ORGANIC LETTERS

2006
Vol. 8, No. 22
5025−5028

Divalent Activation in Temporary Phosphate Tethers: Highly Selective Cuprate Displacement Reactions

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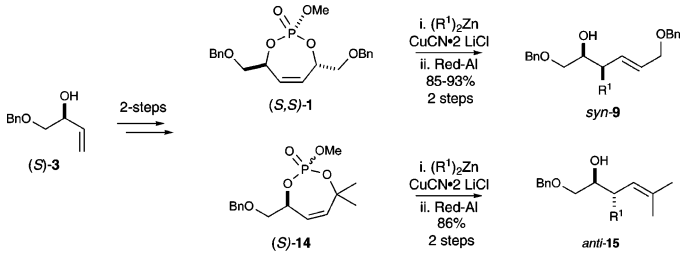
Received July 17, 2006

ABSTRACT



Desymmetrization of a readily derived psuedo-C_2-symmetric monocyclic phosphate via highly diastereoselective *anti*-S_N2' allylic displacement reactions is reported. This method utilizes of a wide variety of zinc-derived organocuprates to afford *E*-1,2-*syn*-configured phosphate acid building blocks. Extension of this protocol to unsymmetric monocyclic phosphates exclusively yields 1,2-*anti*-configured products. Within this study, stereoelectronic factors, coupled with allylic strain, ultimately govern regio- and diastereoselective cuprate reactions, further substantiating the Corey mechanism for organocuprate additions into allylic esters.

We have recently reported use of tripodal-phosphate tethers for coupling of both simple and complex allylic alcohols using ring-closing metathesis (RCM).[1] This method highlights the ability of a phosphate tether to bestow multivalent activation throughout phosphate ester appendages, thereby providing latent leaving group ability yet possessing orthogonal stability. We report herein a new strategy employing phosphate tethers in which a phosphate ester serves a dual role as both tether for coupling two allylic alcohols via ring-closing metathesis (RCM) and as a subsequent leaving group in selective *anti*-S_N2' displacement reactions with organocuprate nucleophiles.

An underlying principle of this approach utilizes the well-documented superiority of phosphates as leaving groups in copper-mediated *anti*-S_N2' displacement reactions, initially highlighted by Yamamoto and co-workers.[2] This feature, where the stereochemistry of an allylic phosphate is inverted in an *anti*-S_N2' displacement, has been successfully employed in previous strategies that exploit high stereospecificity for chirality transfer.[3] Further advances in this area have recently uncovered enantioselective *anti*-S_N2' displacements with chiral Schiff base cuprates as a viable means of desymmetrizing meso-1,3-*syn* allylic phosphates,[4] as well as reagent-controlled asymmetric allylic phosphate displacements catalyzed by copper.[5] The method we report herein initially focuses on the use of symmetry-breaking cuprate additions to readily prepared pseudo-C_2-symmetric monocyclic phosphate **1**. To the best of our knowledge, this system is the

(1) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375−3378.

(2) Initial report of the superiority of phosphate ester leaving groups in *anti*-S_N2' displacements: (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, *4*, 251−253. Proposed mechanism for allylic phosphate displacement via organocuprates: (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3066.

(3) For chirality transfer in *anti*-S_N2' allylic phosphate displacements, see: (a) Belelie, J. L.; Chong, M. *J. Org. Chem.* **2001**, *66*, 5552−5555. (b) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059−1061 and references therein.

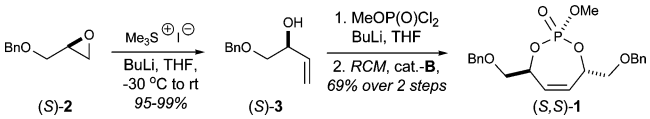
(4) (a) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234−236. (b) Piarulli U.; Claverie, C.; Daubos, Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493−4496.

10.1021/ol061756r CCC: $33.50
Published on Web 09/29/2006

first of its kind where a central phosphate tether imparts divalent activation to the unique doubly allylic phosphate subunit. In the report that follows, intriguing conformational effects have led us to extend the study into unsymmetric phosphates, ultimately providing experimental insight into the Corey mechanism of cuprate displacements.

Our study began with the generation of (*S*,*S*)-monocyclic phosphate **1**, which was achieved in three steps in good overall yields (Scheme 1). Allylic alcohol (*S*)-**3** is readily

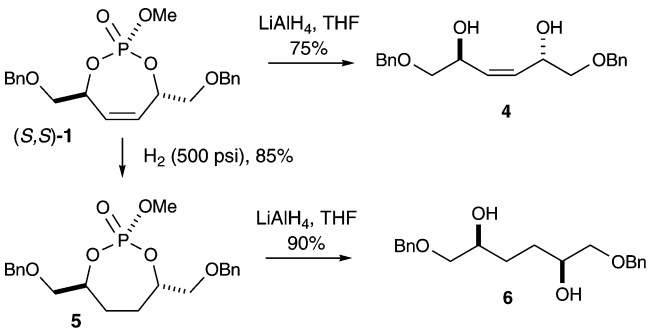
Scheme 1. Synthesis of Monocyclic Phosphate **1**



generated on multigram scale using the Mioskowski−Christie protocol[6] with commercially available glycidol ether (*S*)-**2**. Upon condensation of the alkoxide of **3** with $(MeO)POCl_2$, the phosphate triester tether mediates coupling of two olefins via RCM in good yield using $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (cat.-**B**);[7] use of catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (cat.-**A**) gave poor yields of **1**. Optimized RCM conditions required elevated temperatures (90 °C in toluene) with continuous argon purging.[8]

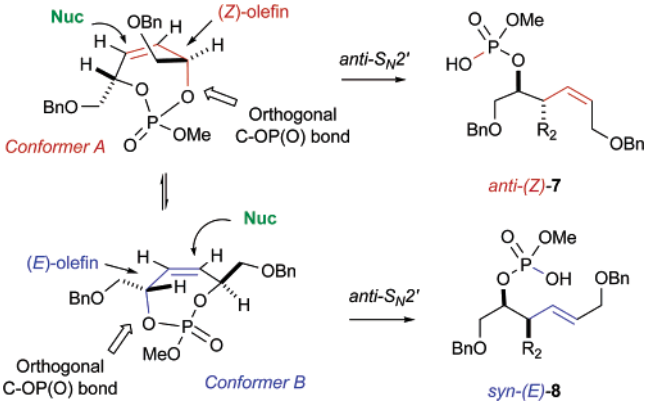
We initially probed several conditions as part of our overarching investigation of orthogonal reactivity patterns within cyclic phosphates containing multiple allylic phosphate positions (Scheme 2). We then shifted focus toward

Scheme 2. Preparation of 1,4-Diols via Phosphate Cleavage



the *anti*-S_N2'-allylic displacement studies using soft organocuprate nucleophiles. A prerequisite for the reaction requires the leaving group to be orthogonal to the system, i.e., coplanar alignment of the σ^* and π^* orbitals. Monocyclic phosphate **1** possesses the ability to align the phosphate

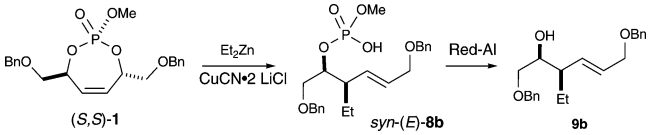
Scheme 3. Possible Modes for Cuprate Addition



moiety in two requisite *anti*-periplanar relationships outlined in Scheme 3. In both conformers we initially anticipated that energies related to the orthogonally aligned phosphate leaving group would be roughly equal in energy, since both are secondary allylic phosphates. When considering only electronic factors, this would imply transition states of equal energy as described by the original Corey mechanism[2b] which invokes a bidentate coordination of incoming cuprate to both π^* and σ^* orbitals, vide infra. Attack of cuprate nucleophiles on **1** can potentially occur through any of four diastereotopic olefinic orbitals. Pseudosymmetry, however, presents two (not four) stereodivergent pathways for *anti*-S_N2'-allylic displacement, ultimately leading to only two possible diastereomeric products.[9] Pathway A occurs through conformer A with addition *anti* to the vicinal CH_2OBn group generating *anti*-(*Z*) diastereomer **7**, while pathway B occurs via conformer B with addition *syn* to the vicinal CH_2OBn group leading to the *syn*-(*E*) diastereomer **8**.

Pleasingly, *anti*-S_N2' displacement of allylic phosphate **1** using $Et_2Zn/CuCN{\cdot}2LiCl$, after acid workup, led to formation of phosphate acid **8b** as a single diastereomer (>20:1) as witnessed by ^{31}P NMR (Scheme 4). Subsequent treatment

Scheme 4. Cuprate Addition/Phosphate Acid Cleavage



with Red-Al led to good yields of homoallylic alcohol **9b**. Initial tentative assignment of the relative stereochemistry within phosphate acid **8b** was made based on the proposed model for cuprate addition and the observed olefinic coupling

(5) (a) Kacprznski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004** *126*, 10676−10681. (b) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130−11131.

(6) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255−1259.

(7) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(8) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869−1874.

(9) Cuprate addition leads to loss of the prochiral phosphorus center, thereby providing only two potential products via four diastereomeric pathways. These pathways correspond to addition *syn*- or *anti*- to the P=O or OMe groups attached to the prochiral phosphorus atom. The other two possible diastereomers, *anti*-(*E*)-**7** and *syn*-(*Z*)-**8** cannot be accessed from (*S*,*S*)-**1** via an *anti*-S_N2'-allylic displacement mechanism. Use of *meso*-**1** would be required to access these two diastereomers.

constant consistent with an (*E*)-configured olefin (J = 15.7 Hz). Unambiguous determination of relative stereochemical relationship at C(2,3) within **9** was ultimately achieved using Karplus analysis of vicinal protons contained within the six-membered ring derived from reductive ozonolysis/acetonide formation of **9**.[10]

The remarkable selectivity for this transformation can be rationalized using Corey's proposed concerted, asynchronous mechanism[2b] for cuprate additions as highlighted in Figure 1. In this mechanism, Corey surmises that the reacting

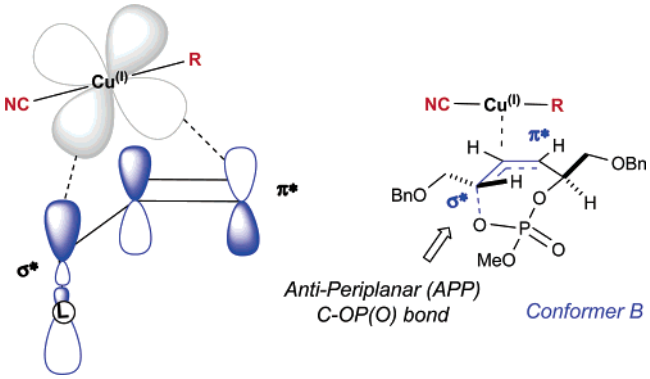
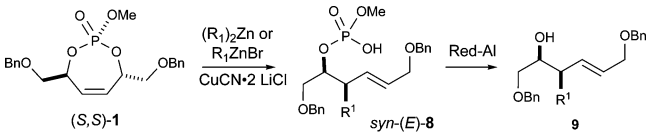


Figure 1. Corey model for rationalizing stereoselectivity.

cuprate simultaneously coordinates both the π* orbital of the olefin and σ* orbital of the phosphate ester leaving group. The asynchronous nature of the transformation predicts a transition state in which substantial bond-lengthening occurs with respect to the σ* bonding orbital. When applied to conformers A and B in **1**, it is anticipated the σ* orbitals are roughly equal in energy, since both are secondary allylic phosphates. Therefore, the stereoselectivity displayed in the cuprate reaction with **1** must ultimately be dictated by the lower steric requirements of conformer B to attain the requisite coplanar alignment of π* and σ* orbitals with the cuprate d-orbital; the greater allylic 1,3-strain ($A^{1,3}$ strain) within conformer A due to the CH_2OBn-side chain disfavors cuprate addition via this conformer (Scheme 3).[11]

Additional reactions of **1** with an array of zinc-based organocuprates gave similar high yields and selectivities when using 4−5 equiv of dialkylzinc-derived organocuprates (entries 1−3, Table 1). Treatment of **1** with 8−9 equiv of the mixed zinc−copper reagents using alkyl halide-derived, functionalized organozinc reagents (entries 4−8, Table 1) provided similar yields and diastereoselectivities. The specified excess reagents were used in all cases to ensure complete consumption of starting materials and overall provided cleaner post-workup mixtures.[12] Following acidic workup,

Table 1. Cuprate Addition/Phosphate Acid Cleavage Sequence



entry	$(R^1)_2Zn$ or R^1ZnBr	phosphate acid - **8** %/dr	homoallylic alcohol - **9**	% yield
1	Me_2Zn (5 equiv)	99/>20:1 **8a**	**9a**	83
2	Et_2Zn (5 equiv)	99/>20:1 **8b**	**9b**	90
3	iPr_2Zn (5 equiv)	99/>20:1 **8c**	**9c**	95
4	c-HexZnI (9 equiv)	99/>20:1 **8d**	**9d**	70
5	BnZnBr (9 equiv)	99/>20:1 **8e**	**9e**	84
6	$CN(CH_2)_3ZnBr$ (9 equiv)	99/>20:1 **8f**	**9f**	31
7	$Cl(CH_2)_4ZnBr$ (9 equiv)	99/>20:1 **8g**	**9g**	71
8	$CH_2{=}CH(CH_2)_3ZnBr$ (9 equiv)	99/>20:1 **8h**	**9h**	65

the phosphate acids were directly subjected to Red-Al to afford corresponding homoallylic substrates **9** in good to excellent yields.

While cleavage of the phosphate acid using Red-Al afforded the majority of products **9** in good yields, lower yields were observed for reductions in which substrates **8** contained functionally sensitive R^1 groups. To circumvent this problem, in situ methylation of the crude phosphate acid using $TMSCHN_2$ produced **10** prior to Red-Al reduction and led to overall higher yields of **9** (Scheme 5).

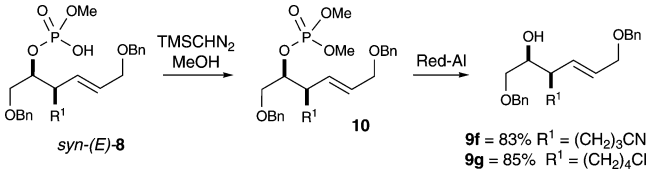
We next turned our attention to the construction of unsymmetric monocyclic phosphates containing similar steric environments with regard to the incoming cuprate, but disparate electronic energies at the σ* orbitals of the leaving phosphate ester (i.e., primary versus secondary allylic phosphate ester leaving groups). In contrast to phosphate **1**, an energetic bias for the corresponding allylic phosphates

(10) (a) See the Supporting Information for acetonide characterization and analysis. (b) Analysis of J_{AC}, J_{BC}, J_{CD} coupling constants provided small coupling values (1.4−2.6 Hz) consistent with the assigned structure. These values were identical to previously reported spectral data when R^1 = Me; see: Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2003**, *5*, 1063−1066.

(11) (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. (b) $A^{1,3}$ strain in acyclic allylic phosphates, see: Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111−2114.

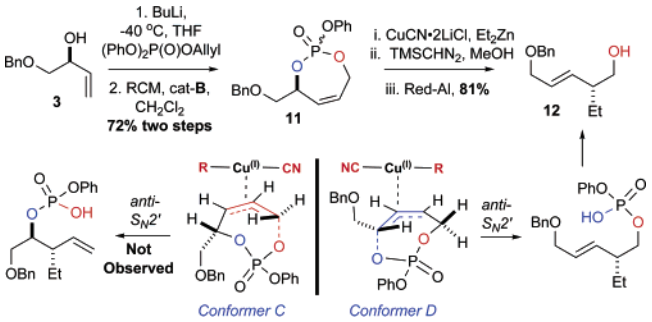
(12) Acid quench and extraction provided clean ^1H and ^{31}P NMR spectra of crude phosphate acids without column chromatography.

Scheme 5. Methylation/Phosphate Cleavage



was thus anticipated. Dioxaphosphacycle **11** was generated via the coupling of one equivalent of allylic alcohol **3** with allyldiphenyl phosphate, followed by RCM to afford **11** in good yields over two steps (Scheme 6). Treatment of **11** with

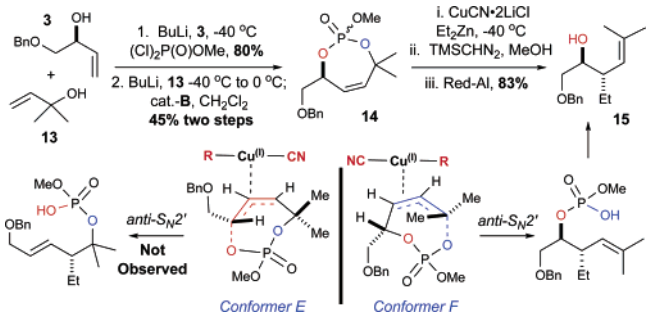
Scheme 6. Unsymmetric Monocyclic Phosphates



3.0 equiv of diethylzinc-derived organocuprates, and subsequent phosphate cleavage, led to formation of a single product **12** produced via cuprate displacement at the secondary allylic phosphate position. In contrast to **1**, no dominant conformational preferences exist between the two described reactive conformations of **11**, indicating that regioselectivity is dictated by electronic effects, vide infra.

This intriguing result led us to explore yet a third paradigm, the unsymmetric cyclic phosphate **14**, containing both secondary and tertiary allylic phosphate positions (Scheme 7). Phosphate **14** was assembled via differential coupling of secondary allylic alcohol **3** and 2-methylbut-3-en-2-ol with dichloromethyl phosphate. The resulting labile acyclic phosphate was immediately subjected to metathesis affording phosphate **14** in moderate yields over the two-step

Scheme 7. Unsymmetric Monocyclic Phosphates



sequence. Treatment of **14** with 3.0 equiv of diethylzinc-derived organocuprate at −40 °C, and subsequent phosphate cleavage, led to formation of a single product **15**. Using the aforementioned Karplus analysis of the resulting acetonide of **15**, unambiguous assignment of *anti*-relationship was established.

The regioselectivity of cuprate displacement in **14** is most surprising in that the requisite conformer F leading to product **15** (Scheme 7) contains an unfavorable $A^{1,3}$ interaction generated by the *gem*-dimethyl moiety. However, the observed selectivity is consistent with the results obtained with **12**, in which the cuprate displaces the more substituted phosphate leaving group. Since the Corey model for cuprate addition predicts significant bond breakage through σ^*, the lower energy σ^* (i.e., the most substituted carbon) in the asynchronous concerted transition state dictates the reaction pathway over substantial $A^{1,3}$ steric interactions.

In rationalizing and summarizing regio- and diastereoselective cuprate additions with symmetric **1** and unsymmetric phosphates **12** and **15**, both steric and stereoelectronic effects appear to play major roles. In the case of **12** and **15**, cuprate displacements proceeded via the more substituted σ^* positions, secondary and tertiary, respectively. When σ^* energies are equivalent as in **1**, allylic strain appears to govern the cuprate addition.

In conclusion, monocyclic phosphates undergo a highly selective *anti*-S_N2' allylic phosphate displacement. Subsequent cleavage affords an array of *syn*-(*E*)-homoallylic alcohols when *pseudo*-C_2-symmetric monocyclic phosphates are employed. In extending this method to unsymmetric phosphates, cuprate addition proceeded through the more substituted allylic phosphate position (lower σ^* energy) with the general reactivity pattern being 1 < 2 < 3, allowing access to *anti*-configured homoallylic alcohols. In probing these systems, the Corey mechanism for allylic organocuprate displacements was examined and further substantiated.

Acknowledgment. This investigation was generously supported by funds provided by the Petroleum Research Fund (PRF 42457-AC, administered by the American Chemical Society), the National Science Foundation (NSF CHE-0503875), and the NIH Dynamic Aspects in Chemical Biology Training Grant (A.W.). We thank Dr. David Vander Velde and Sarah Neuenswander for assistance with NMR measurements and Dr. Todd Williams for HRMS analysis. We kindly acknowledge Daiso Co., Ltd., Fine Chemical Department for donating 100 g of each antipode of both benzyl- and trityl-protected glycidols (e-mail: akkimura@daiso.co.jp) and Materia, Inc., for supplying metathesis catalyst and helpful suggestions. In addition, we thank the reviewers for helpful suggestions.

Note Added after ASAP Publication. The PRF number in the Acknowledgment was incorrect in the version published September 29, 2006; the corrected version was published October 3, 2006.

Supporting Information Available: Experimental details and spectroscopic data of new compounds **1** and **4**−**15** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061756R