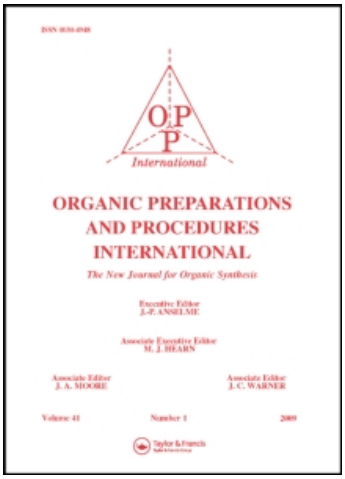


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE PICTET-SPENGLER REACTION: EFFICIENT CARBON-CARBON BOND FORMING REACTION IN HETEROCYCLIC SYNTHESIS

So Won Youn[a]
[a] Department of Chemistry, Pukyong National University, Busan, Republic of KOREA

To cite this Article Youn, So Won(2006) 'THE PICTET-SPENGLER REACTION: EFFICIENT CARBON-CARBON BOND FORMING REACTION IN HETEROCYCLIC SYNTHESIS', Organic Preparations and Procedures International, 38: 6, 505 — 591
To link to this Article: DOI: 10.1080/00304940609356447
URL: http://dx.doi.org/10.1080/00304940609356447

ORGANIC PREPARATIONS AND PROCEDURES INT., 38 (6), 505-591 (2006)

THE PICTET-SPENGLER REACTION: EFFICIENT CARBON-CARBON BOND FORMING REACTION IN HETEROCYCLIC SYNTHESIS

So Won Youn

Department of Chemistry, Pukyong National University
Busan, 608-737, Republic of KOREA
E-mail: sowony@pknu.ac.kr

THE PICTET-SPENGLER REACTION: EFFICIENT CARBON-CARBON BOND FORMING REACTION IN HETEROCYCLIC SYNTHESIS

So Won Youn

Department of Chemistry, Pukyong National University
Busan, 608-737, Republic of KOREA
E-mail: sowony@pknu.ac.kr

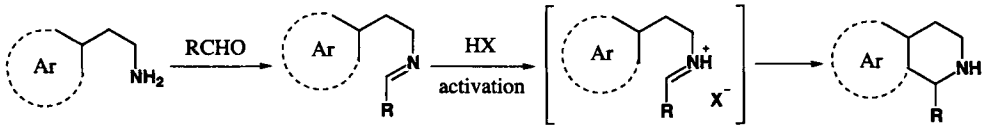
INTRODUCTION

For the last ~100 years, the Pictet-Spengler (P-S) reaction, first reported by Pictet and Spengler in 1911,[1] has been an important reaction for C-C bond formation leading to ring systems referred to as tetrahydroisoquinolines (THIQs) and tetrahydro-β-carbolines (THBCs).[2]

tetrahydroisoquinoline (THIQ) tetrahydro-β-carboline (THBC)

Fig. 1

A typical P-S reaction is a two-step process and involves the condensation of an aliphatic amine (β-arylethylamine or tryptamine) with aldehyde to form an imine, which is most commonly activated by Brønsted acids. Final intramolecular cyclization between a sufficiently reactive, electron-rich aromatic ring and the activated iminium ion results in a *N*-heterocyclic ring *via* a new C-C bond (*Scheme 1*).



Typical Pictet-Spengler Reaction Catalyzed by Bronsted Acid

Scheme 1

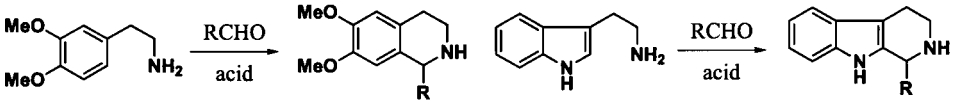
Since its discovery, the P-S reaction has been studied extensively and continues to be a focus of research in total synthesis of natural and unnatural products[3] and in combinatorial applications.[4] The THIQ and THBC ring systems are the core structural moieties of numerous natu-

rally occurring alkaloids as well as synthetic compounds which have interesting medicinal bioactivities, physiological and pharmaceutical effects. Because of the prominent position that the P-S reaction occupies in heterocyclic chemistry, many efforts have been made to improve upon the methodology by applying new reaction conditions, to apply the P-S reaction beyond syntheses of THIQs and THBCs, to develop asymmetric P-S reactions, and to apply it to solid-phase synthesis.

In this review, typical and new synthetic methodologies for the P-S reaction, modification of the traditional procedures, and the synthetic applications of P-S reaction will be discussed.

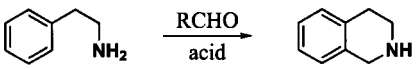
I. BRØNSTED ACID-CATALYZED PICTET-SPENGLER REACTION

The P-S reaction involves the cyclization of electron-rich aryl or heteroaryl groups onto iminium ions generated *in situ* by the condensation of aldehydes with β-arylethylamines. Most often strong Brønsted acids are employed to promote this reaction. Aldehyde-based iminium ion reactions of 3,4-dimethoxyphenethylamine[5] and tryptamine[6] proceed reasonably well, however, the cyclizations of phenethylamine[1, 7] can be difficult with variable results (*Scheme 2*). The P-S



R = H : aq. HCl, 52%; HCO_2H, 87%
R = Ph : H_3PO_4, 71%; CF_3CO_2H, 86%

R = H : aq. H_2SO_4, 65%
R = Me : aq. H_2SO_4, 86%
R = Ph : pH 5.2, 48%; CF_3CO_2H, 64%

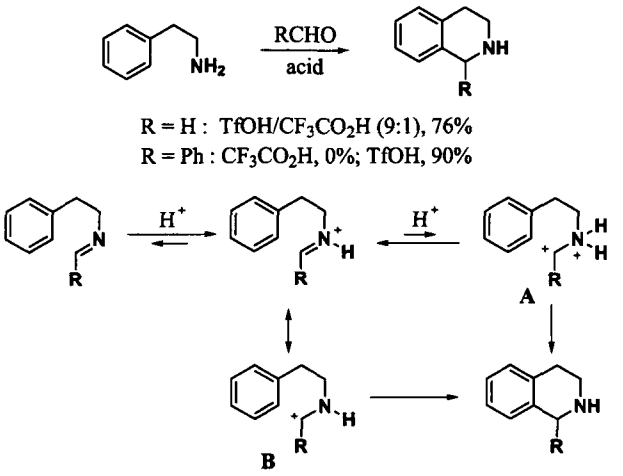


aq. HCl : at 100°C, 36%; at 140°C, trace

Bronsted Acid-Catalyzed Pictet-Spengler Reaction

Scheme 2

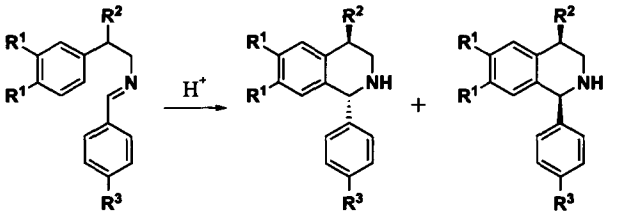
reaction has long been limited to active substrates which bear strongly electron-donating groups such as a methoxy or a hydroxy group on the cyclizing benzene ring. However, Ohwada *et al.* reported superacid-catalyzed P-S reactions of imines of 2-phenethylamine, including the prototype P-S reaction of *N*-methylene-2-phenethylamine, to give the parent and 1-substituted THIQs in moderate to high yields (*Scheme 3*).[8a] The yields are dependent on the acidity of the media. They also found that the prototype cyclization of the parent *N*-methylene-2-phenethylamine is also catalyzed by trifluoroacetic acid (TFA) to give THIQ in good yield, although the cyclization is significantly slower than that catalyzed by superacids. The kinetic studies of the cyclizations revealed that the true electrophiles are the *N,N*-diprotonated imines **A**, *i. e.*, the ammonium-carbenium dications (*Scheme 3*). These findings dispel the notion that the P-S reaction is restricted to activated substrates which bear strongly electron-donating groups on the cyclizing benzene ring.



R = H : TfOH/CF_3CO_2H (9:1), 76%
R = Ph : CF_3CO_2H, 0%; TfOH, 90%

Scheme 3

On the other hand, high stereoselectivities were found in a wide range of superacid-catalyzed P-S reactions. Particularly in the cases of 2-alkyl-*N*-benzylidene-2-phenethylamines, an enhanced stereoselectivity was observed under the superacid conditions as compared with the corresponding weak acid (TFA)-catalyzed (monocationic) cyclization reaction of the *N*-benzylidene-2-(3',4'-dimethoxy)phenethylamines that bear electron-donating groups on the cyclizing aromatic ring (*Scheme 4*).[8b]

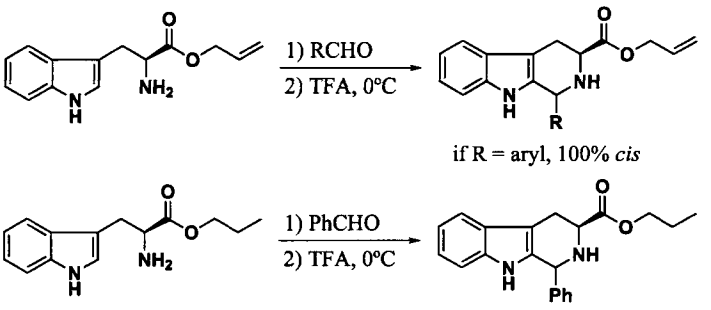


R^2 = Me, Et, *n*-Bu; R^3 = H, Cl *trans* *cis*

R^1 = H : with CF_3SO_3H; 67-95%, *trans/cis* = 80:20 ~ 88:12
R^1 = OMe : with CF_3CO_2H; 91-100%, *trans/cis* = 60:40 ~ 80:20

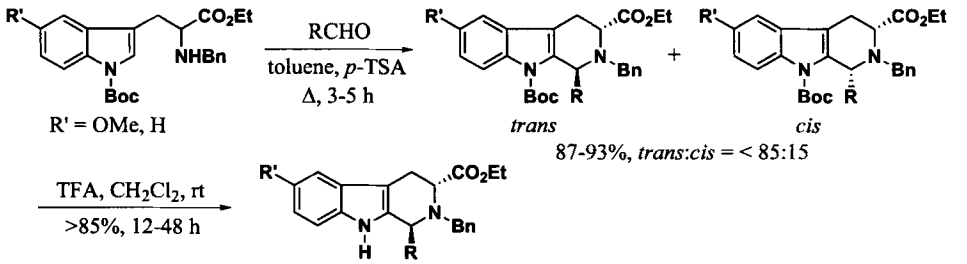
Scheme 4

It was reported that the P-S reaction of tryptophan allyl ester with aryl aldehydes generates *cis*-THBCs in the presence of TFA with complete stereo-control, when the reaction is carried out under kinetically controlled conditions, and with complete retention of optical integrity (*Scheme 5*).[9] The reason for the *cis*-specificity using allyl esters/aryl aldehydes is not clear, but it is possible that π-stacking between the allyl/aryl groups allows the cyclization to proceed through a diaxial intermediate.



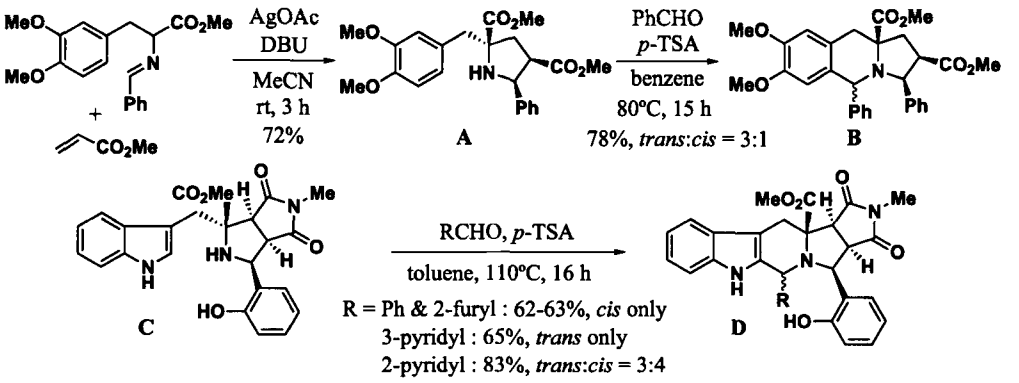
Scheme 5

It was also shown that the P-S reaction proceeds successfully in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA).[10] Hermkens *et al.*[11] had attempted the P-S reaction with a N_a-Boc protected tryptamine in TFA but concluded that ring closure was so slow that N_a-deprotection became a competitive side-reaction. In contrast, the P-S reaction proceeded smoothly between N_a-Boc protected tryptophans and a series of aldehydes in the presence of *p*-TSA with the desired *trans* diastereoselectivity (*Scheme 6*).[10a] The Boc protecting group remained intact in all cases. Although this process provides the *cis* and *trans* diastereomers initially, on removal of the Boc protecting group under acidic conditions, the mixture of *cis* and *trans* isomers was completely converted into the *trans* diastereomer to furnish N_a-H THBCs.



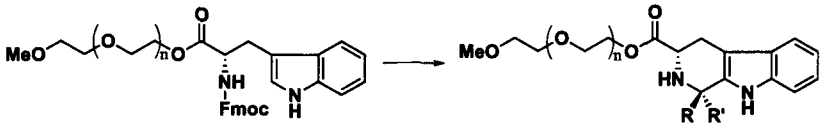
Scheme 6

Grigg *et al.* described that the combination of imine → azomethine ylide → cycloaddition cascades with the subsequent P-S reaction provides ready access to a range of novel nitrogen heterocycles (*Scheme 7*).[10c] The P-S reaction of **A** and benzaldehyde gave **B** as a 3:1 mixture of *trans* and *cis* isomers in 78% yield in the presence of a catalytic amount of *p*-TSA. The P-S reaction (toluene, 110°C, 10 mol% *p*-TSA) of the cycloadduct **C** with various aldehydes proceeded smoothly to give **D** in 62-83% yield. With the exception of **D** for which R is 2-pyridyl, much greater stereoselectivity was observed in the P-S reaction with **D** being obtained as single stereoisomers.



Scheme 7

One-pot condensation of immobilized polymer-bound tryptophan residues with various aldehydes and ketones has been carried out in the presence of *p*-TSA as a catalyst to afford PEG-supported THBCs (*Scheme 8*).[10e] Under these reaction conditions, the use of a *p*-TSA catalyst during the cyclization was found to be advantageous in the improvement of yields and in the isolation of cleaner products.



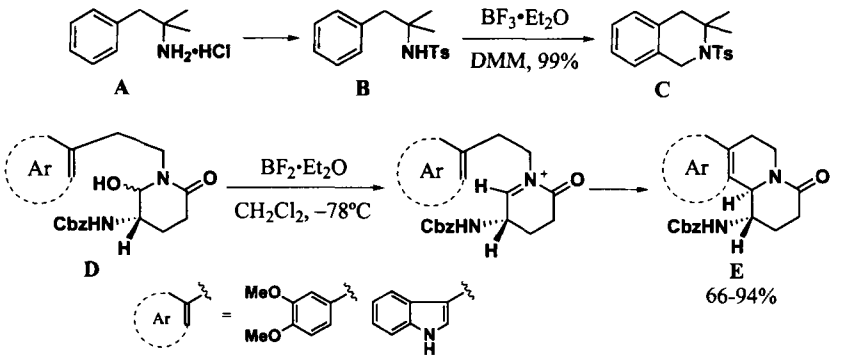
Scheme 8

II. LEWIS ACID- CATALYZED PICTET-SPENGLER REACTION

Although the P-S reaction proceeds efficiently under acidic conditions, other types of promoters are required for acid-sensitive substrates and also to develop an asymmetric version of P-S reaction. Lewis acid-catalyzed P-S reactions are relatively rare and the few reported examples involve highly reactive iminium species which have a heteroatom containing coordinating group.

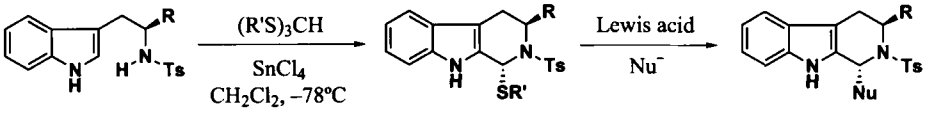
In 1977, Ito and Tanaka reported the ease with which *N*-sulfonylphenethylamines underwent cyclization in the presence of 37% formaldehyde and BF_3•Et_2O.[11a] Any attempt to directly cyclize **A** under the original P-S conditions (HCl, methylal) failed to produce a THIQ in reasonable amounts. Meanwhile, treating **B** in dimethoxymethane (DMM) with BF_3•Et_2O produced THIQ **C** in an isolated yield of 99% (*Scheme 9*).[11b] The DMM serves as the solvent as well as the formaldehyde source, while the BF_3•Et_2O facilitates formaldehyde formation and P-S cyclization. As illustrated in *Scheme 9*, it was described also that the hydroxylactams **D** were

subjected to *N*-acyliminium ion cyclization conditions.[11c] The treatment of **D** with $BF_3 \cdot Et_2O$ at –78°C afforded cyclized products **E** in 66-94% yields.



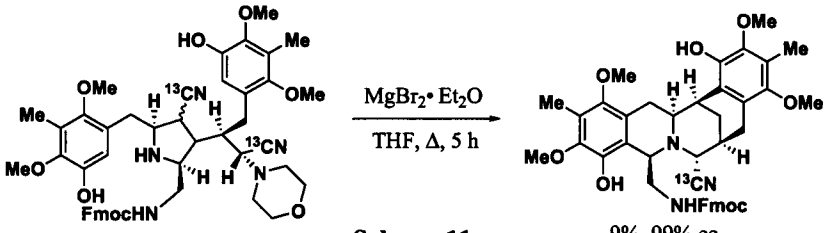
Scheme 9

The synthesis of 1-arylthio- and 1-alkylthio-β-carboline derivatives was developed by reaction of *N*-tosyltryptamines with thioortho esters as electrophiles under Lewis acid conditions (*Scheme 10*).[12] This strategy allows product diversification at C1 without the need for costly aldehyde components and avoids low yields due to competitive self-condensation. Thus, some of the primary limitations of the conventional P-S reaction can be overcome. Among various Lewis acids, addition of $SnCl_4$ to the mixture of the sulfonamide and the thioortho ester in CH_2Cl_2 at –78°C provided the best results. The arylthio or alkylthio groups linked to C1 of the β-carbolines form *N,S*-acetals, which can be useful C-C bond forming precursors. The resulting *N,S*-acetals were used as convenient substrates for the elaboration of 1-substituted THBC derivatives by C-C bond formation *via* tosyliminium ions.



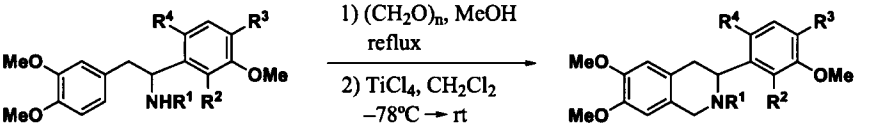
Scheme 10

Aminals have a greater propensity to form imine or iminium ion intermediates under mildly acidic conditions than secondary amino nitriles which, in turn, are more labile than tertiary amino nitriles. Based on these background studies, Meyers *et al.* described that cleavage of the aminal occurs first, followed by trapping of the resultant imine by P-S cyclization, as depicted in *Scheme 11*.[13] Subsequent ionization of the secondary amino nitrile is proposed to initiate a second P-S cyclization. Finally, ionization of the tertiary amino nitrile group leads to internal Strecker reaction to form the pentacyclic product. The best reaction condition for this one-step transformation was heating a solution in THF at reflux in the presence of $MgBr_2 \cdot Et_2O$ (20 equiv). Both P-S cyclizations were believed to proceed with *cis* selectivity, but stereochemical ratios could not be assigned in this experiment.



Scheme 11

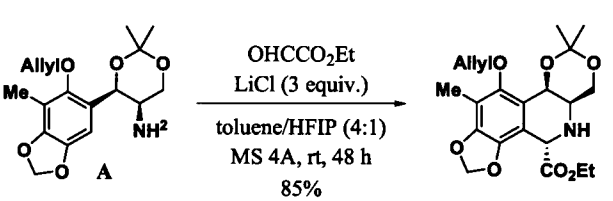
3-Aryl THIQ derivatives were efficiently prepared using $TiCl_4$ at –78°C (*Scheme 12*).[14] The $TiCl_4$-promoted cyclization of *N*-methoxymethyl-*N*-1,2-diarylethylamines *via* iminium ions constitutes an efficient approach to 2'-functionalized-3-aryl THIQs. This mild reaction condition is compatible with the presence of acid-sensitive groups: thus, the 2'-functionalized 3-aryl THIQ could be prepared in high yield without desilylation. Therefore, this is a good alternative to the classical protic acid catalyzed P-S reaction, which gives low yields of desilylated 3-aryl THIQs when applied to the 2'-functionalized amine.



R^1 = H, Me, Bn; R^2 = H, OMe; R^3 = H, OMe
R^4 = H, CH_2CH_2OSi*t*$BuPh_2$

Scheme 12

A P-S reaction between **A** and ethyl glyoxylate under carefully controlled conditions provided the acid-sensitive THIQ in high yield (*Scheme 13*).[15] The benzylic hydroxy group in compound **A** is particularly vulnerable under acidic conditions as a result of the presence of an electron-rich aromatic ring. Indeed, condensation between **A** and ethyl glyoxalate led either to the decomposition of reactants under a variety of acidic conditions or to the recovery of starting materials under mild neutral conditions. It was found that the reaction performed in toluene in the presence of LiBr provided the desired THIQ as a single diastereomer in about 40% yield. Under these conditions, the *trans* isomer became the major product (*trans/cis* = 6/1). When LiCl

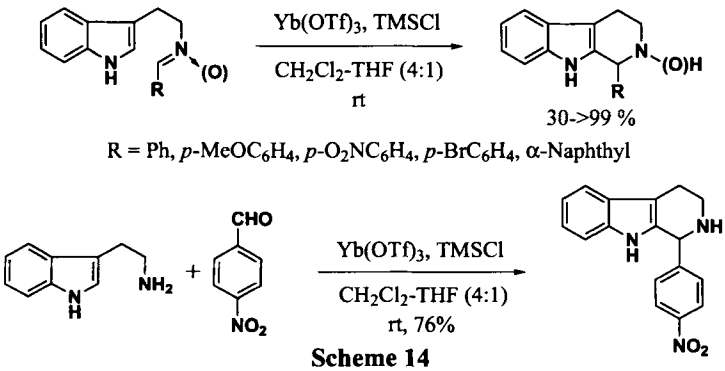


Scheme 13

was used for this reaction, the cooperative effect between LiCl and HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) allowed the P-S reaction of **A** and ethyl glyoxylate to proceed cleanly at room temperature. Adding molecular sieves can further increase the reaction efficiency. Although the exact role of HFIP was unclear, its weak Brønsted acidity (p*K*a = 9.3), strong ionizing power, and hydrogen bond donor ability may be relevant to its unique role in this transformation. Furthermore, the action of both Lewis acid (LiCl) and Brønsted acid (HFIP) might be synergistic, since in the absence of LiCl no reaction occurred at room temperature under otherwise identical conditions. Under the optimized conditions (LiCl, toluene/HFIP = 4/1, room temperature, MS 4 Å, 48 h), the desired P-S reaction took place smoothly to provide exclusively the *trans* isomer in 85% yield. This protocol is highly reliable and can be performed on a multigram scale without erosion of the yield and diastereoselectivity.

Rare-earth metal triflates have been recognized recently as stable, less toxic, and environmentally friendly Lewis acid catalysts. Various reactions have been developed using these catalysts.[16] There are several reports on the P-S reaction catalyzed by rare-earth triflates.

Several reports show that the P-S reactions proceeded in high yields with high regioselectivity in the presence of a catalytic amount of $Yb(OTf)_3$.[17] The P-S reaction of nitrones and imines prepared from *N*-hydroxytryptamine and tryptamine gave the corresponding THBCs in excellent yields in the presence of $Yb(OTf)_3$-TMSCl in a mixture of CH_2Cl_2 and THF (*Scheme 14*).[17a] The reaction of nitrones in CH_2Cl_2-THF (4:1) with $Yb(OTf)_3$ (25 mol%) and trimethylchlorosilane

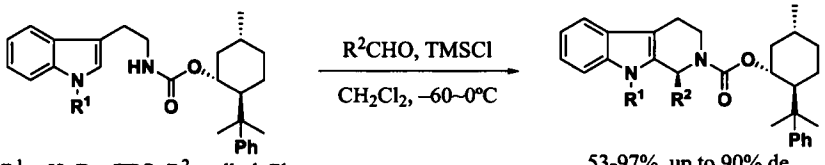


Scheme 14

(TMSCl, 1 equiv) proceeded efficiently, whereas the addition of 1 equiv of $Yb(OTf)_3$ together with TMSCl (1 equiv) was required to promote the reaction of imines prepared from tryptamine. In the case of two-component coupling between tryptamine and *p*-nitrobenzaldehyde, less than 1.0 equiv of $Yb(OTf)_3$ gave the better yields of the corresponding THBC because tryptamine may coordinate with $Yb(OTf)_3$ and prevent imine formation. The two-component reaction was only successful using *p*-nitrobenzaldehyde.

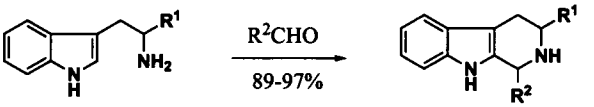
On the other hand, the P-S reaction of tryptamine methylcarbamate with acetaldehyde proceeded faster in the presence of TMSCl alone than a combination of $Yb(OTf)_3$ and TMSCl.[17b]

Other acidic promoters such as $BF_3 \cdot Et_2O$, $ZnCl_2$, $Yb(OTf)_3$, TFA, CSA (10-camphorsulfonic acid) and TMSOTf (trimethylsilyl trifluoromethanesulfonate) gave unsuccessful results. The reaction proceeded using aromatic and aliphatic aldehydes in the presence of TMSCl. A highly diastereoselective P–S reaction using (–)-8-phenylmenthyl carbamate has been also developed (*Scheme 15*).



Scheme 15

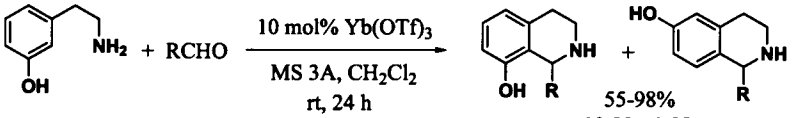
High yielding $Yb(OTf)_3$-catalyzed one-pot P-S reactions of tryptophan methyl ester and tryptamine with aliphatic and aromatic aldehydes were achieved in short reaction times with the aid of microwave irradiation (*Scheme 16*).[17c] Parallel screening was carried out to discover Lewis acids that efficiently catalyze P–S reactions of simple imines. Tryptamine, the imines from which are significantly less reactive due to the absence of the inductively electron-withdrawing carbonyl group in tryptophan, needed the combination of 10 mol% $Yb(OTf)_3$ and 50 mol% [bmim]Cl–$AlCl_3$, N = 0.5, which resulted in a very active catalyst and gave uniformly high yields, either with preformed imines or in one-pot condensations with aldehydes.



$R^1 = CO_2Me$: $Yb(OTf)_3$, CH_2Cl_2, 100°C, microwave
$R^1 = H$: $Yb(OTf)_3$, [bmim]Cl-$AlCl_3$, $N = 0.5$, CH_2Cl_2, 120°C, microwave

Scheme 16

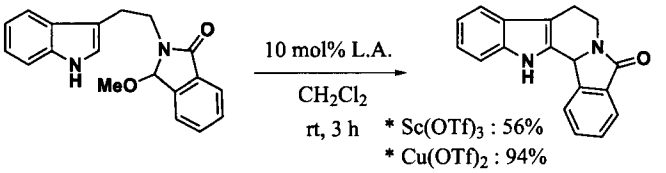
With the help of various dehydrating agents, the catalytic P-S reaction of benzaldehyde and *m*-tyramine proceeded smoothly under mild reaction conditions in high yield with high regioselectivity (*Scheme 17*).[17d] The reactions proceeded in good yields with high regioselectivity when heteroaromatic and aliphatic aldehydes were used, whereas an α,β-unsaturated



Scheme 17

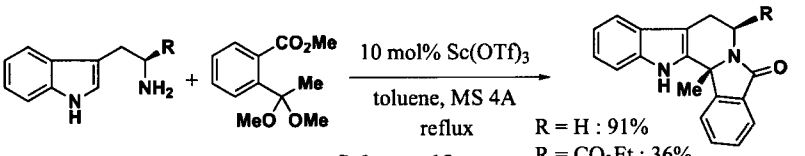
aldehyde caused severe side reactions. When less reactive β-phenethylamine derivatives than *m*-tyramine (e. g. 3-methoxy-β-phenethylamine, 3,5-dimethoxy-β-phenethylamine, and 4-hydroxy-β-phenethylamine) were tried, no cyclized products were obtained and only imine intermediates were produced.

$Sc(OTf)_3$ catalyzed *in situ* generation of the acyliminium ion from α-methoxyindolone and subsequent cyclization to give the corresponding β-carboline in moderate yields (*Scheme 18*).[18a] $Cu(OTf)_2$ promoted the same reaction in a better yield.



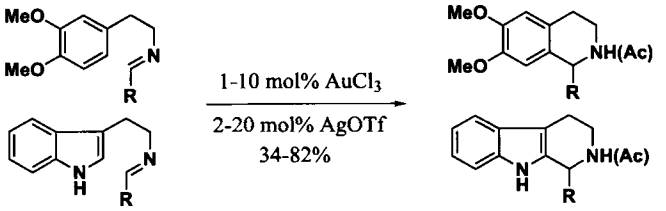
Scheme 18

It was found also that heating a solution of tryptamine and methyl 2-(1,1-dimethoxyethyl)benzoate in toluene in the presence of 10 mol% $Sc(OTf)_3$ and MS 4A gave the β-carboline derivative in excellent yield (*Scheme 19*).[18b] A similar reaction with tryptophan ethyl ester gave the desired product as a single diastereomer.



Scheme 19

Recently we developed mild and efficient $AuCl_3$/AgOTf-catalyzed P-S reactions to afford in good yields a variety of THIQ and THBC ring systems (*Scheme 20*).[19] To enhance the reactivity of the imine, an acylating agent was involved. In our reaction system, various imines obtained by condensation of 3,4-dimethoxyphenethylamine or tryptamine with aldehydes were



R = CO_2Et, aryl, heteroaryl, alkyl, cinnamyl

Scheme 20

used without further purification, and yields were equally good with both electron-deficient and electron-rich aromatic imines as well as aliphatic imines. Heteroaromatic imines, α,β-unsaturated imines, and free (NH) indole-derived imines were all successful in this reaction. It is likely that this reaction proceeds an electrophilic pathway involving imine activation by coordinating gold(III) complex.

III. PICTET-SPENGLER REACTION IN NON-ACIDIC APROTIC MEDIA

It has been reported that the P-S reaction of tryptophan methyl esters with acid-labile aldehydes, which contain functionality such as acetals, esters, amides, and acetonides, in nonacidic, aprotic media (PhH, Δ) permit the synthesis of a wide variety of *cis*- and *trans*-1,3-disubstituted THBCs in high yield (*Scheme 21*).[2b, 20a-c] An important feature of the successful procedure is use of a Dean-Stark trap below the reflux condenser to remove water formed in the reaction.[20d] In every case the effect of substitution of a benzyl group on the aliphatic nitrogen of

40-99%

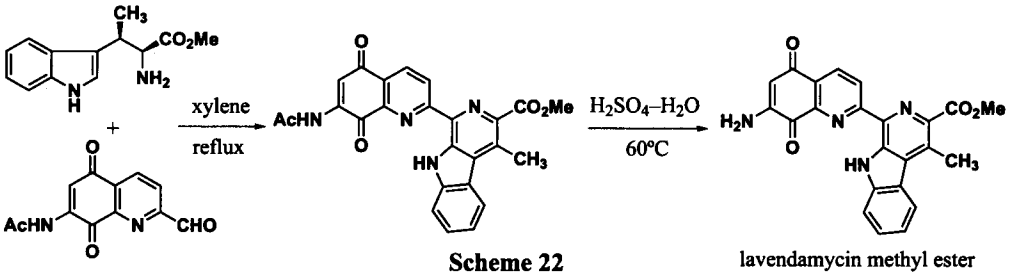
R^1 = H, Me; R^2 = H, CO_2Me; R^3 = H, Bn

R^4 = $HC(OEt)_2$, $CH_2CH_2COCH_2CH_3$, $CH_2CH_2CO_2H$, $CH_2CH_2CO_2Et$, *o*-HOC_6H_4, *o*-AcC_6H_4, Ph

Scheme 21

either tryptamine or tryptophan methyl ester has been to speed the rate of the cyclization and to improve the yield. In contrast, the N_b-isopropyl group leads to lower yields of product which may be due to steric, electronic, or both effects, but in fact is in accord with the greater electron-releasing properties of the isopropyl group as compared to that of the benzyl moiety. The potential of employing high boiling solvents to facilitate the P-S cyclization, without decomposing the aldehydes, is an important advantage of the cyclization in aprotic medium. Later, it was demonstrated that condensation of N_b-benzyltryptophan methyl ester with bulky aldehydes (R^4 = C_6H_{11}, Ph) led, stereospecifically, to the formation of the *trans* diastereomers.[20e]

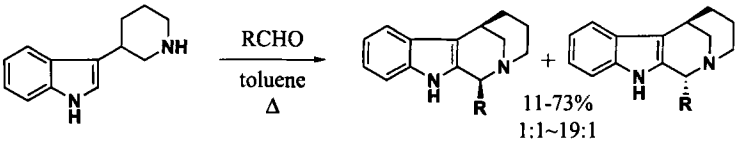
P-S condensation of 7-acetamido-2-formylquinoline-5,8-dione with the methyl ester of (2*RS*,3*SR*)-β-methyltryptophan in refluxing dry xylene for 23 h gave 7-*N*-acetyllavendamycin methyl ester in 79% yield (*Scheme 22*).[21] After hydrolysis in a 70% mixture of H_2SO_4-H_2O, lavendamycin methyl ester was obtained quantitatively.



Scheme 22

lavendamycin methyl ester

New bridged β-carbolines were synthesized *via* a short synthetic route under neutral conditions by refluxing in toluene (*Scheme 23*).[22] The key step of the sequence was a P-S



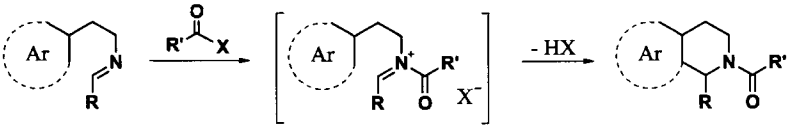
R = Et, *n*-Hex, *n*-Hept, Ph, $(CH_2)_3CH(OEt)_2$, $(CH_2)_3CHNOCH_3$

Scheme 23

condensation employing a cyclic amine and several aldehydes. Under nonacidic, aprotic conditions the bridged THBCs were formed usually in good yield and as a mixture of diastereomers, their ratio depending strongly on the size of the substituent. An excess quantity of aldehyde (10-15 equiv) was required for the reaction due to competitive aldol condensation of the aldehydes to the α,β-unsaturated aldehydes.

IV. ACTIVATED PICTET-SPENGLER REACTION

The P-S reaction shows some disadvantages in terms of product yields when the starting phenethylamines lack activating hydroxyl or alkoxyl groups at the position para to the ring closure, because drastic conditions are usually required to effect the cyclization. A general strategy to increase the reactivity in processes involving imine or iminium intermediates involves generation of the corresponding *N*-acyliminium ions.[2c-d] Owing to the electron-attracting properties of the carbonyl group on nitrogen, the iminium carbon is now more electron-deficient, which causes such *N*-acyliminium ions to be much more reactive as electrophiles than simple *N*-alkyliminium ions. Electron-attracting substituents other than *N*-acyl, such as *N*-sulfonyl, can also be employed in analogues of *N*-acyliminium ion reactions. The condensation of *N*-acyl or *N*-sulfonyl β-phenethylamines with aldehydes, known as the activated P-S reaction, is a well established procedure for the elaboration of THIQs (*Scheme 24*).

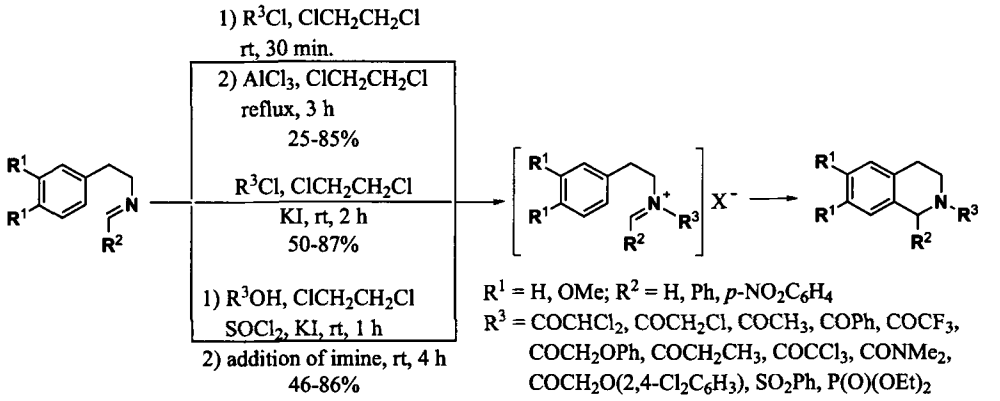


Scheme 24

1. N-Acyl Pictet-Spengler Reaction

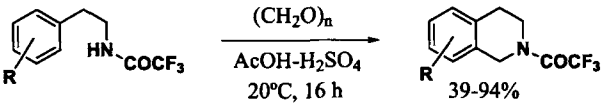
2-Acyl THIQs were obtained from *N*-methylene- or *N*-benzylidene-2-phenylethylamines and acyl chlorides or carboxylic acids/thionyl chloride in the presence of potassium iodide at room temperature (*Scheme 25*).[23a] A number of 2-acyl THIQs were obtained with good results by first *N*-acylating the imine with an acyl chloride and then heating the resultant *N*-acyliminium salt with $AlCl_3$ in 1,2-dichloroethane. A modified, more convenient procedure, which was performed with acyl chloride, a catalytic amount of KI, and an equimolecular amount of the imine in 1,2-dichloroethane at room temperature, was developed and afforded good yields. This

procedure could be improved again by using the corresponding carboxylic acid as starting material. There is a related study in which the reaction of *N*-formyliminium ion with HCHO gave 2-formyl THIQs.[23b]



Scheme 25

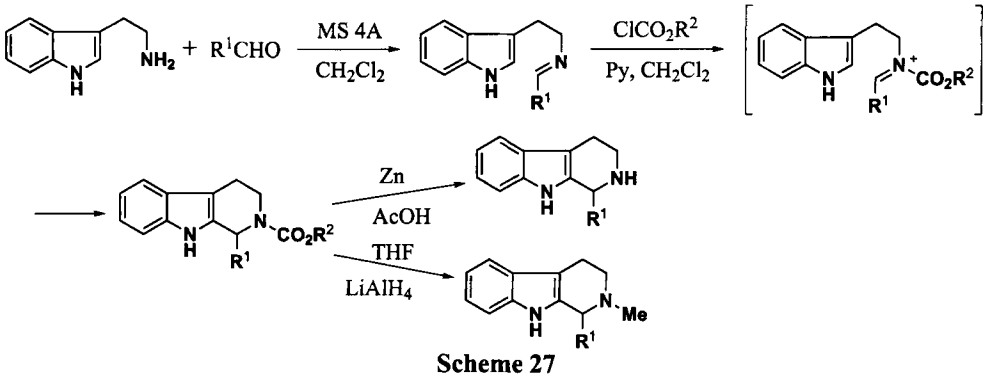
The synthesis of THIQs *via* an intramolecular cyclization of *N*-trifluoroacylated phenethylamines devoid of electron donating groups, with paraformaldehyde mediated by AcOH-H_2SO_4 was described (*Scheme 26*).[24] The paraformaldehyde could be replaced by *s*-trioxane without diminution in yield; however, attempts to extend the utility of this reaction by the use of alkyl or aromatic aldehydes to obtain 1-substituted derivatives were unsuccessful. When the trifluoroacetyl moiety was replaced with acetyl, the yield was unaffected but the rate was considerably slow. In contrast, the use of the benzoyl derivative produced no cyclized product. Replacement of AcOH-H_2SO_4 with TFA or HCO_2H was ineffective for ring closure.



Scheme 26

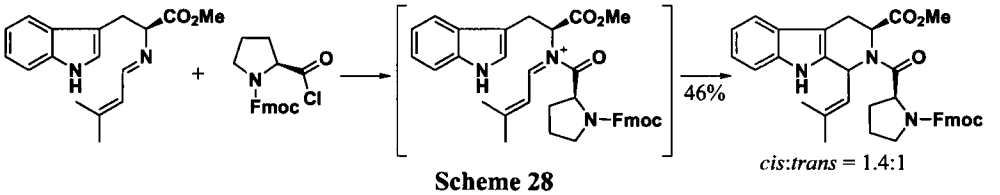
A P-S reaction between tryptamine and aldehydes was achieved through the *N*-acylliminium salt intermediates in the presence of chloroformates[25a] or acetyl chloride (AcCl)[25b] to give the β-carbolines. The P-S reaction of the imines proceeded with chloroformates in the presence of pyridine to give the carbamates which could be converted to the amines by removal of N_b-alkoxycarbonyl group or to N_b-methyl compounds by $LiAlH_4$ reduction (*Scheme 27*).[25a] One-pot reactions of tryptamine and benzaldehyde or 3-methyl-2-butenal with trichloroethyl and methyl chlroformates gave the β-carbolines (56-68%) without isolation of the imines.

Tryptophan analogues were also cyclized by *N*-acyl P-S condensation to yield β-carbolines.[26] Reaction of the imine derived from L-tryptophan methyl ester and senecialdehyde with Fmoc-L-Pro-Cl induced an *N*-acyliminium P-S condensation, yielding a 1.4:1 mixture of *cis* and



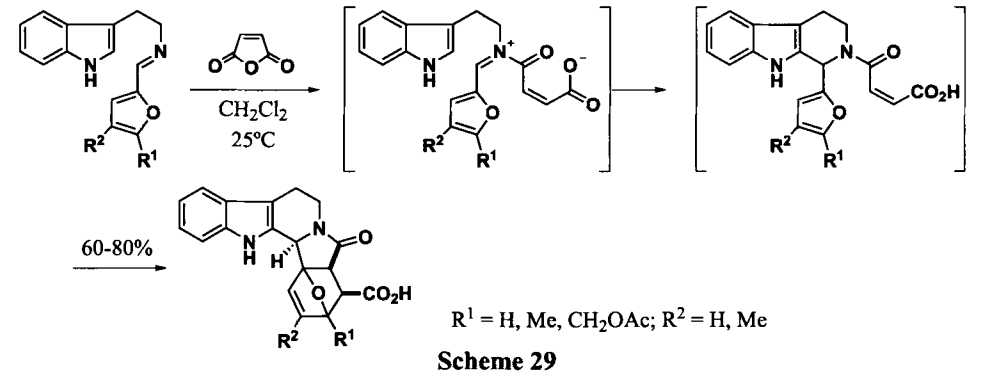
Scheme 27

trans THBCs (*Scheme 28*).[26b] In a previous study with tryptamine,[27] the P-S reaction did not occur with α,β-unsaturated imines and, in an earlier example with isovaleraldehyde and Cbz-L-Pro-Cl,[28] the *trans* epimer predominated. The difference may be due to the use of the bulkier Fmoc group.



Scheme 28

Acylation of the imines, prepared from tryptamine and furaldehydes, with maleic anhydride provided the corresponding hexacyclic nitrogen heterocycles *via* a tandem *N*-acylimminium/P-S/intramolecular Diels-Alder reaction (*Scheme 29*).[29] In this tandem approach, five

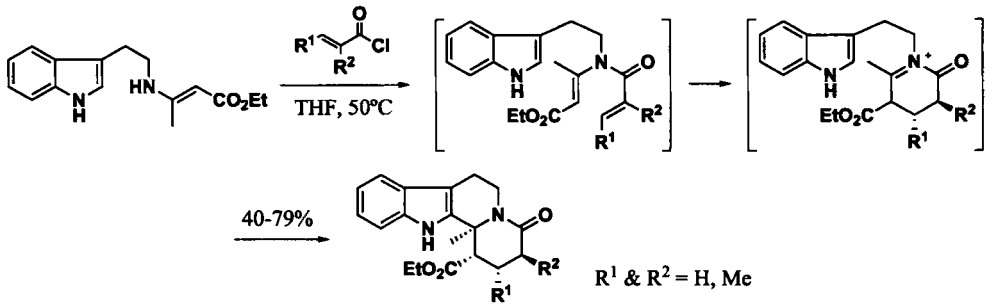


Scheme 29

stereocenters, including a quaternary center and three rings were generated with excellent stereoselectivity. Key to the success of this approach is the use of furaldehyde and maleic anhydride as the aldehyde and anhydride components, respectively. This tandem approach avoids the use of

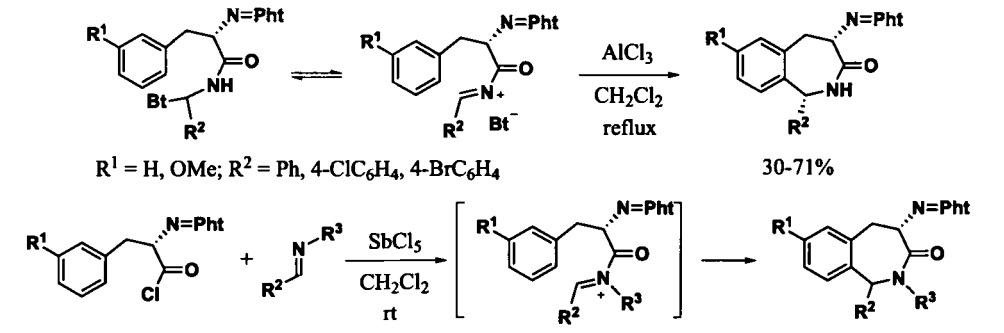
an acid catalyst and higher temperatures to promote the P-S condensation reaction. In addition, use of maleic anhydride introduces a free acid functionality, which could be used as a handle to increase the structural diversity.

It was described that enaminoesters containing a tethered indole or aryl moiety on the amine reacted with substituted maleic anhydrides or acryloyl chlorides to provide pyrrolinone or dihydropyridone products, respectively (*Scheme 30*).[30] The combination of the β-enamino ester with an acryloyl chloride results in an aza-annulation forming a pyridone with a new cyclic β-enamino ester. The indole-tethered dihydropyridones prepared from any of the three acryloyl chlorides (methallyl, crotonyl and acryloyl) could proceed onward to one-pot tetracycle formation *via* the intermediacy of an *N*-acyliminium ion catalyzed by the HCl released from the reaction. In contrast, the aryl-tethered dihydropyridones or pyrrolinones required the aid of TfOH to effect ring closure.



Scheme 30

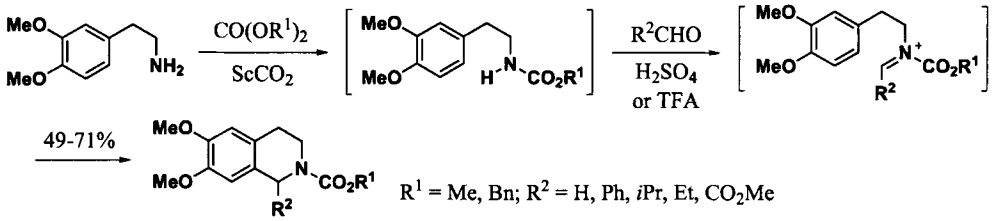
Two versatile syntheses of 1-substituted and 1,2-disubstituted 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones were performed using *N*-acyliminium ions as reactive intermediates (*Scheme 31*).[31] 1-Substituted 2-benzazepinones were synthesized from the benzotriazole (Bt) adducts starting from the corresponding *N*-phthaloyl-phenylalanine amide in the presence of $AlCl_3$, which induced the equilibrium shift towards the *N*-acyliminium ion. Activating



Scheme 31

substituents on the aromatic ring of the amino acid afforded much better yields. In all cases the cyclization resulted in only the *cis* isomer. Meanwhile, a direct way to 1,2-disubstituted benzazepinones was realized by an *N*-acylation of an imine in the presence of $SbCl_5$. The reaction time for *N*-acylation was strongly dependent on the R^3 substituent. Steric hindrance might disfavor the *N*-acylated form. In contrast to the benzotriazole pathway, the strategy through *N*-acylation of an imine gave a diastereomeric mixture. In this reaction, only non-enolizable aldehydes could be used to introduce a 1-substituent (R^2).

Recently, Danheiser *et al.* reported that *N*-acyl P-S cyclizations could be achieved in multiphasic $scCO_2/CO_2$-expanded liquid media *via* the *in situ* formation of carbamate derivatives of β-arylethylamines (*Scheme 32*).[32] Both electron-neutral and electron-rich β-arylethylamines participated in the reaction, which could also be applied to a variety of aliphatic and aromatic aldehydes. An *N*-acyl P-S reaction with methyl glyoxylate was achieved by introducing this aldehyde in the form of its dimethyl acetal derivative.

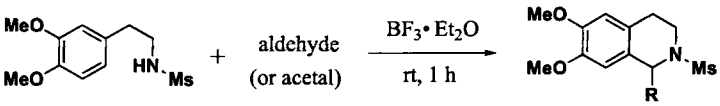


R^1 = Me, Bn; R^2 = H, Ph, *i*Pr, Et, CO_2Me

Scheme 32

2. N-Sulfonyl Pictet-Spengler Reaction

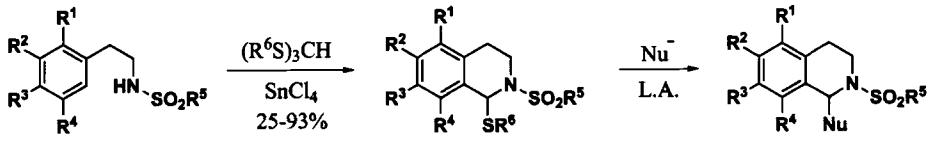
Activation of imine has been achieved also with *p*-toluenesulfonyl chloride (*p*-TsCl) or methanesulfonyl chloride (MsCl) in an *N*-sulfonyliminium-type cyclization.[12, 33] It was described that condensation of sulfonamide with aldehydes or acetals in CH_2Cl_2 and cyclization of the adduct using $BF_3 \cdot Et_2O$ or conc. H_2SO_4 at room temperature afforded the corresponding THIQ as the sole product in excellent yield (*Scheme 33*).[33e]



R = H, CH_2Br, CO_2-(*l*)-menthyl, Bn, CH_2CH_2Ph 58-95%

Scheme 33

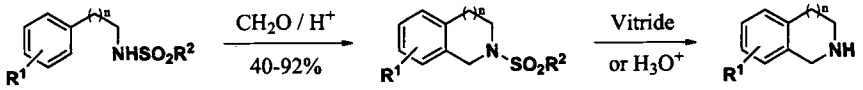
Silveira and Kaufman reported the synthesis of 1-alkylthio- and 1-arylthio-THIQs by means of the activated P-S reaction of *N*-sulfonyl-β-phenethylamines with thioorthoesters as electrophiles in the presence of $SnCl_4$ (*Scheme 34*).[12, 33f] It was shown also that the resulting 1-heterosubstituted THIQ intermediates could be used as sulfonyl iminium ion precursors for C-C bond formation with suitable carbon nucleophiles under Lewis acid assistance, leading to 1-substituted THIQ derivatives.



R^1-R^4 = H, OMe, -OCH_2O-; R^5 = Ts, Cs; R^6 = Ph, Et
* Cs : (1*S*)-10-camphorsulfonyl

Scheme 34

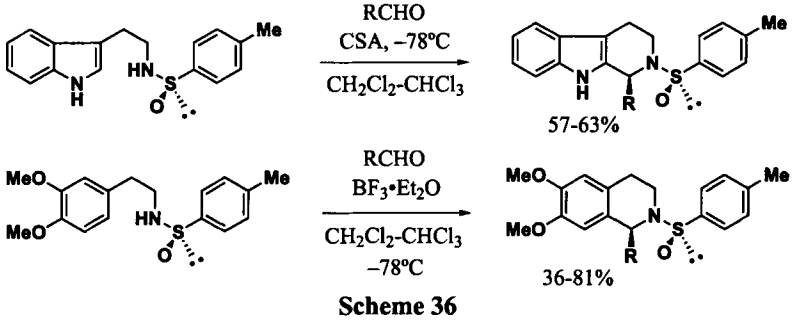
THIQs and ring homologues have been obtained by intramolecular sulfonamidomethylation of *N*-aralkylsulfonamides with formaldehyde formed from *s*-trioxane in acid media followed by desulfonylation under moderate conditions, either by reduction or acid hydrolysis (*Scheme 35*).[34] The use of the highly electron-withdrawing sulfonyl group as the *N*-substituent gave good or high yields of the corresponding heterocycles variously substituted in the aromatic ring, including substrates with a deactivated aromatic ring, and with a six-, seven-, or eight-membered ring. A key feature was the use of moderate conditions for the efficient removal of the sulfonyl group.



n = 1-3; R^1 = H, OMe, Cl
R^2 = 3,4-$Cl_2C_6H_3CH_2$, $PhCOCH_2$, $EtO_2C(CH_2)_2$, $MeO_2C(CH_2)_2$, *o*-$MeO_2CC_6H_4$

Scheme 35

P-S reactions of enantiopure *N*-sulfinyl tryptamines and phenethylamines were carried out under mild acidic conditions to give the corresponding *N*-sulfinyl THBCs and THIQs respectively in good yields with high diastereoselectivity (*Scheme 36*).[35] The chiral auxiliary group could be removed subsequently under mild acidic conditions. (*R*)-*N*-*p*-Tolylsulfinyltryptamine reacted with simple aldehydes in the presence of CSA at –78°C to yield *N*-sulfinyl THBCs in good yield and selectivity, whereas the reaction of (*R*)-*N*-*p*-tolylsulfinylphenylethylamines did not occur under protic acidic conditions at –78°C. Most of the Lewis acids examined led to the

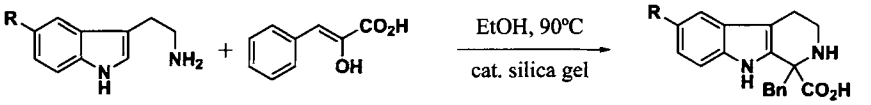


Scheme 36

formation of reactive enamines and undesirable side products, however, $BF_3 \cdot Et_2O$ showed exceptional results, giving the desired product in high yields.

V. PICTET-SPENGLER REACTION USING OTHER METHODS

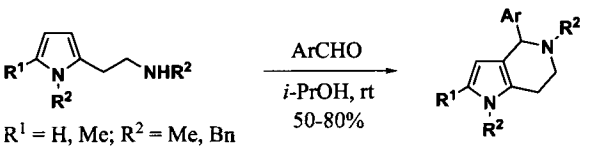
A variety of promoters for P-S reactions have been developed and introduced. There are a few examples using an alcoholic solvent to conduct the P-S reaction.[36] The P-S condensation between phenylpyruvic acid and simple phenethylamine or tryptamine was performed smoothly in silica gel treated EtOH (1 h, 90°C) to afford THIQs (*Scheme 37*).[36b] Silica gel was used as an active surface catalyst, and absolute EtOH was filtered through a silica gel column prior to use, or a small amount of silica gel (~1%) was added to a solution of EtOH.



R = H, OH, OMe

Scheme 37

N,N'-Dialkyl-2-(2-aminoethyl)pyrroles were converted into the fused tetrahydropyrrolopyridines by P-S reaction with aromatic aldehydes in *i*-PrOH within 2–4 h at room temperature (*Scheme 38*).[36c] In contrast to the reported other procedure, this non-catalytic variant of the P-S reaction allowed acidophobic compounds (R^1 = H) to be isolated as free bases in good yields.

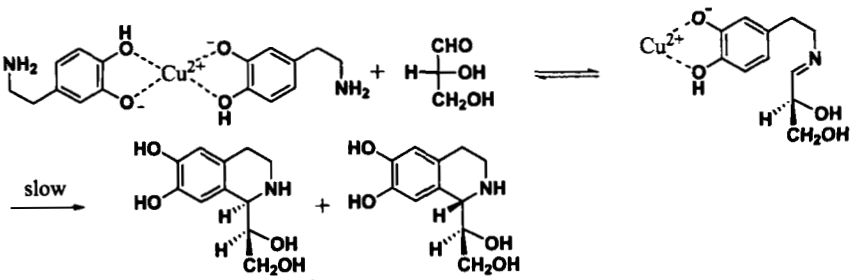


R^1 = H, Me; R^2 = Me, Bn

Scheme 38

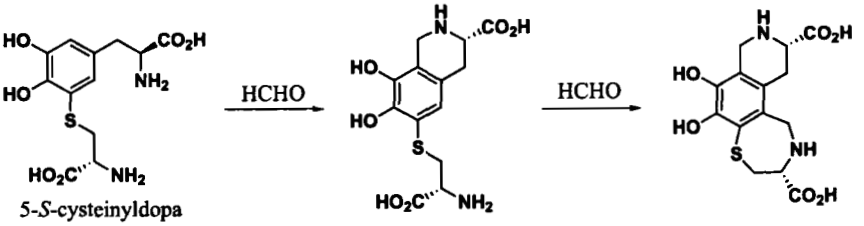
The P-S reaction is known to run efficiently under biomimetic conditions[37] and in vivo.[38] Some research groups have reported the P-S reaction under conditions of relevance for biological environments. Dopamine underwent the P-S reaction with *d*-glyceraldehyde and *d,l*-glyceraldehyde-3-phosphate in 0.05 M phosphate buffer, pH 7.4, and at 37°C to afford THIQs (*Scheme 39*).[39] Transition metal ions commonly occurring in biological systems (e. g. Cu^{2+} and Fe^{3+}) markedly accelerated the formation of products without affecting the diastereomeric ratio. Mechanistic evidence suggested the reversible generation of Schiff base intermediates which undergo stereoselective cyclization according to the Felkin-Anh model. Metal-chelation at the catechol group facilitates the rate-determining nucleophilic attack to the imine moiety by enhancing the electron density at the site of cyclization.

Under biomimetic P-S conditions, *i. e.*, in 0.1 M phosphate buffer pH 7.4 and at 37°C, double condensation of the urinary melanogen 5-*S*-cysteinyldopa with formaldehyde yielded



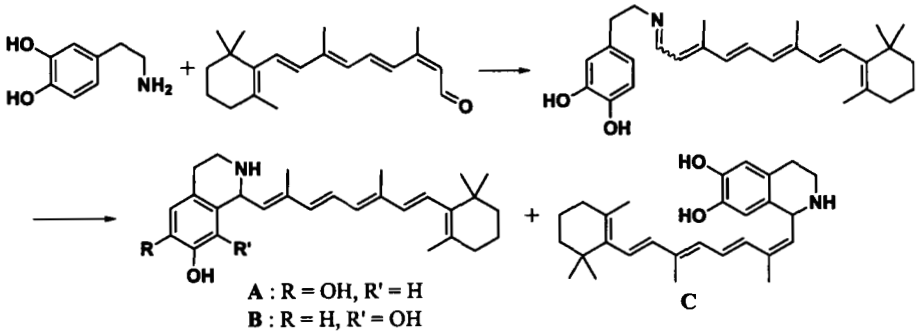
Scheme 39

regioselectively the six-membered ring *ortho* to the activating hydroxyl group as the sole intermediate, followed by the subsequent closure of the seven-membered 1,4-thiazepine moiety (*Scheme 40*).[40] The anomalous regiochemistry underlying formation of the six-membered ring *ortho* to the activating hydroxyl group was rationalized with the aid of AM1/PM3 calculations on the model alkylthiocatechol, predicting a higher HOMO-controlled reactivity on the position *ortho* rather than *para* to the activating hydroxyl group.



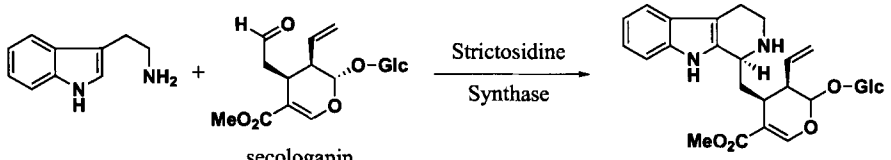
Scheme 40

Some constituents of vitamin A, e. g. 13-*cis*-retinaldehyde, reacted with dopamine under biomimetic environments, 0.1 M phosphate buffer at pH 7.4 with SDS (1–2% w/w), to give the mixture of THIQ retinoid derivatives **A**-**C** (*Scheme 41*).[41] The effect of metal ions, able to be chelated by the catechol system, on product yields was also assessed. Both Cu^{2+} and Fe^{3+} could increase the yields of all the isomers, however, the effect of Fe^{3+} was more pronounced on the yield of **B** probably because iron chelation induces an enhancement of electronic density at position 2.



Scheme 41

Recently an enzymatic P-S reaction was reported where strictosidine synthase catalyzes the stereoselective reaction of tryptamine and secologanin in the first step in the biosynthesis of terpene indole alkaloids to generate strictosidine (*Scheme 42*).[42] Strictosidine synthase could synthesize alternative heterocyclic derivatives, utilizing both the 3-(2-aminoethyl)-benzofuran



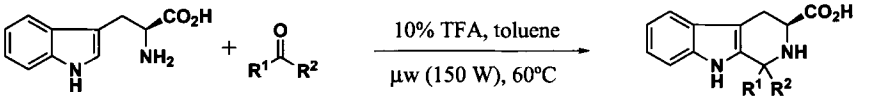
secologanin

Scheme 42

Strictosidine

and benzothiophene analogs, though at a diminished rate relative to the tryptamine substrate. Strictosidine synthase does not readily tolerate substitution at positions 5 and 6 of tryptamine and is most tolerant of substitutions at positions 4 and 7. It was concluded that tryptophan, phenylethylamine, tyramine, histamine, and pyrrole substrates are not tolerated by strictosidine synthase, and the basic indole framework is required for recognition by this enzyme.

P-S condensation can be accelerated by using microwaves,[17c, 43] which have been known to expedite a large array of synthetic organic reactions in conventional solvents.[44] Chu *et al.* reported that P-S reactions of tryptophan with ketones took several days under acidic conditions at ambient temperature to give 1,1-disubstituted THBCs, and therefore they attempted to shorten the reaction time by conventional reflux or microwaves (*Scheme 43*).[43a] They observed that harsh

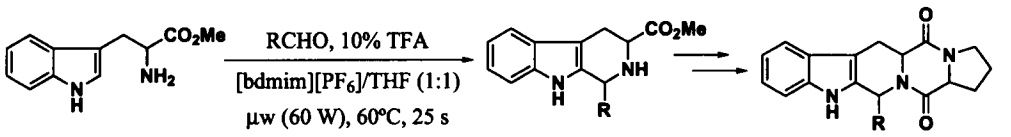


Scheme 43

67-99%

conditions such as conventional reflux or microwaves at high temperatures (e. g., 100°C) gave complete conversion of the starting tryptophan to produce, however, complicated and degraded reaction mixtures. Under milder condition (microwave at 60°C) ketone reactions could be accelerated from days to minutes with high isolated yields (67–99%). The microwave heating was found to be far better than conventional heating in terms of reaction acceleration and this microwave-accelerated P-S reaction was clean, giving the THBC adducts as the only products.

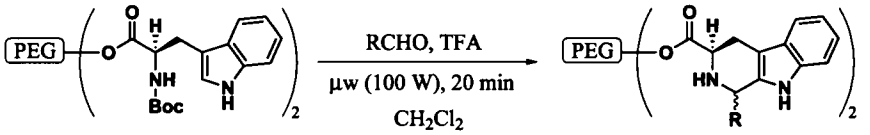
The same group reported a three-step synthesis (P-S, Schotten-Baumann, and intramolecular ester amidation) of THBC-diketopiperazines starting from tryptophan methyl ester using microwave irradiation in the [bdmim][PF_6] ionic liquid at 60°C in overall only 5min with good isolated yields (49–69%) (*Scheme 44*).[43b] The room-temperature ionic liquids are a new class of organic solvents.[45] Because of their negligible vapor pressures and large dipoles, ionic liquids are



Scheme 44

excellent media for microwave-accelerated organic reactions. As the first step of the synthesis, the P-S reaction of tryptophan methyl ester with aldehydes worked effectively in the mixed solvent of [bdmim][PF_6] (1-butyl-2,3-dimethylimidazolium hexafluorophosphate) and THF (1:1, v/v) using TFA and low-power microwaves (60W). Under this microwave condition, it typically required a short reaction time of 25 s to complete the reaction, whereas the same reaction was completed in 7–8 h in conventional solvents such as CH_2Cl_2 at ambient temperature. In addition, reaction times of 8–12 min were needed if the same reactions were conducted using microwave in THF alone. Based on these results it was clearly demonstrated that ionic liquids as reaction media readily accelerate the P-S reaction in the presence of microwaves.

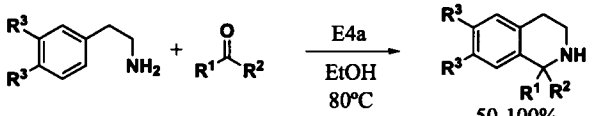
Microwave-assisted P-S condensation of aldehydes with PEG bound tryptophan resulted in the formation of *cis* and *trans* diastereomers of a tricyclic polymer intermediate in around a 1:1 ratio (*Scheme 45*).[43c] The simultaneous addition of TFA and aldehydes resulted in



Scheme 45

the sequential Boc-deprotection, imine formation, and P-S cyclization. This cyclization step, which required 24 h under refluxing conditions in $CHCl_3$, proceeded remarkably faster in 20 min under microwave conditions. Polymer supported intermediates and the polymer itself were stable during the harsh microwave irradiation.

A small pore size zeolite was utilized to promote an environmentally friendly variation of the P-S reaction (*Scheme 46*).[46] The easily separable and recyclable catalyst provided high

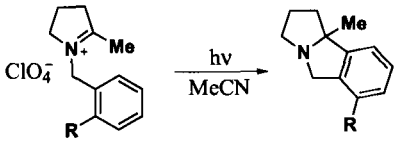


Scheme 46

conversions and a shorter reaction time than the classical AcOH or TFA. Ersorb-4 (E4) is a weakly acidic zeolite-type adsorbent with a 4 Å pore size and has several advantages – it is envi-

ronmentally friendly, nontoxic, recoverable, reusable and inexpensive. The reaction of β-phenylethylamine with aromatic and aliphatic ketones and aldehydes in the presence of acid modified E4a in EtOH resulted in the formation of THIQ in one step and in good yield. Aliphatic ketones and aldehydes gave the corresponding products in poorer yields than aromatic ones. The more acidic KP10 montmorillonite catalyst gave no product because it is unable to bind the water formed during the Schiff base formation.

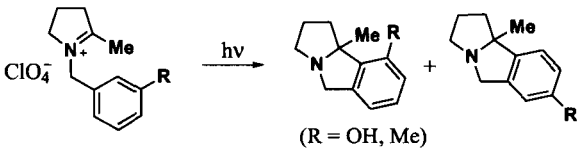
Electron-transfer, photochemical methodology in synthetic approaches for *N*-heterocycle ring construction was introduced. Photoinduced excited-state P-S cyclization of 2-methyl-*N*-xylyl- and 2-methyl-*N*-benzylpyrrolinium perchlorates produced benzopyrrolizidines (*Scheme 47*).[47a] The absence of conjugation of the iminium cation moiety in the 2-methylpyrrolinium salts allowed for light absorption by the aryl ring when irradiations were conducted with light of wavelength greater than 240 nm. Irradiation of an acetonitrile solution of the pyrrolinium perchlorates followed by basic workup gave exclusively the corresponding benzopyrrolizidines.



R = Me (55%), H (80%)

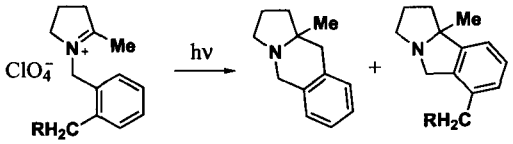
Scheme 47

It was also disclosed that electron-transfer-induced photocyclization processes of a series of *ortho*- and *meta*-substituted 1-benzyl-1-pyrrolinium perchlorates afforded benzopyrrolizidines and benzindolizidines (*Scheme 48*).[47b] These salts were directly irradiated (Vycor, λ > 240 nm) in either MeCN or MeOH. Triplet-sensitized reactions were conducted by irradiation



(R = OH, Me)

R = OH, OSi*t*BuMe$_2$, OMe, Me, CH_2SiMe_3, CH_2Si*t*BuMe$_2$



R = H, $SiMe_3$, Si*t*BuMe$_2$

Scheme 48

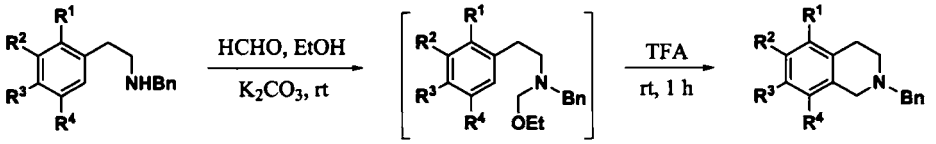
(Pyrex, λ > 290 nm) of acetone solutions. Photoreactions of the *m*-oxybenzyl and *m*-alkylbenzyl salts gave the corresponding benzopyrrolizidines, whereas both pyrrolizidines and indolizidines were obtained by photoreactions of the *o*-alkylbenzyl salts.

VI. MODIFIED PICTET-SPENGLER REACTION

1. Alternative for Aldehydes

The original strategy of the P-S reaction has been modified by employing alternatives for aldehydes as electrophilic components, such as aldehyde equivalents like ketals, acetals,[11b, 33e, 48-50] and enol ethers,[51] thioorthoesters,[12, 33f] chloro(methylthio)acetate,[56] various other α-chloro-α-alkyl/aryl-chalcogeno carbonyls,[57] alkynes,[66-67, 69] enamines,[54, 68] azalactones,[52] perhydro-1,3-heterocycles,[53-55] and Δ^1–piperidines.[58]

A mild and efficient method for the synthesis of THIQs by a modified P-S reaction involving *O,N*-acetals has been developed (*Scheme 49*).[48] The reaction of *N*-benzyl-2-arylethylamines with paraformaldehyde in the presence of K_2CO_3 in EtOH quantitatively afforded *O,N*-acetals, which were treated with TFA to give the THIQs in 44-80% overall yield.

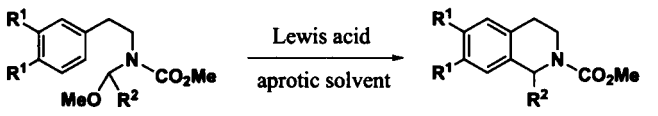


R^1 = H, OMe, OBn; R^2-R^4 = H, OMe

44-80%

Scheme 49

The modified P-S cyclization of *N*-alkoxycarbonyl-*N*-(1-methoxyalkyl)-2-arylethylamine derivatives using Lewis acids in non-protic solvents was described to afford 1-substituted THIQ derivatives in high yields (*Scheme 50*).[49] The advantage of the α-methoxyalkylcarbamates as precursors for P-S cyclization is that they are very stable. THIQs with a Ph or CO_2Me group at



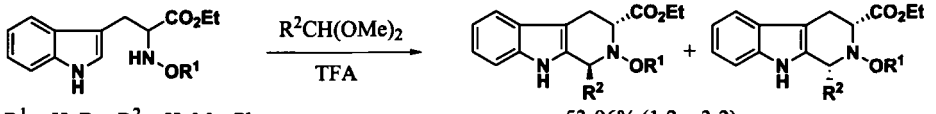
R^1 = H, OMe; R^2 = Ph, CO_2Me, alkyl

63-99%

Scheme 50

the 1-position were obtained using TMSOTf in MeCN in 96-99%, whereas the 1-alkyl substituted THIQs were produced in the best yields in the presence of $TiCl_4$ in CH_2Cl_2. TMSCl was effective only in the case of activated 2-arylethylamine derivatives.

P-S condensations of the *N*-hydroxytryptophan ethyl esters with acetals and aldehydes have been examined in the presence of TFA to yield mixtures of the 2-hydroxy THBCs (*Scheme 51*).[50a]

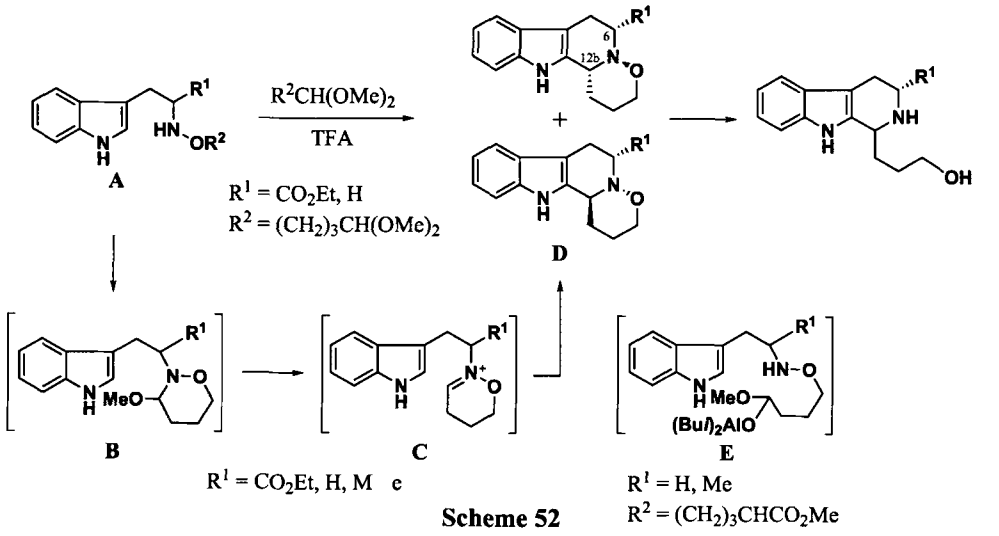


R^1 = H, Bn; R^2 = H, Me, Ph

53-96% (1:2 ~ 3:2)

Scheme 51

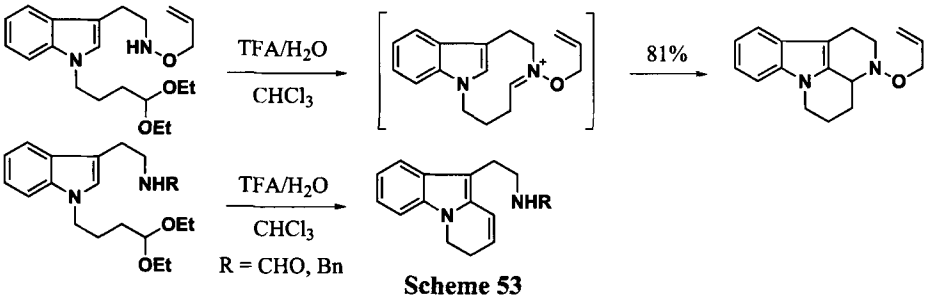
Similarly, it was demonstrated that intramolecular cyclization of N-alkoxy derivatives under acidic or reductive conditions[50b-c] gave the corynanthe analogues (D) in good yields (*Scheme 52*).[50c] An intramolecular P-S reaction of N-alkoxy derivatives (A) with TFA in CH_2Cl_2 occurred, presumably via intermediates **B** → **C**. The cyclizations occurred with high product



Scheme 52

stereoselectivity with a *cis* conformation of the C(6) and C(12b) substituents. The selective reduction of the ester function in **A** (R^2) in the presence of the labile N-O bond with DIBAL in toluene at –70°C, followed by addition of TFA gave the cyclized product **D**. Under the anhydrous acidic conditions intermediate **E** cyclized either *via* **B** → **C** → **D** or *via* an aldehyde intermediate to **C** → **D**. Reductive ring opening of the tetrahydro-1,2-oxazine was accomplished by cleaving the N-O bond with zinc dust in AcOH at 80°C to give the 1,3-disubstituted THBCs.

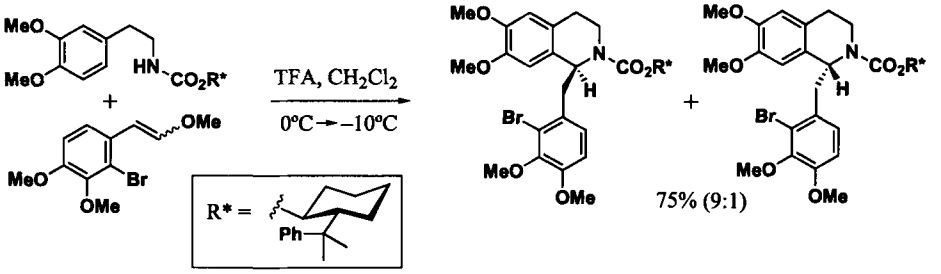
A canthine derivative was synthesized efficiently by intramolecular P-S reaction of N_a-(4,4-diethoxybutyl)-N_b-allyloxytryptamine with TFA/H_2O in $CHCl_3$ (*Scheme 53*).[50d] With N_a-propanal and N_a-pentanal chains, only dimeric and oligomeric compounds were formed, probably because formation has to proceed *via* conformationally disfavored intermediate cyclic



Scheme 53

iminium ions. Cyclization of N_a-butanal functionalized N_b-formyl- or N_b-benzyltryptamines, which are known rate enhancing substituents in the P-S condensation, unexpectedly gave the 3,4-dihydro pyrimidino[1,2-a]indoles, which were formed by a direct electrophilic attack of the protonated aldehydes on the indole 2-position.

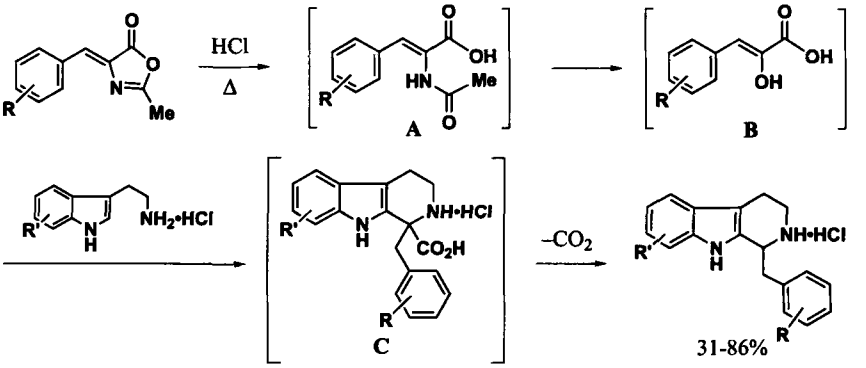
It was found that the asymmetric P-S reaction of enol ether and carbamates which have cyclohexyl-based chiral auxiliaries proceeds with good selectivity with TFA to give THIQ, aporphine and protoberbine alkaloids (*Scheme 54*).[51] The optimum conditions found used 5 equiv of TFA in CH_2Cl_2 at −10°C for 56 h. Lowering the temperature makes the reaction sluggish



Scheme 54

resulting in lower yield, and increasing the reaction time slightly decreases the stereoselectivity. The presence of the C-2 bromine substituent not only led to an increase in the degree of asymmetric induction during the P-S reaction, but was helpful for separation of the diastereomers by chromatography.

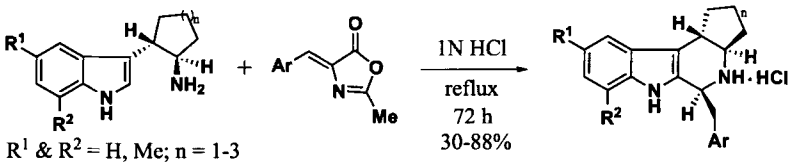
A P-S-like reaction using azalactones as arylacetaldehyde equivalents with tryptamines under acidic conditions has been reported to give rise to the THBCs.[52] While the P-S reaction of tryptamines with phenylacetaldehyde itself works well, the variety of readily available substituted phenylacetaldehydes is quite limited. Admixture of the tryptamine HCl salt and a slight excess of the azalactone in 1 N HCl at reflux for 12-72 h allowed for complete conversion to the THBC (*Scheme 55*).[52a] Strong acidic conditions (1N HCl/reflux) are required to transform the



Scheme 55

azalactone into the reactive arylpyruvic acid **A** which undergoes the P-S reaction with tryptamines, giving rise to the THBC acid **C**. Under acidic thermal conditions **C** decarboxylates to the THBC. Although the phenylpyruvic acid **B** could be detected in solution, the direct involvement of enamide **A** (or protonated azalactone) in imine formation cannot be excluded.

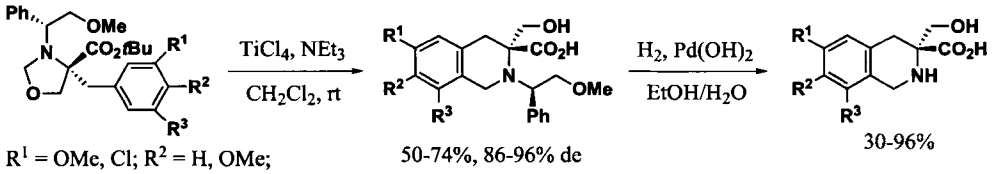
A P-S-like reaction between azalactones and conformationally constrained tryptamines in refluxing 1 N HCl over 72 h gave the corresponding THBCs which were isolated as hydrochloride salts in moderate to good yields (*Scheme 56*).[52b] The observed stereochemical outcome results from both the thermal reaction conditions and the conformational constraints of the starting tryptamines. The final THBC has all the substituents locked in the energetically favoured equatorial orientation.



R^1 & R^2 = H, Me; n = 1-3

Scheme 56

Oxazolidines have been shown to rearrange smoothly into the corresponding THIQs in the presence of $TiCl_4$ *via* intramolecular P-S reactions (*Scheme 57*).[53] Hydrolysis of *tert*-butyl ester occurred during the aqueous work-up. It was found that the addition of a small amount of NEt_3 was crucial for the successfully reproducible reaction because protonation of the starting oxazolidine nitrogen completely inhibits the P-S cyclization and addition of NEt_3 neutralizes uncontrolled acidic traces in the reaction mixture. Resultant THIQs proved to be quite unstable, and were directly submitted to hydrogenolysis, leading to quaternary amino acids. Therefore oxazolidine is a suitable tool for the asymmetric elaboration of various quaternary THIQ carboxylic acids.



R^1 = OMe, Cl; R^2 = H, OMe;
R^1&R^2 = OCH_2O; R^3 = H, OMe

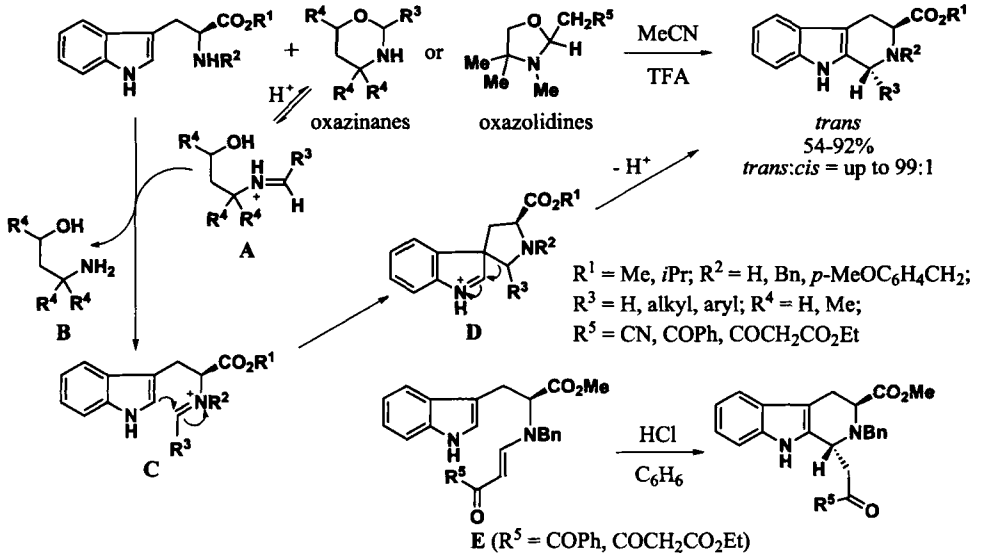
50-74%, 86-96% de

30-96%

Scheme 57

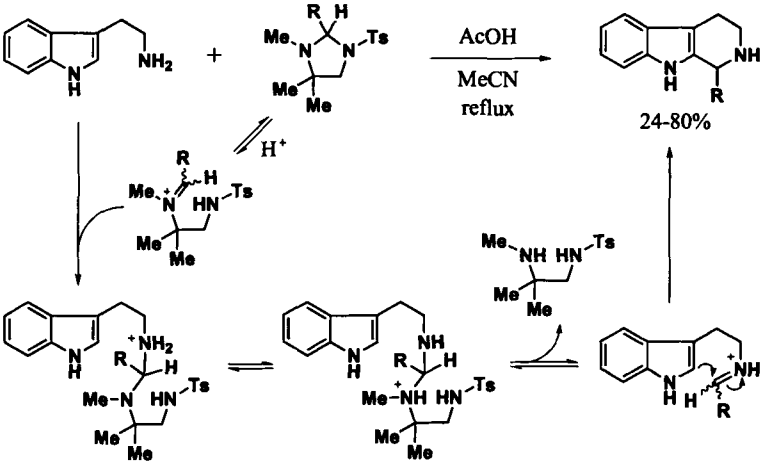
The P-S-like reaction employing perhydro-1,3-heterocycles as synthetic equivalents of several carbonyl compounds has been developed (*Scheme 58*).[54] Acid-catalyzed one-pot condensation of oxazinanes were conducted in MeCN/TFA (10:0.1) or MeCN/AcOH (10:0.1) at reflux to produce various 1,3-disubstituted and 1,2,3-trisubstituted THBCs diastereoselectively. Under the conditions of thermodynamic control 1,2,3-trisubstituted THBCs were formed mainly as *trans* isomers. All these reactions of oxazinanes (existing as ring-chain tautomers) can be visual-

ized to proceed through the formation of an iminium intermediate **C** formed *in situ*, through the loss of appropriate aminopropanol (**B**), followed by spontaneous cyclization by intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety to form a spiroindolenine **D** which rearranges and subsequently deprotonates to yield corresponding THBCs. Reactions of some oxazolidines with N_b-benzyl-L-tryptophane methyl ester furnished acyclic *trans* enamines (**E**), which upon treatment with a saturated benzene solution of HCl at 0°C produced *trans* THBCs.



Scheme 58

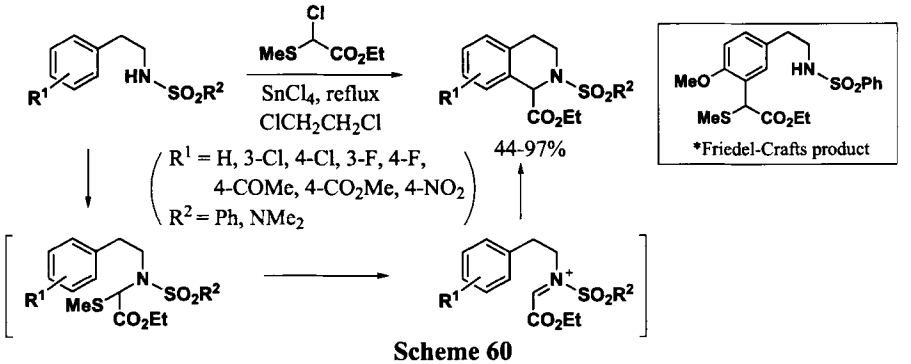
Similarly, imidazolidines reacted with tryptamine in the presence of AcOH to give 1-substituted THBCs (*Scheme 59*).[55a] 2-Substituted 1-tosyl-3,4,4-trimethylimidazolidines transfered



Scheme 59

the substituted fragment (-CHR) to tryptamine to produce cyclic products. The initial step of the transfer process is the opening of the imidazolidine ring to an iminium ion intermediate, which undergoes a nucleophilic attack by the amino group of tryptamine. Further steps involve proton transfer, followed by elimination of an amine moiety. The resulting iminium ion cyclizes to the THBC in a manner analogous to the P-S reaction. This reaction allowed a variety of substituents in the masked aldehydes.

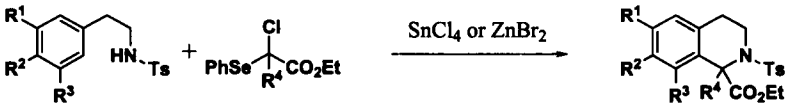
In the P-S reaction, β-phenethylamines bearing an electron withdrawing substituent on the benzene ring usually afford THIQ derivatives in poor yields or do not give any cyclized product. However Sekine *et al.* reported that the reaction of electron deficient *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(methylthio)acetate gave ethyl 2-benzenesulfonyl-THIQ-1-carboxylates in high yields (*Scheme 60*).[56] $AlCl_3$ and $TiCl_4$ gave the Friedel-Crafts product as major product, whereas a weaker Lewis acid such as $SnCl_4$, BF_3•Et_2O and $ZnCl_2$ produced only THIQ through a P-S-like reaction. $SnCl_4$ was the most suitable Lewis acid for this reaction. While cyclization proceeded in high yields when an electron withdrawing substituent is



Scheme 60

on the benzene ring, phenethylamine derivatives bearing a methoxy group on the benzene ring gave only the Friedel-Crafts product quantitatively and the 3,4-dimethoxy derivative gave a mixture of the cyclized product and the Friedel-Crafts product.[56b] On the other hand, the *N,N*-dimethylsulfamoyl derivatives also afforded the cyclized product under similar conditions. In contrast, the *N*-acetyl and the *N*-trifluoroacetyl derivatives yielded only the Friedel-Crafts product.[56b] The $NHSO_2$ group appeared very important for the successful cyclization. The cyclization was not affected by the position of substituent on the benzene ring, and depended on the electron density of the benzene ring and the activity of Lewis acid. Therefore, the alkylation reaction on the nitrogen of *N*-benzenesulfonyl-β-phenethylamines may occur first and then be followed by cyclization through the iminium cation intermediate. Both the electron withdrawing sulfonyl group and the ester group activate the iminium cation carbon enough to allow the electrophilic attack upon the electron deficient benzene ring.

It was shown that the modified P-S cyclization of *N*-sulfonyl-β-phenethylamines with α-chloro-α-phenylselenoacetate/propionate esters under Lewis acid ($SnCl_4$ or $ZnBr_2$) catalysis provided moderate to good yields of the corresponding THIQ derivatives (*Scheme 61*).[57a] Varying degrees of diastereoselection were observed using chiral sulfonamides derived from 1*S*-(+)-10-camphorsulfonic acid and/or chiral esters derived from (-)-menthol. *N*-Sulfonyl-β-phenethylamines containing less activated aromatic rings could furnish the corresponding THIQs using ethyl α-chloro-α-phenylseleno acetate in reasonable yields, albeit longer reaction times or



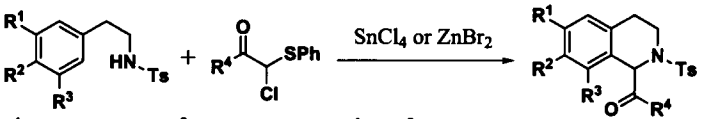
R^1 = H, Me, OMe; R^2 = H, Cl, OMe, OBn;
R^3 = H, OMe; R^4 = H, Me

12-61%

Scheme 61

more rigorous conditions were required. In the case of reactions with ethyl α-chloro-α-phenylselenopropionate, reactivity was clearly different from those of ethyl α-chloro-α-phenylselenoacetate. For example, the highly activated trimethoxy derivative was unable to react, being almost quantitatively recovered, presumably due to strong steric interactions at the ring closure position. On the other hand, less activated β-phenethylamines did not cyclize, probably due to the inability of the selenium reagent to withstand the more drastic reaction conditions required. The similar reaction of *N*-tosyl-β-phenethylamines with ethyl α-chloro-α-phenylselenoacetate catalyzed by $Yb(OTf)_3$ was reported to provide ethyl THIQ-1-carboxylates (22-81%).[57b]

It was reported also that the modified P-S cyclization of *N*-tosyl-β-phenethylamines with α-chloro-α-phenylthioketones afforded 1-benzoyl- and 1-pivaloyl-THIQs (*Scheme 62*).[57c] Yields of cyclized products with α-chloro-α-phenylthioketones were more consistent and generally higher than those with α-chloro-α-phenylselenocarboxylates. The performance of the analogous selenium reagents in this transformation was also attempted, however, its reaction was unsuccessful.

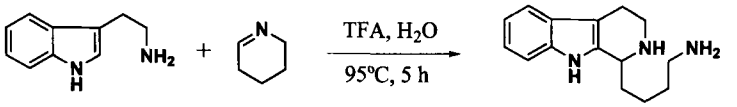


R^1 = H, Cl, OMe; R^2 = H, Me, OMe; R^1 & R^2 = OCH_2O;
R^3 = H, OMe; R^4 = Ph, *t*Bu

32-82%

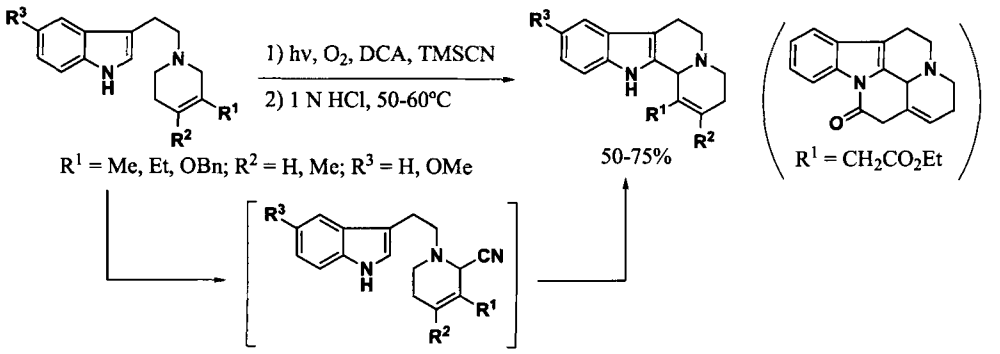
Scheme 62

A one-step synthesis of the β-carboline alkaloid nazlinine from tryptamine and 2,3,4,5-tetrahydropyridine (Δ^1-piperidine) has been performed using TFA as a catalyst for a P-S reaction in water (*Scheme 63*).[58] 2,3,4,5-Tetrahydropyridine is not stable under neutral conditions, due to irreversible imine/enamine dimerization reactions. The corresponding symmetric trimer is easy to handle and dissolving this trimer in water containing one or more equivalents of acid results in a rapid hydrolysis into the protonated monomeric form, which is stable in solution.



Scheme 63

A mild and efficient synthesis of some indoloquinolizidine alkaloids through a P-S cyclization of α-aminonitriles generated *in situ* was described (*Scheme 64*).[59] A photoinduced electron transfer process sensitized by 9,10-dicyanoanthracene (DCA), using TMSCN as

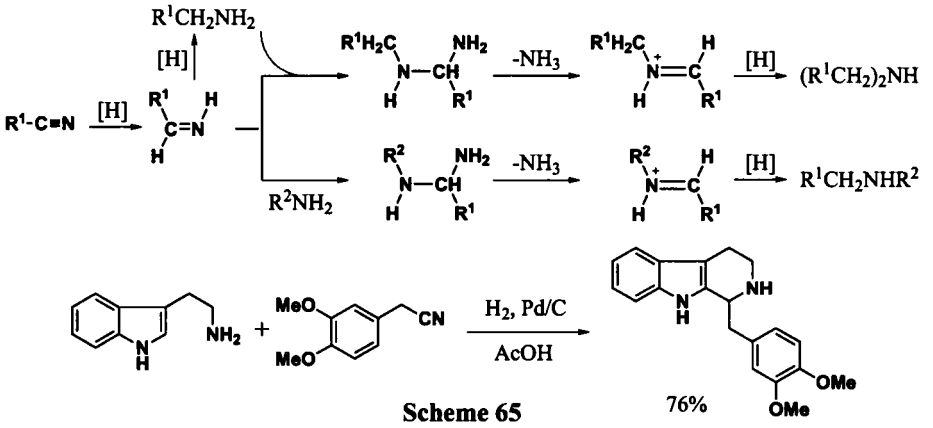


Scheme 64

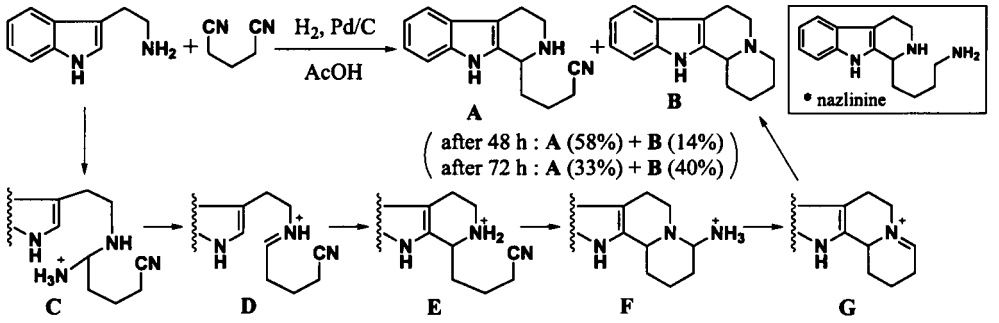
cyanating agent, produced 2-cyano-3-piperideines from tryptamine derivatives. Subsequent acid-catalyzed intramolecular cyclization of 2-cyano-3-piperideine derivatives yielded the corresponding indoloquinolizidines. In this reaction TMSCN was used as a trapping agent for iminium ions and it displayed also a suitable protection towards enamine moieties.

Preparation of THBCs and THIQs was achieved by catalytic hydrogenation of nitrile functionalities.[60] Reductive self-condensation of 3-indole acetonitrile upon catalytic hydrogenation over Pd/C in AcOH yielded 1-(3-indolylmethyl)-THBC along with tryptamine, while hydrogenation of 3,4-dimethoxyphenylacetonitrile failed to give the corresponding THIQ.[60a] However, a cross reaction between 3-indole acetonitrile and 3,4-dimethoxyphenylacetonitrile allowed isolation of 1-(3,4-dimethoxybenzyl)-THBC, which was otherwise prepared by catalytic hydrogenation of a mixture of tryptamine and 3,4-dimethoxyphenylacetonitrile (*Scheme 65*).

Hydrogenation of glutaronitrile in AcOH in the presence of tryptamine yielded 1-(3-cyanopropyl)-THBC (**A**) and indolo[2,3-*a*]quinolizidine (**B**) (*Scheme 66*).[60b] Formation of **B** implies hydrogenation of one nitrile group of glutaronitrile to a protonated imine that is trapped by tryptamine yielding **C**; elimination of NH_3 to iminium ion **D**; P-S cyclization to **E**; hydrogenation of the second nitrile group to a protonated imine that is trapped as aminal **F**; elimination of NH_3 to iminium ion **G**; and finally, hydrogenation to **B**. Nazlinine was not detected in the reaction mixture, indicating that the cyclization to **F** was entropically favored over complete hydrogenation of the intermediate protonated imine.

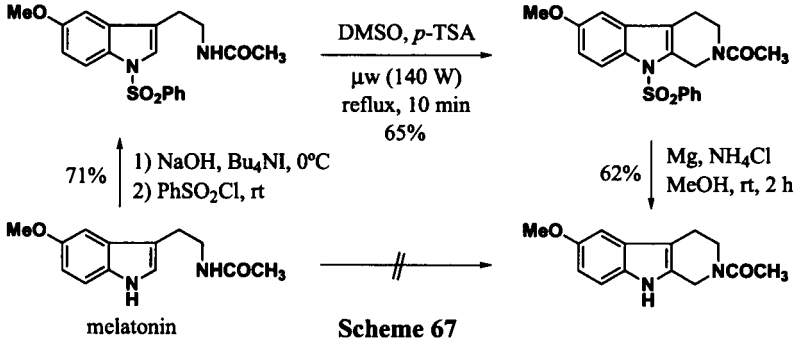


Scheme 65



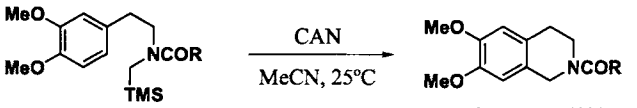
Scheme 66

It was discovered that the rapid microwave-assisted decomposition of DMSO provided formaldehyde for P-S cyclization.[61] Addition of *p*-TSA accelerated the decomposition of DMSO into formaldehyde and then allowed cyclization. Microwave-assisted P-S reactions of benzothiophene, benzofuran, and indole derivatives were conducted in DMSO. Transformation of melatonin itself failed to give THBC. However, N_a-protected melatonin was successfully cyclized to give N_a-protected THBC which was easily deprotected to give the THBC in a good yield (62%) (*Scheme 67*).



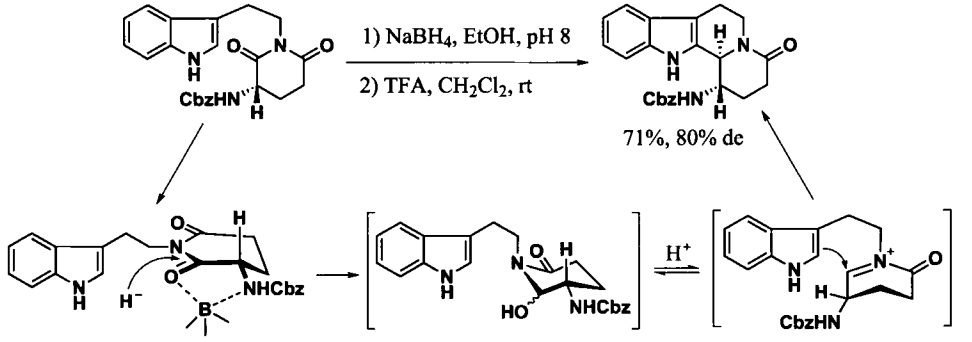
Scheme 67

The oxidative P-S cyclization process can serve as a useful alternative to classical methods.[62] Oxidation reactions of various arylalkyl α-silyl substrates were studied with ceric ammonium nitrate (CAN). Oxidation reactions of the 2-arylethyl α-silylamide and related carbamates were conducted by using 2 equiv of CAN in acetonitrile at 25°C to lead to the THIQs (*Scheme 68*). Oxidation reactions of the chain-shortened arylmethyl-amides and -carbamates, while occurring with lower efficiencies as a result of competitive iminium cation hydrolysis, afforded the corresponding isoindolines. Likewise, the process was successful in the systems that have the amide function endocyclic to the forming *N*-heterocyclic ring. Also this strategy could be employed successfully in the syntheses of benzo- and indolohydroazepines and -hydroazocines. The mild, nonacidic conditions of this oxidative process may be advantageous when applied to systems that possess particularly acid sensitive functionalities, however, one limitation is that it is intolerant of functionality which is oxidatively unstable.



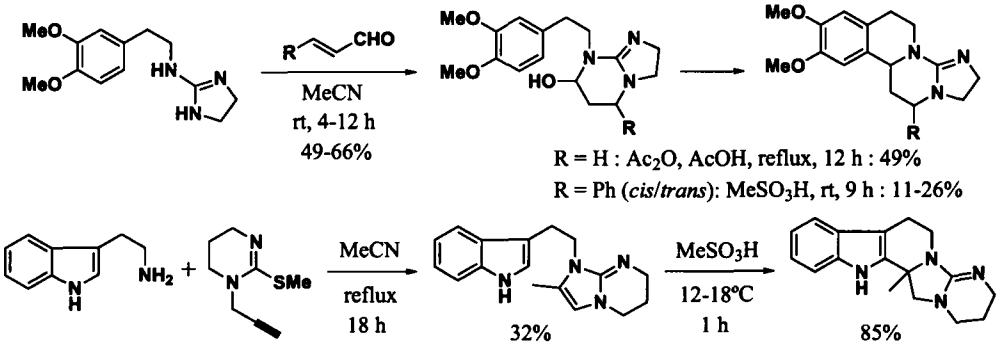
Scheme 68

trans-1-Aminoindolo[2,3-*a*]quinolizidines were synthesised by a highly regioselective imide reduction using $NaBH_4$ and a subsequent, highly diastereoselective intramolecular P-S-like reaction of *N*-acyliminium ions using TFA with 71% yield and good diastereoselectivity (80% de) (*Scheme 69*).[63] The complexation of the reductive species with both the imide carbonyl and the carbamate nitrogen should induce the selective reduction of the imide carbonyl group. Under acidic conditions, the acylcarbinolamine[11c, 64] would then be in equilibrium with the corresponding highly reactive *N*-acyliminium ion. This should favour a fast P-S-like reaction, and thereby avoid any racemisation of the Cα centre. Furthermore, as the reaction is intramolecular, indole attack should occur on the upper less-hindered face thus leading to the *trans* diastereomer.



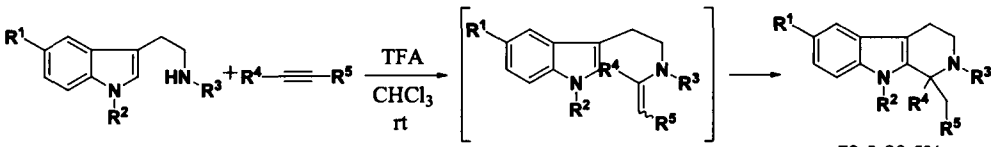
Scheme 69

Esser *et al.* reported a few mechanistically equivalent routes *via* amidinyl-iminium ions to fused isoquinolines and related diverse heterocycles (*Scheme 70*).[65] The reaction of 2-[2-(3,4-dimethoxyphenyl)ethylamino]-4,5-dihydroimidazole with acrolein and cinnamaldehyde gave the corresponding carbinolamines, followed by treatment with acid to result in the formation of imidazo[1',2':1,2]pyrimido[4,3-*a*]isoquinolines, which are also called 8,13,15-triazasteroids. On the other hand, tryptamine reacted with 2-methylthio-1-(2-propynyl)-1,4,5,6-tetrahydropyrimidine to afford the tetrahydroimidazopyrimidine derivative through the 3 sequential reactions in one step; the substitution of the methylthio group, intramolecular amination of the triple bond, and 1,3-H shift. Subsequent transformation under mild conditions yielded the pentacyclic structure with excellent yield. Similarly, the thiophene and pyrrole rings could be used as π-nucleophiles, whereas attempts with furan and imidazole rings were unsuccessful.



Scheme 70

The P-S reaction has been modified by using suitable alkynes.[66-67] The reactions of tryptamines with dimethyl acetylenedicarboxylate (DMAD), methyl propiolate, or butynone produced enamines as intermediates for subsequent P-S reaction (*Scheme 71*).[66a] Protonation of these enamines with TFA led directly to THBCs in high yields.

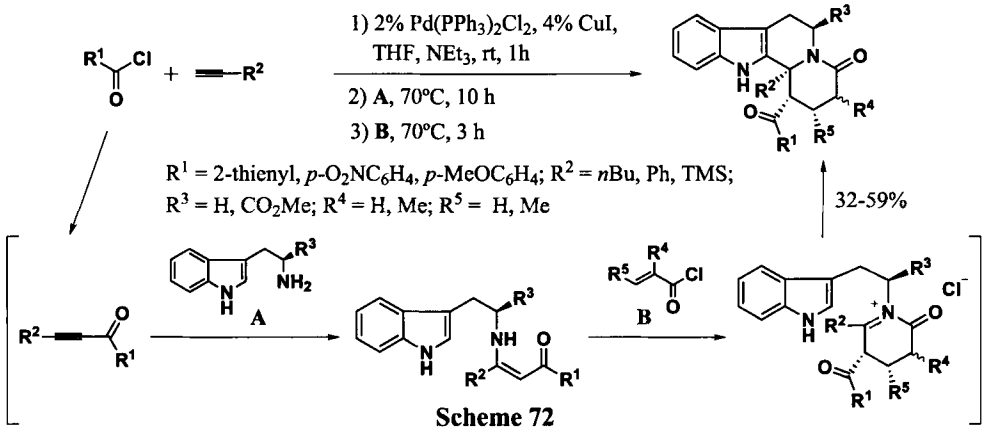


R^1 = H, OMe; R^2 = H, Me; R^3 = H, Et, Bn, CH_2CO_2Me;
R^4 = H, CO_2Me; R^5 = CO_2Me, COMe

Scheme 71

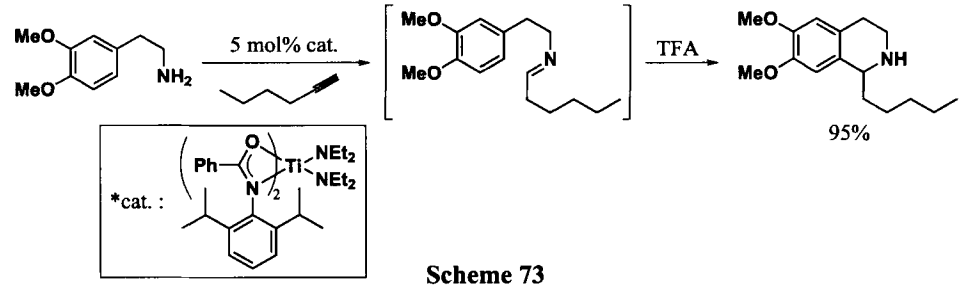
The four-component coupling-amination-aza-annulation-Pictet-Spengler (CAAPS) sequence of acid chlorides, terminal alkynes, tryptamine derivatives, and acryloyl chloride derivatives has been developed to lead to a facile and rapid one-pot access to THBCs in moderate to good yields (*Scheme 72*).[66d] One-pot coupling-amination (CA) sequence of (hetero)aryl acid chlorides, terminal alkynes and primary amines produced (*Z*)-enaminones in excellent yields.

Upon applying tryptamine or L-tryptophane methyl ester as primary amines in the CAA sequence, indolo[2,3-*a*]quinolizin-4-ones were isolated as a result of a subsequent P-S reaction. This process showed excellent diastereoselectivity. The R^2, acyl-R^1, and R^5 substituents were exclusively placed in a *syn–syn* arrangement, whereas with an R^4 substituent other than hydrogen, epimers were formed with moderate selectivity (4.5:1). More interestingly L-tryptophan methyl ester produced the THBC as a single diastereomer.



Scheme 72

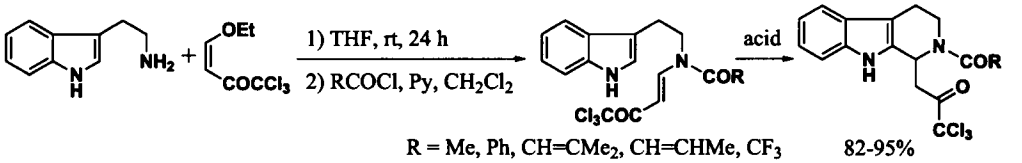
A modified P-S reaction was achieved by hydroamination of terminal alkyl alkynes with 3,4-dimethoxyphenethylamine in the presence of a bulky *bis*-(amidate)titanium-*bis*(amido) complex (*Scheme 73*).[67] This pre-catalyst is effective for anti-Markovnikov regioselective, intermolecular hydroamination of terminal alkyl alkynes with alkyl substituted primary amines to give exclusively the anti-Markovnikov aldimine products. This one-pot synthesis of THIQ avoided the use of a carbonyl-containing substrate and instead regioselective hydroamination with amine gave the reactive imine intermediate. Subsequent acid-catalyzed cyclization resulted in the formation of the corresponding THIQ.



Scheme 73

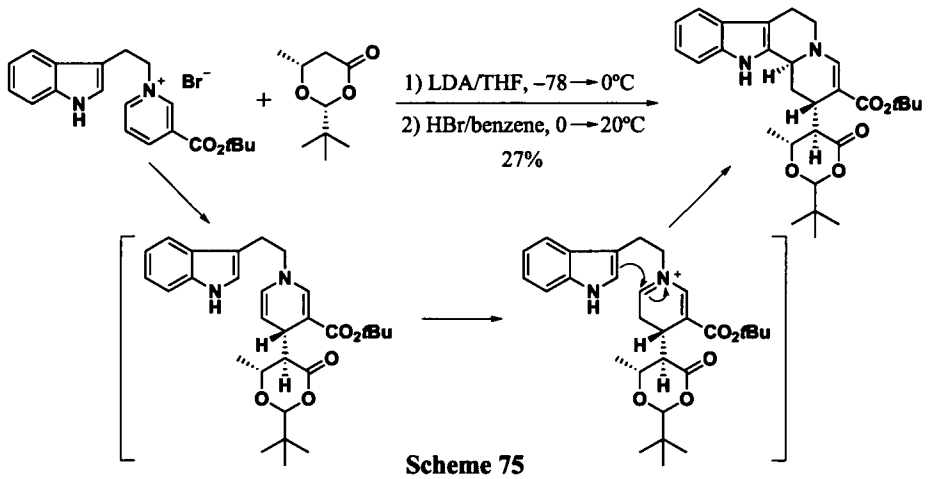
Enamine derivatives have been utilized for a modified P-S reaction.[68] Condensation of tryptamine with 1,1,1-trichloro-4-ethoxy-3-buten-2-one in THF at room temperature for 24 h gave the enamino ketone in 98% yield. Acylation of the resulting enamino ketone, followed by

treatment with TFA or Lewis acids, afforded the THBCs in excellent yields (*Scheme 74*).[68b] Lewis acids like $ZnBr_2$, $TiCl_4$, $SnCl_4$, and TMSOTf have been used and the yields were quite similar, though the use of TMSOTf gave the highest yield (95%). The trichloromethylcarbonyl group in THBCs could be converted easily into an ester moiety by reaction with an alcohol in the presence of K_2CO_3. Interestingly, treatment of non-acylated enamino ketone with TFA did not afford the expected THBC but the 2-substituted indole derivative, presumably by a P-S-retro Michael addition. Similarly, an enamino ketone derived from diethyl (ethoxymethylene)malonate gave the corresponding *N*-acetyl 2-substituted indole derivative by the reaction with TFA followed by acetylation with AcCl in pyridine.



Scheme 74

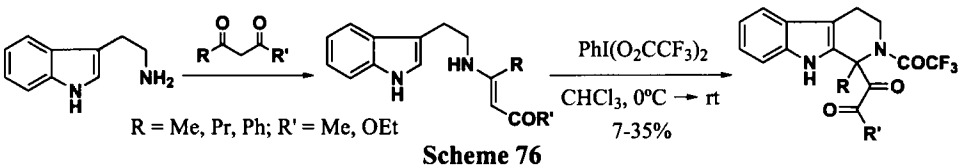
It has been reported that functionalized indolo[2,3-*a*]quinolizines were obtained *via* 1,4-dihydropyridines by the addition of appropriate nucleophiles to pyridinium salts (*Scheme 75*).[68d] The addition of chiral nucleophiles as Na- or Li-salts to pyridinium compounds and the subsequent P-S cyclization to indoloquinolizines proceeded stereoselectively. Several C-C bonds were formed in a one-pot reaction. The dioxan-4-one was used in this reaction as a 9:1 *cis/trans* mixture, because the lithiated *trans*-adduct did not react fast enough to give a detectable adduct with pyridinium salt.



Scheme 75

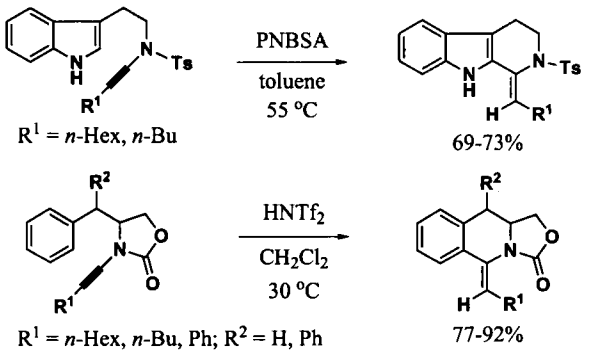
Some related oxidative cyclizations have been introduced. The reaction of enamino carbonyl derivatives of tryptamine with $PhI(O_2CCF_3)_2$ provided 1,1-disubstituted-*N*-trifluoroacetylated THBCs (*Scheme 76*).[68c] On the other hand, the reaction with the enaminone derived

from tryptamine and dimedone did not occur. This oxidative cyclization involves P-S-like cyclization, trifluoroacetylation, and oxidation.



Scheme 76

Recently, it was described that the acid-catalyzed arene-ynamide cyclization was performed *via* a keteniminium ion (*Scheme 77*).[69] $HNTf_2$ and *p*-nitrobenzenesulfonic acid (PNBSA) were effective in promoting the cyclization to give the corresponding THIQs and THBCs, respectively, in good yields. In the case of indole-tethered ynamides, $HNTf_2$ was not successful presumably due to competing protonation of the indole ring when a much stronger Brønsted acid such as $HNTf_2$ was used. On the other hand, protonations of *N*-acyl ynamides required a stronger acid because they are much less reactive than *N*-sulfonyl ynamides given that the nitrogen lone pair is more delocalized into the acyl carbonyl. This modified P-S process showed high stereoselectivity to give the (*Z*)-enamides in all cases.

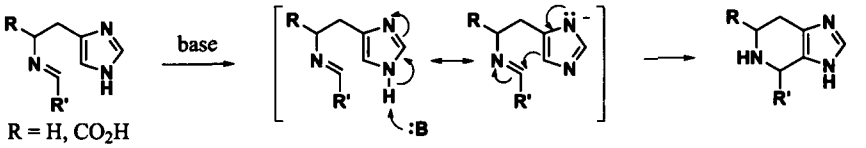


Scheme 77

2. Alternative for Amine Prototypes

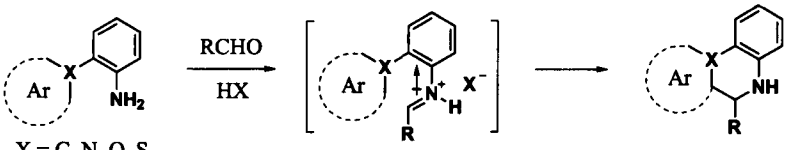
Although the P-S reaction is one of the most powerful methods for C-C bond formation, its application has been limited to only three amine prototypes: tryptophan/tryptamine,[2] histidine/histamine,[70] and dopamine/tyramine,[2] thereby invariably resulting in the formation of THBCs, tetrahydroimidazopyridines, and THIQs. This process is known to be promoted typically by acids. However there are some exceptional, interesting reports in which an alkaline catalyst was used for the P-S reaction involving histamine derived from imidazoles (*Scheme 78*).[70e-f]

On the other hand, the P-S reaction has not usually involved arylamines instead of alkylamines linked to an activated aromatic nucleus. Compared to an alkylamine, an arylamine is less reactive in regard to imine formation with either an aldehyde or a ketone. However, an iminium



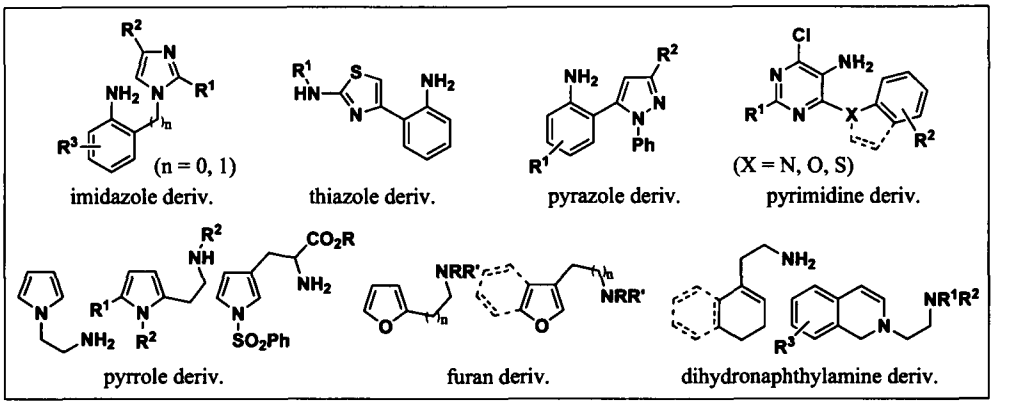
Scheme 78

ion derived from an arylamine will facilitate C-C bond formation more than an alkylamine since enhancement of the electrophilic nature of the iminium intermediate is a driving force for P-S cyclization. Cook *et al.* attributed electrophilicity of the imine double bond as the driving force for P-S cyclization and applied p*K*a values of amines to compare the electrophilicities of the imines.[20c] Comparing the p*K*a values of tryptamine (10.2) and tryptophan methyl ester (7.29) with the aniline (4.2) clearly suggests that the imine derived from an arylamine is more electrophilic since the nitrogen carries a lower electron density than that found for the imines derived from tryptophan methyl ester and tryptamine, respectively. Therefore, the imine derived from an arylamine would undergo the P-S reaction relatively faster than the substrate derived from alkylamines (*Scheme 79*).



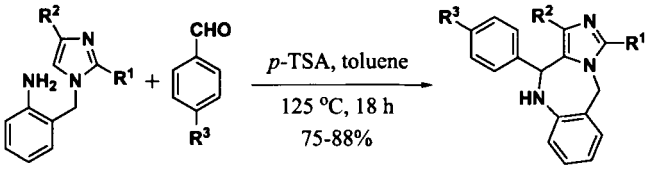
Scheme 79

As shown in *Scheme 80*, many efforts have been made to utilize a variety of activated (hetero)aromatic nuclei and to apply arylamines attached to an activated (hetero)aromatic ring to the P-S reaction for the syntheses of various heterocycles beyond THIQ and THBC derivatives.



Scheme 80

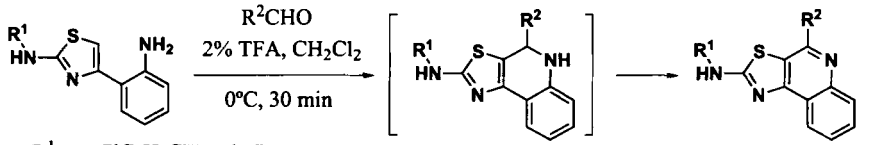
For the first time Kundu *et al.* demonstrated a new application of the P-S reaction by using arylamines instead of alkylamines (*Scheme 81*).[71] Unusual 7-membered heterocycles, triazabenzoazulenes, were obtained by changing the position of the amine functionality in the imidazole ring. The P-S-like reactions of imidazole derivatives with aromatic aldehydes were carried out in the presence of *p*-TSA in toluene at reflux for 18-20 h.



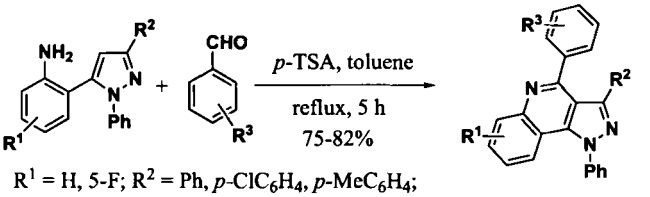
R^1 = *p*-$OMeC_6H_4CH_2$, Ph, $CH_2NHCOPh$;
R^2 = Ph, Me, *p*-$MeOC_6H_4$; R^3 = H, Me, Cl, OEt, NO_2

Scheme 81

Thiazole- and pyrazole-based arylamines have been used for the P-S reaction (*Scheme 82*).[72] The condensation of these substrates with a variety of aldehydes, in the presence of 2% TFA in CH_2Cl_2 at 0°C or *p*-TSA in toluene at reflux, led to the synthesis of thiazoloquinolines and pyrazoloquinolines, respectively. Unlike alkylamines, these arylamines readily underwent P-S-like reactions even with electron-rich aldehydes. Compared with the arylamines linked to the *N*-1 of imidazole described earlier,[71] these C-linked arylamines underwent P-S cyclization faster. This may be attributed to the relative decrease in the p*K*a value of the arylamine linked to the C-4 and C-5 in thiazole- and pyrazole-based arylamines, respectively, which are the already deactivated positions due to the multiply bonded *N*-atom, compared to the p*K*a value of an arylamine linked to the nitrogen, which behaves as an electron donor.



R^1 = *p*-$ClC_6H_4CH_2$, Ph, Bn
R^2 = *p*-$Me_2NC_6H_4$, *p*-$NO_2C_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *o*-OHC_6H_4, 2-furyl

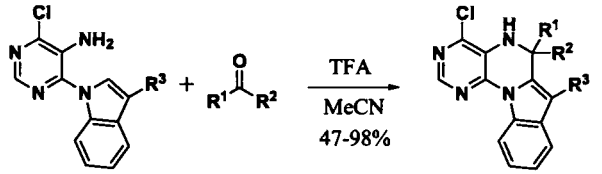


R^1 = H, 5-F; R^2 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4;
R^3 = 4-NMe_2, 4-Br, 2-OMe, 2-OH, 3,4-di-OMe, 4-NO_2

Scheme 82

It was reported that the amino group of pyrimidine was used to form an iminium intermediate with an aldehyde for a P-S-like reaction.[73-74] The iminium ion underwent an intramolecular

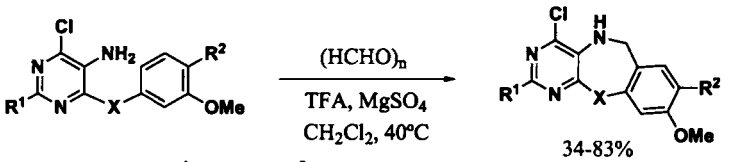
electrophilic cyclization of the adjacent electron-rich (hetero)aromatic ring to yield the 6- or 7-membered ring. Bai *et al.* described that indole-fused pteridines were prepared by the reaction of 5-amino-4-chloro-6-(indol-1-yl)pyrimidine with aldehydes or ketones in the presence of TFA (*Scheme 83*).[73a] The indolylpyrimidine substrates showed unusually high reactivity toward carbonyl compounds. The combination of the pyrimidine ring and the indole ring systems provided some conformational restrictions compared to the classical P-S reaction which has an alkylamine with more freely rotating bonds. These restrictions may help to speed up the cyclization step of the transformations. On the other hand, P-S-like cyclization of 5-amino-4-chloro-6-(*N*-methylanilino)pyrimidine with aldehydes in the presence of TFA produced 7-membered heterocyclic rings, pyrimidine-fused 5,6-dihydrobenzodiazepines.[73b]



R^1 = alkyl, aryl; R^2 = H, Me; R^3 = H, CO_2Me

Scheme 83

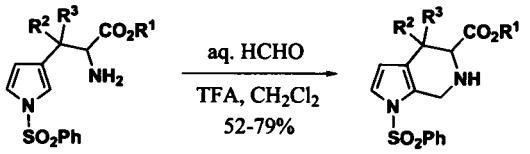
Efficient synthesis of pyrimido[4,5-*b*]-1,4-benzoxazepine, benzothiazepine, and benzodiazepine heterocyles was developed by using a modified P-S reaction of 6-heteroaryl substituted 5-amino-4-chloropyrimidine derivatives with paraformaldehyde under acidic and dehydrating conditions (TFA/$MgSO_4$) (*Scheme 84*).[74] 6-Aminoaryl, 6-oxyaryl, and 6-thioaryl pyrimidine derivatives were used to lead to the desired heterocycles.



X = O, S, NH; R^1 = H, Me; R^2 = H, OMe, O-alkyl

Scheme 84

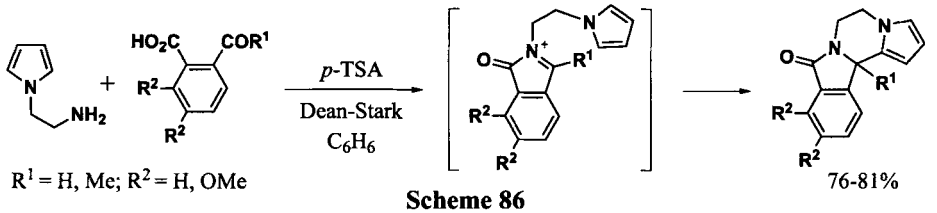
Since Rousseau and Dodd reported the first P-S reaction using pyrrole derivatives to provide the 4,5,6,7-tetrahydro-6-azaindoles (*Scheme 85*),[75a] several research groups have applied



R^1 = Me, Et; R^2 = H, OH; R^3 = H, OH, Me

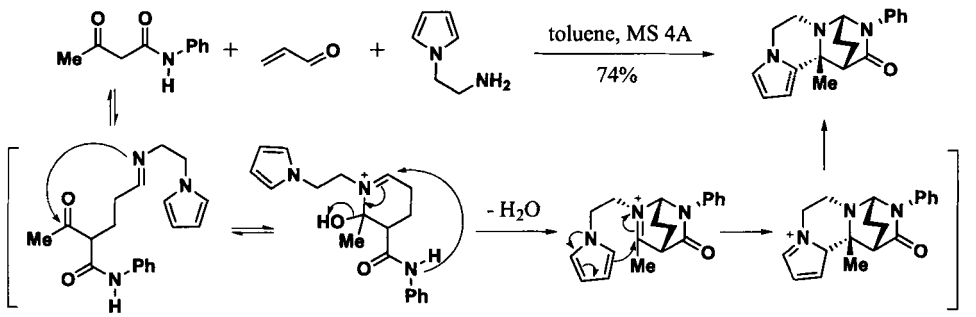
Scheme 85

pyrrole derivatives as the primary amine for P-S reaction.[36c, 75] Dihydropyrrolo[2',1':3,4] pyrazino[2,1-*a*]isoindolones were obtained by the reaction of 2-(1*H*-pyrrol-1-yl)ethylamine with 2-formylbenzoic acids or 2-acetylbenzoic acid in the presence of *p*-TSA with a Dean–Stark apparatus to remove water formed, *via* *N*-acyliminium cation aromatic cyclizations (*Scheme 86*).[75b]



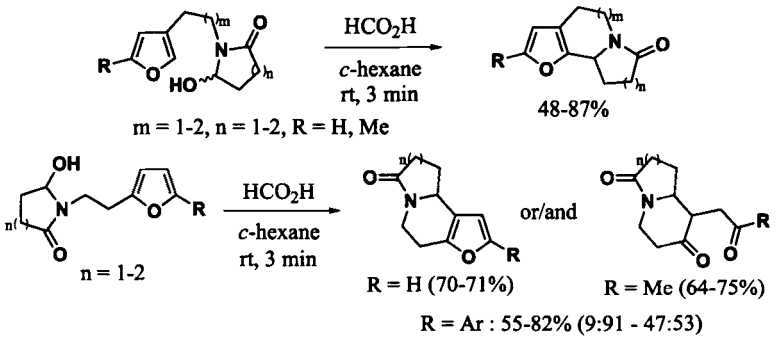
Scheme 86

Rodriguez *et al.* described C-C bond formation *via* a P-S-like intramolecular cyclization involving 1-(2-aminoethyl)pyrrole in the last step of the the multicomponent domino reaction sequence (*Scheme 87*).[75c] Under non-acidic, aprotic conditions, the tetracyclic 2,6-DABCO derivative, having a biologically relevant fused pyrrolopiperazine nucleus, was isolated as one single diastereomer, in good yield and with high chemical purity.



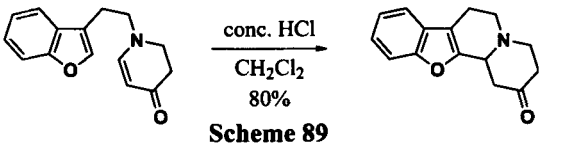
Scheme 87

Studies on the utility of furan or benzofuran moieties for P-S reactions have been demonstrated. The reaction of furan derivatives appending carbinolamides in the presence of HCO_2H in cyclohexane yielded the corresponding fused heterocycles (*Scheme 88*).[76] The outcome of the cyclization event depended on the position of the furan tether attachment (2 vs. 3), tether length, and the furan 5-substituent (R = H, CH_3, aryl). 3-Substituted furans cyclized to form both 6- and 7-membered rings containing furans, such as indolizidine, quinolizidine, pyrrolo[1,2-*a*]azepine, and pyrido[1,2-*a*]azepine ring systems in good to excellent yields. In contrast, 2-substituted furans closed to form only 6-membered rings; however, the products obtained were a function of the furan 5-substituent. The 5-H furans led exclusively to the corresponding furans, indolizidine and quinolizidine, while the 5-CH_3 furans gave only diketone compounds. 5-Arylfurans provided mixtures of furan- and diketone-containing products, with the ratio related to the substitution on the phenyl moiety.



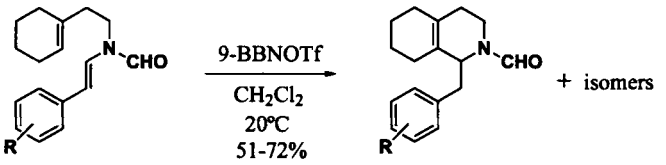
Scheme 88

The P-S cyclization of benzofuran compounds was performed to form the benzofuroquinolizine ring structure (*Scheme 89*).[77] Unlike the case of indoles, no reaction occurred with dilute acid. However, by simply increasing the concentration of the acid, cyclization of enaminone was readily accomplished to provide benzofuroquinolizine ketone in 80% yield.



Scheme 89

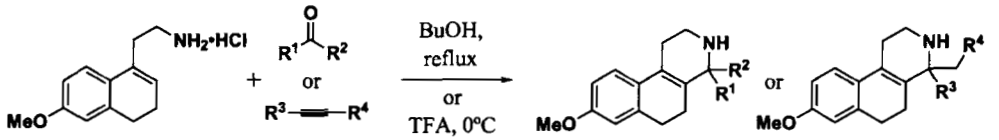
Vinylogous P-S cyclization has been developed to extend the P-S reaction for the synthesis of a variety of isoquinolines.[78-79] The acid-catalyzed cyclization of *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-formyl-2-phenylethenamines produced the corresponding 1-benzyl-2-formyloctahydroisoquinolines under relatively mild conditions (*Scheme 90*).[78] 9-Borabicyclo[3.3.1]non-9-yl (9-BBN) triflate and CF_3SO_3H gave the best results as homogeneous catalysts and the heterogeneous acid $H_3PW_{12}O_{40}$ supported on silica gel was also an active catalyst in this type of cyclization reaction. In all cases a mixture of isomeric octahydroisoquinolines was formed with the 1,2,3,4,5,6,7,8-octahydroisoquinoline as major component.



Scheme 90

A vinylogous P-S cyclization of dihydronaphthylamine derivatives has been carried out using activated aldehydes, ketones, and alkynes to prepare a variety of substituted hexahydrobenzo[*f*]isoquinolines (*Scheme 91*).[79a] The P-S condensation of dihydronaphthylamine

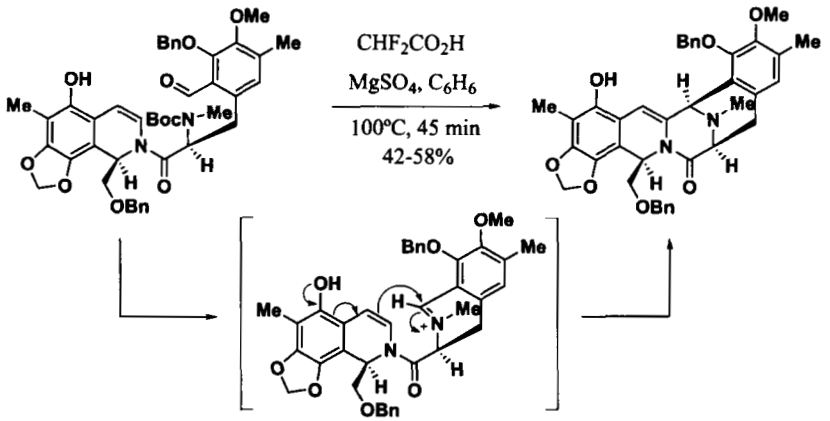
hydrochloride with more electrophilic aldehydes and with cyclic ketones worked very well in an alcoholic solvent. The use of BuOH rather than MeOH as the solvent shortened reaction times and improved product yields. In the case of unactivated ketones, harsh conditions were required to promote the reactions, which were not suitable for acid-sensitive substrates. Therefore, a milder, two-step protocol, which consisted of initial enamine formation at room temperature and subsequent treatment with acid at low temperature, was developed for these cases. Meanwhile, conjugate addition of amine·HCl with activated alkynes afforded the corresponding enamine as a single isomer which underwent smooth cyclization in the presence of TFA to yield hexahydrobenzo[*f*]isoquinolines.



R^1, R^2 = H, CO_2Et, alkyl; R^3 = H, CO_2Me; R^4 = CO_2Me

Scheme 91

Danishefsky *et al.* applied the vinylogous P-S cyclization for a stereospecific formal total synthesis of Ecteinascidin 743 (*Scheme 92*).[79b] The use of an unusual *o*-hydroxystyrene moiety has been developed for the vinylogous P-S reaction. An *o*-hydroxystyrene derivative successfully underwent cyclization to produce a pentacycle upon exposure to 30 equivalents of difluoroacetic acid in benzene.

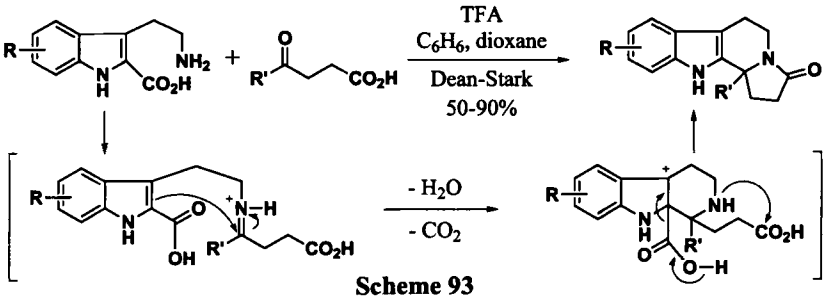


Scheme 92

3. Miscellaneous

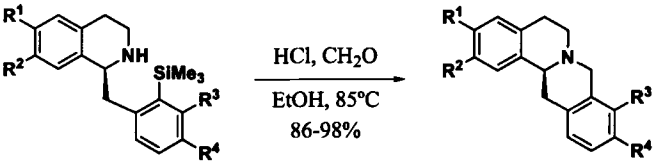
The P-S condensation of various tryptamine-2-carboxylic acids with carbonyl compounds in benzene/dioxane/TFA at reflux with water removal (Dean-Stark trap) afforded directly the corresponding THBCs in good to excellent yields with simultaneous loss of CO_2

(*Scheme 93*).[80] The reaction of tryptamine-2-carboxylic acid with a carbonyl compound forms the Schiff base and then provides the carbocation upon being heated. Loss of a proton and the elements of CO_2 to regenerate the indole double bond provides the desired THBC. The process was quite general for simple aldehydes such as benzaldehyde and cyclohexanecarboxaldehyde to yield the corresponding THBCs, while more reactive electrophiles including α-keto acids and α-keto esters yielded hexahydro-3-oxo-indolizino[8,7-*b*]indoles. It is no longer necessary to remove the 2-carboxylic acid function prior to the execution of the P-S reaction because the elements of CO_2 are lost during the process of cyclization.



Scheme 93

Silyl-directed P-S cyclization of TMS-substituted benzyl THIQs has been performed for the synthesis of protoberberines in excellent yield and complete regioselectivity (*Scheme 94*).[81] Unsubstituted benzylisoquinolines are unreactive under typical P-S conditions apparently because the aromatic ring is insufficiently activated for electrophilic substitution to occur.



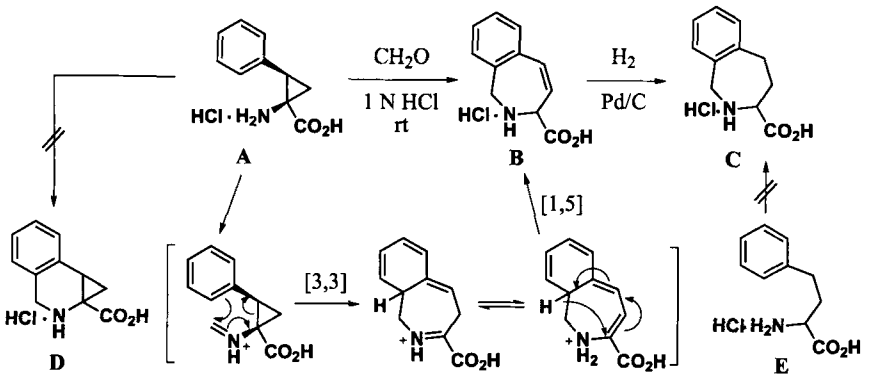
R^1, R^2 = H, OMe, OBn, OCH_2O; R^3, R^4 = H, OMe

Scheme 94

However, 2'-trimethylsilylbenzylisoquinoline gave unsubstituted protoberberine, suggesting that the TMS group is *ipso*-activating. The reactions of 3'-alkoxybenzylisoquinoline derivatives showed the dramatic combined directing and activating effects of TMS substitution. The use of *ipso* direction for protoberberine ring-closure led to the successful syntheses of five naturally-occurring protoberberines, canadine, sinactine, tetrahydropalmatine, corypalmine, and isocory-palmatine.[81b] Cyclizations of 3',4'-dimethoxy-substituted benzylisoquinoline systems proceeded with complete silyl-directed *ipso*-regioselectivity, whereas the analogous 3',4'-methylenedioxy system did not show selectivity.

Tourwé *et al.* demonstrated that the conversion of the iminium ion of *cis*-3-methanophenylalanine to the benzapine involved a novel [3,3]-sigmatropic rearrangement,

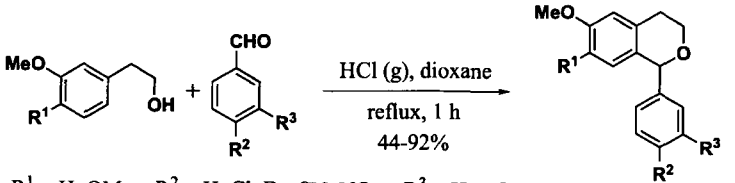
followed by a [1,5]-hydrogen shift (*Scheme 95*).[82] At first, they planned the synthesis of α-amino acid **D** by a P-S cyclization of *cis*-2,3-methanophenylalanine hydrochloride (**A**). However, using 6 N HCl at 100°C, extensive decomposition of **A** occurred. By using milder reaction conditions (rt, 1 N HCl) an almost quantitative conversion of **A** was observed with the formation of 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid **B**, which was reduced by hydrogenation to the more stable tetrahydro-analogue **C**. Interestingly, using the conditions of 6 N HCl at 100°C, P-S cyclization of homophenylalanine **E** to **C** was unsuccessful, giving the recovered starting material **E**.



Scheme 95

VII. OXA-PICTET-SPENGLER REACTION

The oxa-P-S reaction is a variation of the P-S reaction.[83] In the oxa-P-S reaction, a compound such as a 2-phenylethanol reacts with an aldehyde or a ketone to give a 3,4-dihydro-1*H*-benzo[*c*]pyranic (isochromanic) structure. In 1992 Wunsch and Zott described this reaction which was accomplished using $ZnCl_2$/HCl gas, *p*-TSA (2-3 equiv), or Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_4$) as catalysts, and high reaction temperatures.[84a] This method has some disadvantages: harmful, non-recoverable catalysts, and long reaction times (24-66 h). They reported also that activated substrates needed moderately milder conditions.[84b] Later, some new and improved methods for the oxa-P-S reaction have been shown, for example using HCl gas as catalyst in dioxane for only 1 hour (*Scheme 96*).[85]

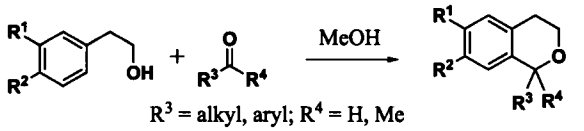


R^1 = H, OMe; R^2 = H, Cl, Br, CN, NO_2; R^3 = H, NO_2

Scheme 96

A facile method to obtain an isochromanic structure was achieved by the oxa-P-S reaction using 2-(3',4'-dihydroxy)phenylethanol with both aldehydes and ketones under very mild

conditions (using catalytic amount of *p*-TSA at 4°C) (*Scheme 97*).[86a] However, this method required a long reaction time (24 h for aldehydes and 48 h for ketones). An activated substrate



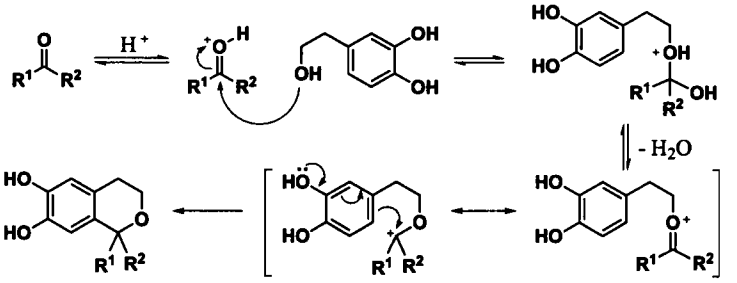
* $R^1 = R^2 = OH$
: with *p*-TSA at 4°C for 24 h (aldehyde) or 48 h (ketone) : 35-95%
: with oleic acid at 21°C for 1 week : 20-40%

* $R^1 = R^2 = OH$ or $R^1 = OH$, $R^2 = H$
: with *p*-TSA & molecular sieve at 4°C for 24 h or 48 h : 80-98%
: with *p*-TSA & Na_2SO_4 at 4°C for 24 h or 48 h : 60-90%

* $R^1 = H$, $R^2 = OH$: no reaction with recovered starting material

Scheme 97

such 2-(3',4'-dihydroxy)phenylethanol underwent the oxa-P-S reaction reaction even using a very mild acid catalyst, such as a fatty acid. In the presence of oleic acid a longer reaction time (1 week) and higher temperature (21°C) were required, nevertheless lower yields were observed than when using *p*-TSA as a catalyst. A high regioselectivity for the aromatic electrophilic substitution was obtained in the activated less hindered aromatic position (*para* to the hydroxyl group). The mechanism was proposed as follows (*Scheme 98*). The first step, the acid-catalyzed formation of the hemiacetal is followed by water loss, which provides the reactive intermediate

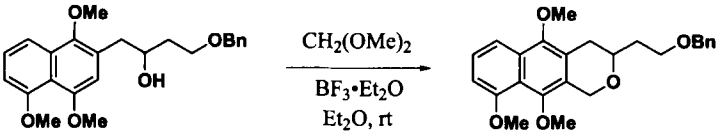


Scheme 98

that finally undergoes intramolecular electrophilic aromatic substitution, in the activated position *para* to the hydroxyl group. Aromatic aldehydes gave higher yields than aliphatic aldehydes, leading the authors to hypothesize that the water elimination step was fundamental. This step occurs more easily with a homobenzylic hemiacetal. To determine whether or not the water elimination step plays a key role in the proposed mechanism, reactions with dehydrating agents, such as molecular sieves and anhydrous Na_2SO_4 were carried out (*Scheme 97*).[86b] The highest yields were obtained when using molecular sieves as the dehydrating agent. Meanwhile, the reaction using 2-(4'-hydroxyphenyl)ethanol instead of 2-(3'-hydroxyphenyl)ethanol did not occur, with

the recovery of unchanged starting material, indicating that the hydroxyl in the *para* position to the reaction site controls the regioselectivity of the reaction.

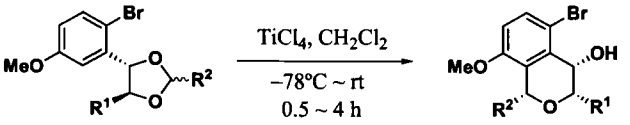
Xu *et al.* applied the oxa-P-S cyclization to a formal total synthesis of deoxyfrenolicin. The reaction of a substituted naphthalene with dimethoxymethane in Et_2O using BF_3•Et_2O afforded an 86% yield of the functionalized naphthopyran (*Scheme 99*).[87]



85%

Scheme 99

It has been discovered that the $TiCl_4$-assisted isomerization of 5-aryl-1,3-dioxolanes produced the 1,3-disubstituted-4-hydroxy-isochromans (*Scheme 100*).[88] The length and nature of the side chains bound to C-2 and C-4 of the dioxolane proved to have influence on the success and stereochemical outcome of the cyclization, probably through complex formation with the catalyst. Methyl groups yield a mixture of 4-hydroxy-isochromans in which the 1,3-*trans* diastereomer predominates, while bulkier substituents give exclusively 1,3-*cis* diastereomers. Functional groups in the C-2 side chain of the dioxolane ring may hinder cyclization by complexation with the promoter.

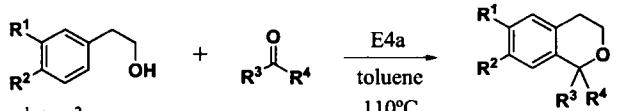


R^1 = $(CH_2)_3CO_2Et$, $(CH_2)_3OBn$, $(CH_2)_3CN$
R^2 = CH_2Br, CH_2SPh, $(CH_2)_3SO_2Ph$, $(CH_2)_3OTBDPS$

26-87%

Scheme 100

The oxa-P-S reaction of 2-phenylethanol derivatives with either aldehydes or ketones was promoted by the modified small pore size zeolite E4a to give isochromans in high yield (*Scheme 101*).[89] Using this catalyst[46] is simple, efficient, cheap, and environmentally-friendly. The catalyst could be recycled without any loss of activity. The optimal reaction conditions were the use of 0.5 g E4a and 2 mmol 2-phenylethanol in toluene as solvent at 110°C.

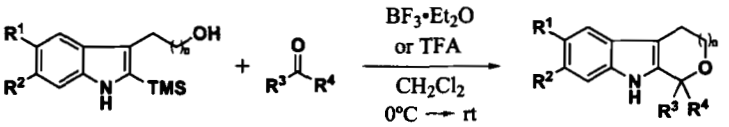


R^1 & R^2 = OMe, H, OCH_2O
R^3 = alkyl, aryl; R^4 = H, Me

64-97%

Scheme 101

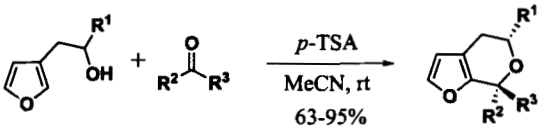
TMS-directed[81] oxa-P-S cyclizations of 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols with various ketones or aldehydes produced the tetrahydro-pyrano[3,4-*b*]indoles (*Scheme 102*).[90] This procedure constitutes a significant improvement of the traditional oxa-P-S reaction by overcoming its limitation to electron-rich or electron-neutral pyranoindoles.[91]



R^1 = H, CN, Cl, NO_2, F, CF_3, CO_2Me; R^2 = H, Cl, CF_3,
R^3 = alkyl, Ph; R^4 = H, alkyl, Ph

Scheme 102

The oxa-P-S reaction of 1-(3-furyl)alkan-2-ols with aldehydes and acetone catalyzed by *p*-TSA gave the corresponding 5,7-disubstituted 4,5-dihydro-7*H*-furano[2,3-*c*]pyrans in good yields (*Scheme 103*).[92] While the reaction with aliphatic aldehydes gave good yields of the cyclized products, using aromatic aldehydes afforded the corresponding products in low yields. This oxa-P-S reaction with aliphatic aldehydes was remarkably stereoselective, giving only *cis* isomer in most cases.



R^1 = $CH(CH_3)_2$, $(CH_2)_8CH_3$, 4-$CH_3C_6H_4$
R^2 = alkyl, R^3 = H or R^2 = R^3 = Me

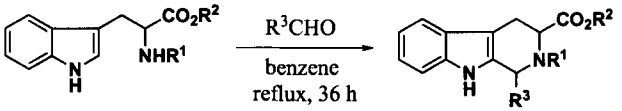
Scheme 103

VIII. ASYMMETRIC PICTET-SPENGLER REACTION

1. Using Chiral Auxiliaries

The P-S reaction has been used for construction of THBC and THIQ ring systems which are widely distributed in various natural products or bioactive compounds. To synthesize these chiral *N*-heterocycles and their analogues for medicinal purposes, asymmetric P-S reaction for the construction of the underlying heterocyclic skeleton in enatiomerically pure form has been developed and successfully employed in numerous alkaloid syntheses.[2-3] Over the past decade a number of asymmetric approaches to the P-S reaction have been reported. In the P-S reaction, the stereogenic C-1 center is generated during the ring closure in a one-pot process and chirality transfer can occur from enantiopure tryptophan esters themselves or the chiral auxiliary introduced to either *N*-protecting group of β-arylethylamine and tryptamine or the aldehyde component, thus inducing diastereoselectivity.

Many asymmetric P-S reactions rely on the use of enantiopure tryptophan esters.[2-3, 9-10, 18b, 20, 54, 66d, 93] The diastereoselective condensation between *N*-alkyltryptophan methyl ester and an aldehyde produces the 1,3-disubstituted THBC framework. The use of a bulky group on the nitrogen, such as a benzyl group, in conjunction with large aldehydes leads preferentially to 1,3-*trans* isomers.[20e, 93f-h] Cook *et al.* have investigated the role of each substituent in the stereoselectivity under nonacidic and acidic conditions (*Scheme 104*).[93i] Even though cyclohexanecarboxaldehyde gave 100% *trans* stereoselectivity of the product, the size of aldehyde had little influence on the diastereoselectivity and the change of methyl ester to isopropyl ester did not improve selectivity. In contrast, the use of a bulky *N*-protective group such as benzyl and diphenylmethyl formed 1,3-*trans* isomer stereoselectively.

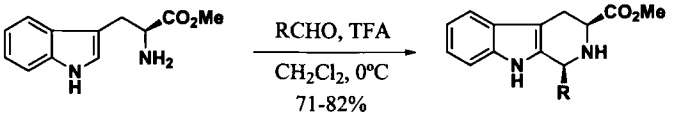


R^1 = H, Bn, $CH(Ph)_2$
R^2 = Me, *i*Pr
R^3 = Me, Pr, *c*Hex

(nonacidic : *trans*:*cis* = 74:26 ~ 100:0
acidic : *trans*:*cis* = 87:13 ~ 100:0)

Scheme 104

cis-1,3-Disubstituted THBCs could be formed with high stereoselectivity by conducting the P-S reaction under conditions of kinetic control (*Scheme 105*).[93j] In a comparative study, the roles of solvent and temperature were investigated. In refluxing benzene, little selectivity was obtained and the temperature rather than the solvent primarily influenced the selectivity. The *cis*-isomers predominated by ratios of about 4:1 when the reactions were carried out in CH_2Cl_2 at 0°C, a lower temperature than commonly used.



R = Ph, alkyl

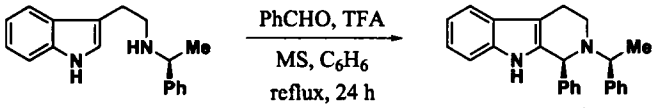
cis:*trans* = 71:29 ~ 83:17

Scheme 105

In the past few years, chiral auxiliary-controlled diastereoselective P-S reactions have been widely studied. Introduction of chiral auxiliaries on the nitrogen atom of the ethylamino side chain of β-arylethylamine or tryptamine, induced diastereoselectivity in several cases.[15, 17b, 31, 35, 51, 52b, 53, 63, 64a, 94] A variety of chiral auxiliaries were introduced including chiral sulfinyl group,[35] α-methylbenzyl group,[95-96] (-)-menthyl derivatives,[17b, 94a] cyclohexyl-based moiety,[51, 94b] and amino acid derivatives.[26-28, 63, 97, 101]

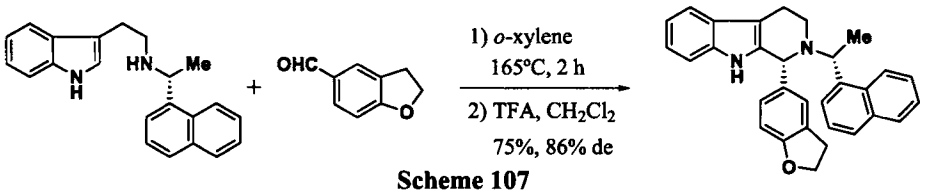
Nakagawa *et al.* described the asymmetric P-S reaction of a tryptamine derivative having an α-methylbenzyl group as a chiral auxiliary and aldehydes *via* an *in situ* generated chiral iminium salt in the presence of Brønsted acids or Lewis acids (*Scheme 106*).[95] The best diastereoselectivity and chemical yield were obtained with benzaldehyde in the presence of TFA

in refluxing benzene. The use of chiral α-methylbenzyl groups showed diastereoslectivity only with specific aldehydes.



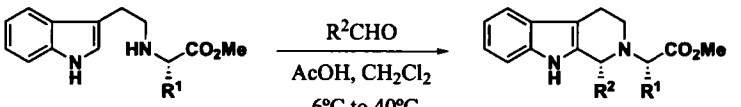
Scheme 106

The use of bulkier α-methylnaphthylamine led to a better diastereoselectivity with 2,3-dihydrobenzo[*b*]furan-5-carboxaldehyde, after acidic equilibration. In this case the reaction only occurred at 165°C in neat *o*-xylene in the absence of acid (*Scheme 107*).[96] The THBCs were obtained as a result of kinetic control under such conditions with 66% de. Interestingly, the minor diastereomer was converted to the major diastereomer under catalysis with TFA in CH_2Cl_2, resulting in the thermodynamically controlled equilibrated ratio 86% de.



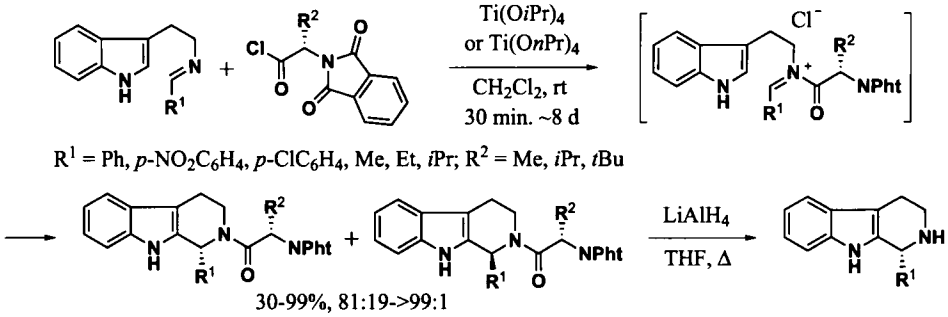
Scheme 107

Waldmann *et al.* developed the asymmetric P-S cyclization of *N*-(β-3-indolyl)ethyl substituted amino acid esters and aldehydes to produce THBCs with high stereoselectivity up to 97% de (*Scheme 108*).[97] The chiral auxiliary was removed by a retro Strecker reaction. The diastereoselectivity increased when the reaction temperature was decreased, and was better with aromatic aldehydes bearing electron-donating groups. In this process *N*-alkyliminium intermediates were generated *in situ* from indolylethyl-substituted amino acid esters and aldehydes. The subsequent cyclization of these only weakly activated electrophiles was rather slow. Consequently, only aromatic aldehydes gave preparatively useful results, whereas aliphatic aldehydes underwent competitive self-aldolization and further undesired side reactions. In addition, to remove the chiral auxiliary from the cyclization products needed a laborious multistep sequence.



Scheme 108

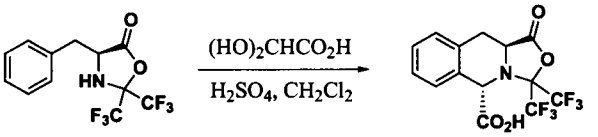
To solve these drawbacks the same group investigated an asymmetric P-S reaction involving *N*-acyliminium ion intermediates instead (*Scheme 109*).[27] Acylation of imines from tryptamine with *N,N*-phthaloyl amino acid chlorides gave THBCs with good diastereoselectivity (up to 99:1) in the presence of titanium alkoxides at room temperature. The reactions employing



Scheme 109

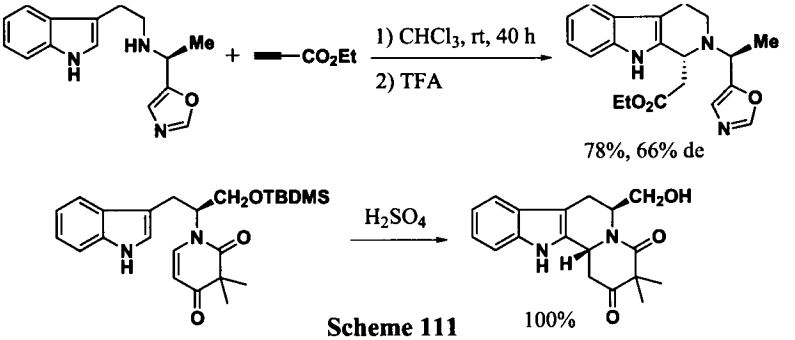
aliphatic imines were complete within several minutes, whereas several days were required for aromatic imines. The electron-withdrawing effect of the *N*-acyl group enhanced the electrophilicity of the iminium intermediates and led to a rapid cyclization. Further, the chiral auxiliary is linked to the resulting THBCs by an amide bond, which is cleavable by simple reduction in a single step. The observed stereoselectivity was rationalized by proposing a transition-state model in which the titanium atom coordinates both the carbonyl group of the *N*-acyliminium ion and the amino acid protecting group.

A diastereoselective synthesis of THIQ-carboxylic acid derivatives has been performed using an oxazolidinone derivative (*Scheme 110*).[98] The asymmetric P-S reaction of hexafluoroacetone-protected phenylalanine with glyoxylic acid hydrate led to a single diastereomer.



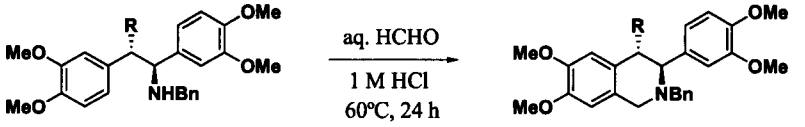
Scheme 110 47%

An asymmetric version of the modified P-S reaction using ethyl propiolate gave the corresponding THBC with modest diastereoselectivity (*Scheme 111*).[99a] On the contrary, completely selectivity was obtained in the similar reaction of a tryptophan derivative. Optically active indolyethylpyridinediones were treated with acids to give the corresponding octahydroindolo[2,3-*a*]quinolizines.[99b]



Scheme 111

A highly enantioselective method for the synthesis of 4-alkyl substituted THIQs was reported by Badía and co-workers. The *anti* amines were subjected to a P-S cyclization procedure employing aqueous HCHO and 1 M HCl at 60°C, yielding the 4-alkyl-3-aryl-THIQs in excellent yield, with no racemization (*Scheme 112*).[100]

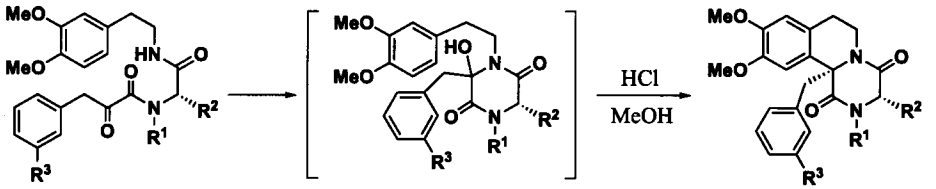


R = Me, Et, *i*Pr, Bn

84-89%, >99% ee

Scheme 112

Czarnocki *et al.* investigated L-amino acids (L-Ala, L-Phe, L-Val, L-Pro) as a source of chirality in the diastereoselective synthesis of THIQ derivatives (*Scheme 113*).[101] The P-S condensation of ketoamides proceeded under very mild conditions (HCl in MeOH at 0°C), affording diketopiperazine derivatives. When L-alanine, L-valine, and L-phenylalanine were used as chiral inductors, no cyclization occurred, probably because the cyclization step is disfavored by a partial or complete enolization that precludes cyclization for either geometric or deactivation reasons. On the contrary, good results were obtained when *N*-methyl-L-amino acids were used as chiral auxiliaries. L-Ala, L-Phe and L-Val gave rise to the *R*-configuration at the newly formed stereogenic center, whereas L-proline led to the prevalence of the (*S*)-diastereomer.

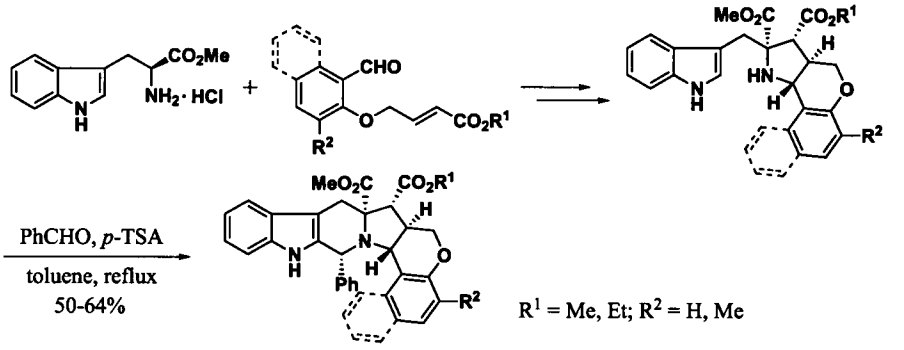


R^1 = Me; R^2 = Me, *i*Pr, Bn; R^3 = H, Cl

Scheme 113

51-92%, 74-100% de

The synthesis of benzo-/naphtha-pyrano-indolizino-indole was performed in good yields by a sequential intramolecular 1,3-dipolar cycloaddition *via* the Ag(I)-catalyzed imine route and subsequent P-S cyclization (*Scheme 114*).[102] The P-S reaction of the cycloadducts with

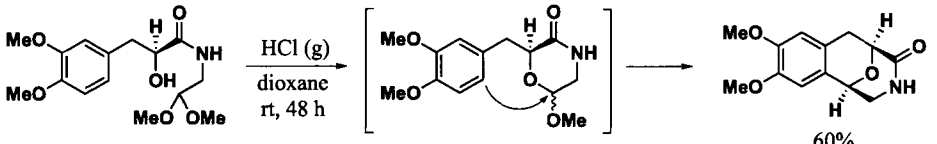


R^1 = Me, Et; R^2 = H, Me

Scheme 114

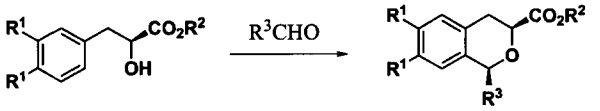
benzaldehyde proceeded smoothly to give the polyfunctional *N*-heterocycles in moderate yields. These reactions were carried out in the presence of *p*-TSA in toluene, using a Dean-Stark apparatus. In all cases only *cis*-isomer was obtained.

The stereoselective preparation of benzomorphan analogues was achieved by an intramolecular oxa-P-S reaction (*Scheme 115*).[103] The carbonyl component, which was masked as an acetal, was connected *via* an amide to the 2-phenylethanol component derived from (*S*)-tyrosine. Treatment of the amide-acetal with HCl in dioxane led to the tricyclic amide as only one diastereomer. This double cyclisation may be started with an intramolecular transacetalisation of the hydroxy group with the acetal function to give the 6-methoxy-1,4-oxazinan-3-one as intermediate. After protonation and methanol elimination a second ring closure finishes the transformation.



Scheme 115

1-Substituted 2-benzopyran-3-carboxylates were synthesized diastereoselectively by an oxa-P-S reaction of optically active phenyllactic acids with benzaldehyde and butyraldehyde under acid catalysis (*Scheme 116*).[104] Mixtures of 1,3-*cis*- and 1,3-*trans*-disubstituted isochromans were obtained with the *cis* diastereomers being favored. The phenyl moiety of phenyllactic acids derived from (*S*)-tyrosine was sufficiently activated for the reaction with aromatic and aliphatic aldehydes and ketones to yield the corresponding isochromans. On the other hand, the oxa-P-S reaction of the unsubstituted (*S*)-3-phenyllactic acid was successful only with aromatic aldehydes.



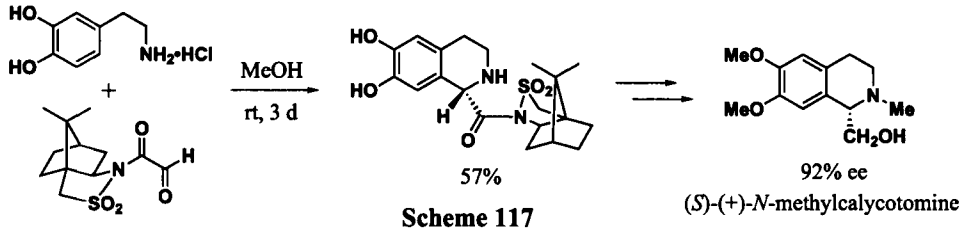
R^1 = H, R^2 = H, R^3 = Ph : $HCl/ZnCl_2$, rt : 67%, 80% de
R^1 = OH, R^2 = Me, R^3 = Ph : HCl/MeOH, rt : 71%, 22% de
R^1 = OH, R^2 = Me, R^3 = *n*-Pr : *p*-TSA/$CHCl_3$: 48%, 16% de

Scheme 116

Chiral aldehydes have also been utilized to lead to stereoselective P-S reactions with β-arylethylamines or tryptamines.[39, 42, 105]

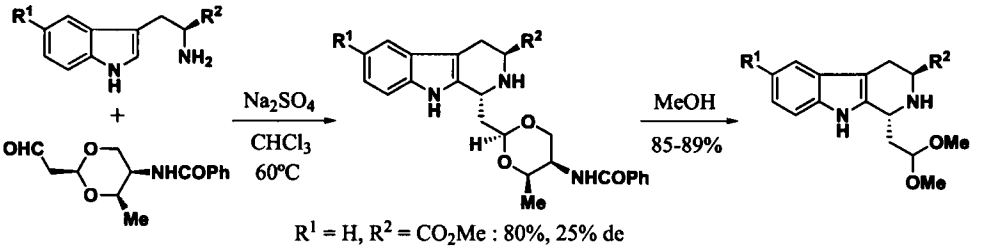
Oppolzer's sultam substituted at nitrogen with a glyoxyloyl group was used as a chiral aldehyde in the P-S reaction with dopamine hydrochloride, forming the corresponding THIQ, which was further converted into (*S*)-(+)-*N*-methylcalycotomine with high enantiomeric purity (92% ee) (*Scheme 117*).[106] The related reaction of tryptamine hydrochloride afforded the THBC with 100% de.

P-S condensation of enantiopure malonaldehyde monocycloacetals with L-tryptophan methyl ester, 5-methoxytryptamine, and tryptamine, respectively, produced the corresponding



Scheme 117

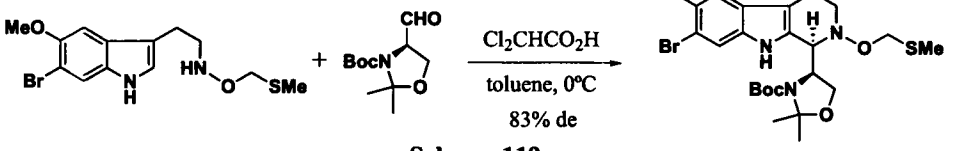
THBCs stereospecifically (*Scheme 118*).[107] The reaction with L-tryptophan methyl ester gave a mixture of two diastereomers, whereas P-S reaction of both 5-methoxytryptamine and tryptamine afforded enantiomerically pure (1*R*)-1-substituted THBCs in high yield.



R^1 = H, R^2 = CO_2Me : 80%, 25% de
R^1 = H, OMe; R^2 = H : 84-86%, 100% de

Scheme 118

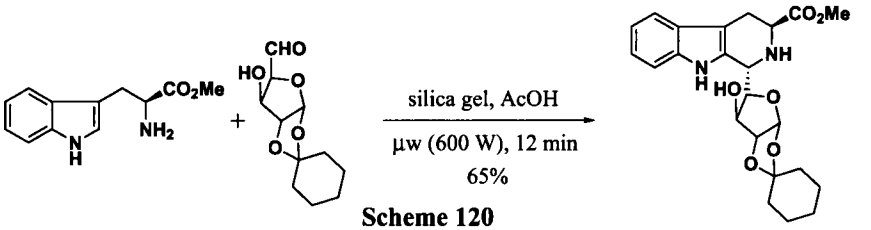
Enantiomerically pure α-aminoaldehydes have been often used to prepare chiral *N*-heterocycles diastereoselectively.[108] Fukuyama *et al.* described the stereocontrolled total synthesis of (-)-eudistomin C by the Brønsted acid-catalyzed diastereoselective P-S reaction.[108e] An initial attempt using a model substrate lacking the bromo and methoxy groups in the indole ring gave the undesired diastereomer as the major product under standard conditions (TFA in CH_2Cl_2, –78°C). Finally, it was found that the reaction in the presence of a catalytic amount of chloroacetic acid or dichloroacetic acid in toluene proceeded smoothly at 0°C to afford the desired diastereomer with high diastereoselectivity (11:1) (*Scheme 119*).



Scheme 119

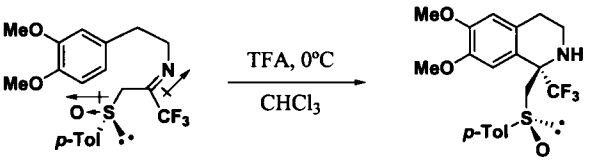
Several P-S condensations of biogenic amines with sugars have been reported.[39, 109] Recently, Giri *et al.* reported the microwave assisted P-S reaction of a sugar derivative on a silica gel support under solvent free conditions (*Scheme 120*).[109f] The reactions of tryptamine and β-phenylethylamine with a sugar derivative under microwave irradiation gave a diastere-

omeric mixture of THBC and THIQ respectively, whereas L- and D-tryptophan methyl esters under the same conditions led to a single diastereomer of the corresponding chiral THBCs stereoselectively.



Scheme 120

The stereoselective synthesis of the quaternary 1-trifluoromethyl THIQ was achieved by the intramolecular P-S cyclization using a sulfinyl group as a removable chiral auxiliary to generate the C-1 quaternary stereogenic center, as well as an activating moiety for the introduction of an oxygen functionality, such as a hydroxyl or a carbonyl (*Scheme 121*).[110] The intramolecular P-S reaction of the (*R*)-β-iminosulfoxide which exists with (*Z*)-geometry, that is with the sulfinylmethyl and the *N*-arylethyl group in *cis* configuration with respect to the C=N bond, produced the desired THIQ as a 6:1 mixture of diastereomers. The stereoselectivity was postulated to result from the *cis* geometry of the C=N bond, with the electron-rich 3,4-dimethoxyphenyl group and stereogenic *p*-tolylsulfinyl group being spatially close, thus minimizing the dipole-dipole interaction between the S=O and C=N bonds and hindering the *si* face of the molecule. On the other hand, the somewhat unusual high reactivity of this ketimine derivative was attributed to the electron-withdrawing effect of the trifluoromethyl group, which strongly increases the electrophilic character of the iminic carbon C-1.

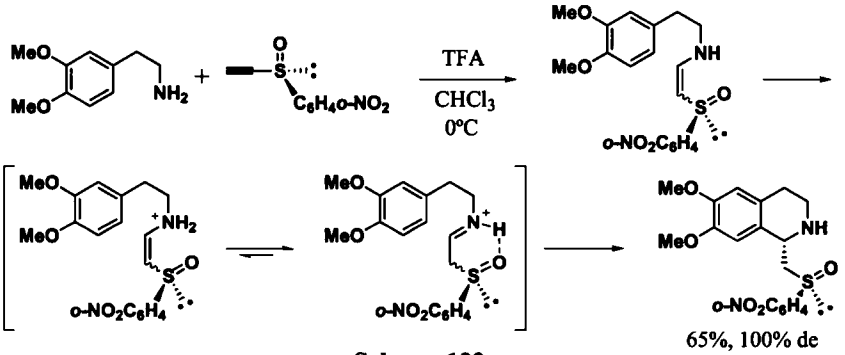


74%, dr = 6:1

Scheme 121

A modified P-S reaction of 2-(3,4-dimethoxyphenyl)ethylamine or tryptamine with a chiral acetylenic sulfoxide in the presence of acid afforded THIQ and THBC skeletons in high to moderate diastereoselectivity (*Scheme 122*).[111] First, a C-N bond was formed through Michael addition of an amine. Without isolation of the Michael adduct β-aminovinyl sulfoxides, a C-C bond was then built by acid, such as TFA or *p*-TSA, induced cyclization of the electron-rich aromatic ring to the β-carbon of the chiral sulfoxide. Control of diastereoselectivity was achieved in this one-pot addition-cyclization sequence. The factors that affected the diastereoselectivity and yield of this reaction were the substituent on the benzene ring of the sulfoxide and the type of acid and solvent used. Remarkable diastereoselectivity was observed in the cyclization of the

β-aminovinyl sulfoxide prepared from 2-(3,4-dimethoxyphenyl)ethylamine and chiral *o*-nitrophenylacetylenic sulfoxide in an acidic medium.

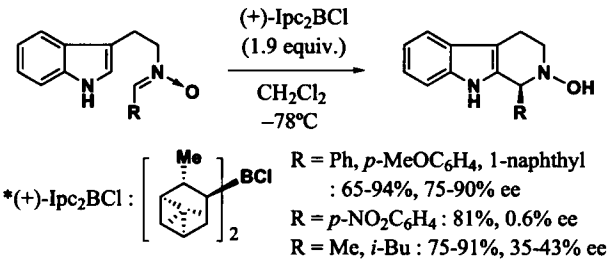


Scheme 122

2. Using Chiral Lewis Acids

Chiral Lewis acids have been used in enantioselective P-S reactions of *N*-hydroxytryptamines but gave only satisfactory results with aromatic aldehydes.[112] The chiral Lewis acid-mediated P-S reaction requires the use of superstoichiometric amounts of a chiral boron reagent, and its scope is restricted to N_b-hydroxytryptamine-derived nitrones.

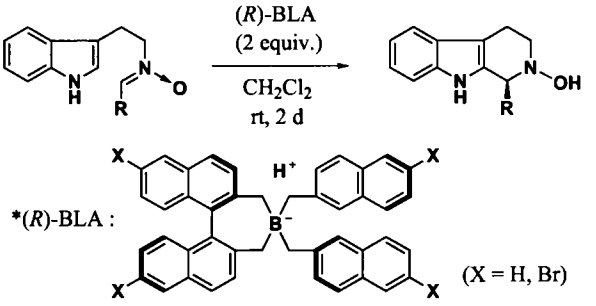
Nakagawa and co-workers have shown that the cyclization of N_b-benzylidenetryptamine catalyzed by diisopinocampheylchloroborane (Ipc_2BCl) gave chiral spiroindolines instead of optically active THBCs.[113] Later, they found that the P-S reaction of N_b-hydroxytryptamine gave the corresponding 1-substituted-2-hydroxy THBCs with up to 90% ee employing (+)-Ipc_2BCl as a chiral Lewis acid catalyst (*Scheme 123*).[112a-b]



Scheme 123

The enantioselective P-S reaction catalyzed by chiral binaphthol-derived Brønsted acid-assisted Lewis acids (BLA) was also demonstrated (*Scheme 124*).[112b-c] The P-S reaction of nitrones, prepared from N_b-hydroxytryptamine with aldehydes, gave the corresponding 1-substituted-2-hydroxy THBC with up to 91% ee. The introduction of bromine at the 6- and 6'-positions of binaphthol had little effect on either the chemical yield or enantioselectivity. Reactions of benzaldehyde derivatives gave the corresponding 2-hydroxy THBCs in high yield

with good to high enantioselectivity up to 91% ee. In particular, the enantiomeric purity of the *p*-$NO_2C_6H_4CHO$ derivative was greatly improved compared with that obtained from the reaction with (+)-Ipc_2BCl, which showed only 0.6% ee. In contrast, bulky naphthyl derivatives and nitrones from aliphatic aldehydes gave THBCs with moderate enantioselectivity. The (*S*)-enantiomers of N_b-hydroxy THBCs were obtained from reactions catalyzed by (*R*)-BLA, except for the reaction of acetaldehyde derivatives. Cyclization with enantiomeric (*S*)-BLA yielded (*R*)-THBC in almost the same chemical and enantiomeric yields, but with opposite facial selectivity.

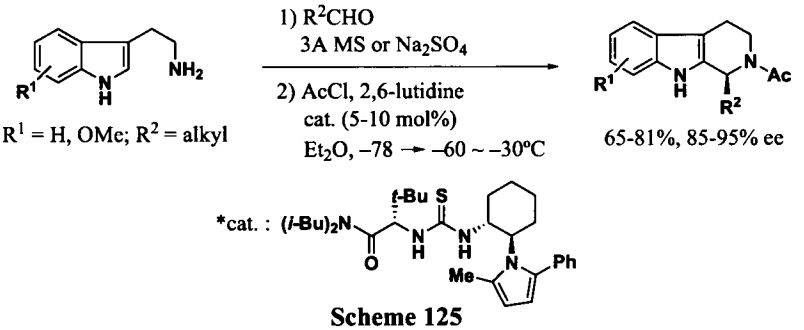


R = Ph, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$: 39-81%, 73-91% ee
R = 1-naphthyl, Me, *i*-Bu : 59-94%, 15-50% ee

Scheme 124

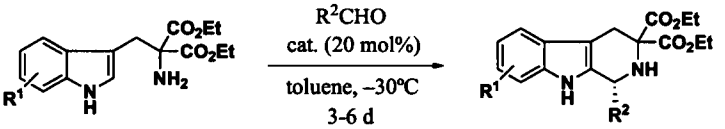
3. Using Chiral Catalysts

Jacobsen *et al.* reported asymmetric *N*-acyl P-S reactions using chiral thiourea derivatives, providing access to a range of *N*-acetyl THBCs in high enantioselectivies (*Scheme 125*).[114] A weakly Lewis basic *N*-acyliminium ion was activated by a chiral hydrogen bond donor. Imines obtained by condensation of tryptamine with aldehydes were used without further purification and the yields of cyclized products for the two-step procedure were generally good. Variation of the indole moiety was tolerated, however, reactions of substrates derived from aromatic aldehydes or trimethylacetaldehyde showed low reactivity.



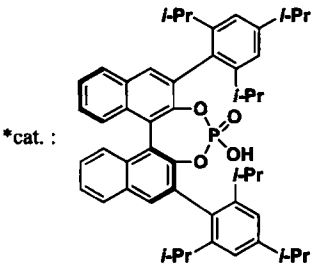
Scheme 125

Recently, List and co-workers demonstrated the highly enantioselective Brønsted acid-catalyzed P-S reaction of various tryptamines with both aromatic and aliphatic aldehydes using a chiral phosphoric acid catalyst (*Scheme 126*).[115] The reaction tolerated a variety of different aldehydes with good results. Both aliphatic unbranched aldehydes and branched aldehydes gave the corresponding THBCs in reasonable to excellent yields and in high ee's. Aromatic aldehydes, especially electron-poor aromatic aldehydes, afforded the THBCs in up to 98% yield and 96% ee. Limitations of this system include the requirement of a geminal diester functionality.



R^1 = H, OMe, OBn; R^2 = alkyl, aryl

40-98%, 62-94% ee



Scheme 126

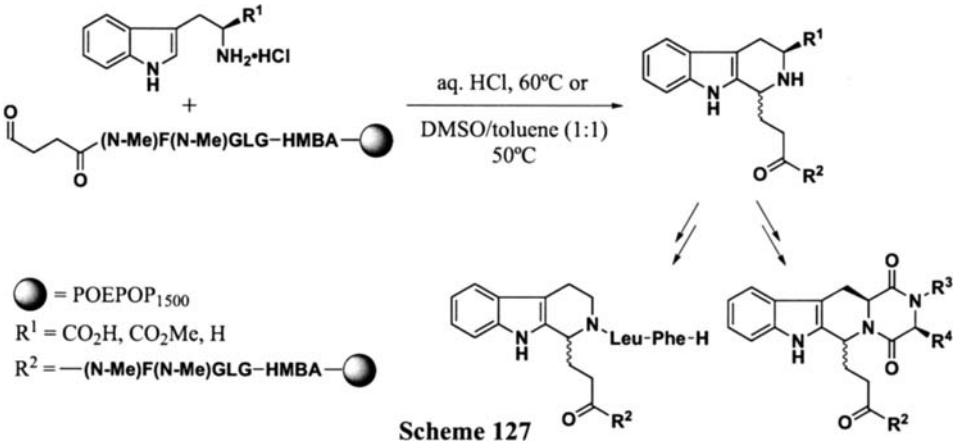
IX. APPLICATIONS OF THE PICTET-SPENGLER REACTION

1. Solid-Phase Synthesis

Natural and synthetic products containing a THBC and THIQ pharmacophore exhibit a wide range of important medicinal bioactivities. Therefore, the heterocyclic skeleton of THBCs and THIQs is an ideal choice for the design of pharmacophore-based combinatorial libraries targeted at drug discovery, through generation of a large number of structurally diverse compounds. Some combinatorial synthetic approaches have been developed to generate molecules containing the THBC and THIQ core structure, both in liquid and in solid phase.[43c, 116] Over recent years, a number of articles on solid phase P-S routes especially to THBCs have appeared. The synthetic strategy is based mainly on the acid-catalyzed P-S condensation of tryptophan analogues with aliphatic and aromatic aldehydes.

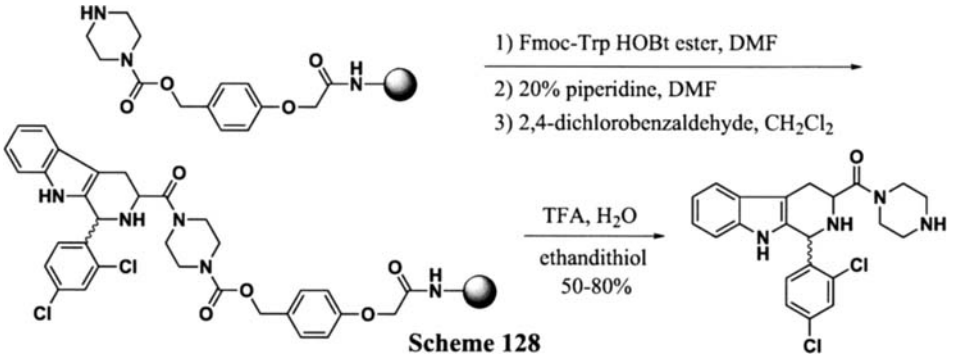
It was reported that *N*-terminal peptide aldehydes were synthesized on a solid support and utilized as electrophiles in P-S condensations leading to THBCs either positioned centrally in a peptide or fused with a diketopiperazine ring in the *N*-terminus of the peptide (*Scheme 127*).[117a] Protection of the two succeeding amide nitrogens was necessary in order to avoid reaction between the aldehyde and backbone amides. The aldehyde was submitted to a range of conditions with tryptophan and histidine, including the methyl esters of these, tryptamine and pheny-

lalanine. Treatment of aldehyde with histidine, histidine methyl ester, and phenylalanine was not successful. On the other hand, tryptophan, its methyl ester, and tryptamine underwent P-S condensations successfully to give the corresponding THBCs in almost 100% purity.



Scheme 127

It is noteworthy that in all reports, with the exception of two examples using polymer-supported aldehydes,[117] tryptophan derivatives were used as substrates, mostly with the tryptophan carboxyl group serving as the means of attachment to the resin. A general solid phase synthesis of THBCs has been described (*Scheme 128*).[118] Coupling of piperazine to 4-nitrophenyl-4-oxycarbonylmethylphenoxyacetyl carbonate resin yielded an amino alkyl urethane resin. The secondary amino groups on the resin were acylated by Fmoc-Trp hydroxybenzotriazole ester or reductively alkylated by Fmoc-tryptophanal. Deprotection of primary amino groups

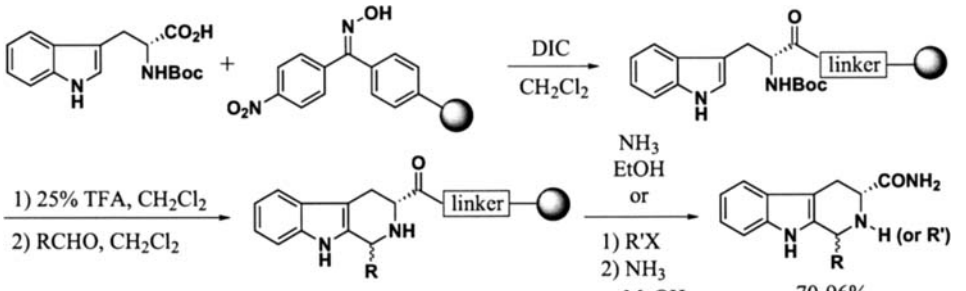


Scheme 128

was followed by condensation of resin bound tryptophan residues or non-peptide structures carrying 3-(2-aminoethyl)indole structures with aldehydes to produce 1-substituted THBCs, which were cleaved from the resin by TFA. THBCs were obtained in relatively high yields under the mild reaction conditions with a wide range of differently substituted aromatic and aliphatic aldehydes, including *N*-protected amino aldehydes. Meanwhile, attempts to generate additional diversity by derivatising the secondary nitrogen at the 2 position of the THBC moiety, by both

reductive alkylation with benzaldehyde and acylation with acid chloride of Fmoc-glycine, were unsuccessful probably due to steric hindrance.

A similar P-S cyclization utilizing tryptophan linked to the Kaiser oxime resin has been reported to give the THBC derivatives, which could be functionalized further by reaction with acylating reagents (*Scheme 129*).[119] The Kaiser oxime resin is stable to acidic conditions and the cleavage by amines and other nucleophiles affords the facile release of products. Boc-L-Tryptophan was attached to the oxime resin by 1,l-diisopropylcarbodiimide (DIC) conditions to

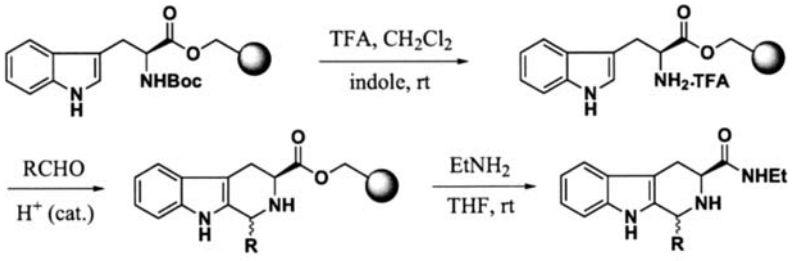


Scheme 129

generate the polymer bound material. Removal of the Boc protecting group with TFA followed by the addition of the aldehydes afforded the THBCs attached to the oxime resin. Nucleophilic cleavage from the resin with ammonia in EtOH afforded the resin-free THBC derivatives as a diastereomeric mixture in high yield and purity. To further functionalize the THBC analogs, resin-bound THBC was treated with an acid chloride, isocyanate or sulfonyl chloride and cleaved by treatment with ammonia in MeOH/CH_2Cl_2 to give the fully functionalized THBC analogs.

Typically, solution-phase P-S reactions are carried out in protic solvents with acid catalysts, conditions not generally amenable to solid-phase reactions since most resins do not swell in protic solvents and acidic conditions exclude the use of acid-cleavable linker strategies. With these solid-phase limitations, Yang *et al.* attempted a solid-phase P-S reaction in benzene or toluene with Fmoc-Trp-Wang resin.[120] While the reaction was very slow at room temperature, reaction at 80°C overnight occurred in moderate purity. The inconvenience of heating and the insolubility of many aldehydes in toluene negated this approach. Next, the authors found that Merrifield resin-bound tryptophan underwent P-S reaction with a variety of aldehydes at room temperature under acidic conditions to give THBCs in excellent yield and purity after cleavage, with the exception of 4-nitrobenzaldehyde (*Scheme 130*).[120] Removal of the Boc group from commercially available Boc-Trp-Merrifield resin under the normal acidic conditions (TFA/CH_2Cl_2 1:1) caused a significant amount of *t*-butyl alkylation to the indole as a side reaction, which was able to be suppressed by addition of indole or thioanisole in the reaction mixture. Reactions were conducted with excess aldehyde in the presence of 10% TFA in CH_2Cl_2. Cleavage of the product from the resin was readily achieved with ethylamine, providing the ethyl

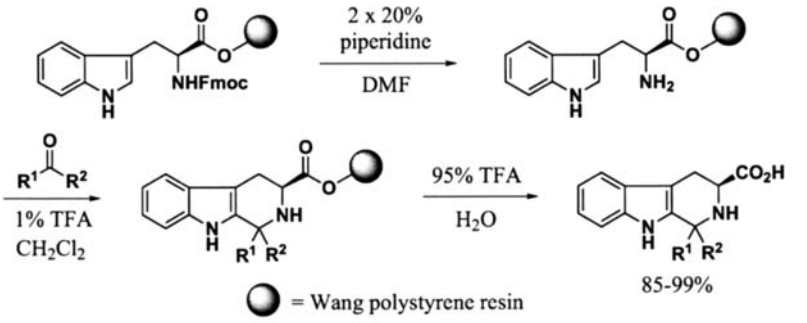
amide. Except for 4-nitrobenzaldehyde, substitution of the benzene ring had little effect on the product purity or yield and aliphatic aldehydes gave somewhat lower purity.



Scheme 130

91-100%

Mayer *et al.* also reported a P-S reaction of polymer bound tryptophan with a variety of aldehydes and ketones under acidic conditions to produce THBCs in excellent yield (*Scheme 131*).[121] Commercially available Fmoc-Trp-Wang resin was treated with 20% piperidine in DMF to give the deprotected resin-bound amine, which then reacted with aldehyde or ketone and 1% TFA in CH_2Cl_2 at room temparature to give the resin-bound THBC. Cleavage from the support was accomplished by suspending and stirring the resin in neat TFA for a period of two hours at room temperature.

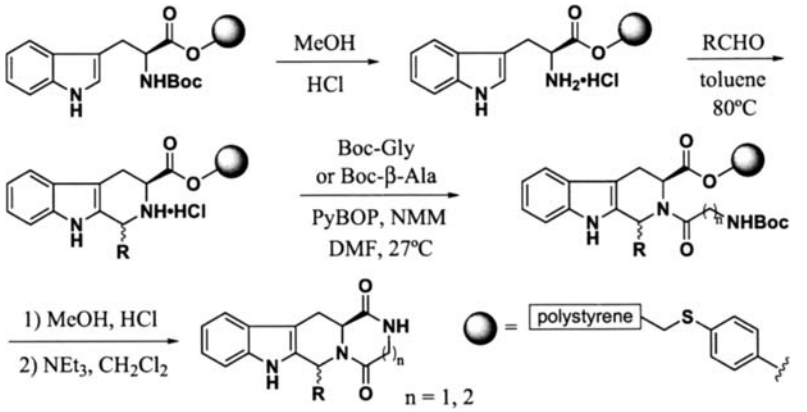


Scheme 131

85-99%

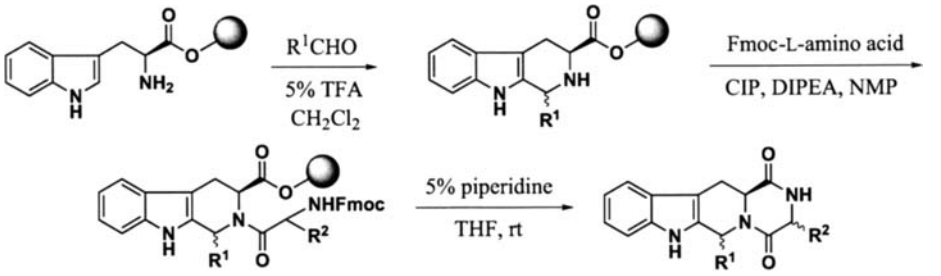
The synthesis of diketopiperazines and seven-membered *bis*-lactams has been developed on Merrifield resin utilizing an acid-stable, amine-cleavable 4-hydroxythiophenol linker or on hydroxyethyl functionalized polystyrene resin.[122] Deprotection of the 4-hydroxythiophenol-linked resin-bound L-Boc-tryptophan was followed by heating (toluene, 85°C, 18 h) in the presence of an aldehyde (6 equiv) without additional acid to provide THBCs with excellent conversion (*Scheme 132*).[122a] In general, both imine formation and subsequent cyclization were tolerant of a wide variety of aliphatic, aromatic and heteroaromatic aldehydes. However, α,β-unsaturated aldehydes and aromatic aldehydes having electron-donating substituents were problematic. Cleavage from the resin with primary amines provided THBC-2-carboxamides. Alternatively, acylation at the carboline 2-position with Boc-glycine and Boc-β-alanine, followed by deprotec-

tion and neutralization, resulted in intramolecular cyclization and cleavage to afford the desired six- and seven-membered *bis*-lactams.



Scheme 132

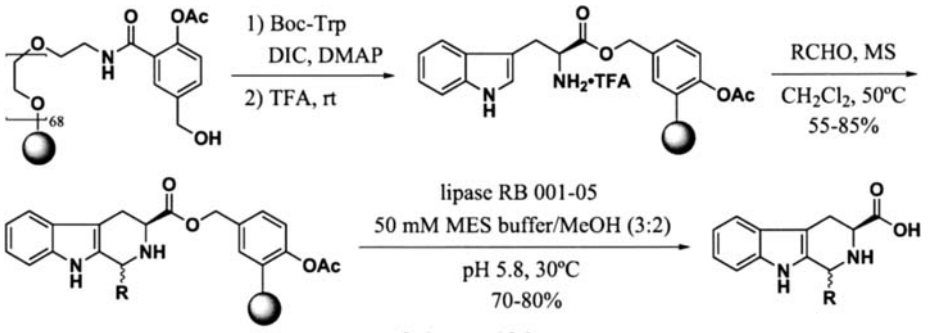
A similar approach was used for the solid-phase synthesis of structural analogs of fumitremorgins, verruculogens and tryprostatins. P-S condensation of hydroxyethyl polystyrene resin-linked L-tryptophan with excess aldehydes provided THBCs in the presence of TFA in CH_2Cl_2 at room temperature (*Scheme 133*).[122b] Use of ketones also led to the desired THBC



Scheme 133

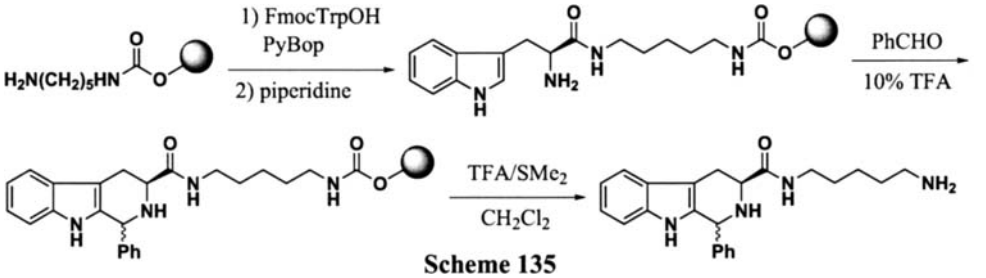
systems, but at a lower rate. Coupling of the resultant secondary amine with Fmoc-protected amino acids occurred with CIP (2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate) and DIPEA (diisopropylethylamine) in NMP. Fmoc-deprotection and subsequent cyclization/cleavage in THF containing 5% piperidine gave the desired diketopiperazines in moderate to high overall yields and high chemical purity.

Utilization of the 4-acyloxy-3-carboxybenzyloxy group as an enzyme-labile linker has been shown to be effective in the solid-phase P-S reaction (*Scheme 134*).[123] The linker was first esterified with Boc-L-tryptophan, and the Boc group was then removed by treatment with TFA. The support-bound tryptophan was then condensed with aliphatic and aromatic aldehydes at 50°C in the presence of molecular sieves to give THBCs. The resin-free THBCs could be released from the polymeric support by lipase RB 001-05 at pH 5.8 in 50 mM MES buffer/MeOH (3:2).



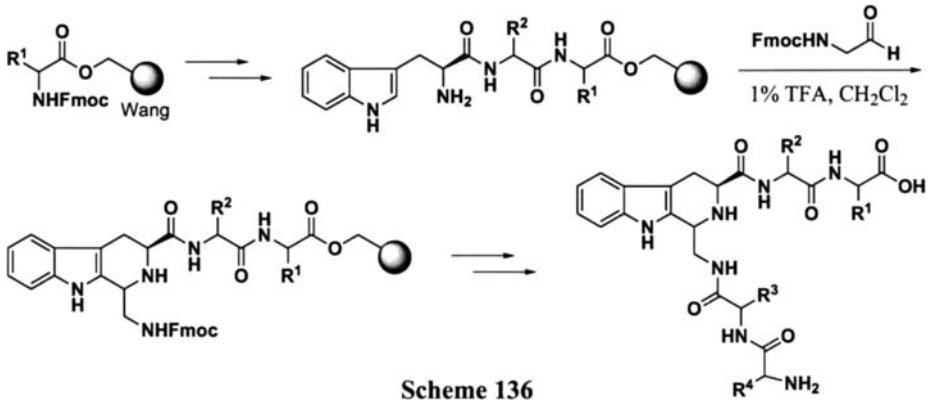
Scheme 134

Yang described the facile cleavage of the carbamate linker of hydroxymethyl polystyrene (*Scheme 135*).[124] The resin bound diamine was acylated with Fmoc-Trp under the standard peptide coupling conditions, followed by Fmoc deprotection. P-S cyclization on a solid support was carried out successfully with 10% TFA in CH_2Cl_2. The carbamate linker of hydroxymethyl polystyrene, an equivalent of Cbz, is stable to a wide range of acidic, basic, and reductive conditions. In contrast, this linker was easily cleaved by treatment with a mixture of TFA and dimethylsulfide at room temperature.



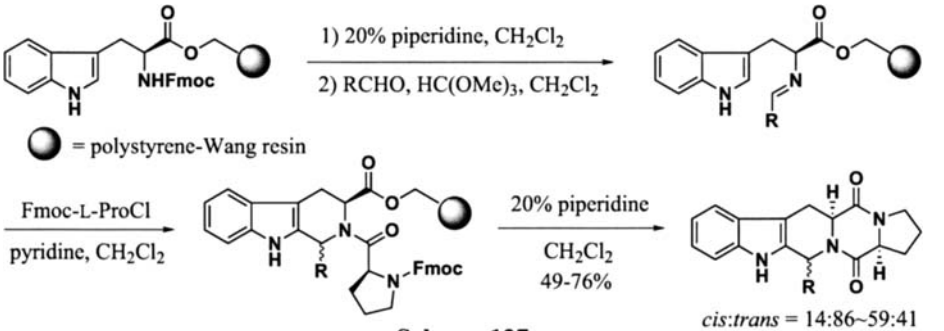
Scheme 135

Solid-phase P-S reactions for the synthesis of THBC-containing peptidomimetics have been shown.[125] Tam and co-workers developed P-S condensation of a resin-bound tryptophan-containing fragment with an Fmoc-amino aldehyde, followed by peptidomimetic chain assembly on the same resin (*Scheme 136*).[125a] The Fmoc group was first removed from Fmoc-amino acid (AA_1) Wang resin, and the second amino acid (AA_2) was attached to the resin using standard coupling conditions. Subsequently, Fmoc-Trp was introduced to the solid support without any side chain protection. After removal of the Fmoc group, a resin-bound free *N*-terminal tryptophan was condensed with a 10 molar equiv excess of Fmoc glycinal in 1% TFA in CH_2Cl_2 at room temperature. The resulting resin-bound THBC heterocycle was deprotected with 20% piperidine in DMF. Elongation of the peptidomimetic backbone (AA_3, AA_4) was performed with a 5 molar equiv excess of Fmoc-amino acids (DIC/HOBt/DMF), followed by piperidine deprotection. The final product was cleaved from the solid support by TFA treatment in essentially quantitative yields, with a purity level typically in excess of 80%.



Scheme 136

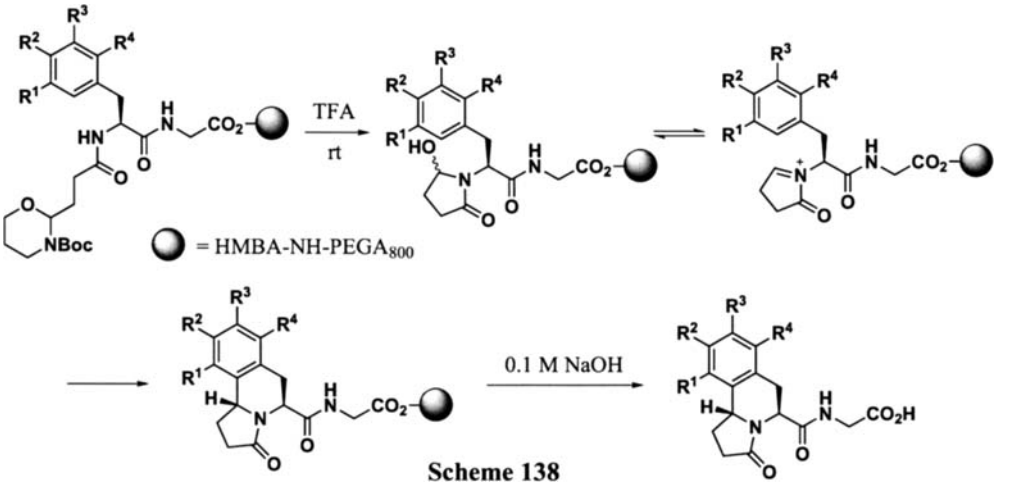
Solid-phase synthesis *via* the intramolecular *N*-acyliminium P-S reaction has been reported by some research groups.[126-127] Ganesan *et al.* demonstrated that L-tryptophan immobilized on polystyrene-Wang resin was sequentially reacted with an aldehyde and Fmoc-amino acid chloride (*Scheme 137*).[126a] This induced *N*-acyliminium P-S reaction to give a mixture of *cis* and *trans* THBCs. Fmoc deprotection by piperidine, with concomitant diketopiperazine formation, resulted in cyclative cleavage of the desired products from the resin.



Scheme 137

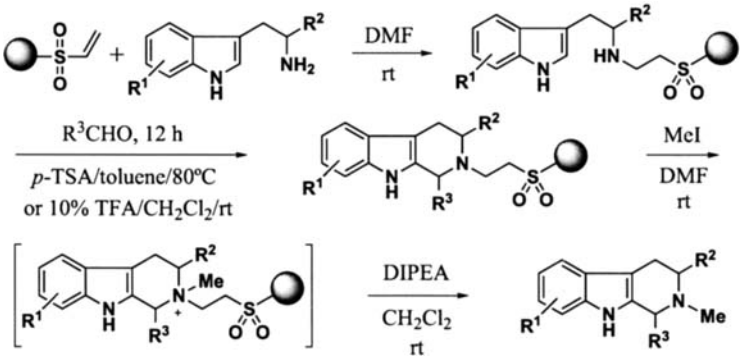
Solid-phase routes toward pyrroloisoquinoline derivatives *via* the intramolecular *N*-acyliminium P-S reaction have been established (*Scheme 138*).[127b] Peptide aldehydes generated from *N*-Boc-1,3-oxazines by acidic conditions underwent intramolecular condensation reactions with the amide nitrogen of a solid-supported peptide backbone, thus forming a 1:1 epimeric mixture of a cyclic 5-hydroxylactam, which in turn was in equilibrium with the corresponding intermediate *N*-acyliminium ion. Under the acidic conditions, a second ring was formed *via* P-S cyclization from the aromatic ring of a neighboring, properly substituted, electron-rich phenylalanine derivative in the peptide sequence. The aromatic substitution pattern of the nucleophilic benzene ring of the phenylalanine derivative and the nature of the acidic reaction media were critically important for the course of the reaction. A range of substitution patterns and substituents were tolerated on the aromatic ring. The reaction was equally efficient for fused aromatic rings, such as pyrene and naphthalenes, incorporated in the peptide backbone as the aryl

alanine derivatives. Both Lewis and Brønsted acids could be employed to effect the cyclization process. This intramolecular reaction was under strict control of stereoselectivity, and only a single stereoisomer was detected in the crude products. Later, the same research group developed the intramolecular *N*-acyliminium P-S reactions using *in situ* generated aldehydes *via* the OsO_4-$NaIO_4$-mediated oxidative cleavage reaction of solid-supported peptide olefins.[127d]



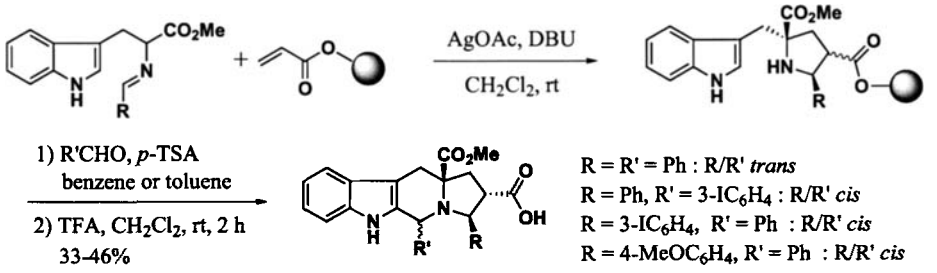
Scheme 138

Shuttleworth and Schultz, respectively, developed solid-phase P-S reactions using tryptamines as the substrates to produce the THBCs with a basic tertiary amine (*Scheme 139*).[128] A vinylsulfonylmethyl polystyrene resin, which is stable under acidic, basic, and thermal conditions, was used as solid support in both reports. Tryptamines were initially supported onto the solid phase *via* 1,4-addition to vinylsulfonylmethyl resin. The supported substrates were treated subsequently with a range of aldehydes in the presence of *p*-TSA in toluene at 80°C[128a] or in the presence of TFA in CH_2Cl_2 at room temperature[128b] for 12 h to afford the THBCs through a P-S reaction. Then, the indole derivatives were activated with methyl iodide and Hoffman elimination mediated by Hünig's base furnished basic tertiary amines in the six-membered heterocyclic rings.



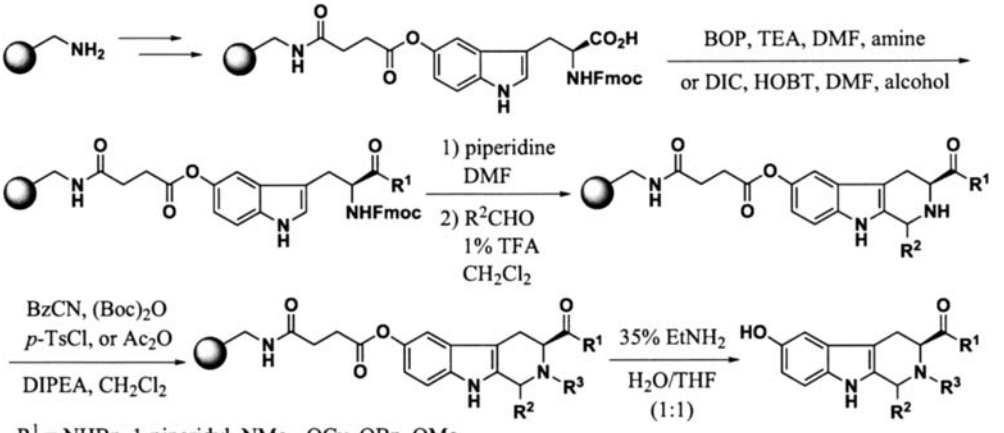
Scheme 139

A solid-phase cascade imine/metalloazomethine ylide/cycloaddition/P-S reaction was reported (*Scheme 140*).[129] Resin-bound cycloadducts were generated by AgOAc-catalyzed imine cycloaddition to a Wang resin acrylate. Solid phase P-S reactions were carried out on the cycloadducts using various aldehydes in the presence of 10 mol% *p*-TSA in benzene (80°C) or toluene (110°C). Resin bound cyclized products were then cleaved from the resin with 1:1 TFA:CH_2Cl_2 at room temperature to afford THBC derivatives in 33-46% yield as mixtures of four isomers of which one was major. Alternatively, the P-S products were cleaved from the resin by transesterification (NaCN/NEt_3 in MeOH/THF) to afford the corresponding methyl esters.



Scheme 140

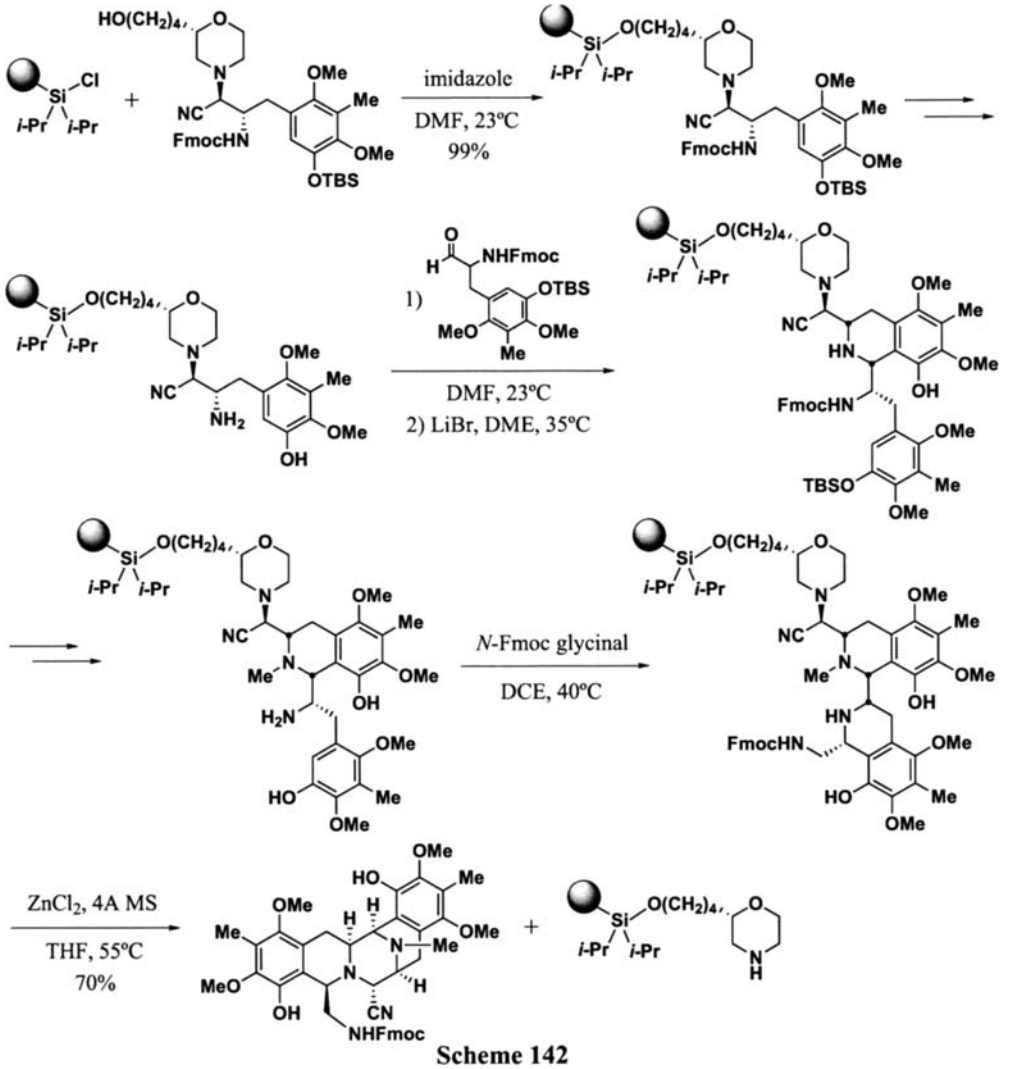
6-Hydroxy-THBCs based on the L-5-OH-tryptophan scaffold have been prepared by several research groups.[130] The commercially available L-5-OH-tryptophan was attached to the solid support through the phenol moiety, by means of a suitable bond that allowed protection of this functional group during the entire synthetic sequence. The resin-bound scaffold could be differently derivatized at the carboxylic acid goup. Lesma *et al.* developed a strategy for a solid-phase synthesis that allowed facile introduction of diversities not only at the C1 position of the carboline skeleton but also, more importantly, at the N2 and at the carboxylic group (*Scheme 141*).[130c] *N*-Fmoc L-5-OH-tryptophan was attached to aminomethyl polystyrene and removal of



Scheme 141

the Fmoc group was followed by treatment of the resin-bound free amine with a 10 M equiv excess of aldehydes in 1% TFA/CH_2Cl_2 at room temperature to afford resin-bound THBCs. To install the R^3 diversity at N2, various kinds of derivatization of the secondary nitrogen at 2 position were performed by reaction with benzoyl cyanide, acetic anhydride, $(Boc)_2O$, or *p*-TsCl to give the corresponding carbamate and *p*-toluensulfonamide derivatives. A high reactivity at N2 was attributed to its distance from the sterically cumbersome solid support. Finally, cleavage of the product from the resin was achieved readily with 35% ethylamine in water/THF (1:1) at room temperature, providing the highly functionalized 6-OH-THBCs.

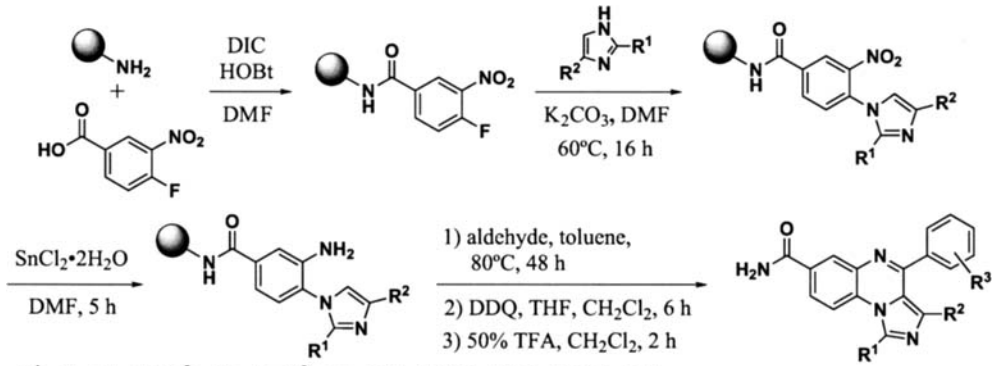
Myers group described the successful adaptation of their prior solution-phase synthesis of saframycin A to a solid-supported synthesis suitable for the preparation of large numbers of diverse saframycin analogues with deep-seated structural modifications (*Scheme 142*).[131]



Scheme 142

Attachment of the *anti*-morpholinonitrile to the solid support was achieved by silyl ether formation with 4-(chlorodiisopropylsilyl)polystyrene in quantitative yield. Addition of a 3-fold excess of the *N*-protected α-amino aldehyde to the amino-terminal intermediate provided the corresponding resin-supported imine, of which treatment with saturated solution of anhydrous LiBr at 35°C in 1,2-dimethoxyethane induced the first stereoselective P-S cyclization reaction, affording the *cis*-THIQ derivative (*cis*:*trans* 7:1). The secondary amino group of the THIQ intermediate was next reductively methylated on the solid phase. Subsequent deprotection of the phenol and primary amino groups of the resulting *N*-alkylation product produced the new amino-terminal resin-bound intermediate, which underwent the second P-S cyclization reaction upon exposure to *N*-Fmoc glycinal in 1,2-dichloroethane at 40°C for 20 h. The resulting *bis*-THIQ derivative was formed in quantitative yield with the required *cis* stereochemistry in the newly formed ring. Then the *bis*-THIQ intermediate was subjected to cyclization-autorelease by warming in the presence of $ZnCl_2$ at 55°C for 1.5 h to afford the saframycin analogue in 53% yield for the 10-step sequence.

A strategy for P-S reaction involving an N1 linked aromatic amine of imidazole and aldehydes was described (*Scheme 143*).[71b] Dihydroimidazoquinoxaline showed moderate stability and, even after purification, it had a tendency to undergo slow oxidation to imidazoquinoxaline. Therefore, a modified P-S strategy for the selective synthesis of imidazoquinoxalines on the solid



Scheme 143

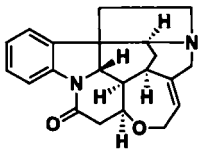
phase was performed. The nucleophilic replacement of fluorine in resin-bound *o*-fluoronitrobenzoic acid with mono- or disubstituted imidazole was followed by reduction of the nitro group to give an N1 linked aromatic amine of the resin-bound imidazole. This was treated subsequently with an aldehyde in toluene at 80°C and then oxidized in the presence of DDQ to afford resin-bound imidazoquinoxalines. Finally, acidolytic cleavage with 50% TFA/CH_2Cl_2 produced the desired imidazoquinoxalines in high yields and purities. Electron-withdrawing and electron-donating substituents on the aldehydes had no significant effect on the yield and purity of the final compounds. The monosubstituted imidazoles furnished compounds in lower yield in comparison to disubstituted imidazoles.

2. Total Synthesis of Indole and Isoquinoline Alkaloids

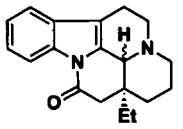
Various naturally occurring alkaloids of the THIQ and THBC type have interesting physiological and pharmaceutical effects and are used for medicinal purposes. THIQs of synthetic, plant and mammalian origin have been studied extensively because of their manifold pharmacological properties.[3] In general, the THIQ family of alkaloids include potent cytotoxic agents that display a range of biological properties such as antitumor and antimicrobial activities. Indole alkaloid natural products are an important source of biologically active compounds.[3, 132] The THBC ring system is present in numerous biologically active indole alkaloids as well as synthetic compounds. One of the most important synthetic methods to synthesize these chiral *N*-heterocycles and their analogues in enantiomerically pure form, which has been successfully employed in numerous alkaloid syntheses, is the P-S reaction.

This review will summarize only the literature that described the total or formal synthesis of THBC, THIQ, and other related heterocyclic alkaloids employing the P-S reaction as a key step, by giving only the fully synthesized alkaloids' structures without synthetic details. Model studies or the construction of the only core structure will not be covered.

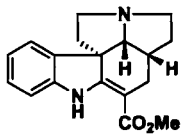
Many reports on the total synthesis of a variety of indole alkaloids have been published (*Scheme 144*): strychnine,[33a] (-)-eburnamonine,[133] (+)-*epi*-eburnamonine,[133] (±)-deethylibophyllidine,[134] (*R*)-(+)-tetrahydroharman,[111] (+)-fumitremorgin B,[135] demethoxyfumitremorgin C,[26b, 126a, 136] tadalafil,[26c] the spirocyclopropane analogues of both (demethoxy)fumitremorgine C and tadalafil,[137] (-)-isovallesiachotamine,[68d, 138] (+)-vallesiachotamine,[68d, 138] (-)-antirhine,[105b] apoyohimbine,[139] (-)-corynantheidine,[140] (-)-corynantheidol,[140] (-)-geissoschizol,[140] (+)-geissoschizine,[140] eudistomins H,[108b] eudistomins I,[108b] (-)-eudistomin C,[108e, 112d] (-)-woodinine,[108b] (-)-(*S*)-brevicolline,[141] (-)-suaveoline,[142] norsuaveoline,[143-144] (-)-raumacline,[145] alstonerine,[146] anhydromacrosalhine-methine,[146] macroline,[147] the enantiomers of both macroline and alstonerine,[148] lavendamycin methyl ester,[21, 149] (-)-vincamajinine,[150] (-)-11-methoxy-17-epivincamajine,[150] (+)-N_a-methyl-16-epipericyclivine,[151-152] (+)-N_a-methylvellosimine,[152] vellosimine,[151-153] (+)-majvinine,[147, 154] (+)-12-methoxy-N_a-methylvellosimine,[155-156] the enantiomer of affinisine,[148] (+)-normacusine B,[152] (+)-10-methoxyaffinisine,[147, 154] (+)-N_a-methylsarpagine,[147, 154] (+)-12-methoxyaffinisine,[155-156] (-)-(*E*)-16-epiaffinisine,[157] (+)-(*E*)-16-epinormacusine B,[157] gardnerine,[158] (+)-dehydro-16-epiaffinisine,[157] (+)-dehydro-16-epinormacusine B,[157] (+)-dehydrovoachalotine,[150] gardnutine,[158] (–)-alkaloid Q_3,[151-152] (–)-panarine,[151-152] (-)-fuchsiaefoline,[155-156] (-)-12-methoxy-N_b-methylvoachalotine,[156] alkaloid G,[144, 157, 159] (+)-ajmaline,[144, 159] macralstonidine,[147, 154] talpinine,[146] talcarpine,[146] 20-deethylenylated subincanadine B,[160] and 19,20-dihydrosubincanadine B.[160]



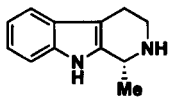
strychnine



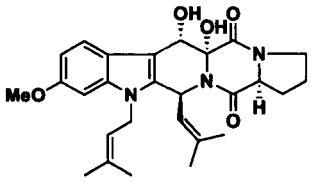
α-H : (-)-eburnamonine
β-H : (+)-*epi*-eburnamonine



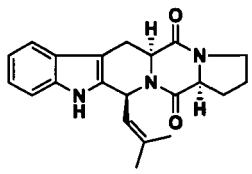
deethylibophyllidine



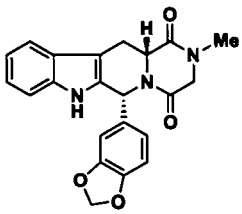
(*R*)-(+)-tetrahydroharman



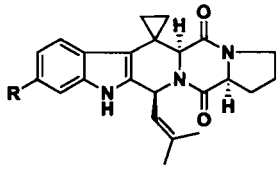
(+)-fumitremorgin B



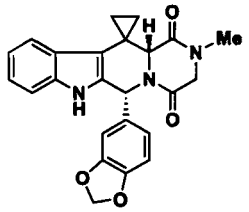
demethoxyfumitremorgin C



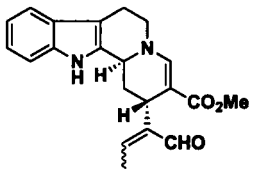
tadalafil



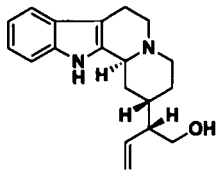
spirocyclopropane analogues of fumitremorgin C (R = OMe) and demethoxyfumitremorgin C (R = H)



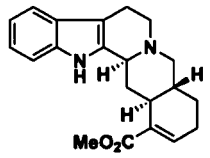
spirocyclopropane analogue of tadalafil



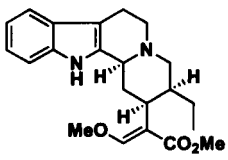
(*Z*)- : (+)-vallesiachotamine
(*E*)- : (-)-isovallesiachotamine



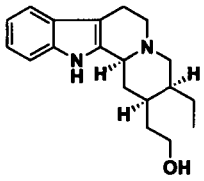
(-)-antirhine



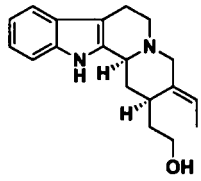
apoyohimbine



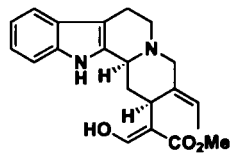
(-)-corynantheidine



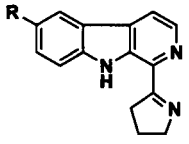
(-)-corynantheidol



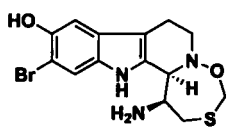
(-)-geissoschizol



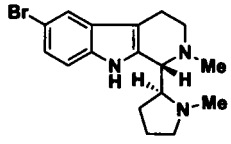
(+)-geissoschizine



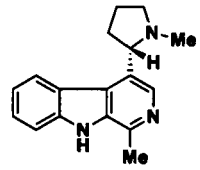
R = H : eudistomin I
R = Br : eudistomin H



(-)-eudistomin C

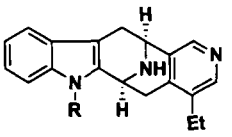


(-)-woodinine

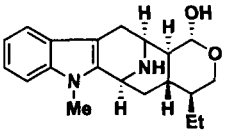


(-)-(*S*)-brevicolline

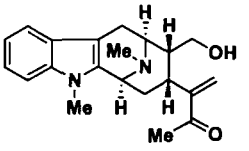
Scheme 144



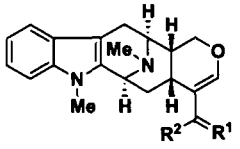
R = Me : (-)-suaveoline
R = H : norsuaveoline



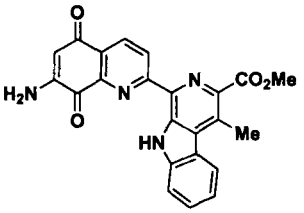
(-)-raumacline



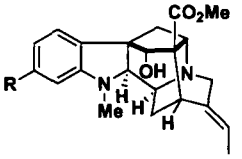
macroline



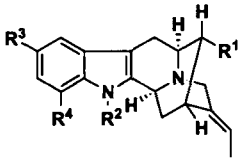
R^1 = O, R^2 = Me : alstonerine
R^1 = CH_2, R^2 = H
: anhydromacrosalhine-methine



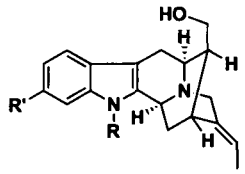
lavendamycin methyl ester



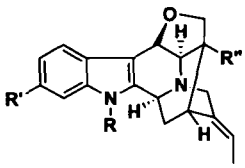
R = H : (-)-vincamajinine
R = OMe : (-)-11-methoxy-17-epivincamajine



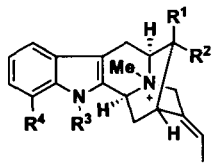
R^1 = CO_2Me, R^2 = Me, R^3 = H, R^4 = H : (+)-N_a-methyl-16-epipericyclivine
R^1 = CHO, R^2 = Me, R^3 = H, R^4 = H : (+)-N_a-methylvellosimine
R^1 = CHO, R^2 = H, R^3 = H, R^4 = H : (+)-vellosimine
R^1 = CHO, R^2 = Me, R^3 = OMe, R^4 = H : (+)-majvinine
R^1 = CHO, R^2 = Me, R^3 = H, R^4 = OMe : (+)-12-methoxy-N_a-methylvellosimine
R^1 = CH_2OH, R^2 = Me, R^3 = H, R^4 = H : affinisine
R^1 = CH_2OH, R^2 = H, R^3 = H, R^4 = H : (+)-normacusine B
R^1 = CH_2OH, R^2 = Me, R^3 = OMe, R^4 = H : (+)-10-methoxyaffinisine
R^1 = CH_2OH, R^2 = Me, R^3 = OH, R^4 = H : (+)-N_a-methylsapargine
R^1 = CH_2OH, R^2 = Me, R^3 = H, R^4 = OMe : (+)-12-methoxyaffinisine



R = Me, R' = H : (-)-(*E*)16-epiaffinisine
R = H, R' = H : (+)-(*E*)16-epinormacusine B
R = H, R' = OMe : gardnerine

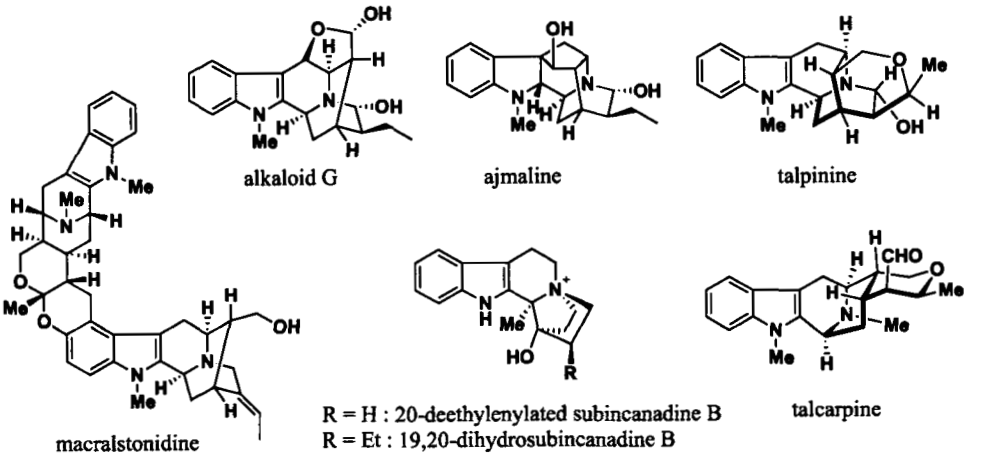


R = Me, R' = H, R" = H : (+)-dehydro-16-epiaffinisine
R = Me, R' = H, R" = CO_2Me : (+)-dehydrovoachalotine
R = H, R' = H, R" = H : (+)-dehydro-16-epinormacusine B
R = H, R' = OMe, R" = H : gardnutine



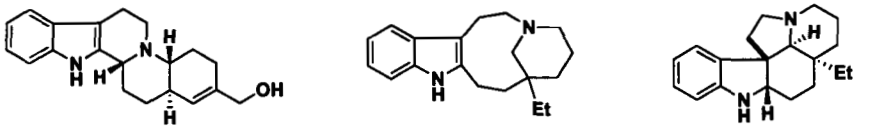
R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = H : (-)-alkaloid Q_3
R^1 = H, R^2 = CO_2^-, R^3 = H, R^4 = H : (-)-panarine
R^1 = H, R^2 = CO_2Et, R^3 = Me, R^4 = OMe : (-)-fuchsiaefoline
R^1 = CH_2OH, R^2 = CO_2Me, R^3 = Me, R^4 = OMe
: (-)-12-methoxy-N_b-methylvoachalotine

Scheme 144 (*continued*)



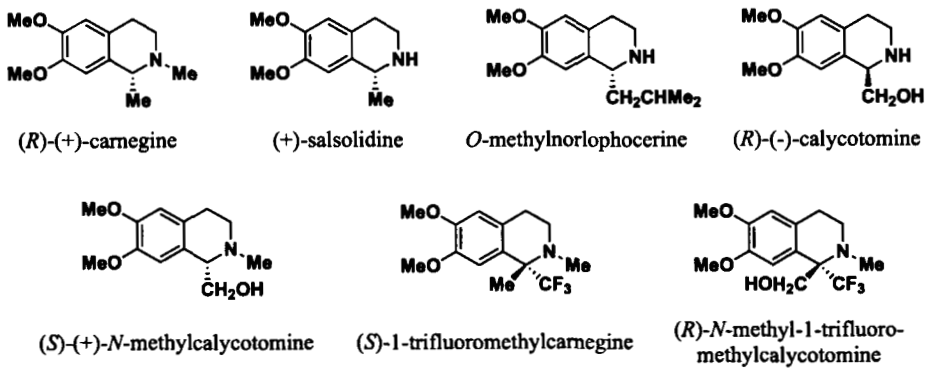
Scheme 144 (*continued*)

Formal syntheses of indole alkaloid (±)-tangutorine,[161] (±)-quebrachamine,[162] and (-)-aspidospermidine[133] were reported (*Scheme 145*).

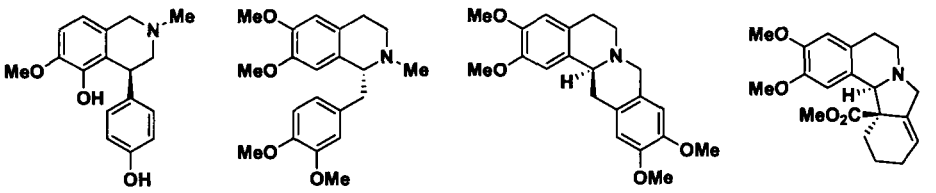


Scheme 145

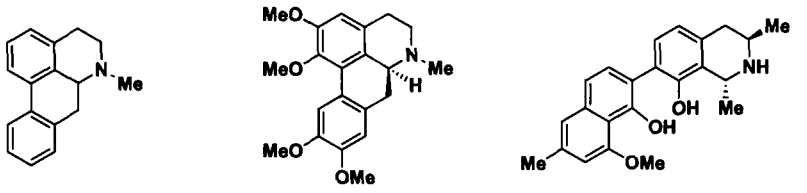
The total syntheses of a variety of isoquinoline alkaloids and a formal total synthesis of ecteinascidin 743[79b] have been reported (*Scheme 146*): (S)-(-)-carnegine[109d, 111] and (*R*)-(+)-carnegine,[111] (+)-salsolidine,[35b] *O*-methylnorlophocerine,[35b] (*R*)-(-)-calycotomine,[109d] (*S*)-(+)-*N*-methylcalycotomine,[106] (*S*)-1-trifluoromethylcarnegine,[110] (*R*)-*N*-methyl-1-trifluoromethylcalycotomine,[110] (*S*)-latifine and its antipode,[163] (*S*)-(+)-laudanosine,[109d] (*R*)-(-)-laudanosine,[51]



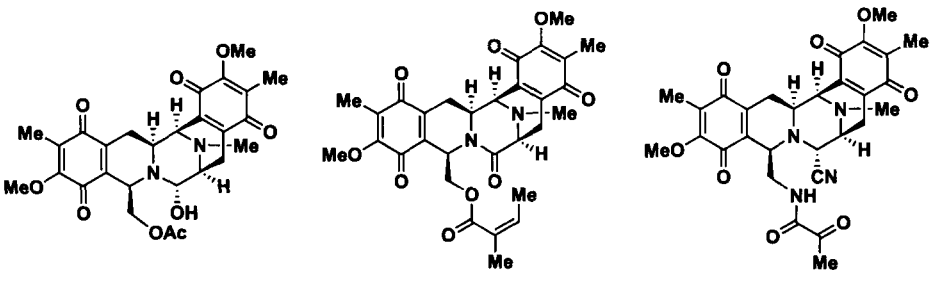
Scheme 146



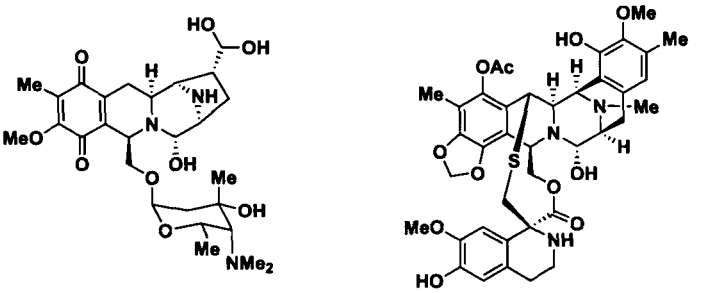
(*S*)-latifine (*R*)-(-)-laudanosine (*S*)-(-)-xylopinine jamitine



aporphine (+)-glaucine dioncophylline B



(-)-jorumycin (-)-renieramycin G (-)-saframycin A

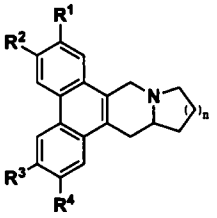


(-)-lemonomycin ecteinascidin 743

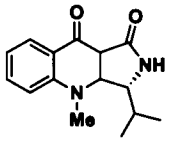
Scheme 146 (*continued*)

(*S*)-(-)-xylopinine,[51] (*R*)-(+)-xylopinine,[164] (±)-jamtine,[165] (±)-aporphine,[166] (+)-glaucine,[51] dioncophylline B,[167] (-)-jorumycin and 3-*epi*-jorumycin,[168] (-)-renieramycin G and 3-*epi*-renieramycin G,[168] (-)-saframycin A,[131, 169] (-)-lemonomycin,[170] and ecteinascidin 743.[171]

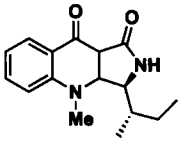
The total syntheses of heterocycles other than β-carboline and isoquinoline derivatives were also achieved (*Scheme 147*): (±)-cryptopleurine,[172] (±)-antofine,[172] (±)-deoxypergularinine,[172] (+)-quinolactacin B,[173] (+)-quinolactacin A2,[173] buflavine,[174] (+)-kalafungin,[175] and (–)-nanaomycin D.[175]



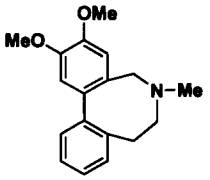
$R^1 = H, R^2 = R^3 = R^4 = OMe, n = 2$: cryptopleurine
$R^1 = H, R^2 = R^3 = R^4 = OMe, n = 1$: antofine
$R^1 = R^2 = R^3 = OMe, R^4 = H, n = 1$: deoxypergularinine



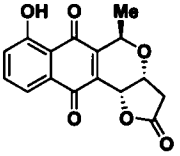
(+)-quinolactacin B



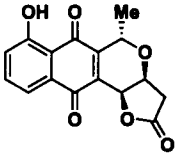
(+)-quinolactacin A2



buflavine



(+)-kalafungin



(-)-nanaomycin D

Scheme 147

X. CONCLUSION

As shown in this review, the P-S reaction has been employed as a key strategy for C-C bond formation in the synthesis of numerous heterocycles including THBCs and THIQs. The THBC and THIQ ring systems are found in various naturally occurring alkaloids as well as synthetic compounds. Due to their valuable medicinal properties, the P-S reaction has attracted the most attention and been extremely well studied.

Over the years, a wide range of synthetic methods have been reported to improve its synthetic efficiency, applying new reaction promoters, a variety of substrates, solid-phase synthesis etc. Most of the stereoselective P-S reactions have used stoichiometric amounts of chiral controllers, however, remarkable progress using chiral catalysts has been recently achieved in the enantioselective synthesis of THBCs.

In view of the continuous development of more efficient, practical, and powerful synthetic methods, the P-S reaction will remain as an important synthetic strategy in the synthesis of numerous heterocyclic target molecules including THBC, THIQ, and their analogues.

Acknowledgments.- The author is grateful to Pukyong National University for generous financial support.

REFERENCES

1. A. Pictet and T. Spengler, *Chem. Ber.*, **44**, 2030 (1911).

2. For reviews, see: (a) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951). (b) E. D. Cox and J. Cook, *Chem. Rev.*, **95**, 1797 (1995). (c) J. Royer, M. Bonin and L. Micouin, *Chem. Rev.*, **104**, 2311 (2004). (d) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, **104**, 1431 (2004).

3. (a) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, **104**, 3341 (2004). (b) T. S. Kaufman, *Synthesis*, 339 (**2005**). (c) K. W. Bentley, *Nat. Prod. Rep.*, **21**, 395 (2004). (d) J. D. Scott and R. M. Williams, *Chem. Rev.*, **102**, 1669 (2002). (e) T. Kametani and K. Fukumoto, "*Isoquinolines Part One*" in "*The Chemistry of Heterocyclic Compounds*", p. 170, G. Grethe, Wiley, N.Y. 1981. (f) G. Jones, "*Comprehensive Heterocyclic Chemistry*", Vol. 2, p. 438, A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984. (g) G. A. Cordell, "*The Alkaloids, Chemistry and Pharmacology*", Vol. 43, Academic Press: New York, 1993. (h) M. Shamma, in "*Organic Chemistry*", Vol. 25, A. T. Blomquist and H. Wasserman, Academic: New York, 1972.

4. For reviews on the solid-phase Pictet-Spengler reaction and on the solid-phase synthesis of nitrogen heterocycles, see: (a) T. E. Nielsen, F. Diness and M. Meldal, *Curr. Opin. Drug. Discuss. Dev.*, **6**, 801 (2003). (b) B. A. Lorsbach and M. J. Kurth, *Chem. Rev.*, **99**, 1549 (1999). (c) R. E. Sammelson and M. J. Kurth, *Chem. Rev.*, **101**, 137 (2001). (d) P. Blaney, R. Grigg and V. Sridharan, *Chem. Rev.*, **102**, 2607 (2002). (e) S. Bräse, C. Gil and K. Knepper, *Bioorg. Med. Chem.*, **10**, 2415 (2002). (f) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky and C. Zechel, *Angew. Chem. Int. Ed. Engl.*, **35**, 2288 (1996).

5. (a) E. Glusa, H. Grüner, A. Hagen, D. Lohmann and H. Foken, *Pharmazie*, **45**, 408 (1990). (b) S. Ruchirwat, M. Chaisupakitsin, N. Patranuwatana, J. L. Cashaw and V. E. Davis, *Synth. Commun.*, **14**, 1221 (1984). (c) R. Sarges, *J. Heterocycl. Chem.*, **11**, 599 (1974). (d) P. Kumar, K. N. Dhawan, K. Kishor, K. P. Bhargava and R. K. Satsangi, *J. Heterocycl. Chem.*, **19**, 677 (1982).

6. (a) E. Späth and E. Lederer, *Chem. Ber.*, **63**, 2102 (1930). (b) S. Akabori and K. Saito, *Chem. Ber.*, **63**, 2245 (1930). (c) G. Hahn and H. Ludewig, *Chem. Ber.*, **67**, 2031 (1934). (d) T. Kawate, M. Nakagawa, K. Ogata and T. Hino, *Heterocycles*, **33**, 801 (1992).

7. H. Kondo and H. Ochiai, *J. Pharm. Soc. Jpn.*, **495**, 313 (1923); *Chem. Abstr.*, **17**, 3032 (1923).

8. (a) A. Yokoyama, T. Ohwada and K. Shudo, *J. Org. Chem.*, **64**, 611 (1999). (b) S. Nakamura, M. Tanaka, T. Taniguchi, M. Uchiyama and T. Ohwada, *Org. Lett.*, **5**, 2087 (2003).

9. L. Alberch, P. D. Bailey, P. D. Clingan, T. J. Mills, R. A. Price and R. G. Pritchard, *Eur. J. Org. Chem.*, 1887 (**2004**).

10. For some recent examples, see: (a) P. Zhang and J. M. Cook, *Tetrahedron Lett.*, **36**, 6999 (1995). (b) R. Grigg, M. Thornton-Pett and G. Yoganathan, *Tetrahedron*, **55**, 8129 (1999).

(c) H. A. Dondas, J. Duraisingham, R. Grigg, W. S. MacLachlan, D. T. MacPherson, M. Thornton-Pett, V. Sridharan and S. Suganthan, *Tetrahedron*, **56**, 4063 (2000). (d) R. Grigg, W. S. MacLachlan, D. T. MacPherson, V. Sridharan, S. Suganthan, M. Thornton-Pett and J. Zhang, *Tetrahedron*, **56**, 6585 (2000). (e) W.-B. Yeh, M.-J. Lin and C.-M. Sun, *Tetrahedron Lett.*, **44**, 4923 (2003).

11. (a) K. Ito and H. Tanaka, *Chem. Pharm. Bull.*, **25**, 1732 (1977). (b) T. J. N. Watson, *J. Org. Chem.*, **63**, 406 (1998). (c) Y. S. Lee, D. J. Cho, S. N. Kim, J. H. Choi and H. Park, *J. Org. Chem.*, **64**, 9727 (1999).

12. C. C. Silveira, L. A. Felix, A. L. Braga and T. S. Kaufman, *Org. Lett.*, **7**, 3701 (2005).

13. A. G. Myers and D. W. Kung, *Org. Lett.*, **2**, 3019 (2000).

14. N. Sotomayor, E. Domfnguez and E. Lete, *Tetrahedron*, **51**, 12159 (1995).

15. (a) X. Chen, J. Chen, M. De Paolis and J. Zhu, *J. Org. Chem.*, **70**, 4397 (2005). (b) M. De Paolis, A. Chiaroni and J. Zhu, *Chem. Commun.*, 2896 (**2003**).

16. S. Kobayashi, M. Sugiura, H. Kitagawa and W. W.-L. Lam, *Chem. Rev.*, **102**, 2227 (2002).

17. (a) R.Tsuju, M. Yamanaka, A. Nishida and M. Nakagawa, *Chem. Lett.*, 428 (**2002**). (b) R. Tsuji, M. Nakagawa and A. Nishida, Tetrahedron: *Asymmetry*, **14**, 177 (2003). (c) N. Srinivasan and A. Ganesan, *Chem. Commun.*, 916 (**2003**). (d) K. Manabe, D. Nobutou and S. Kobayashi, *Bioorg. Med. Chem.*, **13**, 5154 (2005).

18. (a) M. T. El Gihani, H. Heaney and K. F. Shuhaibar, *Synlett*, 871 (**1996**). (b) H. Heaney, M. T. Simcox, A. M. Z. Slawin and R. G. Giles, *Synlett*, 640 (**1998**).

19. S. W. Youn, *J. Org. Chem.*, **71**, 2521 (**2006**).

20. (a) J. Sandrin, D. Soerens, L. Hutchins, E. Richfield, F. Ungemach and J. M. Cook, *Heterocycles*, **4**, 1101 (1976). (b) J. Sandrin, D. Soerens, P. Mokry and J. M. Cook, *Heterocycles*, **6**, 1133 (1977). (c) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro and J. M. Cook, *J. Org. Chem.*, **44**, 535 (1979). (d) M. Jawdosiuk and J. M. Cook *J. Org. Chem.*, **49**, 2699 (1984). (e) F. Ungemach, M. DiPierro, R. Weber and J. M. Cook, *J. Org. Chem.*, **46**, 164 (1981).

21. M. Behforouz, Z. Gu, W. Cai, M. A. Horn and M. Ahmadian, *J. Org. Chem.*, **58**, 7089 (1993).

22. C. Gremmen, B. E. A. Burm, M. J. Wanner and G.-J. Koomen, *Tetrahedron Lett.*, **39**, 1441 (1998).

23. (a) A. P. Venkov and L. K. Lukanov, *Synthesis*, 59 (**1989**). (b) L. K. Lukanov, A. P. Venkov and N. M. Mollov, *Synthesis*, 1031 (**1987**).

24. G. E. Stokker, *Tetrahedron Lett.*, **37**, 5453 (1996).

25. (a) E. Yamanaka, N. Shibata and S.-I. Sakai, *Heterocycles*, **22**, 371 (1984). (b) A. P. Venkov and A. K. Boyadjieva, *Synth. Commun.*, **29**, 487 (1999).

26. (a) S. Nakatsuka, H. Miyazaki and T. Goto, *Chem. Lett.*, 407 (**1981**). (b) H. Wang and A. Ganesan, *Tetrahedron Lett.*, **38**, 4327 (1997). (c) J. D. Revell, N. Srinivasan and A. Ganesan, *Synlett*, 1428 (**2004**).

27. (a) G. Schmidt, H. Waldmann, H. Henke and M. Burkard, *Chem. Eur. J.*, **2**, 1566 (1996). (b) H. Waldmann, G. Schmidt, H. Henke and M. Burkard, *Angew. Chem. Int. Ed. Engl.*, **34**, 2402 (1995).

28. M. Nakagawa, H. Fukushima, T. Kawate, M. Hongu, S.-I. Kodato, T. Une, M. Taniguchi and T. Hino, *Tetrahedron Lett.*, **27**, 3235 (1986).

29. K. Paulvannan, R. Hale, R. Mesis and T. Chen, *Tetrahedron Lett.*, **43**, 203 (2002).

30. M. M. Abelman, J. K. Curtis and D. R. James, *Tetrahedron Lett.*, **44**, 6527 (2003).

31. S. Ballet, Z. Urbanczyk-Lipkowska, D. Tourwé, *Synlett*, 2791 (**2005**).

32. J. R. Dunetz, R. P. Ciccolini, M. Fröling, S. M. Paap, A. J. Allen, A. B. Holmes, J. W. Tester and R. L. Danheiser, *Chem. Commun.*, 4465 (**2005**).

33. (a) R. B.Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, *Tetrahedron*, **19**, 247 (1963). (b) A. H. Jackson and A. E. Smith, *Tetrahedron*, **24**, 403 (1968). (c) D. M. Harrison, *Tetrahedron Lett.*, **22**, 2501 (1981). (d) L. K. Lukanov, A. P. Venkov and N. M. Mollov, *Synthesis*, 204 (**1987**). (e) S.-D. Cho, S.-Y. Song, E.-J. Hur, M. Chen, W.-H. Joo, J. R. Falck, Y.-J. Yoon and D.-S. Shin, *Tetrahedron Lett.*, **42**, 6251 (2001). (f) C. C. Silveira, C. R. Bernardi, A. L. Bragaa and T. S. Kaufman, *Tetrahedron Lett.*, **44**, 6137 (2003).

34. O. O. Orazi, R. A. Corral and H. Giaccio, *J. Chem. Soc., Perkin Trans. 1*, 1977 (**1986**).

35. (a) C. Gremmen, B. Willemse, M. J. Wanner and G.-J. Koomen, *Org. Lett.*, **2**, 1955 (2000). (b) C. Gremmen, M. J. Wanner and G.-J. Koomen, *Tetrahedron Lett.*, **42**, 8885 (2001).

36. (a) T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, H. Ishimaru and K. Wakisaka, *J. Chem. Soc. (C)*, 1805 (**1971**). (b) T. M. Kutchan, G. Shen, V. E. Sutliff and C. J. Coscia, *J. Org. Chem.*, **46**, 1738 (1981). (c) M. V. Raiman, A. V. Pukin, V. I. Tyvorskii, N. De Kimpe and O. G. Kulinkovich, *Tetrahedron*, **59**, 5265 (2003).

37. A. Napolitano, A. Pezzella and G. Prota, *Tetrahedron Lett.*, **40**, 2833 (1999).

38. M. Sandler, S. B. Carter, K. R. Hunter and G. M. Stern, *Nature*, **241**, 439 (1973).

39. P. Manini, M. d'Ischia, R. Lanzetta, M. Parrilli and G. Prota, *Bioorg. & Med. Chem.*, **7**, 2525 (1999).

40. P. Manini, M. d'Ischia and G. Prota, *J. Org. Chem.*, **65**, 4269 (2000).

41. A. Pezzella and G. Prota, *Tetrahedron Lett.*, **43**, 6719 (2002).

42. E. McCoy, M. C. Galan and S. E. O'Connor, *Bioorg. & Med. Chem. Lett.*, **16**, 2475 (2006).

43. (a) F.-M. Kuo, M.-C. Tseng, Y.-H. Yen and Y.-H. Chu, *Tetrahedron*, **60**, 12075 (2004). (b) Y.-H. Yen and Y.-H. Chu, *Tetrahedron Lett.*, **45**, 8137 (2004). (c) W.-J. Chang, M. V. Kulkarni and C.-M. Sun, *J. Comb. Chem.*, **8**, 141 (2006).

44. For recent reviews on microwave-assisted organic synthesis, see: (a) M. Nuchter, B. Ondruschka, W. Bonrath and A. Gum, *Green Chem.*, **6**, 128 (2004). (b) K. M. K. Swamy, W.-B. Yeh, M.-J. Lin and C.-M. Sun, *Curr. Med. Chem.*, **10**, 2403 (2003). (c) B. Wathey, J. Tierney, P. Lidstrom and J. Westman, *Drug Discovery Today*, **7**, 47 (2002). (d) C. O. Kappe, *Curr. Opin. Chem. Biol.*, **6**, 314 (2002). (e) N. S. Wilson and G. P. Roth, *Curr. Opin. Drug Discovery Dev.*, **5**, 620 (2002). (f) A. Lew, P. O. Krutzik, M. E. Hart and A. R. Chamberlin, *J. Comb. Chem.*, **4**, 95 (2002).

45. For recent reviews, see: (a) H. Zhao and S. V. Malhotra, *Aldrichim. Acta*, **35**, 75 (2002). (b) T. Welton, *Chem. Rev.*, **99**, 2071 (1999). (c) R. Sheldon, *Chem. Commun.*, 2399 (**2001**). (d) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, **102**, 3667 (2002).

46. A. Hegedüs and Z. Hell, *Tetrahedron Lett.*, **45**, 8553 (2004).

47. (a) A. J. Y. Lan, R. O. Heuckeroth and P. S. Mariano, *J. Am. Chem. Soc.*, **109**, 2738 (1987). (b) I.-S. Cho and P. S. Mariano, *J. Org. Chem.*, **53**, 1590 (1988).

48. A. Kubo, N. Saito, N. Kawakami, Y. Matsuyama and T. Miwa, *Synthesis*, 824 (**1987**).

49. G. K. Cheung, M. J. Earle, R. A. Fairhurst, H. Heaney, K. F. Shuhaibar, S. C. Eyley and F. Ince, *Synlett*, 721 (**1991**).

50. (a) R. Plate, R. H. M. van Hout, H. Behm and H. C. J. Ottenheijm, *J. Org. Chem.*, **52**, 555 (1987). (b) P. H. H. Hermkens, J. H. v. Maarseveen, C. G. Kruse and H. W. Scheeren, *Tetrahedron Lett.*, **30**, 5009 (1989). (c) P. H. H. Hermkens, J. H. v. Maarseveen, H. W. Berens, J. M. M. Smits, C. G. Kruse and H. W. Scheeren, *J. Org. Chem.*, **55**, 2200 (1990). (d) J. H. van Maarseveen, S. J. E. Mulders, R. W. M. Aben, C. G. Kruse and H. W. Scheeren, *Tetrahedron*, **51**, 4841 (1995).

51. D. L. Comins, P. M. Thakker, M. F. Baevsky and M. M. Badawi, *Tetrahedron*, **53**, 16327 (1997).

52. (a) J. E. Audia, J. J. Droste, J. S. Nissen, G. L. Murdoch and D. A. Evrard, *J. Org. Chem.*, **61**, 7937 (1996). (b) J. Ezquerra, C. Lamas, A. Pastor, P. Alvarez, J. J. Vaquero and W. G. Prowse , *Tetrahedron Lett.*, **37**, 5813 (1996).

53. V. Alezra, M. Bonin, L. Micouin and H.-P. Husson, *Tetrahedron Lett.*, **42**, 2111 (2001).

54. (a) K. Singh and P. K. Deb, *Heterocycles*, **51**, 1509 (1999). (b) K. Singh and P. K. Deb, *Tetrahedron Lett.*, **41**, 4977 (2000). (c) K. Singh, P. K. Deb and P. Venugopalan, *Tetrahedron*, **57**, 7939 (2001).

55. (a) H. C. Hiemstra, H. Bieräugel, M. Wijnberg and U. K. Pandit, *Tetrahedron*, **39**, 3981 (1983). (b) D. Li, Y. Zhang, W. Guo and C. Xia, *Heterocycles*, **65**, 1063 (2005).

56. (a) H. Kohno and Y. Sekine, *Heterocycles*, **42**, 141 (1996). (b) H. Kohno and K. Yamada, *Heterocycles*, **51**, 103 (1999).

57. (a) C. C. Silveira, C. R. Bernardi, A. L. Braga and T. S. Kaufman, *Tetrahedron Lett.*, **40**, 4969 (1999). (b) H.-M. Wang, I.-J. Kang and L.-C. Chen, *Heterocycles*, **60**, 1899 (2003). (c) C. C. Silveira, C. R. Bernardi, A. L. Braga and T. S. Kaufman, *Tetrahedron Lett.*, **42**, 8947 (2001).

58. M. J. Wanner, A. W. Velzel and G.-J. Koomen, *J. Chem. Soc., Chem. Commun.*, 174 (**1993**).

59. J. Santamaria, M. T. Kaddachi and C. Ferroud, *Tetrahedron Lett.*, **33**, 781 (1992).

60. (a) K. Diker, M. D. de Maindreville and J. Lévy, *Tetrahedron Lett.*, **36**, 2497 (1995). (b) K. Diker, K. E. Biach, M. D. de Maindreville and J. Lévy, *J. Nat. Prod.*, **60**, 791 (1997).

61. C. Mésangeau, S. Yous, B. Pérès, D. Lesieur and T. Besson, *Tetrahedron Lett.*, **46**, 2465 (2005).

62. H. J. Kim, U. C. Yoon, Y.-S. Jung, N. S. Park, E. M. Cederstrom and P. S. Mariano, *J. Org. Chem.*, **63**, 860 (1998).

63. P. Ducrot and C. Thai, *Tetrahedron Lett.*, **40**, 9037 (1999).

64. For some examples on the intramolecular P-S-like cyclization using acylcarbinolamines, see: (a) S. Kano, Y. Yuasa and S. Shibuya, *Heterocycles*, **23**, 395 (1985). (b) N. Valls, V. M. Segarra, L. C. Maillo and J. Bosch, *Tetrahedron*, **47** 1065 (1991). (c) H. Heaney and M. O. Taha, *Synlett*, 820 (**1996**).

65. F. Esser, K.-H. Pook and A. Carpy, *Synthesis*, 72 (**1990**).

66. (a) J. Vercauteren, C. Lavaud, J. Lévy and G. Massiot, *J. Org.* Chem., **49**, 2278 (1984). (b) P. D. Bailey, S. P. Hollinshead and Z. Dauter, *J. Chem. Soc., Chem. Commun.*, 1507 (**1985**). (c) P. D. Bailey and S. P. Hollinshead, *Tetrahedron Lett.*, **28**, 2879 (1987). (d) A. S. Karpov, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 1502 (**2004**).

67. Z. Zhang and L. L. Schafer, *Org. Lett.*, **5**, 4733 (2003).

68. (a) J. W. Huffman, *J. Am. Chem. Soc.*, **80**, 5193 (1958). (b) L. F. Tietze and J. Wichmann, *Liebigs Ann. Chem.*, 1063 (**1992**). (c) R. Vohra and D. B. MacLean, *Tetrahedron Lett.*, **34**, 7673 (1993). (d) R. Amann, K. Arnold, D. Spitzner, Z. Majer and G. Snatzke, *Liebigs Ann.*,

349 (**1996**). (e) D. Papadopoulou, I. Papoutsis, S. Spyroudis and A. Varvoglis, *Tetrahedron Lett.*, **39**, 2865 (1998).

69. Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, **7**, 1047 (2005).

70. (a) G. Beke, L. F. Szabo and B. Podanyi, *J. Nat. Prod.*, **65**, 649 (2002). (b) S. M. Hutchins and K. T. Chapman, *Tetrahedron Lett.*, **37**, 4865 (1996). (c) T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 311 (1975). (d) T. Kametani, M. Koizumi, K. Okui, Y. Nishii and M. Ono, *J. Med. Chem.*, **15**, 203 (1972). (e) F. B. Stocker, M. W. Fordice, J. K. Larson and J. H. Thorstenson, *J. Org. Chem.*, **31**, 2380 (1966). (f) D. Heyl, S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, **70**, 3429 (1948).

71. (a) B. Kundu, D. Sawant, P. Partani and A. P. Kesarwani, *J. Org. Chem.*, **70**, 4889 (2005). (b) B. Kundu, D. Sawant and R. Chhabra, *J. Comb. Chem.*, **7**, 317 (2005).

72. S. Duggineni, D. Sawant, B. Saha and B. Kundu, *Tetrahedron*, **62**, 3228 (2006).

73. (a) L. Zheng, J. Xiang, Q. Dang, S. Guo and X. Bai, *J. Comb. Chem.*, **7**, 813 (2005). (b) X. Che, L. Zheng, Q. Dang and X. Bai, *Tetrahedron*, **62**, 2563 (2006).

74. M. A. J. Duncton, L. M. Smith II, S. Burdzovic-Wizeman, A. Burns, H. Liu, Y. Mao, W. C. Wong and A. S. Kiselyov, *J. Org. Chem.*, **70**, 9629 (2005).

75. (a) J.-F. Rousseau and R. H. Dodd, *J. Org. Chem.*, **63**, 2731 (1998). (b) A. R. Katritzky, H.-Y. He and R. Jiang, *Tetrahedron Lett.*, **43**, 2831 (2002). (c) F. Liéby-Muller, T. Constantieux and J. Rodriguez, *J. Am. Chem. Soc.*, **127**, 17176 (2005).

76. S. P. Tanis, M. V. Deaton, L. A. Dixon, M. C. McMills, J. W. Raggon and M. A. Collins, *J. Org. Chem.*, **63**, 6914 (1998).

77. J. Albaneze-Walker, K. Rossen, R. A. Reamer, R. E Volante and E J. Reider, *Tetrahedron Lett.*, **40**, 4917 (1999).

78. G. J. Meuzelaar, E. Neeleman, L. Maat and R. A. Sheldon, *Eur. J. Org. Chem.*, 2101 (**1998**).

79. (a) R. R. Cesati, III and J. A. Katzenellenbogen, *Org. Lett.*, **2**, 3635 (2000). (b) S. Zheng, C. Chan, T. Furuuchi, B. J. D. Wright, B. Zhou, J. Guo and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, **45**, 1754 (2006).

80. (a) K. Narayanan, L. Schindler and J. M. Cook, *J. Org. Chem.*, **56**, 359 (1991). (b) K. Narayanan and J. M. Cook, *J. Org. Chem.*, **56**, 5733 (1991). (c) K. Narayanan and J. M. Cook, *Tetrahedron Lett.*, **31**, 3397 (1990).

81. (a) R. B. Miller and T. Tsang, *Tetrahedron Lett.*, **29**, 6715 (1988). (b) P. S. Cutter, R. B. Miller and N. E. Schore, *Tetrahedron*, **58**, 1471 (2002).

82. J. C. Martins, K. V. Rompaey, G. Wittmann, C. Tömböly, G. Tóth, N. De Kimpe and D. Tourwé, *J. Org. Chem.*, **66**, 2884 (2001).

83. For a review, see: E. L. Larghi and T. S. Kaufman, *Synthesis*, 187 (**2006**).

84. (a) B. Wunsch and M. Zott, *Liebigs Ann. Chem.*, 39 (**1992**). (b) B. Wunsch, M. Zott and G. Hofner, *Arch. Pharm.*, **325**, 733 (1992).

85. (a) A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Grasso, S. Quartarone, M. Zappalà, P. Giusti, V. Libri, A. Constanti and A. G. Chapman, *J. Med. Chem.*, **40**, 1258 (1997). (b) N. Choukchou-Braham, B. Mostefa-Kara, N. Cheikh, M. A. Didi and D. Villemin, *Synth. Commun.*, **35**, 169 (2005).

86. (a) M. Guiso, C. Marra and C. Cavarischia, *Tetrahedron Lett.*, **42**, 6531 (2001). (b) M. Guiso, A. Bianco, C.Marra and C. Cavarischia, *Eur. J. Org. Chem.*, 3407 (**2003**).

87. Y.-C. Xu, D. T. Kohlman, S. X. Liang and C. Erikkson, *Org. Lett.*, **1**, 1599 (1999).

88. D. A. Bianchi, F. Rúa and T. S. Kaufman, *Tetrahedron Lett.*, **45**, 411 (2004).

89. A. Hegedüs and Z. Hell, *Org. Biomol. Chem.*, **4**, 1220 (2006).

90. X. Zhang, X. Li, J. C. Lanter and Z. Sui, *Org. Lett.*, **7**, 2043 (2005).

91. For other oxa-P-S cyclizations, see: (a) R. M. Soll, C. Guinosso and A. Asselin, *J. Org. Chem.*, **53**, 2844 (1988). (b) B. Wuensch, M. Zott, G. Hoefner and G. Bauschke, *Arch. Pharm.*, **328**, 487 (1995). (c) L. M. Cabral, P. R. R. Costa, M. L. A. A. Vasconcellos, E. J. Barreiro and R. N. Castro, *Synth. Commun.*, **26**, 3671 (1996). (d) B. Danieli, G. Lesma, D. Passarella and A. Silvani, *Tetrahedron Lett.*, **41**, 3489 (2000). (e) D. A. Bianchi, M. A. Cipulli and T. S. Kaufman, *Eur. J. Org. Chem.*, **24**, 4731 (2003). (f) S.-Y. Chou, *Heterocycles*, **60**, 1095 (2003).

92. W. H. Miles, S. K. Heinsohn, M. K. Brennan, D. T. Swarr, P. M. Eidam and K. A. Gelato, *Synthesis*, **11**, 1541 (2002).

93. For diastereoselective P-S reactions of tryptophan esters, see: (a) References cited in ref. 10a. (b) P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith and J. M. Vernon, *Tetrahedron Lett.*, **35**, 3587 (1994). (c) L. Deng, K. Czerwinski, J. M. Cook, *Tetrahedron Lett.*, **32**, 175 (1991). (d) G. Massiot and T. Mulumba, *J. Chem. Soc., Chem. Commun.*, 1147 (**1983**). (e) P. H. H. Hermken, J. H. van Maarseveen, P. L. H. M. Cobben, H. C. J. Ottenheijim, C. G. Kruse and H. W. Scheeren, *Tetrahedron*, **46**, 833 (1990). (f) P. D. Bailey, S. P. Hollinshead, N. R. McLay, K. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds and S. D. Wood, *J. Chem. Soc., Perkin Trans. 1*, 431 (**1993**). (g) P. D. Bailey, *Tetrahedron Lett.*, **28**, 5181 (1987). (h) F. Ungemach, M. DiPierro, R. Weber and J. M. Cook, *Tetrahedron Lett.*, **20**, 3225 (1979). (i) E. D. Cox, L. K. Hamaker, M. Li, P. Yu, K. M. Czerwinski, L. Deng, D. W. Bennett, J. M. Cook, W. H. Watson and M. Krawiec *J. Org. Chem.*, **62**, 44 (1997). (j) P. D. Bailey, S. P. Hollinshead and N. R. McLay, *Tetrahedron Lett.*, **28**, 5177 (1987). (k) P. D. Bailey and N. R. McLay, *Tetrahedron Lett.*, **32**, 3895 (1991) and references therein.

94. For selected examples, see: (a) D. L. Comins and M. M. Badawi, *Tetrahedron Lett.*, **32**, 2995 (1991). (b) E. J. Corey and D. Y. Gin, *Tetrahedron Lett.*, **37**, 7163 (1996).

95. (a) T. Soe, T. Kawate, N. Fukui and M. Nakagawa, *Tetrahedron Lett.*, **36**, 1857 (1995). (b) T. Soe, T. Kawate, N. Fukui, T. Hino and M. Nakagawa, *Heterocycles*, **42**, 347 (1996).

96. (a) T. Kawate, M. Yamanaka and M. Nakagawa, *Heterocycles*, **50**, 1033 (1999). (b) W. Jiang, Z. Suia and X. Chen, *Tetrahedron Lett.*, **43**, 8941 (2002).

97. (a) H. Waldmann, G. Schmidt, M. Jansen and J. Geb, *Tetrahedron Lett.*, **34**, 5867 (1993). (d) H. Waldmann and G. Schmidt, *Tetrahedron*, **50**, 11865 (1994).

98. J. Spengler, H. Schedel, J. Sieler, P. J. L. M. Quaedflieg, Q. B. Broxterman, A. L. L. Duchateau and K. Burger, *Synthesis*, 1513 (**2001**).

99. (a) M. Ohba, H. Kubo, T. Fujii, H. Ishibashi, M. V. Sargent and D. Arbain, *Tetrahedron Lett.*, **38**, 6697 (1997). (b) R. H. Huizenga and U. K. Pandit, *Tetrahedron*, **48**, 6521 (1992).

100. J. L. Vicario, D. Badía, E. Domínguez and L. Carrillo, *J. Org. Chem.*, **64**, 4610 (1999).

101. (a) A. Zawadzka, A. Leniewski, J. K. Maurin, K. Wojtasiewicz, A. Siwicka, D. Blachut and Z. Czarnocki, *Eur. J. Org. Chem.*, 2443 (**2003**). (b) A. Zawadzka, A. Leniewski, J. K. Maurin, K. Wojtasiewicz and Z. Czarnocki, *Org. Lett.*, **3**, 997 (**2001**).

102. G. Subramaniyan, J. Jayashankaran, R. D. R. S. Manian and R. Raghunathan, *Synlett*, 1167 (**2005**).

103. B. Wuensch and M. Zott, *Tetrahedron: Asymmetry*, **4**, 2307 (1993).

104. B. Wiinsch and M. Zott, *Liebigs Ann. Chem.*, 39 (**1992**).

105. For selected examples, see: (a) M. Kawai, Y. Deng, I. Kimura, H. Yamamura, S. Araki and M, Naoi, *Tetrahedron: Asymmetry*, **8**, 1487 (1997). (b) B. Danieli, G. Lesma, M. Mauro, G. Palmisano and D. Passarella, *Tetrahedron*, **50**, 8837 (1994).

106. Z. Czarnocki, J. B. Mieczkowsld, J. Kiegiel and Z. Ara?ny, *Tetrahedron: Asymmetry*, **6**, 2899 (1995).

107. L. Bi, M. Zhao, C. Wang, S. Peng and E. Winterfeldt, *J. Org. Chem.*, **67**, 22 (2002).

108. (a) J. Liu, M. Nakagawa and T. Hino, *Tetrahedron*, **45**, 7729 (1989). (b) J. McNulty and I. W. J. Still, *Tetrahedron Lett.*, **32**, 4875 (1991). (c) J. Liu, M. Nakagawa, K. Ogata and T. Hino, *Chem. Pharm. Bull.*, **39**, 1672 (1991). (d) P. Melnyk, P. Ducrot and C. Thal, *Tetrahedron*, **49**, 8589 (1993). (e) T. Yamashita, N. Kawai, H. Tokuyama and T. Fukuyama, *J. Am. Chem. Soc.*, **127**, 15038 (2005).

109. (a) I. M. Piper, D. B. MacLean, I. Kvarnström, and W. A. Szarek, *Can. J. Chem.*, **61**, 2721 (1983). (b) D. B. MacLean, W. A. Szarek and I. Kvarnström, *J. Chem. Soc., Chem. Commun.*, 601 (**1983**). (c) Z. Czarnocki, D. B. MacLean and W. A. Szarek, *J. Chem. Soc., Chem. Commun.*, 1318 (**1985**). (d) Z, Czarnocki, D. B. MacLean and W. A. Szarek, *Can. J. Chem.*, **64**, 2205 (1986). (e) Q. Khuong-Huu, J. Nemlin and J. K. A. Pancrazi, *Tetrahedron*, **48**, 6689 (1992). (f) B. Pal, P. Jaisankar and V. S. Giri, *Synth. Commun.*, **33**, 2339 (2003).

110. P. Bravo, M. Crucianelli, A. Farina, S. V. Meille, A. Volonterio and M. Zanda, *Eur. J. Org. Chem.*, 435 (**1998**).

111. (a) A. W. M. Lee, W. H. Chan and Y. Lee, *Tetrahedron Lett.*, **32**, 6861 (1991). (b) A. W. M. Lee, W. H. Chan, Y. Tao and Y. K. Lee, *J. Chem. Soc. Perkin Trans. 1*, 477 (**1994**).

112. (a) T. Kawate, H. Yamada, T. Soe and M. Nakagawa, *Tetrahedron: Asymmetry*, **7**, 1249 (1996). (b) H. Yamada, T. Kawate, M. Matsumizu, A. Nishida, K. Yamaguchi and M. Nakagawa, *J. Org. Chem.*, **63**, 6348 (1998). (c) T. Kawate, H. Yamada, M. Matsumizu, A. Nishida and M. Nakagawa, *Synlett*, 761 (**1997**). (d) Hino, T.; Nakagawa, M. *Heterocycles*, **49**, 499 (1998).

113. T. Kawate, M. Nakagawa, K. Ogata and T. Hino, *Heterocycles*, **33**, 801 (1992).

114. M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, **126**, 10558 (2004).

115. J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc.*, **128**, 1086 (2006).

116. For selected examples on solid-phase P-S reaction, see: (a) C.-Y. Wu and C.-M. Sun, *Synlett*, 1709 (**2002**). (b) B. A. Bunin, J. M. Dener, D. E. Kelly, N. A. Paras, J. D. Tario and S. P. Tushup, *J. Comb. Chem.*, **6**, 487 (2004). (c) T. R. Kane, C. Q. Ly, D. E. Kelly and J. M. Dener, *J. Comb. Chem.*, **6**, 564 (2004). (d) S.-C. Lee and S. B. Park, *J. Comb. Chem.*, **8**, 50 (2006).

117. (a) T. Groth and M. Meldal, *J. Comb. Chem.*, **3**, 45 (2001). (b) T. Groth and M. Meldal, *J. Comb. Chem.*, **3**, 34 (2001).

118. K. Kalijuste and A. Undén, *Tetrahedron Lett.*, **36**, 9211 (1995).

119. R. Mohan, Y.-L. Chou and M. M. Morrissey, *Tetrahedron Lett.*, **37**, 3963 (1996).

120. L. Yang and L. Guo, *Tetrahedron Lett.*, **37**, 5041 (1996).

121. J. P. Mayer, D. Bankaitis-Davis, J. Zhang, G. Beaton, K. Bjergarde, C. M. Andersen, B. A. Goodman and C. J. Herrera, *Tetrahedron Lett.*, **37**, 5633 (1996).

122. (a) P. P. Fantauzzi and K. M. Yager, *Tetrahedron Lett.*, **39**, 1291 (1998). (b) A. van Loevezijn, J. H. van Maarseveen, K. Stegman, G. M. Visser and G.-J. Koomen, *Tetrahedron Lett.*, **39**, 4737 (1998).

123. B. Sauerbrei, V. Jungmann and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, *37*, 1143 (1998).

124. L. Yang, *Tetrahedron Lett.*, **41**, 6981 (2000).

125. (a) X. Li, L. Zhang, W. Zhang, S. E. Hall and J. P. Tam, *Org. Lett.*, **2**, 3075 (2000). (b) G. K. Tóth, Z. Kele and F. Fülöp, *Tetrahedron Lett.*, **41**, 10095 (2000). (c) J. H. Grimes, Jr., Y. M. Angell and W. D. Kohn, *Tetrahedron Lett.*, **44**, 3835 (2003).

126. (a) H. Wang and A. Ganesan, *Org. Lett.*, **1**, 1647 (1999). (b) D. Bonnet and A. Ganesan, *J. Comb. Chem.*, **4**, 546 (2002).

127. (a) T. E. Nielsen and M. Meldal, *J. Org. Chem.*, **69**, 3765 (2004). (b) T. E. Nielsen and M. Meldal, *J. Comb. Chem.*, **7**, 599 (2005). (c) T. E. Nielsen, S. L. Quement and M. Meldal, *Tetrahedron Lett.*, **46**, 7959 (2005). (d) T. E. Nielsen and M. Meldal, *Org. Lett.*, **7**, 2695 (2005).

128. (a) R. V. Connors, A. J. Zhang and S. J. Shuttleworth, *Tetrahedron Lett.*, **43**, 6661 (2002). (b) T. Y. H. Wu and P. G. Schultz, *Org. Lett.*, **4**, 4033 (2002).

129. H. A. Dondas, R. Grigg, W. S. MacLachlan, D. T. MacPherson, J. Markandu, V. Sridharan and S. Suganthan, *Tetrahedron Lett.*, **41**, 967 (2000).

130. (a) D. Orain, R. Canova, M. Dattilo, E. Klöppner, R. Denay, G. Koch and R. Giger, *Synlett*, 1443 (**2002**). (b) Y.-L. Chou, M. M. Morrissey and R. Mohan, *Tetrahedron Lett.*, **39**, 757 (1998). (c) B. Danieli, P. Giovanelli, G. Lesma, D. Passarella, A. Sacchetti and A. Silvani, *J. Comb. Chem.*, **7**, 458 (2005).

131. A. G. Myers and B. A. Lanman, *J. Am. Chem. Soc.*, **124**, 12969 (2002).

132. (a) L. K. Hamaker and J. M. Cook, "The Synthesis of Macroline Related Alkaloids" in "*Alkaloids: Chemical and Biological Perspectives*", Vol. 9, p. 23, S. W. Pelletier, Elsevier Science: New York, 1995. (b) Y. Ban, Y. Murakami, Y. Iwasawa, M. Tsuchiya and N. Takano, *Med. Chem. Rev.*, **8**, 231 (1988).

133. A. G. H. Wee and Q. Yu, *J. Org. Chem.*, **66**, 8935 (2001).

134. J. Bonjoch, J.-C. Fernàndez and N. Valls, *J. Org. Chem.*, **63**, 7338 (1998).

135. S. Kodato, M. Nakagawa, M. Hongu, T. Kawate and T. Hino, *Tetrahedron*, 44, 359 (**1988**).

136. P. D. Bailey, P. J. Cochrane, K. Lorenz, I. D. Collier, D. P. J. Pearson and G. M. Rosair, *Tetrahedron Lett.*, **42**, 113 (2001).

137. M. Limbach, S. Dalai, A. Janssen, M. Es-Sayed, J. Magull and A. de Meijere, *Eur. J. Org. Chem.*, 610 (**2005**).

138. D. Spitzner and E. Wenkert, *Angew. Chem. Int. Ed. Engl.*, **23**, 984 (1984).

139. J. Leonard, A. B. Hague and M. F. Jones, *Tetrahedron Lett.*, **38**, 3071 (1997).

140. S. Yu, O. M. Berner and J. M. Cook, *J. Am. Chem. Soc.*, **122**, 7827 (2000).

141. S. Mahboobi, W. Wiegrebe and A. Popp, *J. Nat. Prod.*, **62**, 577 (1999).

142. (a) P. D. Bailey and K. M. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 3578 (**2000**). (b) M. L. Trudell, D. Soerens, R. W. Weber, L. Hutchins, D. Grubisha, D. Remett and J. M. Cook, *Tetrahedron*, **48**, 1805 (1992).

143. T. Wang, P. Yu, J. Li and J. M. Cook, *Tetrahedron Lett.*, **39**, 8009 (1998).

144. J. Li, T. Wang, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennett and J. M. Cook, *J. Am. Chem. Soc.*, **121**, 6998 (1999).

145. P. D. Bailey, P. D. Clingan, T. J. Mills, R. A. Price and R. G. Pritchard, *Chem. Commun.*, 2800 (**2003**).

146. P. Yu, T. Wang, J. Li and J. M. Cook, *J. Org. Chem.*, **65**, 3173 (2000).

147. S. Zhao, X. Liao, T. Wang, J. Flippen-Anderson and J. M. Cook, *J. Org. Chem.*, **68**, 6279 (2003).

148. X. Liu, T. Wang, Q. Xu, C. Ma and J. M. Cook, *Tetrahedron Lett.*, **41**, 6299 (2000).

149. (a) M. Behforouz, J. Haddad, W. Cai, M. B. Arnold, F. Mohammadi, A. C. Sousa and M. A. Horn, *J. Org. Chem.*, **61**, 6552 (1996). (b) H. Seradj, W. Cai, N. O. Erasga, D. V. Chenault, K. A. Knuckles, J. R. Ragains and M. Behforouz, *Org. Lett.*, **6**, 473 (2004).

150. J. Yu, X. Z. Wearing and J. M. Cook, *J. Org. Chem.*, **70**, 3963 (2005).

151. J. Yu, X. Z. Wearing and J. M. Cook, *Tetrahedron Lett.*, **44**, 543 (2003).

152. J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippen-Anderson, X. Liao and J. M. Cook, *J. Org. Chem.*, **68**, 7565 (2003).

153. T. Wang and J. M. Cook, *Org. Lett.*, **2**, 2057 (2000).

154. S. Zhao, X. Liao and J. M. Cook, *Org. Lett.*, **4**, 687 (2002).

155. H. Zhou, X. Liao and J. M. Cook, *Org. Lett.*, **6**, 249 (2004).

156. H. Zhou, X. Liao, W. Yin, J. Ma and J. M. Cook, *J. Org. Chem.*, **71**, 251 (2006).

157. J. Yu, T. Wang, X. Z. Wearing, J. Ma and J. M. Cook, *J. Org. Chem.*, **68**, 5852 (2003).

158. H. Zhou, D. Han, X. Liao and J. M. Cook, *Tetrahedron Lett.*, **46**, 4219 (2005).

159. J. Li and J. M. Cook, *J. Org. Chem.*, **63**, 4166 (1998).

160. Y. Liu, S. Luo, X. Fu, F. Fang, Z. Zhuang, W. Xiong, X. Jia and H. Zhai, *Org. Lett.*, **8**, 115 (2006).

161. (a) J. A. Wilkinson, N. Ardes-Guisot, S. Duckia and J. Leonard, *Tetrahedron Lett.*, **46**, 8053 (2005). (b) S. Luo, J. Zhao and H. Zhai, *J. Org. Chem.*, **69**, 4548 (2004).

162. A. G. H. Wee and Q. Yu, *Tetrahedron*, **54**, 13435 (1998).

163. A. Couture, E. Deniau, P. Grandclaudon and S. Lebrun, *Tetrahedron: Asymmetry*, **14**, 1309 (2003).

164. Z. Czarnocki and Z. Ara?ny, *Heterocycles*, **51**, 2871 (1999).

165. A. Padwa and M. D. Danca, *Org. Lett.*, **4**, 715 (2002).

166. G. D. Cuny, *Tetrahedron Lett.*, **45**, 5167 (2004).

167. G. Bringmann, C. Gunter, E. Peters and K. Peters, *Tetrahedron*, **57**, 1253 (2001).

168. J. W. Lane, Y. Chen and R. M. Williams, *J. Am. Chem. Soc.*, **127**, 12684 (2005).

169. A. G. Myers and D. W. Kung, *J. Am. Chem. Soc.*, **121**, 10828 (1999).

170. E. R. Ashley, E. G. Cruz and B. M. Stoltz, *J. Am. Chem. Soc.*, **125**, 15000 (2003).

171. J. Chen, X. Chen, M. Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, **128**, 87 (2006).

172. S. Lebrun, A. Couture, E. Deniau and P. Granddaudon, *Tetrahedron*, **55**, 2659 (1999).

173. X. Zhang, W. Jiang and Z. Sui, *J. Org. Chem.*, **68**, 4523 (2003).

174. P. Sahakitpichana and S. Ruchirawat, *Tetrahedron Lett.*, **44**, 5239 (2003).

175. R. A. Fernandes and R. Brückner, *Synlett*, 1281 (**2005**).

(Received July 18, 2006; in final form September 8, 2006)