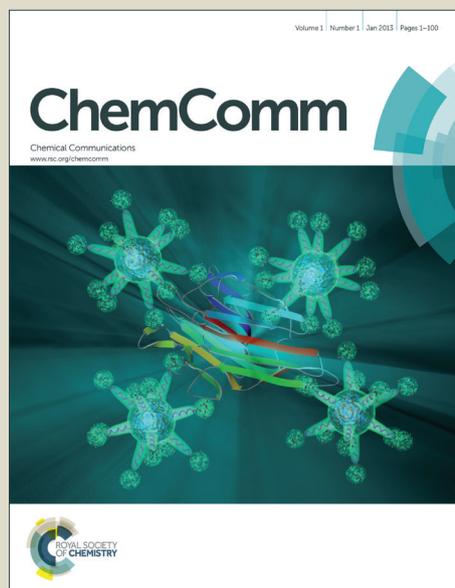


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COMMUNICATION

Spontaneous resolution upon crystallization of allenyl-bis-phosphine oxides

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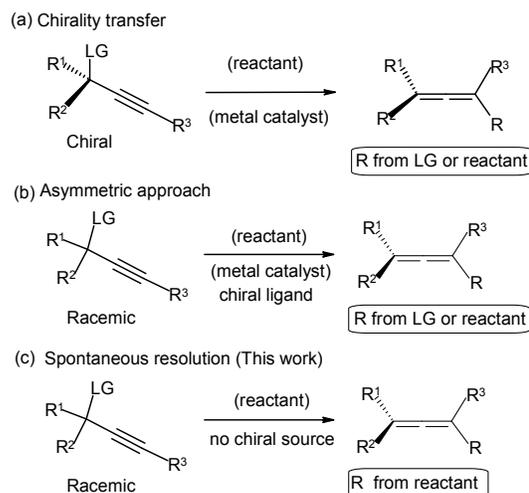
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The first example of 'spontaneous resolution by crystallization' in allene chemistry, by means of crystal structures and solid state CD spectra for the *R* and *S* enantiomers, is presented. These allenes are prepared by the simple reaction of Ph_2PCI with *o*-nitro functionalized propargyl alcohols.

Allenes, in particular optically active allenes, are important building blocks in organic synthesis due to the transfer of axial to central chirality in the final pharmaceutically useful products.¹ Since chiral allenes are present in many natural products, pharmaceuticals² and molecular materials,³ their synthesis and reactivity is a prime area of research activity.⁴ Allenylphosphonates/ allenylphosphine oxides, a subclass of allenes, are also versatile precursors in synthetic chemistry.⁵ An interesting case of asymmetric addition of arylboronic acids to α -keto esters using phosphine containing chiral allenes as ligands to Rh(I) is also reported recently.⁶ Several methods for the synthesis of chiral allenes⁷ including phosphorylated allenes,⁸ by using a chiral auxiliary/source have been developed. In order to obtain chiral allenes from propargylic substrates, there are primarily two major approaches: one by chirality transfer from chiral propargylic substrate (Scheme 1a),⁹ and the other from racemic propargylic substrate by using a chiral ligand (Scheme 1b).¹⁰ In these cases, a chiral source is a must to obtain chiral allenes. A third possibility is by spontaneous resolution by crystallization (Scheme 1c) without using any chiral source, a point not mentioned in the literature so far. Spontaneous resolution through crystallization itself is an important topic in organic synthesis and origin of life.¹¹⁻¹² Herein we disclose our results on the formation of bis-phosphinoylated allenes by using achiral substrates Ph_2PCI (1) and *o*-nitro functionalized propargyl alcohols 2a-f, 3a-c and 4 (Chart 1). More importantly, in the reaction using propargyl alcohols 2a, 2d

and 3a, the chiral allene crystallized spontaneously and in one case both the enantiomers could be successfully separated.



Scheme 1 Formation of chiral allenes using propargylic substrates

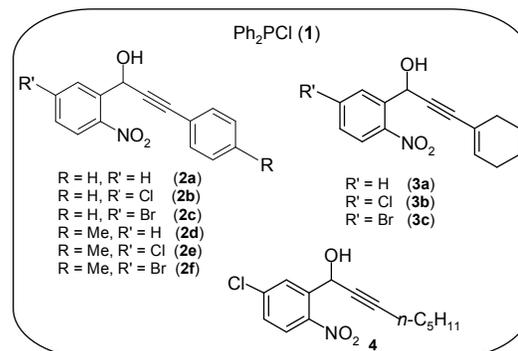
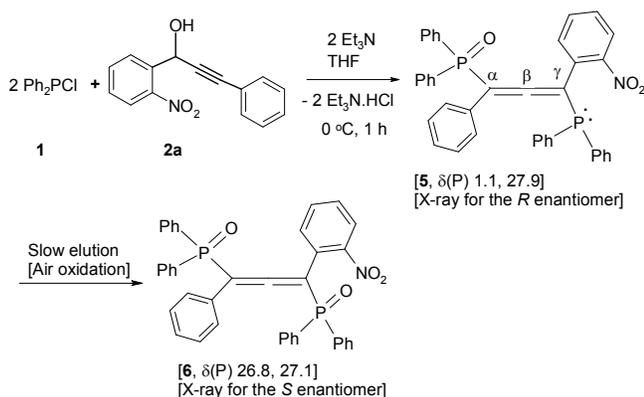


Chart 1 Precursors 1-4 used in the present study

The normal reaction of P(III)-Cl with an equimolar quantity of functionalized propargyl alcohols is expected to lead to mono-phosphinoylated allene.¹³ However, the presence of *o*-functionality leads to novel cyclization leading to rather unexpected heterocycles/fused carbocycles.¹⁴ Interestingly, when we performed the reaction between Ph₂PCl (**1**) and *o*-nitro functionalized propargyl alcohol (**2a**) using 2:1 molar stoichiometry (Scheme 2), the resulting product is the allene **5**, with a *phosphinoyl* group at α position and a *phosphine* group at γ position [X-ray, Figure S1, Supplementary Information]. We could not get good ¹H/¹³C NMR spectra for this compound, because of its oxidative instability that led to the bis-phosphinoyl-allene **6** (X-ray, Figure S1, ESI).¹⁵ Both the compounds **5** and **6** crystallized in the chiral space group *P*2₁2₁ and showed absolute configurations of *R* and *S* respectively (Figure 1). However we were unable to separate both the enantiomers in this case.



Scheme 2. Reaction of **1** with **2a** leading to allenes **5** and **6**.

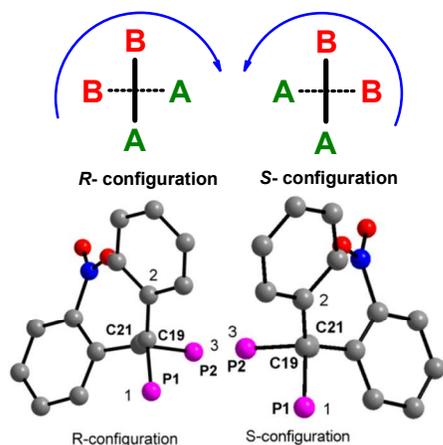
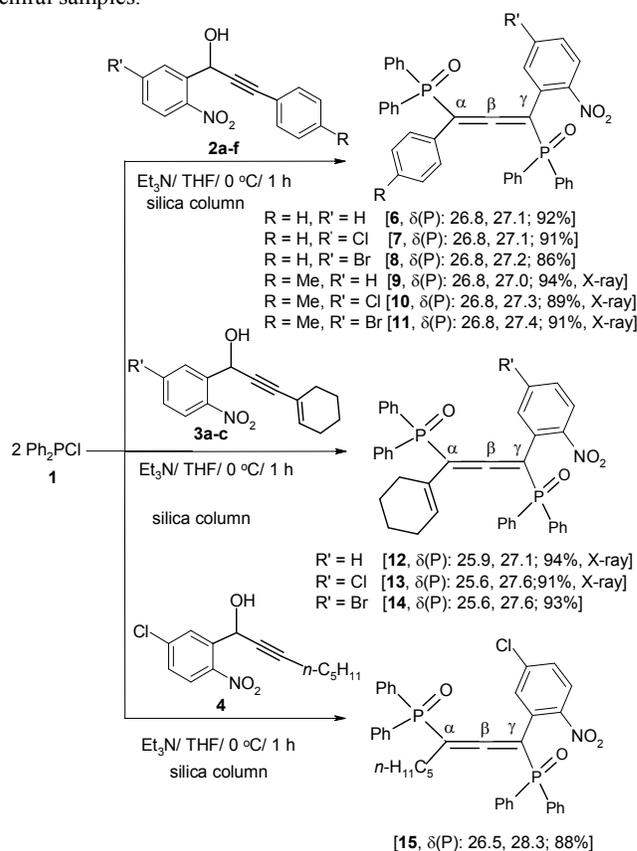


Fig. 1 A diagram showing the (*R*)-configuration for compound **5** and (*S*)-configuration for **6**. **Note:** The view taken is along the C=C=C axis. The numbers 1, 2 and 3 on the structures show the ordering of atoms for deciphering the configuration.

Because of the possibility of spontaneous resolution of enantiomeric allene by crystallization in cases similar to the above, we became interested in this topic and synthesized some more derivatives. In addition, it may be noted that the substitution of allenic CH by a phosphorus moiety is not common. Thus, we treated *o*-nitro functionalized propargyl alcohols **2a-f**, **3a-c** and **4** with Ph₂PCl (**1**) (Scheme 3¹⁶) to obtain the allenyl-(bis)phosphine oxides (**6-15**). Among these structures, **9** and **12** crystallized in the chiral space group *P*2₁2₁. More interesting is the fact that for compound

12, we were able to isolate both the enantiomers (*R* and *S*). These two forms were separated by means of hand-picking. This separation was facilitated by slightly different morphology of these crystals. The overall yield (including *R* and *S* forms) was > 80%. The presence of two sterically interactive tetrahedral Ph₂P(O)C and electron withdrawing *o*-nitro groups may be responsible for the separation of enantiomers with axial chirality. Some carbon atoms of the phenyl groups corresponding to the two phosphorus moieties do come close enough (~3.5 Å). In the general case, it may be possible to observe similar phenomenon wherein sterically interacting substituents are present on the allene. Judgement regarding this effect may have to come from more analogous systems. In the case of compound **12**, we could obtain the CD spectra in the solid state for both the *R* and *S* enantiomers (Figures 2-3). However, we were not able to get significant optical rotation in solution, mainly because of difficulty in separating enough pure crystals. Use of an additional chiral base like Tröger's base [(*5R,11R*)-enantiomer] in the case of **10**, however, did not produce chiral samples.



Scheme 3 Formation of allenyl-bis-phosphine oxides **6-15**

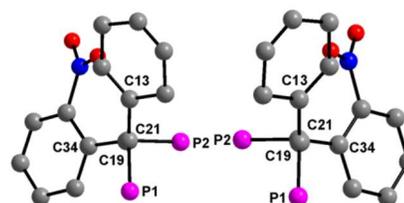


Fig. 2 A picture showing the *R* (left) and *S* (right) configurations in the two enantiomers of **12** separated by hand-picking.

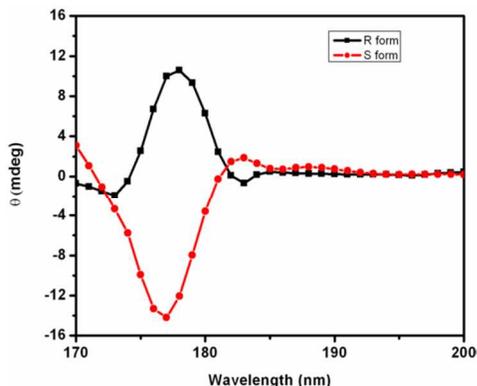
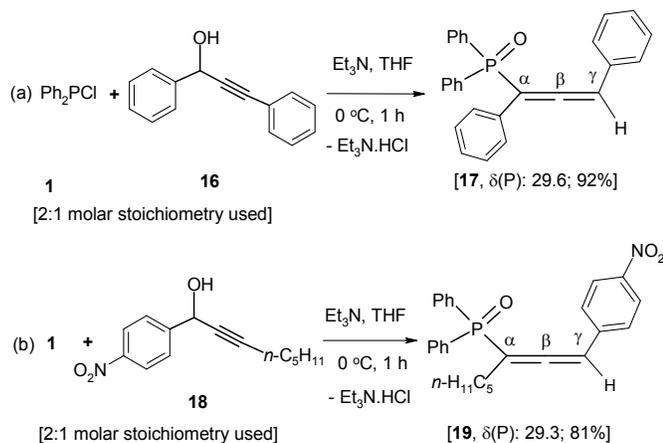


Fig. 3 CD spectra of *R* and *S* forms of crystals of **12**

The bis-phosphinoylated allenes of the type described above are not reported so far in the literature. Hence we wanted to check whether the *o*-NO₂ group on propargyl alcohol is essential or not for the second substitution. However, the 2:1 stoichiometric reaction of **1** with propargyl alcohols **16** or **18** afforded only the mono-phosphinoyl allenes **17** or **19** respectively (Scheme 4). Thus, for the above reaction, *o*-NO₂ group is necessary for the bis-phosphinoylation. The strong electron-withdrawing capacity of the *o*-NO₂ group on this ring and a possible C-H...O hydrogen bonding interaction with the allenic C-H (at γ -carbon) most likely enhances the acidity of the corresponding C-H so that even triethylamine is able to effect further substitution at this carbon.



Scheme 4. Formation of mono-phosphinoylated allenes **17** and **19** from the reaction of Ph₂P(=O)Cl (**1**) with propargyl alcohols **16** and **18**.

In summary, we have separated *R* and *S* enantiomers of allenyl-bis-phosphine oxides *via* spontaneous resolution by crystallization for the first time. X-ray structures as well as CD spectra for *R* and *S* enantiomers of compound **12** have been presented.

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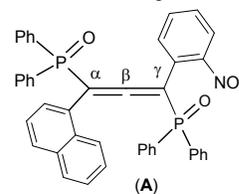
Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental details, X-ray structures of the compounds **5-6** and **9-13**, UV-Visible spectra of compounds **9** and **12**, copies of ¹H/¹³C NMR spectra, and CIF data]. See DOI:

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- 15 X-ray data for compounds **5-6**, **9-11**, (*R*)-**12**, (*S*)-**12** and **13** were collected using Mo K α ($\lambda = 0.71073 \text{ \AA}$) radiation. The structures were solved and refined by standard methods CCDC numbers for the compounds reported herein are: **5** (1041550), **6** (1041551), **9** (1041552), **10** (1041553), **11** (1041554), (*R*)-**12** (1041555), (*S*)-**12** [1041556 and 1051469 (low temperature)] and **13** (1041557).
- 16 We have prepared compound (**A**) to see if slightly larger bulk of the naphthyl group can provide additional examples. So far, crystals suitable for X-ray have not been obtained. However, this result does again prove that the allenic C-H is quite reactive.



(A)
[δ (P): 24.86, 27.30; $J = 13.0$ Hz, 90%]