ORGANIC LETTERS

2007
Vol. 9, No. 26
5501−5504

Remarkable Stereoelectronic Control in the Lewis Base Assisted [2,3]-Rearrangement of Cyclopropenylmethyl Phosphinites

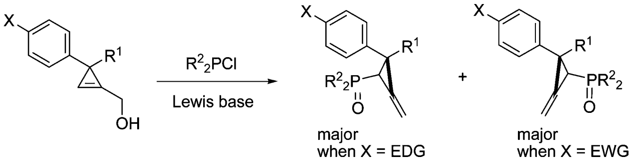
Marina Rubina, Eric W. Woodward, and Michael Rubin*

Department of Chemistry, University of Kansas and Center for Environmentally Beneficial Catalysis, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582

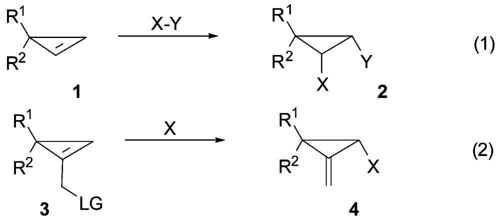
mrubin@ku.edu

Received October 10, 2007

ABSTRACT



A novel 2,3-rearrangement of cyclopropenylmethyl phosphinites to methylenecyclopropylphosphine oxides was demonstrated. It was found that, in striking contrast to the analogous rearrangement known for nonstrained allylic systems, this reaction does not proceed at all upon thermal activation; however, it can be efficiently mediated by Lewis bases. Unique stereoelectronic effects control the diastereoselectivity of this transformation, leading to predominant formation of the more sterically hindered products.



Recent impressive progress in the development of synthetic approaches toward stereodefined cyclopropenes[1] has significantly broadened the scope of useful transformations involving these unique synthons.[2] The extremely reactive double bond of the cyclopropene allows for efficient and selective functionalization of the three-membered ring providing densely substituted cyclopropane derivatives unavailable by alternative cyclization methodologies. Two main approaches of such functionalization include the direct addition of various entities to the cyclopropene double bond (eq 1) and the electrophilic or nucleophilic substitution reactions of cyclopropenes involving a strain-driven shift of the double bond to the exocyclic position (eq 2). While the former approach has been broadly exploited,[2] the second route, leading to valuable methylenecyclopropane (MCP) derivatives,[3] has attracted little attention to date. Most of the known examples of such isomerization involve intermolecular addition of a new entity, and only a few syntheses of optically active methylenecyclopropanes via this method have been demonstrated.[4]

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[1] (a) Doyle, M. P.; Winchester, W. P.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (b) Doyle, M. P.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (c) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233. (d) Liao, L. A.; Zhang, F.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490. (e) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

[2] For recent reviews, see, for example: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

[3] For recent reviews on MCPs, see: (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. See also ref 2a.

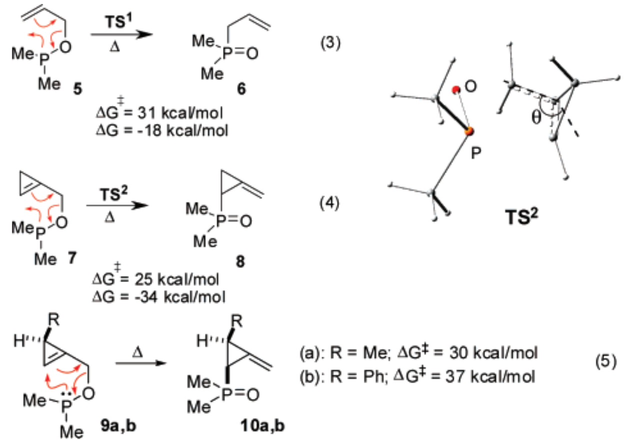
[4] (a) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem.* **2006**, *118*, 4064; *Angew. Chem., Int. Ed.* **2006**, *45*, 3960. (b) Weatherhead-Kloster, R. A.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171. (c) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963.

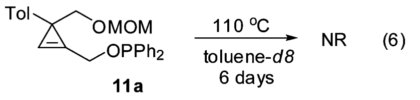
10.1021/ol702473s CCC: $37.00

Herein, we wish to report a novel Lewis base assisted 2,3-rearrangement of 1-cyclopropenylmethyl phosphinites leading to densely substituted cyclopropylphosphine derivatives.[5,6] This methodology represents a valuable alternative to the existing approaches to phosphorylated cyclopropanes, involving trapping of a cyclopropylmetal species with a phosphorus electrophile, which are highly sensitive to steric factors. The discovered unusual promoting effect of the Lewis base additive and unique stereoelectronic control of the selectivity by a very remote substituent are remarkable and set this reaction apart from the majority of the previously reported diastereoselective transformations of cyclopropenes, which are governed by steric or directing effects.

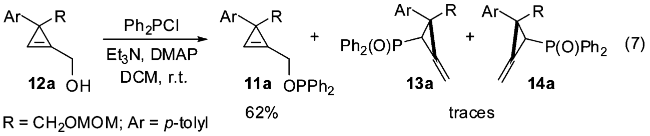
[2,3]-Sigmatropic rearrangements of both allylphosphites[7] and allylphosphinites[8] **5** are well-known; they proceed thermally (at 80−110 °C)[9] via a concerted transition state (**TS^1**)[11] to provide allylphosphine oxide **6** (Scheme 1, eq 3). We hypothesized that the analogous transformation of cyclopropenylphosphinite **7** into MCP **8** should proceed under much milder conditions, urged forward by the significant strain release[10] accompanying migration of the double bond (eq 4). Indeed, DFT computations[11] of a putative rearrangement of **7** into **8** suggested the reaction is highly thermodynamically favorable ($\Delta G = -34$ kcal/mol). However, the activation barrier for the rearrangement of cyclic phosphinite **7** was unexpectedly high, comparable to that for the reaction with acyclic substrate **5** ($\Delta G^\ddagger = 25$ and 31 kcal/mol, respectively).[12] Geometry analysis of the transition state **TS^2** (Scheme 1) suggested that the rather large $\Delta G^\ddagger$ value for the transformation **7**→**8** is primarily associated with severe distortion of the sp^2-hybridized carbon rendering the angle θ between the small cycle plane and the methylene group abnormally small (137°). Introduction of substituents at C-3 of cyclopropene led to further increase of the activation barrier for the concerted reaction (eq 5). Thus, $\Delta G^\ddagger$ values for the rearrangement of the methyl- and phenyl-substituted phosphinites **9a** and **9b** were higher than for the parent system by 5 and 12 kcal/mol, respectively. The results of theoretical modeling indicated that the thermal 2,3-rearrangement of substituted cyclopropenylphosphinites would, most likely, require heating to temperatures not compatible with preservation of the fragile three-membered carbocycle. Indeed, our attempts to perform thermal rearrangement of phosphinite **11a** were unsuccessful: prolonged refluxing in toluene did not provide the expected phosphine oxide and resulted in slow decomposition of the starting material (eq 6).

Scheme 1





Surprisingly, during preparation of phosphinite **11a** from the corresponding cyclopropenylmethanol **12a** and chlorodiphenylphosphine, we detected formation of small amounts of isomeric methylenecyclopropylphosphine oxides **13a** and **14a** (eq 7). Thus, when the reaction was carried out in the presence of triethylamine and DMAP at room temperature, it initially resulted in the rapid formation of phosphinite **11a**. However, when allowed to react overnight, phosphinite **11a** was slowly transformed into phosphinoxides **13a** and **14a** (eq 7). These results clearly indicated the amine plays an important role in assisting the rearrangement of **11** into **13** and **14** and also demonstrated the viability of the direct one-



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[5] For employment of cyclopropylphosphine derivatives in synthesis, see, for example: (a) Molander, G.; Burke, J. P.; Carroll, P. J. *J. Org. Chem.* **2004**, *69*, 8062. (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (c) Meijs, G. P.; Eichinger, P. C. H. *Tetrahedron Lett.* **1987**, *28*, 5559.

[6] For biological studies on phosphorous-containing methylenecyclopropanes, see: (a) Zhou, S.; Brietenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 566. (b) Yan, Z.; Zhou, S.; Kern, E. R.; Zemlicka, J. *Tetrahedron* **2006**, *62*, 2608. (c) Devreux, V.; Wiesner, J.; Goeman, J. L.; van der Eycken, J.; Jomaa, H.; van Calenbergh, S. *J. Med. Chem.* **2006**, *49*, 2656.

[7] (a) Lemper, A. L.; Tieckelmann, H. *Tetrahedron Lett.* **1964**, 3053. (b) Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239. (c) Janecki, T.; Bodalski, R. *Synthesis* **1990**, *9*, 799. (d) Muthiah, C.; Kumar, K. S.; Vittal, J. J.; Swamy, K. C. K. *Synlett* **2002**, 1787.

[8] (a) Liron, F.; Knochel, P. *Chem. Commun.* **2004**, 304. (b) Demay, S.; Volant, F.; Knochel, P. *Angew. Chem.* **2001**, *113*, 1272; *Angew. Chem., Int. Ed.* **2001**, *40*, 1235.

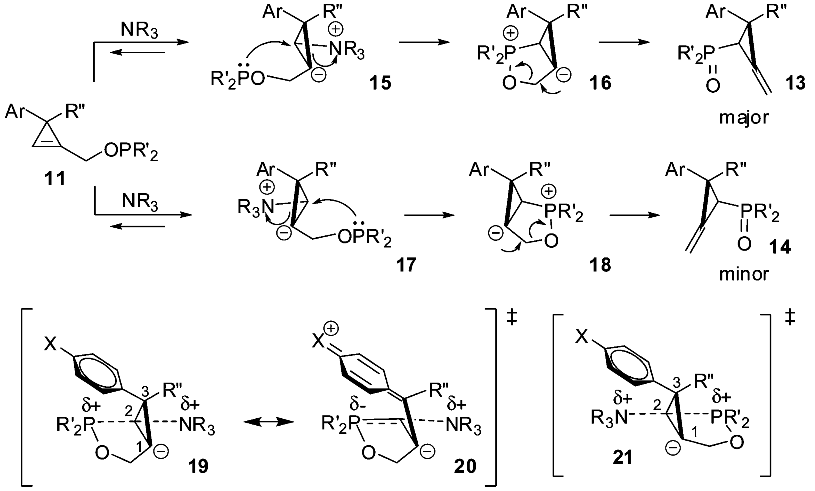
[9] Typical reaction times for this process are 3−12 h. See ref 8a.

[10] Bach, R. D.; Dmitrienko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444.

[11] B3LYP/6−31G(d): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

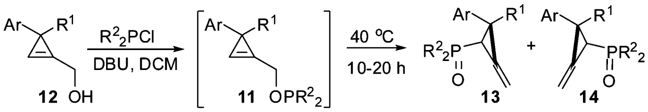
[12] See Supporting Information for details.

Scheme 2. Mechanistic Rationale for the Amine-Assisted Rearrangement



pot transformation of alcohol **12** into phosphinoxides **13** and **14** without isolation of the sensitive phosphinite **11**. Encouraged by this finding and intrigued by the fact that the "thermally improbable", more hindered diastereomer **13** was also observed in notable amounts, we performed systematic screening of a series of different amines.[11] It was found that a number of tertiary amines enabled the phosphinite-to-phosphine oxide rearrangement; however, DBU[13] was particularly efficient in selectively catalyzing the formation of the sterically more hindered phosphine oxide **13** (Table 1).

Table 1. Sequential Phosphinylation/2,3-Rearrangement into Methylenecyclopropylphosphine Oxides



no.	Ar	R^1	R^2	product	yield, %[a]	13/14[b]
1	p-MeC_6H_4	CH_2OMOM	Ph	**13a**, **14a**	86	2.7:1
2	p-MeC_6H_4	CH_2OMOM	i-Pr	**13b**, **14b**	74^{c}	4.0:1
3	p-MeC_6H_4	CH_2OMOM	Cy	**13c**, **14c**	$90^{c,d}$	5.2:1
4	p-MeC_6H_4	CH_2OMOM	t-Bu	**11d**	–	–
5	p-MeC_6H_4	CH_2OMOM	$(i\text{-}Pr)_2N$	**11e**	–	–
6	p-$MeOC_6H_4$	CH_2OMOM	Ph	**13f**, **14f**	90	3.5:1
7	p-FC_6H_4	CH_2OMOM	Ph	**13g**, **14g**	96	1.5:1
8	Ph	CH_2OMOM	Ph	**13h**, **14h**	83^{e}	1.1:1
9	p-$CF_3C_6H_4$	CH_2OMOM	Ph	**13i**, **14i**	91	1:1.3
10	Ph	CO_2Me	Ph	**13j**, **14j**	$47^{c,f}$	2.4:1
11	Ph	CH_2OAc	Ph	**13k**, **14k**	83	2.8:1
12	p-$CF_3C_6H_4$	CH_2OH	Ph	–	0^{g}	–

[a] Combined isolated yields of **13** and **14**. [b] Crude ^1H NMR ratios. [c] Inseparable mixture of **13** and **14**. [d] Reaction ran at 50 °C. [e] Enantiomerically enriched substrate was used; optical yield of 100%. [f] Reaction ran at rt. [g] Complex mixture of products.

Two aspects of this transformation are noteworthy. First, employment of different chlorophosphines revealed that the selectivity toward formation of **13** improved with an increase of electron density on the phosphorus atom (entries 1−3). However, phosphinites **11d**,**e** obtained from very bulky $[(iPr)_2N]_2PCl$ and $(t\text{-}Bu)_2PCl$ failed to undergo rearrangement under these conditions, potentially due to overwhelming steric clashes between the phosphinite moiety and the substituents at C-3 (entries 4 and 5). Second, and very surprisingly, the electronic nature of the para substituent on the aryl ring of cyclopropene has a significant effect on the diastereoselectivity of this rearrangement. Thus, in a series of 3-aryl-substituted cyclopropenes, the diastereoselectivity degraded from the more electron-rich toward the more electron-poor aryl group and finally reversed in the case of the p-CF_3 analogue producing phosphine oxide **13i** as a major product (entries 1 and 6−9). Reactions of ester- and acetyloxymethyl-substituted cyclopropenylmethanols **12j**,**k** followed the general trend predominantly affording more hindered product **13** (entries 10 and 11).

The following mechanism was proposed for this rearrangement (Scheme 2). Initially, addition of an amine to the cyclopropene double bond[14] produces zwitterionic intermediate **15**, thereby releasing the strain and making the phosphinite moiety flexible enough to undergo intramolecular nucleophilic ring closure to form oxophospholanium zwitterion **16**. The latter, upon rapid five-membered ring cleavage, provides phosphine oxide **13**. Minor product **14** is obtained in a similar manner, after initial nucleophilic attack of the amine from the more hindered face, via intermediates **17** and **18** (Scheme 2). The unusual stereoelectronic effects observed in this reaction can be rationalized as follows. According to the Curtin−Hammett principle, rapid thermodynamic equilibrium between **15** and **17**[15] should play a negligible role in stereodifferentiation, which should be rather

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(13) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

(14) For addition of nitrogen nucleophiles to the cyclopropene double bond, see: (a) Franck-Newmann, M.; Miesch, M.; Kempf, H. *Tetrahedron* **1988**, *44*, 2933. (b) Gritsenko, E. I.; Khaliullin, R. R.; Plemenkov, V. V.; Faizullin, E. M. *Zh. Obshch. Khim.* **1988**, *58*, 2733.

(15) The difference in activation energies for steps **11** ⇆ **15** and **11** ⇆ **17** was found to be ca. 3 kcal/mol (B3LYP/6−31G(d)) and was shown to only insignificantly depend on the electronic nature of the aryl substituent.[11]

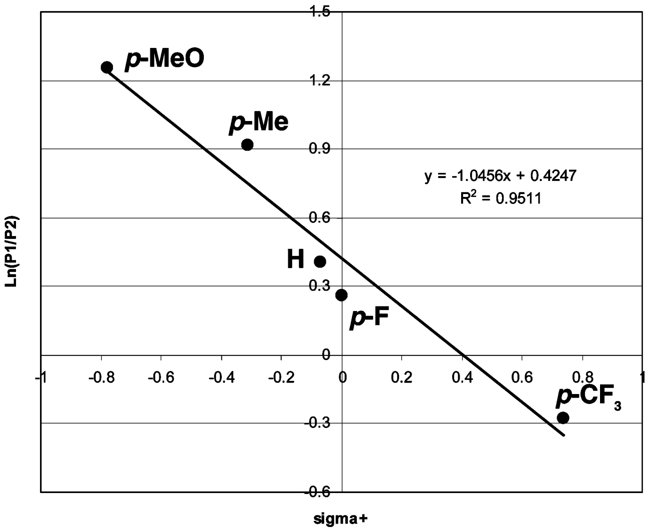

Figure 1. Hammett analysis of diastereoselectivity of the [2,3]-phosphinite-to-phosphine oxide rearrangement.

controlled kinetically on the first irreversible step (**15**→**16** vs **17**→**18**). The latter represents an S$_N$2-type process proceeding via concerted transition states **19** and **21**, respectively. We rationalize that M$^+$-substituents in the aryl ring can contribute to the resonance stabilization of transition state **19** via mesomeric form **20**, making it more favorable than **21**. Remarkably, in contrast to the analogous classical stereoelectronic effects observed in five- and six-membered rings, where maximum orbital overlap is realized for trans substituents at a torsion angle of $\theta = 180°$, in the strained cyclopropane system **21**, the corresponding angle θ (Ar$-$C$^3-$C$^2-$P) $= 125°$ which does not permit proper alignment of the interacting orbitals. However, such resonance is possible for the sterically more hindered transition state **19**, where the torsion angle (again, due to the ring strain) is close to 0°. This mechanistic rationale involving zwitterionic transition states is strongly supported by the observed dependence of the diastereoselectivity on the σ^+-Hammet constants of para substituents in the aryl ring at C-3 (Figure 1).[11]

In conclusion, a novel [2,3]-rearrangement of cyclopropenylmethylphosphinites to methylenecyclopropylphosphine oxides is demonstrated. Having been found thermally impossible due to insurmountable ring strain, this transformation can, however, be efficiently assisted by Lewis bases, which alter the geometry of the transition state via reversible addition to the strained double bond of cyclopropene. Unique stereoelectronic effects of this reaction result in preferential formation of the more sterically hindered products. The described methodology allows for easy introduction of a very important phosphorus functionality into the rigid and densely substituted cyclopropyl scaffold and can be easily amended to the synthesis of optically active 2-phosphorylated methylenecyclopropanes bearing a quaternary chiral center.

Acknowledgment. The support of the National Science Foundation (EEC-0310689) and the University of Kansas REU program (E.W.W.) is gratefully acknowledged.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702473S