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Accessing Brominated Natural Product Motifs Using Phosphoramidite Catalysis

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This article describes the application of a first-generation phosphoramidite catalyst to the construction of the most commonly encountered subunits of bromine-containing natural products. The process is compared with previous efforts, and is found to be complementary to existing methods. Application of the process enables bromocarbocyclisations, bromoetherifications, and bromoallene formation using the common laboratory reagent *N*-bromosuccinimide.

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Introduction

The marine environment provides an abundance of natural products bearing halogen atoms. With them being discovered at a rate exceeding 100 per year, the number of characterised halogenated natural products now stands at ~5000.[1,2] The distribution of these metabolites is heavily skewed towards compounds containing a single halogen atom, with monobrominated compounds being the most numerous. Many of these have the bromine atom appended at an element of chirality (either a stereogenic centre or an axis of chirality).[1,2] Some representative examples are shown in Fig. 1.

In their natural settings, asymmetrically halogenated compounds play multiple roles. Many marine species (including sponges and macroalgae) rely on chemical means to deter predation, and halogenated secondary metabolites are often the 'weapon of choice' for this purpose. For example, panacene (**1**) is accumulated in the mantle of the sea hare *Aplysia brasiliana* because it repels sharks and predatory fish.[3] Similarly, marine organisms that compete for sunlight require chemical defences against colonisation by other organisms. The red alga *Laurencia rigida* deploys (−)-10α-bromo-9β-hydroxy-α-chamigrene (**2**) to prevent colonisation by the green alga *Chlorella fusca*.[4] Other asymmetrically halogenated compounds function as antifouling and antimicrobial agents.[5,6] In the non-natural settings of agrichemical and medicinal research, asymmetrically halogenated compounds display a range of beneficial properties, ranging from insecticidal to anticancer activity.[7–9] A notable example is thyrsiferyl-23-acetate (**4**), which possesses subnanomolar activity against P-388 cells.[10]

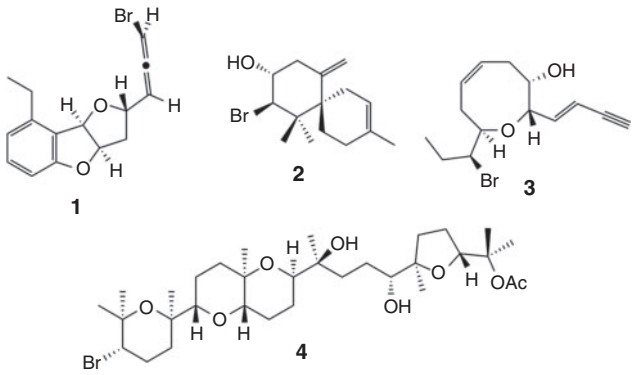


Fig. 1. Selected bromine-containing natural products.

With such a diverse array of potential applications, methods for the rapid generation of these asymmetric organohalogen containing compounds, and in particular organobromine compounds, are of widespread interest. To that end, we recently developed a family of N-heterocycle-flanked 1,1′-bi-2-naphthol (BINOL) phosphoramidites as nucleophilic catalysts.[11,12] Our aim was to employ the phosphoramidite as a bromonium shuttle that would allow us to conduct bromination reactions using the common laboratory reagent *N*-bromosuccinimide (NBS).[13] In order for any proposed catalyst to be generally applicable, it would need to be capable of generating the architectures observed in brominated natural products. In this article, we detail our investigations into the scope of phosphoramidite catalysis for the construction of important natural product motifs.

Results and Discussion

It is known that the predominant biosynthesis of asymmetrically halogenated natural products involves reaction of cyclic bromonium intermediates, which are generated by the action of vanadium bromoperoxidase (VBrPO) enzymes.[14] An examination of asymmetrically brominated compounds revealed three modes of cyclisation that are frequently involved in the biogenesis of these compounds.

Carbocyclisation reactions: as depicted in Fig. 2, the enzymatically generated cyclic bromonium intermediate can react with a carbon nucleophile (typically an alkene) to give a brominated alicyclic ring, such as is seen in luzonesin (**5**).[15]

Bromoetherification and esterification reactions: in this case, cyclic bromonium intermediates react with oxygen nucleophiles – typically alcohols and epoxides, though less

often, carbonyl units. Fig. 3 illustrates how the bromonium species **8** reacts with an internal epoxide to give prelaureatin (**3**).[16]

Bromoallene-forming reactions: in addition to the preceding modes of cyclisation, panacene (**1**) contains a bromoallene moiety that is derived via bromination of an enyne system. As depicted in Fig. 4, cyclisation of *cis*-laurediol (**10**) gives the bromoallene-containing compound hachijojimallene (**9**),[17] with aromatises to give panacene (**1**).[3]

Any laboratory-based brominating reagent that aspires to be widely applicable must, by necessity, be capable of mimicking these common modes of cyclisation. We therefore attempted to synthesise these key natural product motifs in a biomimetic fashion employing N-heterocycle-bearing phosphoramidites as nucleophilic catalysts.

Carbocyclisation Reactions

In 2009, Snyder identified 135 natural products containing substructure **12**, the result of a carbocyclisation reaction (see Scheme 1).[18] This number is doubtless an underestimate of the prevalence of **12** in brominated natural products – a 2013 review identified more than 120 such compounds from a single family of red algae.[9] Synthetically, the most significant advance in brominative methods to access substructure **12** has been the introduction of bromodiethylsulfonium bromopentachloroantimonate (BDSB).[18–20] Developed by Snyder and coworkers, BDSB is able to accomplish previously inaccessible bromocyclisation reactions. For instance, BDSB converted homogeranylbenzene (**13**) into the tricyclic compound **14**, a reaction that could not be performed efficiently using traditional brominating reagents. In order to provide comparisons with BDSB, we elected to study the brominative carbocyclisation of homogeranylbenzene (**13**) using our phosphoramidite-catalysed protocol.

The synthesis of compound **13** is set down in Scheme 2.[20] Geraniol (**15**) was converted into the phosphate ester **16**. Coordination of the phosphate unit to benzylmagnesium chloride helps guide delivery of the nucleophile to the α-position to regioselectively give (*E*)-homogeranylbenzene (**13**) in high overall yield.

Our previous studies on the oxidative stability of *N*-heterocycle-containing BINOL phosphoramidites pointed to the advantage of employing electron-withdrawing groups on an appended triazole ring.[12] Therefore, with **13** in hand, we explored the catalytic activity of the (*S*)-2,4,6-trichlorophenyltriazolyl BINOL phosphoramidite catalyst **17** (TCPT) (Scheme 3). The outcomes of those reactions and relevant literature precedents are presented in Table 1.

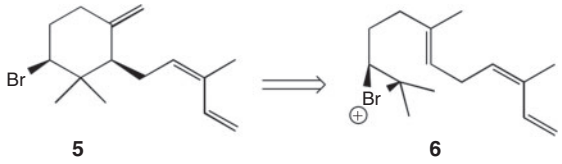


Fig. 2. Substructure generation by carbocyclisation.

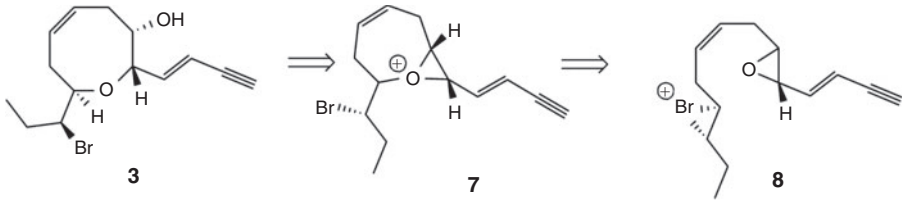


Fig. 3. Substructure generation by bromoetherification.

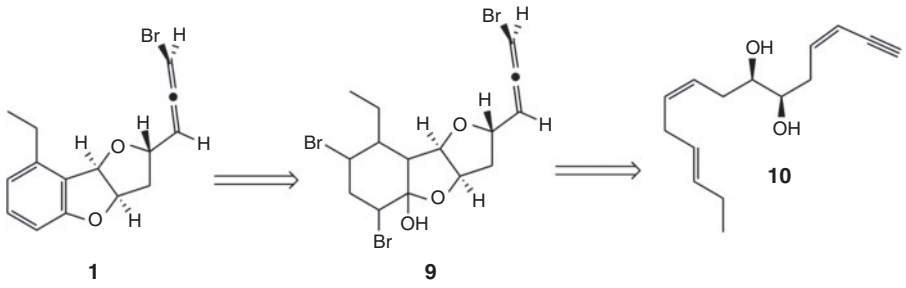
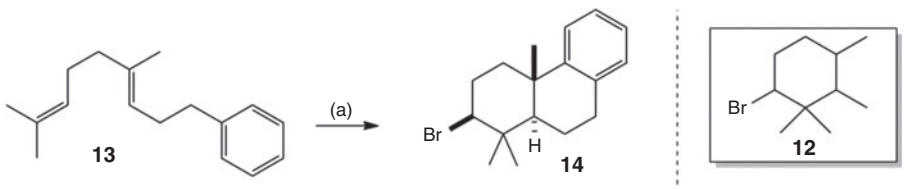


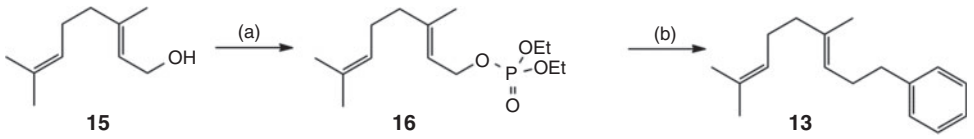
Fig. 4. Substructure generation by bromoallene formation.



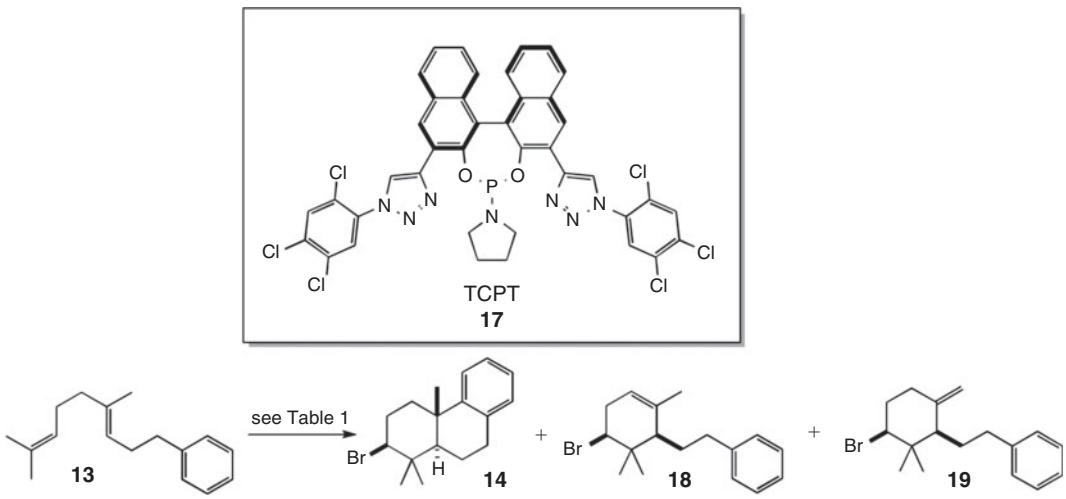
Scheme 1. Bromocyclisation of homogeranylbenzene (**13**). Reagents and conditions: (a) BDSB, $MeNO_2$, −25°C, 5 min, 75 %.

Treatment of **13** with NBS at low temperature resulted in no reaction (entry 1). Snyder has already reported that activated bromonium sources such as bromine and silver(I) (entry 2) and tetrabromocyclohexadienone (TBCO) (entry 3) require polar solvents and deliver the tricyclic compound **14** in low and moderate yield respectively.[20] Similarly, activation of NBS with PPh_3 required long reaction times and was non-selective, returning all possible products.[20] For selective formation of **14**, BDSB was the superior reagent (entry 4).[20] Gratifyingly, adding a suspension of NBS in toluene to solution of TCPT (**17**) and substrate **13** at −78°C resulted in rapid bromocyclisation (<1 min to completion) to give a mixture of **18** and **19** in 76 % yield (entry 6). Concerned that localised heating might be affecting the rate of reaction, solid NBS was cooled with liquid nitrogen before introduction into the reaction vessel. Rapid dissolution of the NBS was observed and the bromocyclisation was complete in less than 5 min. This modified procedure gave an identical product mixture to the initial conditions. We therefore concluded that we had not appreciably perturbed the temperature of the system during the addition of NBS. Entry 7 demonstrates that we were able to reduce the catalyst loading to 2 mol-% without significantly affecting the yield. The phosphoramidite-catalysed bromination protocol complements existing methodologies. Although BDSB is selective for the formation of the tricyclic system, the TCPT system is selective for monocyclisation. Disappointingly, neither of the bromocyclised products **18** or **19** was optically active.

During this work, we did not observe formation of the tetrasubstituted alkene **22** (Scheme 4). The absence of that thermodynamically favourable isomer accords with the observation that the hydrogen atoms that participate in the elimination reaction (designated H^a and H^b on compound **21**) are most favourably oriented with respect to the developing carbocation. Similarly, the absence of the tricyclic compound **14** suggests that the ring closure does not proceed through a concerted Stork–Eschenmoser-type cyclisation, but involves a discrete carbocation intermediate **21**. In non-polar solvents (such as toluene), elimination to form the trisubstituted and exocyclic alkenes **18** and **19** outcompetes the Friedel–Crafts reaction, which would give **14**. As shown in Table 1 (entry 8), when



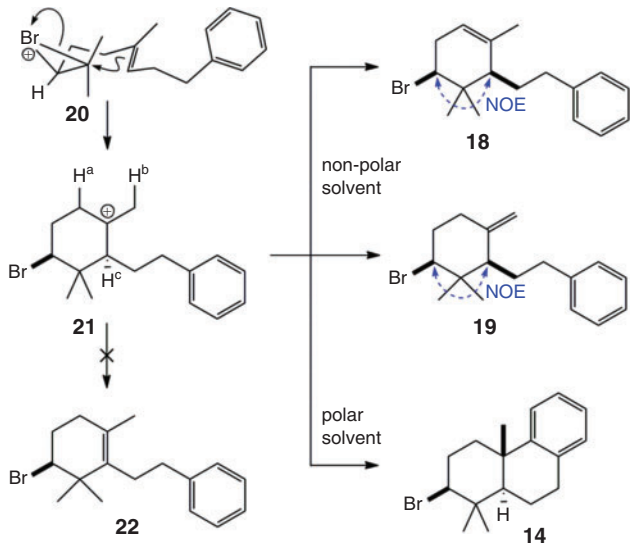
Scheme 2. Synthesis of homogeranylbenzene (**13**). Reagents and conditions: (a) $(EtO)_2POCl$, C_5H_5N, Et_2O, −10°C → room temperature (RT), 93 %; (b) BnMgCl, THF, −40°C, 74 %.



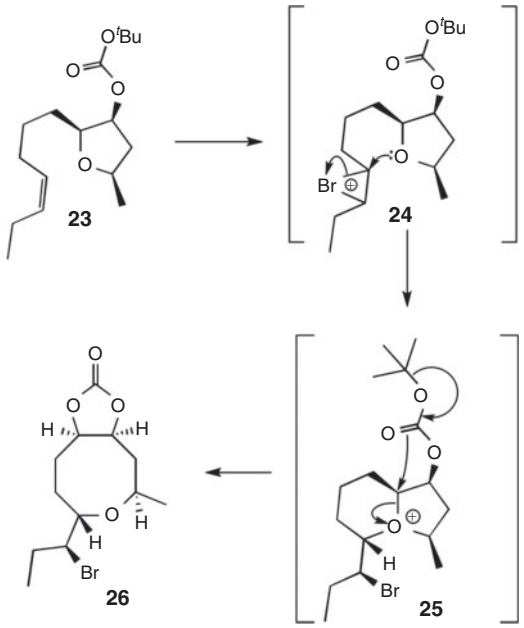
Scheme 3. Bromocyclisation of homogeranylbenzene (**13**).

Table 1. Comparison of the bromocyclisation of homogeranylbenzene (13) with various reagents

Entry	Reagent(s)	Conditions	Solvent	Yield [%] **14**/**18**/**19**
1	NBS	−78°C, 1 h, 4 Å MS	CH_2Cl_2	0/0/0
2	Br_2, $AgBF_4$	−25°C, 5 min	$MeNO_2$	9/<1/<1[20]
3	TBCO	−78°C, 10 min	CH_3CN	27/<1/<1[20]
4	NBS, PPh_3	−78°C, 24 h then −40°C, 6 h	CH_2Cl_2	13/18/13[20]
5	BDSB	−25°C, 5 min	$MeNO_2$	75/<1/<1[20]
6	NBS(*S*)-TCPT (10 mol-%)	−78°C, 10 min, 4 Å MS	Toluene	<1/36/40
7	NBS(*S*)-TCPT (2 mol-%)	−78°C, 10 min, 4 Å MS	Toluene	<1/29/30
8	NBS(*S*)-TCPT (10 mol-%)	−78°C, 10 min, 4 Å MS	CH_2Cl_2	38/15/22



Scheme 4. Pathway to the tetrasubstituted alkene **22**.



Scheme 5. Proposed ring-expanding biosynthesis of medium-ring bromoethers.

increasing the polarity of the solvent from toluene to dichloromethane, the carbocation **21** persists and the formation of **14** is observed.[21] Finally, although the products were racemic, the relative stereochemistry of the newly formed carbocyclic rings **18** and **19** was ascertained by nuclear Overhauser enhancement (NOE) experiments, which demonstrated exclusive formation of the *syn* isomer (Scheme 4).

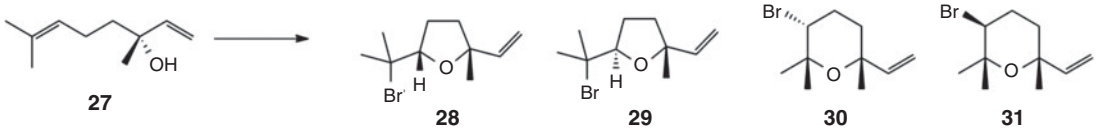
Phosphoramidite catalysis promotes the rapid bromocyclisation reaction to give an important natural product motif. Catalyst loadings between 2 and 10 mol-% were effective. The system showed a proclivity for monocyclisation, which is complementary to the established BDSB reagent.

Bromoetherification and Bromoesterification Reactions

Structures arising from a bromoetherification reaction are abundant in marine natural products. Two families of red algae in particular, *Rhodomelaceae* and *Plocamium*, produce hundreds of such compounds.[9] Cyclic bromoethers ranging from 5- to 12-membered rings have been isolated. Snyder has raised the intriguing possibility that the medium-ring brominated cyclic ethers are produced from smaller cyclic ethers that act as internal nucleophiles during electrophilic brominations (Scheme 5).[22,23] This remarkable result implies that the key to synthesising the members of this class of natural products with medium-ring ethers is to synthesise the corresponding five-membered ethers in a stereodefined fashion. Our initial goal was to show that we could enforce selectivity in the cyclisation of linear terpenoid precursors to give brominated tetrahydrofurans.

Bromocyclisation of (−)-Linalool

We selected (−)-linalool (**27**) as a substrate to explore the reactivity of our catalytic system in promoting the bromoetherification of terpenoid derivatives (Scheme 6). Table 2 shows our results along with comparative efforts by other researchers. The use of a VBrPO-mimic (entry 1) was reported to give both tetrahydrofuran isomers (**28** and **29**) along with both tetrahydropyran isomers (**30** and **31**).[24] Butler and coworkers employed the native enzyme, but under laboratory conditions, this gave an intractable mixture of cyclic ethers that could not be separated (entry 2).[25,26] TBCO has been used to cyclise **27** during the synthesis of the thyrsiferol A (entries 3 and 4).[27,28] That reagent favoured generation of the tetrahydropyran ring system with low levels of diastereoselectivity. Whereas NBS was not capable of effecting the cyclisation (entry 5), in the



Scheme 6. Bromoetherification of linalool (**27**).

Table 2. Comparison of the bromoetherification of linalool (27) with various reagents

Entry	Reagent(s)	Conditions	Solvent	Yield [%] **28**/**29**/**30**/**31**
1	$VO(L)(OEt)_3$, TBHP, NaBr[24]	30°C, 24 h	Propylene carbonate	23/14/27/15
2	VBrPO, NaBr, H_2O_2[25,26]	RT, 1 h	EtOH/buffer (30 : 70)	33 (composition of mixture not quantified)
3	TBCO[28]	0°C, 5 h	$MeNO_2$	17 (**28** + **29**)/38/26
4	TBCO[27]	0°C, 5 h	$MeNO_2$	10/7/38/24
5	NBS	−78°C, 10 min, 4 Å MS	CH_2Cl_2	0/0/0/0
6	NBS(*S*)-TCPT (10 mol-%)	−78°C, 10 min, 4 Å MS	CH_2Cl_2	67/12/0/16

presence of phosphoramidite catalyst **17**, the cyclisation proceeded in high yield (entry 6). In contrast to entries 3 and 4, the phosphoramidite-catalysed process favoured production of tetrahydrofuran **28**. Interestingly, the tetrahydropyran **30** (the major product from the TBCO reaction) was not observed.

As was the case for the carbocyclisations discussed above, phosphoramidite catalysis appears to be complementary to the established reagents. We attribute the ring-size selectivity to a kinetic process. Five-membered ring closures are known to occur more rapidly than the corresponding six-membered ring-closing reactions.[29] By conducting the reaction at low temperature, we were able to enhance the level of selectivity.

Gaining relative stereochemical information for five-membered rings is less straightforward than the corresponding six-membered rings. NOE data are often ambiguous, and in this instance, the products were obtained as oils, precluding the use of X-ray diffraction. Conventional NOE experiments revealed a large number of through-space interactions that were not diagnostic of the relative stereochemistry of **28**.[30] The stereochemistry of the tetrahydrofuran **28** was ascertained by employing a series of NOE experiments in which the mixing time was steadily increased. Through-space cross-relaxation occurs in a time-dependent fashion. At the shortest mixing times, only those nuclei close to the irradiated atom will be capable of being involved in the through-space spin-polarisation transfer. As the mixing time slowly increases, nuclei at increasing distances will be capable of becoming involved in the relaxation process and the corresponding resonances will exhibit NOE enhancements. This allows a time-dependent experiment to differentiate between nuclei that are closer to the irradiated atom than those that are further away.

The histogram in Fig. 5 represents the NOE enhancements observed when H-6 is irradiated as a function of mixing time. It clearly shows that with incremental increases in mixing time, it is the methyl group H-8 and H-9 that show the first increase in signal enhancement. The vinyl proton H-2 only begins to show increased enhancement at relatively long mixing times. Therefore, the relative stereochemistry of the tetrahydrofuran ring must be as depicted in Fig. 5, with the methyl groups in a closer spatial relationship to H-6 than the vinyl unit.

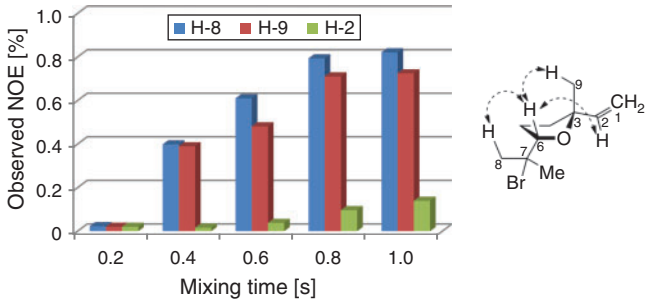


Fig. 5. Time-dependent NOEs of compound **28** when H-6 is irradiated.

These outcomes demonstrate that the phosphoramidite-catalysed process is a competent method for the bromoetherification of unprotected alcohols to give, predominantly, the five-membered ring systems.

Cyclisation of Geranyl Acetate

The bromocyclisation of simple geraniol derivatives in which a carbonyl unit participates as the nucleophile has traditionally been a challenging transformation. Efforts to induce the bromocyclisation of geranyl derivatives using common brominating reagents generally fail,[31] and when successful, the yield of such transformations is low.[32–41] For example, the bromocyclisation of geranyl acetate **32** to give alcohol **35** was reported in 1976 by Wolinsky and Faulkner, who obtained a 20 % yield when using Br_2 in combination with an Ag^I salt (Table 3, entry 1).[37] That result remained the state-of-the-art until Snyder deployed BDSB 33 years later (entry 2).[18] Similarly, efforts to induce the cyclisation enzymatically have also proved troublesome. Use of purified enzyme VBrPO to effect the bromocyclisation of **32** was low-yielding (entry 3).[26] We therefore examined whether the bromocyclisation involving a carbonyl unit as the nucleophile could be effected under phosphoramidite catalysis.

Geranyl acetate (**32**) was synthesised according to the published procedure.[18] When subjected to the action of NBS at low temperature, no background reaction occurred (entry 4). However, when the reaction was repeated in the presence of the phosphoramidite catalyst (**17**), a 1 : 1 mixture of the racemic alkenes **36** and **37** was obtained (entry 5).

The production of the alcohols **34** and **35** has previously been rationalised as shown in Scheme 7.[1,15] The (developing) carbocation from an initial carbocyclisation event is trapped by the carbonyl oxygen to give the stabilised oxonium species **33**. Subsequent cleavage by water gives the observed products. In a similar way, the production of **36** and **37** may result from catalyst (or succinimide anion)-mediated elimination of **33**. However, given the facile elimination observed during the carbocyclisation studies described above, we considered it equally likely that the phosphoramidite-catalysed system did not engage the acetate moiety as a nucleophile, but cyclised in a process akin to that shown in Scheme 4. To discriminate between these possible scenarios, we sought a related substrate for which the engagement of a carbonyl nucleophile would result in an irreversible cyclisation.

Geranyl *tert*-butyl carbonate (**38**, Scheme 8) was synthesised following literature protocols.[18] As carbocation capture by the *tert*-butyl carbonate nucleophile is made irreversible through subsequent fragmentation, this system would establish whether the carbonyl moiety participated in phosphoramidite-catalysed bromocyclisation reactions. As before, treatment of **38** with

Table 3. Comparison of the bromoetherification of geranyl acetate (32) with various reagents

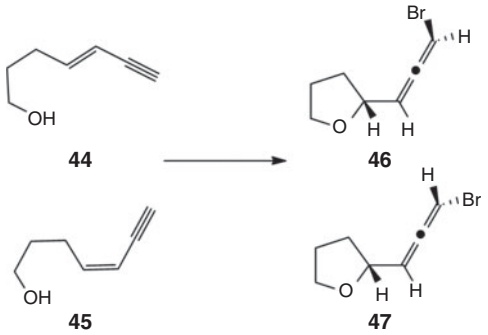
Entry	Reagent(s)	Conditions	Solvent	Yield [%] **34**/**35**/**36**/**37**
1	Br_2, $AgBF_4$	0°C, 24 h	$MeNO_2$	10/10/0/0[37]
2	BDSB	0°C, 24 h	$MeNO_2$	17/63/0/0[18]
3	VBrPO	VBrPO, NaBr, H_2O_2	EtOH/buffer (40 : 60)	0/0/<3/<3
4	NBS	−78°C, 10 min, 4 Å MS	CH_2Cl_2	0/0/0/0
5	NBS(*S*)-TCPT (10 mol-%)	−78°C, 10 min, 4 Å MS	CH_2Cl_2	0/0/31/31

NBS at −78°C did not induce any reaction. However, when the reaction was performed in the presence of the TCPT catalyst (**17**), we again observed a 1 : 1 mixture of alkene isomers **42** and **43**. No trace of bicyclic products **40** and **41** were visible in the ^{1}H NMR spectrum of the crude reaction mixture. We therefore consider it unlikely that the carbonyl moiety was participating in the catalytic bromocyclisation.

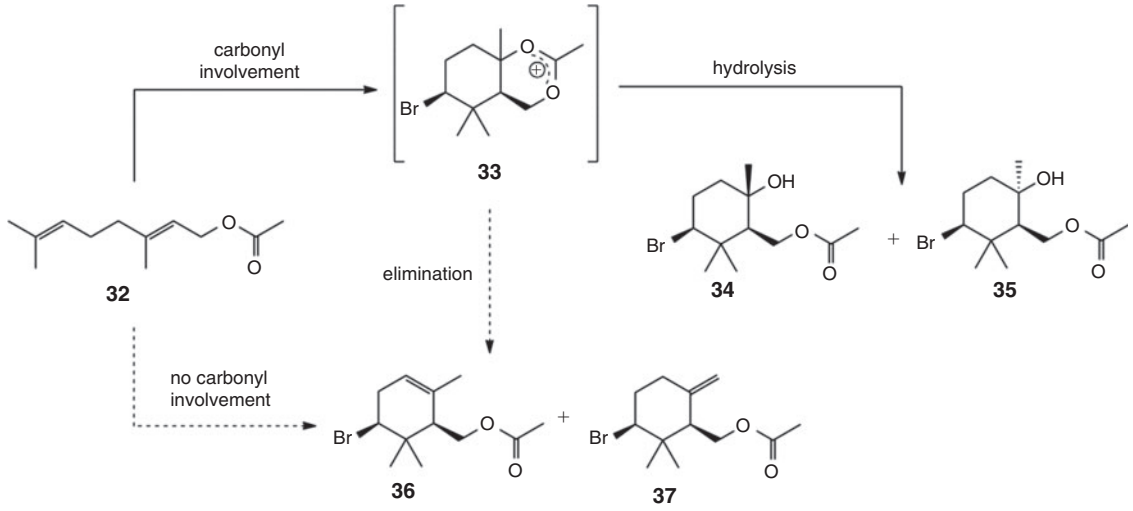
So phosphoramidite catalysis is capable of engaging free alcohols in the cyclisation event, but not the corresponding carbonyl units. Once again, this reactivity pattern is complementary to the established BDSB reagent.

Bromoallene Forming Reactions

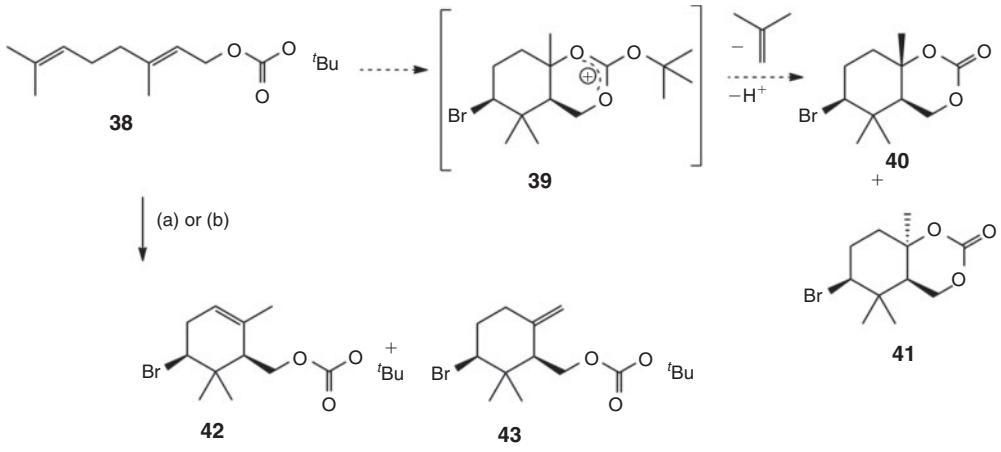
Bromoallenes are surprisingly common in marine natural products. Since the isolation of the first bromoallene-containing natural product, panacene (**1**)[32] (see Figs 1 and 4), the number of compounds containing this functional unit has grown to at least 40.[5] These are predominantly isolated from red algae, and are known to be biogenetically derived from enynes. The key synthetic report in this area is by Braddock and coworkers, who demonstrated that the bromoetherification of linear enynes was stereospecific with respect to the geometry of the starting alkene. Scheme 9 summarises the conclusions of Braddock and coworkers.[42] When the (*E*)-enyne **44** cyclised, bromoallenes **46** and **47** were produced in a 6 : 1 ratio. Attempted cyclisation of the pure (*Z*)-enyne **45** under identical conditions resulted in decomposition. Intriguingly, cyclisation a 1 : 1.6 mixture of **44** and **45** returned a 1 : 1.5 mixture of **46** and **47** quantitatively. This observation suggests that the mechanism is not straightforward and may involve coordination of a bromonium ion between multiple unsaturated moieties.



Scheme 9. Braddock's enyne cyclisations.[42]



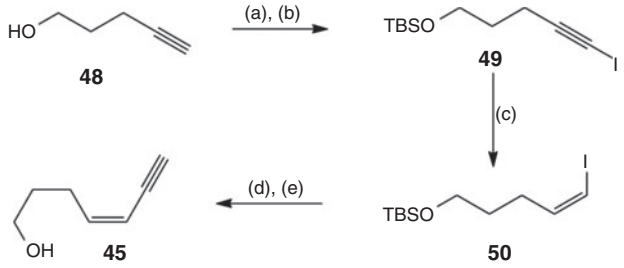
Scheme 7. Bromocyclisation of geranyl acetate (**32**).



Scheme 8. Reagents and conditions: (a) NBS, CH_2Cl_2 −78°C, NR; (b) (*S*)-TCPT **17** (10 mol-%), NBS, CH_2Cl_2, −78°C, 78 % (dr **42** : **43** 1 : 1). NR, no reaction.

Given those outcomes, we initially targeted cyclisation of the (*Z*)-enyne **45** in order to test whether phosphoramidite catalysis could complement existing methods of bromoallene generation. The synthesis of **45** is depicted in Scheme 10. Protection of 4-pentyn-1-ol (**48**) as the silyl ether and iodination gave **49**.[43] It is known that ethynyl iodides can be reacted with diimide to give the (*Z*)-configured alkene without over-reduction to the alkane, provided that careful attention is paid to the stoichiometry and concentration of reactants.[44] In this instance, when two equivalents of the diimide precursor tosylhydrazide were employed, compound **49** was reduced to stereochemically pure **50**[45] without over-reduction. Subsequent Sonogashira coupling of the iodoalkene with trimethylsilylacetylene and double deprotection gave the desired (*Z*)-enyne **45**.[46]

When subjected to the action of NBS at low temperature, (*Z*)-enyne **45** was recovered unchanged (Scheme 11). However, in the presence of the phosphoramidite catalyst (*S*)-TCPT **17**, we were pleased to observe that bromoallene formation occurred cleanly at −78°C. Surprisingly, and in contrast to Braddock's work,[42] the bromoallenes **46** and **47** were generated as a 1 : 1 mixture.



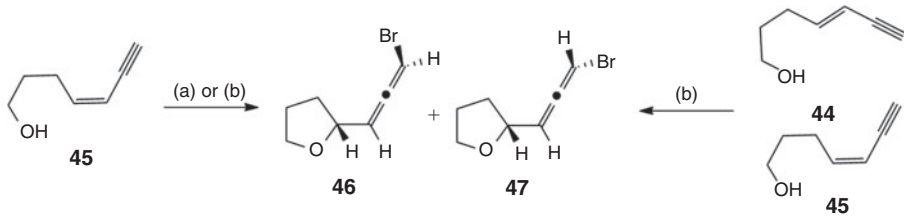
Scheme 10. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, room temperature (RT), 60 h; (b) I_2, KOH, MeOH/H_2O (5 : 1), 0°C → RT, 16 h, 74 % (2 steps); (c) $TsNHNH_2$, NaOAc, THF/H_2O (1 : 1), Δ, 15 h, 86 %; (d) TMSC≡CH, $Pd(PPh_3)_4$, CuI, THF/NEt_3 (1 : 1), RT, 16 h; (e) TBAF, THF, −10°C → 0°C, 3 h, 91 % (2 steps).

To probe the origin of the 1 : 1 product ratio, we synthesised a 1 : 1.6 mixture of (*E*)-enyne **44** and (*Z*)-enyne **45** according to Braddock's procedure.[42] When this mixture was subjected to the phosphoramidite-catalysed conditions, we again observed a 1 : 1 ratio of the bromoallene products **46** and **47**. There is evidence for the coordination of Lewis bases to the halonium ion in the transition states of certain Lewis base-promoted bromolactonisations.[47] The lack of stereospecificity in this instance suggests that the phosphoramidite system proceeds through a more α-bromocation-like intermediate, allowing bond rotation and access to both diastereomers.

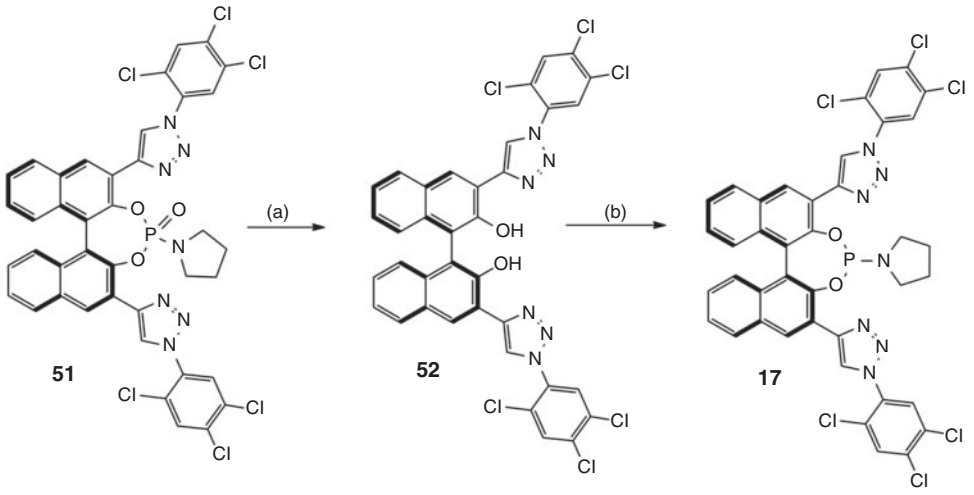
The phosphoramidite-catalysed bromination of enynes delivers bromoallenes in high yield. The process is not stereospecific. In a total synthesis setting, the cyclising alcohol would almost certainly be attached to a stereogenic centre, perhaps allowing a diastereoselective process that is independent of the enyne geometry. Work to that end is currently under way in our laboratory.

Catalyst Recovery

In each of the foregoing processes, exposure of the crude mixture to the air resulted in aerobic oxidation of the phosphoramidite catalyst **17** to give the phosphoramidate **51** (see Scheme 12). Therefore, the preferred method for catalyst recovery was filtration of the crude reaction mixture to remove succinimide, followed by an extractive workup. The oxidised



Scheme 11. Reagents and conditions: (a) NBS, CH_2Cl_2, 4-Å molecular sieves (MS), −78°C, NR; (b) (*S*)-TCPT **17** (10 mol-%), NBS, 4 Å MS, CH_2Cl_2, −78°C, 82 % (dr **46** : **47** 1 : 1). (NR, no reaction).



Scheme 12. Reagents and conditions: (a) HCl (10 M in H_2O), CH_2Cl_2/MeOH (1 : 9), room temperature (RT), 16 h, 99 %; (b) PCl_3, toluene, Δ, 16 h, then $(CH_2)_4NH$, 0°C → RT, 0.5 h, 91 %.

phosphoramidate **51** was substantially more polar than the cyclisation products and was recovered chromatographically, after elution of the desired cyclisation products. Recovery of **51** was typically 98 %. As shown in Scheme 12, cleavage of the phosphorus(v) unit to regenerate the diol **52** was facile. The phosphoramidite **17** was then regenerated, with no loss of optical rotation.[11,12]

Conclusion

This article describes our use of phosphoramidite catalysis to construct several bromine-containing motifs that are commonly encountered in natural products. The reactivity of this system was found to be complementary to the current gold-standard reagent, BDSB. The phosphoramidite-catalysed carbocyclisation of homogeranylbenzene proceeded in high yield and diastereoselectivity, and monocyclisation was highly favoured. The bromoetherification of the unprotected tertiary allylic alcohol, linalool, favoured formation of the tetrahydrofuran product. In contrast to BDSB, carbonyl units were not nucleophilic enough to engage in cyclisation during the phosphoramidite-catalysed process. And finally, the phosphoramidite-catalysed bromination of enynes led to the corresponding bromoallenes. Reaction with diastereomerically pure linear enynes demonstrated that the process was not stereospecific, which opens avenues for substrate-controlled processes.

In conclusion, phosphoramidite catalysis permits the use of the stable and readily available brominating reagent NBS for the synthesis of a range of brominated natural product motifs.

Experimental

General Experimental

Reagent-grade dichloromethane and triethylamine were freshly distilled from calcium hydride. Tetrahydrofuran and methanol were collected using an Innovative Technology Inc. PureSolv™ solvent purification system. Tosyl hydrazide,[48] diethyl chlorophosphate,[49,50] geranyl diethyl phosphate,[20] 5-*tert*-butyldimethylsilyloxypent-1-yne,[51] 1-iodo-5-*tert*-butylsimethylsilyloxypent-1-yne,[43] and TBCO[52,53] were synthesised according to literature procedures. All other solvents and reagents were used as received from commercial sources. Melting points were determined using a Stanford Research Systems Optimelt automated melting point system and are uncorrected. Infrared spectra were acquired neat on a Bruker Alpha-E attenuated total reflection (ATR) spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX300 (^{1}H frequency 300 MHz, ^{13}C frequency 75 MHz) or Bruker Avance DPX500 (^{1}H frequency 500 MHz, ^{13}C frequency 125 MHz). ^{1}H chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26) or tetramethylsilane (δ 0.00) as reference and are reported as chemical shift (δ_H), relative integral, multiplicity (s, singlet; br, broad; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet), and coupling constants (J) reported in Hz. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 77.16) as internal reference and are reported as chemical shift (δ_C), multiplicity (assigned from distortionless enhancement by polarisation transfer (DEPT) experiments). NMR assignments were made on the basis of heteronuclear single quantum coherence (HSQC), heteronuclear multiple-bond correlation (HMBC), nuclear Overhauser effect spectroscopy (NOESY), and homonuclear correlation spectroscopy (COSY) 2D experiments. High-resolution mass spectra (HRMS) were recorded on a Bruker ApexII Fourier-transform ion cyclotron resonance mass spectrometer with a 7.0-T magnet, fitted with an off-axis analytical electrospray ionisation (ESI) source. Column chromatography was performed using Grace Davidson 40–63-μm (230–400 mesh) silica gel using distilled solvents. Analytical thin-layer chromatography was performed using preconditioned plates (Merck TLC silica gel 60 F254 on aluminium) and visualised using UV light (254 and 365 nm) and ethanolic anisaldehyde.

Representative Bromination Procedure

A representative protocol for the bromocyclisation reactions is as follows: a solution of substrate (0.50 mmol, 1.0 equiv.) and (*S*)-TCPT catalyst **17** (0.05 mmol, 0.10 equiv.) in CH_2Cl_2 (10 mL) was stirred (7 h) over activated 4-Å molecular sieves (0.5 g). The mixture was cooled to −78°C and a solution of NBS (0.50 mmol 1.0 equiv.) in CH_2Cl_2 (10 mL) was added over 5 min via syringe pump. The solution was stirred (5 min) at −78°C, then quenched via the addition of a solution of sodium sulfite (5 % in water, 20 mL) and allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the organic extracts combined with the organic partition of the reaction mixture and washed with water (50 mL), brine (50 mL), dried over sodium sulfate, and concentrated. Column chromatography was used to isolate the product(s).

(E)-3,7-Dimethylocta-2,6-dien-1-yl diethyl phosphate **16**[20]

To a mixture of geraniol (10 mL, 58 mmol, 1.0 equiv.), pyridine (19 mL, 0.23 mol, 4.1 equiv.), and diethyl ether (100 mL) at −10°C was added, dropwise, diethyl chlorophosphate (10 mL, 69 mmol, 1.2 equiv.) and the reaction stirred, while being allowed to warm slowly to room temperature (16 h). The mixture was cooled to 0°C and quenched via addition to a solution of sodium hydroxide (1.0 M in water, 200 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts washed with water (2 × 100 mL), brine (50 mL), and dried over sodium sulfate. Column chromatography (ether) gave the product (15.6 g, 93 %) as a colourless oil. ν_{max} (neat)/cm^{-1} 2980, 1275, 1101, 1035. δ_H (300 MHz, $CDCl_3$) 5.33 (1H, m), 5.01 (1H, m), 4.50 (2H, dt, J 7.5, 0.5), 3.99–4.07 (4H, m), 1.94–2.08 (4H, m), 1.60 (3H, s), 1.60 (3H, s), 1.26 (6H, dt, J 7.1, 0.9). δ_C (75 MHz, $CDCl_3$) 142.3 (C), 131.7 (C), 123.4 (CH), 118.8 (CH, J_{C-P} 6.4), 63.9 (CH_2, J_{C-P} 5.5), 63.4 (2C, CH_2, J_{C-P} 6.1), 39.3 (CH_2), 26.0 (CH_2), 25.5 (CH_3), 17.5 (CH_3), 16.2 (CH_3), 15.9 (2C, CH_3, J_{C-P} 6.5).

(E)-(4,8-Dimethylnona-3,7-dien-1-yl)benzene **13**[20]

A solution of benzyl chloride (0.230 mL, 2.00 mmol, 2.0 equiv.) in THF (10 mL) was cooled to 0°C and added over 30 min to ground magnesium turnings (97 mg, 4.00 mmol, 4.0 equiv.), activated with a crystal of mercury(II) chloride. The solution was stirred at 0°C (1 h), then cooled to −40°C and added to a solution of **16** (290 mg, 1.00 mmol, 1.0 equiv.) in THF (2.0 mL) at −40°C. The mixture was stirred, being allowed to warm gradually to room temperature (4 h). The reaction was quenched with saturated aqueous ammonium chloride (15 mL), then extracted with ethyl acetate/hexanes 1 : 1 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 mL), then brine (20 mL), dried over sodium sulfate and concentrated. Column chromatography (ethyl acetate/light petroleum 1 : 99) gave **13** (2.6 g, 74 %) as a

slightly yellow oil. R_f 0.76 (CH_2Cl_2/hexanes 1 : 4). ν_{max} (neat)/cm^{-1} 3052, 2965, 1495, 1376, 1109, 835. δ_H (300 MHz, $CDCl_3$) 7.37 (2H, dd, *J* 7.2, 1.8), 7.26–7.36 (3H, m), 5.32 (1H, tt, *J* 7.2, 1.1), 5.24 (1H, m), 2.09–2.82 (8H, m), 1.80 (3H, s), 1.73 (3H, s), 1.68 (3H, s). δ_C (75 MHz, $CDCl_3$) 142.3 (C), 135.6 (C), 131.2 (C), 128.4 (2C, CH), 128.1 (2C, CH), 125.6 (CH), 124.4 (CH), 123.6 (CH), 39.7 (CH_2), 36.2 (CH_2), 29.9 (CH_2), 26.8 (CH_2), 25.7 (CH_3), 17.6 (CH_3), 15.9 (CH_3).

(2-((1R,5S*)-5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl) ethyl)benzene* ***18*** *and (2-((1R*,3S*)-3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)ethyl)benzene* ***19***[20]

These compounds were synthesised using the representative procedure in toluene. They were obtained, after column chromatography using CH_2Cl_2/hexanes (1 : 19), as a colourless oil comprising a 1 : 1.1 mixture of **18** and **19** (76 %), R_f 0.40 (CH_2Cl_2/hexanes 1 : 9). ν_{max} (neat)/cm^{-1} 2952, 1675, 1649, 1363, 1232. *Compound* ***18***: δ_H (300 MHz, $CDCl_3$) 7.26–7.33 (2H, m), 7.16–7.23 (3H, m), 5.25 (1H, br s), 4.18 (1H, dd, *J* 9.0, 7.2), 2.88 (1H, ddd, *J* 16.2, 11.0, 5.3), 1.81–2.62 (5H, m), 1.80 (3H, br s), 1.67 (1H, dddd, 17.6, 13.7, 7.1, 5.0), 1.07 (3H, s), 0.90 (3H, s). δ_C (100 MHz, $CDCl_3$) 142.7 (C) or 142.4 (C), 136.7 (C), 126.0–128.6 (3C, CH) 121.0 (CH), 65.3 (CH), 49.7 (CH), 39.1 (C), 37.5 (CH_2), 36.1 (CH_2), 35.5 (CH_2), 31.8 (CH_2), 28.5 (CH_3), 22.4 (CH_3), 16.7 (CH_3). *Compound* ***19***: δ_H (300 MHz, $CDCl_3$) 7.26–7.33 (2H, m), 7.16–7.23 (3H, m), 5.01 (1H, s), 4.77 (1H, s), 4.11 (1H, dd, *J* 11.4, 5.7), 2.81 (1H, ddd, *J* 13.9, 10.3, 4.5), 1.81–2.62 (7H, m), 1.13 (3H, s), 0.84 (3H, s). δ_C (100 MHz, $CDCl_3$) 145.7 (C), 142.7 (C) *or* 142.4 (C), 126.0–128.6 (3C, CH) 109.2 (CH_2), 67.4 (CH), 52.3 (CH), 42.0 (C), 38.1 (CH_2), 37.5 (CH_2), 34.9 (CH_2), 28.6 (CH_2), 28.4 (CH_3), 15.7 (CH_3).

(2R,5S)-5-(2-Bromopropan-2-yl)-2-methyl-2-vinyltetrahydrofuran ***28***[27,28]

This compound was synthesised using the representative procedure. It was obtained as a colourless oil (67 %). This compound elutes last among the four isomers produced in the cyclisation. A pure sample of **28** may be obtained by preparative thin-layer chromatography (ether/light petroleum 2 : 98). α_D^{24} +6.0 (*c* 1.0, $CHCl_3$). R_f 0.60 (ether/hexanes 1 : 19). ν_{max} (neat)/cm^{-1} 2970, 1260, 1091, 1065, 1018, 916, 801. δ_H (500 MHz, $CDCl_3$) 5.99 (1H, dd, *J* 17.4, 10.8), 5.22 (1H, dd, *J* 17.4, 1.4), 4.99 (1H, dd, *J* 1.4, 10.8), 3.99 (1H, app t, *J* 6.8), 1.77–2.08 (4H, m), 1.75 (3H, s), 1.72 (3H, s), 1.30 (3H, s). δ_C (125 MHz, $CDCl_3$) 144.0 (CH), 111.7 (CH_2), 86.1 (CH), 84.0 (C), 68.4 (CH), 37.6 (CH_2), 31.6 (CH_3), 29.2 (CH_3) 29.0 (CH_2), 25.7 (CH_3). *m/z* (+ESI) (relative intensity) 321 (97), 319 (100), 257 (39, MNa^+), 255 (38, MNa^+). *m/z* (HRMS, +ESI) 255.03563, calc. for $C_{10}H_{17}{}^{79}BrONa$ 255.03550 [M + Na]; 257.03361, calc. for $C_{10}H_{17}{}^{81}BrONa$ 257.03345.

((1R,5S*)-5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl) methyl Acetate* ***36*** *and ((1R*,3S*)-3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)methyl Acetate* ***37***[18,26]

These compounds were synthesised using the representative procedure. They were obtained, after column chromatography (ethyl acetate/hexanes 1 : 49), as a colourless oil comprising a 1 : 1 mixture of **36** and **37** (62 %). R_f 0.55 (ethyl acetate/hexanes 1 : 50). ν_{max} (neat)/cm^{-1} 2952, 2925, 1754, 1395, 1232. *Compound* ***36***: δ_H (300 MHz, $CDCl_3$) 5.35 (1H, br s), 4.50–4.37 (2H, m), 4.35 (1H, dd, *J* 11.8, 3.9 Hz), 2.06 (3H, s), 2.59–1.64 (3H, m), 1.49 (3H, s), 1.21 (3H, s), 0.95 (3H, s). δ_C (75 MHz, $CDCl_3$) 171.2 (C), 133.9 (C), 122.3 (CH), 64.0 (CH), 63.8 (CH_2), 49.1 (CH), 35.1 (C), 29.9 (C, CH_2), 28.6 (CH_3), 21.9 (CH_3), 21.3 (CH_3), 16.6 (CH_3). *Compound* ***37***: δ_H (300 MHz, $CDCl_3$) 4.95 (1H, s), 4.66 (1H, s), 4.50–4.37 (2H, m), 4.13 (1H, dd, *J* 9.9, 7.1), 2.03 (3H, s), 2.59–1.64 (3H, m), 1.23 (3H, s), 0.91 (3H, s). δ_C (75 MHz, $CDCl_3$) 171.2 (C), 144.0 (C), 110.1 (CH_2), 66.1 (CH), 62.7 (CH_2), 51.2 (CH), 36.3 (C), 35.3 (CH_2), 29.9 (C, CH_2), 28.4 (CH_3), 21.2 (CH_3), 17.5 (CH_3). *m/z* (EI) (relative intensity) 216 (8), 214 (9), 135 (100), 119 (30), 107 (40), 93 (37), 79 (10), 43 (97).

((1R,5S)-5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl) methyl tert*-Butyl Carbonate* ***42*** *and ((1R,3S)-3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)methyl* tert*-Butyl Carbonate* ***43***

These compounds were synthesised using the representative procedure. They were obtained, after column chromatography (ethyl acetate/hexanes 1 : 99), as a colourless oil comprising a 1 : 1 mixture of **42** and **43** (65 %). R_f 0.70 (ethyl acetate/hexanes 1 : 50). ν_{max} (neat)/cm^{-1} 2927, 1747, 1649, 1394, 1364, 1232. *Compound* ***42***: δ_H (300 MHz, $CDCl_3$) 5.39 (1H, br s), 4.39–4.53 (2H, m), 4.39 (1H, α, dd, *J* 11.8, 3.9), 1.64–2.63 (2H, m), 1.52 (3H, s), 1.45 (9H, s) or 1.43 (9H, s), 1.24 (3H, s), 0.98 (3H, s). δ_C (75 MHz, $CDCl_3$) 153.5 or 153.1 (C), 134.1 (C), 122.6 (CH), 64.4 (CH), 63.6 (CH_2), 49.4 (CH), 34.9 (C), 29.9 (CH_2), 28.6 (CH_3), 27.8–27.9 (3C, CH_3), 21.7 (CH_3), 18.3 (CH_3), 16.5 (CH_3). *Compound* ***43***: δ_H (300 MHz, $CDCl_3$) 4.99 (1H, s), 4.67 (1H, s), 4.39–4.53 (2H, m), 4.17 (1H, dd, *J* 9.9, 7.1), 1.64–2.63 (4H, m), 1.52 (3H, s), 1.45 (9H, s) or 1.43 (9H, s), 1.26 (3H, s), 0.93 (3H, s). δ_C (75 MHz, $CDCl_3$) 153.5 or 153.1 (C), 144.3 (C), 109.8 (CH_2), 66.4 (CH), 62.9 (CH_2), 51.9 (CH), 36.1 (C), 35.3 (CH_2), 29.9 (CH_2), 28.4 (CH_3), 27.8–27.9 (3C, CH_3), 18.1 (CH_3), 17.7 (CH_3). *m/z* (EI) (relative intensity) 216 (18), 214 (19), 135 (100), 119 (27), 93 (23), 43 (86).

*(Z)-5-*tert*-Butyldimethylsilyloxy-1-iodopent-4-yne* ***49***[43]

To a solution of **48** (1.0 mL, 11 mmol, 1.0 equiv.) in DMF (30 mL) was added *tert*-butyldimethylchlorosilane (2.1 g, 14 mmol, 1.3 equiv.), then imidazole (1.8 g, 26 mmol, 2.5 equiv.). The mixture was stirred at room temperature (60 h), then filtered. The filtrate was diluted with hexanes (100 mL), washed with water (3 × 100 mL), brine (100 mL), dried over sodium sulfate and passed through a plug of silica, washing with CH_2Cl_2/hexanes 1 : 9 (50 mL), and concentrated to give a colourless oil. This colourless oil was taken up in methanol (25 mL) and a solution of potassium hydroxide (1.5 g, 27 mmol, 2.5 equiv.) in water (7 mL) added. The mixture was cooled to 0°C and stirred with protection from light while iodine (4.1 g, 16 mmol, 1.5 equiv.) was added in small portions, allowing the brown colour of dissolved iodine to dissipate between portions. The mixture was stirred for a further 16 h, while being allowed to warm to room temperature. The reaction mixture was partitioned between hexanes (100 mL) and water (100 mL). The aqueous partition was washed with hexanes (50 mL) and the hexane wash combined with the organic partition of the reaction mixture, and washed with water (3 × 100 mL), brine (50 mL), dried over $NaSO_4$, and concentrated. Column chromatography (ether/light petroleum 1 : 9) gave **49** (2.6 g, 74 %) as a slightly yellow oil. R_f 0.25 (EtOAc/hexanes 1 : 50). ν_{max} (neat)/cm^{-1} 2190, 1471, 1253, 1007, 835, 776. δ_H (300 MHz, $CDCl_3$) 3.67 (2H, d, *J* 6.1), 2.44 (2H, t, *J* 7.0), 1.72 (2H, dt, *J* 13.9, 6.4), 0.88 (9H, s), 0.03 (3H, s). δ_C (75 MHz, $CDCl_3$) 94.2 (C), 61.3 (CH_2), 31.4 (C), 25.9 (3C, CH_3), 18.3 (CH_2), 17.3 (CH_2), −5.3 (2C, CH_3), −7.1 (CI).

*(Z)-5-*tert*-Butyldimethylsilyloxy-1-iodopent-4-ene **50**[45]*

A solution of **49** (1.61 g, 4.96 mmol, 1.0 equiv.) in THF (5 mL) was added to a stirred solution of tosyl hydrazide (1.85 g, 9.93 mmol, 2.0 equiv.) and sodium acetate (1.22 g, 14.9 mmol, 3.0 equiv.) in water (5 mL) and the mixture heated to reflux (16 h) with strict exclusion of light. The reaction mixture was poured onto a solution of ammonium chloride (5 % in water, 100 mL) and the resulting mixture extracted with ethyl acetate/hexanes 1 : 9 (3 × 20 mL). The combined organic extracts were washed with water (2 × 100 mL), brine (50 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/hexanes 1 : 200) gave **50** as a slightly yellow oil (1.39 g, 86 %). R_f 0.25 (ether/hexanes 1 : 200). δ_H (300 MHz, $CDCl_3$) 6.17–6.23 (2H, m), 3.64 (2H, t, *J* 6.3), 2.21 (2H, t, *J* 5.5), 1.67 (2H, tt, *J* 6.3, 5.5), 0.90 (9H, s), 0.06 (6H, s). δ_C (75 MHz, $CDCl_3$) 141.1 (CH), 82.6 (CH), 62.5 (CH_2), 31.5 (CH_2), 31.2 (CH_2), 26.1 (3C, CH_3), 18.4 (C), −5.7 (2C, CH_3). *m/z* (EI) (relative intensity) 326 (MH^+, 1), 269 (100), 164 (15), 75 (45).

*(Z)-Hept-4-en-6-yn-1-ol **45**[46]*

To a mixture of **50** (1.39 g, 4.26 mmol, 1.00 equiv.), copper(I) iodide (60 mg, 0.32 mmol, 0.074 equiv.) and tetrakistriphenylphosphinepalladium(0) (200 mg, 0.17 mmol, 0.041 equiv.) in THF (10 mL) was added triethylamine (10 mL), then trimethylsilylacetylene (1.5 mL, 11 mmol, 2.5 equiv.). The mixture was stirred (16 h), then partitioned between water (100 mL) and hexanes (20 mL). The aqueous partition was extracted with hexanes (2 × 20 mL) and the organic extracts combined with the organic partition of the reaction mixture and washed with saturated aqueous ammonium chloride (2 × 20 mL), water (100 mL), brine (100 mL), and dried over sodium sulfate. The solution was passed through a plug of silica, washing with ether/hexanes: 1/9. Volatile components were removed under vacuum to give (*Z*)-1-*tert*-butyldimethylsilyloxy-7-trimethylsilylhept-4-en-6-yne[54] as a colourless oil. ν_{max} (neat)/cm^{-1} 2954, 2121, 1610, 1447, 1054. δ_H (300 MHz, $CDCl_3$) 5.94 (1H, dt, *J* 10.9, 7.4), 5.47 (1H, dt, *J* 10.9, 1.5), 3.63 (2H, t, *J* 6.5), 2.36 (2H, ddt, *J* 9.9, 7.4, 1.5), 1.64 (2H, tt, *J* 6.5, 9.9), 0.90 (9H, s), 0.19 (6H, s), 0.05 (3H, s). δ_C (75 MHz, $CDCl_3$) 145.1 (CH), 109.5 (CH), 62.9 (CH_2), 32.0 (CH_2), 27.1 (CH_2), 26.1 (3C, CH_3), 18.5 (C), 0.2 (3C, CH_3), −5.1 (2C, CH_3). *m/z* (EI) (relative intensity) 296 (MH^+, 2), 239 (100), 133 (89), 73 (74). This bis-silylated compound was deprotected in the next step without further purification.

The sample of (*Z*)-1-*tert*-butyldimethylsilyloxy-7-trimethylsilylhept-4-en-6-yne prepared as described above was taken up in THF (20 mL) and cooled to −10°C. A solution of tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 8.7 mL, 2.0 equiv.) was added slowly and the mixture stirred (1 h), being allowed to warm to 0°C. The reaction was quenched with water (10 mL), then partitioned between water (100 mL) and ethyl acetate/hexanes 1 : 1 (20 mL). The aqueous partition was extracted with ethyl acetate/hexanes 1 : 1 (2 × 20 mL) and the organic extracts combined with the organic partition of the reaction mixture and washed with water (100 mL), brine (100 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/hexanes 3 : 7) gave **45** (1.15 g, 91 %, 2 steps) as a colourless oil. R_f 0.35 (ethyl acetate/hexanes 3 : 7). ν_{max} (neat)/cm^{-1} 3340, 3300, 3040, 2956, 2894, 2111, 1445, 1059, 745. δ_H (300 MHz, $CDCl_3$) 6.02 (1H, ddt, *J* 10.8, 7.6, 0.9), 5.50 (1H, ddt, *J* 10.8, 2.3, 1.4), 3.67 (2H, t, *J* 6.5), 3.10 (1H, ddt, *J* 2.3, 0.9, 0.5), 2.44 (1H, dddt, *J* 7.6, 7.4, 1.4, 0.5), 2.25 (1H, s), 1.64 (1H, tt, *J* 7.4, 6.5). δ_C (75 MHz, $CDCl_3$) 145.1 (CH), 108.9 (CH), 81.9 (CH), 80.4 (C), 62.0 (CH_2), 31.4 (CH_2), 26.5 (CH_2). *m/z* (ESI) (relative intensity) 111 (39, MH^+), 93 (100), 51 (34).

(2R)-2-((S*)-3-Bromopropa-1,2-dien-1-yl)tetrahydrofuran **46** and (2R*)-2-((R*)3-Bromopropa-1,2-dien-1-yl) tetrahydrofuran **47**[42]*

A solution of **45** (205 mg, 1.86 mmol, 1.0 equiv.) and (*S*)-TCPT catalyst (163 mg, 0.185 mmol, 0.10 equiv.) in CH_2Cl_2 (20 mL) was dried by stirring over 4-Å molecular sieves (7 h), then cooled to −78°C and a suspension of NBS (330 mg, 1.85 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) added via syringe pump over 5 min. The solution was stirred at −78°C (3 h), then quenched with a solution of sodium sulfite (5 % w/v in H_2O, 10 mL) and allowed to warm to room temperature. The mixture was filtered, then partitioned between water (50 mL) and ethyl acetate/hexanes 1 : 1 (10 mL). The aqueous partition was extracted with ethyl acetate/hexanes 1 : 1 (2 × 10 mL) and the organic extracts combined with the organic partition of the reaction mixture and washed with water (2 × 100 mL), brine (100 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/light petroleum 1 : 9) gave a slightly yellow oil consisting of equal proportions of **46** and **47** (288 mg, 82 %). R_f 0.53 (light petroleum/ether 7 : 3). *Compound **46***: δ_H (300 MHz, $CDCl_3$) 6.03 (1H, dd, *J* 5.7 1.9), 5.42 (1H, dd, *J* 5.7 5.4), 4.52–4.56 (1H, m), 3.75–3.90 (2H, m), 2.02–2.14 (1H, m), 1.87–2.00 (2H, m), 1.71–1.86 (1H, m). δ_C (75 MHz, $CDCl_3$) 201.3 (C), 102.4 (C), 75.7 (CH), 68.3 (CH_2), 31.5 (CH_2), 25.5 (CH_2). *Compound **47***: δ_H (300 MHz, $CDCl_3$) 6.04 (1H, dd, *J* 5.7 1.6), 5.40 (1H, dd, *J* 5.9 5.7,), 4.52–4.56 (1H, m), 3.75–3.90 (2H, m), 2.02–2.14 (1H, m), 1.87–2.00 (2H, m), 1.71–1.86 (1H, m). δ_C (75 MHz, $CDCl_3$) 201.2 (C), 102.8 (C), 75.1 (CH), 73.9 (CH), 68.2 (CH_2), 31.5 (CH_2), 25.3 (CH_2). *m/z* (EI) (relative intensity) 158 (8), 156 (7), 71 (100).

Catalyst Recycling

The yield for the installation of the phosphoramidite moiety is higher than in our previous report.[11,12] Rather than the standardised workup employed for comparative purposes in our study of structure–activity, here we desired simply to maximise production of the desired phosphorus(III)-centred catalyst **17**. To this end, the crude mixture was diluted with ethyl acetate to precipitate pyrrolidinium chloride, filtered under a flow of nitrogen, volatile components removed under vacuum, and a toluene solution of the residue immediately subjected to column chromatography (WARNING: the highly exothermic adsorption on silica of this mixture can be mitigated by using a buffer of alumina above the main silica column. Dichloromethane is unsuitable for loading this crude mixture onto a chromatographic medium. Toluene is preferred.)

Supplementary Material

Copies of NMR spectra of compounds **18**, **19**, **28**, **42**, **43**, **46**, and **47** are available on the Journal's website.

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