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CARBONYLATIVE PALLADIUM-CATALYZED REACTIONS OF LACTAM-, LACTONE-, AND THIOLACTONE-DERIVED VINYL TRIFLATES AND PHOSPHATES FOR THE SYNTHESIS OF N-, O-, AND S-HETEROCYCLES

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In occasion of the celebration of the 80th birthday of Professor Emeritus, Akira Suzuki

Abstract – A full account of our most recent studies on the chemistry of lactam-, lactone-, and thiolactone-derived vinyl triflates and phosphates is reported. In this review we focus on the use of these versatile electrophiles in Pd-catalyzed carbonylative reactions. They provide, through alkoxycarbonylation, aminocarbonylation and carbonylative Suzuki-Miyaura reactions, a straightforward and convenient access to useful intermediates for the synthesis of N-, O- and S-heterocyclic and natural compounds.

CONTENTS

1. INTRODUCTION

Cyclic ketene aminal and acetal triflates (i.e. lactam-, imide-, and lactone-derived vinyl triflates, Figure 1), and the corresponding phosphates, are established useful intermediates in the synthesis of natural products and heterocyclic compounds.[1,2] Since the first works appeared in the nineties,[3] the conditions for a variety of palladium- and nickel-catalyzed coupling reactions of these intermediates with organotin, organozinc, and organoboron derivatives, have been found as well as for Sonogashira and Heck reactions, exchange with metals and coupling with organocuprates.[4,5] When we first come across lactam-derived vinyl triflates,[6] no examples of Suzuki-Miyaura coupling reactions were known, and so, concomitantly with Coudert's group in France,[7] we started a program aimed at studying the Pd-catalyzed cross-coupling reactions of these intermediates,[8] aware of the numerous advantages of boron derivatives (in particular boronic acids and esters) over other organometals in terms of stability to air and moisture, low toxicity and environmental impact (besides many of them being commercially available).

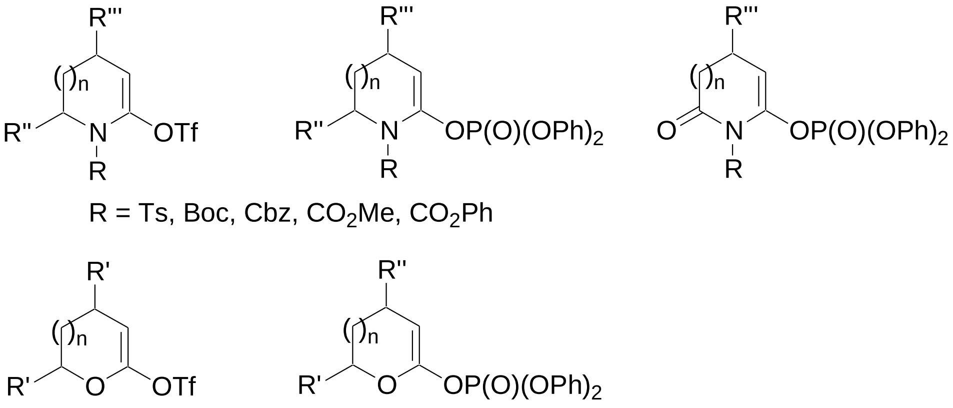
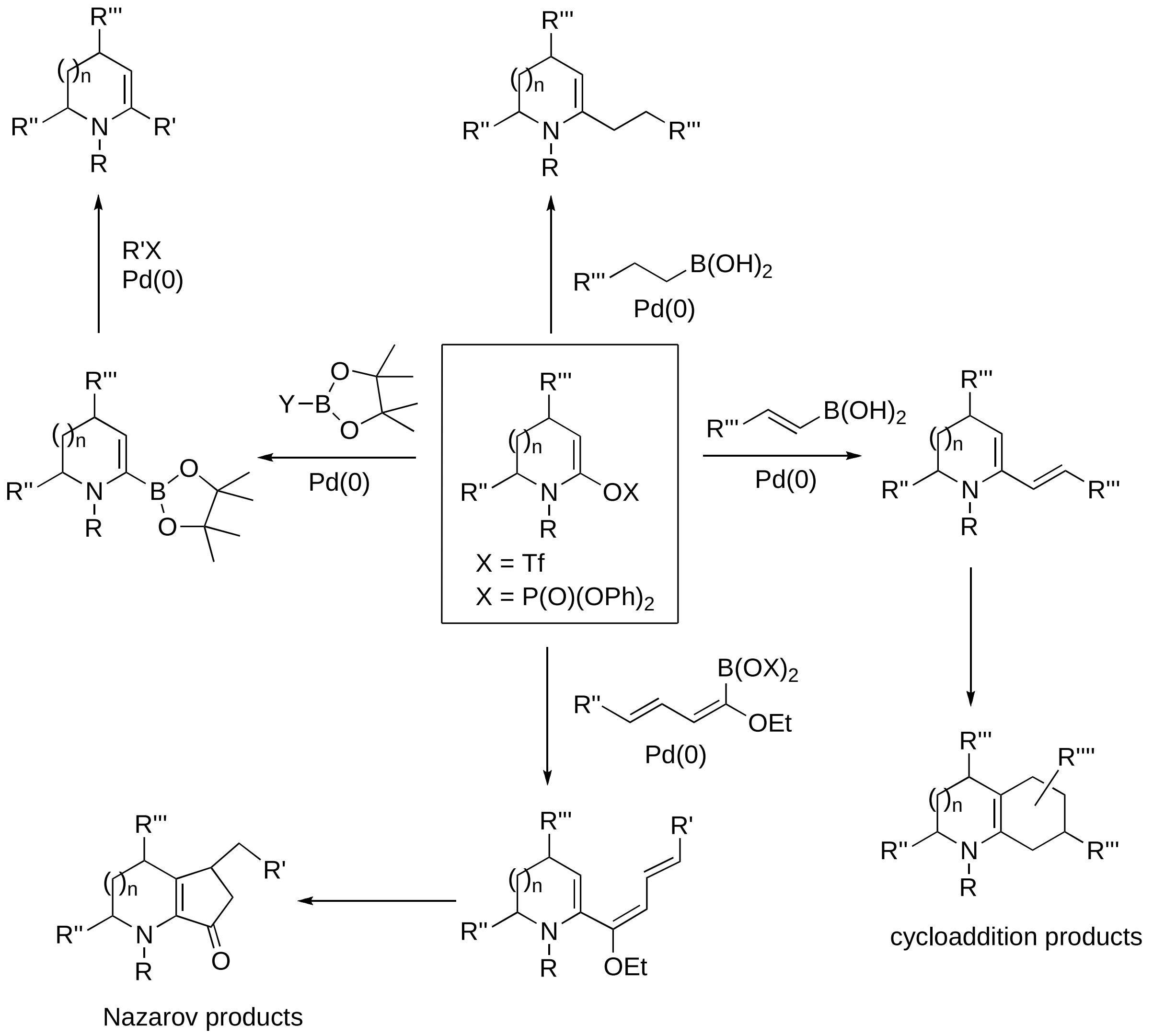


Figure 1

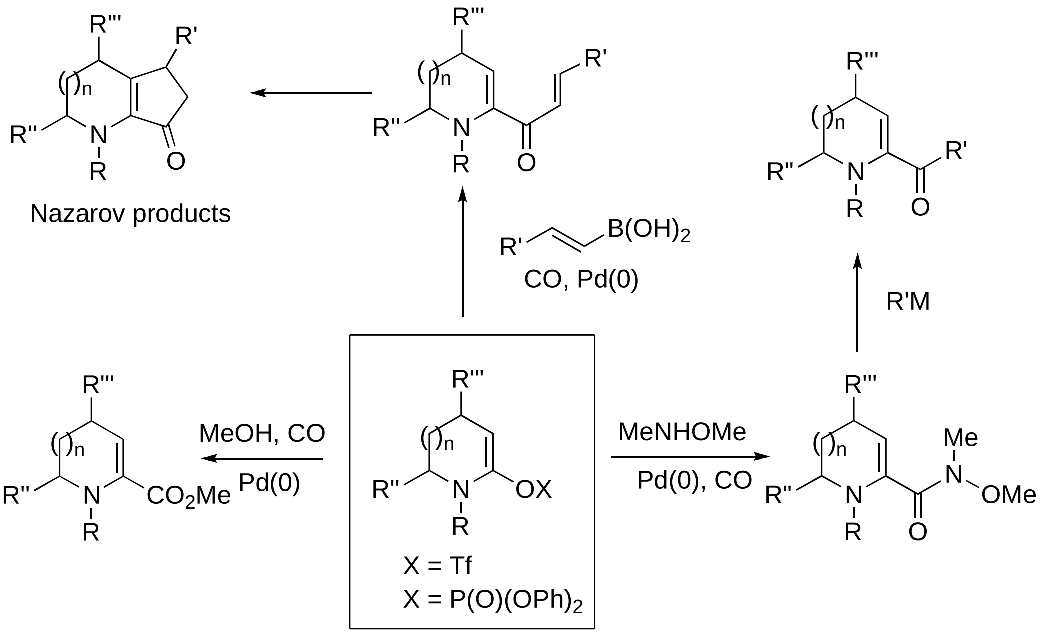
Thus, conditions were found for the Suzuki-Miyaura coupling with alkyl and alkenyl boronic acids and esters,[9,10] as well as α-alkoxydienylboronates (Scheme 1).[11] Moreover δ-valerolactam-derived vinyl triflates were converted into the corresponding vinyl boronates by Pd-catalyzed coupling with bis(pinacolato)diboron or pinacolborane, which resulted in an umpolung. This boronate efficiently coupled under Pd catalysis with aryl and heteroaryl bromides to give the corresponding 2-substituted piperidines in excellent yields, thus further expanding the scope of these triflates.[12] The conjugated alkoxytrienes obtained by the Pd-catalyzed coupling reaction of lactam-derived vinyl triflates with α-alkoxydienylboronates were used as intermediates for the Nazarov reaction, as these compounds undergo a 4π electrocyclization process under acidic conditions to afford cyclopenta-fused piperidines in good yields.[11,13] The coupling products with alkenylboronic acids and esters were instead used as useful dienes for cycloaddition reactions affording octahydroquinoline derivatives (Scheme 1).[10]



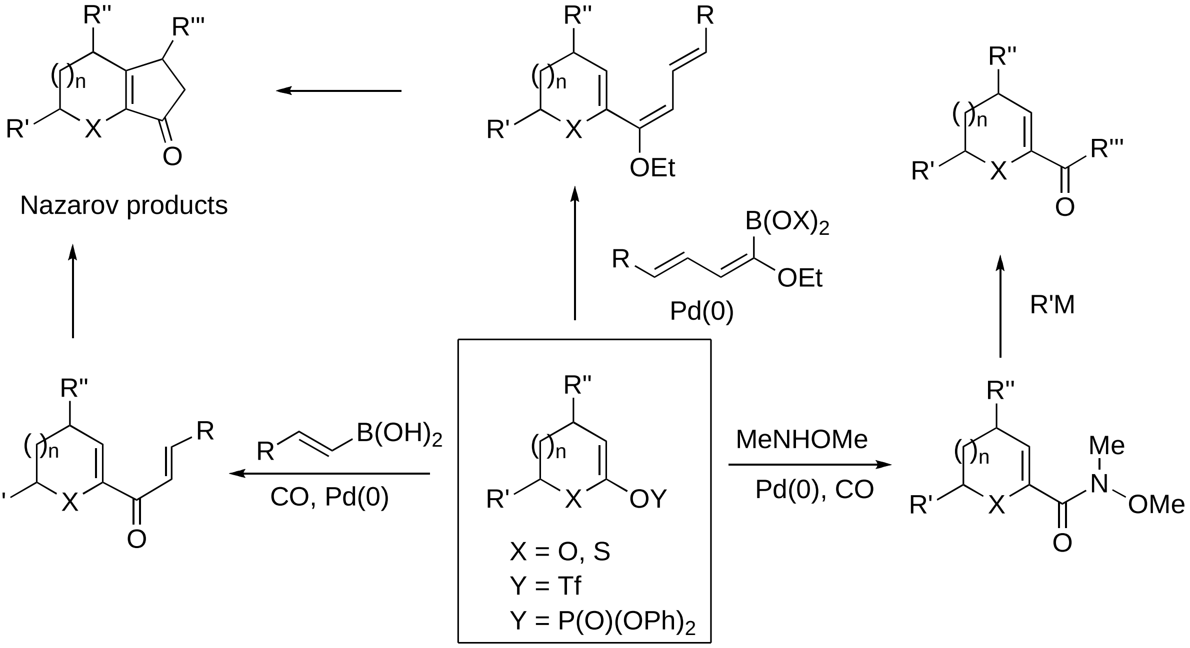
Scheme 1

A review on this work and, in general, on the stability and reactivity of lactam-derived vinyl triflates and phosphates has been published.[14] The stability of cyclic ketene aminal (and acetal) triflates and phosphates is an issue of great importance, as several and sometimes unpredictable factors can determine their rapid decomposition. Small structural modification of the heterocyclic nucleus, the N-protecting group, the heterocycle substituents, and traces of acidity (even on storage in fridge), all can affect the rate of degradation of these intermediates,[14] which for these reasons are often used as a crude reaction mixture just after their preparation or purified through basic alumina or silica gel neutralized by an amine.

More recently, our work was focussed on the carbonylative couplings of cyclic ketene aminal triflates and phosphates (Schemes 2) and the extension of these reactions to lactone-derived vinyl triflates and phosphates (Scheme 3). We employed also thiolactone-derived vinyl triflates, a class of electrophiles never used for cross-coupling processes before.



Scheme 2

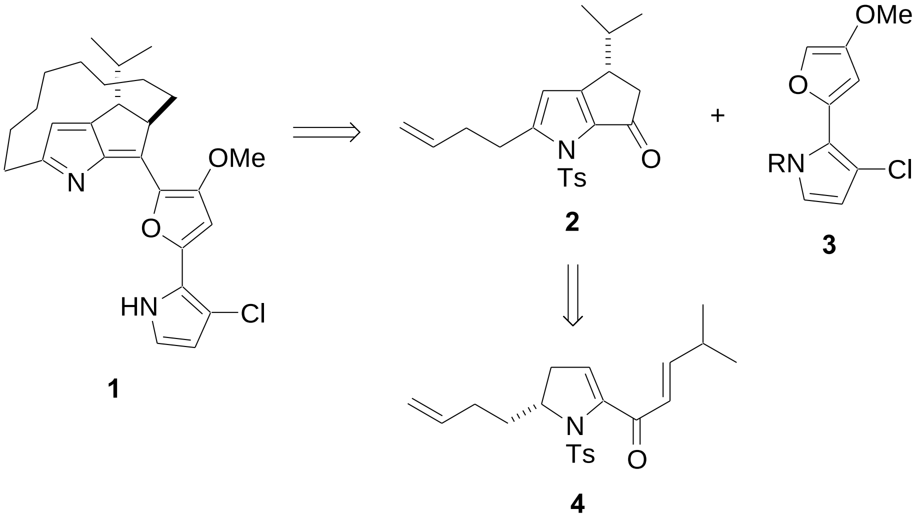


Scheme 3

As depicted in Scheme 3, O- and S-containing triflates and phosphates were also used in non-carbonylative Suzuki-Miyaura coupling reactions as we were interested in preparing suitable intermediate for the Nazarov reaction for the synthesis of cyclopenta-fused O- and S-heterocycles.[5,11,15,16] This reviews deals mainly with the results obtained in our studies on the Pd-catalyzed carbonylative reactions of lactam-, lactone- and thiolactone-derived vinyl triflates and phosphates, that is alkoxycarbonylations, aminocarbonylations, and Suzuki-Miyaura carbonylative cross-couplings, and the application of the formed products to the synthesis of natural and heterocyclic compounds.

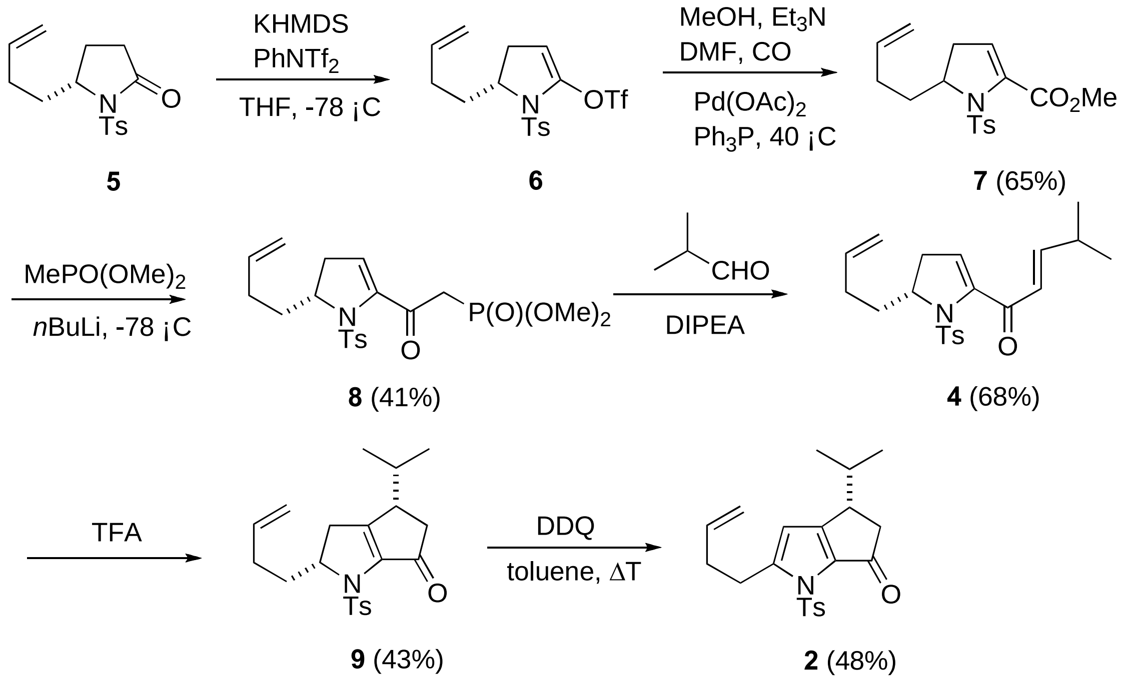
2. ALKOXYCARBONYLATION REACTIONS

Methoxycarbonylation reactions have been carried out on lactam-derived vinyl triflates (and phosphates) a number of times to prepare useful intermediates for the synthesis of natural products.[1,17] We recently exploited such a chemistry for the enantioselective synthesis of roseophilin,[18], 4-hydroxypipecolic acids,[19] and fagomine.[20]

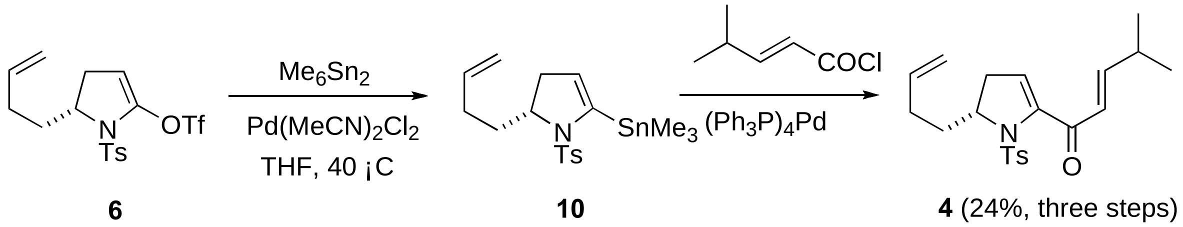


Scheme 4

Roseophilin (**1**, Scheme 4) is a macrocyclic pigment isolated from *Streptomyces griseoviridis* that exhibits potent cytotoxicity against human cancer cell lines.[21] This, and the unique ansa-bridged cyclopenta[b]pyrrole structural core of roseophilin, have stimulated the interest of several groups in the partial or total synthesis of this heterocycle.[22] Among the various synthetic procedures to prepare roseophilin, we decided to revise the one reported by Fuchs in which 13 steps were necessary for the preparation of key isopropyl-substituted ketopyrrole **2** in racemic form.[23] Based on our findings about the remote stereocontrol in the Nazarov reaction,[11,15,16] we envisioned a faster route to obtain bicyclic ketopyrrole **2** in enantiopure form by electrocyclization of pyrroline **4** (Scheme 4) in which the properly oriented buten-3-yl chain on the N-heterocycle would control the absolute stereochemistry of the C4 atom, bearing the isopropyl group, in a Nazarov reaction. Thus *N*-tosyl pyrrolidinone **5** (Scheme 5) was converted into the corresponding vinyl triflate **6** which was directly used without prior purification in the subsequent Pd-catalyzed carbonylation reaction. The carbonylation was realized under standard conditions (10% $Pd(OAc)_2$, Ph_3P, Et_3N, CO) in the presence of MeOH to give methyl ester **7** in 65% overall yield. This ester was then converted into the corresponding Horner-Emmons-Wadsworth reagent **8** (41%) and finally reacted with isobutyric aldehyde to afford the requisite dienone **4**. The same dienone was also prepared by a shorter and more convergent procedure as depicted in Scheme 6. Triflate **6** was initially converted into the corresponding stannane **10** by a Pd-catalyzed coupling reaction with Me_6Sn_2. Then, crude stannane **10** was coupled with 4-methyl-2-pentenoyl chloride in the presence of $(Ph_3P)_4Pd$ as a catalyst in refluxing toluene. At the time, this was the first Stille coupling of lactam-derived vinyl stannanes with acyl chlorides, and in the present case provided **4** in 24% over three steps. Unfortunately the umpolung of **6** could not be realized by borylation as in the case of the corresponding six-membered lactam derivatives[12] as this triflate decomposed quickly during the reaction with both bis(pinacolato)diboron and pinacolborane.



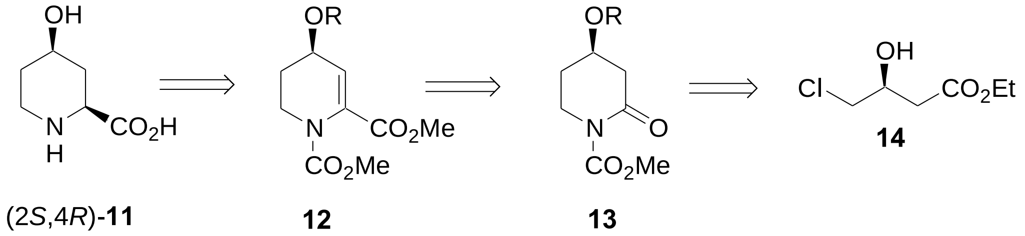
Scheme 5



Scheme 6

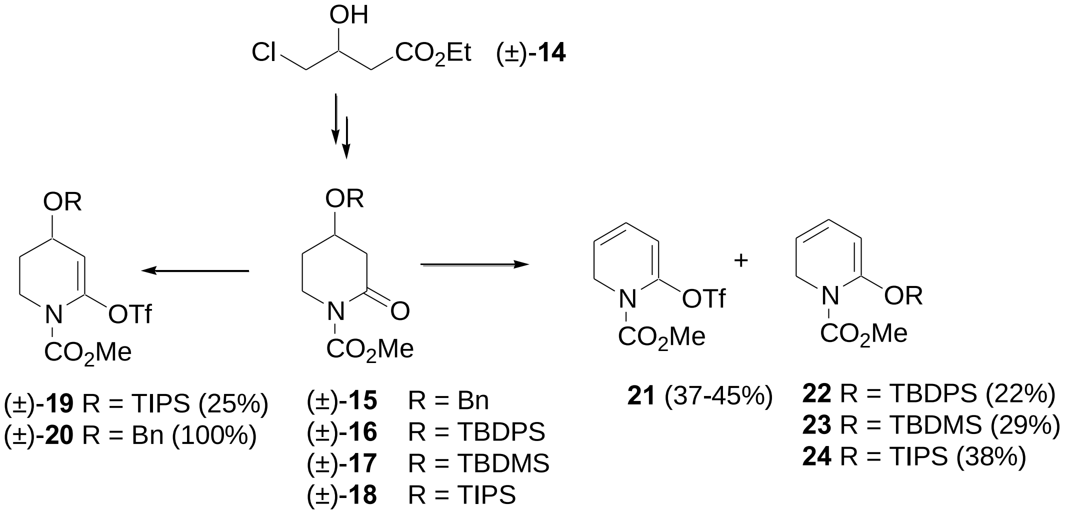
To complete the synthesis, compound **4** was dissolved in pure TFA and the electrocyclization was complete in 20 h to give (2*R*,4*S*)-**9** (Scheme 5) as a single diastereomer (43% yield after chromatography) possessing a 2,4-cis relative stereochemistry as established by NOESY studies. Compound **9** was finally subjected to oxidation yielding target compound (4*S*)-**2** in 48% after chromatography.

The low stability of the pirrolidinone-derived vinyl triflate **6**, which could not be stored in fridge for more than 24 h and had to be used without purification, was due to the augmented ring strain compared to *δ*-valerolactam-derived vinyl triflates. Based on our own experience, these are generally much more stable, can be purified by chromatography and be stored for months in fridge. Thus it was quite a surprise to observe the rapid degradation of 4-*O*-silyloxy-substituted *δ*-valerolactam-derived vinyl triflates and phosphates during and after their preparation as possible intermediates in the synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid.[19] (2*S*,4*R*)-4-hydroxypipecolic acid **11** (Scheme 7) was isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[24] and is a constituent of cyclodepsipeptide antibiotics such as virginiamycin S2.[25] It is also embedded in the structure of some NMDA receptor antagonists,[26] and HIV-protease inhibitors.[27] Because of its importance in medicinal chemistry, numerous enantioselective synthesis of **11** have been reported.[28]



Scheme 7

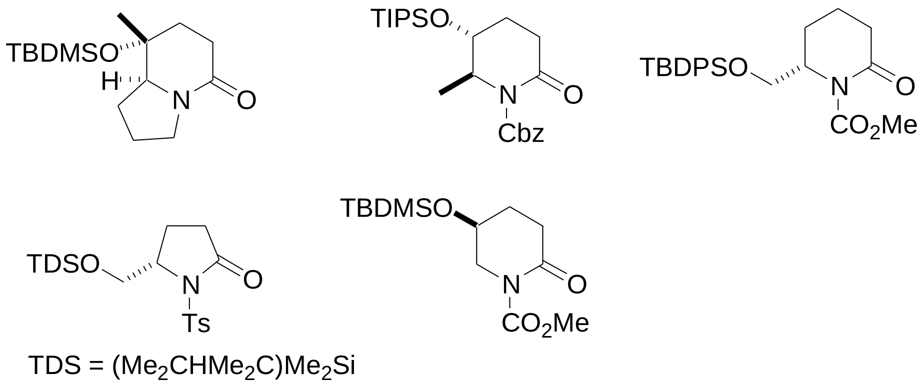
We envisaged a synthetic route to enantiopure (2*S*,4*R*)-4-hydroxypipecolic acid **11** (Scheme 7) from commercial ethyl (3*S*)-4-chloro-3-hydroxybutanoate **14**, in which the key step was the stereocontrolled hydrogenation of tetrahydropyridine-2-carboxylate derivative **12**. This in turn could be obtained by Pd(0)-catalyzed methoxycarbonylation of a vinyl triflate prepared from enantiopure lactam **13**. A bulky substituent (TBDPS or TBDMS group) on the hydroxy group of **12** should direct the reduction to the less hindered face of the double bond providing the target cis product.



Scheme 8

To test this hypothesis, we started from racemic ethyl 4-chloro-3-hydroxybutanoate **14** (Scheme 8) to prepare requisite *N*-protected piperidinones **16-18** having a bulky protection already installed on the 4-hydroxy group.[19] We first attempted the conversion of lactam **16** into the corresponding vinyl triflate by treatment with KHMDS in THF at – 78 °C and then quenching the enolate with *N*-phenyl triflimide. However, only elimination to give **21** (45% after chromatography) occurred. Moreover the signals of

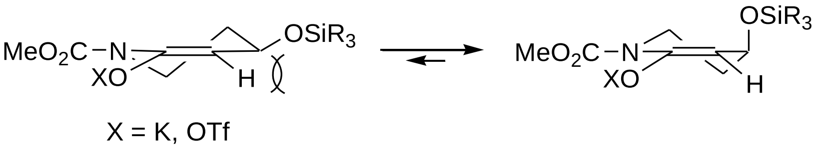
2-O-silylated compound **22** (1:2 ratio with **21**) were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Repeating the experiment with the TBDMS-protected lactam **17**, also in this case elimination was the major pathway, together with the formation of a relatively greater amount of the silyl enol ether **23** (29% after chromatography). As the last attempt, we prepared also the TIPS (triisopropylsilyl) ether **18**,[29] on the grounds of the reported greater stability to basic conditions of the TIPS ethers compared to TBDPS and TBDMS ethers.[30] In this case the ^{1}H NMR analysis of the crude reaction mixture revealed that only a minor part of the starting material was converted into the corresponding vinyl triflate **19** (25% after chromatography), whereas the remaining product was silyl enol ether **24**. 4-Silyloxy substituted lactams appear therefore unsuitable for the preparation of the corresponding vinyl triflates. On the other hand, structurally different lactams containing silyloxy groups were successfully converted into the corresponding triflates by other authors (Figure 2),[14] so the problem in our case was due to the allylic position of the silyloxy group.



TDS = $(Me_2CHMe_2C)Me_2Si$

Figure 2

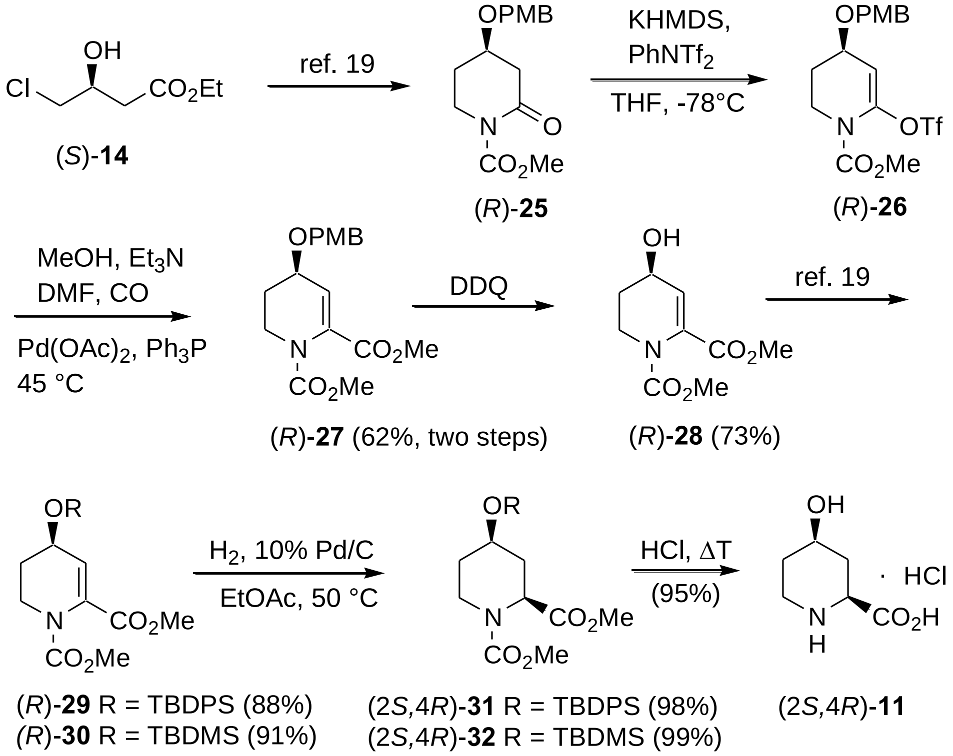
A possible cause of the strong tendency of enolates (or triflates) from **16**, **17** and **18** to give the elimination products is the A(1,2) strain between the olefinic proton on C-3 and the bulky equatorial silyloxy group after formation of the enolate (Scheme 9).



X = K, OTf

Scheme 9

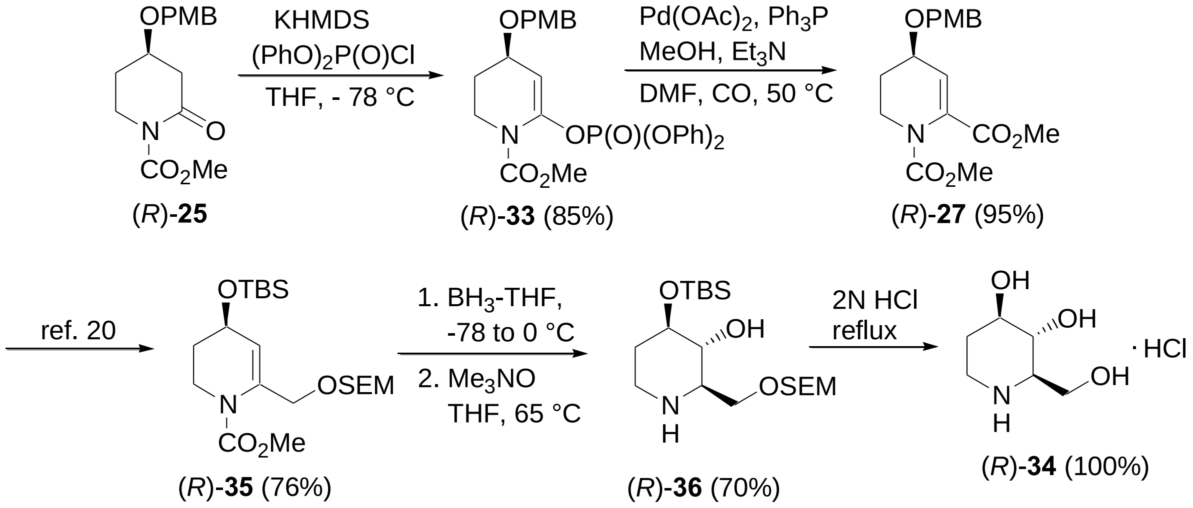
To reduce the strain, the 4-silyloxy group adopts an axial orientation[31] more subject to elimination under the reaction conditions for stereoelectronic reasons. Interestingly we observed also migration of the silyl group to the enolate O atom, which must have occurred intermolecularly. Instead, the 4-benzyloxy group of compound **15** (Scheme 8), and the 4-[*p*-methoxybenzyloxy] group of (*R*)-**25** (Scheme 10) resisted under the basic conditions so that enantiopure vinyl triflate (*R*)-**26** (Scheme 10) could be quantitatively prepared and subjected to Pd-catalyzed methoxycarbonylation under standard conditions to give key intermediate (*R*)-**27**. This was converted into the 4-silyloxy derivatives (*R*)-**31** and (*R*)-**32** which were hydrogenated providing, after exhaustive hydrolysis, target pipecolic acid (2*S*,4*R*)-**11** with excellent stereoselectivity (cis/trans ratio from 17:1 to 23:1).



Scheme 10

The procedure to prepare enantiopure protected hydroxy ester (*R*)-**27** was later improved (Scheme 11) by switching from triflate **26** to the corresponding phosphate (*R*)-**33** which proved much more stable and, of course, economically convenient to prepare. Based on the high facial selectivity in the hydrogenation conditions and having in mind the synthesis of (+)-fagomine (**34**) (Scheme 11), we thought that the same stereocontrol could occur in a hydroboration reaction. (+)-Fagomine is a 1,2-dideoxy-azasugar isolated from *Castanospermum australe* (Leguminosae)[32] and the seeds of Japanese buckwheat *Fagopyrum esculentum* (Polygonaceae)[33] which exhibits strong antihyperglycemic effect in streptozocin-induced diabetic mice and in potentiation of the glucose-induced insulin secretion.[34] Thus, phosphate (*R*)-**33** was prepared by treatment of (*R*)-**25** with a slight excess of KHMDS (0.5 M solution in toluene) in THF at -78 °C, followed by addition of diphenylchlorophosphate. Phosphate (*R*)-**33** could be purified by chromatography on silica gel (85%) consequently allowing higher and reproducible yields in the subsequent carbonylative step (from 86 to 95% in various experiments).

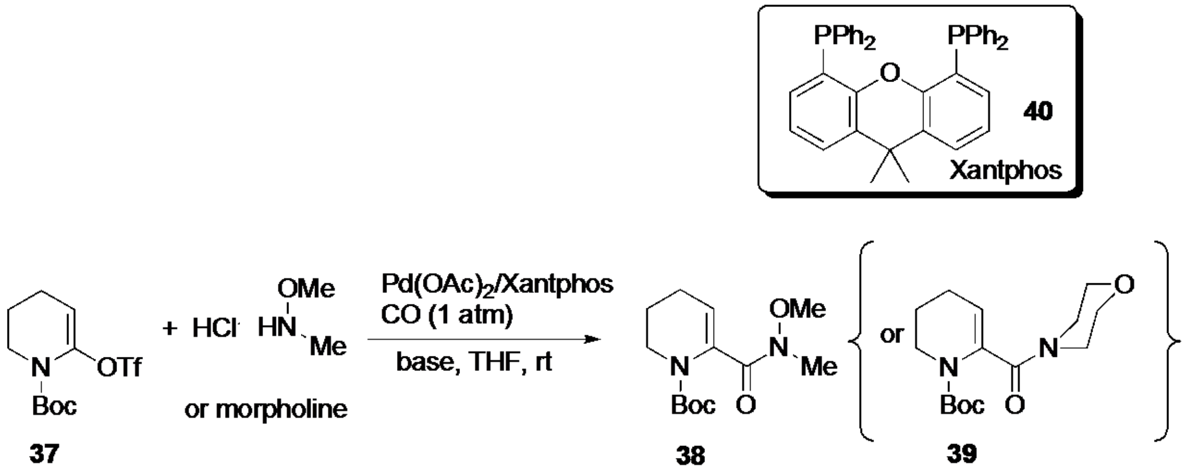
After deprotection to (*R*)-**28** (Scheme 10), conversion into the corresponding TBS (*t*-butyldimethylsilyl) ether, reduction of the methyl ester with DIBAL-H, and protection as the SEM [(β-(trimethylsilyl)ethoxy)methyl] ether (*R*)-**35**, the hydroboration/oxidation steps proceeded smoothly to give (*R*)-**36** as the desired distereoisomer (Scheme 11). Thus, as in the case of the hydrogenation, the bulky 4-silyloxy group, which in (*R*)-**35** is axially oriented to remove the A(1,2)-strain with 3-H, effectively directed the hydroboration to the opposite face, providing, after oxidation, (*R*)-**36**. Exhaustive deprotection provided eventually (+)-fagomine **34** in 23% overall yield.[20]



Scheme 11

3. AMINOCARBONYLATION REACTIONS

Due to our studies on Nazarov reaction, we were particularly interested in new and convenient synthetic sequences leading to conjugated dienones. To this aim, Weinreb amides could be considered versatile intermediates, hence we undertook an investigation aimed at exploiting heterocyclic derived triflates in aminocarbonylative coupling leading to the syntheses of heterocyclic Weinreb amides. Moreover, in order to establish this as a general method for the synthesis of heterocyclic acylated derivatives, reactions with various nucleophiles were thereafter considered.[35]



Scheme 12

First experiments were conducted under Buchwald' s conditions in his aminocarbonylative coupling of aryl bromides;[36] then, triflate **37** was treated with 2% of $Pd(OAc)_2$, Na_2CO_3 (3 equiv), and Xantphos **40** as the supporting ligand in toluene as a solvent under 1 atm pressure of CO (Scheme 12).

Table 1. Sinthesis of Weinreb Amides from Heterocyclic Vinyl Triflates

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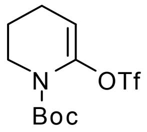
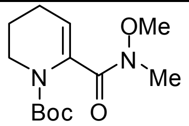
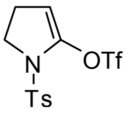
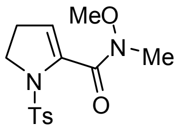
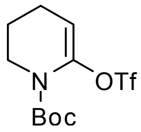
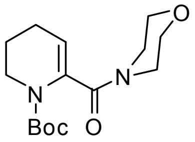
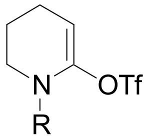
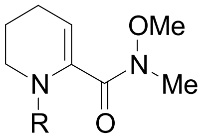
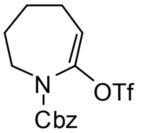
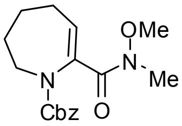
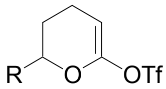
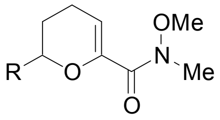
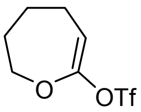
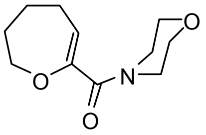
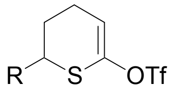
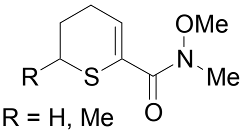
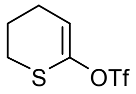
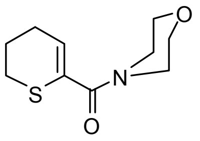
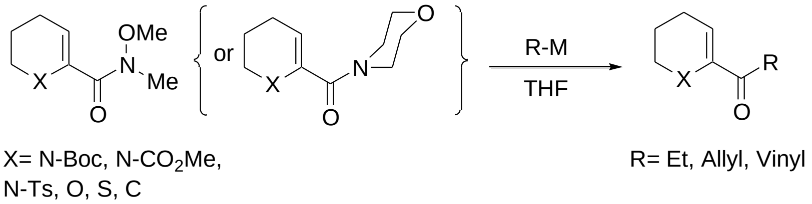
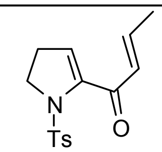
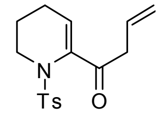
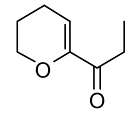
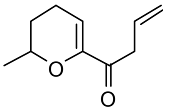
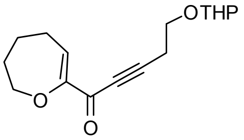
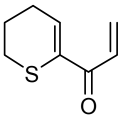
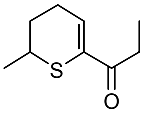
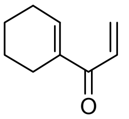
1			78
2			75
3			57
4	 R =CO_2Me, Ts		64-68
5			72
6	 R = H, Me		76-83
7			90
8	 R = H, Me	 R = H, Me	68-70[b]
9			66

[a]Yields refer to flash chromatography purified products. [b]Experiments were conducted with anhydrous DCM and Et_3N as a base without substantial variations in yield.

After 3 h at rt, we observed the complete disappearance of the starting triflate and obtained the amide in 55% yield after chromatography. With THF as a solvent, the yield of the amide **38** after flash chromatography purification rose to 78%. The use of Xantphos proved to be mandatory as experiments conducted with dppp or dppf in the role of ligands gave only lower conversions. Xantphos is a bidentate ligand developed by van Leeuwen and initially used for the hydroformylation reaction.[37] It possesses a wide bite angle (110°) and flexibility range (97-133°), and these characteristics are believed to impart a dynamic coordination environment that may be important for catalyst activity and stability in Pd- and other transition-metal-catalyzed processes.[38] The optimized experimental conditions were thus applied to the synthesis of a series of heterocyclic Weinreb amides as reported in Table 1. As for the lactam-derived *N*-methyl-*N*-methoxy amides, *N*-CO_2Me and *N*-tosyl protected amides were recovered in good yields (entry 4, Table 1), and in these cases, the crude reaction mixtures could be filtered through a short pad of Celite and directly used for subsequent reactions. Different ring sizes are well-tolerated, so that the pyrrolidinone-derived amide (entry 2) and the caprolactam-derived amide (entry 5) were isolated in good yields. The same experimental conditions were applied to the synthesis of lactone-derived (entries 6-7) and thiolactone-derived amides (entries 8-9). As morpholine derivatives proved to act as Weinreb amide analogues,[39] when morpholine was used as an amine in the aminocarbonilative process, the corresponding amides were successfully obtained in 57%, 90% and 66% yield respectively. Moreover, the procedure could be rewardingly applied to the carbocyclic system as well; a 58% yield of the cyclohexanone-derived amide was obtained, though in this case a slight amount of carbonylated homocoupling product was detected. We then decided to inspect the reactivity of the amides reported in Table 1 with organometallic reagents, namely Grignard and organolithium reagents. First experiments were conducted on nitrogen amides with discouraging results: as a matter of fact, with carbamates as protecting groups (Boc, CO_2Me, Cbz) the amides showed an inadequate reactivity and were recovered unchanged even under drastic reaction conditions such as the use of a strong excess of an organometallic reagent (up to 5 equiv. of BuLi, vinyl or ethylmagnesium bromide) or high temperatures. Satisfactory results on lactam derived *N*-tosyl amides were at last obtained with allyl magnesium bromide as a nucleophile, as the corresponding ketones were isolated in excellent yields (entries 1 and 2, Table 2, 91% and 90% respectively). Concerning the unexpected low reactivity of *N*-carbamate protected Weinreb amides, on the basis of our experimental data we could only presume that both conformational aspects and metal-chelation phenomena are accountable to explain the observed reactivity.[40] Satisfactory results have been obtained with oxygen, thio or carbocycle amides (Table 2). The reactions with ethyl, allyl or vinyl magnesium bromide all proceeded smoothly at -78°C and afforded quite pure ketones in less than 1 hour. Provided that the sequence is feasible, the vinylation reaction using the commercial available and cheap vinyl magnesium bromide could be considered of remarkable synthetic worth. In the case of caprolactone derived amide (entry 5), the reaction with THP protected lithium but-3-yn-1-ol efficiently proceeded at -78 °C and was complete within 30 min, affording the corresponding conjugated enynone in an 87% yield after flash chromatography purification.

Table 2. Conversion of heterocyclic amides into functionalized ketones



entry	product	T (°C)	Yield %[a]
1		-78	91
2		-78	90
3		-78	76
4		-78	78
5		-78	87
6		-78	80
7		-78	72
8		-78	94

[a] Yield after chromatographic purification.

4. CARBONYLATIVE SUKUKI-MIYAURA COUPLING REACTIONS

Although carbonylative cross-couplings are powerful synthetic tools, no examples of such reactions were known to have been carried out on ketene aminal and acetal triflates and phosphates when we started to evaluate the possibility of forming new C–C bonds through carbonylative cross-coupling reactions involving organometallic reagents. Stille carbonylative processes were well known and widely used.[41] However, since tin compounds are toxic, we opted to investigate the carbonylative Pd-catalyzed coupling reactions of ketene aminal and acetal triflates with boronic acids. Due to the current interest in the Nazarov reaction of unsymmetrical dienones having one of the double bond embedded in a heterocyclic structure,[11,15,16,18, 42] we first evaluated the use of substituted vinylboronic acids (Figure 3) as the coupling partners, and extended this study to a thiolactone-derived enol triflate as an example of a class of electrophiles that have never been used in any kind of metal-catalyzed coupling process.[43]

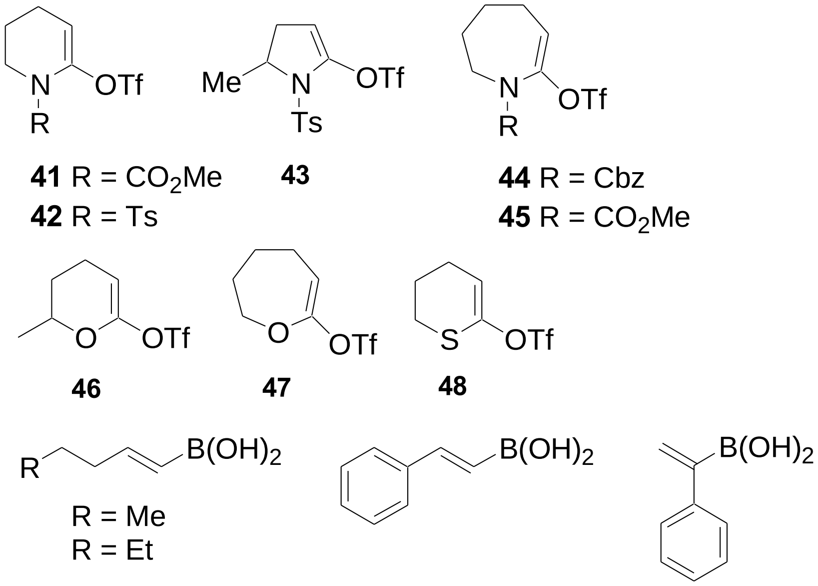
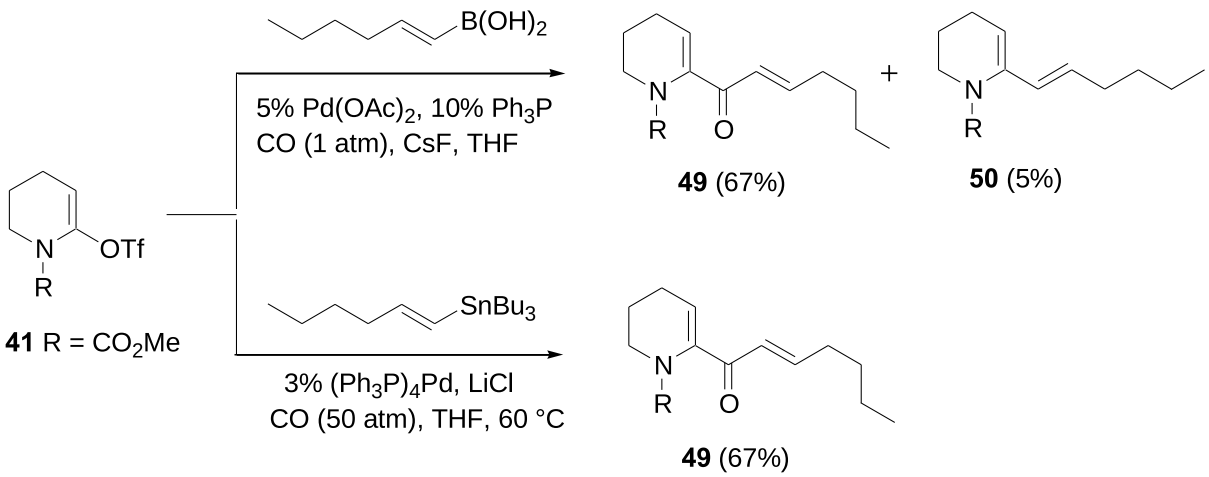


Figure 3

An initial survey of the conditions for the carbonylative coupling of cyclic ketene aminal triflate **41** (Scheme 13) resulted in 5% $Pd(OAc)_2$/10% Ph_3P being the best catalyst system in anhydrous THF when carrying out the reaction in the presence of CsF (3 equiv) to generate the negatively charged, four-coordinate boron "ate" complex that is required for the transmetalation step. So, with triflate **41** and 2 equiv of (*E*)-1-hexenyllboronic acid, at room temperature and under atmospheric pressure of carbon monoxide, we observed the rapid formation of the carbonylative coupling product **49**, which was obtained in 67% yield after chromatography. The non-carbonylated coupling product **50** was also obtained in 5% yield. For a comparison, we carried out also the carbonylative Stille coupling of triflate **41** with (*E*)–tributyl 1–hexenylstannane (Scheme 13) under standard conditions, which resulted in a much slower reaction, as it proceeded only at high CO pressure (50 atm) and temperature (60 °C), to provide the coupling product in 67% yield.[44]



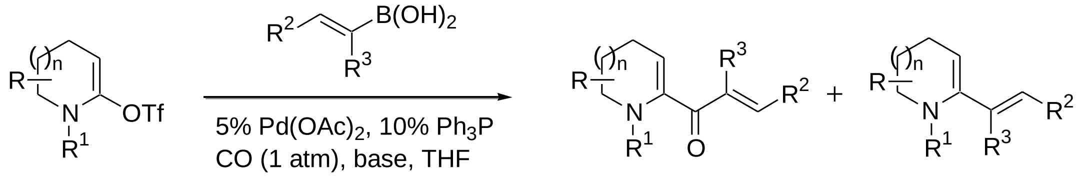
Scheme 13

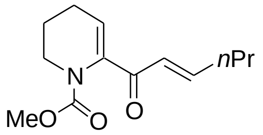
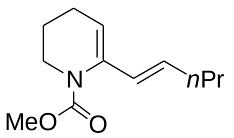
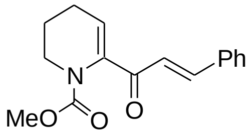
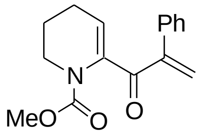
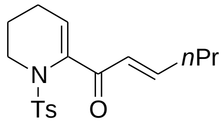
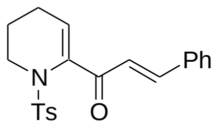
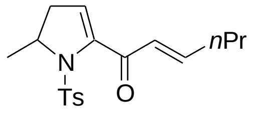
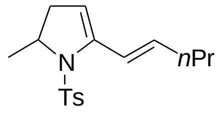
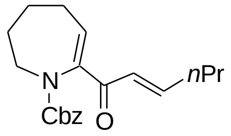
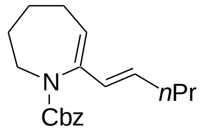
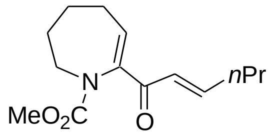
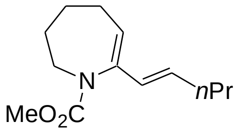
To explore the scope of the reaction, a series of structurally different vinyl triflates derived from lactams, lactones, and one thiolactone (Figure 3) were subjected to Suzuki-Miyaura carbonylative coupling with various alkenylboronic acids (Tables 3 and 4). Of these triflates, **43**, **46** and **47** were unstable compounds prone to quickly decompose. Therefore they were used without purification just after their preparation.

The results of the carbonylative coupling of triflates **41**-**45** derived from differently protected (*N*-tosyl, *N*-Cbz, *N*-CO_2Me) five-, six-, and seven-membered lactams were really satisfactory (Table 3). We were particularly pleased to obtain the coupling product between five-membered heterocyclic triflate **43** and 1-pentenylboronic acid (entry 6) in 77% yield as this procedure could represent a better alternative to that previously proposed for the preparation of a roseophilin synthetic precursor.[18] As the yield of the carbonylative coupling under standard conditions was barely acceptable with seven-membered ring triflate **45** (48%), being relatively high the amount of the non-carbonylated product (18%), the reaction of triflates **44** and **45** with (*E*)-1-pentenyllboronic acid was carried out in the presence of dppf [1,1’-bis-(diphenylphosphino)-ferrocene] as a ligand, which is reported to increase the relative amount of the carbonylated product in Suzuki-Miyaura carbonylative processes.[45] We thus obtained the carbonylated coupling products in good chromatographic yield (62 and 61%, respectively, entries 7 and 8), together with a lower amount of by-products (11-13%).

As the first attempts of carbonylative coupling of the crude reaction mixture containing cyclic ketene acetal triflate **46**, performed under standard conditions with 5 mol % of $Pd(OAc)_2$, provided a lower relative amount of the carbonylated product (42% yield). Also with this triflate the reaction was carried out in the presence of dppf as a ligand (Table 4, entry 1), which provided a higher ratio between the carbonylated (50%) and non carbonylated product (6%).

Table 3. Carbonylative Suzuki-Miyaura coupling of Triflates 41-45[a]

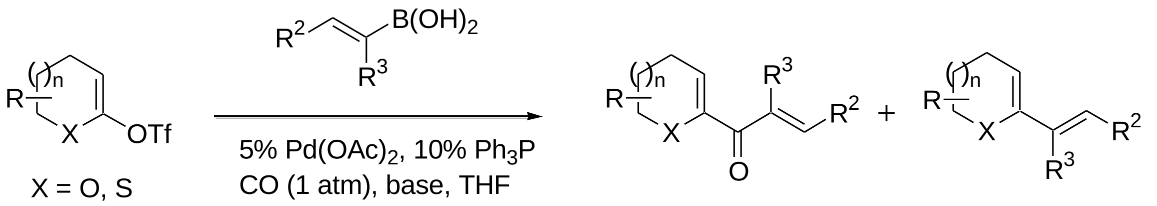


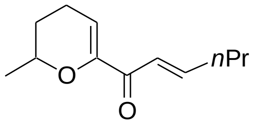
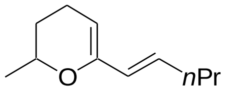
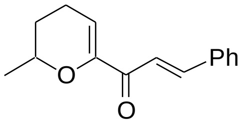
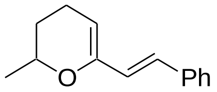
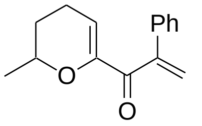
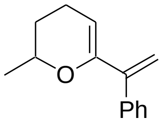
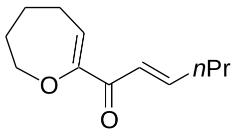
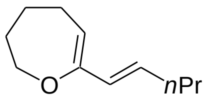
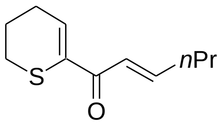
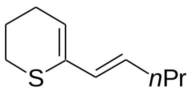
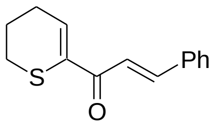
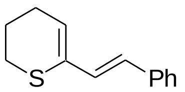
entry	triflate	product	(%)[b]		(%)[b]
1	**41**		79		12
2	**41**		83	-	
3	**41**		68	-	
4	**42**		69	-	
5	**42**		60	-	
6	**43**		77		13
7[c]	**44**		62		13
8[c]	**45**		61		11

[a]Reactions carried out on 0.5-1.5 mmol of substrates at rt with 5 mol % of catalyst [Pd(OAc)$_2$] and 10 mol % of Ph$_3$P, 2 equiv of boronic acid and 3 equiv of CsF. All reactions were complete after 3-4 h. [b]Yield after chromatography. [c]Reaction carried out in the presence of dppf as a ligand.

These conditions were applied to the coupling of **46** with the other boronic acids, obtaining in both cases the carbonylated products in acceptable chromatographic yield after two steps (entries 2 and 3). The carbonylative coupling of crude triflate **47** with (*E*)-1-pentenyllboronic acid in the presence of dppf provided the desired compound only in 32% yield, together with less than 6% of the non carbonylated product (entry 4). Degradation of unstable triflate **47** took place to a great extent under these conditions and we believe that also for the six-membered ketene acetal triflates partial decomposition of the substrates causes generally lower yield than with the lactam derivatives.

Table 4. Carbonylative Suzuki-Miyaura Couplings of Triflates 46-48[a]



entry	triflate	product	(%)[b]	product	(%)
1	**46**		50		6
2	**46**		51		4
3	**46**		52		6
4	**47**		32		6
5[c]	**48**		56		22
6[c]	**48**		57		19

[a]Reactions carried out on 0.5-1.5 mmol of substrates at room temperature in the presence of 5 mol % of catalyst [Pd(OAc)$_2$] and 6.25 mol % of dppf, 2 equiv of boronic acid and 3 equiv of CsF. All reaction were complete after 3-4 h by TLC. [b]Overall yield over two steps after chromatography. [c]Reaction carried out in the presence of CsOAc as a base and 10 mol % of Ph$_3$P.

Finally, for the carbonylative coupling of dihydrothiopyranyl triflate **48** with (*E*)-1-pentenyllboronic acid or (*E*)-styrylboronic acid, the best results in terms of yield and product ratio were obtained by using CsOAc as a base (entries 5 and 6) and the reaction products were isolated in good overall yield (56 and

57%, respectively) after the two steps.

An important observation is that, despite the reactions being carried out under 1 atm of CO, the non-carbonylative Suzuki-Miyaura coupling, in each optimized conditions, appears as a minor problem with cyclic aminal and acetal triflates as non-carbonylated products are always obtained in less than 13% yield. This is not true for thiolactam-derived vinyl triflate **48**. Surely the heteroatom has a certain influence on the relative amount of the products and reasonably this is related to the electron density on C2 that in turn is greatly dependant on the electronegativity of the heteroatom present in the ring. With S-containing heterocyclic triflate **48** the higher electron density on C2 could slow down the adsorption of CO by the palladium complex determining the formation of a higher amount of the non-carbonylated product.

5. THE NAZAROV REACTION

The Nazarov reaction is one of the most powerful process for constructing five-membered carbocyclic systems, having found its applications in the synthesis of several natural products.[46,13,18] The Nazarov reaction of N- and O-heterocyclic divinyl ketones and their synthetic equivalents depicted in Figure 4 has been in particular the subject of several recent studies.[11,15,16,18,42,47,48] The cyclization forms structurally interesting cyclopenta-fused heterocyclic compounds (Figure 4) due to their presence in natural and biologically active compounds.[46,49] The presence of the heteroatom has a striking influence on the reactivity of these systems, as it makes the ring closure of the corresponding pentadienyl cations possible even in the presence of catalytic amounts of Brønsted or Lewis acids at room temperature, whilst the corresponding carbocyclic substrates do not generally react unless more drastic conditions are used.

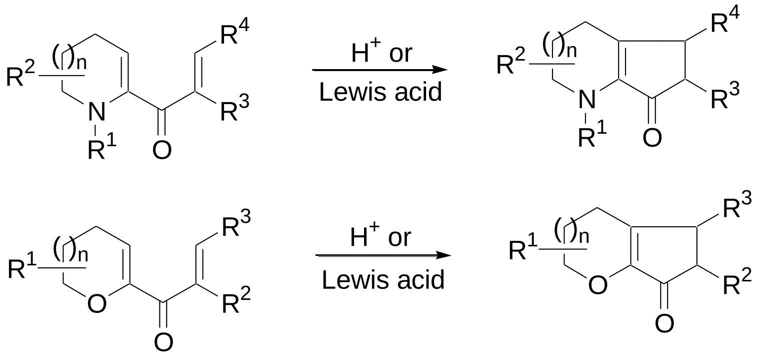
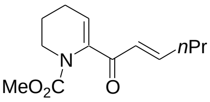
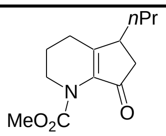
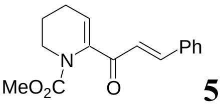
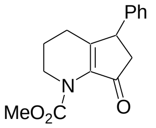
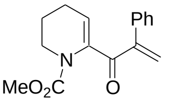
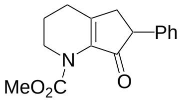
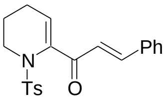
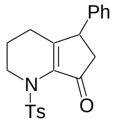
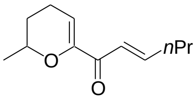
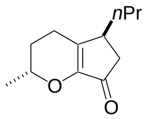
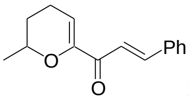
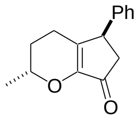
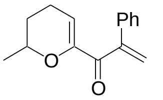
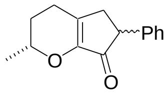
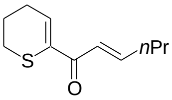
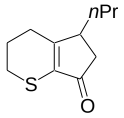
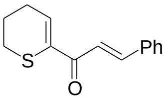
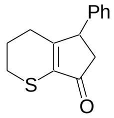


Figure 4

The carbonylative reactions carried out in our laboratories and reported in sections 3 and 4 allow for the rapid preparation of the unsymmetrical divinyl ketones (Figure 4) required for the Nazarov reaction. Very recently we have in fact applied those procedures for the preparation of a series of N,- O, and S-containing heterocyclic divinyl ketones for a comparative study on the Lewis- and Brønsted acid-catalyzed,[16,50] and organocatalytic[51] Nazarov reaction.

Table 5. Lewis acid-catalyzed Nazarov Reaction of Dienones 51-59

Entry	Dienone	Lewis Acid	T (°C)	Time (h)	product	Yield (%)
1	 **51**	$Sc(OTf)_3$ (3%) $In(OTf)_3$ (15%)	55 35	3 12		86 85
2	 **52**	$In(OTf)_3$ (10%)	55 20	2.5 4		83 81
3	 **53**	$Sc(OTf)_3$ (10%)	22	20		64
4	 **54**	$Sc(OTf)_3$ (3%)	55	6.5		55
5	 **55**	$Sc(OTf)_3$ (3%)	0	4		65[a]
6	 **56**	$Sc(OTf)_3$ (10%) $In(OTf)_3$ (3%)	0 20	1 1		63[b] 64
7	 **57**	$Sc(OTf)_3$ (3%)	20	1.5		53[c]
8	 **58**	$Sc(OTf)_3$ (3%)	20	1		67
9	 **59**	$Sc(OTf)_3$ (3%) $In(OTf)_3$ (3%)	20 20	1 1		73 72

[a] trans/cis ratio = 9:1. [b] trans/cis ratio = 20:1. [c] trans/cis = 1.2:1

Among various Lewis acids, metal triflates, and in particular $Sc(OTf)_3$ and $In(OTf)_3$, were the most efficient in catalyzing the electrocyclization process. $Sc(OTf)_3$ and $In(OTf)_3$ are the most Lewis acidic among the catalysts tested as the two cations Sc^{3+} and In^{3+} possess a high charge to radius ratio.[52] With *N*-CO_2Me protected dienones **51-53**, all reactions were successfully carried out at either room temperature or slight heating in the presence of 3-15 mol % of the catalyst (Table 5, entries 1-3). The Nazarov reaction of the 2-alkoxy-1,4-dien-3-one **55** provided, after 4 h at 0 °C in the presence of 3 mol %

of $Sc(OTf)_3$, the Nazarov product (entry 5) in 65% yield after chromatography. Cyclization of **56** was fast with 10 mol % of $Sc(OTf)_3$ at 0 °C as well as in the presence of 3 mol % of $In(OTf)_3$ at 20 °C. Both Nazarov products (entries 5 and 6) were obtained as a mixture of diastereomers in 9:1 and 20:1 ratio respectively. The relative stereochemistry of the major isomers was 2,5-trans, which is in accordance with the results obtained in the mineral acid-catalyzed Nazarov reaction of analogous substrates.[15] It is interesting to notice that the Lewis acid has no effect in varying the sense of conrotation with respect to the mineral acid-catalyzed process,[16] the 2,5-trans products being obtained as the major diastereomers.

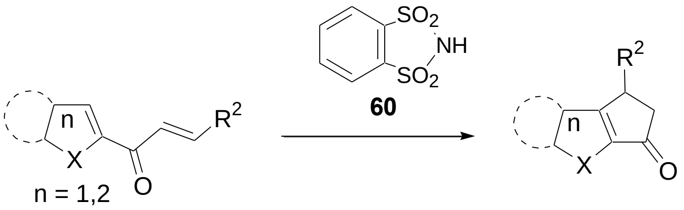
The cyclization of **57** was carried out at room temperature in the presence of 3 mol % of $Sc(OTf)_3$ (entry 7). In this case a 1.2:1 mixture of diastereomers was isolated by chromatography in 53% yield. Also the cyclization of thiopyranyl derivatives **58** and **59** was very fast, as the Nazarov products (entries 8 and 9) were obtained in good yield just after 1 h at room temperature.

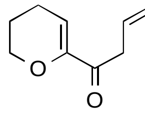
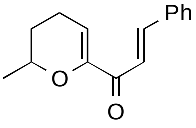
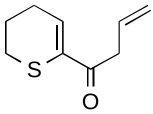
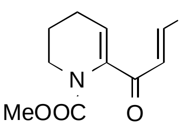
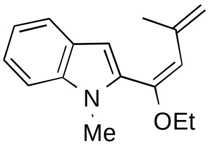
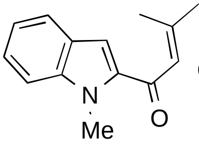
The (high) relative rates of cyclization of heteroatom-containing dienones **51**-**59** can be explained on the basis of the role of the heteroatom in stabilizing the positive charge which develops in the transition state of the process,[16] but also, bidentate binding of the Lewis acid to the substrate (C=O and heteroatom) could help the two vinyl moieties in adopting the proper s-cis/s-trans orientation for the cyclization.

6. NEW TRENDS IN NAZAROV CYCLIZATION

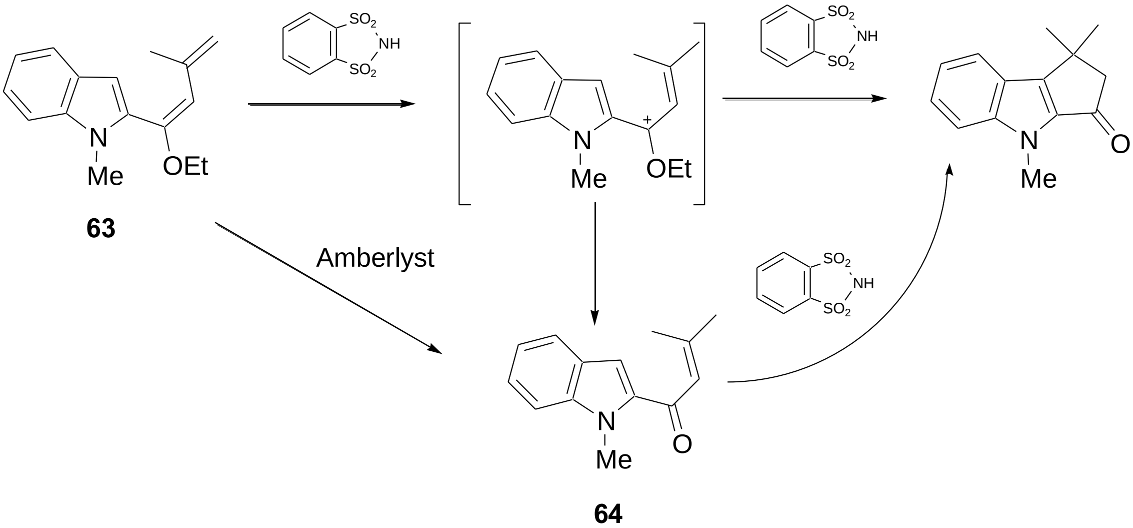
The development of progressively milder acid promoters is mandatory for the Nazarov reaction to be accounted as a versatile synthetic tool. Interestingly, the process could be promoted by both Lewis and Brønsted acids, but while Lewis acid catalysis is well assessed and allows the use of extremely mild conditions coupled with a high level of regio- and diastereo/enantioselectivity[53,42,43] further efforts are required to improve protic acid catalysis in the context of the Nazarov cyclization. Among the organic Brønsted acids, Rouden *et al.* demonstrated the efficiency of a catalytic amount of TsOH in promoting the Nazarov cyclization on α-alkoxydienones.[54] The sulfonic acid resin Amberlyst 15® proved to be an efficient catalyst with suitable substrates.[11,15] In recent times Rueping *et al.* described the first organocatalytic enantioselective Nazarov reaction on activated dienones with BINOL (1,1'-binaphtol) derived *N*-triflyl phosphoramides.[47] Recently, *o*-benzenedisulfonimide (**60**; Table 6) has been reported to act in catalytic amounts, as a safe, nonvolatile, and recyclable Brønsted acid.[55] *o*-Benzenedisulfonimide has thus been evaluated as a catalyst in Nazarov electrocyclization. Some preliminary experiments conducted on β-damascone, an unpolarized and β-trisubstituted dienone that is reported to undergo ring closure under very harsh conditions,[56] gave encouraging results. Thus, on continuing our studies on the Nazarov cyclization of dienones in which one of the double bonds is embedded in an heterocyclic framework, a series of heterocyclic derived dienones were considered for the electrocyclization promoted by the *o*-benzenedisulfonimide (Table 6).

Table 6. ***o*-Benzendisulfonimide catalyzed cyclization of heterocyclic dienones**



Entry	**60** mol (%)	Substrate	Solvent	Time (h)/T (°C)	Yield
1	30	 **61**	toluene	3 / 100	70
2	10	**61**	no	0.5 / 60	51
3	30	 **56**	toluene	0.3 / 100	66 *trans:cis* 5 : 1
4	30	**56**	toluene	6 / 60	66 *trans:cis* 7 : 1
5	30	 **62**	ECOENG212	2 / 60	65
6	5	 **52**	CH_2ClCH_2Cl	3.5 / 80	78
7	10	 **63**	CH_2ClCH_2Cl	0.2 / rt	43
8	50	 **64**	CH_2ClCH_2Cl	20 / 80	45
9	30	**63**	CH_2ClCH_2Cl	5.5 /80	65

Compounds **61** and **62** (Table 6) were synthesized through the reaction of allyl magnesium bromide with the corresponding Weinreb amides,[35] while **56** and **52** through a carbonylative Suzuki-Miyaura cross coupling between lactone- or lactam-derived vinyl triflates and (*E*)-styrylboronic acid.[19,44,50] Palladium catalyzed Suzuki coupling between 1-methyl-1*H*-indol-2-yl trifluoromethanesulfonate and the suitable α-ethoxydienylboronate afforded **63** in excellent yields. All the starting compounds were supposed to take advantage of the presence of a heteroatom in the α-position of the dienone, nonetheless it should be pointed out that in the case of allyl derivatives **61** and **62** an isomerization of the terminal double bond must occur before the cyclization process takes place. In Table 6, a selection of the most significant data obtained in the various experimental conditions is reported. A satisfactory yield was obtained using compound **61** in toluene for 3h at 100 °C (entry 1). Due to the low environmental impact of **60**, we were particularly interested in evaluating solvent-free conditions (entry 2). The catalyst could be easily recovered from the work-up of the reaction mixture through a rapid rinse of the organic layer with water, and thus reused for further experiments without loss of catalytic activity. Optimized conditions allowed recovery of the cyclization product at a yield of 51%. In the case of **56** (entry 4), the cyclization proceeds with good diastereoselectivity with a 7:1 ratio in favour of the *trans* diastereoisomer. This result is in accordance with the data obtained with analogous substrates both under Brønsted acid[15,11] and Lewis acid[50] catalysis. Furthermore, it is worth emphasizing that *o*-benzenedisulfonimide is efficient in promoting the Nazarov cyclization also in the case of thio derivative **62** in the ionic liquid ECOENG 212 (entry 5). Azacycle derivatives **52** and **63** are considered in entries 6 and 7. In these cases the reaction proceeds in dichloroethane at 80 °C with a 5% catalyst loading with a 78% yield for **52**. Particularly efficient was the cyclization of **63** (entry 7). After 10 min at 25 °C the TLC control showed the disappearance of the starting material and the formation of two new products, the expected cyclic product together with the open chain ketone **64** in a 2:1 ratio.



Scheme 14

We have previously demonstrated that in the conversion of alkoxydienyl heterocyclic derivatives into cyclic products by Amberlist 15®-catalyzed Nazarov reaction, the divinyl ketone **64** is not an intermediate of the reaction pathway (Scheme 14).[11] However, *o*-benzenedisulfonimide was efficient in converting **64** into the cyclic product in a separate process (entry 8) even though an higher amount of catalyst and longer reaction time were required. The efficiency of **60** as a catalyst can be entirely exploited in the direct and complete conversion of **63** using slightly stronger conditions (entry 9), the cyclic product was recovered in a 65% yield. It is remarkable to point out that Amberlyst 15® failed in the direct conversion of **63** into the corresponding cyclopentenone; in that case **64** was recovered as the only product and then cyclized with neat TFA. The metal-free procedure proposed allows the use of a safe, nonvolatile and recyclable organic promoter with a loading factor which is not larger than 30%.

7. CONCLUSIONS

The use of lactam-, lactone- and thiolactone-derived vinyl triflates and phosphates in palladium-catalyzed carbonylative reactions furnishes a valuable synthetic tool towards heterocyclic frameworks. In this review we first described the reactivity of heterocyclic-derived enol triflates and phosphates in alkoxycarbonylation reactions and the use of the products as key intermediates in the synthesis of natural compounds such as roseophilin, (+)-fagomine, and (2*S*,4*R*)-4-hydroxypipecolic acid. Aminocarbonylation was exploited to synthesize heterocyclic Weinreb amides that were successfully reacted with various nucleophiles to obtain divinyl ketones possessing the right electronic arrangement to undergo a Nazarov electrocyclization. Furthermore, divinyl ketones were obtained resorting to a Suzuki-Miyaura carbonylative process between heterocyclic enol triflates and vinyl boronic acids. By means of the herein proposed synthetic approach, heterocyclic bicyclic frameworks become readily and straightforwardly accessible structures.

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