Table I. Synthesis of Diols (2) and Allylic Alcohols (3) (See eq 1)[a]

entry	phosphinoyl aldehydes (1) no.	R^1	R^2	diols (2) R^3	no.	ds ratio[b,c,d]	yield (%)[e]	allylic alcohols yield (%)[f]
1	**1a**	CH_3	CH_3	*i*-Pr	**2a**	–[g]	84	84[h]
2	**1b**		$-(CH_2)_5-$	C_6H_{11}	**2b**	–[g]	87	93
3	**1c**	CH_3	Et	$PhCH_2CH_2$	**2c**	14:1	82	92
4	**1d**	CH_3	$(CH_3)_2C{=}CHCH_2$	*i*-Pr	**2d**	14:1	85	90[h]
5	**1e**	CH_3	Bn	CH_3	**2e**	28:1	94[i]	95[h]
6	**1e**	CH_3	Bn	$PhCH_2CH_2$	**2f**	43:1	89	94
7	**1e**	CH_3	Bn	*t*-Bu	**2g**	≥45:1	32[j]	98
8	**1f**	CH_3	*i*-Pr	*i*-Bu	**2h**	>99:1	94	91
9	**1g**	CH_3	Ph	$PhCH_2CH_2$	**2i**	–[k]	80	77
10	**1h**	Et	*i*-Pr	*n*-Pr	**2j**	7.5:1	81	91[h]

[a] For a representative experimental for the synthesis of **2** and **3** see the supplementary material. [b] The term ds refers to the diastereofacial selectivity for these reactions. Only threo diols were obtained. [c] Determined by ^{31}P NMR spectroscopy of the crude product mixture. Accuracy of the analysis by ^{31}P NMR spectroscopy was established by demonstrating that the *E*/*Z* ratio of allylic alcohols **3d,e,j** (by ^1H NMR of the crude product mixture), prepared from crude diols **2d,e,j**, was the same as the reported ds. [d] After purification of the diol by either flash chromatography (fc) or recrystallization (r), ds generally improved significantly: e.g. **2c**, 59:1 (r); **2d**, >99:1 (r); **2e**, 34:1 (fc); **2f**, 57:1 (fc); **2g**, >99:1 (fc); **2i**, >99:1 (r); **2j**, >99:1 (fc). [e] Isolated yield (%). [f] Unless otherwise noted, yields for **3** are based on elimination from purified diol **2**. The *E*/*Z* ratio of products was always equal to the ds of the purified or crude diol **2**. [g] Only the threo diol was obtained. [h] Crude **2** was used. Therefore, the yield is based on starting aldehyde **1**. [i] 1.1 equiv of acetaldehyde were used. [j] 41% of starting material (**1e**) was recovered. Approximately 20% of homocoupled products from **1e** was observed by ^{31}P NMR spectroscopy. [k] Not determined due to the presence of several other minor resonances in the ^{31}P NMR spectrum of the crude product mixture.

With high diastereofacial selectivity in hand all that remained to complete the proposed synthesis of allylic alcohols shown in eq 1 was to perform the Horner–Wittig elimination reaction.[16] This was accomplished using an excess of sodium hydride (4 equiv) in refluxing tetrahydrofuran (ca. 20–60 min).[8] Yields of the allylic alcohols were always high, and the elimination can be performed on the crude diols (**2**) (Table I). Alternatively, purification of the diols either by recrystallization or chromatography generally results in significant or complete enrichment of the major isomer (see Table I).

In summary, we have developed an efficient and stereospecific synthesis of 3,3-disubstituted allylic alcohols that employs the chelation assisted pinacol cross-coupling reaction as a key step. Extension of this chemistry to asymmetric syntheses of this class of alcohols is clearly feasible by beginning with enantiomerically pure chelating aldehydes. The high diastereofacial selectivity observed in these reactions also warrants further study. In particular, if the conformational properties of chelated **1** are responsible for this selectivity, then other chelation-controlled addition reactions to these aldehydes should be possible.[17] Such reactions could lead to a general and stereospecific synthesis of trisubstituted alkenes.

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Supplementary Material Available: Representative procedures for syntheses of aldehydes **1**, diols **2**, and allylic alcohols **3** and ^1H and ^{13}C NMR, mass spectra, and elemental analyses data for all compounds (11 pages). Ordering information is given on any current masthead page.

(13) To our knowledge, diastereofacial selective additions of this magnitude, to a prochiral carbonyl bearing three non-hydrogen α-substituents, two of which are methyl and ethyl, is without precedent. For examples of chelation-controlled addition reactions to α-hydroxy(or alkoxy) carbonyls bearing two different non-hydrogen substituents, see: (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (c) Cram, D. J.; Allinger, J. *Ibid.* **1954**, *76*, 4516. (d) Cram, D. J.; Elhafez, F. A. A. *Ibid.* **1952**, *74*, 5828. For an additional example related to this area see: Reetz, M. T. *Nach. Chem. Tech. Lab.* **1981**, *29*, 165.

(14) For reviews of chelation-controlled addition reactions, see: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(15) The term "chelation-control" is used to identify a predictive model for the stereochemical outcome of these reactions (Figure 1). This model is not meant to suggest what the reactive intermediates are in these reactions.

(16) Buss, A. D.; Greeves, N.; Mason, R.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **1985**, 2307.

(17) Recently, Warren and co-workers have achieved high stereochemical control in the reduction of α-diphenylphosphinoyl ketones (i.e. $Ph_2P(O)CHRC(O)R'$ using sodium borohydride in the presence of cerium chloride. Elliott, J.; Hall, D.; Warren, S. *Tetrahedron Lett.* **1989**, *30*, 601.

Stereoselective Alkylations of Chiral, Phosphorus-Stabilized Benzylic Carbanions

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Summary: A series of 6-substituted 2-benzyl-3-*tert*-butyl-1,3,2-oxazaphosphorinanes was prepared in racemic and enantiomerically pure form. The diastereoselectivity of alkylation of the derived anions was examined as a function of ring substitution pattern, base, solvent, electrophile, and enantiomeric composition.

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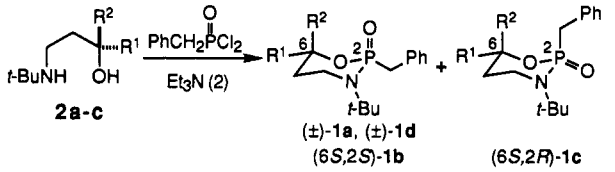
The use of anionic organophosphorus reagents for carbon–carbon single bond formation[1] pales in comparison to their application in olefinations. Moreover, despite the potential for chiral modification of phosphorus, only a few reports have appeared in recent years documenting asymmetric reactions of phosphorus-stabilized anions in a chiral environment.[2,3] As part of a general program of the chemistry of chiral, phosphorus-stabilized anions (structure, reactivity, selectivity),[4] we have undertaken a thorough investigation of their alkylation behavior. We report herein that highly selective alkylations of phosphorus-stabilized, benzylic carbanions can be achieved using a readily available chiral auxiliary.[4c]

The selection of the auxiliary was guided by several criteria: (1) accessibility in scalemic form, (2) ease of incorporation and recovery, and (3) strong conformational bias in the anion. The initial design was based on the Seyden–Penne model for the structure of the anion which incorporated a C–Li bond in an orthogonal orientation.[5] However, our own studies have recently refined this picture and shown that there is no C–Li bond and the rotational barrier in the anion is extremely low.[4a,6] Thus, the *auxiliary* must be designed such that the anion will have a strong rotamer bias. This was deemed best accomplished by differentiating the two sides of the phosphorus with sterically disparate groups, e.g. *N-tert*-butyl and O-electron pair. Thus, a series of 2-benzyl-3-*tert*-butyl-1,3,2-oxazaphosphorinanes 1[7] was envisioned to the probe the dissymmetric environment about phosphorus.

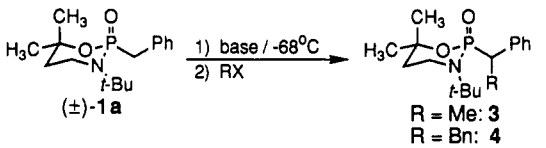
Table I. Preparation of Substrates 1a–d



educt	R^1	R^2	product	yield, %
2a	Me	Me	**1a**	55
(*S*)-**2b**[a]	Me	H	**1b**[b]	49
	Me	H	**1c**[b]	28
2c	H	H	**1d**	24

[a] 99% ee. [b] Ratio 1.8:1.

Table II. Alkylation of Racemic 1a



base	solvent	RX	ratio[a]	yield, %[b]
t-BuLi	THF	MeI	98:2	88
t-BuLi	THF[c]	MeI	99:1	62
t-BuLi	DME[c]	MeI	99:1	–
t-BuLi	Et_2O[c]	MeI	98:2	–
KHMDS	THF[c]	MeI	98:2	–
t-BuLi	THF[c]	Me_2SO_4	98:2	–
t-BuLi	THF	BnBr	96:4	78

[a] Determined by HPLC. [b] Isolated yield of the major diastereomer. [c] DMPU added (2 equiv).

Scheme I

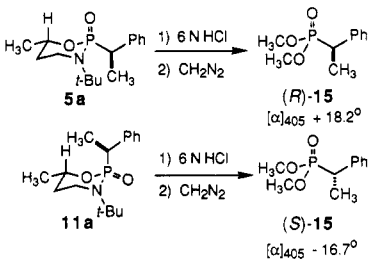
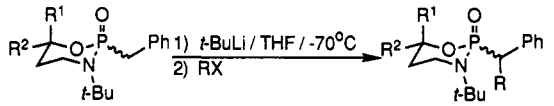


Table III. Alkylation of 1b, 1c, and 1d



educt	RX	ratio[a]	products	yield, %
1b	MeI	95:5	**5a:5b**	85[b]
1b	$(MeO)_2SO_2$	92:8	**5a:5b**	67[b]
1b	$ClCH_2OBn$	92:8	**6a:6b**	74[b]
1b	*n*-BuLi	93:7	**7a:7b**	78[b]
1b	$BrCH_2CO_2Bn$	94:6	**8a:8b**	46[b]
1b	$ICH_2CH{=}CH_2$	90:10	**9a:9b**	86[b]
1b	BnBr	84:16	**10a:10b**	70[b]
1c	MeI	83:17	**11a:11b**	96[c]
1c	BnBr	55:45	**12a:12b**	98[c]
1d	MeI	90:10	**13a:13b**	81[b]
1d	BnBr	70:30	**14a:14b**	71[c]

[a] HPLC. [b] Isolated yield of major diastereomer. [c] Isolated yield of both diastereomers.

The substrates **1a–d** were prepared by combining benzylphosphonic dichloride[8] with the readily available *N-tert*-butyl-1,3-amino alcohols **2a–c**[4c,9] (Table I). The optically active oxazaphosphorinanes, **1b** and **1c**, were separated chromatographically, and their stereostructures were assigned by ^{31}P and ^{1}H NMR spectroscopy and were ultimately secured by X-ray crystallography (vide infra).

Orienting alkylation studies were performed with racemic **1a** by varying the base, solvent, additive, and elec-

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(2) For asymmetric alkylations, see: (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (b) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *Chem. Scr.* **1985**, *25*, NS5. (c) Bartlett, P. A.; McLaren, K. L. *Phosphorus Sulfur* **1987**, *33*, 1. (d) Hanessian, S.; Bennani, Y.; Delorme, D. *Tetrahedron Lett.*, in press.

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(4) (a) Denmark, S. E.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 864. (b) Denmark, S. E.; Cramer, C. J. *J. Org. Chem.* **1990**, *55*, 1806. (c) Denmark, S. E.; Marlin, J. E. *J. Org. Chem.* **1987**, *52*, 5742. (d) Denmark, S. E.; Rajendra, G.; Marlin, J. E. *Tetrahedron Lett.* **1989**, *30*, 2469.

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(6) (a) Denmark, S. E.; Miller, P. C.; Wilson, S. R., manuscript submitted. (b) Cramer, C. J., unpublished calculations.

(7) All new compounds have been fully characterized by ^{1}H (300 or 500 MHz), ^{13}C (75 or 125 MHz), and ^{31}P (121 MHz) NMR, IR, mass spectrometry, microanalysis and optical rotation.

(8) (a) Morita, T.; Okamoto, Y.; Sakurai, H. *Tetrahedron Lett.* **1978**, *19*, 2523. (b) Bhongle, N. N.; Notter, R. H.; Turcotle, J. G. *Synth. Commun.* **1987**, *17*, 1071.

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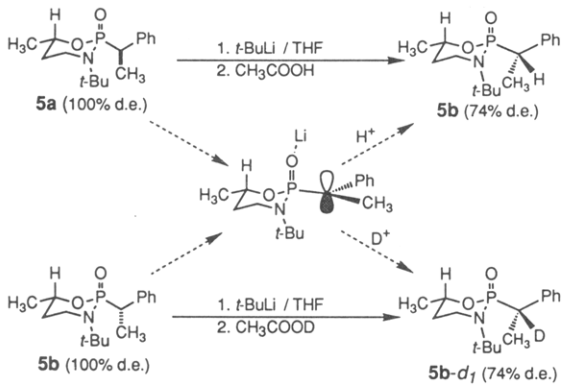
Scheme II



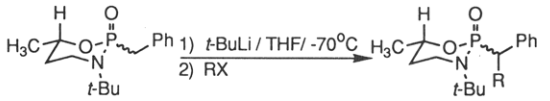
trophile. As summarized in Table II, *the alkylations were highly selective and independent of solvent, additive, and base.* While *n*-BuLi could also be used, *t*-BuLi was found to give cleaner reactions. Interestingly, as opposed to the electrophile-dependent alkylation selectivity of sulfoxide-stabilized carbanions,[10] both methyl iodide and dimethyl sulfate yielded a 98:2 ratio of the crystalline, easily separable methylated diastereomers.

In the optically active series, we found that the alkylation of Li^+**1b**$^-$ also occurred with high diastereoselectivity in a range of 95:5 (MeI) to 84:16 (BnBr).[16] This trend is in contrast to enolate alkylations where MeI is the least selective electrophile.[11] Surprisingly, the epimer Li^+**1c**$^-$, reacted with low stereoselectivity.[12]

The stereochemical course of alkylation was determined by X-ray crystallographic analysis of **10a**, the major benzylation product of Li^+**1b**$^-$. The newly created stereogenic center was found to possess the *R* configuration. Thus, electrophilic attack occurred on the *re* face of (2*S*,6*S*)-Li^+**1b**$^-$. The major alkylation products from reaction of Li^+**1c**$^-$ were shown to possess the opposite (*S*) configuration by comparison of the optical rotation of the dimethyl phosphonates **15** derived from **5a** and **11a** (Scheme I). Thus, the local chirality of the anion (phosphorus configuration) dominates the stereochemical course of alkylation.

The poor selectivity in alkylation of Li^+**1c**$^-$ was unexpected based on the simple picture of anion structure and local environment. Moreover, the higher selectivity observed in the alkylation of Li^+**1d**$^-$ (Table III) also rules out simple steric approach control.[13] To probe the origin of the erosion in selectivity we investigated the contributions of two potentially significant factors: stereoselective, kinetic anion formation[14] and aggregation effects.[15]

Table IV. Comparison of Scalemic and Racemic 1b and 1c



educt	RX	ratio[a]	products	yield, %
(+)-**1b**	MeI	95:5	**5a**:**5b**	85[b]
(±)-**1b**	MeI	93:7	**5a**:**5b**	84[b]
(+)-**1b**	BnBr	84:16	**10a**:**10b**	70[b]
(±)-**1b**	BnBr	84:16	**10a**:**10b**	83[b]
(−)-**1c**	MeI	83:17	**11a**:**11b**	96[c]
(±)-**1c**	MeI	83:17	**11a**:**11b**	76[c]
(−)-**1c**	BnBr	55:45	**12a**:**12b**	96[c]
(±)-**1c**	BnBr	55:45	**12a**:**12b**	98[c]

[a] HPLC. [b] Isolated yield of major product. [c] Isolated yield of combined products.

As shown in Scheme II deprotonation–reprotonation (deuteration) of pure epimers **5a** and **5b** led to the same 87:13 mixture of products. *Thus, the reaction must proceed though a common intermediate* and stereoselective deprotonation, if present, is irrelevant. This result is consistent with the low anion rotational barrier.[6]

A very important difference among the anions which may contribute to their different alkylation selectivity is that Li^+**1a**$^-$ and Li^+**1d**$^-$ are racemic while Li^+**1b**$^-$ and Li^+**1c**$^-$ are scalemic. If the reactive species were dimeric, $(Li^+$**1b**$^-)_2$ and $(Li^+$**1c**$^-)_2$ *must be homochiral* while $(Li^+$**1a**$^-)_2$ and $(Li^+$**1d**$^-)_2$ can be either homochiral or heterochiral. To test the effect of aggregate structure on diastereoselectivity, racemic Li^+**1b**$^-$ and Li^+**1c**$^-$ were alkylated. The comparison of the racemic and scalemic anions is compiled in Table IV. Using both MeI and BnBr, the products were formed with the same diastereoselectivity independent of enantiomeric composition. Thus, either the aggregate structure is not responsible for the different alkylation selectivities or the reactive species are monomers.

In summary, the alkylation of Li^+**1a**$^-$ and Li^+**1b**$^-$ proceeds with high diastereoselectivity and **1b** provides easy access to optically active alkylphosphonic acids. An explanation of the differing alkylation selectivities of Li^+-**1a**–**d**$^-$ requires an extensive ring conformational analysis which, together with further studies of electrophilic substitution, will be the subject of forthcoming reports.

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Supplementary Material Available: A listing of crystal and positional parameters, bond lengths, angles and torsional angles for **10a** and preparation and full characterization of **1a**, **1b**, **1c**, **3a**, **5a**, and **11a**/**b** (21 pages). Ordering information is given on any current masthead page.

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(11) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1.

(12) The alkylations were shown to be under kinetic control as Li^+**1c**$^-$ failed to epimerize **12b**.

(13) X-ray crystallography established that the major product (**13a**) is in the same configurational series as **5a**.

(14) Durst, T.; Fraser, R. R.; McClory, M. R.; Swingle, R. B.; Viau, R.; Wigfield, Y. Y. *Can. J. Chem.* **1970**, *48*, 2148.

(15) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(16) **Note Added in Proof.** We have recently discovered that the *smaller N*-isopropyl analogue of **1b** reacts with uniformly higher selectivity, 98:2 (MeI), 97:3 (BnBr); Chen, C.-T., unpublished observations in these laboratories.