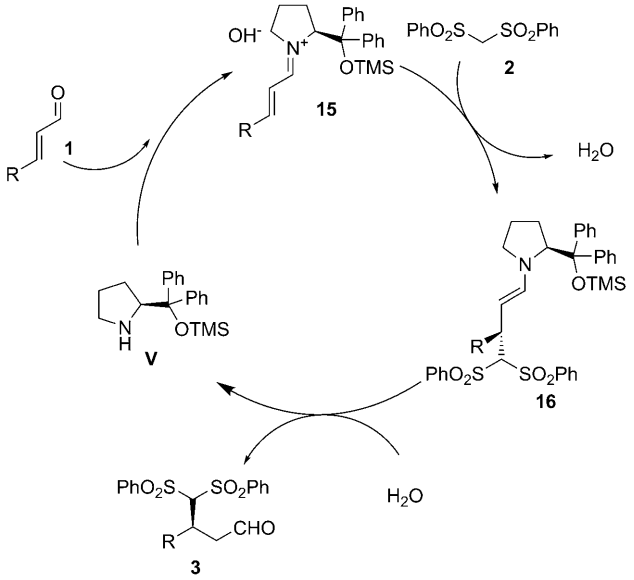
The stereochemical outcome of the reaction can be easily rationalized by the mechanistic proposal outlined in Scheme 5. Thus, efficient shielding of the *Re*-face of the chiral iminium intermediate **15** by the bulky aryl groups of **V** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **15**. This mechanism is in accordance with those proposed for other amine-catalyzed reactions between nucleophiles and enals.[17]

Both deuterium- and ^{13}C-labeled amino acids have found wide use in metabolite studies. For example, in 1980, Tanaka et al. described a metabolism study of valine in vitamin B12-folate deficiency in rats using valine chirally labeled with ^{13}C and deuterium.[18] In 1997, Meinwald synthesized L-(2*S*,3*S*)-4,4,4-[$^2H_3$]valine in eight steps in low overall yield, employing the Sharpless epoxidation of allyl alcohols as the source of chirality and using highly valuable deuterium starting materials.[19] Furthermore, the synthetic route only affords this diastereomer.

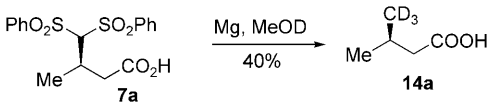
Very recently, Soai et al. reported on the use of cryptoenantiomers and/or of isotope-enantiomers as chirality inducers in the autocatalytic diisopropylzinc addition to pyrimidyl-5-carbaldehydes.[20] In this context, we examined the possibility of applying the present methodology to the synthesis of isotope-enantiomers. We envisaged an easy entry to deuterium-labeled compounds by simply using CD_3OD (a common NMR solvent) with magnesium in the desulfonylation step. To test this idea, we treated carboxylic acid **7a** in deuterated methanol and Mg, and obtained the chiral deuterolabelled compound **14a** in moderate yield (Scheme 6). This methodology allows us to synthesize both enantiomers of **14a** simply by changing the enantiomer of the catalyst. In addition, the use of ^{13}C-labeled bis(phenylsulfonyl)methane would result in the formation of the chirally ^{13}C-labelled compound **14a**. As described in the literature, **14a** could be



Scheme 4. Determination of absolute configuration and scope of the reaction.



Scheme 5. Proposed mechanism.



Scheme 6. Synthesis of chiral deutero-labeled isoamylic acid.

a convenient starting compound for synthesizing valine in an organocatalytic fashion by the α-amination protocol reported by List[21] and Jorgensen and co-workers[22] or by the method described by Aberhardt and Weiller[23] starting from isoamyl alcohol.

In summary, we have described a practical, inexpensive, and powerful methodology that constitutes an organocatalytic alternative for organometallic 1,4-additions. We have developed an asymmetric methyl or alkyl addition to α,β-unsaturated aldehydes with excellent yields and enantioselectivities. This versatile reaction can also be used in the synthesis of isotope-enantiomers, making this procedure highly valuable for the synthesis of interesting compounds for biological studies or for the investigation of autocatalytic asymmetric processes.

Experimental Section

In a vial, bis(phenylsulfonyl)methane (**2**) (74 mg, 0.25 mmol) and catalyst **V** (16 mg, 0.05 mmol) were added to toluene (2 mL). Next, unsaturated aldehyde **1a** (0.375 mmol, 1.5 equiv) was added and the reaction mixture was stirred at 4 °C overnight. The crude product was purified by column chromatography to afford the final compound **4a**.

Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): $\delta = 9.65$ (s, 1H), 7.90–7.83 (m, 4H), 7.70–7.61 (m, 2H), 7.57–7.47 (m, 4H), 4.77 (m, 1H), 3.28–3.12 (m, 2H), 2.92 (dd, $J_1 = 7.0$ Hz, $J_2 = 18.7$ Hz, 1H), 1.39 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz. $CDCl_3$): $\delta = 200.1$, 139.4, 138.9, 134.5, 134.4, 129.4, 129.1, 129.0, 85.2, 47.3, 28.0, 18.2 ppm; HRMS $[M+H]^+$: calculated for $[C_{17}H_{19}O_5S_2]^+$: 347.1254; found: 347.1255; $[\alpha]_D^{25} = +6.7$ ($c = 1.2$, $CHCl_3$, 93 % *ee*).

Acknowledgements

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Keywords: enantioselective addition · isotope effects · organocatalysis · sulfones · unsaturated aldehydes

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