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Asymmetric [2,3]-Wittig Rearrangements with Chiral, Phosphorus Anion-Stabilizing Groups

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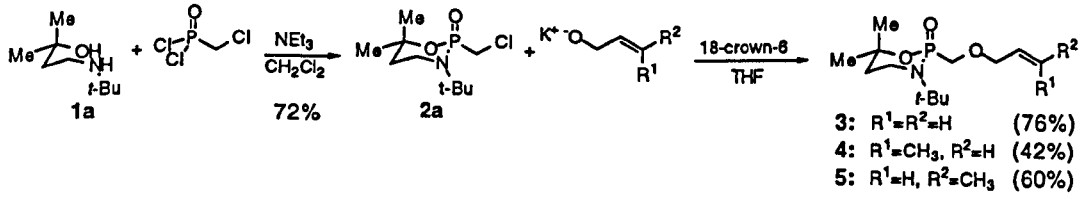
Abstract: The [2,3]-Wittig rearrangement of a chirally-modified phosphorus stabilized anion proceeds readily and with excellent diastereo- and enantioselectivity for allyloxymethyl and (Z)-2-butenyloxymethyl derivatives.

The [2,3]-Wittig rearrangement belongs to an important subgroup of sigmatropic rearrangements that have found extensive application in the synthesis of complex organic molecules.[1] Due to the ease of construction of the allylic ether precursors and the high and predictable levels of stereocontrol, creative solutions to problems in both acyclic and macrocyclic stereoselection have been devised with one of the many variants of the [2,3]-Wittig rearrangement. Moreover, the use of chiral auxiliary-based asymmetric modifiers have not escaped attention in this arena, and several successful applications are on record.[2] Previous disclosures from these laboratories have documented the ability of chiral, phosphorus anion-stabilizing groups to influence the rate and stereochemical outcome of the Claisen rearrangement.[3] In this scenario, the anion is peripheral to the pericyclic system while in the [2,3]-Wittig rearrangement, the electrons of the anion are integral to the 6π Huckel array. We describe herein the facile and highly stereoselective [2,3]-Wittig rearrangements of chiral allyloxymethyl phosphonamidates.[4]

Orienting studies were carried out using a racemic 1,3,2-oxazaphosphorinane controller group derived from achiral amino alcohol **1a**.[5] The amino alcohol was coupled with chloromethylphosphonic dichloride in the presence of triethylamine to afford racemic 2-chloromethyl-1,3,2-oxazaphosphorinane **2a**[6] in 72% yield (Scheme 1). The synthesis of the rearrangement substrates, **3**, **4** and **5**, involved a rather difficult displacement of the chloride which was accomplished by treatment of **2a** with the appropriate potassium alkoxide in the presence of a stoichiometric amount of 18-crown-6 to afford the corresponding racemic 1,3,2-oxazaphosphorinanes.

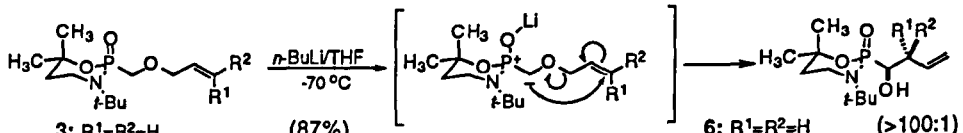
Scheme 1



Deprotonation of **3-5** with *n*-BuLi in THF at -70 °C generated the phosphorus-stabilized anion which underwent the [2,3]-Wittig rearrangements to afford the 1'-hydroxy-3-butenyl-1,3,2-oxazaphosphorinanes **6**, **7** and **8** in good yields (Scheme 2). In the rearrangements of **3** and **4**, a single product was observed as determined by ^{1}H NMR spectroscopy prior to purification. In the case of **3**, the rearrangement was complete within 30 min, while in the case of **4**, the rearrangement took significantly longer (12 h). Oxazaphosphorinane **5**, when treated

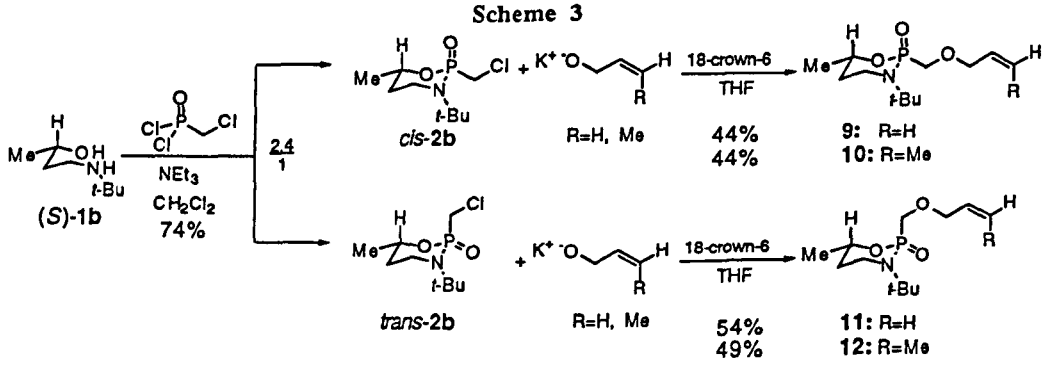
with *n*-BuLi under the same conditions, underwent rearrangement in 3.5 h to afford a 2.6:1 mixture of two diastereomeric products as determined by ^{1}H NMR spectroscopy. Since **4** underwent rearrangement to afford a single diastereomer, it was assumed that **5** afforded a mixture of epimers at the methyl-bearing stereogenic center (i.e. **7** and **8**). Thus, the chiral phosphorus auxiliary can be effective in controlling the diastereofacial selectivity at both prostereogenic centers in the [2,3]-Wittig rearrangement. However, we were not able to assign the relative configurations of the newly created centers. Thus, we next assayed the ability of an enantiomerically pure auxiliary to carry out this transformation to afford enantiomerically pure rearrangement products that could be correlated to known compounds.

Scheme 2



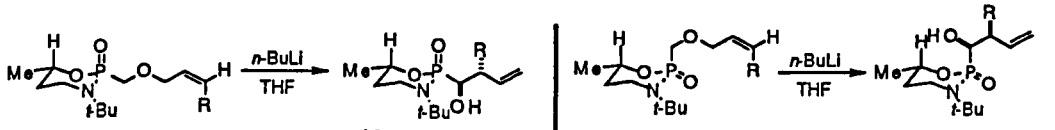
To achieve this objective, we selected amino alcohol (*S*)-**1b** because of its structural similarity to amino alcohol **1a** and because of its ready accessibility on a large scale in high enantiomeric purity.[3a,5] Chiral HPLC analysis indicated an enantiomeric enrichment of 99% ee. Treatment of (*S*)-**1b** with chloromethylphosphonic dichloride afforded a 2.4:1 mixture of the 2-chloromethyl-1,3,2-oxazaphosphorinanes which were separated by silica gel column chromatography to afford enantiomerically pure samples of *cis*-**2b** and *trans*-**2b** (Scheme 3). Assignment of the configuration at phosphorus was not as straightforward as usual. From our own experience, as well as that of others, the ^{31}P NMR chemical shift of the *cis* diastereomer is customarily downfield relative to that of the *trans* diastereomer and the ^{1}H NMR chemical shift for $H_{ax}C(6)$ in the *cis* diastereomer appears downfield relative to the *trans* diastereomer.[5,7] Compounds *cis*-**2b** and *trans*-**2b** did not conform to this trend. Assignment of configuration at phosphorus was based on the fact that all of the derivatives prepared from *cis*-**2b** and *trans*-**2b** did fit the trend. Additionally, we have noted a correlation in these compounds between the sign of the optical rotation and the configuration at phosphorus such that the dextrorotatory isomer possesses the *S* configuration at phosphorus, while the levorotatory isomer has the *R* configuration. This trend holds for **2b** and **9-12**.

Scheme 3



The 2-allyloxymethyl-1,3,2-oxazaphosphorinanes **9**, **10**, **11** and **12** were prepared as described above for the racemic series. The (*E*)-allyloxides were not pursued in this series in light of the poor rearrangement diastereoselectivity observed for **5**. The [2,3]-Wittig rearrangements of **9**-**12** were carried out as described for the racemic compounds (*n*-BuLi / THF). The reactions proceeded cleanly and reproducibly at low temperature and were complete within 2 h for **9** and **11**. For compounds **10** and **12**, the rearrangements were significantly slower but were complete within 14 h. The substrates **9**, **11** and **12** underwent rearrangement to afford 1'-hydroxy-3-butenyl-1,3,2-oxazaphosphorinanes **13**, **15** and **16** respectively. In each case, only one diastereomeric product was detected as determined by ^{1}H NMR spectroscopy of the crude reaction mixtures (Scheme 4). The indicated selectivities are signal to noise measurements in the ^{1}H NMR spectra.

Scheme 4



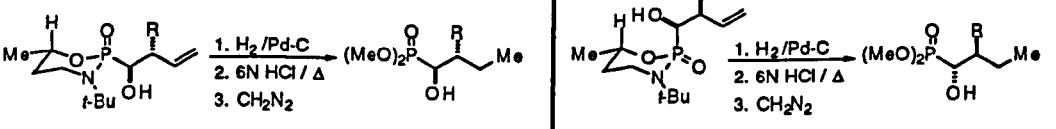
9: R=H (-64 °C/2h) 74% **13**: R=H (>100:1)
10: R=Me (-72 °C/14h) 74% **14**: R=CH_3 (9:1)

11: R=H (-64 °C/2h) 72% **15**: R=H (>100:1)
12: R=Me (-72 °C/14h) 88% **16**: R=Me (>94:1)

1,3,2-Oxazaphosphorinane **10** underwent rearrangement to afford a 9.3:1 mixture of diastereomeric products **14**. The ratio of was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and remained unchanged after chromatography. It is assumed that the minor isomer bears the opposite configuration at C(2') (methyl-bearing center). This assumption was supported by the subsequent degradation of **14** and **16** to 2-methylbutyric acid in which the hydroxy-bearing stereocenter has been removed (*vide infra*). The magnitude of the optical rotation was lower for the acid derived from the mixture of **14** ((*R*)-(-)-**19**: $[\alpha]_D^{29}$= -14.6 (c = 0.4, $CHCl_3$)) than for the acid derived from **16** ((*S*)-(+)-**19**: $[\alpha]_D^{29}$ = +17.1 (c = 0.4, $CHCl_3$)).

The last task was to remove the amino alcohol auxiliary and to determine the absolute configuration of the rearrangement products. The auxiliary was removed (after hydrogenation of the olefin) by heating the 1,3,2-oxazaphosphorinanes to reflux in 6 N HCl. The resulting phosphonic acids were purified by ion exchange column chromatography (BIORAD AG 50W-X8). The amino alcohol could be recovered as the hydrochloride salt in approximately 66% yield by flushing the column with 1 N HCl. The phosphonic acids were esterified with CH_2N_2 to afford the dimethyl phosphonic esters (*S*)-**17**, (1*S*,2*R*)-**18**, (*R*)-**17** and (1*R*,2*S*)-**18** (Scheme 5).

Scheme 5



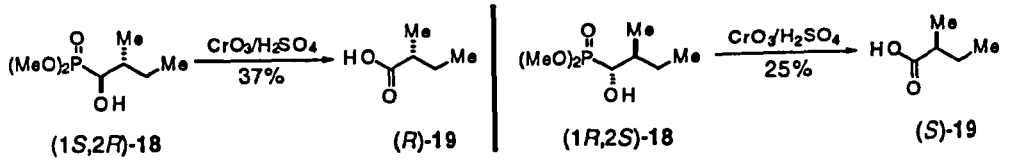
13: R=H 80% (*S*)-**17**: R=H
14: R=Me 77% (1*S*,2*R*)-**18**: R=Me

15: R=H 78% (*R*)-**17**: R=H
16: R=Me 69% (1*R*,2*S*)-**18**: R=Me

The configuration of the hydroxy-bearing stereocenters was determined for compounds (*S*)-(+)-**17** and (*R*)-(-)-**17** by comparison of the sign of the optical rotation with that of dimethyl (1-hydroxypropyl)phosphonate, for which the configuration is known[8] and for which an independent synthesis has been carried out.

The configuration of the methyl-bearing stereocenters was determined by comparison of the sign of the optical rotation after oxidative cleavage of phosphonates (1*S*,2*R*)-**18** and (1*R*,2*S*)-**18** to afford the known 2-methylbutyric acids[9] (*R*)-(-)-**19** and (*S*)-(+)-**19** respectively (Scheme 6).

Scheme 6



We have previously noted in Claisen rearrangements and in alkylations of *P*-stabilized anions that the configuration at phosphorus controls the creation of the stereogenic centers.[3a,5,7] Consistent with these observations, the diastereomeric oxazaphosphorinanes **9(10)** and **11(12)** afforded the opposite sense of asymmetric induction in the [2,3]-Wittig rearrangement and lead to enantiomeric products. The overall stereochemical outcome can be understood in terms of a chelation model recently advanced for *P*-alkoxymethyl anions[7] and will be described in a full account.

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REFERENCES AND NOTES

(1) Reviews: (a) Marshall, J. A. In *Comprehensive Organic Synthesis;* Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3; pp 975-1014. (b) Brückner, R. In *Comprehensive Organic Synthesis;* Winterfeldt, E., Ed.; Pergamon Press: Oxford, 1991; Vol. 6; pp 873-908. (c) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (d) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594.

(2) For selected examples see: (a) Mikami, K.; Kasuga, T.; Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4185. (b) Uchikawa, M.; Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4577. (c) Takahashi, O.; Mikami, K.; Nakai, T. *Chem. Lett.* **1987**, 69.

(3) (a) Denmark, S. E.; Marlin, J. E. *J. Org. Chem.* **1987**, *52*, 5742. (b) Denmark, S. E.; Stadler, H.; Dorow, R. L.; Kim, J.-H. *J. Org. Chem.* **1991**, *56*, 5063.

(4) The [2,3]-Wittig rearrangement with an achiral phosphonate anion stabilizing group has recently been reported. (a) Gulea-Pucarescu, M.; About-Jaudet, E.; Collignon, N. *J. Organomet. Chem.* **1994**, *464*, C14. (b) The use of chiral menthyl phosphonates for asymmetric [2,3]-Wittig rearrangement is described in the accompanying Letter.

(5) Denmark, S. E.; Dorow, R. L. *J. Org. Chem.* **1990**, *55*, 5926.

(6) All new compounds have been fully characterized by ^{1}H, ^{13}C and ^{31}P NMR, IR, MS, elemental anaylsis and optical rotation where appropriate.

(7) Denmark, S. E.; Chen, C.-T. manuscript submitted.

(8) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1969**, 4647.

(9) Kenyon, J.; Phillips, H.; Pittman, V. P. *J. Chem. Soc.* **1935**, 1072.

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