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PAPER

Synthesis of geminal bisphosphonates *via* organocatalyzed enantioselective Michael additions of cyclic ketones and 4-piperidones†

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A Michael addition reaction of cyclic ketones and piperidones to a vinyl phosphonate is described. The reaction, catalyzed by chiral diamines, produced geminal γ-oxobisphosphonates in high yields (up to 92%) and very high *ees* (up to >99%). Disubstituted ketones gave *drs* of up to 8 : 92. The synthesis and characterization of several new compounds with potential biological activity is described.

Introduction

Millions of doses of bisphosphonates are used annually throughout the world for the treatment and prevention of bone disorders, such as osteoporosis, Paget's disease and bone-related cancers.[1] Compounds **A–D** (Fig. 1) are examples. Bisphosphonates contain P–C–P(O)(OH)$_2$ moieties and they are hydrolysis-resistant analogues of pyrophosphate, P–O–P(O)(OH)$_2$, a unit found in many molecules essential for life, such as DNA, RNA, proteins, enzymes, ATP, phospholipids, and so on. Hence they have a huge potential as targets for pharmaceutical applications. Recent studies *in vitro* and *in vivo* showed that some are potent inhibitors of parasitic protozoa responsible for diseases considered by the World Health Organization as major tropical diseases. These include *Trypanosoma cruzi*, the pathogen that causes Chagas' disease,[2] *T. brucei*, which causes sleeping sickness,[3] and *Plasmodium falciparum*, responsible for malaria.[3a,4] Some bisphosphonates also activate cells known to possess potent antitumour activity, the γδ T cells, which means that they could control a broader range of tumours.[5]

Studies to investigate the mode of action of bisphosphonates[6] and discover molecular targets for drug design found, as potential candidates, the enzymes farnesyl diphosphate synthase (FPPS) and hexokinase. FPPS plays an important role in the mevalonate/cholesterol biosynthetic pathway, in protein prenylation, and the generation of isoprenoid lipids.[6] Hexokinase catalyzes the first step in glycolysis.[7] Both enzymes are strongly inhibited by certain geminal bisphosphonates. X-ray crystallography studies showed that the binding of risedronate-related compounds to FPPS is stereospecific,[8] which suggests that chiral bisphosphonates could become important pharmaceutical targets in the future, better capable of interacting with the allosteric sites of proteins. This concept is supported by a recent structure activity relationship (SAR) study, which showed that the two enantiomers of **E**, a phosphonocarboxylate analogue of minodronate **D**, had significantly different activities,[9] and that [(+)-**E**] was the most potent selective inhibitor known of Rab geranylgeranyltransferase, another enzyme in the mevalonate pathway. This was the first report ever that a change in the configuration of the chiral center resulted in large differences in the activity of this type of compounds. Bisphosphonates are known to have few or no toxic side effects. Their properties are related to the nature of the functional substituents on the geminal carbon atom. Yet, despite the fact that they have many applications, there have been very few reports on the development of methods to synthesize chiral bisphosphonates.

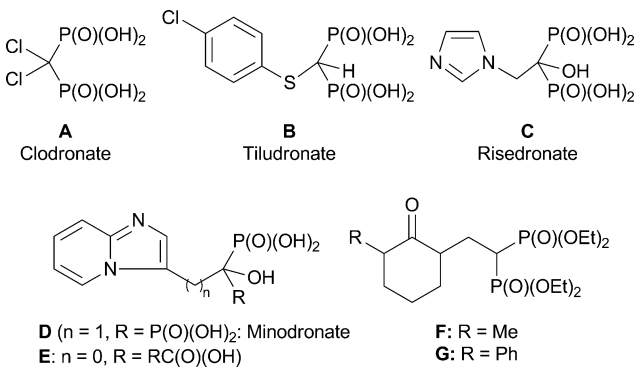
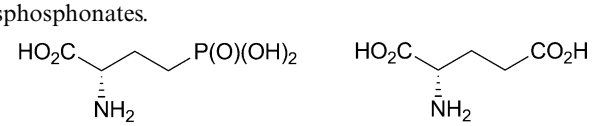


Fig. 1 Biologically active geminal bisphosphonates.



Our research interests in the Michael addition reaction[10] brought our attention to a class of phosphonates reported as having, in their racemic forms, potent anti-arthritic and anti-inflammatory activity.[11] They are 4-oxobisphosphonates, *e.g.* **F**

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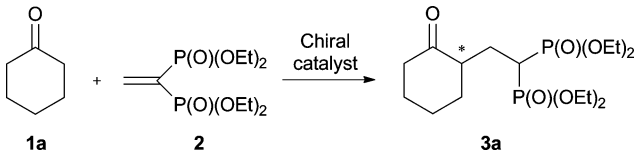
and **G** (Fig. 1), and an enantioselective Michael addition reaction of ketones to vinylbisphosphonate would be one of the obvious ways to access chiral analogues. Besides the potential to have anti-arthritic and anti-inflammatory activity, they could be further transformed into compounds with other useful properties,[12] *i.e.* they could be converted by the Strecker or by the Bucherer–Bergs reaction into chiral α,α-disubstituted amino acids bearing a 4-bisphosphonyl moiety. These compounds would be structural analogues of L-2-amino-4-phosphonobutanoic acid (L-AP4)[13] **H**, a known antagonist of the metabotropic glutamate receptors, mGlu, end receivers of information from L-glutamate **I**, the major excitatory neurotransmitter in the central nervous system.[14] mGlu plays a key role in fundamental processes like neural development, learning and memory, and is implicated in a variety of acute and chronic CNS disorders, being a potential target for therapeutic intervention. Thus a library of these compounds may reveal important new leads for pharmaceutical development.

The Michael addition reaction is a powerful tool for C–C bond formation and for the elaboration of complex molecules from simple substrates. Applications to the synthesis of phosphonates have been recently reviewed.[15] There have been a few reports on the conjugate addition reaction of carbon nucleophiles to geminal vinyl bisphosphonates: Grignard reagents,[16] organolithium compounds,[17] and carbanions generated with sodium ethoxide,[18] tertiary amines,[11b] lithium amide base,[11a,19] or inorganic base.[18] Catalytic asymmetric methods are still rare.[20] To the best of our knowledge, besides a report on the use of Ni(II)-Schiff base complexes to promote the addition of nitroacetates to ethyledenebisphosphonates,[21] only organocatalysts were used to achieve chiral induction.

The application of organocatalysis[22] in phosphonate chemistry has been recently reviewed.[23] The addition of aldehydes to a vinylidene bisphosphonate catalysed by a diphenylprolinol silyl ether was reported to give γ-geminal bisphosphonate aldehydes in high yields and *ees* of up to 97%.[24–26] Dihydroquinine was used to catalyse the addition of prochiral β-ketoesters to vinylidene bisphosphonates to provide highly substituted adducts in high yields and *ees* of up to 99%.[27] We recently communicated the first examples of the enantioselective addition of ketones to tetraethyl methylenediphosphonate, catalyzed by chiral diamines.[28] In order to create a library of 4-oxobisphosphonates for SAR studies, we have now explored this reaction further and applied it to a wide range of cyclic ketones and piperidones, substances often used as advanced intermediates in the synthesis of biologically active piperidines,[29] but which may also be active by themselves.[30] The full details of the work are presented here.

Results and discussion

Prior to our short communication, the organocatalyzed asymmetric Michael addition reaction of ketones to electron-deficient olefins had been reported by others[21] and by us[10c] with other acceptors, *i.e.* nitroalkenes, enones, vinyl sulfones, alkylidene malonates, maleimides, α,β-unsaturated aldehydes, imides, α-substituted vinyl cyanoacetates, acetylenic esters, but not with vinyl bisphosphonates. We chose as a model reaction for our studies the addition of cyclohexanone to tetraethyl vinylidene bisphosphonate (Scheme 1).



Scheme 1 The Michael addition of cyclohexanone to bisphosphonate **2**.

To explore the possibility of asymmetric induction *via* enamine catalysis, the amines shown in Fig. 2 were tried as organocatalysts. A ten-fold excess of ketone, commonly used in organocatalyzed addition reactions, and 10 mol% catalyst, were used as starting conditions for a preliminary screening. Piperazine, a catalyst we found useful in the Michael addition of aldehydes to β-nitrostyrenes,[10d] did not react, neither did its 1-methyl derivative. There was also no reaction in the presence of catalyst **V**. Commercially available (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine **III**, a proline derivative that has in the past been successfully used in other organocatalyzed reactions,[21,31] gave a single phosphorus-containing product, as determined by ^{31}P NMR spectroscopy, which was isolated by chromatography and identified as the desired Michael addition adduct.

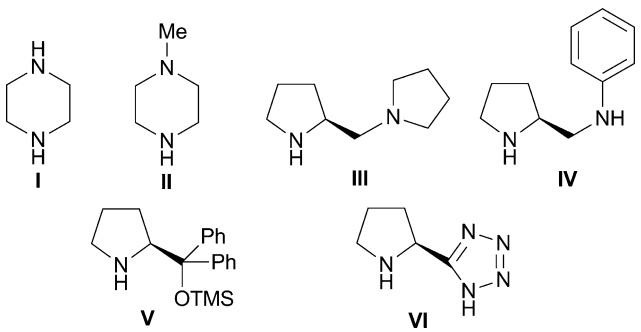


Fig. 2 The organocatalysts screened.

Afterwards the reaction conditions were optimized using diamine **III** as catalyst. The nature of the solvent did not have a large influence on the outcome of the reaction (Table 1), with *ees* varying between 30 and 34%, except for the ionic liquid [bmin]PF_6, which gave an improvement of 10%, but a lower yield of product was obtained. The reaction could also be carried out successfully in brine, but more than 3 days were needed for complete conversion of the substrate rather than the typical 17 h necessary in the other solvents, with no benefits in terms of asymmetric induction. When the salt was changed to LiCl, the best *ee* was obtained in CH_2Cl_2 at

Table 1 Effect of the solvent on the asymmetric Michael addition of cyclohexanone to tetraethyl vinylidene bisphosphonate catalyzed by **IV**[a]

Entry	Solvent	Time [h]	Conversion [%]	*ee*[b] [%]
1	CH_2Cl_2	17	100	32
2	CH_2ClCH_2Cl	17	100	34
3	$CHCl_3$	17	100	30
4	EtOH	17	100	32
5	DMF	17	100	32
6	[bmin]PF_6	17	100	46
7	Brine	89	100	36

[a] Conditions: room temperature, bisphosphonate (1 mM) : ketone : catalyst 1 : 10 : 0.1. [b] Determined by ^{13}C NMR spectroscopy.

Table 2 The effect of additives, catalyst load and temperature on the Michael addition reaction[a]

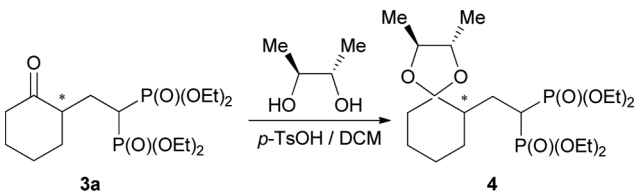
Entry	Solvent	Additive	Time [h]	Conversion [%]	*ee*[b] [%]
1	CH_2Cl_2	None	17	100	32
2	CH_2Cl_2	PhCOOH	17	100	40
3	CH_2Cl_2	LiCl	17	50	48
4	CH_2Cl_2	LiCl	24	100	24
5	CH_2Cl_2	CH_3COOH	17	100	20
6	CH_2Cl_2	CH_3COOH	17	100	36
7	CH_2Cl_2	*p*-TsOH·H_2O	40	50	6
8[c]	CH_2Cl_2	PhCOOH	17	100	30
9[d]	CH_2Cl_2	PhCOOH	168	63	26
10	CH_3CN	LiCl	17	100	30
11	THF	PhCOOH	17	100	26
12	Toluene	PhCOOH	17	100	30
13[e]	CH_2Cl_2	PhCOOH	17	100	32

[a] Conditions: r.t., with bisphosphonate (1 mM) : ketone : catalyst : additive 1 : 10 : 0.1 : 0.1. [b] Determined by ^{13}C NMR spectroscopy. [c] Reaction with 20 mol% catalyst + additive. [d] Reaction at 0 °C. [e] Reaction with catalyst **IV**.

$t_{\frac{1}{2}}$, but unfortunately it dropped as the reaction proceeded (Table 2, entries 3 and 4).

The effect of catalyst load and the presence of acids as additives was also investigated, but the results did not vary much. A higher induction was obtained in [bmin]PF_6, but the yield of product obtained in this reaction was lower than in CH_2Cl_2. Finally, a combination of 10 mol% diamine **III** and PhCOOH in dichloromethane (Table 2, entry 2) were selected as optimum conditions for further studies. Two additional diamines, **IV** and **VI**, were tried as potential catalysts with these conditions, but they gave no additional improvement in the results.

The enantiomeric excess of the product of these reactions was determined by ^{13}C NMR spectroscopy, from the ratio of the signals of the diastereoisomeric acetals **4** obtained after reaction of **3a** with (*S*,*S*)-2,3-butanediol in the presence of *p*-TsOH[32] (Scheme 2).



Scheme 2 Acetal synthesis for *ee* determination.

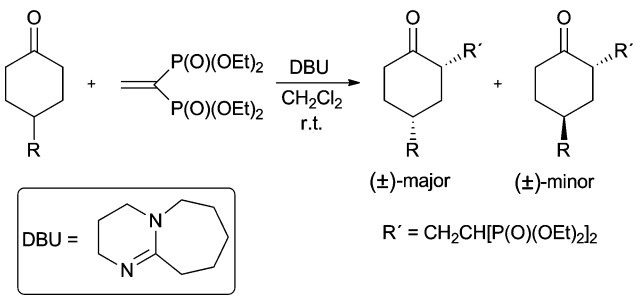
In order to explore further the potentialities of the reaction, the method developed was then applied to a wide range of ketones. The reactions proceeded smoothly at room temperature to give the desired 2,4-disubstituted Michael adducts in high yields (Table 3). No condensation products formed, as indicated by ^1H NMR spectroscopy.

As shown in the table, the reactivity of 4-substituted cyclohexanones was similar, with 4-phenycyclohexanone reacting the fastest (entry 2). Diastereoselectivities, determined from the ratio of signals in ^{31}P NMR spectra of the crude products, were moderate, varying from 12 to 1 to 2.5 to 1. The enantiomeric excesses were high, going up to 88% with the bulkiest substituent, *tert*-butyl, providing the greatest enantiocontrol (entry 5).

The diastereoselectivity of the major product was found to be *trans* from a NOESY spectrum of **3c**. The presence of a cross peak between a multiplet at 2.89–3.01 ppm (H-1′) and a doublet at 1.26 ppm (C-5′–CH_3) indicated a close spatial relationship (*syn*) between these two protons, which is only possible if the compound had a *trans* configuration. When 2-phenylcyclohexanone was used as substrate, there was no reaction in CH_2Cl_2. The reaction was possible in [bmin]PF_6, but the conversion was only 80% after 7 days (entry 3) and 20% of an unknown additional product formed too. Product **6** was found to be racemic. This suggests that the presence of the bulky α-substituent hinders enamine formation and the reaction may even proceed *via* the formation of an intermediate enolate instead of an enamine, with the chiral diamine acting as a base. In this case prochiral enolate faces could have led to transition states of more comparable energies, and the final product was racemic.

The monoacetal of 1,4-cyclohexanedione **1f** was also used as a substrate for the reaction, giving product **3f** in moderate yield and a good enantioselectivity of 64%. Enantioselective alkylation of **1f** provides a route to α-alkylated 1,4-cyclohexanedione derivatives, which are also important building blocks for the synthesis of natural products.[33]

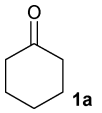
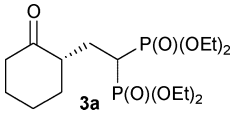
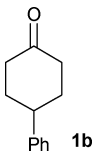
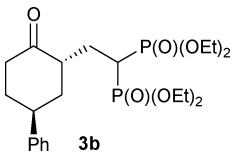
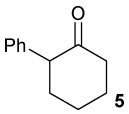
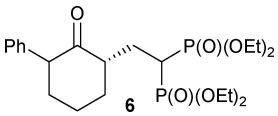
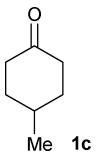
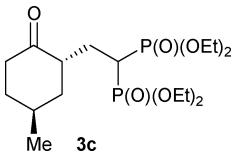
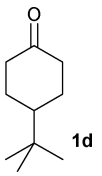
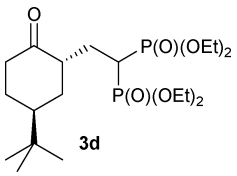
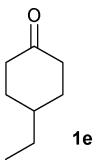
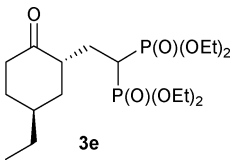
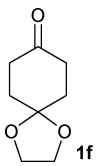
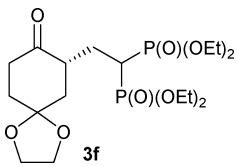
The enantiomeric excesses of the disubstituted ketones **3b–f** and **6** were determined by HPLC. For this purpose, it was necessary to prepare racemic standards for comparison of retention times, and this was done *via* a Michael addition reaction of ketone enolates formed in the presence of DBU to vinyl bisphosphonate **2**, in an adaptation of the method developed by Schlachter *et al.*[11a] and Nugent *et al.*[11b] for the synthesis of geminal bisphosphonates **F** and **G** (Scheme 3). For ketones with no absorption in the UV-VIS region of the spectrum, a method to convert them into their hydrazones by reaction with 2,4-dinitrophenylhydrazine (Scheme 4) was used.[34] These reactions were selective, giving the products cleanly in 17 h at r.t. When the hydrazone-forming reactions are mediated by catalytic amounts of acid, no racemization is found to occur.[34b] Presumably the compounds isolated are the more stable *E*-isomers.



Scheme 3 The Michael addition to vinylidene bisphosphonate catalyzed by DBU. The relative configuration observed for the major product is opposite to that obtained with the chiral catalyst.

The Michael addition reaction was also applied to the alkylation of cyclopentanone and some derivatives, but they showed different reaction patterns from the cyclohexanones. Cyclopentanone was very reactive. When the ketone and the bisphosphonate were reacted in the usual 10 : 1 ratio, there was complete conversion to products within 1.5 h. However, a 6 : 94 mixture of 2-monosubstituted to 2,5-disubstituted cyclopentanone was obtained (Scheme 5). With a 1 : 1 ratio of ketone to bisphosphonate, after 1 h there was already 60% conversion, but the same product

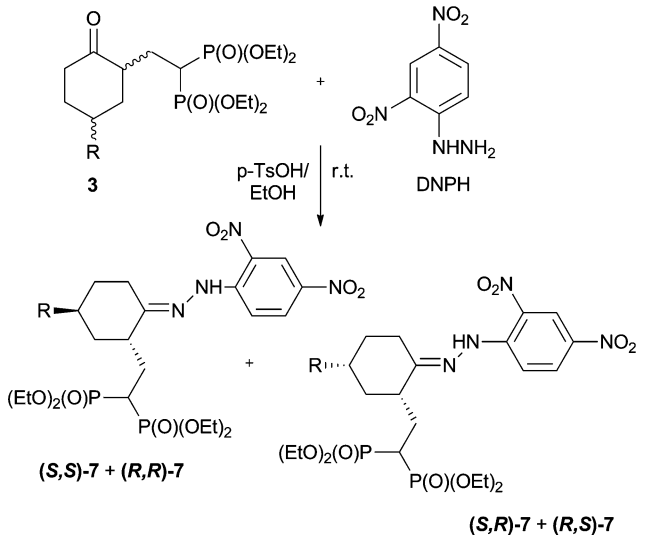
Table 3 Asymmetric Michael addition of cyclohexanones to tetraethyl vinylidene bisphosphonate[a]

Entry	Ketone	Product	Time	Yield[b] [%]	*dr*[c] [*cis*/*trans*]	*ee*[d] [*cis*/*trans*]
1	 **1a**	 **3a**	17 h	61	—	40
2	 **1b**	 **3b**	7 h	78	8 : 92	62 : 76
3[e]	 **5**	 **6**	7 d	80	14 : 86	0
4	 **1c**	 **3c**	17 h	86	18 : 82	83 : 71
5	 **1d**	 **3d**	17 h	92	30 : 70	88 : 78
6	 **1e**	 **3e**	17 h	72	30 : 70	86 : 77
7[f]	 **1f**	 **3f**	25 h	62	—	64

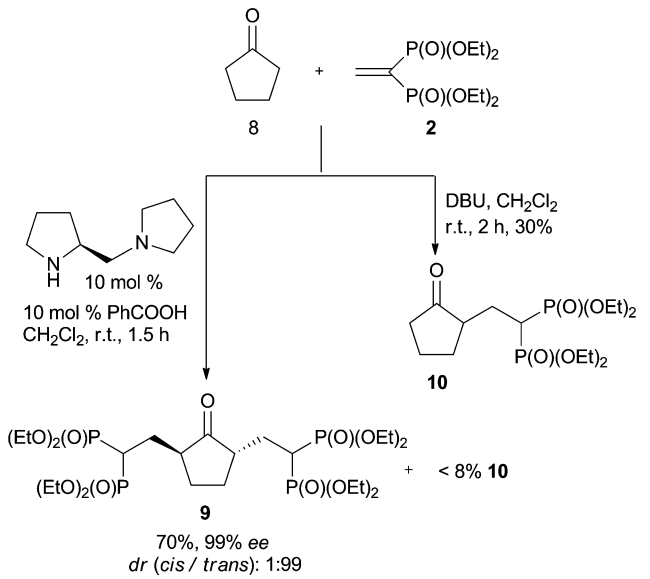
[a] Conditions: r.t., bisphosphonate (1 mM) : ketone : catalyst : PhCOOH = 1 : 10 : 0.1 : 0.1. [b] After isolation by column chromatography. [c] Determined by ^{31}P NMR spectroscopy. [d] Determined by ^{13}C NMR spectroscopy (entry 1), or by chiral HPLC neat, or after conv. into 2,4-dinitrophenylhydrazones (entries 4–7). [e] Reaction in [bmin]PF_6, conv. shown. [f] A ratio of bisphosphonate (1 mM) : ketone = 1 : 4 was used.

distribution was obtained. Thus, either the 2-monosubstituted cyclopentanone is much more reactive towards the catalyst than the unsubstituted ketone, or an enamine intermediate reacts with the vinyl phosphonate to produce an iminium salt that is so reactive, that after protonation it is deprotonated again to form a new enamine, before hydrolysis takes place. Hence there is a second addition, and the disubstituted product is preferentially obtained. Disubstituted cyclopentanone **9** is chiral and has a high optical rotation ($[\alpha]_D^{22}$ −30.2, c = 0.69) in $CHCl_3$. This indicates that the compound is *trans* disubstituted, with C_2 symmetry, since a *cis*-disubstituted compound would be *meso* and optically inactive. Bisphosphonate **9** has to be chromatographed fast on silica gel, else it decomposes partially *via* a retro-Michael reaction. In contrast to this reaction, when the preparation of a racemic sample was attempted with the DBU-promoted addition, the product obtained was primarily mono-substituted, even when the reaction was allowed to proceed for 17 h, with a 4 : 1 bisphosphonate to ketone ratio, and a 3-fold excess of DBU. In order to obtain a racemic substrate for HPLC analysis, bisphosphonate **9** was refluxed in ethanolic KOH for 17 h, which resulted in full racemization, as evidenced by the optical rotation of the product. DNPH derivatives were subsequently prepared.

1-Indanone showed a similar behaviour to 2-phenylcyclohexanone. When the reaction was attempted with a



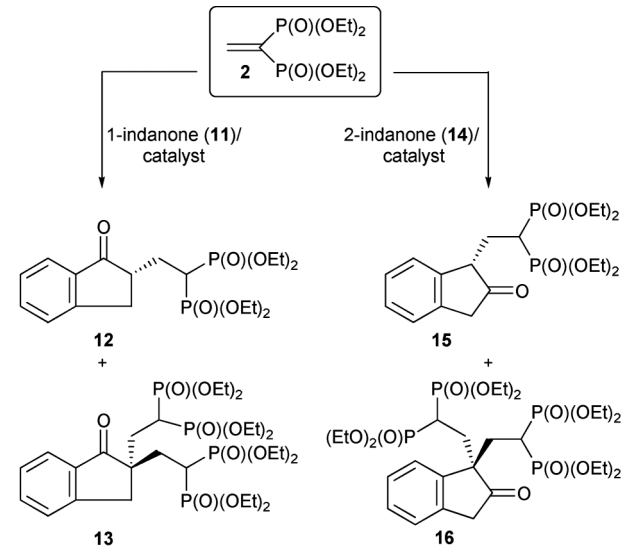
Scheme 4 The synthesis of DNPH adducts for *ee* determination by HPLC.



Scheme 5 The Michael addition reaction of cyclopentanone to vinyl bisphosphonate **2**.

5 : 1 ratio of ketone to bisphosphonate, after 17 h there were only traces of product. Bisphosphonate **12** could eventually be prepared in 81% yield after a 46 h reflux. Unfortunately this product was racemic. Dialkylated indanone **13** was also obtained in low amount (Scheme 6). The synthesis of bisphosphonate **12** had been previously described, in a DBU catalyzed reaction.[11] Under our standard conditions, a 34 : 66 mixture of monosubstituted to disubstituted indanone was obtained.

The alkylation of 2-indanone was also attempted. This substrate was very reactive, and under standard conditions the enamine-catalyzed reaction was complete in just over 1.5 h. However, a mixture of approx. 70 : 30 of monosubstituted **15** to disubstituted ketone **16** was obtained, plus small amounts of non-phosphorus-containing condensation products. When the ratio of the reagents was lowered to 3 : 1 2-indanone to bisphosphonate, there was complete conversion in 17 h, with a similar product distribution.



Catalyst	Product distribution	
	12 / 13	**15 / 16**
Chiral diamine / PhCOOH	92 : 8	70 : 30
DBU	34 : 66	12 : 82

Scheme 6 The Michael addition reaction of 1-indanone and 2-indanone.

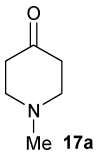
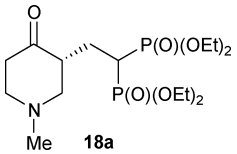
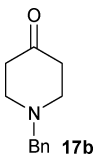
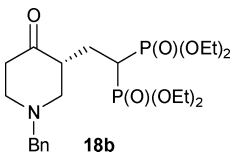
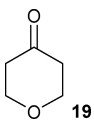
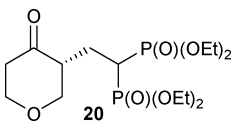
Very small amounts of other products also formed, which made product isolation difficult. In addition, some decomposition was also observed during chromatography. Although this product could be isolated pure enough for spectroscopic identification, it was never pure enough to allow an unambiguous determination of the enantiomeric excess, and hence this was abandoned.

The DBU promoted reaction gave, under standard conditions, a complex mixture of products. After optimization, it was possible to obtain one product selectively by running the reaction for 2 h in an ice bath. However, only disubstituted product was obtained. This product was identical to the disubstituted product obtained in the enamine-catalyzed reaction. Unlike the reaction with cyclopentanone, with 2-indanone the second alkylation took place on the same carbon atom, showing the large preferential formation of the trisubstituted enolate over the disubstituted one for the second addition. The presence of two substituents could be confirmed by the integration in the ^{1}H NMR spectrum and by mass spectrometry. Disubstitution on the same carbon atom could be unambiguously confirmed by a DEPT experiment, which showed, besides the presence of signals corresponding to CH_2 groups of the POEt moieties and the methylene groups β to phosphorus, the presence of an additional CH_2 signal at 42.85 ppm.

In order to further examine the potentialities of the enamine promoted reaction, it was decided to extend the substrate range to 4-tetrahydropyranone and 4-piperidones. The results are presented in Table 4. There was smooth addition in all cases to give the desired bisphosphonates as single reaction products. The 4-piperidones obtained had high enantioselectivities of up to 90%. However, it was found that these compounds racemized partially during chromatography on silica gel, and hence the enantiomeric excesses shown in Table 4 were determined prior to chromatographic purification.

The reaction with 4-tetrahydropyranone gave the product in a high yield of 88%, but with a lower asymmetric induction, similar to that obtained in the reaction of unsubstituted cyclohexanone.

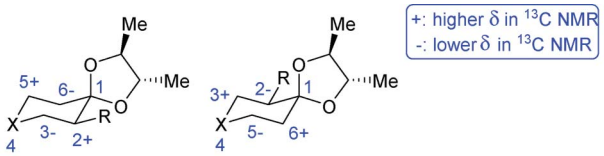
Table 4 Asymmetric Michael addition of 4-piperidones and 4-tetrahydropyranone to tetraethyl vinylidene bisphosphonate[a]

Entry	Ketone	Product	Time [%]	Yield[b] [%]	*ee*[c] [%]
1	 **17a**	 **18a**	5	58	90
2	 **17b**	 **18b**	6	61	65
3	 **19**	 **20**	17	88	40

[a] Conditions: r.t., bisphosphonate (1 mM) : ketone : catalyst : PhCOOH = 1 : 10 : 0.1 : 0.1. [b] After isolation by column chromatography. [c] Determined by ^{13}C NMR spectroscopy (entry 3), or by chiral HPLC.

These results show that this new method of synthesis of geminal 4-oxobisphosphonates has wide applicability and may be used for target oriented synthesis with substrates containing other functional groups.

In these reactions, the absolute configuration of the major enantiomer produced was determined by ^{13}C NMR spectroscopy. The spectra of the diastereomeric acetals **4** was used and the empirical method of Lèmiere *et al.*[35] As a consequence of the Cahn–Ingold–Prelog sequence rules, acetals of 2-substituted cyclohexanone **3a** fitted the model derived for 2-benzylcyclohexanone (Fig. 3). The configuration of **3a** was found to be 2*S*. A similar result was obtained for bisphosphonate **20**. The absolute configuration is believed to be the same for the other products obtained, assuming that they were formed by enamine catalysis and similar reaction pathways.



The data for **4** and **21** fit the empirical model for the 2*S* configuration.

C NMR chemical shifts of the acetals used for the assignment of the absolute configuration

Isomer	δC-1	δC-2	δC-3	δC-4	δC-5	δC-6
4 major	109.9	42.3	24.5	29.2	23.3	36.8
4 minor	110.0	43.1	25.0	28.9	23.8	36.3
21 major	107.2	42.8	69.1	-	65.9	36.8
21 minor	107.2	43.5	69.0	-	66.0	36.4

Fig. 3 Determination of the absolute configuration of **3a** and **20**.[35]

The absolute configuration determined is consistent with the preferential formation of an *anti* enamine (Fig. 4) in which the double bond is oriented away from the bulky substituent at position 2 of the pyrrolidine ring. Reaction can then take place at the *Re* face as in **K**, or the *Si* face as in **L**. When the catalyst is protonated, phosphonate approach to the *Re* face gives a tight acyclic synclinal transition state **K**, which can be stabilized by electrostatic interactions between a) the partially positive nitrogen atom of the enamine, b) the partially negatively charged oxygen atom of the phosphonate group and c) the protonated nitrogen atom on the second pyrrolidine ring. If attack were to occur on the *Si* face, the nitrogen atom of the second ring would be too far away from the reaction centre and the stabilization brought about by factor c) would not take place. This reaction model proposed is in agreement with Seebach's model for Michael addition reactions with pre-formed enamines from pyrrolidines.[36] In our reactions in aprotic media the products also had a 2*S* configuration. Presumably under these conditions the nitrogen atom on the second ring stabilizes the partially positively charged phosphorus atom in transition state **M**.

The relative configuration, which was established to be *trans* for **3c**, can be explained by an axial approach of the electrophilic vinyl bisphosphonate to an enamine in which the 6-membered ring is in the more stable chair-like conformation, and both the bulky pyrrolidine ring and the 4-methyl group occupy an equatorial position as in **O**. In this way 1,3-allylic strain as well as 1,3-diaxial interactions are minimized (Fig. 5). This is in general agreement with existing knowledge on reactions of pyrrolidine enamines of 1,4-disubstituted cyclohexanones.[37]

Overall the results provide further evidence supporting the current wave of thought that in organocatalytic reactions mediated by chiral amines, enamines are involved as intermediate species.

Conclusion

We have developed a method for the diastereo- and enantioselective synthesis of functionalized geminal bisphosphonates, which are chiral structural analogues of biologically active compounds. The organocatalyzed Michael addition reaction protocol developed could be successfully applied to 4-substituted cyclohexanones, piperidones and cyclopentanones, and it gave several new geminal 4-oxobisphosphonates in high yields, good diastereoselectivities and very high enantioselectivities. Aromatic substitution at position 2 of the ring retarded the reaction considerably, and although products could be obtained, they were racemic. Studies to evaluate the biological activity of these compounds are under way.

Experimental

Synthesis of substrates

Tetraethyl vinylbisphosphonate (2). This compound was prepared from paraformaldehyde and commercially available tetraethyl methylenebis(phosphonate) according to a literature procedure.[38]

1,4-Cyclohexanedione monoethylene acetal (1f). This monoacetal used as a substrate in Michael addition reactions was prepared

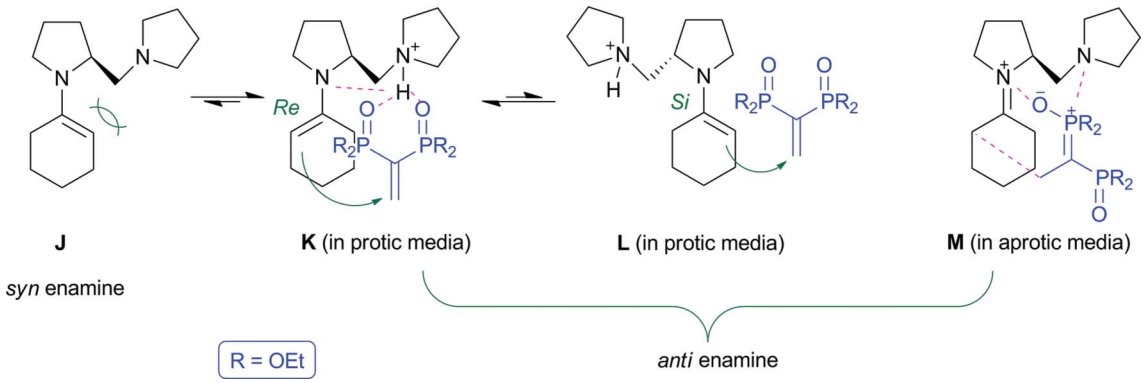


Fig. 4 Proposed facial selectivity for the transition state.

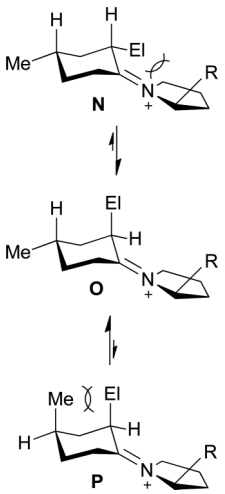


Fig. 5 The preferred conformation for the addition reaction.

from 1,4-cyclohexanedione and ethylene glycol according to a literature procedure.[39]

General procedure for the asymmetric Michael addition reaction. To vinyl *gem*-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (10.0 mmol), (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.1 mmol) and benzoic acid (0.1 mmol). The solution was stirred at room temperature, under argon, for the times specified. The reaction was then quenched with a concentrated solution of ammonium chloride, and the products were extracted with dichloromethane. The combined extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel. In some cases, as specified for each compound in the supporting information,† the presence of benzoic acid in the crude product interfered with product isolation during chromatography. The work-up procedure was then modified to resolve this problem as follows: when the reaction was complete, water was added, the mixture was treated with a saturated solution of $NaHCO_3$ and the product was extracted with dichloromethane. The organic phase was then washed successively with a 1 M HCl solution and with water, filtered through anhydrous Na_2SO_4, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

Tetraethyl [2-(5′-*tert*-butyl-2′-oxocyclohexyl)ethylidene]bisphosphonate (3d). Prepared from ethylidene bisphosphonate **2** and 4-*tert*-butylcyclohexanone, according to the general procedure. The product was obtained as a 70 : 30 (*trans*/*cis*) mixture of diastereoisomers, as determined by ^{31}P NMR spectroscopy. The crude product was purified by column chromatography on silica gel with 1 : 1 acetone/$CHCl_3$ to give product **3d** as a mixture of two diastereoisomers, in the form of a colourless viscous liquid (78 mg, 92%). The diastereoisomers separate partially during chromatography, but complete separation requires several chromatographies. **Major diastereoisomer**: δ_H (400 MHz; $CDCl_3$) 0.89 (s, 9 H, 3 × CH_3 of *t*-Bu), 1.33 (m, 12 H, $OCCH_3$), 1.45–1.60 (m, 2 H, 2 × 3′-H), 1.63–1.84 (m, 2 H, 2 × 4′-H), 1.87–2.04 (m, 2 H, $PCCH_2$), 2.24–2.56 (m, 4 H, PCHP + 1′-H + 2 × 6′-H), 2.75–2.86 (m, 1 H, 1′-H), 4.03–4.26 (m, 8 H, OCH_2) ppm; δ_C (100 MHz; $CDCl_3$) 16.37 (4 × $OC\underline{C}H_3$), 25.71 (CH_2, $PCCH_2$), 27.27 (3 × CH_3 of *t*-Bu), 29.67 (Cq, *t*-Bu), 31.50 (CH_2, C-4′), 32.52 (CH_2, C-5′), 33.78 (CH, t, J_{CP} 133.4 Hz, PCHP), 38.62 (CH_2, C-6′), 41.72 (CH_2, C-3′), 46.70 (CH_2, C-1′), 62.64 (m, CH_2, 4 × OCH_2), 215.0 (Cq, C═O); δ_P (162 MHz; $CDCl_3$) 23.67, 24.06; *m*/*z* 455 (M+1, 3), 454 (M^+, 12), 397 (16), 351 (7), 317 (24), 301 (22), 289 (10), 288 (100), 273 (5), 271 (5), 261 (29), 244 (6), 233 (14), 205 (6), 187 (8), 177 (6), 171 (5), 165 (6), 159 (8), 152 (21), 136 (5), 122 (7), 112 (5), 110 (7), 109 (7), 98 (7), 97 (8), 96 (5), 95 (7), 83 (10), 82 (6), 81 (8), 79 (5), 72 (23), 70 (5), 69 (12), 67 (9), 59 (32), 57 (18), 55 (20), 54 (5); **minor diastereoisomer**: δ_H 0.84 (s, 9 H, 3 × CH_3 of *t*-Bu), 1.00–1.18 (m, 1 H, 6′-H), 1.18–1.44 (m, 1 H, 4′-H), 1.24–1.31 (m, 12 H, $OCCH_3$), 1.49–1.69 (m, 2 H, PCCH + 5′-H), 1.97–2.13 (m, 2 H, 4′-H + 6′-H), 2.19–2.37 (m, 3 H, PCCH + 2 × 3′-H), 2.71 (tq, 1 H, *J* 4.9, 9.0, 23.7 Hz, PCHP), 2.81–2.95 (m, 1 H, 1′-H), 4.00–4.22 (m, 8 H, OCH_2) ppm; δ_C 16.44 (4 × $OC\underline{C}H_3$), 26.35 (CH_2, $PCCH_2$), 27.67 (3 × CH_3 of *t*-Bu), 29.03 (CH_2, C-4′), 29.72 (Cq, *t*-Bu), 32.47 (CH, t, J_{CP} 164.7 Hz, PCHP), 35.98 (CH_2, C-6′), 41.74 (CH_2, C-3′), 47.00 (CH, C-5′), 47.52 (CH, m, C-1′), 62.60 (m, 4 × OCH_2), 213.3 (Cq, C═O); δ_P (162 MHz; $CDCl_3$) 23.62, 24.28; *m*/*z* 456 (M+2, 0.2), 455 (M+1, 2), 454 (M^+, 10), 397 (10), 317 (20), 301 (22), 289 (14), 288 (80), 261 (28), 260 (10), 233 (15), 204 (32), 202 (100), 187 (11), 171 (11), 167 (31), 152 (22), 149 (33), 144 (25), 133 (16), 132 (12), 118 (12), 117 (34), 116 (20), 115 (37), 109 (17), 105 (18), 104 (28), 99 (10), 98 (11), 93 (10), 91 (17), 89 (13), 79 (10), 77 (17), 76 (19), 74 (12), 69 (10), 67 (10), 63 (11), 57 (34), 58 (10), 55 (18), 51 (12), 50 (13), 46 (12), 45 (26) (Found C,

50.62; H, 9.05 (major + minor). Calcd for $C_{20}H_{40}O_7P_2$: C, 52.86; H, 8.87). The enantiomeric excesses were determined by HPLC on a chiral column after conversion of the diastereoisomers into their 2,4-dinitrophenylhydrazones,[34] (Chiralpak AD-H, 16% *i*-PrOH in hexane, 1.0 mL min^{-1}, 365 nm): t_R = 14.5 (*cis*, major), 25.6 (*trans*, major), 40.1 (*cis*, minor), 45.8 (*trans*, minor) min, relative to the racemic sample prepared with DBU as base.

General procedure for the Michael addition reaction catalyzed by DBU. This procedure, used for the preparation of racemic standards, is a modification of the method described by Nugent *et al.*[11] for analogous compounds. To vinyl *gem*-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (1.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.0 mmol). The solution was stirred at room temperature, under argon, for one hour. Water was then added, and the products were extracted with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

***rac*-Tetraethyl [2-(5′-*tert*-butyl-2′-oxocyclohexyl)ethylidene]bisphosphonate.** Prepared from ethylidene bisphosphonate **2** and 4-*tert*-butylcyclohexanone, according to the general procedure. The product was obtained as a 25 : 75 (*trans*/*cis*) mixture of diastereoisomers as determined by ^{31}P NMR spectroscopy. The crude product was purified by column chromatography on silica gel with 3 : 2 acetone/$CHCl_3$ to give the product as a mixture of two diastereoisomers, in the form of a colourless viscous liquid (39 mg, 41%). The diastereoisomers separate partially during chromatography, but complete separation requires several chromatographies. The spectroscopic data of the product agrees with that of the product obtained in the asymmetric reaction.

General procedure for the synthesis of 2,4-dinitrophenylhydrazine adducts[34]. The bisphosphonate (0.20 mmol) was dissolved in ethanol (1.0 mL) and 2,4-dinitrophenylhydrazine (0.20 mmol) was added, followed by a catalytic amount of *para*-toluenesulfonic acid. The mixture was stirred at room temperature for 17 h. An aqueous saturated solution of sodium bicarbonate was added, and the compound was extracted with dichloromethane. The combined organic extracts were washed with water, filtered through anhydrous sodium sulfate, and the solvent was then removed in a rotary evaporator, to give a yellow-orange solid.

Dinitrophenylhydrazine adduct of tetraethyl [2-(5′-*tert*-butyl-2′-oxocyclohexyl)ethylidene]bisphosphonate (7a). Prepared from **3f** (from the major diastereoisomer of the DBU-catalyzed reaction) and dinitrophenylhydrazine according to the general procedure. The crude product was purified by preparative TLC on silica gel with EtOAc/acetone 3 : 2 as eluent to give **7a** as an orange hygroscopic solid (34 mg, 77%). δ_H (400 MHz; $CDCl_3$) 0.89 (s, 9 H, 3 × CH_3, *t*-Bu), 1.06 (q, 1 H, *J* 13 Hz), 1.24–1.40 (superimp. m, 1 H), 1.26–1.40 (m, 12 H, 4 × $OCCH_3$), 1.44–1.56 (m, 1 H), 1.80–1.94 (m, 1 H), 2.00 (td, *J* 2.0, 4.8 Hz, 1 H), 2.04–2.16 (m, 2 H), 2.60–2.80 (m, 1 H), 2.82–3.06 (m, 3 H), 4.08–4.32 (m, 8 H, 4 × OCH_2), 8.19 (d, 1 H, *J* = 9.2 Hz, H-6″), 8.28 (dd, 1 H, *J* 2.4, 9.2 Hz, H-5″), 9.12 (d, 1 H, *J* 2.4 Hz, H-3″), 11.28 (s, 1 H, N-NH); δ_C (100 MHz; $CDCl_3$) 16.40–16.54 (m, CH_3, 4 × $OCCH_3$), 25.03 (d, CH_2, J_{CP} 6 Hz, $PCCH_2$), 27.18 (CH_2, C-4′), 27.52 (CH_3, 3 × CH_3 of *t*-Bu), 28.02 (CH_2, C-3′), 34.48 (d, CH, J_{CP} 134 Hz, PCH), 36.68 (CH_2, C-6′), 42.00 (Cq, *t*-Bu), 42.44–42.60 (m, CH, PCCCH), 47.27 (CH, C-5′), 62.20–62.77 (m, CH_2, 4×OCH_2), 116.7 (CH, C-6″, Ar), 123.5 (CH, C-3″, Ar), 128.9 (Cq, C-2″, Ar), 130.0 (CH, C-5″, Ar), 137.6 (Cq, C-4″, Ar), 145.5 (Cq, C-1″, Ar), 162.4 (C═N); δ_P (162 MHz; $CDCl_3$) 24.36, 24.61; *m*/*z* 634 (M^+, 2), 599 (13), 515 (16), 487 (10), 452 (31), 435 (22), 407 (13), 379 (11), 377 (20), 351 (14), 317 (19), 301 (52), 289 (22), 288 (100), 273 (16), 267 (13), 261 (46), 260 (12), 245 (13), 233 (31), 217 (13), 205 (21), 200 (11), 189 (20), 187 (19), 177 (30), 165 (26), 158 (22), 152 (34), 137 (17), 135 (10), 125 (14), 110 (11), 109 (49), 108 (10), 93 (12), 57 (47), 46 (10) (Found C, 48.80; N, 8.55; H, 7.11. Calcd for $C_{26}H_{44}N_4O_{10}P_2$: C, 49.10; N, 8.83; H, 6.99).

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Notes and references

1 R. G. G. Russell, *Bone*, 2011, **49**, 2–19 special issue on bisphosphonates.
2 (*a*) J. A. Urbina, B. Moreno, S. Vierkotter, E. Oldfield, G. Payares, C. Sanoja, B. N. Bailey, W. Yan, D. A. Scott, S. N. J. Moreno and R. Docampo, *J. Biol. Chem.*, 1999, **274**, 33609–33615; (*b*) R. Docampo, *Curr. Pharm. Des.*, 2001, **7**, 1157–1164; (*c*) R. Docampo and S. N. J. Moreno, *Curr. Drug Targets: Infect. Disord.*, 2001, **1**, 51–61; (*d*) J. A. Urbina, *Acta Trop.*, 2010, **115**, 55–68.
3 (*a*) M. B. Martin, J. S. Grimley, J. C. Lewis, H. T. Heath III, B. N. Bailey, H. Hendrick, V. Yardley, A. Caldera, R. Lira, J. A. Urbina, S. N. J. Moreno, R. Docampo, S. L. Croft and E. Oldfield, *J. Med. Chem.*, 2001, **44**, 909–916; (*b*) E. Kotsikorou, Y. Song, J. M. W. Chang, S. Faelens, Z. Tovian, E. Broderick, N. Bakalara, R. Docampo and E. Oldfield, *J. Med. Chem.*, 2005, **48**, 6128–6139.
4 (*a*) M. B. Martin, J. M. Sanders, H. Kendrick, K. de Luca-Fradley, J. C. Lewis, J. S. Grimley, E. M. van Bussel, J. R. Olsen, G. A. Meints, A. Burzynska, P. Kafarski, S. L. Croft and E. Oldfield, *J. Med. Chem.*, 2002, **45**, 2904–2916; (*b*) S. Ghosh, J. M. W. Chan, C. R. Lea, G. A. Meints, J. C. Lewis, Z. S. Tovian, R. M. Flessner, T. C. Loftus, I. Bruchhaus, H. Kendrick, S. L. Croft, R. G. Kemp, S. Kobayashi, T. Nozaki and E. Oldfield, *J. Med. Chem.*, 2004, **47**, 175–187.
5 (*a*) D. Simoni, N. Gebbia, F. P. Invidiata, M. Eleopra, P. Marchetti, R. Rondanin, R. Baruchello, S. Provera, C. Marchioro, M. Tolomeo, L. Marinelli, V. Limongelli, E. Novellino, A. Kwaasi, J. Dunford, S. Buccheri, N. Caccamo and F. Dieli, *J. Med. Chem.*, 2008, **51**, 6800–6807; (*b*) Y. Zhang, A. Leon, Y. Song, D. Studer, C. Haase, L. A. Koscielski and E. J. Oldfield, *J. Med. Chem.*, 2006, **49**, 5804–5814; (*c*) J. M. Sanders, S. Ghosh, J. M. Chan, G. Meints, H. Wang, A. M. Raker, Y. Song, A. Colantino, A. Burzynska, P. Kafarski, C. T. Morita and E. Oldfield, *J. Med. Chem.*, 2004, **47**, 375–384.
6 (*a*) F. H. Ebetino, A.-M. L. Hogan, S. Sun, M. K. Tsoumpra, X. Duan, J. T. Triffitt, A. A. Kwaasi, J. E. Dunford, B. L. Barnett, U. Oppermann, M. W. Lundy, A. Boyde, B. A. Kashemirov, C. E. McKenna and R. G. G. Russell, *Bone*, 2011, **49**, 20–33; (*b*) E. Oldfield, *Acc. Chem. Res.*, 2010, **43**, 1216–1226; (*c*) H. Fleisch, *Endocr. Rev.*, 1998, **19**, 80–100.
7 C. E. Sanz-Rodriguez, J. L. Concepción, S. Pekerar, E. Oldfield and J. A. Urbina, *J. Biol. Chem.*, 2007, **282**, 12377–12387.
8 L. Widler, K. A. Jaeggi and J. R. Green, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **144**, 5–8.
9 C. E. McKenna, B. A. Kashemirov, K. M. Błażewska, I. Mallard-Favier, C. A. Stewart, J. Rojas, M. W. Lundy, F. H. Ebetino, R. A. Baron, J. E. Dunford, M. L. Kirsten, M. C. Seabra, J. L. Bala, M. S. Marma, M. J. Rogers and F. P. Coxon, *J. Med. Chem.*, 2010, **53**, 3454–3464.
10 (*a*) A. M. M. Phillips and T. A. Modro, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1875–1879; (*b*) M. T. Barros, C. D. Maycock and A. M. Faísca Phillips, *Tetrahedron: Asymmetry*, 2005, **16**, 2946–2953; (*c*) M. T. Barros and A. M. Faísca Phillips, *Molecules*, 2006, **11**, 177–196; (*d*) M. T. Barros and A. M. Faísca Phillips, *Eur. J. Org. Chem.*, 2007, 178–185.
11 (*a*) S. T. Schlachter, L. A. Galinet, S. K. Shields, D. G. Aspar, C. J. Dunn, N. D. Staite and R. A. Nugent, *Bioorg. Med. Chem. Lett.*, 1998,

8, 1093–1096; (*b*) R. A. Nugent, S. T. Schlachter, M. Murphy, C. J. Dunn, N. D. Staite, N. A. Galinet, S. K. Shields, H. Wu, D. G. Aspar and K. A. Richard, *J. Med. Chem.*, 1994, **37**, 4449–4454.
12 (*a*) P. Savignac and B. Iorga, *Modern Phosphonate Chemistry*, CRC Press, Boca Raton, 2003, chapter 7, pp. 319–404; for a recent review on the synthesis and reactions of oxophosphonates see; (*b*) A. Atmani, F. Memmou and J.-P. Bouillon, *C. R. Chim.*, 2009, **12**, 963–1001.
13 See, for example M. B. Robinson, S. L. Crooks, R. L. Johnson and J. F. Koerner, *Biochemistry*, 1985, **24**, 2401–2405 and references therein.
14 M. G. Moloney, *Nat. Prod. Rep.*, 2002, **19**, 597–616.
15 For recent reviews on the Michael addition reaction in the synthesis of phosphonates see: (*a*) T. Janecki, J. Kędzia and T. Wąsek, *Synthesis*, 2009, **8**, 1227–1254; (*b*) T. Minami and J. Motoyoshiya, *Synthesis*, 1992, 333–349.
16 M. L. Lolli, L. Lazzarato, A. DiStilo, R. Fruttero and A. Gasco, *J. Organomet. Chem.*, 2002, **650**, 77–83.
17 S. H. Szajnman, A. Montalvetti, Y. Wong, R. Docampo and J. B. Rodriguez, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3231–3235.
18 G. Sturtz and J. Guervenou, *Synthesis*, 1991, 661–662.
19 R. A. Nugent, C. J. Dunn, N. D. Staite, M. J. Murphy, S. T. Schlachter, D. G. Aspar, S. K. Shields and L. A. Galinet, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **109**, 229–232.
20 For recent general reviews on catalytic asymmetric conjugate addition reactions see: (*a*) M. Thirumalaikumar, *Org. Prep. Proced. Int.*, 2011, **43**, 67–129; (*b*) J.-X. Ji and A. S. C. Chan, Catalytic Asymmetric Conjugate Addition, in *Catalytic Asymmetric Synthesis*, ed I. Ojima, Wiley-VCH, New Jersey, 3rd edn, 2010, ch. 8; for recent reviews on organocatalytic asymmetric conjugate addition reactions see: (*c*) N. Li, G. H. Xi, Q. H. Wu, W. H. Liu, J. J. Ma and C. Wang, *Chinese J. Org. Chem.*, 2009, **29**, 1018–1038; (*d*) D. Enders, C. Wang and J. W. Bats, *Angew. Chem., Int. Ed.*, 2008, **47**, 7539–7542; (*e*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, **14**, 2065–2092; (*f*) S. Sulzer-Mossé and A. Alexakis, *Chem. Commun.*, 2007, 3123–3135; (*g*) C. Bressy and P. I. Dalko, in *Enantioselective Organocatalysis*, ed P. I. Dalko, Wiley-VCH, Weinheim, 2007, ch. 2; (*h*) D. Almasi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299–365; (*i*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, **11**, 1701–1716; (*j*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, **12**, 1877–1894.
21 Y. Kato, Z. H. Chem, S. Matsunaga and M. Shibasaki, *Synlett*, 2009, 1635–1638.
22 (*a*) For recent general reviews in organocatalysis see, for example H. Pellissier, *Recent Developments in Organocatalysis*, ed. J. J. Spivey, Springer, Cambridge, 1st edn, 2010, RSC Catalysis series, vol. 3; (*b*) S. Bertelsen and K. A. Jorgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178–2189; (*c*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638–4660; (*d*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007.
23 L. Albrecht, A. Albrecht, H. Krawczyk and K. A. Jörgensen, *Chem.–Eur. J.*, 2010, **16**, 28–28.
24 S. Sulzer-Mossé, M. Tissot and A. Alexakis, *Org. Lett.*, 2007, **9**, 3749–3752.
25 S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli and Y. Filinchuk, *Chem.–Eur. J.*, 2009, **15**, 3204–3220.
26 For recent reviews on the use of chiral amines as organocatalysts see: (*a*) P. M. Pihko, I. Majander and A. Erkkila, *Top. Curr. Chem.*, 2010, **291**, 29–75; (*b*) L.-W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, 2009, (14), 1807–1821; (*c*) G. Amarante and F. Coelho, *Quim. Nova*, 2009, **32**, 469–481; (*d*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138–6171; (*e*) F. Peng and Z. Shao, *J. Mol. Catal. A: Chem.*, 2008, **285**, 1–13; (*f*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569.
27 M. Capuzzi, D. Perdicchia and K. A. Jørgensen, *Chem.–Eur. J.*, 2008, **14**, 128–135.
28 M. T. Barros and A. M. Faísca Phillips, *Eur. J. Org. Chem.*, 2008, **15**, 2525–2529.
29 P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953–2989.
30 See, for example, N. Rameshkumar, A. Veena, R. Ilavarasan, M. Adiraj, P. Shanmugapandiyan and S. K. Sridhar, *Biol. Pharm. Bull.*, 2003, **26**, 188–193 and references therein.
31 For a first report on the use of this compound as an organocatalyst see S. Saito, M. Nakadai and H. Yamamoto, *Synlett*, 2001, 1245–1248.
32 For a method on the determination of the enantiomeric purity of chiral ketones using their butane-2,3-diol acetals see H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, 1977, 2183–2186.
33 D. Enders, A. Nühring and J. Runsink, *Chirality*, 2000, **12**, 374–377.
34 For previous descriptions on the use of aromatic hydrazines to derivatize ketones for configuration studies see, for example: (*a*) Y. Kawai, M. Hayashi and N. Tokitoh, *Tetrahedron*, 2005, **61**, 5049–5055; (*b*) Y. Kawai, M. Hayashi and N. Tokitoh, *Tetrahedron Lett.*, 2002, **43**, 465–467.
35 G. L. Lemière, R. A. Domisse, J. A. Lepoivre, J. C. Alderweireldt, H. Hiemstra, H. Wynberg, J. B. Jones and E. J. Toone, *J. Am. Chem. Soc.*, 1987, **109**, 1363–1370.
36 (*a*) S. J. Blarer, W. B. Schweizer and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 1637–1654; (*b*) D. Seebach and J. Golinski, *Helv. Chim. Acta*, 1981, **64**, 1413–1423.
37 For *cis–trans* equilibration in 2,*x*-disubstituted cyclohexanones see, for instance, F. Johnson, L. G. Duquette, A. Whitehead and L. C. Dorman, *Tetrahedron*, 1974, **30**, 3241–3251.
38 C. R. Degenhardt and D. C. Burdsall, *J. Org. Chem.*, 1986, **51**, 3488–3490.
39 B. J. Lambert, *J. Am. Chem. Soc.*, 1967, **89**, 1836–1840.

