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First Enantioselective Organocatalytic Conjugate Addition of Aldehydes to Vinyl Phosphonates

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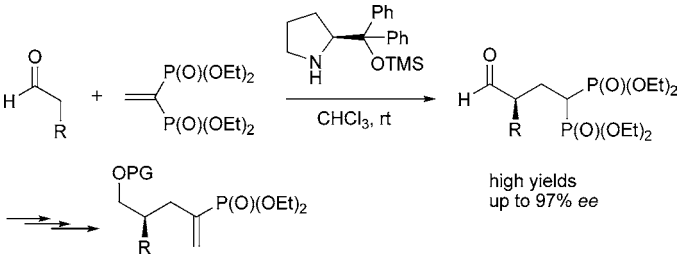
ABSTRACT



Chiral amines catalyze the enantioselective conjugate addition of aldehydes to vinyl phosphonates in high yields and with enantioselectivities up to 97% ee. This novel process provides synthetically useful chiral γ-geminal phosphonate aldehydes which can be easily converted in a few steps into chiral β-substituted vinyl phosphonates with conservation of the optical purity.

Besides transition-metal complexes and enzymes, organocatalysis has recently emerged as a new field in asymmetric synthesis.[1,2] The efficiency and the scope of organocatalysis and particularly aminocatalysis have been broadly established since the rediscovery of the proline-catalyzed intermolecular aldol reaction.[3] Chiral secondary amines have proven to be effective catalysts for these reactions by covalently activating the carbonyl compounds either via nucleophilic enamines or electrophilic iminium ions.[4] Among the wide variety of methods, the asymmetric conjugate addition (ACA) catalyzed by pyrrolidine analogues has become of major significance for the stereoselective formation of C−C bonds.[5] In this context, our laboratory has developed 2,2′-bipyrrolidine derivatives for the Michael addition of aldehydes and ketones to nitroolefins with high stereocontrol.[6] An improvement of selectivity for bulky aldehydes was further achieved by Kanger and us with 3,3′-bimorpholine derivative, incorporating the morpholine structural motif instead of pyrrolidine one.[7] More recently, we have described the first enantioselective conjugate addition of aldehydes to vinyl sulfones catalyzed by our diamines with enantioselectivities up to 80%

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ee.[8] In contrast to cinchona catalysts,[9] the presence of geminal bis-sulfone groups on the olefin was required for the reactivity of this pyrrolidine-type catalysis.

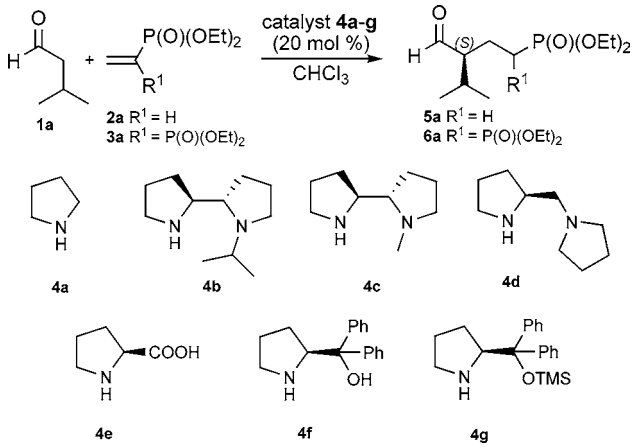
To broaden the scope of our methodology and to confirm our hypothesis of bis-activated Michael acceptors, vinyl phosphonates were selected as electrophilic olefins owing to their easy access from commercial sources and their potential for offering synthetic versatile intermediates. Despite the great interest on vinyl phosphonates,[10] only Enders has reported diastereoselective conjugate addition of modified ketone via SAMP hydrazone activation.[11] It is also worth noting that conjugate addition of lithium salt of Schöllkopf's bislactim ether to vinylphosphonate constitutes a highly stereoselective key step in the synthesis of α-amino γ-phosphonate aldehyde.[12] However, it remains challenging to develop a direct enantioselective catalytic method for the cornerstone ACA of carbonyl donors.

Herein, we present the first enantioselective organocatalytic conjugate addition of aldehydes to vinyl phosphonates using diphenylprolinol silyl ether **4g**, providing optically active γ-*gem*-phosphonate aldehydes in good yields and with high stereoselectivities, which can be easily converted into chiral β-substituted vinyl phosphonates with conservation of the optical purity.

In view of the previously mentioned hypothesis, we initially evaluated the reactivity of vinyl phosphonates **2a**−**3a** in the conjugate addition of isovaleraldehyde **1a** using pyrrolidine **4a** as the organocatalyst (Table 1, entries 1 and 2). As expected, we found that the Michael reaction was only effected with the vinyl bis-phosphonate **3a** (Table 1, entry 2).[13] This behavior was confirmed by performing the reaction with N-*i*-Pr-2,2′-bipyrrolidine (*i*-PBP) **4b** catalyst (Table 1, entries 3 and 4). No reaction occurred with vinyl monophosphonate **2a** (Table 1, entry 3), whereas full conversion was achieved in 1 h with vinyl bis-phosphonate **3a** (Table 1, entry 4). Consequently, contrary to nitroolefins,[14,15] we assume that this type of Michael acceptor should bear geminal bis-electron-withdrawing groups in order to enable the aminocatalyzed conjugate addition of carbonyl donors. Next, the stereochemical outcome was examined by screening various pyrrolidine-core organocatalyts for the Michael reaction of isovaleraldehyde **1a** to vinyl bis-phosphonate **3a**, and some representative results are shown in Table 1. Despite its excellent catalytic activity, *N*-isopropyl-(2*S*,2′*S*)-bipyrrolidine **4b** led to moderate yield and low enantioselectivity whatever the temperature (Table 1, entries 4 and 5). The reaction rate and the enantioselectivity were decreased when the isopropyl substituent in **4b** was exchanged for a methyl group in **4c** (Table 1, entry 6). Although (*S*)-(+)-(1-pyrrolidinylmethyl)pyrrolidine **4d** catalyzed the reaction as fast as diamine **4b**, it was revealed to be unselective (Table 1, entry 7). Neither (*S*)-proline **4e** nor (*S*)-diphenylprolinol **4f** have generated the 1,4-adduct **6a** after 48 h (Table 1, entries 8 and 9). Then, we were interested in (*S*)-diphenylprolinol silyl ether **4g** extensively explored by Jørgensen in various organocatalytic reactions[16] and innovatively reported by Hayashi[15d] as an exceptional catalyst for the Michael reaction of aldehydes to nitroolefins.

To our delight, (*S*)-diphenylprolinol silyl ether **4g** was found to induce particularly high stereocontrol for the ACA

Table 1. Optimization Studies for the Oragnocatalytic ACA of Isovaleraldehyde **1a** to Vinylphosphonates **2a**−**3a**[a]



entry	Michael acceptor	cat.	reaction cond	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	**2a**	**4a**	rt, 96 h	0		
2	**3a**	**4a**	rt, 1 h	100	80	
3	**2a**	**4b**	rt, 96 h	0		
4	**3a**	**4b**	rt, 1 h	100	71	31
5	**3a**	**4b**	0 °C, 5 h	100	75	33
6	**3a**	**4c**	0 °C, 24 h	84	55	29
7	**3a**	**4d**	0 °C, 5 h	100	70	15
8	**3a**	**4e**	rt, 48 h	0		
9	**3a**	**4f**	rt, 48 h	0		
10	**3a**	**4g**	rt, 12 h	100	80	90
11	**3a**	**4g**	0 °C, 18 h	100	82	80
12	**3a**	**4g**	60 °C, 12 h	100	71	91
13[e]	**3a**	**4g**	rt, 12 h	100	49	83
14[f]	**3a**	**4g**	rt, 15 h	100	81	85

[a] Performed with **1a** (3.33 mmol), **2a** or **3a** (0.333 mmol), and **4a**−**g** (0.066 mmol). [b] Determined by ^{1}H NMR on the crude material. [c] Isolated yields after purification by column chromatography. [d] Determined by ^{1}H NMR on imidazolidines **8a** and **9a** derived from Michael adduct **6a** and *N*,*N*-dimethyl-1,2-diphenylethylenediamine **7**; see Scheme 1. [e] Performed with H_2O/EtOH 95:5. [f] Performed with 10 mol % of catalyst **4g**.

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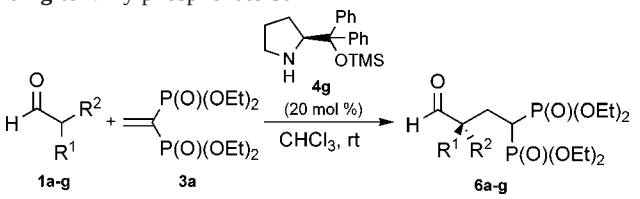
of isovaleraldehyde **1a** to vinyl bis-phosphonate **3a**. The reaction was complete within 12 h at room temperature in the presence of 20 mol % of catalyst **4g** in $CHCl_3$, and the adduct **6a** was afforded in good yield (80%) and with excellent enantioselectivity (90% ee; Table 1, entry 10). A decrease in the enantiomeric excess (from 90 to 80% ee) was observed upon decreasing the temperature (Table 1, entry 10 vs 11). Heating the reaction did not improve the enantiocontrol and decreased the yield (entry 12). Changing $CHCl_3$ to a mixture of H_2O/EtOH (95:5) gave lower yield and selectivity (Table 1, entry 10 vs 13). The catalyst loading could be reduced to 10 mol % with still high level of enantioselectivity (Table 1, entry 14).

With the optimized conditions in hand (Table 1, entry 10), the generality of the reaction for different aldehydes was demonstrated, with the results summarized in Table 2.

Extensive variation in steric demands of the aldehyde substituent can be realized, affording γ-gem-phosphonate aldehydes **6a**−**e** in good yields (75−85%) and with high enantioselectivities (75−97% ee; Table 2 entries 1−5). The more hindered the aldehyde, the better was the stereoinduction. The best asymmetric outcome was attained using the bulkier 3,3-dimethylbutyraldehyde **1b** (Table 2, entry 2). Not only branched aldehydes (Table 2, entries 1 and 2) but also linear aldehydes, such as valeraldehyde **1c** and propionaldehyde **1e** can also be employed to reach good ee values (Table 2, entries 3 and 5). Interestingly, the benzyl moiety can be introduced with good level of stereocontrol (Table 2, entry 4). Unfortunately, pent-4-enal **1f**, bearing a terminal double bond, gave the Michael adduct **6f** in moderate yield and with low enantiomeric excess, but it should be noted that this reaction is unprecedented (Table 2, entry 6). Delightfully, the challenging formation of quaternary carbon center was achieved in good yield using isobutyraldehyde **1g** as nucleophile and pyrrolidine **4a** as organocatalyst (Table 2, entry 7).

Table 2. Scope of the Organocatalytic ACA of Aldehydes **1a**−**g** to Vinylphosphonate **3a**[a]

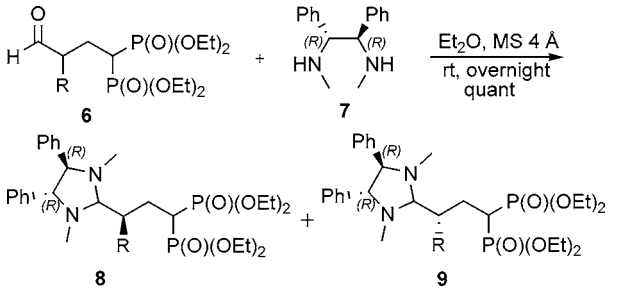


entry	aldehyde/ product	R^1, R^2	time (h)	yield[b] (%)	ee[c] (%)
1	**1a/6a**	*i*-Pr, H	12	80	90 (*S*) (+)
2	**1b/6b**	*t*-Bu, H	12	85	97 (+)
3	**1c/6c**	*n*-Pr, H	12	75	86 (+)
4	**1d/6d**	Bn, H	12	81	85[d] (+)
5	**1e/6e**	Me, H	8	75	75 (+)
6	**1f/6f**	allyl, H	12	65	46 (+)
7[e]	**1g/6g**	Me, Me	24	80	

[a] Performed with **1a**−**g** (3.33 mmol), **3a** (0.333 mmol), and **4g** (0.066 mmol). [b] Isolated yields after purification by column chromatography. [c] Determined by ^{1}H NMR on imidazolidines **8** and **9** derived from Michael adduct **6** and *N*,*N*-dimethyl-1,2-diphenylethylenediamine **7**; see Scheme 1. [d] ee was confirmed by chiral SFC. [e] Performed with pyrrolidine **4a** (0.066 mmol).

In view of the high molecular weight and the non-UV active groups in the Michael adducts **6a**−**f**, their optical purity could not be evaluated by usual chiral separative techniques. To overcome this problem, the compounds were converted into diastereomeric imidazolidine **8** and **9** with *N*,*N*-dimethyl-(1*R*,2*R*)-diphenylethylenediamine **7** (Scheme 1).[17] The use of (*R*,*R*)-diamine **7** for the derivatization of chiral aldehydes **6a**−**f** provides ^{1}H and ^{31}P NMR spectra with different signals for each diastereomeric imidazolidine **8** and **9**.[18,19] Moreover, the enantiomeric excess of the Michael adduct **6d** with a phenyl moiety was confirmed by chiral

Scheme 1. Determination of the Enantiomeric Excess of the Michael Adduct **6** by ^{1}H NMR via Derivatization of Imidazolidines **8** and **9**



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SFC, proving the efficiency of the NMR determination of the enantiomeric purity.

The determination of the absolute configuration[18b,20] allowed us to postulate a Michael acceptor attack from the *Si*-face of the *E*-enamine in accordance with previous studies (Figure 1).[16a] Indeed, the selectivity of the organocatalytic

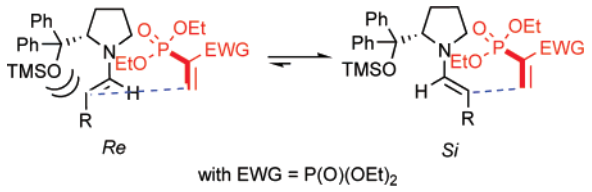
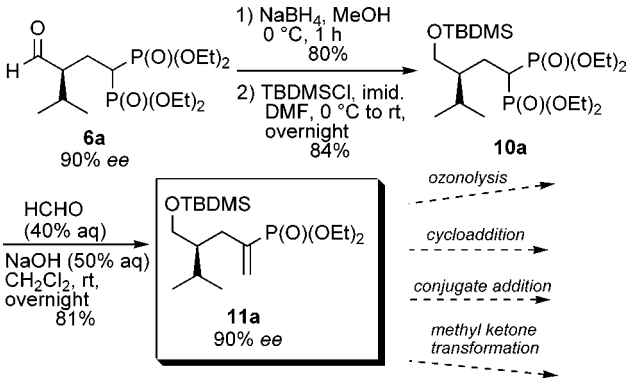


Figure 1. Proposed transition state.

ACA could be explained by an acyclic synclinal transition state based on Seebach's model[21] in which there could be favorable electrostatic interactions between the nitrogen of the enamine and the phosphonate moiety. The bulky aryl and silyl groups would promote the selective formation of the *E*-enamine and selective shielding of its *Re*-face.

To illustrate the synthetic utility of this methodology, the enantioenriched γ-*gem*-phosphonate aldehyde **6a** was easily converted into β-substituted vinyl phosphonate **11a** with no loss of enantioselectivity (Scheme 2). Reduction of compound **6a** with $NaBH_4$ and subsequent protection of the primary alcohol with TBDMS group afforded the corresponding γ-*gem*-phosphonate-protected alcohol **10a** in high overall yield (84%). Then, the HEW reaction with aqueous formaldehyde using 50% aqueous NaOH solution[22] provided

Scheme 2. Functionalization of Michael Adduct **6a**: A New Route to Enantioenriched β-Substituted Vinyl Phosphonate **11a**



the enantioenriched β-substituted vinyl phosphonate **11a** in high yield (81%) with retention of the enantiomeric excess (90% ee).[23] This new versatile building block could be involved in a variety of synthetic transformations such as ozonolysis, cycloaddition, conjugate addition, methyl ketone formation.[10,24]

In conclusion, we have disclosed the first enantioselective organocatalytic conjugate addition of aldehydes to vinyl phosphonates in good yields and with high enantioselectivity. To generate some reactivity of this pyrrolidine-type catalysis, the presence of geminal-bis-electron-withdrawing groups on the Michael acceptor was demonstrated to be necessary. We have also updated the use of chiral diamine auxiliaries for determining the enantiomeric purity of chiral aldehydes via diastereomeric imidazolidines. The optically active γ-*gem*-phosphonate aldehydes are useful tunable chiral synthons as exemplified by the synthesis of β-substituted vinyl phosphonate with no loss of enantioselectivity.

Acknowledgment. We thank Dr. Richard Frantz (University of Geneva) for valuable advice and constructive discussions.

Supporting Information Available: Experimental procedures, ^1H, ^{13}C, and ^{31}P spectra, and chiral separations for compounds **6a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) An excess of (*R*,*R*)-diamine **7** was used to avoid kinetic resolution. Several sets of signals for diastereomeric imidazolidine mixture **8** and **9** were detected by ^1H NMR and mostly by ^{31}P NMR analysis with significant differences in chemical shifts; see the Supporting Information.

(20) ^1H NMR spectrum of diastereomeric imidazolidines derived from (*S*)-bis((phenylsulfonyl)ethyl)-3-methylbutanal and diamine **7** 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 **6a** and the same configuration was assumed for the other products **6b**−**f**; see the Supporting Information.

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