Asymmetric Conjugate Additions of Chiral Allyl- and Crotylphosphonamide Anions to α,β-Unsaturated Carbonyl Compounds: Highly Stereocontrolled Access to Vicinally Substituted Carbon Centers and Chemically Asymmetrized Chirons

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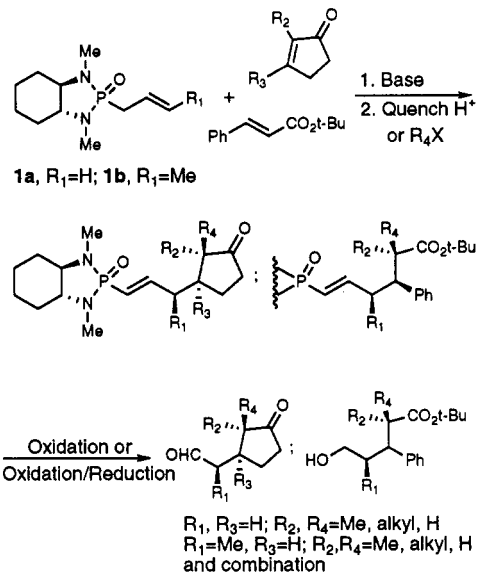
Summary: Reactions of anions derived from chiral nonracemic allyl and crotyl bicyclic phosphonamides with α,β-unsaturated cyclic ketones, esters, lactones, and lactams take place at the γ-position of the reagents and lead to diastereomerically pure or highly enriched products of conjugate addition. The option to quench the corresponding enolates with various alkyl halides offers a versatile approach to vicinal substitution including the generation of quaternary carbon centers.

In spite of significant recent advances in asymmetric 1,4-conjugate addition reactions,[1] involving chiral catalysts or substrates containing a chiral auxiliary, relatively few examples are known in which the transferred carbon moiety is *an allylic-type anion and part of a chiral reagent*.[2-5] In the only reported example of an *allylphosphonyl anion*, high levels of asymmetric inductions have been reported by Hua and co-workers[5] for three unsubstituted simple cyclic enones[5a] and for 3,4-dihydro-4-oxo-(2*H*)-pyridine-L-carboxylate.[5b] In another instance, individual enantiomers of allylic phosphine oxides have shown good to excellent selectivity toward cyclopentenone as reported by Haynes and co-workers.[4] With such phosphorus-based reagents, it is operationally imperative to work with stereochemically defined reagents, hence, the necessity to separate enantiomers or diastereomers.[6] Furthermore, the limited examples of asymmetric conjugate additions to α,β-unsaturated carbonyl compounds beyond simple cycloalkenones[4,5] warrant the development of a more general approach to this important problem.

We report herein on highly stereocontrolled asymmetric 1,4-conjugate additions to α,β-unsaturated cyclic ketones, lactones, lactams, and esters with anions of allyl and crotyl chiral phosphonamides that are readily available in enantiomerically pure form.[7]

Scheme I



The deployment of a series of vicinal carbon substituents with specific configurations in the products is achieved through a choice of (*R,R*)- or (*S,S*)-reagents, a preselection of substituents on the enone portion, and the option to quench the resulting enolates with a variety of electrophiles. *In this manner it is possible to generate as many as three contiguous stereogenic centers containing a combination of secondary, tertiary, and quaternary substituents at will and in a single step* as illustrated in Scheme I for a cyclopentenone motif and for *tert*-butyl cinnamate. Oxidative cleavage leads to products corresponding to the formal conjugate addition of an acetaldehyde or a propionaldehyde anion equivalent to α,β-unsaturated carbonyl compounds.

Table I lists a number of relevant examples with excellent diastereoselectivities. Thus, mono-, di-, and trisubstituted cyclopentanones are obtained virtually as single diastereomers (entries 1-4).[8] The inclusion of HMPA[9] was found to enhance the ratio of γ-1,4-addition and to improve the stereoselectivity in the case of 3-methylcyclohexenone (entry 6). The scope of these conjugate addition reactions is greatly expanded by the

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(1) For recent reviews, see: 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. *Topics Stereochem.* **1991**, *20*, 87 and references cited therein.

(2) For a review on asymmetric conjugate additions with sulfoxide-stabilized carbanions, see: Walker, A.-J. *Tetrahedron: Asymmetry* **1992**, *3*, 961. Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Striling, C. J. M., Eds.; Wiley-Interscience: New York, 1988; p 823. Solladié, G. In *Asymmetric Synthesis*; Morison, J. D., Ed.; Academic Press: New York, 1983, Vol. 2, p 157. Barbashyn, M. R., Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 4, p 227.

(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.; Bharathi, S. N.; Panagadan, J. A.; Isujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (c) See also: Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144.

(4) For 1,4-conjugate additions of allylic chiral phosphine oxide anions, see: (a) Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58. (b) See also: Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162.

(5) For 1,4-conjugate additions of chiral allylic phosphonyl anions, see: (a) Hua, D. H.; Chan-Yu-King, R.; McKie, J.-A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026. (b) Hua, D. H.; Chen, J. S.; Saha, S.; Wang, H.; Roche, D.; Bharathi, S. N.; Chan-Yu-King, R.; Robinson, P. D.; Iguchi, S. *Synlett* **1992**, 817.

(6) Hua, D. H.; Ostrander, R. A.; Chan-Yu-King, R.; McKie, J.-A. *Org. Prep. Proc. Int.* **1989**, *21*, 225.

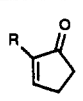
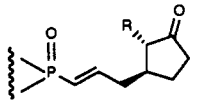
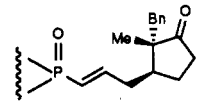
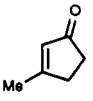
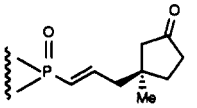
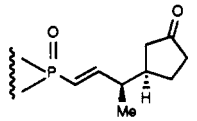
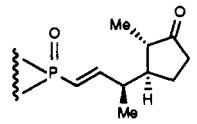
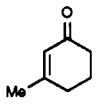
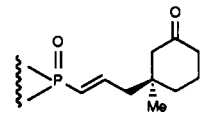
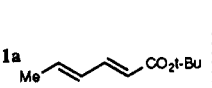
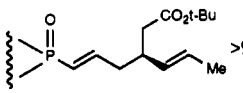
(7) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7659 and references cited therein. See also supplementary material.

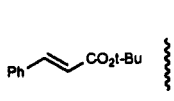
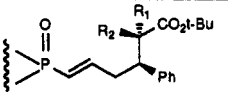
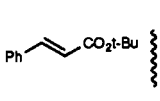
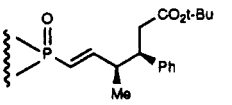
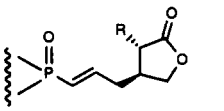
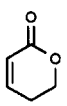
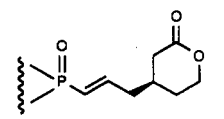
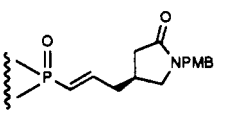
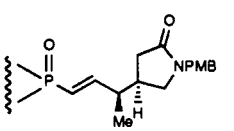
(8) With 3-methylcyclopentenone and the crotyl reagent **1b**, only 1,2-attack took place with the α-carbanion. In other instances attack at the carbonyl site could be suppressed in the presence of HMPA (Table I, entry 6).

(9) See, for example, the case of alkylthio allylic anions, see: Binns, M. R.; Haynes, R. K., Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573. Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790 and references cited therein.

0022-3263/93/1958-5032$04.00/0

Table I. 1,4-Conjugate Additions with Reagents 1a and 1b

entry	reagent	substrate	product[a]	ratio[b]	yield[c] (%)
1	1a				
		R=H	**2a**, R=H ; $[\alpha]_D$ +40.0° (c 1.43)	93:7	88
		R=Me	**2b**, R=Me; $[\alpha]_D$ +33.5° (c 1.50)	93:7	80
2	1a			>99:1	80
			3; $[\alpha]_D$ +48.6° (c 1.20)		
3	1a			95:5	75
			4; $[\alpha]_D$ +17.4° (c 1.22)		
4	1b			96:4	96[d]
			5; $[\alpha]_D$ +28.2° (c 2.85)		
5	1b			94:6	74
			6; $[\alpha]_D$ +7.6° (c 2.00)		
6	1a			90:10	62[e]
			7; $[\alpha]_D$ -5.0° (c 1.85)		
7	1a			>99:1	76[f]
			8; $[\alpha]_D$ +6.7° (0.95)		

entry	reagent	substrate	product[a]	ratio[b]	yield[c] (%)
8	1a				
			9a, R_1R_2=H; $[\alpha]_D$ -5,8° (c 1.90)	>99:1	80
			9b, R_1=H,R_2=Me; $[\alpha]_D$ +11.2° (c 1.45)	>99:1	24
			9c, R_1=Me,R_2=H; $[\alpha]_D$ -3.5° (c 2.12)	>99:1	50
9	1b			>99:1	94
			10; $[\alpha]_D$ -1.9° (1.10)		
10	1a				
			11a, R=H ; $[\alpha]_D$ -16.1° (1.00)	>99:1	93
			11b, R=Bn; $[\alpha]_D$ -8.7° (0.80)	>99:1	67[g]
11	1a				
			12; $[\alpha]_D$ +3.0° (c 1.00)	93:7	48[h]
12	1a				
			13; $[\alpha]_D$ +2.6° (c 1.75)	99:1	60[hi]
13	1b				
			14; $[\alpha]_D$ -2.3° (c 2.20)	95:5	51[hk]

[a] Typical procedure: To the anion of reagent (1 mmol, from THF, BuLi, −78 °C, ~1 min) was added the substrate (1.2 mmol, THF). After being stirred at −78 °C for 0.5 h, the reaction mixture was quenched with NH_4Cl or with MeOH (**2b**, **6**), MeI (**9b**, **9c**), or BnBr (**3**, **11b**), followed by usual workup. See supplementary material for procedures and details. [b] Ratios 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 4, 5, 7–9, 12, 13), from ^{13}C NMR spectra of cyclic acetal derivatives with (*R*,*R*)-2,3-butanediol after oxidative cleavage (entries 1–3, 6, 10, 11).[5a] Corresponding racemic products were analyzed for comparison. See supplementary material. [c] Yield of isolated product after flash chromatography. Optical rotations were recorded in chloroform. [d] Stereochemistry proposed based on entry 9. [e] 1 mol equiv of HMPA was used. [f] The 1,6-addition product from γ-attack (7%) was also found. [g] After DBU equilibration. [h] Starting allylphosphonamide was recovered. [i] Toluene as solvent, NaHMDS as base. [k] Toluene as solvent.

superb stereoselectivity observed in the unprecedented case of acyclic α,β-unsaturated esters and dienic esters (entries 7–9).[10] The stereochemical versatility and preparative value of these unique stereodifferentiating reagents is further demonstrated in the case of α,β-unsaturated lactones and lactams with the option of trapping of the corresponding enolates with alkyl halides (entries 10–13). Toluene was found to be the solvent of choice in the case of the α,β-unsaturated lactam (entries 12 and 13).[11] The absolute configurational identity of the adducts was established by a combination of spectroscopic and chemical methods, by X-ray crystallography, and by comparison with known compounds.

The consistently high diastereoselectivities in the additions of allyl and crotyl phosphonamide anions such as **1a** and **1b**,[12,13] respectively, can be rationalized on the basis of their unique structures and topologies.[14] We propose that the *si* face selectivities with the (*R*,*R*)-reagents is the result of a favored transition state in which the cation-

(10) For an isolated example of the addition of α-lithiated phosphonates to α,β-unsaturated esters, see: Yamaguchi, M.; Tsukamoto, Y.; Hayashi, A.; Minami, T. *Tetrahedron Lett.* **1990**, *31*, 2423.

(11) Selectivity of conjugate addition was drastically diminished with a coordinating N-protective group (t-Boc, Ts).

(12) For achiral allylic phosphonamides, see: Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1969**, *34*, 3053. Evans, D. A.; Tackacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371. For the preparation of chiral nonracemic analogs, see: Koeller, K. J.; Spilling, C. D. *Tetrahedron Lett.* **1991**, *32*, 6297. See also refs 7 and 14.

(13) For structural and theoretical aspects of phosphorus-based allylic anions, see: (a) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A., Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5423. (b) Denmark, S. E.; Rajendra, G.; Marlin, J. E. *Tetrahedron Lett.* **1989**, *30*, 2469. See also: Denmark, S. E.; Cramer, C. J. *J. Org. Chem.* **1990**, *55*, 1813.

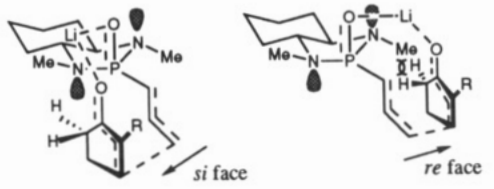


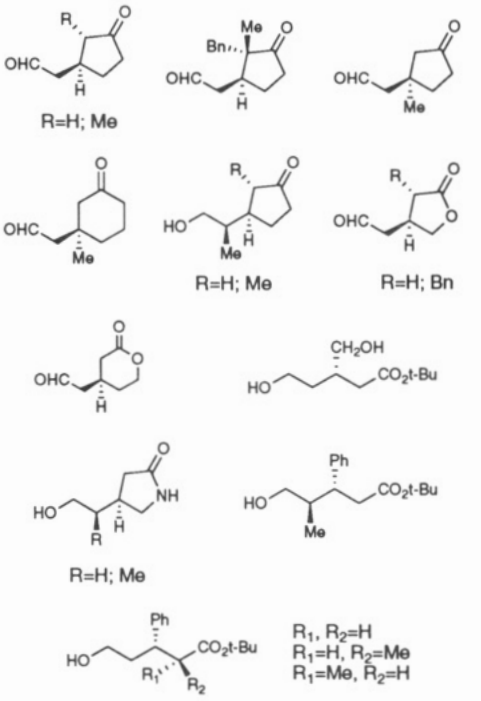
Figure 1.

chelated substrates are best accommodated within the "left-cleft" of the reagents (Figure 1). This may also correspond to a *trans*-decalinoid transition state previously proposed by Haynes and co-workers[4] for allylic sulfoxides and phosphine oxides.

The use of the allylic phosphonamide reagents **1a,b** and their enantiomers for asymmetric conjugate additions offers several advantages, including (a) ease of preparation of the reagents in enantiomerically pure form, (b) excellent selectivity in single-stage additions and in tandem asymmetric addition–alkylation, (c) wide scope of α,β-unsaturated carbonyl compounds, and (d) excellent predictive power based on the model proposed in Figure 1. Oxidative cleavage (O_3, CH_2Cl_2, −78 °C) and standard manipulation of functional groups generate a variety of enantiomerically pure (or highly enriched) chirons, which can be used as versatile templates in synthesis. A few representative compounds prepared from the initial adducts are shown in Chart I.

With the paucity of methods now available to prepare acyclic, cyclic, and heterocyclic compounds[15] containing contiguous carbon substituents including quaternary centers[16] in enantiomerically pure form, numerous applications of this methodology in the synthesis of natural

Chart I



and unnatural products and related compounds are evident.[17] It should be noted that the oxidation–reduction products resulting from the adducts **8** and **9a** in Table I are *chemical equivalents of asymmetrization processes normally accomplished with esterases and dialkyl 3-substituted glutarates with variable stereoselectivity*.[18] Furthermore, the symmetry elements in these adducts are such that diastereomeric or enantiomeric products can be obtained by adjustment of end groups, thus expanding their utility as chirons in synthesis. Further details regarding the scope and mechanistic features of these asymmetric reactions will be reported in due course.

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Supplementary Material Available: Experimental procedures, compound characterization data, and selected spectra (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754; *Chim. Script.* **1984**, *88*, 1419. Hanessian, S.; Bennani, Y. *Tetrahedron Lett.* **1990**, *31*, 6461, 6465. See also ref 7.

(15) For examples of chiral lactams and pyrrolidines of medicinal interest, see: Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814; **1993**, *58*, 36. Nielsen, L.; Brehm, L.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1990**, *33*, 71 and references cited therein.

(16) See, for example: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(17) For many examples of natural product synthesis starting with cyclic and acyclic compounds containing multiple stereogenic centers, see: Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley-Interscience: New York, 1989. Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH Publishers, Inc.: New York, 1988; *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press, Inc.: New York, 1984, 1989; Vols. 1 and 2 and references cited therein.

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