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Enantioselective Organocatalytic Conjugate Addition of Aldehydes to Vinyl Sulfones and Vinyl Phosphonates as Challenging Michael Acceptors

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Abstract: Chiral amines with a pyrrolidine framework catalyze the enantioselective conjugate addition of a broad range of aldehydes to various vinyl sulfones and vinyl phosphonates in high yields and with enantioselectivities up to >99% *ee*. This novel process provides synthetically useful chiral γ-*gem*-sulfonyl or phosphonyl aldehydes which can be widely functionalized with retention of the enantiomeric excess. Mechanistic insights including DFT calculations are explored in detail.

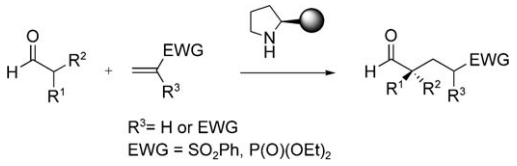
Keywords: aldehydes · amines · asymmetric synthesis · Michael addition · organocatalysis

Introduction

Besides transition-metal complexes and enzymes, organocatalysis is now well-recognized as a powerful tool for the preparation of optically active compounds.[1,2] The pioneering reports of the proline intermolecular aldol reaction[3] and iminium ion catalysis' concept[4] set the stage for an explosion of aminocatalysis over the last few years. Chiral secondary amines have proven to be effective aminocatalysts by covalently activating the carbonyl partners either via nucleophilic enamine or electrophilic iminium species.[5] Among the wide variety of methods available, the asymmetric conjugate addition (ACA) catalyzed by pyrrolidine analogues is of considerable importance for stereoselective C–C bond forming reactions.[6] Direct Michael addition of carbonyl donors via enamine activation represents a particularly attractive route, affording versatile functionalized adducts in an atom-economical manner. Several electron-withdrawing groups on the Michael acceptor, including nitro,[7,8] carbonyl,[7f,9] and ester,[7i,10] groups, have been successfully exploited in aminocatalysis. Nevertheless, expanding the scope of Michael acceptors still remains an important challenge.

In this context, after developing efficient 2,2′-bipyrrolidine and 3,3′-bimorpholine derivatives for ACA of aldehydes and ketones to nitroolefins,[8] we focused on less extensively explored vinyl sulfones and vinyl phosphonates due to their easy access from commercial sources and their potential for offering highly tunable chiral intermediates. In the past, considerable efforts have been devoted to the development of ACA to vinyl sulfones.[11,12] Although the reaction of preformed enamines with vinyl sulfones has been known for some time,[13] only sporadic examples lead to enantioenriched adducts,[14] and the use of organocatalysis in this area remains elusive.[15] Moreover, despite the great interest in vinyl phosphonates,[16] few reports describe the formation of chiral γ-phosphonate carbonyl compounds through ACA.[17] With a view to generalizing the scope of pyrrolidine-based catalysis, we have recently communicated the first enantioselective organocatalytic conjugate addition of aldehydes to vinyl sulfones[18] and to vinyl phosphonates[19] (Scheme 1).

Herein, we describe improved conditions and catalysts for these ACA, which result in higher yields and enantioselec-



Scheme 1. ACA of aldehydes to vinyl sulfones and vinyl phosphonates catalyzed by chiral amines.

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tivities for a broad range of aldehydes. In addition, the synthetic utility of optically active Michael adducts as useful chiral synthons is exemplified by various functionalizations. We also present mechanistic insights including DFT calculations for the N-*i*Pr-(2*S*,2′*S*)-bipyrrolidine (*i*PBP) catalyst.

Results and Discussion

The vinyl sulfones and vinyl phosphonates used for this study are compiled in Figure 1. Some of these compounds (**1**, **2**, **3**, **6**) were purchased from commercial suppliers; others (**4**, **5**, **7**) were prepared according to literature procedures (see Supporting Information).[20–22]

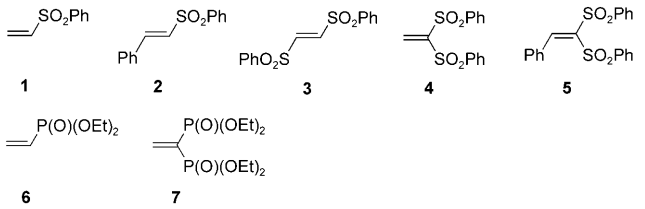
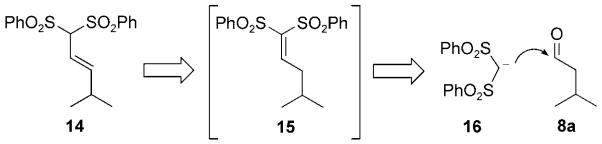


Figure 1. Vinyl sulfones **1**–**5** and vinyl phosphonates **6**, **7** studied.

Reactivity—mono-activated vs bis-activated vinyl sulfones: At the outset of our studies, we evaluated the reactivity of vinyl sulfones **1**–**5** towards catalytic conjugate addition. Isovaleraldehyde **8a** was selected as our model substrate due to its low tendency to do a self-aldol reaction and 25 mol% of pyrrolidine was used as the organocatalyst (Table 1). A large excess of aldehyde (10 equiv) was employed to force an equilibrium to favor the Michael adduct. Inspired by our previous work on nitroolefins,[8] chloroform was used as the solvent.

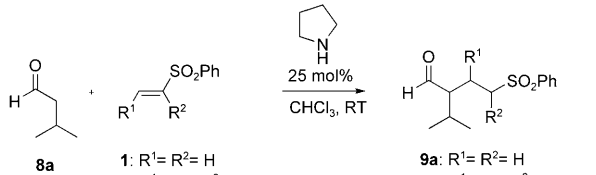
No or scarcely any reaction occurred with mono-activated vinyl sulfones **1**–**3** (entries 1–3) whereas complete conversion was achieved in 30 minutes with vinyl bis(sulfone) **4** in moderate yield (entry 4). This suggested that the reactivity of pyrrolidine-catalyzed conjugate addition of aldehydes requires geminal bis(sulfonyl) groups on the olefin.

In view of the investigation of the diastereoselectivity of the reaction, we were interested in β-substituted vinyl bis(sulfones). Owing to difficulties in the synthesis of β-alkyl vinyl bis(sulfones) due to their propensity to isomerize into the more stable allylic bis(sulfone),[23] we opted for grafting a phenyl appendage at the β-position through a modified Knoevenagel procedure.[24] Surprisingly, under pyrrolidine catalysis, β-phenyl bis(sulfone) **5** underwent a retro-Knoevenagel reaction, releasing bis(phenylsulfonyl)methane anion **16** which reacted with isovaleraldehyde **8a** to give allylic bis(sulfone) **14** after suitable isomerization (Table 1, entry 5, Scheme 2).



Scheme 2. Mechanism of formation of allylic bis(sulfone) **14**.

Table 1. Reactivity of vinyl sulfones **1**–**5**.



Entry	Vinyl sulfone	*t*	Product	Conv.[a] [%]	Yield[b] [%]
1	**1**	4 d	**7a**	0	–
2	**2**	4 d	**8a**	0	–
3	**3**	4 d	**9a**	<10	–
4	**4**	30 min	**10a**	100	53
5	**5**	30 min	**14**[c]	100	–

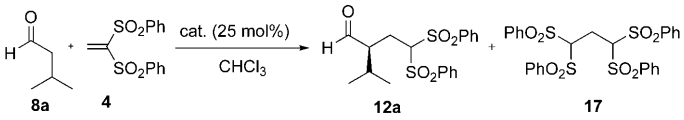
[a] Determined by ^{1}H NMR of the crude material. [b] Isolated yields after purification by column chromatography on silica gel. [c] For the formation of **14**, see Scheme 2.

We therefore focused our attention on vinyl bis(sulfone) **4** and performed an extensive screen of reaction conditions.

ACA of aldehydes to vinyl sulfones—Optimization of reaction conditions: The modest yield obtained previously (53%, Table 1, entry 4) could be explained by the formation of tetrasulfone by-product **17**, arising from 1,4-addition of bis(phenylsulfonyl)methane anion **16**, generated in situ, to vinyl bis(sulfone) **4** (Table 2 and Section on Mechanistic Insights) (Table 1, entry 4 vs Table 2, entry 1). Moreover, the sensitivity of γ-sulfonyl aldehyde **12a** also accounts for the precedent modest yield. Indeed, purification on silica gel (53% yield) gave unsatisfactory results whereas a significant improvement was observed by using Florisil (75% yield) Table 1, entry 4 vs Table 2, entry 1).

The stereochemical outcome was next examined by testing a range of pyrrolidine-core organocatalysts for the Michael reaction of isovaleraldehyde **8a** with vinyl bis(sulfone) **4**, with the results summarized in Table 2. We first found that decreasing the temperature to −60 °C gave higher enantioselectivity (entries 2–3 vs entry 4). It was also apparent that the selectivity of 2,2′-bipyrrolidine derivatives **18a**–**f** relies on the steric hindrance of the tertiary amine (entries 4–9). Either a primary group on the nitrogen such as N-Bn **18c** (entry 6) and N-Me **18d** (entry 7) or a too bulky group such as *N*-*c*Hex **18b** (entry 5) and *N*-3-pentyl **18e** (entry 8) were revealed to be unselective. Surprisingly, hydrochloride salt **18f** did not catalyze the reaction (entry 9). Moreover, the smaller the group, the higher the quantity of by-product **17**. Significantly, the proportion of tetrasulfone **17** becomes lower as the substituent becomes bulkier. Actually, the most interesting result from the 2,2′-bipyrrolidine

Table 2. ACA of isovaleraldehyde **8a** to vinyl bis(sulfone) **4**; catalyst screening.



8a (10 equiv) **4** **12a** **17**

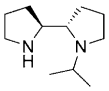
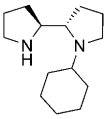
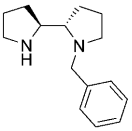
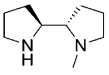
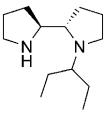
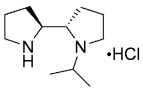
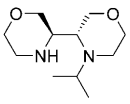
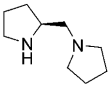
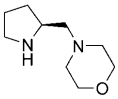
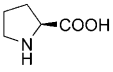
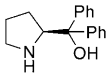
Entry	Catalyst	Reaction condition	Conv.[a] [%]	Yield[b] [%]	*ee*[c] [%]
1	 pyrrolidine	RT, 30 min	100	75 (19)[d]	–
2	 *i*PBP **18a**	RT, 30 min	100	65 (18)[d]	57
3		−30 °C, 1 h	100	62 (16)[d]	63
4	 **18b**	−60 °C, 2 h	100	71 (13)[d]	75
5		−60 °C, 2 h	100	43 (17)[d]	58
6	 **18c**	−60 °C, 2 h	100	27 (31)[d]	45
7	 **18d**	−60 °C, 2 h	100	23 (50)[d]	54
8	 **18e**	−60 °C, 2 h	100	69 (6)[d]	47
9	 **18f**	−60 °C, 2 h	0	–	–
10	 *i*PBM **18g**	−60 °C, 2 h	100	79 (0)[d]	55
11[e]	 **18h**	−60 °C, 2 h	100	25 (4)[d]	19
12	 **18i**	−60 °C, 2 h	100	38 (2)[d]	53
13[e]	 L-proline	−60 °C, 2 h	n.d.[f]	n.d.[f]	n.d.[f]

Table 2. (Continued)

Entry	Catalyst	Reaction condition	Conv.[a] [%]	Yield[b] [%]	*ee*[c] [%]
14	 **18j**	−60 °C, 2 h	0	–	–

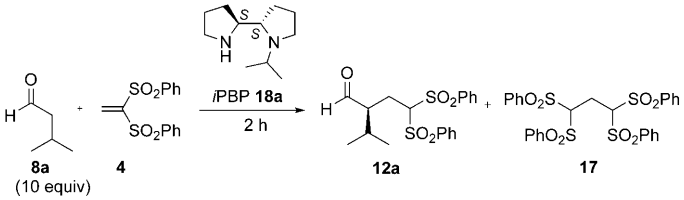
[a] Determined by ^{1}H NMR on the crude material. [b] Isolated yields after purification by column chromatography on Florisil. [c] *ee* values were determined by SFC. [d] Proportion of tetrasulfone by-product **17** determined by ^{1}H NMR of the crude material. [e] The reaction was sluggish and led to many by-products. [f] Not determined.

derivatives was obtained with the secondary *i*Pr group **18a** (71 % yield, 75 % *ee*) (entry 4). Replacement of the bicyclic five-membered ring by a six-membered ring prevented the formation of tetrasulfone **17** which improved the yield from 71 to 79 % but also decreased the enantioselectivity (entry 4 vs 10). Interestingly, mono-substituted pyrrolidinylmethyl diamines **18h**, and **18i** provided only traces of by-product **17** which stems from their low tendency to add to vinyl bis(sulfone) **4** (entries 11–12). However, diamines **18h** and **18i** gave Michael adduct **12a** in low yield (entries 11–12). In this series, the tertiary amine had to be composed of a morpholine moiety to achieve good enantioselectivity (entry 11 vs entry 12). Moreover, neither L-proline nor diphenylprolinol **18j** afforded the desired Michael adduct **12a** (entries 13–14). From these results, *i*PBP **18a** was found to be the best catalyst for the reaction (Table 2, entry 4).

Influence of the solvent as well as catalyst loading were next evaluated (Table 3). Chlorinated solvent ($CHCl_3$, CH_2Cl_2) achieved the highest yields and enantioselectivities (entries 1–3). The use of anhydrous $CHCl_3$ decreased the amount of by-product **17** with respect to purum $CHCl_3$ (entry 2 vs entry 1). All other solvents tested were rather disappointing. No conversion was obtained with anhydrous CH_3CN (entry 5), whilst MeOH (entry 4) or anhydrous THF (entry 6) provided lower yields and *ee* values in comparison to anhydrous $CHCl_3$ which gave the best results (entry 2). It should be emphasized that the enantioselectivity and chemical yield including proportion of by-product **15** depends on the catalyst loading. The greater the quantity of *i*PBP **18a** employed, the better the enantioselectivity and the yield (entries 2, 7–11). Hence, 25 mol % of *i*PBP **18a** in $CHCl_3$ was the best compromise with regard to selectivity and reactivity (entry 2).

Other experiments concerning the concentration of aldehyde **8a** and sequence of reagent addition were conducted (Table 4). As widely described,[1,2] the larger the concentration of aldehyde, the cleaner the reaction and the better the enantioselectivity (entry 1 vs entries 3–4). The excess of aldehyde forces an equilibrium favouring the Michael adduct, and consequently restricting side reactions. The requirement of a large excess of aldehyde was confirmed by the slow addition of isovaleraldehyde **8a** which led to many by-products (entry 2). Finally, the slow addition of vinyl bis(sulfone) **4**

Table 3. Effect of solvent and catalyst loading.



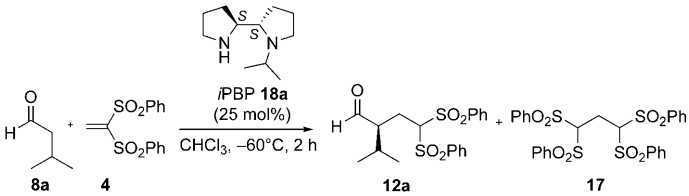
Entry	Catalyst loading [mol%]	Solvent	T [°C]	Yield[a] [%]	ee[b] [%]
1[c]	25	$CHCl_3$	−60	71 (18)[d]	75
2[e]	25	$CHCl_3$	−60	71 (13)[d]	75
3	25	CH_2Cl_2	−78	50 (23)[d]	66
4	25	MeOH	−60	65 (18)[d]	35
5	25	CH_3CN	−45	n.d.[f]	n.d.[f]
6	25	THF	−78	15 (19)[d]	15
7	5	$CHCl_3$	−60	15 (4)[d]	34
8	10	$CHCl_3$	−60	40 (13)[d]	34
9	15	$CHCl_3$	−60	68 (11)[d]	52
10	30	$CHCl_3$	−60	70 (19)[d]	75
11	40	$CHCl_3$	−60	70 (20)[d]	80

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee*'s were determined by chiral SFC. [c] Purum $CHCl_3$ without prior purification. [d] Proportion of tetrasulfone by-product **17** determined by ^{1}H NMR of the crude material. [e] $CHCl_3$ extra dry, with molecular sieves, filtered over basic alumina. [f] Not determined.

suppressed the formation of by-product **17**, but with a decrease of enantiomeric excess (entry 5).

ACA of aldehydes to vinyl sulfones catalyzed by *i*PBP—Scope of aldehydes: With the optimized conditions in hand for *i*PBP **18a** catalyst, we next enlarged the scope of the reaction with a variety of aldehydes (Table 5). Overall, the asymmetric induction depended on the steric bulk of the aldehyde partner. Isovaleraldehyde **8a** and 2-cyclohexylacetaldehyde **8b** afforded their respective adducts **12a** and **12b** in good yields and enantioselectivities (entry 1–2). The best asymmetric outcome was attained using bulkier 3,3-dimethylbutyraldehyde **8c**, with 80% *ee* (entry 3). Linear aldehyde such as valeraldehyde **8d** produced adduct **12d** in good yield but with moderate enantiomeric excess (entry 4). Although substrate **8e** showed similar reactivity, no stereoselectivity was observed (entry 5). This methodology was also applied to the challenging formation of quaternary carbon centers with α,α-disubstituted aldehydes but required a higher temperature (RT) for complete conversion (entries 6–8). Thus, the reaction of isobutyraldehyde **8f** as nucleophile and pyrrolidine as organocatalyst led to α,α-dimethyl-γ,γ-sulfonyl aldehyde **12f** in good yield (entry 6). The differentiation between methyl and ethyl in 3-methylbutyraldehyde **8g** was obviously not enough to provide good stereocontrol (entry 7). Finally, 2-phenylpropionaldehyde **8h** reacted very slowly with no selectivity, probably due to the enolizable benzylic protons under basic catalysis (entry 8).

Table 4. Effect of aldehyde concentration and sequence of reagent addition.

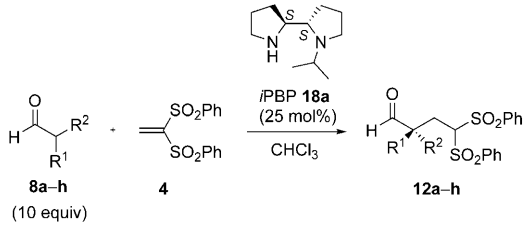


Entry	Equivalent aldehyde **8a**	Yield[a] [%]	ee[b] [%]
1	10	71 (13)[c]	75
2[d]	10	n.d.[e]	n.d.[e]
3	2	43 (33)[c]	45
4	5	53 (25)[c]	58
5[f]	10	78 (0)[c]	63

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee*'s were determined by chiral SFC. [c] Proportion of tetrasulfone by-product **17** determined by ^{1}H NMR of the crude material. [d] Slow addition of isovaleraldehyde **8a** (1 h30). [e] Not determined (sluggish reaction). [f] Slow addition of vinyl bis(sulfone) **4** (1 h 30 min).

Improved conditions and catalyst for ACA of aldehydes to vinyl sulfones—Diphenylprolinol silyl ether: Although we have demonstrated the efficiency of the first organocatalytic ACA of aldehydes to vinyl sulfones in terms of yield and reactivity, the previous set of reaction conditions was substrate dependent and *ee* values higher than 80% could not be reached using *i*PBP **18a** (Table 5). With a view to improving our methodology, we were interested in (*S*)-diphenylprolinol

Table 5. ACA of aldehydes **8a–h** to vinyl bis(sulfone) **4** catalyzed by *i*PBP **18a**.

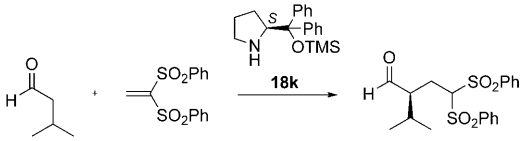


Entry	Aldehyde/Product	R^1	R^2	Reaction conditions	Yield[a] [%]	ee[b] [%]
1	**8a/12a**	*i*Pr	H	−60°C, 2 h	71	75 (+)[c]
2	**8b/12b**	*c*Hex	H	−60°C, 2 h	71	70 (+)[c]
3	**8c/12c**	*t*Bu	H	−60°C, 2 h	78	80 (+)[c]
4	**8d/12d**	*n*Pr	H	−60°C, 2 h	76	53 (+)[c]
5	**8e/12e**	Me	H	−60°C, 2 h	72	0[d]
6[e]	**8f/12f**	Me	Me	RT, 1 h	73	–
7	**8g/12g**	Et	Me	RT, 4 h	59	12 (+)[c]
8	**8h/12h**	Ph	Me	RT, 7 h	14 (15)[f]	0

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee*'s were determined by chiral SFC. [c] Sign of the optical rotation. [d] *ee* determined on the corresponding primary alcohol **31e**. [e] Reaction performed with 50 mol% of pyrrolidine. [f] Conversion determined by ^{1}H NMR of the crude material.

silyl ether **18k** for promoting ACA of isovaleraldehyde **8a** to vinyl bis(sulfone) **4** (Table 6). Indeed, catalyst **18k** was extensively explored by Jørgensen in various organocatalytic reactions,[25] and innovatively reported by Hayashi as an exceptional catalyst for the Michael reaction of aldehydes to nitroolefins.[7f] Pleasingly, (*S*)-diphenylprolinol silyl ether **18k** was found to induce particularly high stereocontrol for the ACA of isovaleraldehyde **6a** to vinyl bis(sulfone) **4**. Thus, the Michael adduct **12a** was obtained in high yield (88%), with excellent enantioselectivity and without the formation of tetrasulfone by-product **17** (93% *ee*; Table 6, entry 1). (*S*)-Diphenylprolinol silyl ether **3a** was revealed to be an especially active catalyst owing to its bulky substituents. It is worth noting that (*S*,*S*)-*i*PBP **18a** and (*S*)-diphenylprolinol silyl ether **18k** afforded the same major enantiomer (+)-(*S*)-**12a** which involves the same facial selectivity according to steric shielding (See Section on DFT Calculations).

Table 6. ACA of isovaleraldehyde **8a** to vinyl bis(sulfone) **4** catalyzed by (*S*)-diphenylprolinol silyl ether **18k**; optimisation of reaction conditions.



8a **4** **12a**

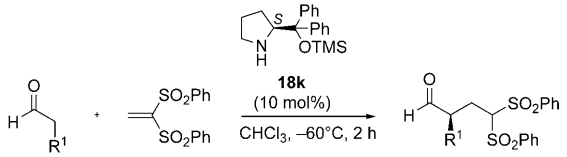
Entry	Equivalent aldehyde **8a**	Cat. loading [mol%]	Solvent	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	10	25	$CHCl_3$	−60	88	93 (+)[c]
2	10	25	hexane	−60	81	87
3	10	25	toluene	−60	87	93
4	10	25	toluene	−78	87	92
5	10	25	$CHCl_3$	RT	83	90
6	10	25	H_2O/EtOH (95:5)	RT	45	72
7	10	10	$CHCl_3$	−60	90	92
8	10	5	$CHCl_3$	−60	89	91
9	10	1	$CHCl_3$	−60	90	86
10	2	10	$CHCl_3$	−60	89	89

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee* values were determined by chiral SFC. [c] Sign of the optical rotation.

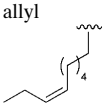
Our next task was optimize the reaction conditions for catalyst **18k** (Table 6). A short solvent survey revealed the suitability of nonpolar solvents (entries 1–3). The best results in terms of yields and enantioselectivity were achieved with both chloroform (entry 1) and toluene (entry 3). When the reaction in toluene was performed at a lower temperature (−78°C), no improvement was observed (entry 3 vs 4). For practical purposes, chloroform was chosen as the solvent in the subsequent studies. To our delight, the reaction in chloroform could also be carried out at room temperature with conservation of high yield and enantioselectivity (entry 1 vs 5). However, changing chloroform to a mixture of H_2O/EtOH (95:5)[26] drastically decreased either yield or enantiomeric excess (entry 5 vs 6). The catalyst loading could be reduced to 10 mol% or even to 5 mol%, without compromising both yield and enantioselectivity (entries 7–8). Due to the fact that we were interested in performing these reactions on a large scale, it was pleasing to find that only 1 mol% of (*S*)-diphenylprolinol silyl ether **18k** was required to provide Michael adduct **12a** in 90% yield and with 86% *ee* (entry 9). Finally, it is worthy of note that the reaction could also be performed using only 2 equivalents of isovaleraldehyde **8a** with still high yield and *ee* (entry 10).

To probe the scope of the improved methodology, a broad range of aldehydes was next considered (Table 7). Extensive variation in steric demands of the aldehyde substituent can be realized, affording γ-*gem*-sulfonyl aldehydes **12a–e**, **i–j** in good yields (77–90%) and with high enantioselectivities (76–98% *ee*; entries 1–7). Once again, hindered aldehydes accessed the highest *ee* values, with up to 98% *ee* for 3,3-dimethylbutyraldehyde **8c** (entries 1–3). Not only branched aldehydes (entries 1–3) but also linear aldehydes, such as valeraldehyde **8d** and propionaldehyde **8e** can also be employed to reach good enantioselectivity (entries 4–5). Interestingly, the allyl moiety can be introduced with good level of stereocontrol (entry 6). From a synthetic point of view, (*Z*)-undec-8-enal (**8j**), bearing a *cis* double bond, gave the Michael adduct **12j** in good yield and with 93% *ee* (entry 7).

Table 7. ACA of aldehydes **8a–e**, **i–j** to vinyl bis(sulfone) **4** catalyzed by (*S*)-diphenylprolinol silyl ether **18k**.



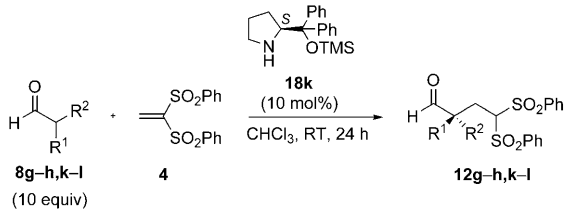
8a–e,i–j (10 equiv) **4** **12a–e,i–j**

Entry	Aldehyde/Product	R^1	Yield[a] [%]	*ee*[b] [%]
1	**6a/10a**	*i*Pr	90	92
2	**6b/10b**	*c*Hex	86	83
3	**6c/10c**	*t*Bu	90	98
4	**6d/10d**	*n*Pr	87	85
5	**6e/10e**	Me	85	76
6	**6i/10i**	allyl	88	92
7	**6j/10j**		77	93

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee*'s were determined by chiral SFC.

(*S*)-Diphenylprolinol silyl ether **18k** also proved to be an efficient catalyst for the straightforward construction of chiral quaternary carbon centers with α,α-disubstituted aldehydes (Table 8). Despite the unfruitful preliminary result with 3-methylbutyraldehyde **8g** (entry 1), we anticipated that higher differenciation between the α-substituents would provide better stereoinduction. Pleasingly, 2-phenylpropionaldehyde[27] **8h** underwent reaction with vinyl bis(sulfone) **4** in good yield and with promising enantiomeric excess de-

Table 8. ACA of aldehydes **8g–h**, **k–l** to vinyl bis(sulfone) **4** catalyzed by (*S*)-diphenylprolinol silyl ether **18k**.



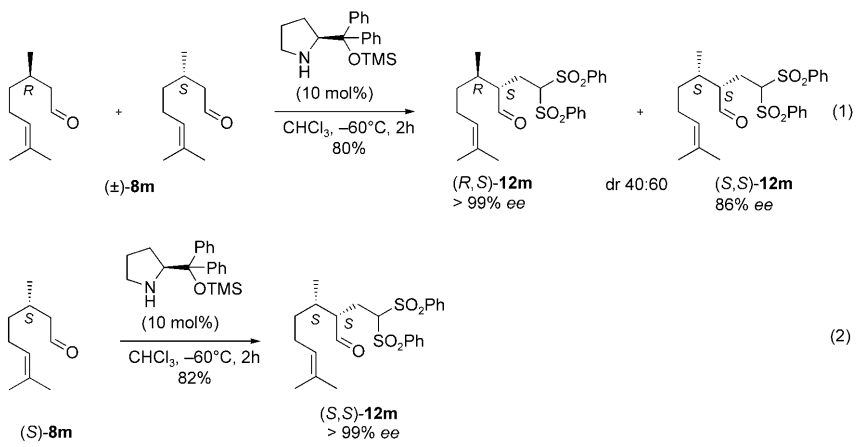
Entry	Aldehyde/Product	R^1	R^2	Yield[a] [%]	*ee*[b] [%]
1	**6g/10g**	Et	Me	75	12
2	**6h/10h**	Ph	Me	78	47
3	**6k/10l**	1-naphthyl	Me	76	91
4	**6l/10l**	*c*Hex	Me	71	64

[a] Isolated yields after purification by column chromatography on Florisil. [b] *ee*'s were determined by chiral SFC.

spite the presence of a very labile proton at the α-position of the carbonyl (entry 2). Replacement of phenyl group with the bulkier 1-naphthyl group resulted in a higher enantioselectivity of 91% *ee* (entry 3). By grafting cyclohexylmethyl appendages, chiral quaternary carbon center was formed in good yield and with 64% *ee* (entry 4). Thus, we have demonstrated that our methodology is also suitable for chiral quaternary carbon center formation, reaching to good enantioselectivity.

Consistently, higher yields and *ee* values were achieved with (*S*)-diphenylprolinol silyl ether **18k** in comparison to (*S*,*S*)-*i*PBP **18a** The most obvious cases were represented by propionaldehyde **8e** and 2-phenylpropionaldehyde **8h** for which (*S*,*S*)-*i*PBP **18a** could induce any stereoinduction whereas catalyst **18k** generated moderate to good enantioselectivities (Table 5, entry 5 vs Table 7, entry 5 and Table 5, entry 8 vs Table 8, entry 2).

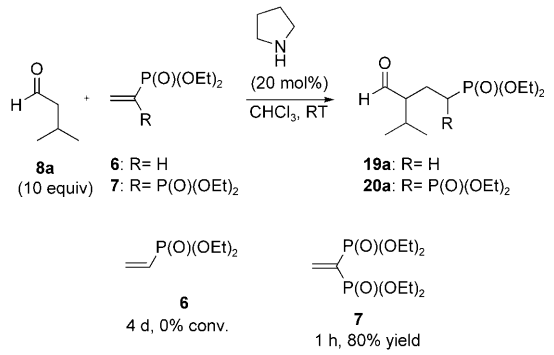
Citronellal **8m** was then selected as donor partner in order to examine the plausibility of kinetic resolution (Scheme 3). Racemic (±)-citronellal **8m** underwent reaction with vinyl bis(sulfone) **4** with excellent enantioselectivity with respect to the diastereomers but without significant selectivity in the kinetic resolution [dr *syn*/*anti* 40:60, Scheme 3, Equation (1)]. By performing the reaction with enantiopure (*S*)-citronellal **8m**, the Michael adduct (2*S*,3*S*)-**12m** is obtained in nearly pure form [>99% *ee*, Scheme 3, Equation (2)].[28] It is worth noting that a higher enantioselectivity for Michael adduct (*S*,*S*)-**12m** was observed when the reaction is performed with pure (*S*)-citronellal **8m** and (*S*)-**18k** catalyst in comparison with racemic (±)-citronellal **8m** [Scheme 3, Equation (2) vs (1). This can be considered as a match situation between (*S*)-citronellal and (*S*)-**18k** catalyst. From the result obtained with racemic (±)-citronellal **8m**, it seems that (*R*)-citronellal **8m** and the same catalyst does not afford as high diastereoselectivity. In this mismatch combination, the formation of the minor (*R*,*R*)-diastereomer **12m** affects the optical purity of of (*S*,*S*)-**12m** obtained from (*S*)-citronellal **8m**. Therefore, the observed *ee* of (*S*,*S*)-**12m** obtained from the racemic citronellal is lower than expected, and this can also explain the 40:60 diastereomeric ratio. Compound **12m** constitutes a highly useful chiral intermediate for the synthesis of natural products due to its citronellal scaffold improved by the introduction of a versatile *gem*-sulfonyl group.[29]



Scheme 3. ACA of citronellal **8m** to vinyl bis(sulfone) **4** catalyzed by (*S*)-diphenylprolinol silyl ether **18k**.

ACA of aldehydes to vinyl phosphonates—Reactivity: to broaden the scope of our methodology and to confirm our hypothesis on the requirement of bis-activated Michael acceptors, vinyl phosphonates were selected as electrophilic olefins. We initially evaluated the reactivity of vinyl phosphonates **6–7** in the conjugate addition of isovaleraldehyde **8a** using pyrrolidine as catalyst (Scheme 4). As previously emphasized for vinyl sulfones, we found that the Michael reaction was only effected with vinyl bis(phosphonate) **7** (Scheme 4). No reaction occurred with vinyl mono-phosphonate **6** whereas full conversion was achieved in 1 h with vinyl bis(phosphonate) **7** (Scheme 4). Consequently, we assume that the Michael acceptor, with the exception of nitroolefins[7] and methyl vinyl ketone,„[7f,9] should bear geminal bis-electron withdrawing groups in order to enable the aminocatalytic ACA of carbonyl donors.

ACA of aldehydes to vinyl phosphonates—Optimisation of reaction conditions: The stereochemical outcome of the ACA of isovaleraldehyde **8a** to vinyl bis(phosphonate) **7** was next explored with a short array of pyrrolidine-core organocatalysts (Table 9). Despite its excellent catalytic activity, *i*PBP **18a** led to moderate yield and low enantioselectivity no matter the temperature (entries 1–2). It is notable that vinyl bis(sulfone) **4** is more reactive than vinyl bis(phosphonate) **7** which is underlined by the lack of reactivity at −30°C of the latter Michael acceptor (Table 5, entry 1 vs Table 9, entry 3). The reaction rate and the enantioselectivity were di-



Scheme 4. Pyrrolidine-catalyzed conjugate addition of isovaleraldehyde **8a** to vinyl phosphonates **6–7**. Comparison of reactivity.

Table 9. ACA of isovaleraldehyde **8a** to vinyl bis(phosphonate) **7**. Optimization of reaction conditions.

Entry	Catalyst[a]	Reaction conditions	Conv.[b] [%]	Yield[c] [%]	*ee*[d] [%]
1		$CHCl_3$, RT, 1 h	100	71	31
2	*i*PBP **18a**	$CHCl_3$, 0 °C, 5 h	100	75	33 (+)[e]
3		$CHCl_3$, −30 °C, 48 h	0	–	–
4	**18d**	$CHCl_3$, 0 °C, 24 h	84	55	29
5	**18h**	$CHCl_3$, 0 °C, 5 h	100	70	15
6	L-proline	$CHCl_3$, RT, 48 h	0	–	–
7	**18j**	$CHCl_3$, RT, 48 h	0	–	–
8		$CHCl_3$, RT, 12 h	100	80	90 (+)[e]
9		$CHCl_3$, 0 °C, 18 h	100	82	80
10		$CHCl_3$, 60 °C, 12 h	100	71	91
11		H_2O/EtOH (95:5), RT, 12 h	100	49	83
12	**18k**	$CHCl_3$, RT, 15 h	100	81	85

[a] Entries 1–11: 20 mol%, entry 12: 10 mol%. [b] Determined by ^{1}H NMR of the crude material. [c] Isolated yields after purification by column chromatography on silica gel. [d] *ee*'s were determined by ^{1}H NMR on the corresponding imidazolidines **21a–22a** derived from Michael adduct **20a** and *N*,*N*-dimethyl-1,2-diphenyl ethylene diamine (**23**), see Scheme 5. [e] Sign of the optical rotation.

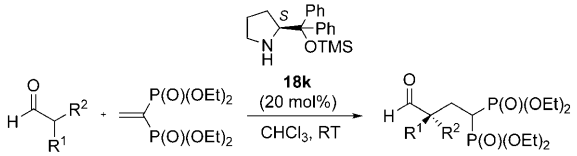
minished when the isopropyl substituent in catalyst **18a** was exchanged by a methyl group in **18d** (entry 4). Although diamine **18h** catalyzed the reaction as fast as diamine **18a**, it was revealed to be unselective (entry 5). Neither L-proline nor (*S*)-diphenylprolinol **18j** generated the Michael adduct **20a** after 48 h (entries 6–7).

Delightfully, (*S*)-diphenylprolinol silyl ether **18k** was found to induce particularly high stereocontrol for the ACA of isovaleraldehyde **6a** to vinyl bis(phosphonate) **7**. The reaction was complete within 12 h at room temperature in the presence of 20 mol% of catalyst **18k** in $CHCl_3$ and furnished Michael adduct **20a** in good yield (80%) and with excellent enantioselectivity (90% *ee*; entry 8). A decrease in the enantiomeric excess (from 90 to 80% *ee*) was observed upon decreasing the temperature (entry 8 vs 9). Heating the reaction did not improve the enantiocontrol and decreased the yield (entry 10). Changing $CHCl_3$ to a mixture of H_2O/EtOH (95:5) gave lower yield and selectivity (entry 8 vs 11). The catalyst loading could be reduced to 10 mol% while retaining a high level of enantioselectivity (entry 12).

ACA of aldehydes to vinyl phosphonates—Scope of aldehyde: With the optimized conditions in hand (Table 9, entry 8), the generality of the reaction for various aldehydes was demonstrated, with the results summarized in Table 10.

Good to high enantioselectivities were obtained with regard to the aldehyde substituent, ranging from 75–97% *ee* (entry 1–5). Interestingly, phenetylaldehyde **8n** afforded equally good *ee* value (entry 4). Unfortunately, pent-4-enal **8i**, bearing a terminal double bond, gave the Michael adduct **20i** in moderate yield and with low enantiomeric excess (entry 6). The challenging formation of quaternary carbon center was achieved in good yield using isobutyralde-

Table 10. ACA of aldehydes **8a**, **c-f**, **h**, **i**, **n** to vinyl bis(phosphonate) **7** catalyzed by (*S*)-diphenylprolinol silyl ether **18k**.

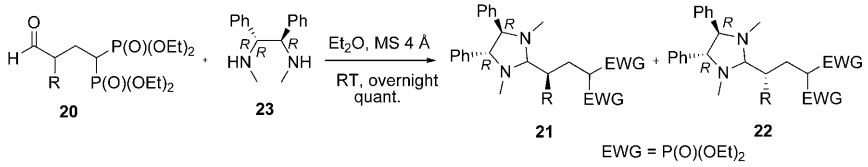


Entry	Aldehyde/Product	R^1	R^2	Yield[a] [%]	*ee*[b] [%]
1	**8a/20a**	*i*Pr	H	80	90 (*S*) (+)[c]
2	**8c/20c**	*t*Bu	H	85	97
3	**8d/20d**	*n*Pr	H	75	86
4	**8n/20n**	Bn	H	81	85[d]
5	**8e/20e**	Me	H	75	75
6	**8i/20i**	allyl	H	65	46
7[e]	**8f/20f**	Me	Me	80	–
8[f]	**8h/20h**	Ph	Me	–	–

[a] Isolated yields after purification by column chromatography on silica gel. [b] *ee*'s were determined by ^{1}H NMR on the corresponding imidazolidines **21–22** derived from Michael adduct **20** and **23**, see Scheme 5. [c] Sign of the optical rotation. [d] *ee* was confirmed by chiral SFC. [e] Performed with 20 mol% of pyrrolidine. [f] No conversion was observed after 48 h at RT.

hyde **8f** as nucleophile and pyrrolidine as organocatalyst (entry 7). However, phenylpropionaldehyde **8h** was not reactive enough to undergo the conjugate addition (entry 8).

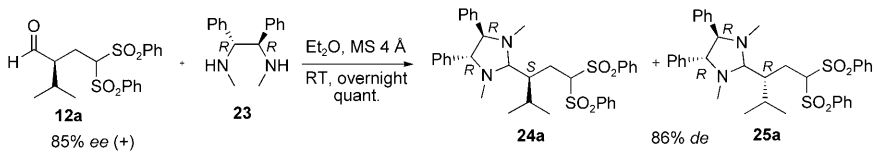
Determination of the *ee* of γ-*gem*-phosphonate aldehydes: In view of the high molecular weight and non-UV active groups in Michael adducts **20**, the optical purity could not be attributed by usual chiral separative techniques. Consequently, the enantiomeric excess of γ-*gem*-phosphonate aldehydes **20** was determined by ^{1}H NMR analysis through the formation of diastereomeric imidazolidine **21**–**22** with (*R*,*R*)-diamine **23** (Scheme 5).[30,31]



Scheme 5. Determination of the *ee* of γ-*gem*-phosphonate aldehydes **20**.

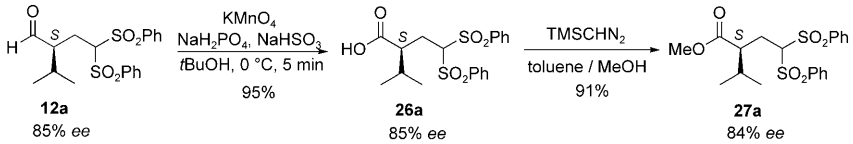
The use of (*R*,*R*)-diamine **23** for the derivatization of chiral aldehydes **20** provides ^{1}H and ^{31}P NMR spectra with different signals for each diastereomeric imidazolidine **21** and **22**.[32] Very mild conditions are required for this transformation (Et_2O, molecular sieves, room temperature) and an excess of (*R*,*R*)-diamine **23** was used to avoid kinetic resolution. The enantiomeric excess was determined on the crude diasteromeric imidazolidine mixture **21**–**22** to prevent the selective enrichment of one diastereoisomer. In one instance, the enantiomeric excess of the Michael adduct **20n** with a phenyl moiety could be confirmed by supercritical fluid chromatography (SFC), proving the efficiency of the NMR spectroscopy for determination of the enantiomeric excess.

Determination of the absolute configuration γ-*gem*-phosphonate aldehydes: The absolute configuration of the adduct **20a** was established by analogy with known Michael adduct **12a**, (*S*)-bis(phenylsulfonyl)ethyl)-3-methylbutanal (85% *ee*) (Scheme 6). As for diastereomeric imidazolidines **21a**–**22a**, the ^{1}H NMR spectrum of diastereomeric imidazolidines **24a**–**25a** shows a major deshielded signal and a minor shielded one for the same benzylic proton. Consequently, we ascribed the (*S*) absolute configuration to the (+)-Michael adduct **20a** and the same spatial arrangement was assumed for the other products **20**.



Scheme 6. Determination of the absolute configuration of γ-*gem*-phosphonate aldehydes **20a** (Scheme 5, R = *i*Pr) by analogy with known γ-*gem*-sulfonyl aldehyde **12a**.

Synthetic utility of γ-*gem*-sulfonyl aldehydes and determination of their absolute configuration: the applicability of γ-*gem*-sulfonyl aldehydes as highly tunable synthons was illustrated by a variety of synthetic transformations involving the aldehyde as well as the sulfonyl groups. The large scale synthesis of the chiral Michael adduct **12a** was carried out with only 1 mol% of (*S*)-diphenylprolinol silyl ether **18k** with still high level of enantioselectivity (85% *ee*). We first chose to selectively manipulate the aldehyde functionality. The Michael adduct (*S*)-**12a** with 85% *ee* was easily oxidized into carboxylic acid **26a** in 95% yield after a brief $KMnO_4$ exposure with no loss of enantioselectivity. Further transformation into methyl ester **27a** was achieved in high yield by the addition of $TMSCHN_2$ to confirm the optical purity of 84% *ee* (Scheme 7).[33]

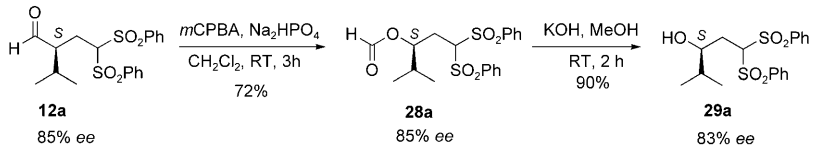


Scheme 7. Methyl ester derivatization of optically active of γ-*gem*-sulfonyl aldehyde **12a**.

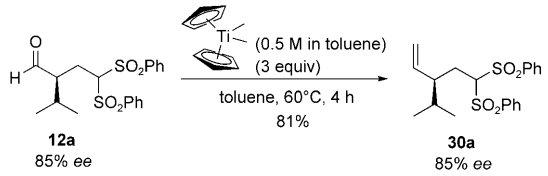
Conversely, Baeyer–Villiger oxidation of the (*S*)-adduct **12a** followed by saponification of formyl ester compound **28a** furnished secondary alcohol **29a** in high yield with perfect retention of configuration (Scheme 8).[34]

We also managed to perform methylenation of aldehyde (*S*)-**12a** with freshly prepared Petasis reagent[35] giving the vinyl derivative **30a** with conservation of the *ee* (Scheme 9). It is pertinent to note that the corresponding Wittig reagent as well as Horner–Wadsworth–Emmons reagent induced only epimerisation of aldehyde (*S*)-**12a**, probably due to their basic propertities.

Besides the obvious synthetic utility of the aldehyde moiety, we also considered the transformation of the sulfonyl groups.[36] After suitable reduction and protection of the primary alcohol **31a** as its TBDMS ether **32a** with reten-

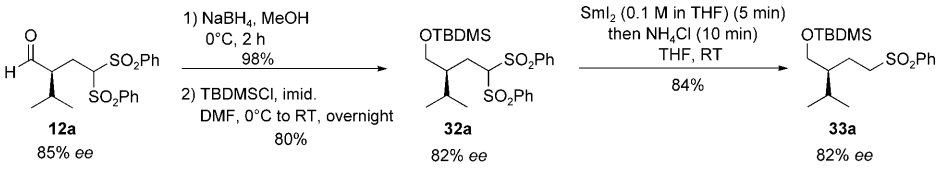


Scheme 8. Secondary alcohol derivatization of optically active of γ-*gem*-sulfonyl aldehyde **12a**.



Scheme 9. Methylenation of optically active of γ-*gem*-sulfonyl aldehyde **12a**.

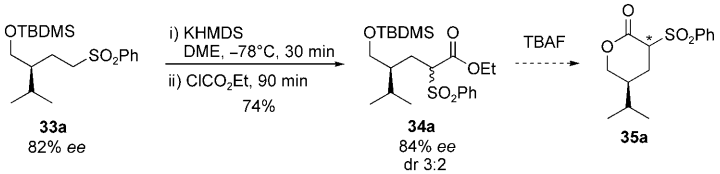
tion of the optical purity, freshly prepared samarium diiodide,[37,38] efficiently mediated reductive monodesulfonylation of γ-*gem* sulfonyl protected alcohol **32a** to give a potentially nucleophilic reagent **33a** in good yield and with 82% *ee* (Scheme 10).[39] It is worth noting that the exact sequence of reagent addition is critical for the reaction. Indeed, addition of *gem*-sulfonyl compound **32a** to a solution of SmI_2 in THF gave only partial conversion (40%) whereas the reverse addition led to full conversion.



Scheme 10. Reduction–protection and subsequent monodesulfonylation of optically active of γ-*gem*-sulfonyl aldehyde **12a**.

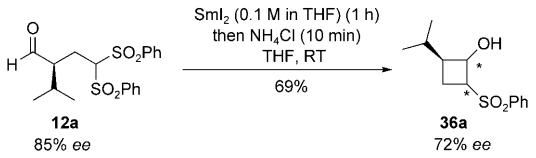
Next, α-deprotonation of compound **33a** with KHMDS and subsequent addition of ethyl chloroformate afforded the acylated product **34a** in 74% yield as a mixture of diastereomers (3:2) with 84% *ee* (Scheme 11).[40] Chiral synthon **34a** could easily access enantioenriched valerolactone **35a** which is a ubiquitous structural intermediate in natural product synthesis.[41]

We also investigated the intramolecular reductive cyclization of γ-geminal bis(sulfone) aldehyde **12a** in order to obtain cyclobutanol **36a** which could be an interesting chiral building block for total synthesis.[37b,42] The intramolecular



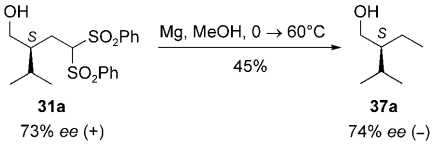
Scheme 11. Towards the synthesis of enantioenriched valerolactone **35a**.

samarium Barbier reaction gave the desired cyclobutanol **36a** in good yield as a single diastereomer although a small degree of racemisation was observed (Scheme 12).



Scheme 12. Synthesis of cyclobutanol **36a**.

Finally, we were interested in effecting bis-desulfonylation[11h,k–l] by exchanging the sulfonyl groups of primary alcohol **31a** with hydrogens (Scheme 13). Reduction with Raney Nickel[43] even with ultrasound activation led to the recovery of starting material **31a**. Only one sulfonyl group was reductively cleaved with aluminium amalgam (Al/Hg)[44] in 75% conversion after 5 d. Seemingly, these reducing reagents were not suitable for totally removing non-activated geminal bis(sulfones). Fortunately, the bis-desulfonylation can be performed using activated magnesium turnings in MeOH.[45] Hence, alcohol **37a** was obtained in 45% yield with no loss of enantioselectivity (74% *ee*). Usefully, the *S* absolute configuration of the Michael adduct **12a** was determined by comparison of the optical rotation of the resulting alcohol **37a** with literature.[46] It was



Scheme 13. Bis-desulfonylation of alcohol **31a**; determination of the absolute configuration of γ-*gem*-sulfonyl aldehydes **12a**.

assumed that the spatial arrangement of the other Michael adducts **12** was the same.

The absolute configuration of Michael adducts **12** was confirmed by X-ray analysis of carboxylic acid **26c** derived from γ-*gem*-sulfonyl aldehyde **12c** (Figure 2).

Many other synthetic transformations of Michael adducts **12** could be envisaged for the remaining aldehyde and sulfonyl groups. For instance, naphthalene-catalyzed lithiation of sulfones and the in situ reaction of the resulting organolithium with aldehydes and halogen compounds could be investigated to broaden the scope of the synthetic utility of Michael adduct **12**.[38b,47] Moreover, the presence of a double

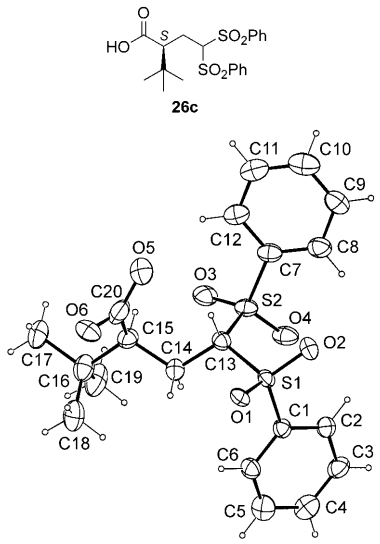
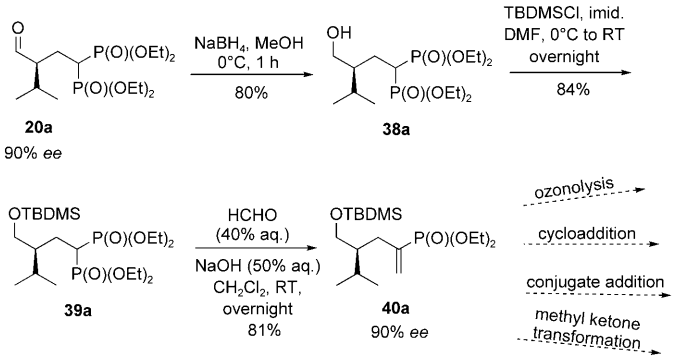


Figure 2. X-ray crystal structure of (*S*)-carboxylic acid **26c** derived from γ-*gem*-sulfonyl aldehyde **12c**. CCDC 662357 (**26c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

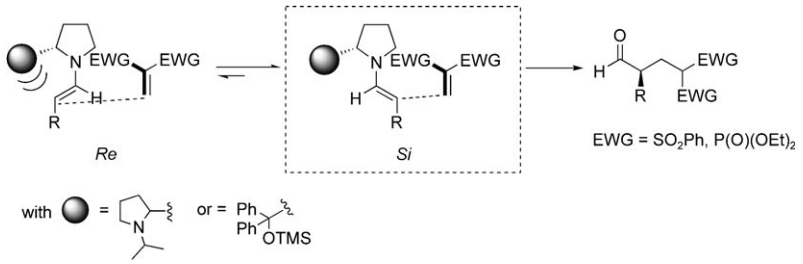


Scheme 14. Functionalization of γ-*gem*-phosphonate aldehyde **20a**; a new route to enantioenriched β-substituted vinyl phosphonate **40a**.

carbon–carbon bond on Michael adducts **12i,j,m** supplies new opportunities such as ozonolysis, cross-metathesis, radical cyclization[48] after appropriate transformations.

Synthetic application of γ-*gem* sulfonyl phosphonates: To illustrate the synthetic utility of this methodology, the enantioenriched γ-*gem*-phosphonate aldehyde **20a** was easily converted into β-substituted vinyl phosphonate **40a** with no loss of enantioselectivity (Scheme 14). Reduction of compound **20a** with $NaBH_4$ and subsequent protection of the primary alcohol **38a** with a TBDMS group affords the corresponding γ-*gem*-phosphonate protected alcohol **39a** in high overall yield. The HWE reaction with aqueous formaldehyde using 50% aqueous NaOH solution[49] provides the enantioenriched β-substituted vinyl phosphonate **40a** in high yield (81%) with retention of the enantiomeric excess (90% *ee*).[50] This new versatile building block could be involved in a variety of synthetic transformations such as ozonolysis, cycloaddition, conjugate addition or methyl ketone formation.[16,51]

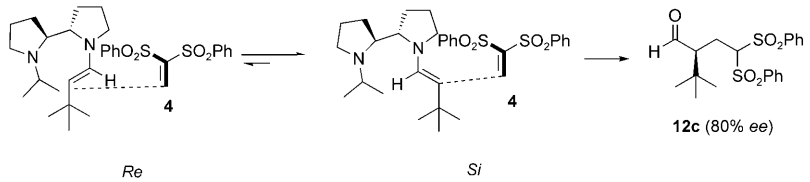
Proposed transition-state model: The determination of the absolute configuration allowed us to postulate a Michael acceptor attack from the *Si* face of the (*E*)-enamine according to steric shielding (Scheme 15).[6c,25a] The selectivity of the organocatalytic ACA could be explained by an acyclic synclinal transition state based on Seebach's model[52] in which there are favourable electrostatic interactions between the nitrogen of the enamine and the electron-withdrawing group of the Michael acceptor. As the selectivity depends on steric hindrance, the very bulky diphenyl silyl ether moiety induced better enantioselectivity than the *N*-*i*Pr-pyrrolidine moiety (93% *ee* vs 75% *ee*, see Table 6, entry 1 vs Table 5 entry 1). It is worth noting that (*S*,*S*)-*i*PBP **18a** and (*S*)-diphenylprolinol silyl ether **18k** afforded the same major enantiomer (+)-(*S*)-**12a** which involves the same face selectivity due to steric shielding. The bulky group on the catalyst framework would promote the selective formation of the *anti* enamine and selective shielding of the *Re* approach. Consequently, the less hindered *Si* transition state is well favored compared to the *Re* and leads to the (*S*)-**12a** adduct (R = *i*Pr) (Scheme 15).



Scheme 15. Proposed transition state for the organocatalytic ACA of aldehydes to vinyl bis(sulfones) and vinyl bis(phosphonates) according to steric shielding.

The origin of the selectivity in the organocatalytic ACA of aldehydes to vinyl sulfones has also been investigated for *N*-*i*Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP) catalyst by density functional theory (DFT) using the PBE1PBE/6-31G* method[53] within the Gaussian03 package.[54]

Transition-state modeling by DFT calculations: In the following preliminary account of computational modeling we focus mainly on the structure of the transition states of the enamine, derived from (*S*,*S*)-*i*PBP **18a** and 3,3-dimethyl butyraldehyde **8c**, and vinyl sulfone **4**, since their properties can provide the best indications (leads) for understanding of



Scheme 16. Studied case for the transition state modeling by DFT calculations.

the observed selectivity (Scheme 16) (Computational methods, see Supporting Information).

Indeed, on the reactant side the potential energy surface for enamines is quite complex, nevertheless the conformational search provided five low energy minima within a 4 [kcal mol^{-1}] range. All five minima belong to (*E*)-enamines and the lowest energy conformer corresponds to *anti* enamine. Although, the selective steric shielding of the *Re* face is apparent, at least to a certain degree, from the optimized structure of this reactant, it could not provide a full rationale for the observed selectivity.

One of the key factors that can enhance the selectivity of the Michael-acceptor attack of the (*E*)-enamine is the ability of this system to develop the stabilizing electrostatic interactions at the transition state between the nitrogen of the enamine and sulfone oxygen atoms. For the reaction pathway leading to the *Si*-face adduct (Figure 3), our modeling revealed a progressive increase of the negative charge on the oxygen atoms. When comparing the charges between the reactant and transition state **II-TS** it increased, respectively, from −0.397 to −0.425 for O1 and from −0.409 to −0.438 for O2 (Figure 3). These two oxygen atoms are quite close and equidistant with respect to the enamine nitrogen (3.428 and 3.491 Å, respectively). The charge build-up on oxygen atoms in the **II-TS**, together with relatively short distances between the involved atoms, allow for improved electrostatic interactions.

During the *Re* approach (Figure 4), when compared to the reactant, the negative charge on the two crucial oxygen atoms decrease in the transition state **V-TS** with computed charges for atoms O3 and O4 of −0.417 and −0.461, respectively (Figure 4). In addition, the latter oxygen is further apart from the enamine nitrogen (4.072 Å). Such charge depletion and elongation of oxygen–nitrogen distance is in contrast with what was observed for the attack of the *Si* face. The optimized geometry parameters of **V-TS** are clearly less favorable for the electrostatic interactions between the enamine and sulfone moieties. At the origin of this structural perturbation is the steric hindrance between the bulky substituent and the O4. Particularly, one of the hydrogens (attached to C10, see Figure 4) comes into close contact with this oxygen atom. This type of unfavorable interaction is absent in the **II-TS** structure (Figure 3), setting thereby the stage for the improved electrostatic interactions and providing further stabilization of the transition state for the *Si* approach. Indeed, in the **II-TS** transition state, the bulky substituent is extending its C10–C12 moiety away form the incoming sulfone (Figure 3).

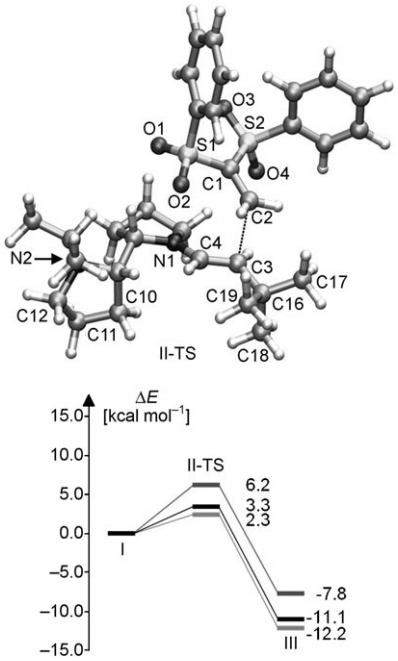


Figure 3. Schematic energy profile for ACA to the *Si* face of the (*E*)-enamine, together with the optimized structure (top) of the transition state.

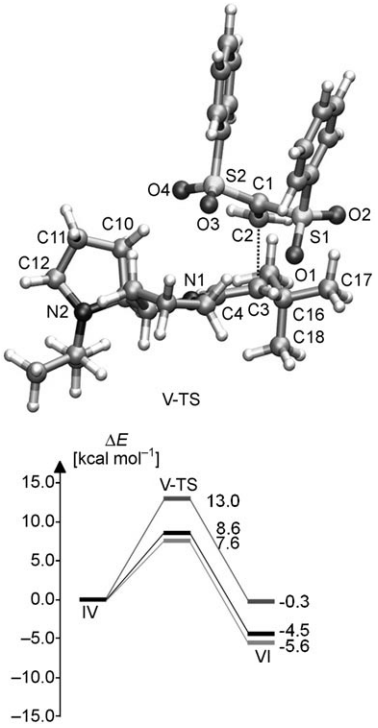


Figure 4. Schematic energy profile for ACA to the *Re* face of the (*E*)-enamine, together with the optimized structure (top) of the transition state.

The present modeling can also be used to evaluate whether the *tert*-butyl substituent on the enamine can additionally be involved in the face selectivity of the vinyl sulfone addition. Indeed, for the vinyl sulfone approach to the *Re* face, one of the vinyl hydrogens develop two close contacts with the *tert*-butyl substituent. In the **V-TS** geometry (Figure 4), this steric hindrance translates into H···H distances of 1.966 and 2.258 Å. Again the analogous steric interference is less severe in the **II-TS** transition state of the *Si* face attack (Figure 3).

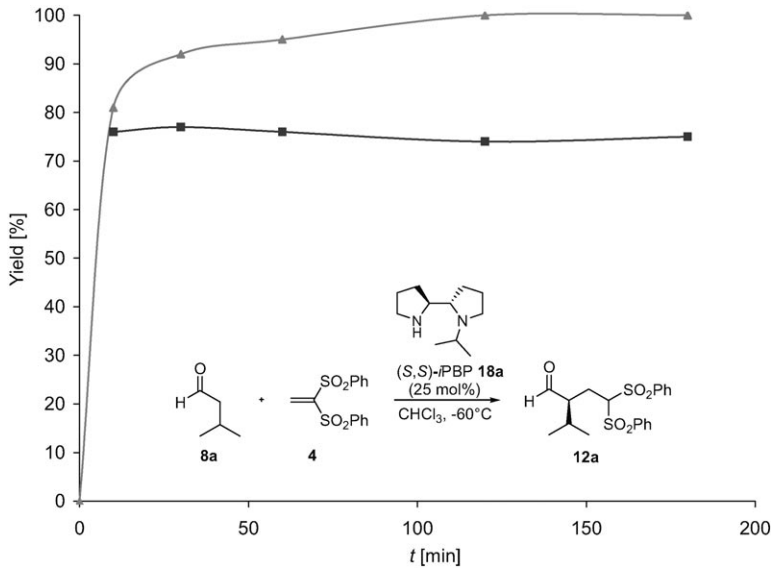


Figure 5. *ee* Values (■) as a function of time, conversion: ▲.

The favorable and unfavorable interactions described above are reflected in clearly different energy barriers for the two modes of addition. Expressed in terms of relative energies, the barrier for the vinyl sulfone **4** addition to the *Si* face amounts to 2.4 kcal mol^{-1}, while the barrier for the *Re* approach is 5.3 kcal mol^{-1} higher. The incorporation of the ZPE correction only marginally changes the energy profile. Since all stationary points of the potential energy surface were characterized by the vibrational analysis, we were able to apply the thermal corrections and compute the free energy (right column in Table 11). When comparing the free energies, the energy difference $\Delta\Delta G$ between the two transition states further increased to 6.8 kcal mol^{-1}. These preliminary DFT results not only correlate well with the reported experimental results, but they also provide the rationale for the origin of the observed selectivity. The modelling of the solvent effects is currently in progress.

Table 11. Relative energies and relative free energies [kcal mol^{-1}] for ACA to (*E*)-enamines at the PBE1PBE level of theory.

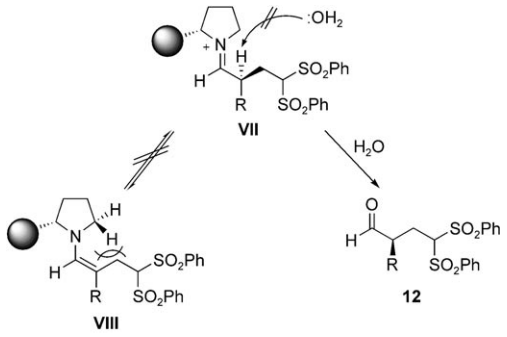
Face	Species	ΔE[a]	ΔE(ZPE)[b]	ΔG[c]
Si	**I**	0.0	0.0	0.0
	II-TS	2.4	3.3	6.2
	III	−14.1	−11.1	−7.8
Re	**IV**	0.0	0.0	0.0
	V-TS	7.7	8.6	13.0
	VI	−7.6	−4.5	−0.3

[a] Relative energies. [b] ZPE corrected relative energies. [c] Relative free energies at 25 °C.

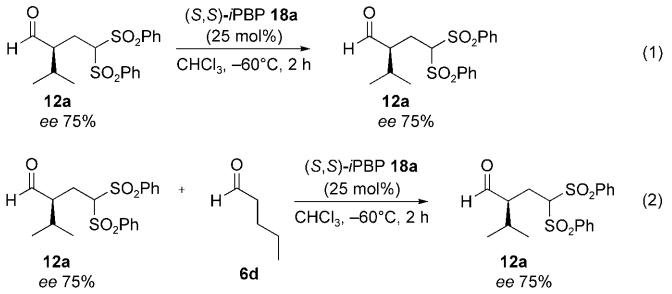
Mechanistic insights: In order to establish the role of (*S*,*S*)-*i*PBP in ACA, we investigated advanced mechanistic studies on this catalytic system. The stability of the chiral center in the product is as important as its enantioselective formation. Consequently, we first conducted an epimerisation study by monitoring the enantiomeric excess as a function of time (Figure 5). Plotting the *ee* of the Michael adduct **12a** versus time gave a near straight line (■) which indicates there is no epimerisation during the reaction.

The absence of racemisation was also previously determined by observing that the *ee* of aldehyde **12a** was almost similar to the one of the corresponding primary alcohol **31a** (see Scheme 10). In accordance with Jørgensen's explanation,[25a] the stability of the chiral center during the reaction could arise from the steric hindrance of the aminocatalyst (*S*,*S*)-*i*PBP **18a** and especially (*S*)-diphenylprolinol silyl ether **18k**.[25a] This undesired pathway is generally prevented because the formation of the bulky disubstituted enamine species **VIII** is disfavored in comparison to the iminium **VII** hydrolysis leading to enantioenriched Michael adduct **12** (Scheme 17). This phenomenon is also in agreement with kinetic control.

To obtain further information on the influence of kinetic control in our reaction, Michael adduct **12a** (75 % *ee*) was subjected to standard conditions [Scheme 18, Eq. (1)]. Neither variation of enantiomeric excess nor formation of vinyl bis(sulfone) **4**, that is, retro-addition, were observed which corroborates our kinetic control hypothesis. This trend was



Scheme 17. Proposed transition state for the organocatalytic ACA of aldehydes to vinyl bis(sulfones) and vinyl bis(phosphonates) according to steric shielding.



Scheme 18. Evaluation of kinetic control.

confirmed by reacting a less hindered aldehyde such as valeraldehyde **6d** and compound **12a** which led only to the recovery of Michael adduct **12a** with no loss of enantioselectivity [Scheme 18, Eq. (2)].

NMR spectroscopy was also investigated to gain insight into the intermediates of the catalytic cycle. Preliminary results indicated the formation of by-product **17** in large amounts (Hb) and the addition of (*S*,*S*)-*i*PBP **18a** to vinyl bis(sulfone) **4** which trapped the catalyst as product **41** (Ha) (Figures 6 and 7). The reaction evolved into a 1:4 ratio of Michael adduct **12a** to by-product **17**, suggesting a slow transformation of trapped catalyst **41** into the desired 1,4-adduct **12a**.

It is clear that the temperature as well as the sequence of reagent addition could influence the proportion of by-product **17**. Indeed, the introduction of (*S*,*S*)-*i*PBP **18a** last to the reaction mixture at −60 °C prevented the formation of tetrasulfone **17** (Figures 6 and 8). This result was experimentally confirmed and led to an increase of the chemical yield from 71 to 82 %. Unfortunately, no improvement of enantioselectivity was observed showing that the structure of the catalyst or more precisely its steric hindrance mainly governs the stereoinduction. Unfortunately, neither iminium **42** nor enamine **43** intermediates (Figure 9) were detected by these ^{1}H NMR experiments (Figure 6). However, the formation of the enamine intermediate **43** derived from isovaleraldehyde

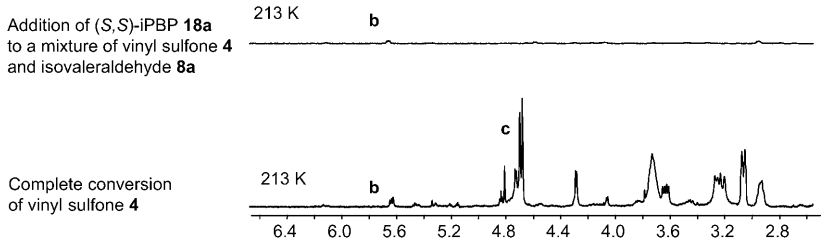


Figure 8. ^{1}H NMR study: addition of (*S*,*S*)-*i*PBP **18a** to a mixture of isovaleraldehyde **8a** and vinyl bis(sulfone) **4**.

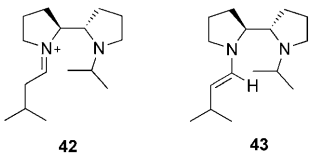


Figure 9. Iminium **42** and enamine **43** derived from isovaleraldehyde **8a** and and (*S*,*S*)-*i*PBP **18a**.

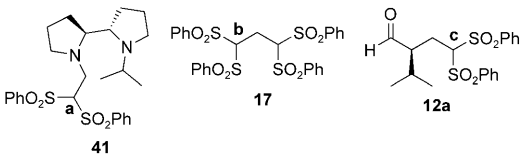


Figure 6. Identified compounds by NMR spectroscopy.

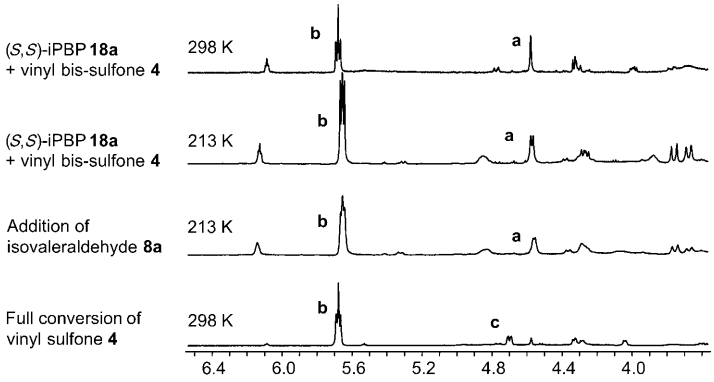


Figure 7. ^{1}H NMR study: Addition of isovaleraldehyde **8a** to a mixture of vinyl bis(sulfone) **4** and (*S*,*S*)-*i*PBP **18a**.

6a and (*S*,*S*)-*i*PBP **18a** during the reaction was confirmed by ESI-MS method (see Supporting Information).

Finally, we studied linear/non-linear effects in ACA of isovaleraldehyde **8a** to vinyl bis(sulfone) **4** catalyzed by (*R*,*R*)-*i*PBP **18a** (Figure 10). Plotting the *ee* value of catalyst **18a** versus that of the Michael adduct **12a** gave a slight negative non-linear relationship. Diastereomeric active species are not in accordance with our transition sate model based on steric shielding in which there is probably no H-bonding or aggregation in solution. No solid phase was observed excluding an explanation by physical phase behavior.[55] Appa-

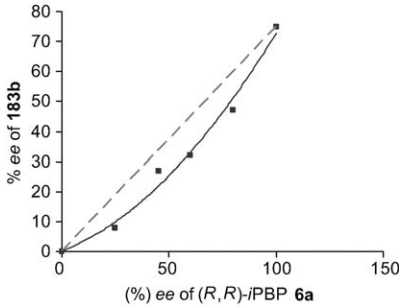


Figure 10. Slight non-linear effect in the ACA of isovaleraldehyde **6a** to vinyl bis(sulfone) **4** catalyzed by (*R*,*R*)-*i*PBP **18a**.

rently, there is neither epimerisation nor influence of the addition of the enantioenriched Michael adduct **12a** in the reaction conditions suggesting that there is no interaction between the chiral catalyst and the chiral product (see Figure 5 and Scheme 17). However, reversible trapping of the catalyst as compound **41** (Figure 6) could decrease the amount of available catalyst and consequently this phenomenon of reservoir effect would explain the observed negative nonlinear effect.

Conclusion

We are in the "golden age of organocatalysis", and organocatalytic reactions are recognized as a powerful tool for the preparation of optically active compounds. The use of chiral amines such as pyrrolidine analogues for the enantioselective Michael reaction via enamine activation represents an important breakthrough in modern asymmetric synthesis. We have demonstrated the high potential of the organocatalytic ACA via enamine activation by expanding the scope of Michael acceptors. Hence, we disclosed the first intermolecular enantioselective organocatalytic conjugate addition of aldehydes to vinyl sulfones and vinyl phosphonates with high enantioselectivity. The principle of double activation through the presence of geminal electron-withdrawing groups on the olefin was demonstrated for inducing reactivity. Although 2,2′-bipyrrolidine derivatives **18a–e** proved to be interesting organocatalysts for these reactions (up to 80% *ee*), a catalytic system with diphenylprolinol silyl ether **18k** is more flexible allowing the reaction to proceed without the formation of by-products in various solvents and with excellent enantioselectivity regardless of temperature, catalyst loading, the quantity of aldehyde, or nature of aldehyde (up to 99% *ee*). We were also gratified to see that our methodology proceeded efficiently towards the formation of chiral quaternary carbon centers (up to 91% *ee*). The determination of the absolute configuration as well as DFT calculations allowed us to postulate a *Si* transition state via an acyclic synclinal Seebach's model. Hence, the asymmetric induction depends on highly steric shielding involving an enamine intermediate. This novel enantioselective organocatalytic ACA led to optically active γ-*gem*-sulfonyl aldehydes and γ-*gem*-phosphonate aldehydes as useful tunable chiral synthons as exemplified by various functionalizations with conservation of the optical purity.

Experimental Section

For experimental procedures, characterizations, chiral separations, crystallographic information files (CIF) and DFT calculations, see Supporting Information.

ACA of aldehydes to vinyl sulfones (General procedure 1): To a solution of 1,1-bis(benzenesulfonyl)ethylene (**4**; 50 mg, 0.162 mmol, 1 equiv) in dry chloroform filtered on basic alumina (1.5 mL) was added aldehyde **8** (1.62 mmol, 10 equiv) at the appropriate temperature, and then pyrrolidine (0.08 mmol, 50 mol%) or diphenylprolinol silyl ether **18k** (0.0162 mmol, 10 mol%). The evolution of the reaction was controlled by TLC until completion. The solution was hydrolysed with sat. aq. NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on Florisil using a mixture of cyclohexane (*c*-Hex) and ethyl acetate (AcOEt).

(2*S*)-Bis(phenylsulfonyl)ethyl)-3-methylbutanal (12a): From isovaleraldehyde (**8a**; 1.62 mmol, 10 equiv, 0.18 mL), 1,1-bis(benzenesulfonyl)ethylene (**4**; 0.162 mmol, 1 equiv, 50 mg) and **18k** (0.0162 mmol, 10 mol%, 5.3 mg) according to GP 1 (2 h, −60 °C) to give a yellow oil as crude product which is purified by column chromatography on Florisil (*c*-Hex/AcOEt 2:1) to obtain a pale yellow oil (57.5 mg, 90%). The enantiomeric excess was determined by chiral SFC (chiralcel OJ column, 2 mL min^{-1}, 200 bar, MeOH 10%-2–1–25%, 30 °C, t_R = 4.14 (*R*), 5.80 min (*S*)); $[\alpha]_D^{20}$ = +44.5 (*c* = 1.45 in $CHCl_3$, 92% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H), 7.96–7.88 (dd, *J* = 24.1, 7.4 Hz, 4H), 7.73–7.67 (m, 2H), 7.60–7.53 (m, 4H), 4.71–4.68 (dd, *J* = 9.1, 3.1 Hz, 1H), 2.94–2.90 (m, 1H), 2.54–2.47 (m, 1H), 2.17–2.11 (m, 2H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.94 ppm (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.99 (1CHO), 137.89 (1$C_{quat.}$), 137.74 (1$C_{quat.}$), 134.75 (1CH), 134.57 (1CH), 129.78 (1CH), 129.37 (1CH), 129.186 (1CH), 129.14 (1CH), 80.55 (1CH), 54.67 (CH), 28.62 (1CH), 21.51 (1CH_2), 19.84 (1CH_3), 19.04 ppm (1CH_3); MS (EI mode): *m*/*z* (%): 396 (1), 225 (28), 169 (12), 145 (14), 143 (25), 141 (11), 134 (13), 125 (49), 97 (15), 91 (17), 83 (19), 81 (10), 79 (12), 78 (25), 77 (100), 69 (13), 67 (10), 55 (35), 51 (35); IR ($CHCl_3$): $\tilde{\nu}$ = 3065w, 3020w, 2964w, 2928w, 2873w, 1724s, 1585m, 1448m, 1331s, 1311m, 1157s, 1079s cm^{-1}. HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{22}O_5S_2$ 417.08046, found 417.08063 $[M+Na]^+$.

For the other Michael adducts **12** and their derivatives, see Supporting Information.

ACA of aldehydes to vinyl phosphonates (General procedure 2): To a solution of tetraethyl ethylidenebis(phosphonate) (**7**; 100 mg, 0.33 mmol, 1 equiv) in $CHCl_3$ (3 mL) was successively added aldehyde **8** (3.33 mmol, 10 equiv) and then pyrrolidine (0.066 mmol, 20 mol%) or **18k** (0.066 mmol, 20 mol%) at RT. The reaction was monitored by TLC until complete conversion. The reaction mixture was hydrolyzed with aq. sat. NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOH 9:1) to afford 1,4-adduct **20**. The enantiomeric excess were determined by ^{1}H and ^{31}P NMR on imidazolidine **21–22** which were prepared by adding successively molecular sieves and *N*,*N*-dimethyl-1*R*,2*R*-diphenyl ethylene diamine (**23**; 25 mg, 0.103 mmol, 4 equiv) to a solution of compound **20** (10 mg, 0.025 mmol, 1 equiv) in diethyl ether (3 mL) at room temperature. After stirring overnight at room temperature, the reaction mixture was filtered over Celite, washed with diethyl ether (2×5 mL) and concentrated in vacuo to give the diastereomeric mixture of imidazolidine **21–22** (quant.).

(*S*)-2-Isopropyl-4,4′-ethylphosphonate-butanal (20a): Compound **20a** was prepared from **7** and isovaleraldehyde **8a** according to GP 2. After purification, compound **20a** was obtained as a pale yellow oil (102 mg, 80%). The enantiomeric excess was determined by ^{1}H and ^{31}P NMR on imidazolidines **21a–22a** derived from compound **20a** and (*R*,*R*)-diamine **23**: ^{1}H NMR (400 MHz, C_6D_6): δ = 4.57–4.55 (*R*,*R*,*S*), 4.51–4.48 ppm (*R*,*R*,*R*); ^{31}P NMR (162 MHz, C_6D_6): δ = 25.75 (*R*,*R*,*S*), 25.41–25.21 ppm (*R*,*R*,*R*). The absolute configuration of compound **20a** was established by analogy with imidazolidines **269b–270b** derived from known Michael adduct (*S*)-bis(phenylsulfonyl)ethyl)-3-methylbutanal (**12a**; 85% *ee*) and imidazolidines **24a–25a**. $[\alpha]_D^{20}$ = +21.5 (*c* = 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (d, *J* = 1.52 Hz, 1H), 4.21–4.14 (m, 8H), 2.82–2.77 (m, 1H), 2.51–2.21 (m, 2H), 2.19–2.05 (m, 1H), 1.99–1.87 (m, 1H), 1.36–1.02 (m, 12H), 1.00 (d, *J* = 10.1 Hz, 3H), 0.98 ppm (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.92 (1CHO), 63.12–62.72 (m, 4CH_2), 56.16–56.02 (m, 1CH), 34.61 (t, 1CH), 28.88 (1CH), 21.62 (1CH_2), 20.10 (1CH_3), 19.53 (1CH_3), 16.61–16.55 ppm (m, 4CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.41–23.12 ppm; MS (EI mode) *m*/*z*

(%): 386 (2), 357 (11), 289 (119, 288 (100), 261 (32), 249 (20), 242 (15), 233 (14), 215 (17), 177 (12), 165 (10), 159 (13), 152 (51), 109 (11), 41 (12), 29 (17); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{32}O_7P_2$: 386.162331 and found 386.161380 $[M]^+$.

For the other Michael adducts **20** and their derivatives, see Supporting Information.

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