Alkylation of Chiral, Phosphorus-Stabilized Carbanions: Substituent Effects on the Alkylation Selectivity

Scott E. Denmark* and Chien-Tien Chen

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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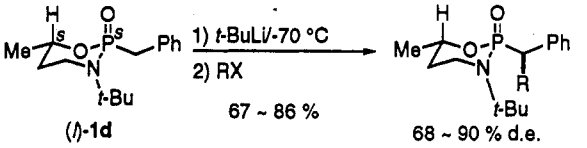
Summary: The alkylation of a series of enantiomerically pure cis and trans 3-substituted 2-benzyl-6-methyl-1,3,2-oxazaphosphorinane 2-oxides was found to be sensitive to the bulk of the *N*-substituents.

The synthesis and utility of phosphonic acids and phosphonate derivatives have emerged as areas of significant research activity.[1] Our interest in the preparation of these compounds derives from the exploration of the chemistry of phosphorus-stabilized anions in the domains of structure[2] and reaction stereoselectivity.[3] One of the primary goals is the design and development of chirally modified reagents which can effect highly stereoselective asymmetric transformations of the anion for general access to chiral phosphorus[4] and non-phosphorus-containing compounds.[4a,5] Reports from these laboratories have demonstrated the utility of anions derived from chiral phosphonamidate (*l*)-**1d** in asymmetric alkylation, Scheme 1.[3a] We have subsequently undertaken a thorough survey of *N*-substituents and have examined their influence on the alkylation selectivity. Herein we disclose that extremely selective and general alkylations of phosphorus-stabilized carbanions can be accomplished by fine tuning the *N*-substituents.

The original design of the auxiliary for **1d** was made on the basis of the strongly dissymmetric environment around the anionic center due to the sterically disparate groups, i.e., *N*-*tert*-butyl and O-electron pair, and a strong rotamer bias in the anion. To evaluate the importance of the

Scheme 1



N-substituent, several *N*-alkyl-1,3-amino alcohols **2a–c** and **2e** were prepared from ethyl (*S*)-3-hydroxybutyrate by analogy to the synthesis of the corresponding *N*-*tert*-butyl analog.[6] The oxazaphosphorinane 2-oxides, (*l*)-**1a–c** and (*u*)-**1a–c**, were synthesized from benzylphosphonic dichloride[7] and the appropriate 1,3-amino alcohols **2a–c** to afford the easily separable, crystalline products in good overall yields (78–89%), Table 1.[8] The extreme steric bulk in **2e** retarded its direct cyclization with benzylphosphonic dichloride. An alternative route involving the Arbuzov reaction[9] of phosphite **3e** (trans/cis:15/1)[10] with benzyl bromide (or benzyl tosylate[11]) in warm acetonitrile was employed to produce (*l*)-**1e** and (*u*)-**1e** in a ratio of 7.3:1 (or 11:1). Their stereostructures were assigned spectroscopically by analogy with **1d** whose absolute configuration was confirmed by X-ray crystallographic analysis[3a] and by the diagnostic downfield shift of HC(6) in the cis isomer.[12]

The alkylation studies were first carried out with (*l*)-**1a–c** and **1e** by adopting the optimized reaction conditions for (*l*)-**1d** reported previously and by examining MeI and BnBr as test electrophiles. As summarized in Table 2, the methylations proceeded with high diastereoselectivity in a range of 90/10 (R = $C(C_2H_5)_3$) to 97/3 (R = *i*-Pr and Et) and were uniformly more selective than the corresponding benzylations. Among the *N*-substituents surveyed, the *N*-isopropyl-(2*S*,6*S*)-1,3,2-oxazaphosphorinane (*l*)-**1c** gave the best alkylation selectivities. Interestingly, the results revealed that even a small *N*-group like methyl exhibited superior diastereoselectivity as compared to the *N*-*tert*-butyl and *N*-(1,1-diethyl)propyl (*tert*-heptyl) analogs.

The *N*-isopropyloxazaphosphorinane 2-oxide ((*l*)-**1c**) underwent highly diastereoselective alkylation with a variety of electrophiles, Table 3. In all cases the alkylation

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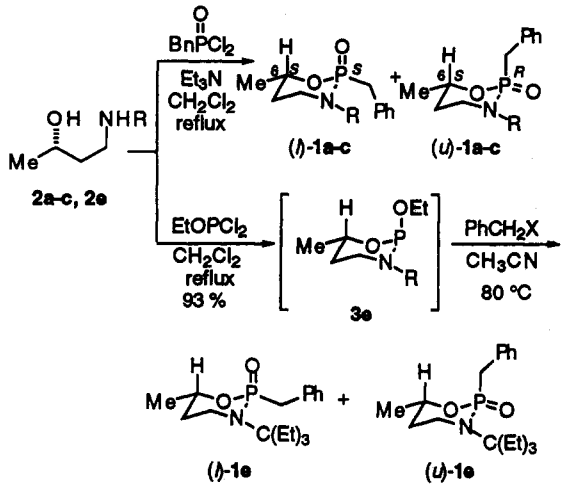
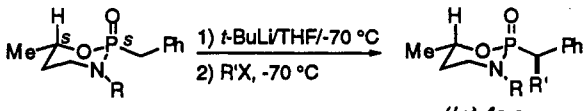
Table 1. Preparation of Substrates 1a–c and 1e



R	ratio (*l*:*u*)[a]	product	yield,[d] % (*l*:*u*)
Me	1.1:1	**1a**	43:38
Et	1:1.3	**1b**	28:50
i-Pr	1.9:1	**1c**	57:32
C(Et)$_3$	7.3:1[b,c]	**1e**	72:9[b,c]

[a] Ratio determined by ^{31}P NMR. [b] BnBr was used. [c] Ratio (11:1) and yield (68:6.5) when BnOTs was used. [d] Isolated yield.

Table 2. Alkylation with Oxazaphosphorinane 2-Oxide (*l*)-1a–e



educt	R	R′X	product	ratio (*l*,*u*:*l*,*l*)[b]	yield,[c] %
(*l*)-**1a**	Me	MeI	**4a**	95:5	85
(*l*)-**1b**	Et	MeI	**4b**	97:3	89
(*l*)-**1c**	*i*-Pr	MeI	**4c**	97:3	93
(*l*)-**1d**	*t*-Bu[a]	MeI	**4d**	95:5	85
(*l*)-**1e**	C(Et)$_3$	MeI	**4e**	90:10	85
(*l*)-**1a**	Me	BnBr	**5a**	90:10	71
(*l*)-**1b**	Et	BnBr	**5b**	91:9	84
(*l*)-**1c**	*i*-Pr	BnBr	**5c**	94:6	89
(*l*)-**1d**	*t*-Bu[a]	BnBr	**5d**	84:16	83
(*l*)-**1e**	C(Et)$_3$	BnBr	**5e**	80:20	67

[a] Data from ref 3a. [b] Determined by HPLC. [c] Isolated yield.

Table 3. Alkylation of Oxazaphosphorinane 2-Oxide (*l*)-1c[a]

R′X	product	ratio (*l*,*u*:*l*,*l*)[b]	yield,[c] %
MeI	**4c**	97:3	93
n-BuI	**6**	99.4:0.6	95
i-BuI	**7**	100:0	94
i-PrI	**8**	97.5:2.5	82[d]
allyl bromide	**9**	98:2	89
BnBr	**5c**	94:6	89
BnOCH$_2$Cl	**10**	1.5:98.5[e]	84

[a] All reactions were carried out as shown in Table 2. [b] Determined by HPLC. [c] Isolated yield. [d] With 17% of recovered (*l*)-**1c**. [e] Due to priority change.

products **4c**, **5c**, and **6**–**10** were formed in high yield (82–95%) with excellent diastereoselectivity (88–100% de). The alkylation with a β-branched alkyl halide, i.e., *i*-BuI, afforded a single diastereomer (*l*,*u*)-**7** in 95% yield. A secondary alkyl halide, i.e., *i*-PrI, was also found to react smoothly leading to a 97/3 ratio of the isopropylated products **8** in 82% yield along with recovered (*l*)-**1c** (17%).

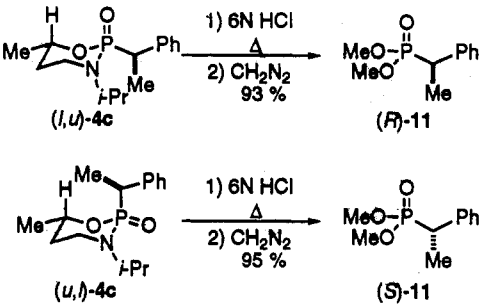
As opposed to the trend in the alkylation behavior of *cis*-oxazaphosphorinane 2-oxide (*l*)-**1a-e**, in the methylations of the trans stereoisomers (*u*)-**1a-d** the steric bulk of the *N*-substituents has little influence on the diastereoselectivity (83/17–85/15), Table 4. However, significant improvement in diastereoselection can be attained by the employment of very large *N*-*tert*-heptyl analog (*u*)-**1e** (95/5).

Table 4. Methylation with Oxazaphosphorinane 2-Oxide (*u*)-1a–e[a]

educt	R	product	ratio (*u*,*l*:*u*,*u*)[b]	yield,[c] %
(*u*)-**1a**	Me	**4a**	83:17	99
(*u*)-**1b**	Et	**4b**	85:15	99
(*u*)-**1c**	*i*-Pr	**4c**	85:15	100
(*u*)-**1d**	*t*-Bu[d]	**4d**	83:17	96
(*u*)-**1e**	C(Et)$_3$	**4e**	95:5	97

[a] All reactions were carried out as shown in Table 2. [b] Determined by HPLC. [c] Isolated yield. [d] Data from ref 3a.

Scheme 2



The stereochemical course of alkylation in the cis series was determined by spectroscopic correlation of **4c** with the alkylation product **4d** (from (*l*)-**1d**) whose absolute configuration at the newly created stereogenic center was found to possess the *R* configuration by X-ray crystallographic analysis.[3a] Furthermore, the assignment of *R* configuration was secured by comparison of the optical rotations of dimethyl phosphonate **11** derived from both (*l*,*u*)-**4c** and (*l*,*u*)-**4d**,[3a] Scheme 2. Thus, the electrophilic attack occurred preferentially from the *re* face of Li$^+$**1**$^-$. The major alkylation products in the trans series were assigned in a similar fashion, Scheme 2. Thus, (*u*,*l*)-**4c** provided **11** of opposite (*S*) configuration. Thus, the stereochemical course of alkylation was controlled by the local asymmetric environment provided by the phosphorus stereogenic center, and either enantiomer of dimethyl phosphonate **11** can be obtained by diastereoselective alkylation.

To gain insight into the origin of stereocontrol, we found that a nearly linear steric energy relationship (δ = –0.084, r = –0.995) was obtained when the logs of [% de (**5a-c**)/% de (**5a**)] were correlated with the appropriate Taft steric substituent constants *Es* from (*l*)-**1a** (R = Me) to (*l*)-**1c** (R = *i*-Pr).[13] This empirical consistency of steric control effects by increasing the steric bulk of *N*-substituents (from *N*-Me to *N*-*i*-Pr) strongly indicates that very similar reactive conformations of the anions in (*l*)-**1a–c** are involved in the alkylation, and the size of R plays a crucial role in the facial bias of the anions. The erosion of diastereoselectivity observed in the case of sterically demanding substituents such as (*l*)-**1d** and (*l*)-**1e** suggested subtle changes on the conformations of the heterocyclic rings. The adverse gauche interaction between the anionic

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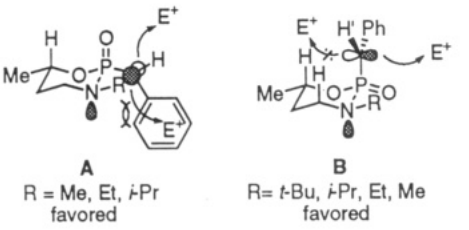
Scheme 3



moiety and the *N-tert*-heptyl (or *N-tert*-butyl) group seems responsible for such changes. The delicate conformational equilibria of oxazaphosphorinane 2-oxides is well documented by conformational studies in solution[12b,c,14a] and structural features in the solid state.[14]

The results of alkylation in the cis series can be rationalized in terms of the parallel anion conformer **A**, Scheme 3.[15] The electrophilic attack takes place predominantly from the side opposite to the nitrogen substituent. Thus, when the R group becomes larger, the diastereoselectivity increases. On the other hand, the unexpected steric independence from *N*-Me to *N*-*t*-Bu in the methylations in the trans series can be understood by the orthogonal anion rotamer **B**. Since the stereocontrol elements in **B** are the axial hydrogens in the heterocycle, increasing the steric bulk of R would have little consequence on the diastereoselection.

In summary, the alkylation of $Li^+(l)$-**1c**$^-$ and $Li^+(u)$-**1e**$^-$ proceeds with uniformly high selectivity and provides access to either antipode of α-alkylphosphonic acids and phosphonates. The conformation of the phosphorus heterocycle, the conformational bias of the anion, and the steric bulk of the *N*-substituents are key factors in controlling the diastereoselectivity of alkylation. Further studies to address these important issues in thiophosphoryl-stabilized anions are currently underway.

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Supplementary Material Available: Preparation and full spectroscopic characterization of **1a–c,e**, **2a–c,e**, **4a–c,e**, **5a–c,e**, and **6–10** are provided (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.

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(15) The nitrogen atom in **A** is formulated as pyramidal on the basis of our X-ray crystal structures of diazaphosphorinane 2-oxide anions[2] and the X-ray structure of the anion derived from the *P*-isopropyl analog of **1d** which displays a pyramidal nitrogen; Miller, P. C.; Wilson, S. R. unpublished results from these laboratories.