Asymmetric Conjugate Additions of Chiral Phosphonamide Anions to α,β-Unsaturated Carbonyl Compounds. A Versatile Method for Vicinally Substituted Chirons

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Reactions of anions derived from chiral nonracemic allyl, crotyl, and cinnamyl bicyclic C_2-symmetrical phosphonamides with α,β-unsaturated cyclic ketones, esters, lactones, and lactams take place at the γ-position of the reagents. The products are diastereomerically pure or enriched β-substituted carbonyl compounds. The method also provides easy access to vicinal substitution of as many as three stereogenic centers including in some cases quaternary carbon atoms, in a one-pot sequence.

Introduction

Asymmetric 1,4-addition reactions to α,β-unsaturated carbonyl compounds are among the most frequently used methods for stereoselective C−C bond construction.[1] The utilization of chiral sulfur- and phosphorus-based stabilized allylic-type anions has shown great promise as a powerful method in asymmetric Michael-type reactions.[2−7]

Individual enantiomers of allylic phosphine oxides prepared by Haynes and co-workers[4] were shown to undergo 1,4-additions to cyclopentenones with good to excellent stereoselectivity. Hua and co-workers[5] reported high levels of stereoselectivity in 1,4-additions of 2-allyl-1,3,2-oxazaphospholidine 2-oxides to simple α,β-unsaturated cyclic ketones and 3,4-dihydro-4-oxo-(2*H*)-pyridine-L-carboxylate. Denmark and co-workers[6] described high levels of stereocontrol in 1,4-additions of anions derived from 2-allyl-1,3,2-oxazaphosphorinane 2-oxide to simple carbocyclic enones. Similar results were achieved by Fuji and co-workers,[7] who have used allyl and crotyl phosphonates prepared from 1,1′-binaphthalene-2,2′-diol in the same type of reaction.

The majority of the above-cited examples consist of additions to cyclic enones, and it remains unclear whether other classes of α,β-unsaturated carbonyl compounds, such as lactones, lactams, esters, etc., would provide the same degree of stereo- and regiochemical efficiency. Another practical problem associated with most of the above-mentioned methods is the need to secure single enantiomers of the phosphorus reagents, since diastereomeric reagents have exhibited different levels of selectivity.[8] Separations of diastereomeric reagents are usually done by fractional crystallization or by chromatography.[8]

Our laboratory has had a long-standing interest in the design, synthesis, and applications of phosphorus-containing chiral reagents based on phosphonamides derived from (*R*,*R*)- and (*S*,*S*)-*N*,*N*-dialkyl-1,2-diaminocyclohexanes.[9] These can be easily prepared from the corresponding commercially available *trans*-1,2-diaminocyclohexanes, which can be resolved with D- or L-tartaric acid on a large scale.[10] Like the alkyl analogues,[11,12] allylic phosphonamides[13] are easily prepared by condensation of allyl-, crotyl-, and cinnamylphosphonic dichlorides, for example, with the corresponding (*R*,*R*)- or (*S*,*S*)-*N*,*N*-dialkyl-1,2-diaminocyclohexane.[14] Scheme 1

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(1) Leonard, J. *Contemp. Org. Synth.* **1994**, *1*, 387. Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 77. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 201. See also: Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1991**, 20, 87 and references therein.

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(3) For 1,4-conjugate additions of chiral allylic sulfoxide anions, see: (a) Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719. (b) Hua, D. H. Bharati, S, N.; Panagadan, J. A.; Isujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (c) See also: Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharati, S. N. *J. Org. Chem.* **1993**, *58*, 2144.

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(7) Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036.

(8) Hua, D. H.; Ostrander, R. A.; Chan-Yu-King, R.; Mckie, J.-A. *Org. Prep. Proc. Int.* **1989**, *21*, 225. Freeman, R.; Haynes, R. K.; Loughlin, W. A.; Mitchell, C.; Stokes, J. P. *Pure Appl. Chem.* **1993**, *65*, 647.

(9) For a review on the design and applications of chiral 1,2-diaminocyclohexane-based reagents in asymmetric synthesis, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.

(10) Glasbol, F.; Steenbol, P.; Sorensen, S. B. *Acta Chem. Scand.* **1980**, *26*, 3605.

(11) (a) Hanessian, S.; Bennani, Y. L.; Delorme, D. *Tetrahedron Lett.* **1990**, *31*, 6461. (b) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837.

(12) For the alternative preparation see: Koeller, K. J.; Spilling, C. D. *Tetrahedron Lett.* **1991**, *32*, 6297.

(13) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1969**, *34*, 3053. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5652; **1968**, *90*, 6816.

(14) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *Chim. Scr.* **1985**, *25*, 5.

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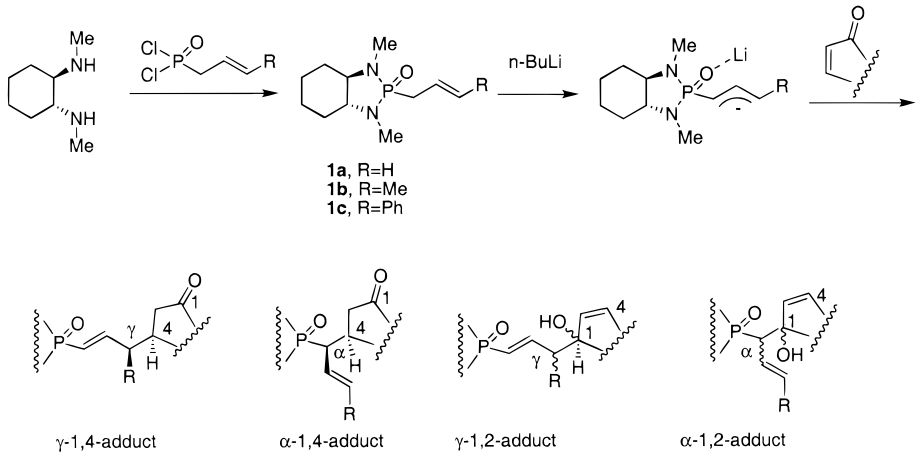
Scheme 1



shows the sequence of reactions leading to the formation of stabilized allylic-type phosphonamide anions, and the regiochemical issues[15] resulting from reactions with an α,β-unsaturated ketone. In addition, there is the challenge of stereochemical control, particularly with regard to the synthesis of preparatively useful γ-1,4-adducts.

Phosphonamides **1a**−**c** are crystalline, diastereomerically pure compounds which can be converted to their anions with *n*-BuLi at −78 °C, and used directly in 1,4-additions to α,β-unsaturated carbonyl compounds. We have previously reported the utility of alkyl, allyl, and related chiral bicyclic phosphonamides such as **1a** and **1b** in the asymmetric olefination of cyclohexanones.[16] Other applications can be found in the asymmetric synthesis of α,α′-dialkyl-,[14] α-alkyl-α′-halo-,[12] α-alkyl-α′-amino-,[17a,c] and α-alkyl-β-aminophosphonic acids.[17b] Phosphonamide anion technology developed in our laboratory has also been useful in natural product synthesis.[18,19] Chiral nonracemic phosphonamides have been studied in connection with carbanion-accelerated Claisen rearrangements.[20]

In a preliminary communication,[21] we reported the highly stereocontrolled 1,4-additions of allylic phosphonamide anions **1a** and **1b** to a variety of α,β-unsaturated carbonyl compounds. The option to trap the corresponding enolates with a variety of electrophiles allowed the generation of as many as three contiguous stereogenic centers with high levels of diastereoselectivity. As a logical extension of these results, we also reported the asymmetric synthesis of acyclic motifs in which three or more contiguous stereogenic centers were generated in single-stage or sequential Michael-type reactions, respectively.[22,23] Utilizing anions derived from chiral bicyclic γ-chloroallyl phosphonamides, we also reported the asymmetric syntheses of enantiopure substituted cyclopropanes[24] and aziridines.[25]

In this paper, we present a detailed account of the use of allylic phosphonamide anions in asymmetric 1,4-addition reactions to α,β-unsaturated cycloalkenones, lactones, lactams, and esters (Scheme 2). The adducts have been further transformed into chirons containing contiguous functional groups that could find utility in total syntheses.

Results and Discussion

Addition to Cyclopentenones and Cyclohexenones. Treatment of **1a** and **1b** with 1.2 equiv of *n*-BuLi at −78 °C for 1−2 min generated the corresponding lithiated anions that reacted with cyclic ketones within 30 min. Depending on the substrate and quenching electrophile, this methodology afforded substituted cyclopentanones having one, two, and three contiguous asymmetric centers with high diastereomeric purity. Methanol was a better quenching agent in the reactions with 2-methylcyclopentenone (Table 1, entries 2 and 6), since the use of NH_4Cl resulted in a significant loss of stereoselectivity at the α-position of the ketone. Entries 3, 4, and 7 represent examples of creating quaternary stereogenic centers at α- and β-positions in the cyclopentanone and cyclohexanone cores.[26] Addition of **1a** to 3-methylcyclohexenone under standard conditions was not a regioselective process, leading to a ∼2:1 mixture of γ-1,4- and γ-1,2-adducts with poor stereoselectivity (66% de) for the desired γ-1,4-adduct. However, addition of 1 equiv of HMPA[4] to the reaction mixture enhanced the

(15) For factors influencing the regioselectivity of phosphonamide-stabilized allylic anion addition, see: (a) Denmark, S. E.; Cramer, C. J. *J. Org. Chem*. **1990**, *55*, 1806. (b) Cramer, C. J.; Denmark, S. E.; Miller, P. C.; Dorow, R. L.; Swiss, K. A.; Wilson, S. R. *J. Am. Chem. Soc*. **1994**, *116*, 2437. See also: (a) Corey, E. J.; Cane, D. E. *J. Org. Chem*. **1969**, *34*, 3053. (b) Ahlbrecht, H.; Farnung, W. *Chem Ber*. **1984**, *117*, 1. (c) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371. (d) Birse, E. F.; McKenzie, A.; Murray, A. W. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1039. (e) Hata, T.; Nakajima, M.; Sekine, M. *Tetrahedron Lett*. **1979**, 2047; see also ref 29.

(16) (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc*. **1984**, *106*, 5754. (b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett*. **1992**, *33*, 7655. (c) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett*. **1992**, *33*, 7659.

(17) (a) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett*. **1990**, *31*, 6465. (b) Hanessian, S.; Bennani, Y. L.; Herve, Y. *Synlett* **1993**, 35. (c) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272.

(18) (a) Paquette, L. A.; Wang, T.-Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455. (b) Wang, T.-Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc*. **1996**, *118*, 1309.

(19) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett*. **1995**, *36*, 4579.

(20) Denmark, S. E.; Stadler, H.; Dorow, R. L.; Kim, J.-H. *J. Org. Chem*. **1991**, *56*, 5063.

(21) (a) Hanessian, S.; Gomtsyan, A.; Payne, A.; Herve, Y.; Beaudoin, S. *J. Org. Chem*. **1993**, *58*, 5032. (b) Hamme, A. T.; Paquette, L. A. *Chemtracts:Org. Chem*. **1994**, *7*, 24.

(22) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett*. **1994**, *35*, 7509.

(23) For a recent review on sequential reactions see: Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

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(25) Hanessian, S.; Cantin, L.-D. *Tetrahedron Lett*. **2000**, *41*, 787.

(26) See for example: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 388. Fuji, K. *Chem. Rev*. **1993**, *93*, 2037. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

Scheme 2

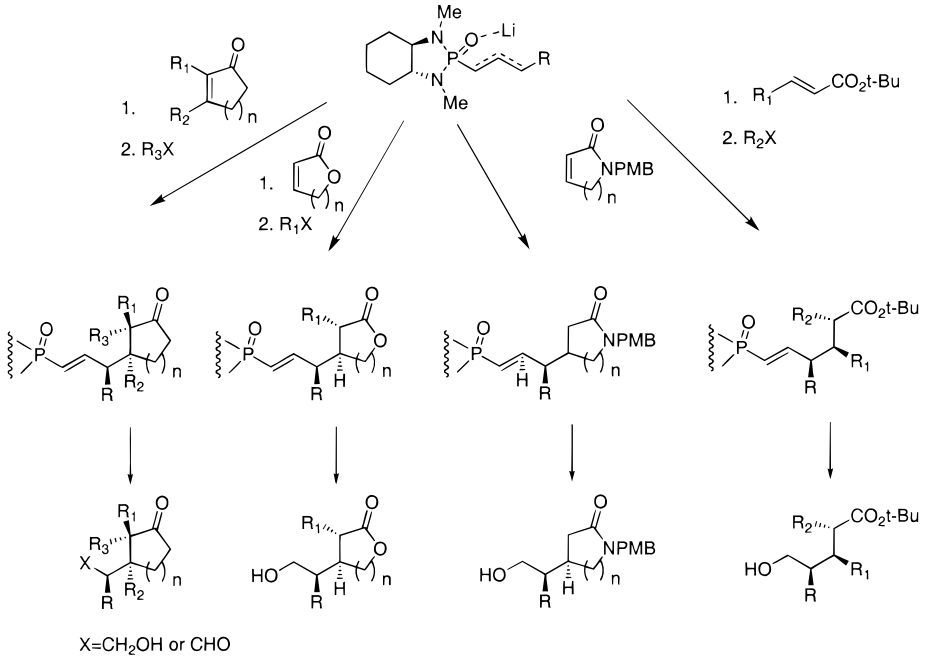
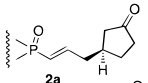
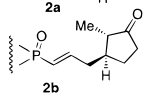
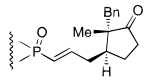
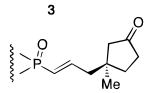
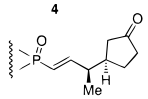
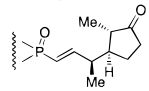
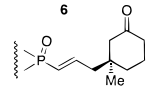


Table 1. 1,4-Conjugate Addition Reactions of 1a and 1b with α,β-Unsaturated Cyclic Ketones

Entry	Reagent	Substrate	Quench	Product	Ratio[a]	Yield[b] (%)
1	**1a**		NH_4Cl	 **2a**	93:7	88
2	**1a**		MeOH	 **2b**	93:7	80
3	**1a**		BnBr	 **3**	>99:1	80
4	**1a**		NH_4Cl	 **4**	95:5	75
5	**1b**		NH_4Cl	 **5**	96:4	96
6	**1b**		MeOH	 **6**	94:6	74
7	**1a**		NH_4Cl[c]	 **7**	90:10	62

[a] Determined from ^1H, ^{13}C, and ^{31}P NMR parameters (all entries) and further substantiated from ^{13}C NMR spectra of cyclic ketal−acetal derivatives with (*R,R*)-2,3-butanediol after oxidative cleavage (entries 1-4 and 7) and Mosher esters of products after oxidative cleavage and reduction (entries 5 and 6). [b] Yield of isolated product after flash chromatography. [c] Reaction done in the presence of HMPA (1 equiv).

stereochemical purity of **7** to 80% de with an increase in yield to 62% (Table 1, entry 7). The reaction between 3-methylcyclopentenone and **1b** afforded a mixture of 1,2-addition products only. The nature of the solvent, additives, and external ligands is known to affect the regioselectivity in conjugate addition reactions.[27−29]

Generally, diastereoselectivities were determined by analysis of ^1H, ^{13}C, and ^{31}P NMR spectra of the vinylic phosphonamide adducts, and further corroborated by spectral analysis of cleavage products either as bisdioxolanes or as Mosher esters (Scheme 3).

Accordingly, all the adducts listed in Table 1 resulting from addition of allyl reagent **1a** (entries 1−4 and 7) were converted to bisdioxolanes via *δ*-keto aldehydes (Scheme 3), and their diastereomeric ratios were determined by ^{13}C NMR according to Hiemstra and Wynberg.[30] For the adducts from the crotyl reagent **1b** (Table 1, entries 5 and 6) a different cleavage procedure was devised to avoid possible racemization at the aldehyde side chain (Scheme 4). Thus, the carbonyl group in **5** and **6** was reduced and the mixture of alcohols protected as a silyl ether. Ozonolysis of the vinyl phosphonamide segment gave an alcohol which was converted to the corresponding Mosher esters **8a** and **8b** in each case after the carbonyl group in the cyclopentane ring was reinstalled by removal of the silyl group followed by oxidation with PDC. It should be noted that, in the majority of examples shown in Table 1, the degrees of diastereoselectivity obtained from ^1H, ^{13}C, and ^{31}P NMR spectra of 1,4-adducts were in close agreement with the values obtained from ^{19}F NMR of Mosher esters. In isolated instances when de values for products before and after cleavage were not concordant, the value determined for the cleavage product was chosen to determine the stereoselectivity of the particular 1,4-addition reaction.

The newly created asymmetric center on the cyclopentanone ring in **2a** (Table 1, entry 1) was assigned an (*S*)-

(27) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790. Ager, D. J. East, M. B. *J. Org. Chem.* **1986**, *51*, 3983. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Org. Chem.* **1989**, *54*, 1960.

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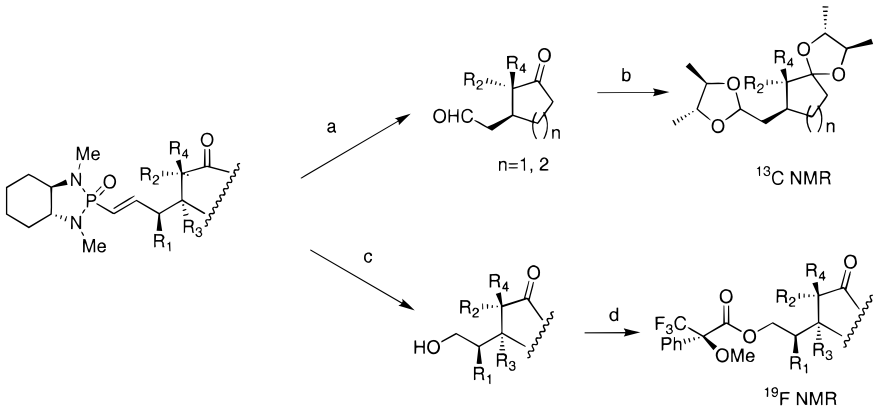
(29) For a review on regioselectivity in the additions of heteroatom-stabilized allylic anions, see: Katritsky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665.

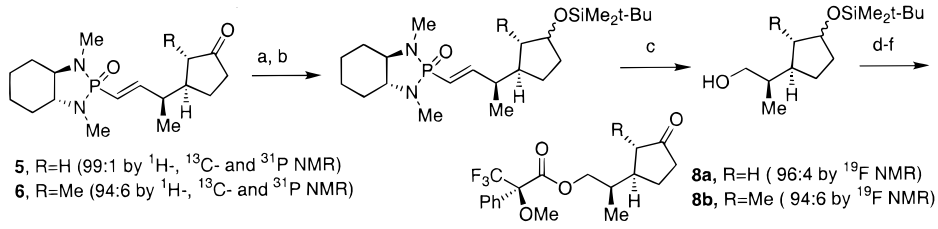
(30) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183.

Scheme 3[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, then Me_2S; (b) 3 equiv of (2*R*,3*R*)-2,3-butanediol, 0.05 equiv of *p*-TsOH; (c) O_3, CH_2Cl_2−MeOH, −78 °C, then $NaBH_4$; (d) (+)-Mosher acid chloride, Py−CCl_4, 1 h, rt, then 3-dimethylamino-1-propylamine.

Scheme 4[a]



[a] Reagents and conditions: (a) $NaBH_4$; (b) TBDMS−Cl; (c) O_3, CH_2Cl_2−MeOH, −78 °C, then $NaBH_4$; (d) Mosher reagent; (e) TBAF, AcOH; (f) PDC.

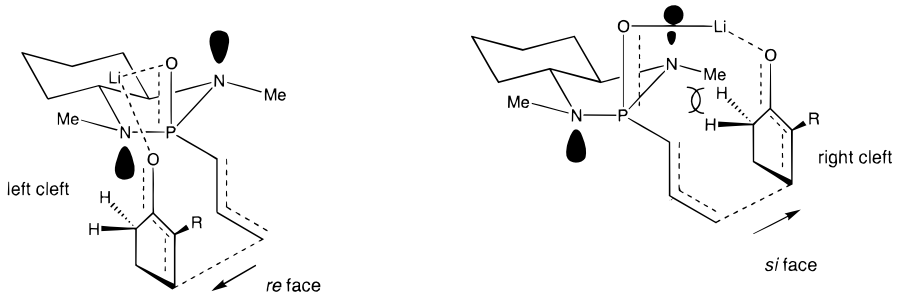


Figure 1. "Cleft" concept for the reaction transition state.

configuration on the basis of a comparison of the optical rotation value with that reported for a degradation product. [5a]

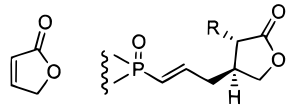
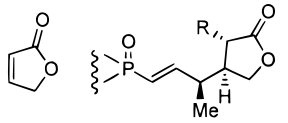
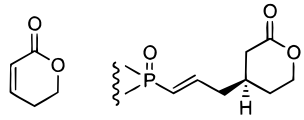
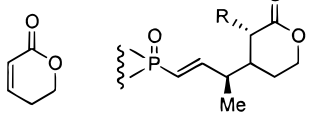
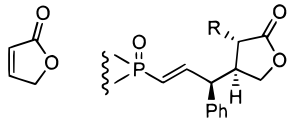
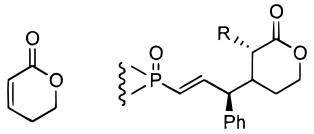
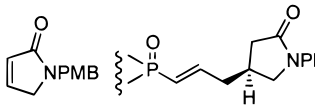
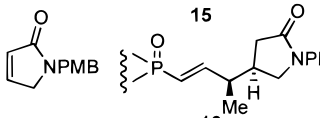
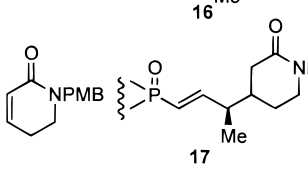
To rationalize the high levels of stereocontrol in the additions of lithiated allyl and crotyl phosphonamides to α,β-unsaturated cyclic ketones, we propose an approach of the enone component from the "left cleft" [21a] of the Li-coordinated reagent, resulting in a *re*-face attack (Figure 1). An approach from the "right cleft" is less favorable due to the steric interaction between the *N*-Me group of the phosphonamide and H atoms of the enone. A key requirement for the correct relative positioning of the reagent and substrate is the anchoring of a lithium cation on polarized P═O and C═O groups. Haynes[31] has proposed *cis*- and *trans*-decalinoid Li-chelated transition states to explain selectivities of 1,4-addition reactions with related reagents.

Addition to Lactones and Lactams. To the best of our knowledge there are no precedents in the literature for the successful asymmetric conjugate reactions between allylic phosphonamide anions and α,β-unsaturated lactones and lactams. In the only reported attempt[7] of the addition of an allyl binaphthylphosphonate to a five-membered α,β-unsaturated lactone, a mixture of products resulting from α- and γ-attack by the reagent with poor stereoselectivity was observed.

Allyl, crotyl, and cinnamyl phosphonamides **1a**−**c** undergo remarkably stereoselective 1,4-additions to lactones and lactams (Table 2). Diastereoselection in most examples with five- and six-membered lactones is virtually complete. Little if any erosion of stereoselectivity was observed when the intermediate enolates were quenched with alkyl halides to provide lactones with up to three contiguous stereogenic centers. In the case of benzylated lactone **9b,** prepared from allyl reagent **1a** (entry 1),

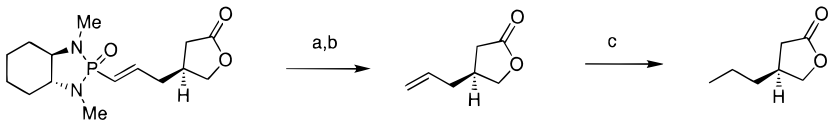
(31) For discussions about relevant 10-membered transition states, see: (a) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411. (b) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423.

Table 2. 1,4-Conjugate Addition Reactions of 1a−c with α,β-Unsaturated Lactones and Lactams[a]

Entry	Reagent	Substrate	Product	Ratio[b]	Yield[c]
1	**1a**		**9a**, R=H **9b,** R=Bn	>99:1 >99:1	93 67[d]
2	**1b**		**10a**, R=H **10b**, R=Me **10c**, R=Bn **10d**, R=allyl	98:2 96:4 98:2 98:2	80 70 75 60
3	**1a**		**11**	93:7	48
4	**1b**		**12a,** R=H **12b**, R=Me	>99:1 93:7	65 63
5	**1c**		**13a,** R=H **13b**, R=Me	>99:1 >99:1	75 70
6	**1c**		**14a,** R=H **14b**, R=Me	98:2 >99:1	70 67
7	**1a**		**15**	99:1	60[e]
8	**1b**		**16**	95:5	51[f]
9	**1b**		**17**	75:25	96

[a] The reaction mixture was quenched with NH_4Cl or with MeI (**10a**, **12b**, and **13b**), BnBr (**9b** and **10c**), or allyl bromide (**10a**). [b] Determined from ^1H, ^{13}C, and ^{31}P NMR parameters (all entries) and further substantiated from ^{13}C NMR spectra of cyclic ketal−acetal derivatives with (*R*,*R*)-2,3-butanediol after oxidative cleavage (entry 1) and Mosher esters of products after oxidative cleavage and reduction (entries 2, 3, and 7-9). [c] Yield of isolated product after flash chromatography. [d] After DBU equilibration. [e] Toluene as solvent, NaHMDS as base. [f] Toluene as solvent.

Scheme 5[a]



9a **18** **19**

19, $[\alpha]_D$ -5.6 (c=0.9, EtOH)
lit. -7.3° (EtOH)

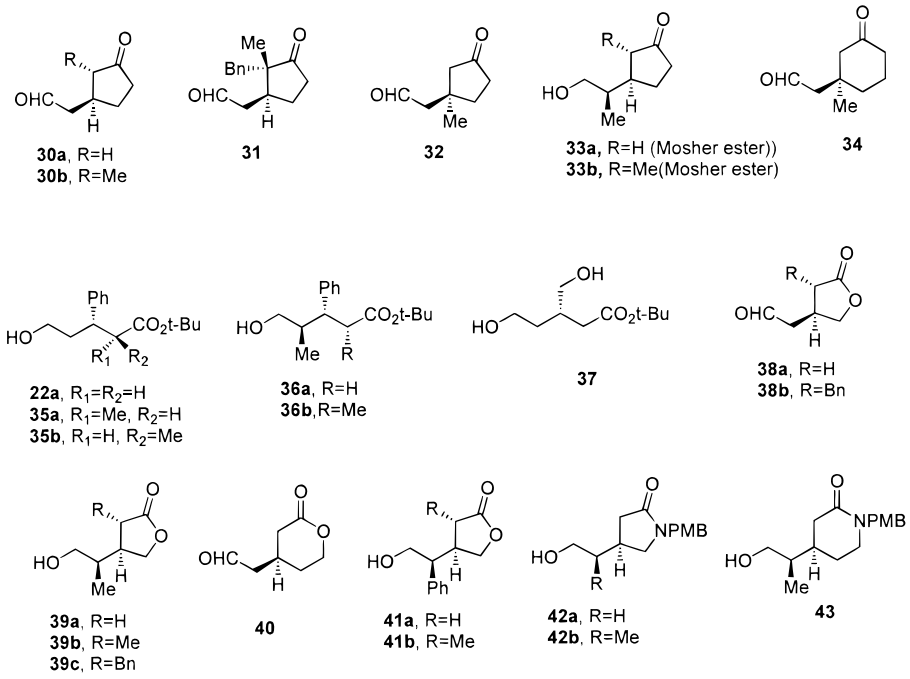
[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, then Me_2S, 95%; (b) $MeP(Ph_3)Br$, *n*-BuLi, THF, −50 °C, 58%; (c) H_2, Pd/C, $CHCl_3$, 99%.

followed by treatment with benzyl bromide, it was necessary to equilibrate the product with DBU to obtain a single isomer. In contrast, reactions with crotyl reagent **1b**, followed by addition of an electrophile to the corresponding enolates, proved to be highly stereoselective (Table 2, entries 2 and 4, adducts **10b**−**d** and **12b**). The 1,4-additions and trapping of lactone enolates with cinnamyl phosphonamide reagent **1c** were also highly stereoselective (Table 2, entries 5 and 6). The adducts **13a**, **14a** and **13b**, **14b** have two and three contiguous stereocenters, including a phenyl appendage on the acyclic chain. Easy access to highly functionalized chiral nonracemic lactones made this technology a method of choice for the key step in the total synthesis of (+)-acetoxycrenulide by Paquette and co-workers.[18]

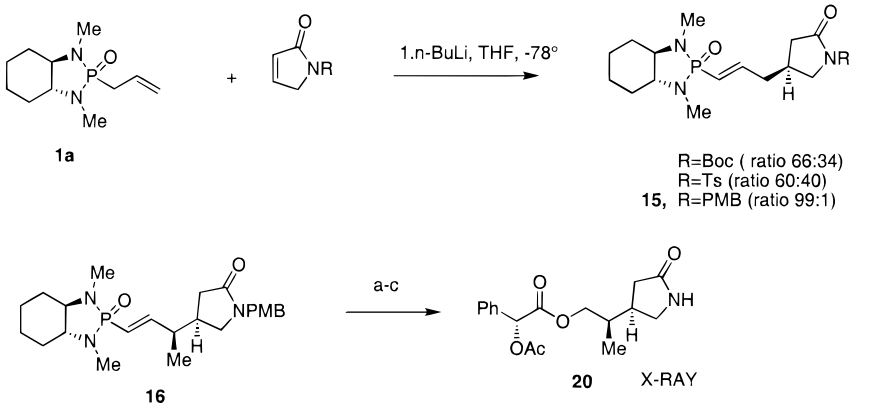
As in the case of ketones, initial assessment of stereoselectivity was done by the analysis of ^1H, ^{13}C, and ^{31}P NMR of addition products. In addition, Mosher ester and bisdioxolane adducts of the lactone aldehydes obtained after ozonolytic cleavage were used to confirm the initial diastereoselectivities. To establish the absolute stereochemistry for conjugate addition to lactones, compound **9a** was converted to the known compound **19**[32] in three steps (Scheme 5). It is noteworthy to point out that the ozonolytic cleavage and subsequent reduction of the lactone adducts **9**, **10**, and **13** (Table 2) did not result in ring expansion to δ-lactones (see later); the product of

(32) Mukayama, T.; Fujimoto, K.; Hirose, T.; Takeda, T. *Chem. Lett.* **1980**, 635.

Chart 1



Scheme 6[a]



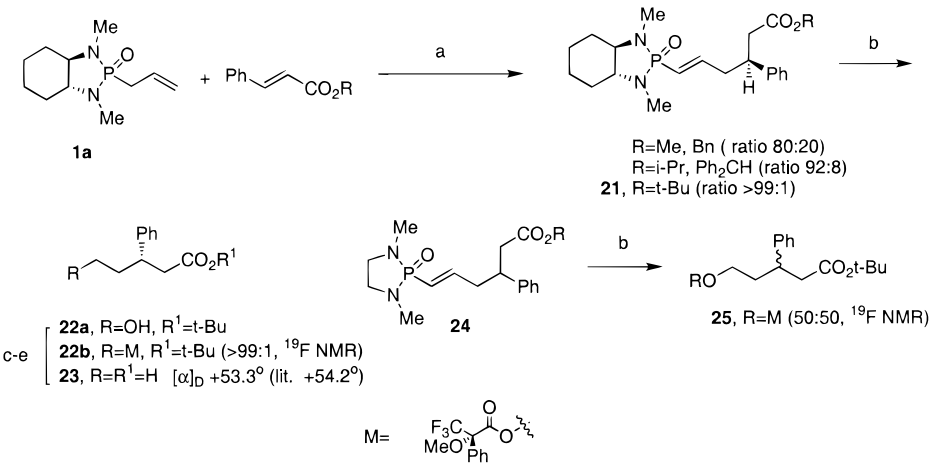
[a] Reagents and conditions: (a) O_3, CH_2Cl_2−MeOH, −78 °C, then $NaBH_4$; (b) (*R*)-OAc-mandelic acid, DCC; (c) CAN, MeCN−H_2O.

oxidative cleavage and reduction was found to be the racemic *δ*-lactone as a result of equilibration between two *ω*-hydroxy lactones of symmetrical structures. It was possible to isolate the corresponding aldehydes (see Chart 1, compound **40**).

The nature of the *N*-protecting group in α,*β*-unsaturated lactams exhibits a significant effect on the stereoselectivity of the process. Initially, we observed very poor stereocontrol with *N*-Boc and *N*-Ts protecting groups (Scheme 6). We attributed these results to a possible coordination of the *N*-protecting groups to the lithium cation, which presumably alters the favored approach from the left cleft of the (*R*,*R*)-reagent as discussed above (Figure 1). To substantiate this assumption, we found that stereoselectivity was markedly increased with the use of the noncomplexing *p*-methoxybenzyl (PMB) group. Thus, reaction of *N*-PMB α,*β*-unsaturated pyrrolidinone with allyl and crotyl reagents **1a** and **1b** led to adducts **15** and **16** with excellent stereochemical outcome (Scheme 6, Table 2, entries 7 and 8). Toluene was a solvent of choice in both cases, and NaHMDS replaced BuLi in the synthesis of **15** to provide a higher yield. In the case of the six-membered lactam (Table 2, entry 9) the diastereomeric ratio of conjugate addition adducts dropped to 75:25. Diastereoselectivities were determined by analyzing ^{19}F NMR spectra of Mosher esters after oxidative cleavage, reduction to the primary alcohol, and esterification. To validate the reliability of assignments of absolute configuration of the newly formed centers in the lactam series, we prepared the mandelate **20** (Scheme 6) in four steps by ozonolysis of **16**, followed by reductive workup with $NaBH_4$, condensation with (*R*)-(−)-*O*-acetylmandelic acid, and deprotection of the PMB group. X-ray crystallographic analysis confirmed the structure and absolute stereochemistry of **20**, and of the lactone adducts in Table 2 by analogy.

Addition to α,*β*-Unsaturated Esters. Anions of allylic phosphonamides undergo highly stereocontrolled conjugate additions to α,*β*-unsaturated esters. In our initial studies, we found that the reaction of **1a** with methyl or benzyl *trans*-cinnamates gave a mixture of *γ*-1,4-adducts with only a 80:20 ratio of diastereomers (Scheme 7). The stereoselectivity of the process improved to 92:8 by employing secondary alkyl esters such as

Scheme 7[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then aq NH_4Cl; (b) O_3, CH_2Cl_2−MeOH, −78 °C, then $NaBH_4$; (c) CBr_4, Ph_3P, THF; (d) Bu_3SnH, AlBN; (e) KOH, MeOH, 55% for three steps.

Table 3. 1,4-Conjugate Addition Reactions of 1a with α,β-Unsaturated esters

Entry	Reagent	Substrate	Quench	Product	Ratio[a]	Yield[b] (%)
1	**1a**	Ph, CO_2t-Bu	NH_4Cl	**21**	>99:1	80
2	**1a**	Ph, CO_2t-Bu	MeI	**21a** (X-RAY) + **21b**	>99:1	50
					>99:1	24
3	**1b**	Ph, CO_2t-Bu	NH_4Cl	**26**	>99:1	94
4	**1b**	Ph, CO_2t-Bu	MeI	**27**	92:8	87
5	**1a**	Me, CO_2t-Bu	NH_4Cl	**28**	>99:1	76[c]

[a] Determined from ^1H, ^{13}C, and ^{31}P NMR parameters (all entries) and further substantiated from Mosher esters of products after oxidative cleavage and reduction (entries 1-5). [b] Yield of isolated product after flash chromatography. [c] The γ-1,6-addition product (7%) was also found.

2-propyl or diphenylmethyl. Remarkably, addition to *tert*-butyl *trans*-cinnamate afforded a single diastereomer **21** (Table 3, entry 1). Oxidative cleavage and reduction under standard conditions led to **22a**, which gave a single Mosher ester, **22b** (Scheme 7). Since the Mosher ester group in **22b** is separated from the newly formed asymmetric center by two carbon atoms, we chose to confirm the stereochemical purity by an alternative route. Thus, we synthesized the achiral vinyl phosphonamide **24** (Scheme 7), and converted it to a racemic Mosher ester, **25**. Two well-separated peaks with a 1:1 ratio in the ^{19}F NMR spectrum ultimately confirmed the stereochemical purity of the adduct **22b**. The (*S*)-absolute configuration at the benzylic carbon atom of adduct **21** was established by converting it to the known acid **23**[33] in four steps (Scheme 7). Thus, ozonolysis of **21**, followed by reductive workup, gave the alcohol, which was brominated with CBr_4/Ph_3P; the product was reduced with Bu_3SnH and then hydrolyzed with aq KOH to produce **23** in 55% overall yield.

As in the cyclic enone series, we were successful in quenching the intermediate enolates with electrophiles for the acyclic series as well. A sequential conjugate addition of **1a** to *tert*-butyl *trans*-cinnamate, followed by addition of methyl iodide (Table 3, entry 2), led to a 2:1 mixture of *anti*- and *syn*-adducts **21a** and **21b**, which were separated by chromatography. The structure of the major isomer **21a** was unequivocally assigned by X-ray analysis.

Conjugate addition of the crotyl reagent **1b** to *tert*-butyl *trans*-cinnamate afforded a single adduct, **26** (Table 3, entry 3). Trapping the enolate with methyl iodide was equally stereocontrolled to give **26a** with three contiguous stereogenic centers, essentially in one operation (Scheme 8, Table 3, entry 4). Structural and stereochemical assignments were conclusively established by NOE data on the corresponding lactone **29a** and an X-ray structural analysis of **29b** (Scheme 8).

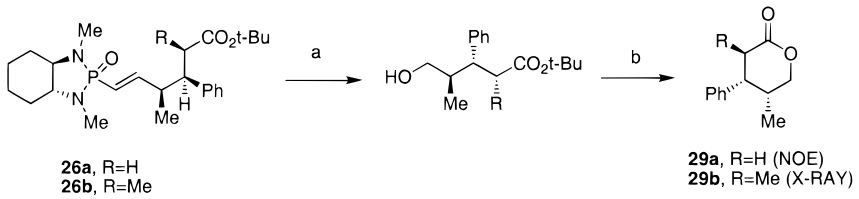
We were pleased to find that the reaction of **1a** with *tert*-butyl sorbate was highly regio- and stereoselective to give the 1,4-adduct **27** as the major isomer (Table 3, entry 5). Boyle and Kishi[19] have used adduct **27** in their structural studies of the natural product fumonisin B.

Finally, in an extension of the 1,4-addition reactions in the acyclic series, we reacted **1a** with isopropyl crotonate to give the 1,4-adduct in excellent stereoselectivity, albeit in 38% yield. The 1,4-additions of allyl phosphonamide anions are more efficient with cinnamates compared to crotonates, possibly due to a more favorable reduction potential at the β-carbon atom when an aromatic group is present, as well as to the prevalence of a favored *s-trans* conformation.[34] The stereochemical outcome of phosphonamide anion additions to acyclic α,β-unsaturated esters (Scheme 7, Table 3) can be rationalized by considering the proposed alignment of Li-coordinated reactants to approximate favorable transition

(33) Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613.

(34) For a discussion of enone conformations in conjugate reduction, see: Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1441.

Scheme 8[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2−MeOH, −78 °C, then $NaBH_4$; (b) CF_3CO_2H, CH_2Cl_2, rt.

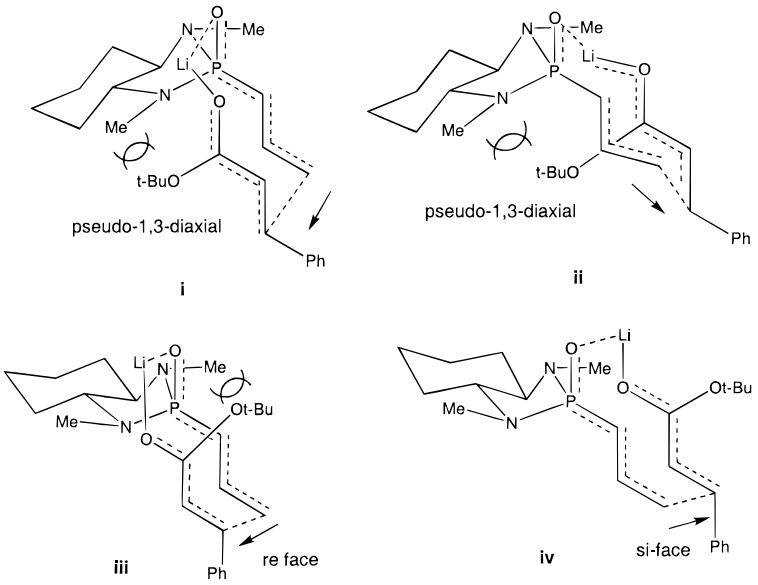


Figure 2. (i) Disfavored left cleft *trans*-dacalinoid chair−chair-type TS. (ii) Disfavored right cleft *trans*-decalinoid chair−chair-type TS. (iii) Disfavored left cleft *cis*-decalinoid boat−boat-type TS. (iv) Favored right cleft *cis*-decalionoid boat−boat-type TS.

states (Figure 2). Adopting a pictorial expression according to Haynes,[31] we can explain the stereochemical outcome of the additions to *tert*-butyl cinnamate, for example, by a favored *si*-face approach of the stabilized γ-stabilized anion as in panel iv.

Conclusion

Asymmetric 1,4-addition reactions using anions of enantiomerically pure allyl phosphonamide reagents **1a**−**c** offer practical routes to a variety of enantiopure or highly enriched branched carbocyclic, heterocyclic, and acyclic compounds (Chart 1). Some of the acyclic chirons obtained by oxidative cleavage of the adducts can be viewed as products of effective chemical asymmetrization (Chart 1, **36b**, and **37**), as opposed to enzymatic asymmetrization accomplished with esterases and dialkyl 3-substituted glutarates.[35] Good to excellent stereoselectivity was achieved in generating stereogenic centers in one-pot addition−alkylation sequences. Of particular preparative significance is the successful adaptation of these reactions to acyclic α,β-unsaturated esters, with the generation of three contiguous stereogenic centers in one operation. The unique structural, topological, and symmetry-related features of the allylic phosphonamide reagents are mostly responsible for the excellent stereo- and regiocontrol in these 1,4-addition reactions. The easily accessible (*S*,*S*)-reagents can lead to compounds in the enantiomeric series.

(35) (a) Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. (b) See also: Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and the chemical shifts are reported in parts per million on the δ scale with $CHCl_3$ as reference. ^{31}P NMR spectra were recorded at 121 MHz with 85% H_3PO_4 as reference. ^{19}F spectra were recorded in $CDCl_3$ at 282.2 MHz. IR spectra were recorded as films. MS and HRMS spectra were recorded using electron ionization or by the FAB technique. Organic solvents were dried by standard methods. α,β-Unsaturated ketones and lactones were distilled before use. Other commercially obtained reagents were used without further purification. Flash chromatography was performed on 230−400 mesh silica gel. Thin-layer chromatography (TLC) was performed on glass plates coated with a 0.02 mm layer of silica gel 60 F-254. Optical rotations were measured in $CHCl_3$ at 23 °C.

(3a*R*,7a*R*)-2-Allyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzadiazaphosphole 2-Oxide, 1a. To a cooled solution of (1*R*, 2*R*)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine[9] (3 g, 21.1 mmol) and Et_3N (4.7 g, 46.6 mmol) in benzene (80 mL) was added allylphosphonic dichloride according to Corey and Cane[13] (3.7 g, 23 mmol) in benzene (80 mL) within 1 h at 0 °C. The reaction mixture was stirred at ambient temperature for 18 h, and the salts were filtered and washed with ethyl acetate (100 mL). The filtrate was concentrated, and the residue was purified by silica gel

chromatography (95:5 ethyl acetate−MeOH) to give 4.50 g (92%) of the product: mp 45−46 °C (hexane); $[\alpha]_D$ −51.1° (*c* 1.85; $CHCl_3$); ^{1}H NMR δ 5.85−5.70 (1H, m C*H*═CH_2), 5.20−5.10 (2H, m, CH═CH_2), 2.59 (3H, d, J = 12.0 Hz, NCH_3), 2.56 (3H, d, J = 13.4 Hz, NCH_3), 2.85−2.45 (4H, M, 2CHN, PCH_2), 2.15−1.80 (4H, m, cyclohexane), 1.40−1.00 (4H, m, cyclic); ^{13}C NMR δ 129.2 (d, J = 10 Hz), 118.5 (d, J = 13.1 Hz), 64.2 (d, J = 7.9 Hz), 64.2 (d, J = 4.9 Hz), 33.6 (d, J = 109.6 Hz), 29.4, 28.3 (d, J = 9.9 Hz), 27.9 (d, J = 4.7 Hz), 27.8; HRMS calcd for $C_{11}H_{21}N_2OP$ 228.1391, found 228.1384.

(3a*R*,7a*R*)-2-Crotyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzadiazaphosphole 2-Oxide, 1b. The crotyl phosphonamide was prepared from (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (2.1 g, 14.8 mmol) and crotylphosphonic dichloride[13] (2.9 g, 16.9 mmol) by using the procedure described above for the synthesis of **1a**: yield 3.33 g (93%); mp 29−30 °C; $[\alpha]_D$ −68.0° (*c* 0.94; $CHCl_3$); ^{1}H NMR δ 5.55 (1H, m, 10.3, 11.7 Hz, 2NCH_3), 2.09−1.73 (4H, m, cyclohexane), 1.70 (3H, m, $CHCH_3$), 1.40−1.05 (4H, m, cyclic); ^{13}C NMR, δ 129.1, 121.0, 64.0, 31.7, 30.3, 29.3, 28.2, 27.9, 27.7, 23.8, 17.5; ^{31}P δ 42.90; HRMS calcd for $C_{12}H_{23}N_2OP$ 242.1546, found 242.1530.

(3a*R*,7a*R*)-2-Cinnamyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzadiazaphosphole 2-Oxide, 1c. 1c was prepared according to the method described for **1b**, from the diamine (0.46 g, 3.2 mmol) and cinnamylphosphonic dichloride[34] (0.8 g, 3.5 mmol) in benzene. Purification of the crude product by silica gel chromatography gave the title compound **1c** (0.84 g, 87%) as a white solid: mp 57−58 °C; $[\alpha]_D$ +76° (*c* 1.25, $CHCl_3$); ^{1}H NMR δ 7.45 (5H, m, Ph), 6.53 (1H, m, CH−C*H*pH), 6.23 (1H, m, C*H*═CHPh), 2.90 (4H, m P(O)CH_2, C*H*N), 2.54 (6H, 2d, J = 11.15 Hz, NMe), 2.09−1.73 (4H, m, cyclohexane); ^{13}C NMR δ 137, 129.5, 127.13, 126.91, 134, 121, 64.75, 32.13, 31.5, 30.7, 29.7, 28.5, 27.87, 27.56, 23.7, 20.21; ^{31}P δ 42.10; HRMS calcd for $C_{17}H_{25}N_2OP$ 304.1880, found 304.1878.

General Procedure for 1,4-Addition. To a solution of allyl phosphonamide (1 mmol) in THF (10 mL) was added *n*-BuLi (1.2 mmol, 1.6 or 2.5 M solution in hexane) at −78 °C under argon. A solution of α,*β*-unsaturated carbonyl compound (1.2 mmol) in THF (5 mL) at −78 °C was added immediately via cannula. The reaction mixture was stirred at −78 °C for 30 min, slowly quenched with saturated aqueous NH_4Cl or with MeOH, with MeI (10 equiv), with BnBr (5 equiv), and with allyl bromide (5 equiv) and allowed to warm to ambient temperature. The mixture was diluted with EtOAc (50 mL) and washed with brine (20 mL) and water (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The resulting crude product was purified by column chromatography (EtOAc−MeOH). Individual yields are listed in Tables 1−3; physical constants (IR and ^{1}H, ^{13}C, and ^{31}P NMR data and copies of spectra) can be found in the Supporting Information.

General Procedure for the Oxidative Cleavage of 1,4-Addition Products. (a) A −78 °C solution of 1,4-addition product (0.3 mmol) in dry CH_2Cl_2 (13 mL) was treated with a stream of O_3 in O_2 until starting material could not be detected by TLC (∼20−30 min). The reaction flask was flushed with argon to remove residual O_3, and then Me_2S (0.5 mL) was added. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. Purification of the reaction mixture by silica gel chromatography (hexane −EtOAc) provided an aldehyde. Corresponding ketal−acetals were prepared by the reaction of the aldehyde with (*R*,*R*)-2,3-butanediol and TsOH according to the literature.[5a] (b) This procedure was the same as (a) except instead of CH_2Cl_2 a mixture of CH_2Cl_2−MeOH (1.5:1) was used and instead of Me_2S $NaBH_4$ (5 equiv) was used. Resulting alcohols were transformed to Mosher esters according to the literature.[36]

(3*S*)-Allyl Butyrolactone, 18. A 2.5 M solution of *n*-BuLi in hexanes (0.19 mL, 0.475 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (0.17 g, 0.475 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min and then cooled to −50 °C. The ylide was added dropwise by cannula to a −50 °C solution of the aldehyde formed from the ozonolysis of **9a** (0.058 g, 0.452 mmol) in THF (3 mL). The mixture was stirred at −50 °C for 1 h and then stirred at ambient temperature overnight. The reaction mixture was quenched with glacial AcOH, stirred for 30 min, and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by flash chromatography (hexanes−EtOAc, 3:1) to give volatile olefin **18** (0.033 g, 58%); $[\alpha]_D$ −3.20° (*c* = 0.25); IR (film) 1775 cm^{-1}; ^{1}H NMR δ 5.80−5.67 (m, 1H), 5.15−5.08 (m, 2H), 4.40 (dd, J = 9.0 and 7.2 Hz, 1H), 4.00 (dd, J = 9.0 and 5.7 Hz, 1H), 2.70−2.17 (m, 5H).

19. Compound **18** (0.033 g, 0.262 mmol) was dissolved in chloroform (3 mL) and hydrogenated over 10% palladium on carbon for 30 min. The catalyst was removed by filtration and the solvent evaporated at ambient temperature to give pure lactone **19** (0.033 g, 99%). $[\alpha]_D$ −5.6° (*c* 0.90, EtOH) (lit.[30] $[\alpha]_D$ −7.3° for the (*S*)-lactone); IR (film) 1775 cm^{-1}; ^{1}H NMR δ 4.42 (dd, J = 9.0 and 7.5 Hz, 1H), 3.92 (dd, J = 9.0 and 7.0 Hz, 1H), 2.67−2.50 (m, 2H), 2.23−2.14 (m, 1H), 1.48−1.28 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 73.2, 35.3, 35.1, 34.4, 20.4, 13.7; HRMS calcd for $C_7H_{12}O_2$ 129.0924, found 129.0921 $(M + H)^+$.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR data, IR data, mass spectral data, $[\alpha]_D$ values, copies of ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra, and X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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