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Highly Convergent Synthesis of Chiral Bicyclophosphinates by Domino Hydrophosphinylation/Michael/Michael Reaction

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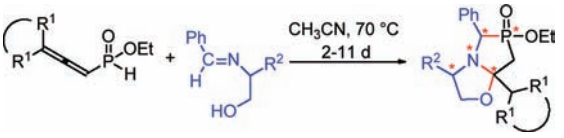
ABSTRACT



Diastereoselective domino reactions of iminoalcohols and allenyl *H*-phosphinates produce chiral phosphorus bicycles in a regio- and stereoselective fashion. A predictive model for diastereoselection is used for these new chiral phosphinic esters.

Modern organic synthesis has benefited from the development of highly selective methods for the efficient construction of potentially useful target molecules. Domino or cascade reactions which are the combination of multiple transformations in a single pot are now routinely employed in the synthesis of complex and even chiral target molecules constituting a powerful tool for organic chemists.[1] Often mild and environmentally friendly, domino reactions also provide a shortened and atom-economical synthesis, substantially decreasing the wastes associated with the production of organic compounds. Toward the goal of improving chemical efficiency, the ability to execute sequential reactions in one pot is conceptually challenging. Hence, in modern organic chemistry, the conception of new domino reactions has emerged as an exciting brain bender puzzle to solve synthetic problems.

Allenes have been demonstrated to be an important class of chemicals, but they remain underused because these functions are often thought to be highly reactive.[2] Despite this putative drawback, they were recently involved as useful intermediates in several addition[3] or cyclization reactions.[4]

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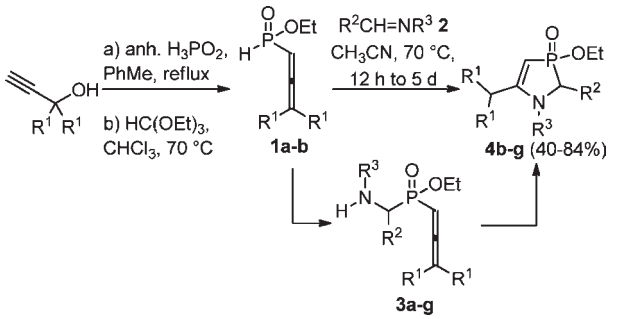
In this context, we focused on *H*-phosphinylallene reagents, a surprisingly quite stable class of both nucleophilic and electrophilic allenes where the electronic properties of the two unsaturated carbon−carbon bonds determine the chemo- or regioselectivity of their reactions.[5] Seeking to develop streamlined phosphorus heterocyclic syntheses, we begun to explore the combination of a useful bicyclic ring formation involving P−C, C−O, and C−N bond-forming processes in a single step using *H*-phosphinyl allenes.[6]

Allenyl *H*-phosphinic esters **1a**,**b** were obtained in two steps from the combination of anhydrous hypophosphorous acid with, respectively, 2-methyl-3-butyn-2-ol and 1-ethynyl-1-cyclohexanol in 90% and 85% yields.[7] Afterward, allenyl *H*-phosphinic acids were quantitatively esterified under neutral conditions by the reaction of triethylorthoformate in refluxing chloroform leading to the corresponding allenyl *H*-phosphinates **1a,b**. These reagents were then allowed to react with imines **2a**−**d** (Table 1). The rate and the yield of the reaction were strongly dependent on the starting imines **2**; using benzaldehyde *N*-phenylimine (entry 1, Table 1), only hydrophosphinylation reaction took place resulting in the formation of a diastereomeric mixture of the α-aminophosphinyl allene **3a** in 75% yield. Whatever the activating agents (PTSA, $BF_3 \cdot OEt_2$, Ag^+, Pd^{2+}, NaH, *t*-BuOK), no cyclization product was observed from allene **3a**, whereas for a stronger nucleophile (R^3 = benzyl, entries 2−7, Table 1), we obtained the 1,3-azaphospholenes **4b**−**g** in 40−84% yields in acetonitrile at 70 °C with modest diastereoselectivity.[8]

On the basis of those results, we decided to examine the behavior of iminoalcohols **5** in such a cyclization process. Some of these imines would embed a chiral center associated with a hydroxy function featuring another nucleophilic reacting center. The reaction of allenes **1a,b** with imines **5** derived from (*R*)- or (*S*)-phenylglycinol, (*S*)-2-amino-butanol or ethanolamine resulted in the formation of the corresponding 1-oxa-3-aza-6-phosphabicyclo[3.3.0]octanes **6a**−**e** in 45−80% yields after chromatography on silica gel (Table 2).

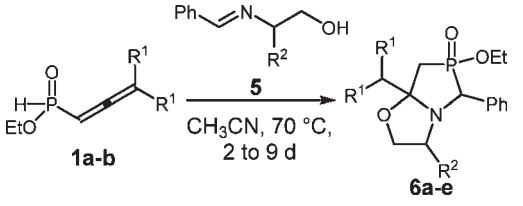
Table 1. Synthesis of 1,3-Azaphospholenes **4b**−**g**



entry		R^1	R^2	R^3	time	isolated yield[a]	diastereomer ratio
1	**3a**	Me	Ph	Ph		75[b]	49/51
2	**4b**	Me	Ph	Bn	12 h	84	56/44
3	**4c**	Me	pCF$_3$-C$_6$H$_4$	Bn	4 d	75	40/60
4	**4d**	Me	*i*Pr	Bn	2 d	49	49/51
5	**4e**	$(CH_2)_5$	Ph	Bn	5 d	80	52/48
6	**4f**	$(CH_2)_5$	pCF$_3$-C$_6$H$_4$	Bn	5 d	76	51/49
7	**4g**	$(CH_2)_5$	*i*Pr	Bn	5 d	45	49/51

[a] Most of the reactions were conducted on a scale of 3.12 mmol of allene. [b] Only phosphinyl allene **3a** was obtained during the reaction, and no cyclization product **4a** was observed.

Table 2. Synthesis of 1-Oxa-3-aza-6-phosphabicyclo-[3.3.0]octanes **6a**−**e**



	R^1	R^2	time (d)	isolated yield[a]	diastereomer ratio
6a	Me	(*R*)-Ph-	7	65	50/50
6b	Me	(*S*)-Ph-	7	70	50/50
6c	Me	(*S*)-Et-	4	45	41/11/33/15[b]
6d	Me	H-	2	80	32/15/30/23[b]
6e	-$(CH_2)_5$-	(*S*)-Ph-	11	56	50/50

[a] Most of the reactions were conducted on a scale of 3.12 mmol of allene. [b] Major diastereomers are epimers at the phosphorus centers.

To confirm the structure, one diastereomer of **6a** was crystallized for X-ray crystallographic analysis. Two different crystals were obtained and both adopted chiral space group $P2_12_12_1$. X-ray structures of polymorphs **6a-I** and **6a-II** of phosphabicyclo[3.3.0]octane **6a** are

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given in Figure 1. The two polymorphs exhibited similar conformations: oxazaphosphabicyclooctane adopted as expected a *cis* ring junction where the pyramidal nitrogen and all of the substituents on chiral carbons were on the convex face of the molecule. The two polymorphs differed mainly by the orientation of the methyl group of ethyl phosphinic ester function as illustrated in Figure 1.[9]

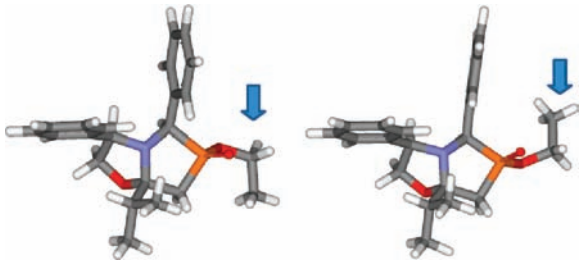

Figure 1. X-ray of polymorphs of phosphabicyclo[3.3.0]octane **6a-I** and **6a-II**.

In agreement with the formation of the aminophosphinyl allene **7**, we assumed that the first step of the reaction was the diastereoselective imine hydrophosphination. ^{31}P NMR monitoring confirmed the formation of four diastereomers **7**. Their chemical shifts around 40 ppm, together with the disappearance of the $^{1}J_{PH}$ coupling, were consistent with the α-aminophosphinate linkage (Scheme 1). When R^2 = Ph, a 41/40/9/10 diastereomeric ratio was observed, confirming that R^2 acted as a stereocontroller.[10] Then a 5-*endo-dig* amino-Michael reaction on the C_2 allenyl group followed by an isomerization of the resulting double bond and a 5-*exo-trig* reaction of oxygen afforded compounds **6a**. Interestingly, no azaphospholene intermediate **8** was observed and final bicycles **6a** at 62 ppm were formed. We were pleased to obtain only two diastereomers of **6a** arising from the major pair of diastereomers

We assumed that a hydrophosphinylation reaction of imine took place under kinetic control (Scheme 1).[11] In aprotic solvent, the stereochemical outcome of the reaction was mainly controlled by the possibility of formation of a five-membered intramolecular H-bonded ring.[12] Then, the preferential formation of the major diastereomer pair of **6a** could be explained by the control exerted by the alcohol present in imine **5** and the steric hindrance induced by the phenyl group on the *si* face (Scheme 1). Hence, formation of intermediates **7** occurred by the delivery of the racemic allenylphosphinate **1a** to the less hindered *re* face of the imine. With these precedents in mind, we also thought about the possibility of a kinetic resolution of the racemic allenylphosphinate **1a** under these double asymmetric induction conditions. Unfortunately, no or very low level of double diastereodifferentiation were seen in such conditions.

The next step was the formation of azaphospholene **8**. Afterward, the stereoselective oxa-Michael reaction required the presence of an adequate electron-deficient insaturation. The stereochemical outcome of such cyclization was influenced by the previously created stereocenters of the azaphospholene ring. We suspected that diastereomers **6a** were formed under thermodynamically controlled conditions. To demonstrate this hypothesis, a proton exchange reaction was carried out. It was conducted after ring closure from a pure sample of **6a** and was validated by the ^{1}H and ^{13}C NMR experiments in deuterated methanol (Figure 2).

The proton exchange between the deuterium atom of methanol and hydrogen atoms of methylene group PCH_2 was fast and complete deuteration took place in the NMR tube at room temperature in less than five minutes. The ABX proton signal at 2.30 ppm completely disappeared in ^{1}H NMR according to the deuteration of the carbon atom. Similarly in ^{13}C NMR, the doublet signal at 28.83 ppm which should become a doublet of quintuplet also disappeared due probably to the combination of a high multiplicity and the loss of NOE enhancement. Moreover, FAB mass spectrometry data in an aprotic matrix (NPOE) gave a *m*/*z* ratio equal to 388 consistent with $C_{22}H_{27}D_2O_3NP$ formula.

The full configuration of both diastereomers of **6a** was confirmed and elucidated by NOESY correlations and ^{1}H NMR (Figure 3). H-1 and H-2 proton were easily attributed through their difference of chemical shifts due to a strong shielding for hydrogen H-2 contacting phenyl ring ($\Delta\delta$ = 0.72 and 0.78 ppm). The NOESY correlation of H-2 to H-3 on both diastereomers led to the assignment of *cis* phenyl-isopropyl group stereochemistry. Relative configuration at phosphorus was determined by comparison of the chemical shifts of the protons of ethyl ester methylene. According to the X-ray data, the *trans* Ph-OEt stereoisomer showed weakly diastereotopic protons ($\Delta\delta$ = 0.03 ppm) respectively at 3.98 ppm (H_a) and 4.01 ppm (H_b) whereas the *cis* one exhibited a greater difference ($\Delta\delta$ = 0.48 ppm, δ_{Ha} = 3.23 ppm and δ_{Hb} = 3.71 ppm). Diastereomers of **6a** were only epimer at the phosphorus atom.

Specific rotations were determined for both diastereomers of **6a** and **6b**. As expected, the *trans*-**6a** and *trans*-**6b** have respectively a +73.1° and −72.5° specific rotation, whereas the *cis*-**6a** and *cis*-**6b** presented

(9) The X-ray crystallographic coordinates have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 785343 and 785344. These data can be obtained free of charge from Cambridge Crystallographic Data Centre: http://www.ccdc.cam.ac.uk/data_ request/cif. See also the Supporting Information for more crystallographic details.

(10) Taking into account that phosphinyl allene was racemic, the diastereoselectivity was 81/19.

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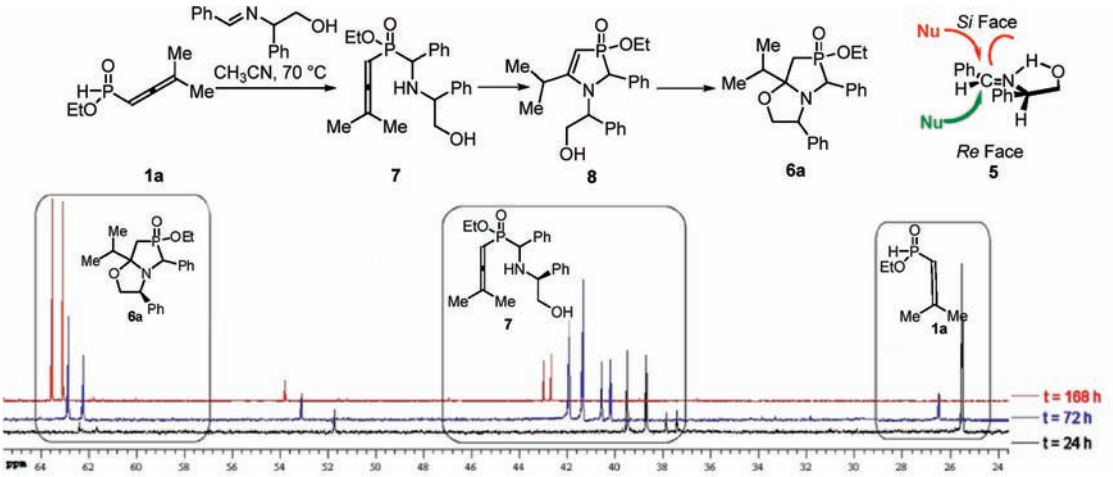
Scheme 1. Proposed Mechanism for the Formation of 1-Oxa-3-aza-6-phosphabicyclo[3.3.0]octane **6a**



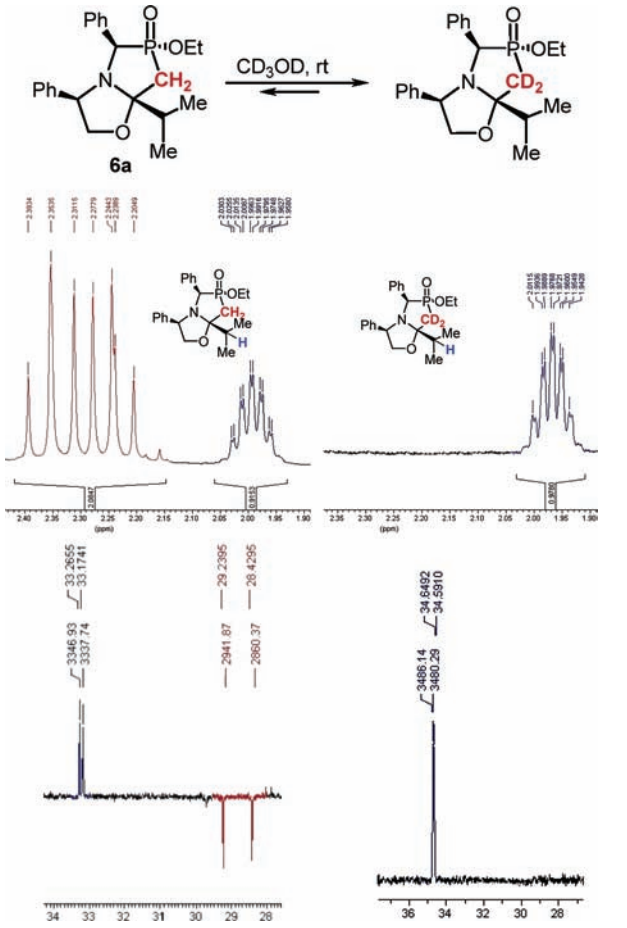


Figure 2. ^{1}H and ^{13}C NMR spectra of hydrogen/deuterium exchange of **6a**.

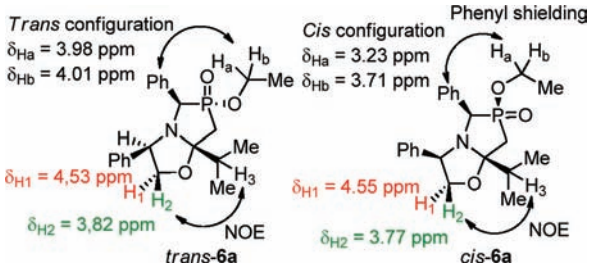


Figure 3. Absolute configuration of 1-oxa-3-aza-6-phosphabicyclo-[3.3.0]octane diastereomers of **6a**.

+14.1° and −13.5°, confirming the influence of the stereogenic center on the chiral iminoalcohol starting materials.

In summary, we have developed a new, practical, and diastereoselective domino reaction for the synthesis of highly functionalized and chiral phosphorus bicycles from simple iminoalcohols and allenyl *H*-phosphinates. A predictive model for diastereoselection was used along with the attribution of all chiral centers of the molecules. Further work on these chiral bicyclic structures will be related to the free chiral phosphinic acids which could be used as chiral Brønsted acid in metal-free enantioselective catalysis.

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Supporting Information Available. Synthetic procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.