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# Phosphine organocatalysis in the synthesis of natural products and bioactive compounds.

Catherine Gomez, Jean-François Betzer, Arnaud Voituriez and Angela Marinetti<sup>\*[a]</sup>

*During the last few years, synthetic methods based on phosphine organocatalysis have experienced extremely fast developments. This short overview is intended to demonstrate that these methods can afford suitable tools for the constitution of either focused or DOS inspired libraries of small molecules for biological screening. It also reports selected examples where these organocatalytic methods have been used conveniently as key steps in the formal or total synthesis of complex natural products. Especially, synthetic applications of the inter- and intramolecular cyclizations of unsaturated substrates have been considered in this review.*

## Introduction

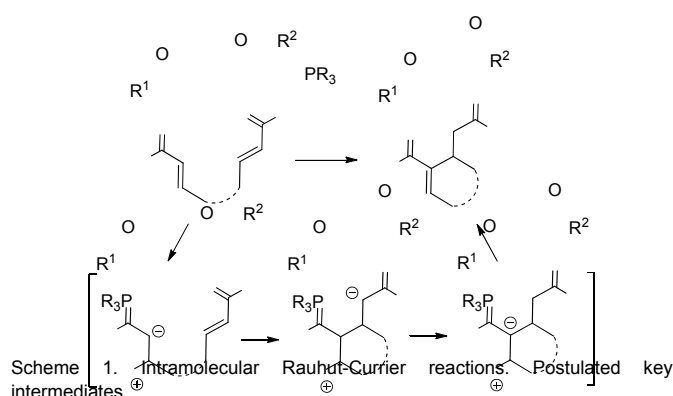
Phosphine organocatalysis has received increasing attention in recent years, most notably because it represents an efficient and practical method to build densely functionalized cyclic compounds from simple and easily available starting materials.<sup>[1]</sup>

This review is intended to demonstrate the synthetic potential of nucleophilic phosphine organocatalysis by highlighting selected applications (a) as key steps in the synthesis of complex natural products, (b) as tools for the synthesis of large libraries of bioactive compounds for pharmaceutical applications, (c) in the synthesis of core structures of natural products and analogues.

From this overview, it appears that despite the supposedly low handiness of trivalent phosphorus derivatives, phosphine catalysis is perfectly suited to the development of fine chemistry processes.

## Rauhut-Currier reactions

The so-called Rauhut-Currier reaction (or vinyllogous Morita-Baylis-Hillman reaction) has been disclosed initially as a practical method for the dimerization of electron-deficient olefins, such as acrylonitrile or acrylates, in the presence of nucleophilic phosphorus catalysts.<sup>[2]</sup> Its intramolecular variant shown in Scheme 1 generates cyclic olefins from 1,n-dienes (n=5,6) activated by electron-withdrawing groups.<sup>[3]</sup> The phosphorus catalyst is assumed to add to one of the olefin functions. The resulting zwitterionic intermediate will undergo then an intramolecular conjugate addition to the second Michael acceptor. Finally, a proton transfer and the subsequent elimination of the phosphine complete the catalytic cycle.



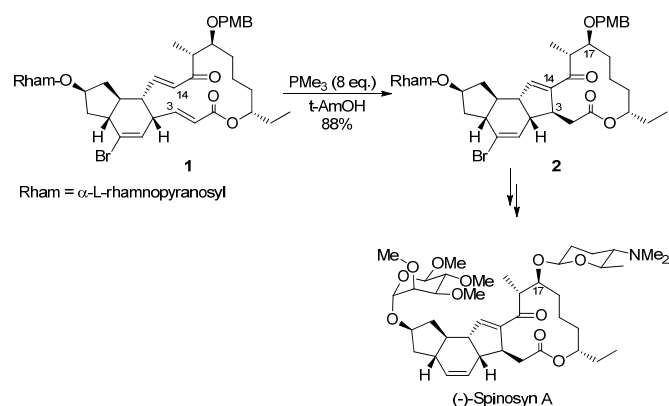
From the very beginning this intramolecular reaction has been proposed as a key step in the synthesis of natural products, as illustrated hereafter.

## Total synthesis of natural products

The Rauhut-Currier reaction has been proposed by Roush as a key step in the retrosynthetic pathway to **(-)-spinosyn A**, a polyketide natural product with insecticidal activity.<sup>[4]</sup> The tricyclic *as*-indacene core of **spinosyn A** has been built by a reaction sequence involving at first a transannular Diels-Alder reaction to create the cyclohexene moiety. Then, an intramolecular Rauhut-Currier reaction was used to form the fused five-member ring of the tricyclic nucleus, as shown in Scheme 2. Thus, treatment of **1** with  $\text{PMe}_3$  in *tert*-amyl alcohol resulted in the stereoselective

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formation of the C<sub>3</sub>-C<sub>14</sub> bond. The cyclization afforded a 95:5 mixture of epimers with opposite configurations at C<sub>3</sub>, the desired stereoisomer **2** being the major one. In optimized conditions a large excess (8 equivalents) of PMe<sub>3</sub> was used to accelerate the cyclization reaction and thereby minimize the main side-reaction, that is an alkoxide induced olefin migration.

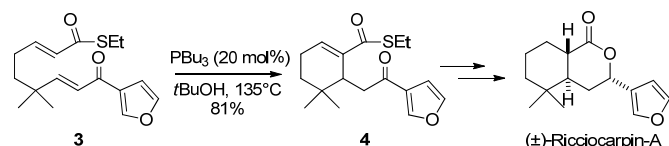


Scheme 2. Synthesis of (-)-Spinosyn A through an intramolecular Rauht-Currier reaction.

The total synthesis of (-)-spinosyn A was completed then by removal of the bromine substituent and installation of the forosamine unit at C(17)-OH. The synthesis involved 23 steps in the longest linear sequence and proceeded in 3% overall yield.

In further studies Roush applied an analogous Diels-Alder/Rauht-Currier reaction sequence to the assembly of the as-indacene ring system of FR182877, a new antimetabolic agent isolated from a strain of *Streptomyces*.<sup>[5]</sup>

Another synthetic target has been **ricciocarpin-A**, a potent molluscicidal, isolated from the liverwort *Ricciocarpus natans*, which has attracted attention for fighting against tropical human parasitic diseases. Its core structure contains a six member ring that Krische envisioned to build by means of a phosphine-promoted Rauht-Currier reaction on the enone/thienoate substrate **3** (Scheme 3).<sup>[6]</sup> The reaction takes place under PBu<sub>3</sub> catalysis at a 20 mol% catalyst loading, giving 81% yield of the desired cyclohexene **4**. The presence of the thienoate function is crucial here to ensure good chemoselectivity and high yields in the Rauht-Currier reaction, with respect to analogous reactions involving substrates with enoate or enal type functions.



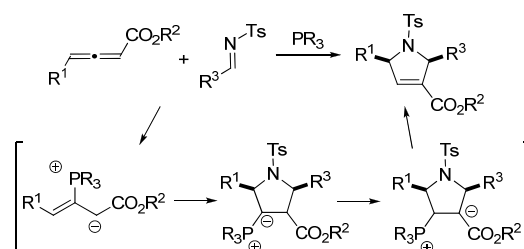
Scheme 3. Total synthesis of Ricciocarpin-A, involving an intramolecular Rauht-Currier reaction as the key step.

After this cyclization step, the total synthesis of ricciocarpin-A has been achieved by a concise, two step sequence involving a reduction/lactonisation process (NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 55% yield) followed by a diastereoselective reduction of the intracyclic olefin function (NaBH<sub>4</sub>, Py, 25°C, 78% yield).

This method is particularly convenient since the unsymmetrical starting diene already incorporates all carbons of the ricciocarpin-A skeleton.

### [3+2] and [4+2] cyclizations on imines

The phosphine catalysed [3+2] annulations of aldimines with allenates or substituted alkynoates have been introduced by Xiyun Lu as an efficient synthetic approach to highly functionalized 3-pyrrolines.<sup>[7]</sup> PBu<sub>3</sub> and PPh<sub>3</sub> are suitable catalysts at a catalyst loading of 10-20 mol%. They operate via an initial activation of the allene or the alkyne substrates, as typified in Scheme 4.



Scheme 4. Phosphine catalyzed [3+2] annulations of allenates with imines.

The method has been applied to allenic esters and ketones, that were combined with *N*-tosyl, *N*-phosphoryl and *N*-thiophosphorylimines. Starting from  $\gamma$ -substituted allenates (R<sup>1</sup>≠H) or alkynes, these reactions proceed with high diastereoselectivity, leading to *syn*-2,5-disubstituted pyrrolines as the major products. Enantioselective variants are also known.<sup>[8]</sup>

More recently Kwon has shown that starting from  $\alpha$ -substituted allenates, the reaction with imines under phosphine catalysis also enables the diastereoselective synthesis of tetrahydropyridines via the formal [4+2] cycloadditions illustrated in Scheme 5.<sup>[9]</sup>



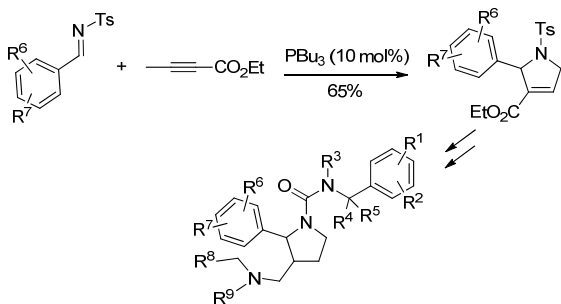
Scheme 5. Phosphine catalyzed [4+2] annulations of allenates with imines

The catalytic methods in Scheme 4 and Scheme 5 have been successfully applied so far to both targeted syntheses of bioactive compounds with pyrroline or tetrahydropyridine substructures, and diversity oriented syntheses. Selected examples are shown hereafter.

### Synthesis of bioactive pyrrolines and tetrahydropyridines

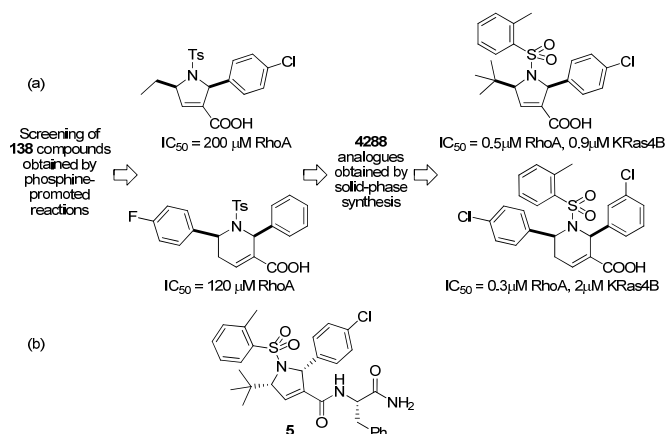
A series of pyrrolidine derivatives possessing neurokinine inhibitory properties have been patented by Pfizer.<sup>[10]</sup> The key step of their synthesis is a [3+2] cycloaddition reaction between *N*-tosylimines and ethyl but-2-ynoate, catalyzed by 10 mol% of tributylphosphine. These reactions, shown in Scheme 6, have been carried out at a 0.25 mol scale (30 mL ethyl butynoate). Subsequent functional group transformations have afforded the

desired pyrrolidines as racemic compounds. The required enantiopure compounds have been accessed by separation of suitable intermediates by chiral HPLC.



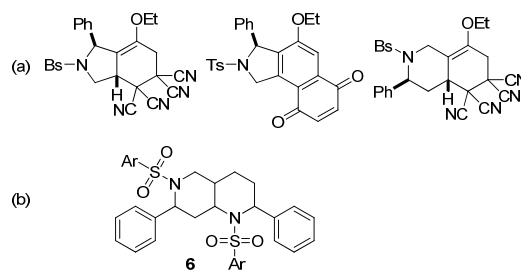
Scheme 6. Synthesis of neurokinine inhibitors by phosphine catalyzed [3+2] annulations of ethyl but-2-ynoate with tosylimines.

By taking advantage of analogous [3+2] and [4+2] cyclizations between allenates, or butynoates, and imines, Kwon developed a combinatorial library of nitrogen heterocycles. These compounds were screened as inhibitors of protein geranylgeranyltransferase type I (GGTase-I).<sup>[11]</sup> At first 138 heterocycles were produced and tested. In a second time, 4288 analogues were obtained by solid-phase synthesis. Two of these molecules inhibit the GGTase I of geranylgeranylate RhoA and K-Ras4B, with submicromolar IC<sub>50</sub> values (scheme 7a). After further screening and improvement of the molecular backbone, Tamanoi and Kwon have highlighted the highly promising pyrroline **5** which inhibits GGTase-I activity, blocks protein geranylgeranylation and induces tumor inhibition in human pancreatic cancer xenograft models (scheme 7b).



Scheme 7. Libraries of pyrroline/tetrahydropyridine derivatives screened as GGTase-I inhibitors.

A diversity-oriented-synthesis (DOS) approach led Kwon to also synthesize multicyclic tetrahydropyridines by phosphine-catalyzed cycloaddition reactions, followed by Tebbe and Diels-Alder reactions (Scheme 8a).<sup>[12]</sup> Some of these molecules inhibit the migration and invasion of breast cancer and might serve for the development of antimetastatic agents.



Scheme 8. Examples of potential anticancer compounds obtained by phosphine-promoted cyclizations.

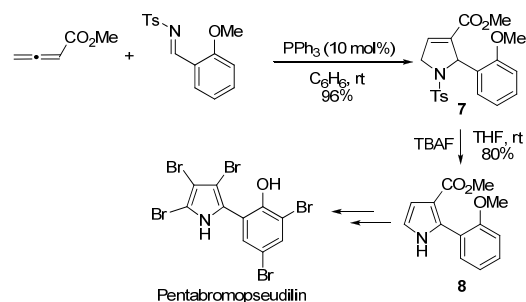
Finally, a DOS strategy based on phosphine-catalyzed cyclizations has been applied also to the search of new activators of endothelium-driven immunity. Among the 642 compounds synthesized, octahydro-1,6-naphthyridin-4-ones (see **6** in scheme 8b) have been identified as a new group of small molecules displaying the desired activity.<sup>[13]</sup>

Generally speaking, the Kwon's and Pfizer's studies mentioned in this section demonstrate the suitability of phosphine organocatalysis to DOS approaches, as well as to the constitution of large libraries of small molecules for biological screening. Extremely varied structures can be obtained quickly, without the use of special equipment or particular knowledge.

### Formal or total synthesis of natural products

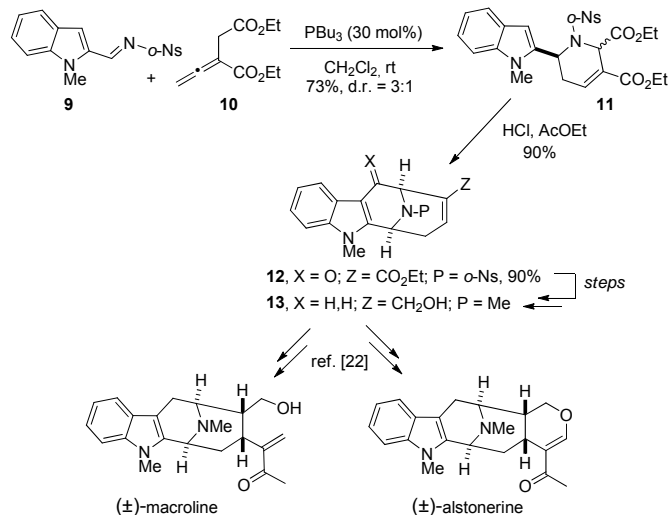
The [3+2] cycloadditions between allenates or propiolates and imines shown in Scheme 4 have been applied to the synthesis of natural products, as shown hereafter.

One of the very first examples is the Lu's synthesis of **pentabromopseudilin**,<sup>[14]</sup> a marine antibiotic isolated from *Pseudomonas bromoutiliz*, *Chromobacteria* and *Alteromonas luteoviolaceus*. The nitrogen heterocycle **7** was obtained in 96% yield from methyl 2,3-butadienoate and *N*-tosyl-2-methoxybenzalimine under PPh<sub>3</sub> catalysis. Treatment of the 3-pyrroline **7** with tetra-*n*-butyl ammonium fluoride induced a tandem desulfination-dehydrogenation reaction affording the pyrrole unit **8**. A sequence involving hydrolysis of the ester moiety and subsequent decarboxylation, followed by demethylation (Na<sub>2</sub>S, NMP) and bromination (Py.HBr<sub>3</sub> in EtOH) led to the desired pentabromopseudilin in 26% yield for the four step sequence.



Scheme 9. Synthesis of Pentabromopseudilin by phosphine-catalyzed [3+2] cycloaddition between allenates and imines.

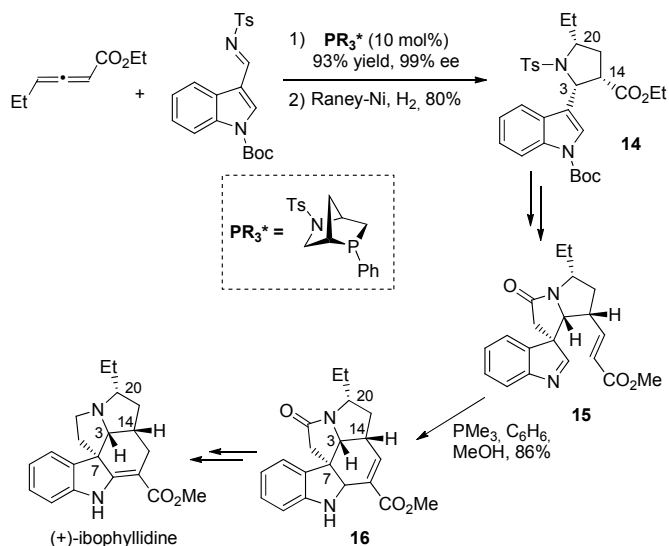
In 2005 Kwon had envisioned the phosphine-triggered [4+2] annulation of  $\alpha$ -substituted 2,3-butadienoates with imines (Scheme 5) as an entry into macroline indole alkaloids, including **( $\pm$ )-macroline** and **( $\pm$ )-alstonerine** (Scheme 10).<sup>[15]</sup> These indole alkaloids were isolated from the root bark of *Alstonia* and exhibit a wide range of biological activities such as hypotensive, anti-amoebic, antimalarial and cytotoxic properties.



Scheme 10. Formal Syntheses of ( $\pm$ )-macroline and ( $\pm$ )-alstonerine via a phosphine-catalyzed [4+2] annulation.

The phosphine-promoted [4+2] cyclization is the initial step of the reaction sequence leading to the polycyclic core structure of these alkaloids. The 2-indolylimine **9** reacts with the  $\alpha$ -substituted 2,3-butadienoate **10** upon exposure to a catalytic amount of tributylphosphine (30 mol%). The reaction affords the functionalized tetrahydropyridine **11** in 73% yields as a 3:1 mixture of diastereomers. The mixture was treated with HCl in order to induce epimerization of the carbon center bearing the ester function and concomitant intramolecular Friedel-Crafts acylation of the indole ring. This process gives the bridged bicycle **12** in 90% yield. This compound was transformed then into the key intermediate **13** ( $Z = \text{CH}_2\text{OH}$ ,  $P = \text{Me}$ ) by the following sequence: (i) Fukuyama's denosylation; (ii) *N*-methylation by the Eschweiler-Clarke reaction; (iii) deoxygenation with  $\text{ZnI}_2$ - $\text{NaBH}_3\text{CN}$ ; (iv) reduction of the ester with DIBAL. Previous work from Cook has shown that further manipulations of this common intermediate **13** can produce both ( $\pm$ )-macroline and ( $\pm$ )-alstonerine.<sup>[16]</sup>

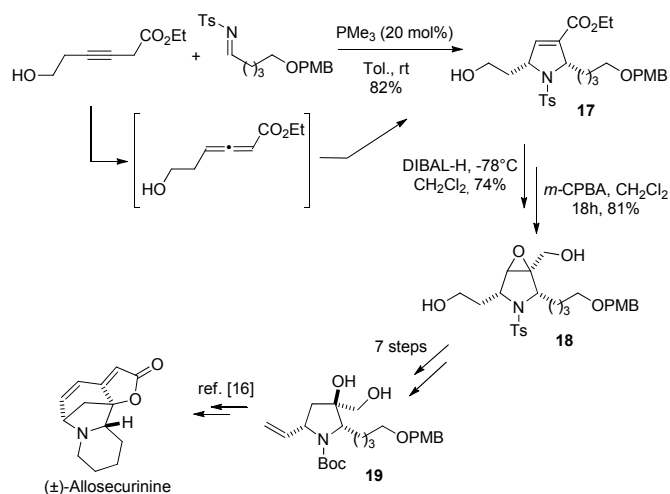
More recently, Kwon<sup>[17]</sup> has reported an efficient enantioselective total synthesis of **(+)-ibophyllidine**, a fused pentacyclic indole alkaloid, originally isolated from the plant *Tabernaemontana iboga*. The synthetic procedure involves two distinct phosphine promoted reactions allowing formation of the pyrrolidine and cyclohexene rings respectively. The key step is the asymmetric [3+2] annulation between a  $\gamma$ -substituted allenolate and a tosyl imine bearing an indole moiety, as shown in Scheme 11.



Scheme 11. Asymmetric total synthesis of (+)-ibophyllidine.

This annulation reaction proceeded extremely well, on a multigram scale, in the presence of the chiral bicyclic phosphine shown in Scheme 11. It delivered the desired 3-pyrroline in very high yield, diastereoselectivity and enantioselectivity (93% yield, *syn*-isomer, 99% ee, at a 10% catalyst loading). The phosphorus catalyst is a novel *trans*-L-4-hydroxyproline derived phosphine that has been specifically designed and prepared by the same authors. The enantiomerically pure pyrroline was subjected to diastereoselective hydrogenation of the double bond, under Raney-Ni catalysis, to deliver the all-*syn*-pyrrolidine **14** in 80% isolated yield, with total stereocontrol. The key intermediate **14** was transformed then into the spirocyclic indolenine derivative **15** in six steps. At this point, a second phosphine promoted process, that is an intramolecular  $\text{PMe}_3$  promoted aza-Morita-Baylis-Hillman reaction, has been implemented for building the six-member ring of **16** (86% yield). This unique pathway successfully addresses the challenges of synthesis and stereocontrol of the pentacyclic ibophyllidine framework in 15 steps and 13% overall yield.

The versatility and efficiency of phosphine promoted [3+2] cycloadditions on aldimines has been illustrated by Loh with the formal synthesis of **( $\pm$ )-allosecurinine** (Scheme 12).<sup>[18]</sup> *Allosecurinine* is a *Securinega* alkaloid, isolated from plants of the *Euphorbiaceae* family, which display antimalarial, antibiotic and antifungal properties. The [3+2] cycloaddition between 3-alkynoates and imines was used for the synthesis of the suitably functionalized, *syn*-2,5-disubstituted 3-pyrroline **17**. In this case trimethylphosphine promotes both the isomerization of the alkyne into a  $\gamma$ -substituted allenolate and the subsequent [3+2] cycloaddition reaction. This *in situ* isomerization of easily available alkynes avoids the more complicated preparation of the  $\gamma$ -substituted allenolates. The cyclization reaction takes place with total control of the relative stereochemistry of the stereogenic carbons of **17** (82% isolated yield, as the single *syn*-diastereomer).

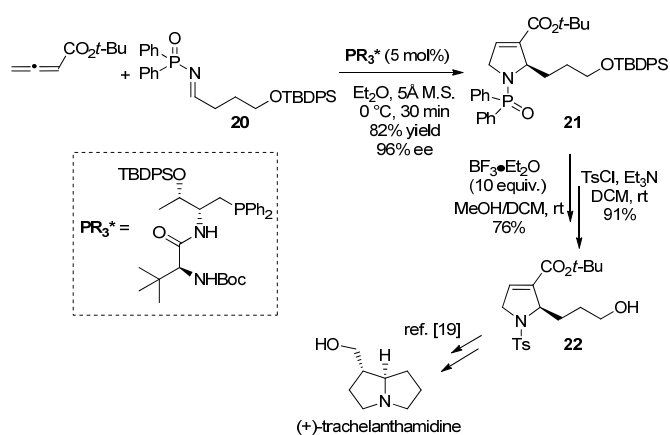


Scheme 12. Formal synthesis of (±)-Allosecurinine.

In the subsequent steps of the synthesis, Loh has taken advantage of the insaturation of pyrroline to introduce a third stereogenic center, *via* epoxide **18**. The regioselective opening of the epoxide followed by a few subsequent steps of functional group transformation, delivered the key intermediate **19**. The synthesis of allosecurinine from pyrrolidine **19** had been described by Kerr in 2008.<sup>[19]</sup>

In 2012, Yixin Lu *et al.* have adapted the [3+2] cyclization methodology to the enantioselective, formal synthesis of the pyrrolizidine alkaloid **(+)-trachelanthamidine** (Scheme 13).<sup>[20]</sup> Beside enantiocontrol, the major challenge of this work was to enable aliphatic imines to undergo stereoselective cyclizations. To this end, a very effective chiral catalyst, a dipeptide-based bifunctional phosphine shown in Scheme 13 was designed which afforded the desired pyrrolines at low temperature, in a very short reaction time. The cycloadducts were obtained in good yields, with high enantioselectivities (95-99% ee).

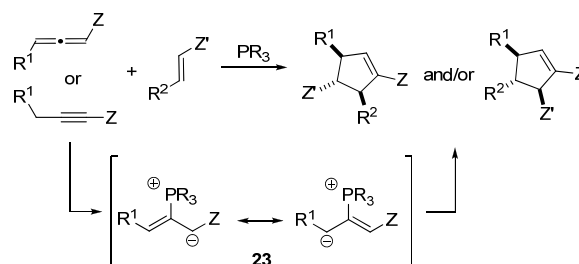
For the formal synthesis of **(+)-trachelanthamidine**, the [3+2] cyclisation has been carried out on the *N*-diphenylphosphinoyl protected imine **20** to afford the corresponding 3-pyrroline **21** in 82% yield and 96% ee. The *N*-diphenylphosphinoyl group was removed by treatment with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  and the subsequent installation of a tosyl group led to pyrroline **22**, a known intermediate in the total synthesis of trachelanthamidine.<sup>[21]</sup>



Scheme 13. Formal synthesis of **(+)-trachelanthamidine** *via* enantioselective [3+2] cyclisation between an *N*-diphenylphosphinoyl imine and *t*-butyl allenolate.

## [3+2] cyclizations on olefins

Since 1995, the [3+2] annulations of electron-deficient olefins and allenes or alkynes, under phosphine catalysis, have been known as suitable approaches to functionalized cyclopentenes.<sup>[22]</sup> Starting from both allenes and alkynes, the process supposedly involves the same zwitterionic phosphonium salts **23** generated by nucleophilic addition of the phosphine to the  $\beta$ -carbon of the allene, or by addition to the alkyne and subsequent proton shift. These intermediates give Michael type additions through either their  $\alpha$ - or  $\gamma$ -carbons, leading to the isomeric  $\alpha$ - and  $\gamma$ -adducts respectively.

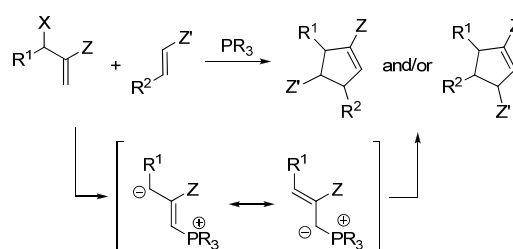


Scheme 14. Synthesis of cyclopentenes *via* [3+2] cyclizations on allenes or alkynes.

As a general trend,  $\alpha$ -addition is preferred in the case of monosubstituted and 1,1,2-trisubstituted olefins, while acyclic 1,2-disubstituted olefins mainly afford  $\gamma$ -adducts.

The method has been adapted to the stereoselective synthesis of non-natural cyclic aminoacids, or polycyclic core-structure of natural products as well as to total syntheses.

An alternative approach to cyclopentene derivatives is the [3+2] cyclization between olefins and allylic halides or carbonates under phosphine catalysis (Scheme 15).<sup>[23]</sup>

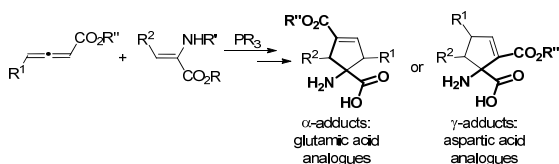


Scheme 15. Synthesis of cyclopentenes *via* [3+2] cyclizations involving allylic substrates.

This method has been applied notably to the synthesis of spirocyclic oxindoles, a key core structure found in some series of natural products.

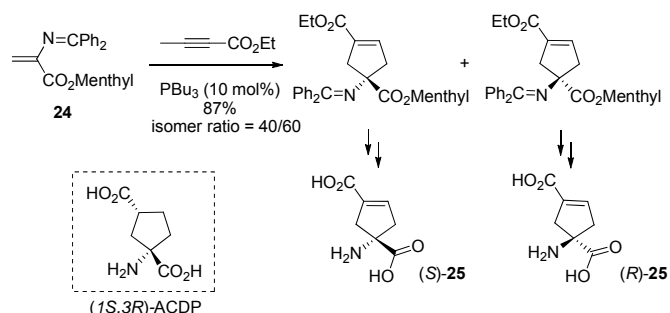
## Synthesis of non-natural analogues of natural products

The phosphine-promoted [3+2] cyclizations above have been adapted to the synthesis of non-natural  $\alpha$ -aminoacids. By starting from allenolates and dehydroaminoacids as olefinic partners,  $\alpha$ -adducts will afford cyclic glutamic acid analogues while  $\gamma$ -adducts will produce aspartic acid analogues (Scheme 16).



Scheme 16. Constrained amino acid analogues via [3+2] cyclization.

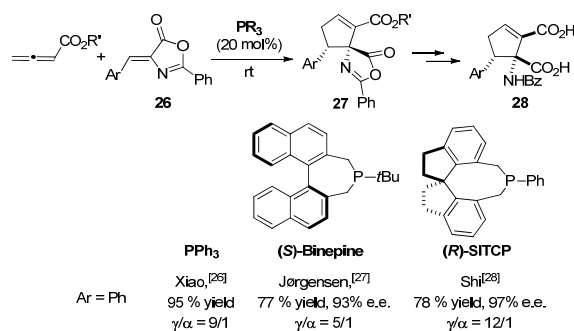
In this field, the pioneering work of Pyne has targeted conformationally restricted *L*-glutamate analogues. Inspired by the known potential of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACDP) as therapeutic agent for the treatment of neurodegenerative diseases, Pyne synthesized a dehydroanalogue as well as some 5-substituted derivatives under phosphine catalysis.<sup>[24]</sup>



Scheme 17: Synthesis of conformationally restricted *L*-glutamate analogues.

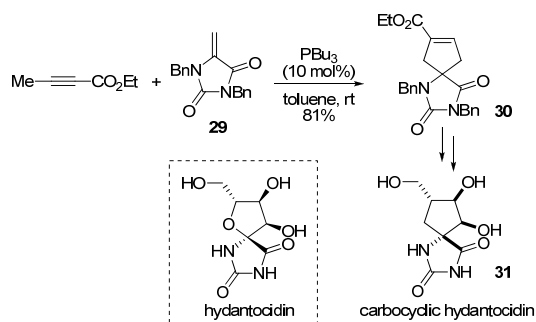
Cyclisation between the *l*-menthyl 2-aminoacrylate derivative **24** and ethyl but-2-ynoate gave exclusively the  $\alpha$ -adducts in 87% yield and a 40/60 diastereomers ratio (Scheme 17). Separation of individual diastereomers by preparative HPLC and further chemical transformations afforded enantiomerically pure samples of the desired cyclopentenyl derivatives **25**. (*S*)-**25** proved to be a relatively potent agonist for mGlu5 ( $EC_{50}$  =  $18 \pm 6$   $\mu$ M) and mGlu2 ( $EC_{50}$  =  $45 \pm 10$   $\mu$ M) receptors.

Cyclic analogues of aspartic acid have been prepared by Xiao and Chen<sup>[25]</sup> via the triphenylphosphine-promoted [3+2] cycloaddition of 2-phenyl-4-arylidene-5(4*H*)-oxazolones **26** with allenolate. Generally good yields, high diastereoselectivity and regioselectivities in favour of the  $\gamma$ -adduct were obtained (Scheme 18). Efficient enantioselective variants were developed later by the groups of Jørgensen<sup>[26]</sup> and Shi<sup>[27]</sup> independently. (*S*)-*t*-Bu-Binepine and (*R*)-SITCP afforded the desired oxazolones **27** in up to 95% and 99% e.e. respectively. These products could be easily transformed in the corresponding conformationally restricted cyclopentenyl aspartic acid analogues **28**.



Scheme 18: Synthesis of cyclic analogues of aspartic acid by [3+2] cycloaddition reactions.

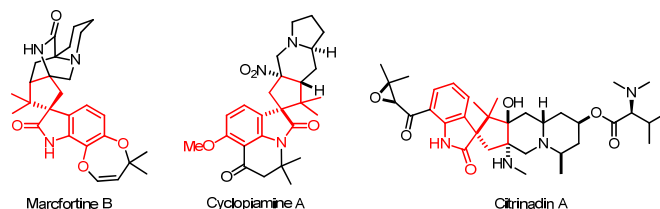
In a different application, the phosphine-catalyzed [3+2] cycloaddition of ethylbutynoate to 5-methylenehydantoin **29** allowed Pyne to prepare **carbocyclic analogues** of the potent herbicide **hydantocidin** (Scheme 19).<sup>[28]</sup> In the cyclization step, under tributylphosphine catalysis, the desired  $\alpha$ -regioisomer of the spirocyclic product **30** was obtained in 81% yield. Seven additional steps furnished the carbocyclic hydantocidin derivative **31** in racemic form, with moderate control of the diastereoselectivity.



Scheme 19: Carbocyclic analogues of the potent herbicide hydantocidin.

## Synthesis of core substructures of natural products

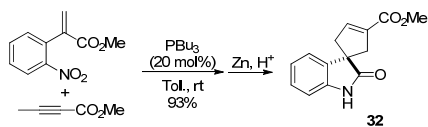
The **spiro-cyclopentene-2-oxindole** backbone is present in numerous natural product and drug candidates (for relevant examples, see Scheme 20). For their synthesis, initial studies from Pyne have envisioned a multistep procedure, while, in the last few years, several research groups have developed efficient one-step syntheses.



Scheme 20: Natural products with spiro-cyclopenteneoxindole core structures.

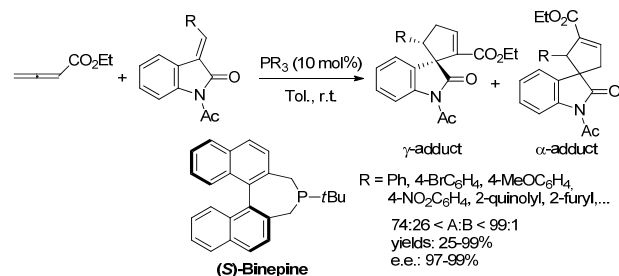
The Pyne's approach involves a tributylphosphine-catalyzed [3+2] cycloaddition between 2-(2-nitrophenyl)propenoate and 2-butynoate, followed by a reductive cyclization reaction. The

corresponding spirooxindole derivative **32** was obtained in 90% yield.<sup>[29]</sup> This cycloaddition reaction was also performed with a chiral propiolamide, derived from the Oppolzer's sultame. It gave a 3.3/1 diastereoisomeric ratio in a combined 66% yield.



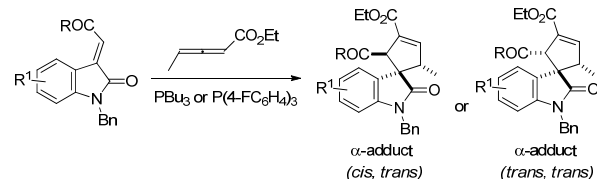
Scheme 21: Two-step synthesis of spirocyclopentene-2-oxindoles.

In 2010 our group developed the first synthetic approach to spirocyclopenteneoxindoles by phosphine-promoted [3+2] cyclization of allenes on arylidene oxindoles (Scheme 22).<sup>[30]</sup> Both racemic and enantioselective procedures have been established, leading to the desired spirocycles in generally good yields, high regioselectivities and high enantioselectivities when (*S*)-*t*-Bu-Binaphthylphosphine was used as the chiral catalyst (up to >99% e.e.).



Scheme 22: Enantioselective [3+2] cyclization of allenes on arylidene oxindoles.

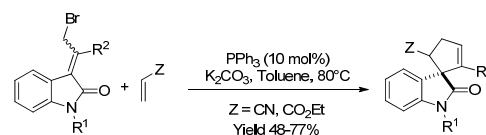
The same strategy has been extended by Min Shi to the synthesis of spiro-cyclopentene-2-oxindoles with trisubstituted cyclopentene moieties, by starting from a  $\gamma$ -substituted allene, i.e. ethyl penta-2,3-dienoate (Scheme 23).<sup>[31]</sup>



Scheme 23: [3+2] cyclization of ethyl penta-2,3-dienoate on 2-oxoethylidene-indolin-2-ones.

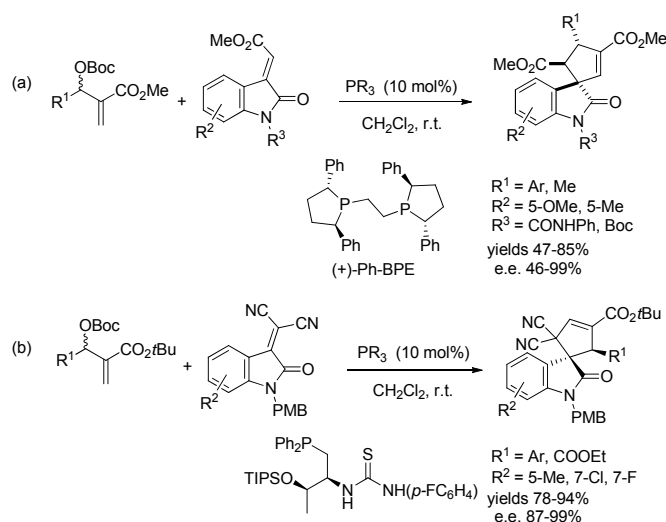
The  $\alpha$ -adducts were obtained as mixtures of two diastereomers, with opposite relative configurations of the quaternary carbon at the ring junction and the adjacent CH(COR) carbon. The diastereoselectivity of these reactions proved to be controlled by the nature of the phosphorus catalyst: PBU<sub>3</sub> gave mainly the *cis-trans* isomer, while P(4-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> afforded the *trans-trans* isomer with >20:1 isomer ratios in most cases.

The synthesis of the spiro-cyclopentene-2-oxindoles by [3+2] cycloaddition of olefins with allylic bromides has been reported initially by Shanmugam (Scheme 24).<sup>[32]</sup> Isatin derived allylic bromides were reacted with ethyl acrylate or acrylonitrile to give the desired 3-spirocyclopenten-2-oxindoles in moderate to good yields as single isomers.



Scheme 24: [3+2] cycloaddition reactions of allylic bromides.

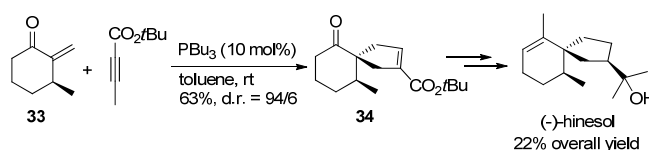
The alternative strategy which consists in reacting an isatin derived olefin with an allylic carbonate has been implemented later by Barbas and Shi. Barbas obtained spirocyclopentene-2-oxindoles derivatives by cycloaddition between Morita-Baylis-Hillman carbonates and 2-oxindolin-3-ylidene acetates. Excellent yields, regioselectivities and enantioselectivities were attained with Ph-BPE as the catalyst (Scheme 25a).<sup>[33]</sup> Independently Shi<sup>[34]</sup> and Lu<sup>[35]</sup> reported analogous cyclizations involving 2-(2-oxindolin-3-ylidene)malononitriles. By using an *L*-threonine-derived chiral phosphine, Lu obtained the 3-spirocyclopenten-2-oxindoles in high yields, moderate to high regioselectivities (1:1 to 25:1 isomers ratios) and ee.s up to 99% (Scheme 25b).



Scheme 25: Spirooxindoles by enantioselective [3+2] cycloadditions of allylic carbonates.

## Formal or total synthesis of natural products

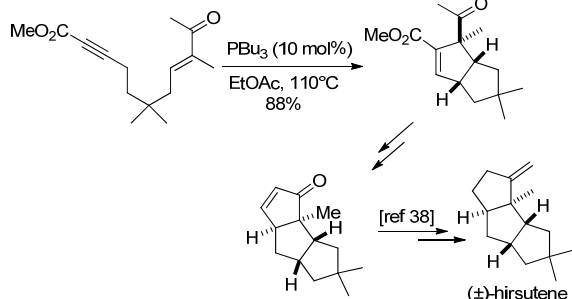
The [3+2] cyclization between olefins and alkynes has been applied to the formal or total synthesis of a few natural products. X. Lu and Y. Du realized the first total synthesis of (*-*)-hinesol, an active ingredient of cerebral circulation and metabolism improver, by a Bu<sub>3</sub>P-catalyzed [3+2] cyclization of (*S*)-3-methyl-2-methylenecyclohexanone **33** with *tert*-butyl 2-butynoate (Scheme 26).<sup>[36]</sup> In this key step, the desired spiro-carbocycle **34** was obtained in 63% yield, with high regio- and diastereoselectivity (d.r. = 94/6). Finally, (*-*)-hinesol was synthesized in 10 total steps and 22% overall yield from 2-cyclohexenone.



Scheme 26: Total synthesis of (*-*)-hinesol.

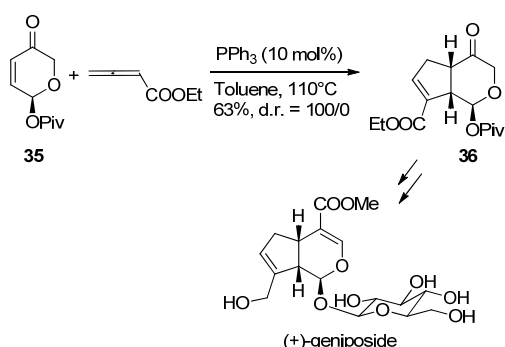


Krische and Wang have developed a formal synthesis of ( $\pm$ )-**hirsutene** based on an intramolecular phosphine-promoted [3+2] cyclisation reaction (Scheme 27).<sup>[37]</sup> This key step occurred in 88% yield with total control of the relative stereochemistry of the three contiguous stereogenic centers. After that, an advanced precursor of hirsutene<sup>[38]</sup> was obtained in 4 steps.



Scheme 27: Formal synthesis of ( $\pm$ )-hirsutene.

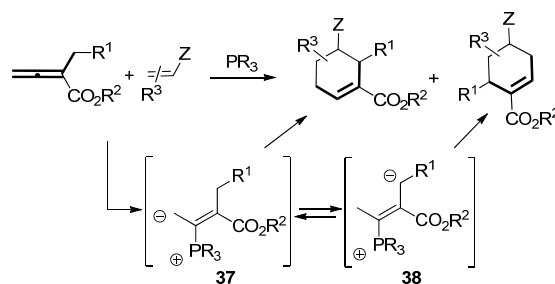
Krische also achieved the asymmetric total synthesis of the iridoid  $\beta$ -glucoside (**+**)-**geniposide**. A diastereoselective phosphine-catalysed [3+2] cyclisation reaction allowed the rapid construction of the *cis*-fused cyclopenta[c]pyran iridoid ring system.<sup>[39]</sup> Indeed, the reaction of ethyl-2,3-butadienoate with (*S*)-5-oxo-5,6-dihydro-2H-pyran-2-yl pivalate **35**, catalyzed by 10 mol% of PPh<sub>3</sub> in toluene at 110°C gave the desired bicycle **36** in 63% yield as a single stereoisomer (Scheme 28). Ten additional steps allowed the synthesis of the (**+**)-geniposide.



Scheme 28: Total synthesis of the iridoid  $\beta$ -glucoside (**+**)-geniposide.

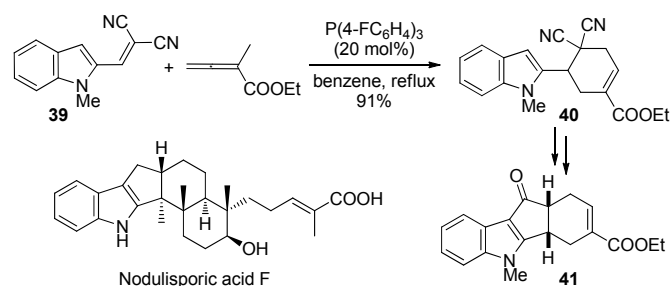
## [4+2] cyclizations on olefins

In 2007, the Kwon's group has disclosed a facile access to cyclohexenes *via* phosphine catalysed [4+2] annulations between electron-poor olefins and  $\alpha$ -substituted allenates.<sup>[40]</sup> In these reactions, the allenate behaves as the four-carbon synthon, due to the involvement of the  $\beta'$ -carbon in the cyclization process. Two different regioisomers can be formed depending on the substrate and the catalyst used. They result from Michael type additions of intermediates **37** and **38**, respectively, to the electron-poor olefin (Scheme 29).



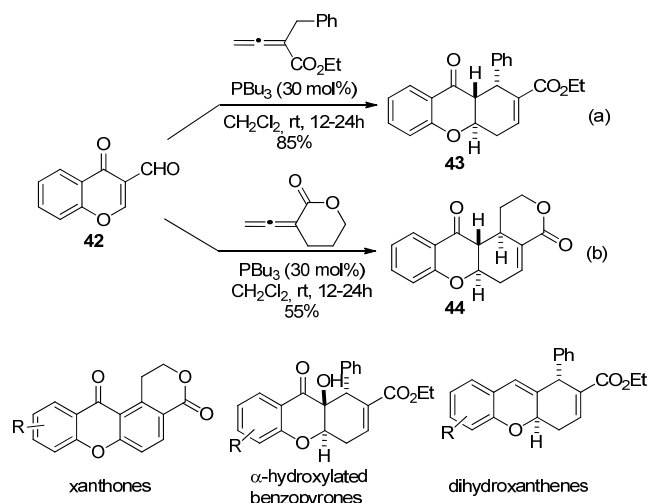
Scheme 29: Synthesis of cyclohexenes *via* [4+2] cyclizations.

The potential utility of these [4+2] annulations for the synthesis of biologically active natural products has been demonstrated by the synthesis of the **tetracyclic framework of Nodulisporic acid F** (Scheme 30).<sup>[40]</sup> A [4+2] annulation of ethyl  $\alpha$ -methylallenoate and the activated *N*-Me-2-indolylidene malononitrile **39** has been carried out in the presence of 20 mol% of phosphorus catalyst. The choice of the catalyst is crucial for an optimal control of the reaction outcome. Indeed the desired product (which results from  $\beta'$ -addition) was obtained preferentially by using a moderately nucleophilic catalyst, namely *tris*-(*p*-fluorophenyl)phosphine. The reaction led to a single regioisomer of cyclohexene **40** in a 91 % isolated yield. Starting from **40**, the tetracyclic framework **41** of the natural compound was accessed *via* an intramolecular Houben-Hoesch reaction, *i.e.* an acid catalysed acylation of the indole subunit.



Scheme 30: Synthesis of the tetracyclic framework of Nodulisporic acid F.

More recently, Kumar has developed a phosphine-catalyzed diastereoselective access to tricyclic and tetracyclic **cyclohexene-fused-chromone rings** that can be further elaborated into natural ring systems.<sup>[41]</sup> For instance, 3-formylchromone **42**, that proved more reactive than chromone itself, could be converted into the tricyclic and tetracyclic benzopyrones **43** and **44** shown in Scheme 31 by a cascade [4+2] annulation-deformylation sequence. In the presence of tributylphosphine (30 mol%), the reaction takes place with high, or total control of the relative configurations of three stereogenic centres.



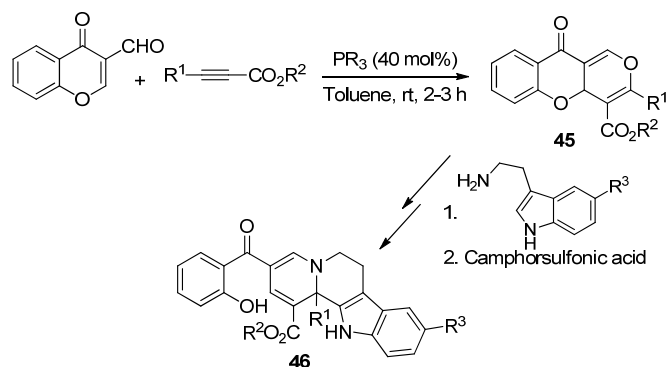
Scheme 31: Cascade synthesis of benzopyrones and related ring systems.

Further elaboration of the cyclization products offers concise accesses to xanthone rings by dehydrogenation, to  $\alpha$ -hydroxylated benzopyrones by oxidation, as well as to dihydroxanthenes via reduction of the keto-function (Scheme 31). Thus, this strategy led to compound collections displaying structural features of natural products, which are oriented mainly toward drug discovery and chemical biology research.

## [4+2] cyclizations between enals and alkynes

Both phosphine and amine organocatalysis also afford a flexible access to **tricyclic benzopyrone** structures, such as **45** (Scheme 32), by [4+2] cyclizations between 3-formylchromones and alkynes.<sup>[42]</sup> Compounds of this class have been reported recently as inhibitors for bacterial metallo- $\beta$ -lactamases and antibiotic candidates. Unlike all other [4+2] cyclizations quoted in this review, this cyclization process involves a four-atom component including an heteroatom, namely the oxygen atom of the formyl function.

The same benzopyrone derivatives **45** served as versatile starting points for multistep reaction cascades leading to tetracyclic **indoloquinolizine** scaffolds which are characteristic of many polycyclic monoterpene.<sup>[43]</sup> Among others, the natural-product inspired indoloquinolizine **46** has been prepared as a new modulator of centrosome integrity with antiproliferative effects on cancer cells.

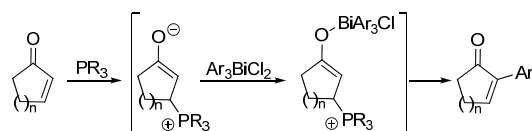


Scheme 32: A cascade synthesis of indoloquinolizines based on a [4+2] annulation on 3-formylchromone.

These results are expected to inspire new drug discovery programs in future works.

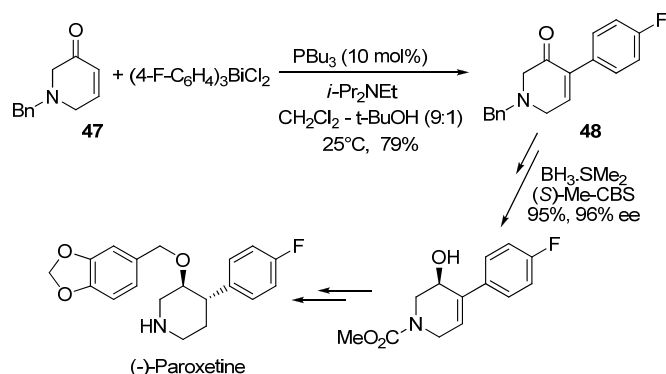
## $\alpha$ -Arylation of enones

The activation of cyclic enones and  $\beta$ -substituted enals by conjugated addition of nucleophilic phosphines has been used by Krische as a suitable strategy for the regioselective  $\alpha$ -arylation of these substrates. Trapping of the phosphonium-enolates by hypervalent aryl-bismuth reagents, followed by aryl transfer to the  $\alpha$ -position affords the desired arylated enone (Scheme 33).<sup>[44]</sup>



Scheme 33: Phosphine catalyzed  $\alpha$ -arylation of enones

The method has been applied as the initial step in the total synthesis of **(-)-paroxetine**, a GlaxoSmithKline antidepressant drug marketed as Paxil (Scheme 34).<sup>[45]</sup>  $\alpha$ -Arylation has been conducted on the dihydropyridinone **47** with triarylbi-muth dichloride, in the presence of tributylphosphine and Hünig's base to afford the desired product **48** in 79% yield. The asymmetric synthesis of (-)-Paroxetine relies then on an oxaborolidine-catalyzed 1,2-reduction of the enone-function as the enantioselective key step (95% yield, 96% ee).



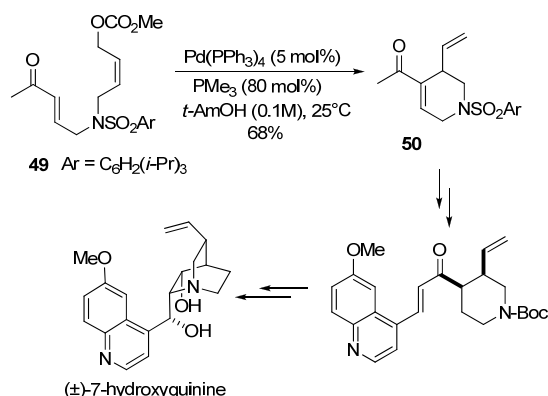
Scheme 34: Total synthesis of (-)-paroxetine.

The synthetic sequence delivers (-)-paroxetine in eight steps, with an overall 21% yield from **48**.

## Phosphine-palladium(0) dual catalysis

Combining transition metal catalysis and organocatalysis enables concomitant activation of two latent reaction partners and allows unprecedented transformations to be achieved. This is typified in Scheme 35 by a dual-catalysis process first reported by Krische in 2004,<sup>[46]</sup> which combines a phosphine-mediated nucleophilic activation of the enone moiety of **49** with a palladium(0)-promoted electrophilic activation of the allylic portion of the same substrate.<sup>[47]</sup> This results in an intramolecular Tsuji-Trost nucleophilic substitution reaction leading to the cyclic derivative **50**. Optimized reaction conditions include the use of  $\text{PMe}_3$  (80

mol%) and Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) as the catalysts. The reaction proceeds at r.t. in *t*-amyl alcohol and delivers **50** in 68% yield.



Scheme 35: Total synthesis of (±)-7-hydroxyquinine.

Compound **50** served as a key intermediate in the total synthesis of (±)-7-hydroxyquinine. *Rac*-7-hydroxyquinine was obtained from **50** in eight steps and 24% overall yield (Scheme 35). This stereoselective route involved less than half the number of steps previously reported for the syntheses of the same quinine derivative. In the Krische's work, an analogous strategy has been applied also to the formal synthesis of (±)-quinine from **50**.

## Summary and Outlook

In summary, recent studies from various research groups demonstrate the potential of phosphine-promoted catalytic reactions, both in the synthesis of complex molecular structures, including chiral species, and in the diversity-oriented synthesis of bioactive compounds.

However, it is worth mentioning that, compared to the known variety of phosphine-promoted processes, only a few of them have been applied so far to such oriented syntheses of specifically targeted compounds. Asymmetric processes are even more underdeveloped, in terms of both methodological studies and synthetic applications. Therefore, new developments in the field of phosphine organocatalysis can be easily anticipated in the near future.

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