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Lactam-derived Vinyl Triflates and Phosphates in the Synthesis of N-Heterocycles

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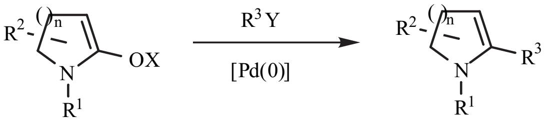
Abstract: In the last decade there has been a growing interest in the coupling reactions of lactam-derived vinyl triflates and phosphates. The usefulness and versatility of these lactam derivatives in organic synthesis will be highlighted in this review that deals with the methods for their preparation, their stability and reactivity, and applications to the synthesis of natural compounds.

Keywords: Catalysis, coupling, lactams, palladium, phosphates, triflates.

The functionalization of lactams by Pd-catalyzed and non-catalyzed coupling reactions of their vinyl triflate **1** and phosphate **2** derivatives (Scheme **1**) has received a growing attention in the last decade as a tool for the synthesis of N-containing heterocycles. In marked contrast to the widely used vinyl triflates (and phosphates) from ketones or lactones, the corresponding lactam derivatives **1** and **2** had not been employed until Isobe reported the Pd-catalyzed coupling of the *N*-benzoyl protected δ-valerolactam-derived vinyl triflate with (trimethylsilyl)acetylene [1,2] and almost contemporary works by Comins [3] and Murai [4] on similar substrates appeared in the literature.



1 X = SO_2CF_3 (Tf)
2 X = $P(O)(OPh)_2$ or $P(O)(OEt)_2$
R^1 = Cbz, CO_2Ph, Boc,
CO_2Me, Ts, Bz

Scheme 1.

With the first report by Hiemstra and Speckamp on triflates from five-membered lactams, the bases for the successive full exploitation of these compounds were laid [5]. Since then, Heck, Stille, Suzuki-Miyaura, Sonogashira, carbopalladation and other reactions have been carried out on substrates **1** and **2** in order to obtain key intermediates in various synthetic sequences aimed at the preparation of natural compounds. The scope of this mini review is to highlight the usefulness and versatility of non-aromatic lactam-derived vinyl triflates and phosphates in organic synthesis. The methods for the preparation of **1** and **2** and their stability will be analyzed first. The Pd-catalyzed and non-catalyzed reactions described in the literature (and their applications to natural product synthesis) will follow, organized by type of coupling. Heteroaromatic triflates and phosphates are not treated because of their close resemblance, in terms of stability and reactivity, to aromatic triflates.

PREPARATION AND STABILITY

Vinyl triflates **1** are prepared by enolate formation from the corresponding lactams (generally using strong bases such as LHMDS or KHMDS) and trapping with triflic anhydride, *N*,*N*-bis(trifluoromethanesulfonyl) aniline (*N*-phenyltriflimide) or *N*-(5-chloro-2-pyridyl)triflimide (Comins' reagent) [3,6]. The route involving triflic anhydride was found not to be reproducible in terms of yields [7-8], whereas both the triflimides afforded vinyl triflates in usually excellent yields after silica gel chromatography, at least for six-membered derivatives (Table. **1**) [3-4,9-10]. The advantage of using Comins' reagent stands in avoiding toxic HMPA, but using KHMDS as a base allows one to successfully employ the cheaper *N*-phenyltriflimide.

The reason behind the belated utilization of vinyl triflates **1** and phosphates **2** is probably the limited, or lack of, stability that has been generally attributed to these compounds in terms of resistance to aqueous work-up or chromatography and tendency to decomposition on standing at rt or in the course of the coupling step subsequent to their preparation. Isobe himself had already reported in its pioneering work that a seven-membered *N*-benzoyl triflate could not be successfully used in the coupling with (trimethylsilyl)acetylene because of its instability [1] and both Isobe and Comins observed that five-membered triflates rapidly decompose [3] or are sensitive to aqueous work-up [2]. The first insights into which structural features are necessary for a lactam-derived vinyl triflate **1** to be of useful stability were given by Hiemstra and Speckamp [7]. Vinyl phosphates from *N*-alkyl substituted lactams suffer from a phosphate-phosphonate rearrangement which occurs to some extent during their preparation and which becomes complete upon exposure to additional base [11]. This could have hampered the use of lactam-derived vinyl phosphates as coupling partners until Nicolaou's report on *N*-alkoxycarbonyl protected phosphates **2** [12]. The phosphate-phosphonate rearrangement is not observed in the course of their preparation, even when the base (KHMDS) is added to

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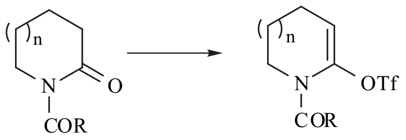
Table 1. Preparation of Lactam-Derived Vinyl Triflates



3-9

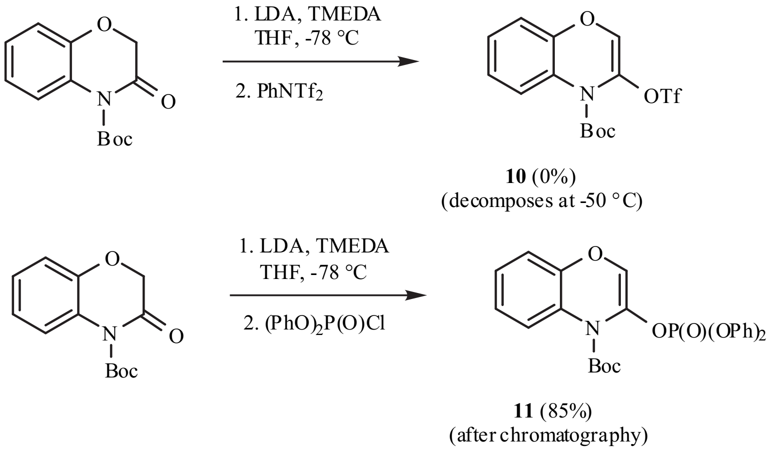
entry	n	R	conditions^a	product	yield (%)^b	reference
1	1	Ph	A	**3**	94	[4]
2	1	Ph	B	**3**	87	[3]
3	1	OPh	B	**4**	90	[3]
4	1	OPh	A^c	**4**	29	[3]
5	1	OBn	A	**5**	92	[9]
6	1	O*t*-Bu	A	**6**	75	[9]
7	1	O*t*-Bu	A	**6**	89	[4]
8	1	OMe	A	**7**	89	[10]
9	2	OBn	A	**8**	67	[4]
10	2	OBn	A	**8**	65	[9]
11	2	OPh	B	**9**	54	[3]

^{a}Conditions: (A) LHMDS, HMPA, $PhNTf_2$, THF, -78 °C; (B) LHMDS, Comins' reagent, THF, -78 °C. ^{b}After purification by chromatography. ^{c}Without HMPA.

a mixture of the lactam and phosphoryl chloride [12]. Moreover, these phosphates enjoy a remarkable stability, often superior to that of their triflate counterparts as illustrated in the examples reported in (Scheme **2**) (compare stability of **10** and **11**) [13-14], thus being useful and less expensive (due to the cost of the reagents employed for their preparation) alternatives to compounds **1**.

Ring size, *N*-protection, and ring substituents are all factors that affect the stability of **1** and **2**. In particular for phosphates **2**, it appears that N-protection by an electron withdrawing group is the only requisite for stability, even to silica gel flash chromatography, irrespective of the ring size (Scheme **3**) [12]. For triflates **1**, ring size and substituents also control the stability of these derivatives, although a six-membered ring, when coupled with an electron withdrawing N-protecting group, ensures sufficient stability so that compounds such as **5** and **6** (Table. **1**) are not only obtained in high yield after chromatography, but can also be stored for weeks at room temperature, for several months at 4 °C, and even recovered unreacted after hours at 80 °C under coupling conditions [9]. Some illustrative examples on the effect of N-substituent, ring size and ring substituents on the stability of triflates are reported in (Table. **2**).

From these data it emerges that pyrrolidinone triflates are, probably due to augmented ring strain, the most labile derivatives (entries 1, 2, 4 and 5) and, in order for them to be of sufficient thermal stability, a high electron withdrawing group as the Ts is essential in these cases

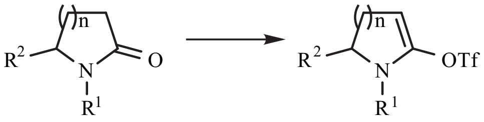


10 (0%)
(decomposes at -50 °C)

11 (85%)
(after chromatography)

Scheme 2.

Table 2. Preparation and Stability of Lactam-Derived Vinyl Triflates



5, 8, 12-18

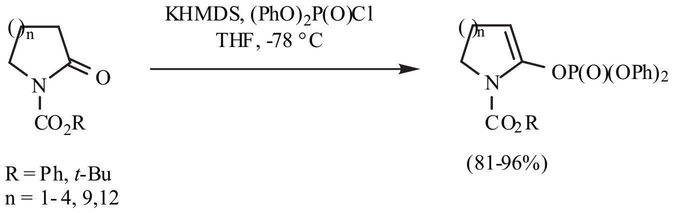
entry	n	R^1	R^2	conditions[a]	product	yield (%)[b]	stability	reference
1	1	COPh	H	A	**12**	30-60	decomposes during couplings	[2,4]
2	1	Ts	H	B	**13**	0 (100)	decomposes during chromatography	[7,8]
3	1	Ts	EtO	B	**14**	97	stable at rt for short periods	[7,8]
4	1	Boc	EtO	B	**15**	0 (0)	not formed	[7,8]
5	1	Ts	CH_2OTDS	B	**16**	(100)	limited, not chromatographed	[8]
6	2	Cbz	H	A	**5**	92	stable	[9]
7	2	Ts	EtO	B	**17**	96	stable	[7,8]
8	2	Ts	Me	A	**18**	53	stable	-[c]
9	3	Cbz	H	A	**8**	65	partially decomposes during couplings	[9]

[a] Conditions: (A) LHMDS, HMPA, $PhNTf_2$, THF, - 78 °C; (B) KHMDS, Comins' reagent, THF, - 78 °C; [b] Yields after chromatography. In brackets the yield of the crude product is reported. [c] Occhiato, E. G.; Prandi, C., unpublished material.

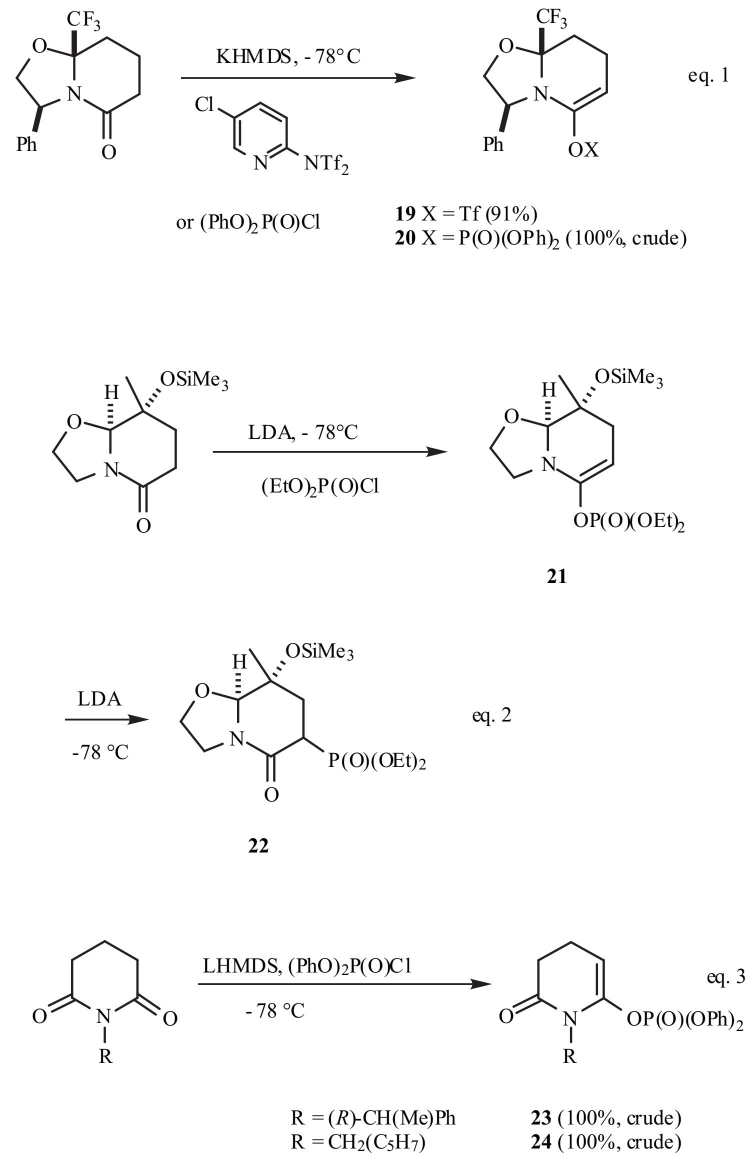
together with a further electronegative substituent (the ethoxy group) at the α position (entry 3). In case these five-membered triflates decompose during chromatography (entries 2 and 5), however, they can be directly used without purification in the next coupling step [8]. As for the six-membered derivatives, the stability of the triflates appears to be irrespective of the ring substitution and the type of N electron withdrawing group, as illustrated by the entries 6-8. With regard to 7-membered vinyl triflates (as *N*-CO_2Ph and *N*-Cbz), while these compounds could be isolated after chromatography in acceptable yields (54-67%) [3-4,9], they display a lower stability and tend to decompose to the corresponding lactam in the successive Pd-catalyzed coupling reactions [1-2,9], although decomposition has not always been observed as in the case of some alkylation reactions [4].

Two particular cases that must be cited concerning the stability are those reported in (Scheme **4**). In eq. 1 the formation of chiral enantiopure triflate **19** and phosphate **20** is reported [15]. Both compounds proved quite stable (at least under basic conditions) and could be successfully used in coupling reactions. Because of the lack of a suitable N protection, their formation and successive use is striking but the presence of two strong electronegative groups (the oxygen atom and the CF_3 group) at the α positions to the N atom could explain the relative stability. Also, since the decomposition pathway of these triflate and phosphate derivatives seems to be the hydrolysis of the O-S or O-P bond, the relatively bulky groups present in **19** and **20** could confer further stability by hampering to some extent the hydrolytic nucleophilic attack. On the other hand, as shown in eq. 2, the formation of a closely related phosphate (**21**), without the CF_3 group, has been reported, although this intermediate was not isolated and thus comparison of its stability with that of **20** cannot be made. Phosphate **21** instead underwent fast phosphate-phosphonate rearrangement at low temperature in the presence of an excess of LDA [16].

With the reactions reported in eq. 3 (Scheme **4**), it has been possible to demonstrate that also imides are good candidates for the generation of vinyl triflates or phosphates [17-18]. The second, unreacted carbonyl group can stabilize the structure in the same way as the electron withdrawing N substituent present in compounds **1** and **2**. Phosphates **23** and **24** proved more stable than the corresponding triflates but they had to be used in the subsequent coupling reactions without purification since chromatography on neutral alumina caused partial decomposition.



Scheme 3.

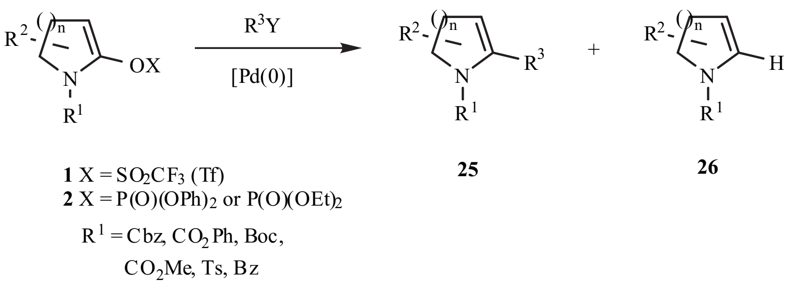


Scheme 4.

REACTIVITY AND APPLICATION TO THE SYNTHESIS OF N-HETEROCYCLES

Alkylation and Allylation Reactions

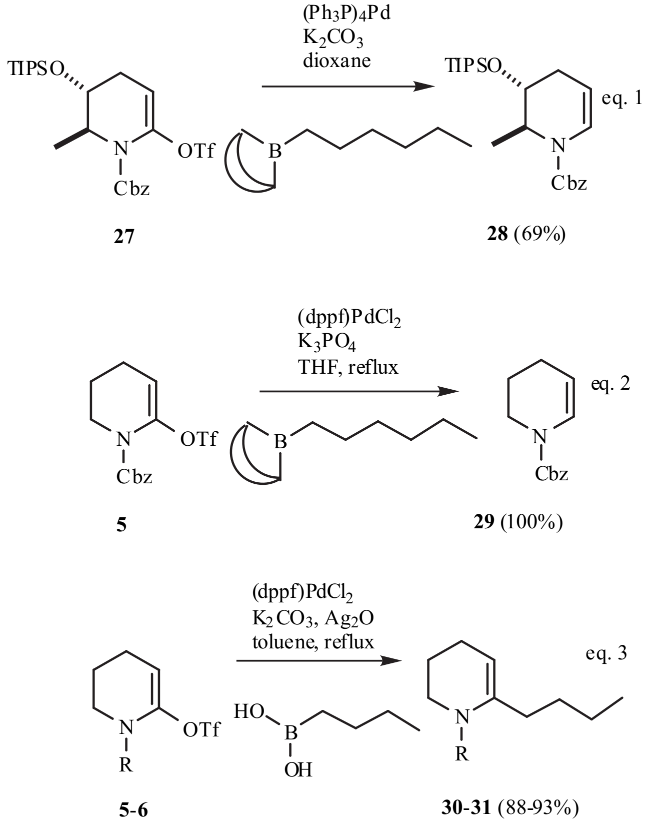
Organometallic coupling reactions have rarely been carried out on triflates **1** and phosphates **2** for the introduction of an alkyl group and no applications of such transformations to the synthesis of natural products or other N-heterocycles have been reported so far. What limits this sp^3-sp^2 coupling (Scheme **5**) is the β-hydride elimination which takes place after the transmetalation step and often leads to the complete formation of the α-unsubstituted product **26**. This concurrent reaction has been observed for triflates **1** in Pd-catalyzed reactions, in particular for *B*-alkyl Suzuki-Miyaura and Zn-alkyl couplings [7,19], whereas for reactions with organocuprates a possible Cu-TfO exchange



Scheme 5.

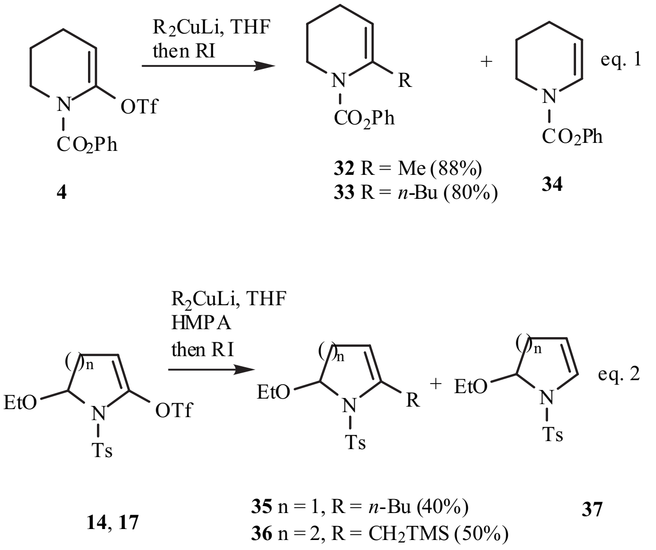
forming a vinyl organocopper which gives the α-unsubstituted by-product **26** (Scheme **5**) upon workup has been suggested [3]. However, in some cases suitable reaction conditions have been found that allow high yields in the coupling product to be obtained.

Since its disclosure by Suzuki and Miyaura [20], the *B*-alkyl coupling reaction has become one of the most important methods for C-C bond formation, with a growing use in the synthesis of complex natural compounds [21]. This synthetic procedure, which involves addition of 9-BBN-H to an olefin followed by the Pd(0)-catalyzed coupling with a vinyl halide or triflate, has been successfully applied by Sasaki and co-workers to lactone-derived vinyl triflates and phosphates in the course of the synthetic work towards complex marine polycyclic ethers such as brevetoxin, ciguatoxin, and gambierol [22-26]. It is therefore puzzling that when the same protocol was applied to vinyl triflate **27** [19], the β-H elimination was found to be the major pathway (Scheme **6, eq. 1**). Identical results were obtained by Occhiato (unpublished material) with triflate **5** (or **6**) (Scheme **6, eq. 2**). However, changing from alkylboranes derived from hydroboration with 9-BBN-H to alkyl boronic acids as the coupling partners, the coupling with triflates **5-6** was successfully carried out in the presence of Ag_2O using 3% (dppf)$PdCl_2$ as a catalyst in anhydrous toluene (eq. **3**, Scheme **6**), the β-H elimination being almost completely suppressed [9, 27]. With the corresponding seven-membered derivatives lower yields were obtained (22%) due to degradation of the starting material [9].



Scheme 6.

Alkylation was satisfactorily carried out also with organocuprates (R_2CuLi) (Scheme **7**) [3,4,8]. In particular, Comins found that quenching the reaction with the corresponding alkyl iodide (prior to workup) leads to improved yields in the coupling product, the extent of the α-unsubstituted product **34** formation being completely suppressed (eq. **1**). This result suggests the formation of a vinyl organocopper intermediate, possibly through a metal-TfO exchange. Worst results were achieved with triflates **14** and **17**. In these cases modest yields (40-50%) were obtained by carrying out the reaction in the presence of HMPA as a co-solvent and by adding the corresponding alkyl iodide before workup. Without HMPA, the formation of **37** prevailed (Scheme **7, eq. 2**) [8].



Scheme 7.

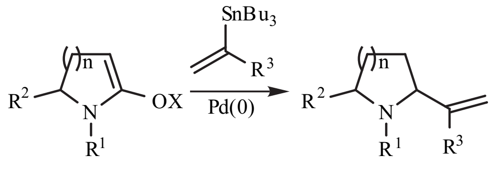
Alkylation of lactam-derived vinyl phosphates has been reported only for eight-membered derivative **38**, in particular a $Ni(acac)_2$-catalyzed coupling reaction of a Grignard reagent lacking β-hydrogens (Scheme **8, eq. 1**) [12]. Unfortunately, no other alkylation examples of phosphates **2** have been reported, so it is not possible to say if they suffer from the β-elimination problem like the corresponding triflates. The first reported allylation reaction has also been carried out on phosphate **38** (scheme **8, eq. 2**) under Pd(0) catalysis and using tributyl(allyl)tin as the nucleophile with an excess of LiCl. In this case, the allylation product was obtained in 93% yield [12]. This result appears superior to the corresponding Suzuki-Miyaura coupling which employs allylboron pinacolate (Scheme **8, eq. 3**), although work aimed at improving the yields of **41** and **42** was not carried out [9].

SP^2-SP^2 COUPLING: INTRODUCTION OF VINYL GROUPS

The vinylation reaction of triflates **1** and phosphates **2** has been carried out by exploiting Stille type coupling of tributyl(vinyl)tin or other simple organotin derivatives [3,5,8,12,13]. Some significant vinylation reactions by Stille type coupling are reported in (Table. **3**) [3,8,12] and (Scheme **9**) [13,17].

Interesting, among them, is the use of tributyl(1-ethoxyvinyl)tin for the synthesis of the corresponding vinyl derivatives **44** and **46** (entries 2 and 4) which, after hydrolysis (Scheme **10**) afford α-acyl substituted N-

Table 3. Vinylation of Lactam-Derived Vinyl Triflates and Phosphates

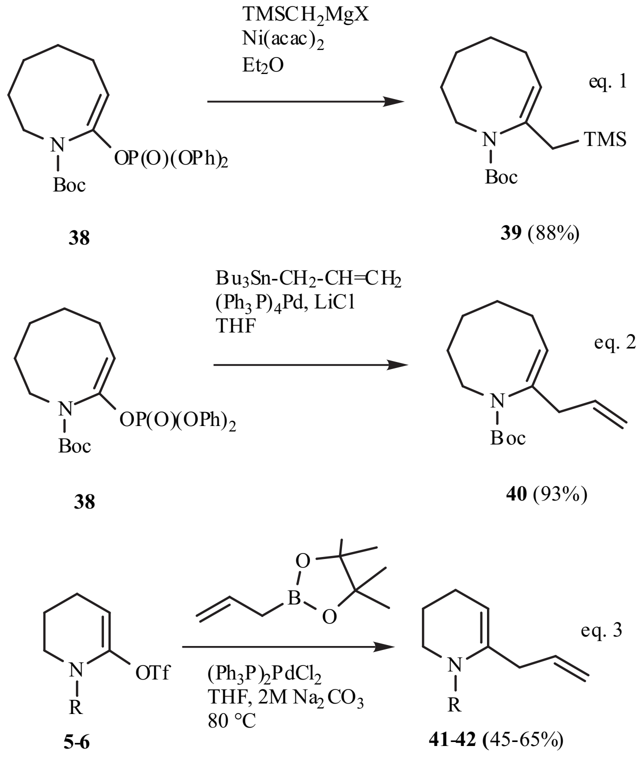


43-51

entry	n	R^1	X	R^2	R^3	conditions^a	product	yield (%)^b	reference
1	1	Ts	Tf	EtO	H	A	**43**	78	[8]
2	1	Ts	Tf	EtO	EtO	B	**44**	64	[8]
3	2	Ts	Tf	EtO	H	A	**45**	83	[8]
4	2	Ts	Tf	EtO	EtO	B	**46**	67	[8]
5	2	CO_2Ph	Tf	H	H	C	**47**	78	[3]
6	1	CO_2Ph	$P(O)(OPh)_2$	H	H	C	**48**	65	[12]
7	2	CO_2Ph	$P(O)(OPh)_2$	H	H	C	**49**	80	[12]
8	3	CO_2Ph	$P(O)(OPh)_2$	H	H	C	**50**	76	[12]
9	12	CO_2Ph	$P(O)(OPh)_2$	H	H	C	**51**	73	[12]

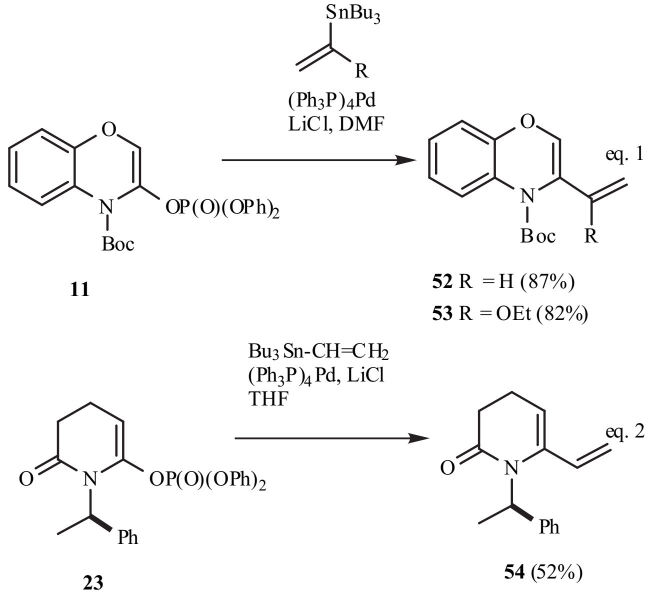
^{a}Conditions: (A) $Pd(MeCN)_2Cl_2$, Ph_3As, NMP, rt; (B) $(Ph_3P)_2PdCl_2$, DMF, 40 °C; (C) $(Ph_3P)_4Pd$, LiCl, THF, heat. ^{b}Yields after chromatography.

heterocycles [5,8]. This theme will be successively expanded by the use of α-alkoxystyrylboronates [10].



Scheme 8.

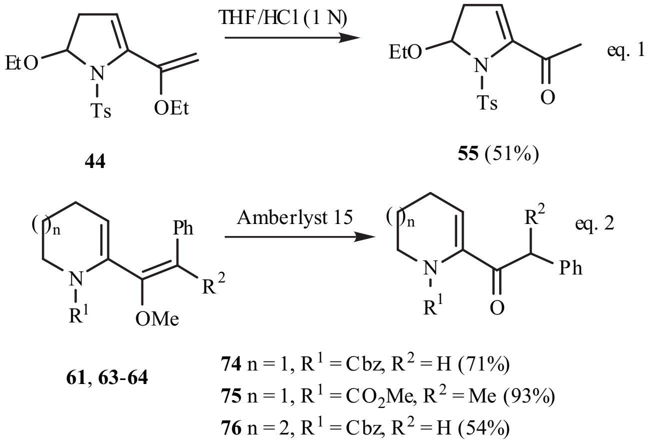
Structurally diverse alkenylboronic acids and esters have only recently been employed under Pd(0) coupling for the functionalization of these lactam derivatives [9,10,17,28]. Some examples are reported in (Table. **4.**, Schemes **11** and **12**).



Scheme 9.

The reactions have been carried out under 5% $(Ph_3P)_2PdCl_2$ catalysis in THF, in the presence of 2 M Na_2CO_3 (aq) as a base and by using the boronic esters obtained by addition of catecholborane to the alkyne (Table. **4.**, entries 1-5) [9,28], α-methoxystyrylboronates (entries 6-9) [10], α-ethoxydienylboronates (Scheme **11**) [10], and alkenylboronic acids (Scheme **12**) [17]. In particular, coupling with α-methoxystyrylboronates (Table. **4.**, entries 6-9) furnished products which gave α-acyl substituted N-heterocycles (Scheme **10, eq. 2**) **74-76** in good yields under mild acidic conditions (Amberlyst 15 in chloroform, rt) [10]. Surprisingly, hydrolysis under the same conditions of coupling products **65-67** (Scheme **11**) afforded cyclopentafused N-heterocycles after a Nazarov electrocyclization of a pentadienyl cation intermediate [10]. Finally, a Suzuki-Miyaura coupling has been used in place of the classical Stille reaction for the introduction of the unsubstituted vinyl moiety: glutarimide-derived vinyl phosphate **23** (Scheme **12**) underwent Suzuki-Miyaura coupling under the above conditions with vinylboronic acid *n*-butyl ester affording vinyl derivative **54** in 77% (compare with the Stille coupling reported in Scheme **9, eq. 2**) [17], without formation of the product deriving from the possible, competing Heck reaction often reported for vinylboronic esters [29-30].

Vinylation of triflates **1** and phosphates **2** leads to the formation of 2-(*N*-acylamino)-1,3-dienes which proved to be very useful partners in cycloaddition reactions for the synthesis of octahydroquinoline derivatives and other heterocycles [8,12,15,17,28,31]. Further interest in these studies was stimulated by the substantial lack of information on the behavior of 2-(*N*-acylamino)-1,3-dienes in cycloaddition reactions. A strikingly anomalous regiochemical preference, in contrast to the predictions based on HOMO diene-LUMO dienophile interactions, has been observed in the cycloadditions of dienes **77** and **80** (Scheme **13**) with ethyl acrylate (eqs **1** and **3**) (and other dienophiles, eq. 2) to give octahydroquinolines **78** and **81**, respectively, both as 1:1 epimeric mixtures. Diastereopure compounds **82** and **83** were instead obtained in good yields with a regiochemistry in accordance to theoretical anticipations when acrylates bearing (1*R*)-(+)-2,10-camphorsultam as a chiral auxilary (Scheme **13**, eqs **4** and **5**) were used as coupling partners [31]. Two examples in which a chiral auxiliary has been linked to the dienes are known. Conformationally constrained diene **84**, prepared by Stille coupling of **20** with tributyl(vinyl)tin, reacted with ethylacrylate to give diastereopure cycloadduct **85** in 68% yield with a normal regiochemical preference (Scheme **14**). This compound was then easily elaborated to enantiopure decahydroquinoline **86** [15].



44

55 (51%)

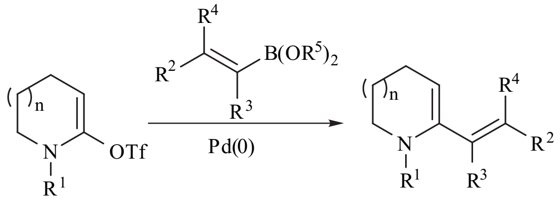
61, **63-64**

74 n = 1, R^1 = Cbz, R^2 = H (71%)
75 n = 1, R^1 = CO_2Me, R^2 = Me (93%)
76 n = 2, R^1 = Cbz, R^2 = H (54%)

Scheme 10.

Dienes **54**, **72** and **73** (Schemes **15** and **16**), which bear a simple and inexpensive chiral auxiliary on the N atom, were reacted with various dienophiles such as maleimides, acrylates and acrylamides, with or without Lewis acids being present. With *N*-phenylmaleimide, the highest endo/exo (13:1) and facial selectivities in favor of products **87-89** were achieved at low temperature (-18 °C), but de values never exceeded 74%. However, crystallization afforded diastereopure compounds in acceptable 52-64% yield. With chiral acrylamides (Scheme **16**) exo products **91** and **94** were formed but with low (2 :1) facial selectivity [17].

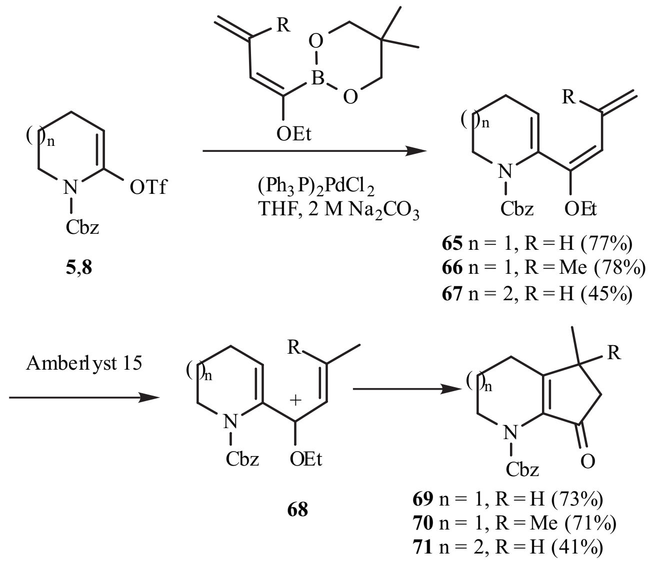
Table 4. Vinylation of Lactam-Derived Vinyl Triflates



56-64

entry	n	R^1	R^2	R^3	R^4	conditions[a]	product	yield (%)[b]	reference
1	1	Boc	*n*-Bu	H	H	A	**56**	82	[9,28]
2	1	Cbz	*n*-Bu	H	H	A	**57**	86	[9]
3	1	Boc	Ph	H	H	A	**58**	76	[9,28]
4	1	Boc	Et	Et	H	A	**59**	77	[9,28]
5	2	Cbz	*n*-Bu	H	H	A	**60**	56	[9]
6	1	Cbz	H	OMe	Ph	B	**61**	81	[10]
7	1	Cbz	Me	OMe	Ph	B	**62**	64	[10]
8	1	CO_2Me	Me	OMe	Ph	B	**63**	68	[10]
9	2	Cbz	H	OMe	Ph	B	**64**	50	[10]

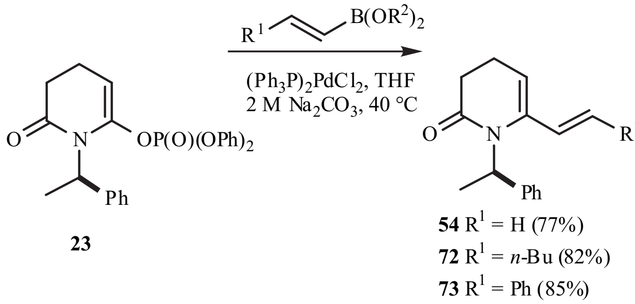
[a] Conditions: (A) $(Ph_3P)_2PdCl_2$, THF, 2 M Na_2CO_3, 40-50 °C, boronates as 2-(1-alkenyl)-1,3,2-benzodioxaboroles; (B) $(Ph_3P)_2PdCl_2$, THF, 2 M Na_2CO_3, 40-50 °C, boronates as substituted 5,5-dimethyl-2-(1-alkenyl)-1,3,2-dioxaborinanes. [b] Yields after chromatography.



Scheme 11.

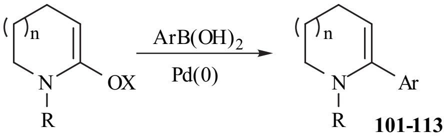
SP^2-SP^2 COUPLING: INTRODUCTION OF ARYL AND HETEROARYL GROUPS

The arylation of triflates **1** and phosphates **2** has been carried by Pd(0)-catalyzed cross-coupling reaction of organozinc, organotin and, more recently, organoboron compounds. Arylation by coupling of organozinc derivatives has been successfully carried out on different substrates, however only with PhZnCl as the nucleophile, in THF and in the presence of $(Ph_3P)_4Pd$ as a catalyst [7,12,15]. A limited number of tributyl(aryl)tin derivatives have been used for achieving arylation of phosphate **11** in excellent yields [13]. More extensive studies were performed by using aryl and heteroarylboronic acids in the coupling steps [9,28,32,33,34]. This is justified by the fact that boronic acids are favored reagents due to their stability to air and moisture, low toxicity and limited side reactions in the coupling reaction. Moreover a large number of them is currently available and more are being commercialized. Such couplings were first reported in 1999 for triflate **95**, an intermediate in the synthesis of a cytochrome P450$_{17\alpha}$ inhibitor [32], and for phosphate **11** (Scheme **17**) [34]. In the former case, an higher reactivity of the five-membered triflate was observed. Further work has been then carried out on simpler triflates [9, 28] and phosphates [33] (Table. **5**) and the procedure applied to the synthesis of functionalized 1,5-diaza-cis-decalins [35].



Scheme 12.

Table 5. Arylation of Lactam-Derived Vinyl Triflates and Phosphates



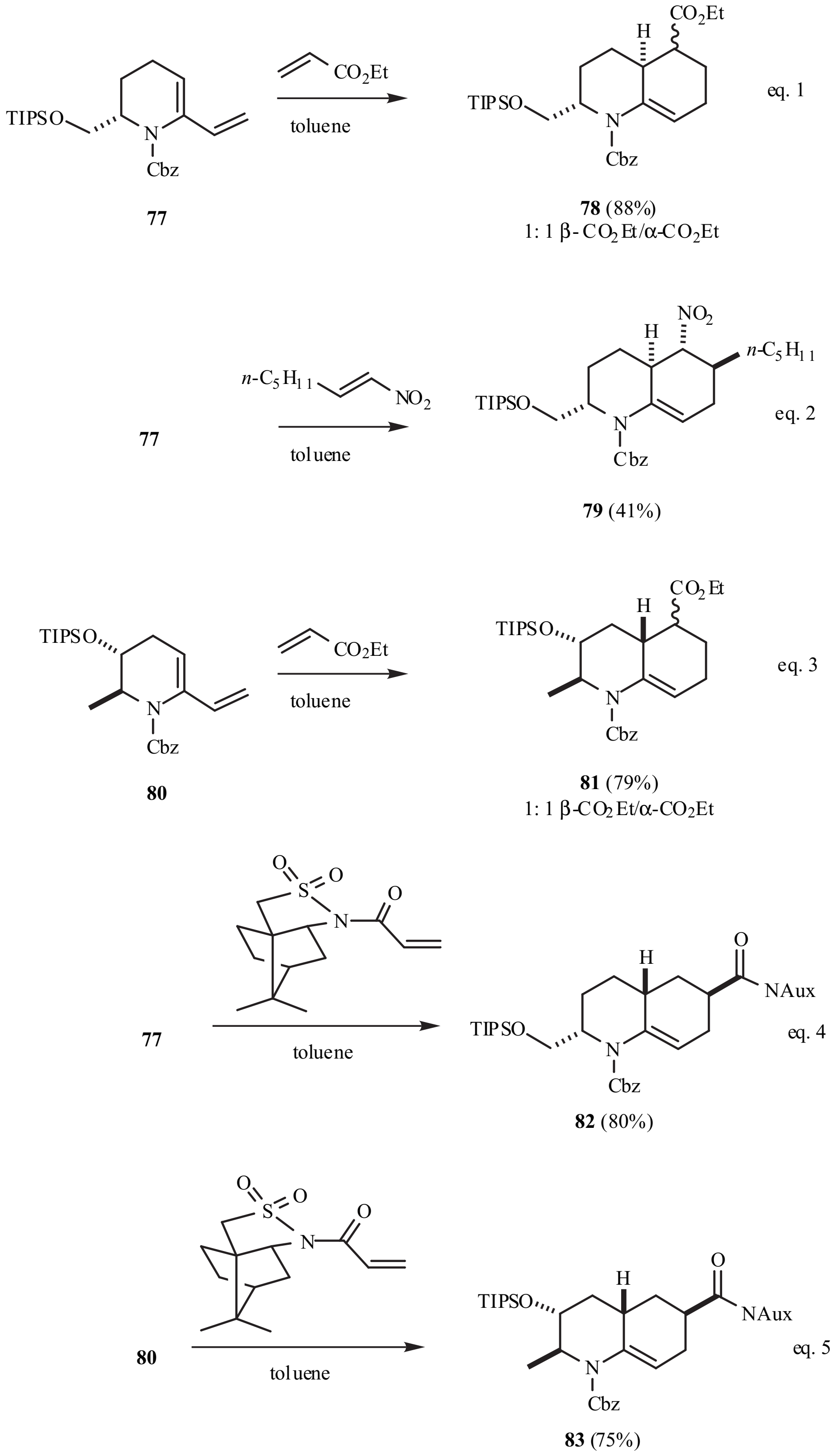
entry	n	R	X	Ar	conditions^a	product	yield (%)^b	reference
1	1	Boc	Tf	Ph	A	**101**	85	[9,28]
2	1	Cbz	Tf	Ph	A	**101**	84	[9]
3	1	Boc	Tf	furan-2-yl	A	**102**	94	[9]
4	1	Boc	Tf	thiophen-2-yl	A	**103**	91	[9]
5	2	Cbz	Tf	Ph	A	**104**	57	[9]
6	1	Boc	Tf	pyrid-3-yl	A	**105**	91	[28]
7	1	CO_2Ph	$P(O)(OPh)_2$	Ph	B	**106**	89	[33]
8	1	CO_2Ph	$P(O)(OPh)_2$	*p*-methoxyphenyl	B	**107**	95	[33]
9	1	CO_2Ph	$P(O)(OPh)_2$	naphthalen-1-yl	B	**108**	90	[33]
10	1	CO_2Ph	$P(O)(OPh)_2$	furan-2-yl	B	**109**	90	[33]
11	1	CO_2Ph	$P(O)(OPh)_2$	benzothiophen-2-yl	B	**110**	77	[33]
12	8	Boc	$P(O)(OPh)_2$	Ph	B	**111**	94	[33]
13	8	Boc	$P(O)(OPh)_2$	naphthalen-1-yl	B	**112**	93	[33]
14	8	Boc	$P(O)(OPh)_2$	furan-2-yl	B	**113**	94	[33]

[a] Conditions: (A) $(Ph_3P)_2PdCl_2$, THF, 2 M Na_2CO_3, 40-50 °C; (B) $(Ph_3P)_4Pd$, DME, 2 M Na_2CO_3, EtOH, reflux. [b] Yields after chromatography.

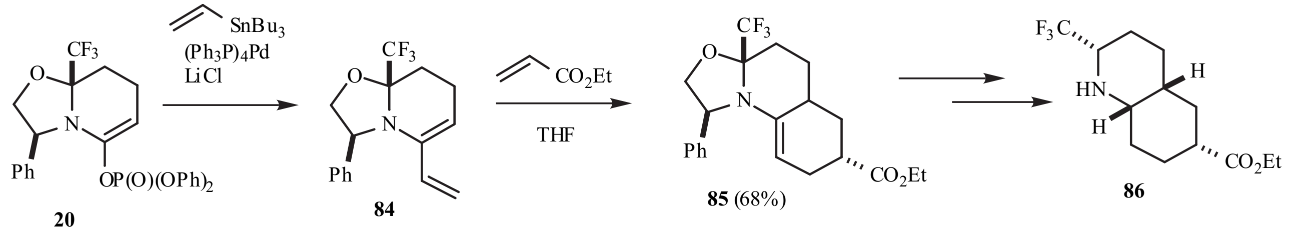
In all cases excellent yields (usually >85% after chromatography), irrespective of the N protection and ring size, have been obtained in these Suzuki-Miyaura couplings carried out in the presence of aqueous bases. The aryl- and heteroaryl piperidines obtained following this protocol constitute ideal precursors for the construction of complex heterocyclic systems likely to be of interest in medicinal chemistry.

SP-SP^2 COUPLING: INTRODUCTION OF AN ALKYNYL GROUP

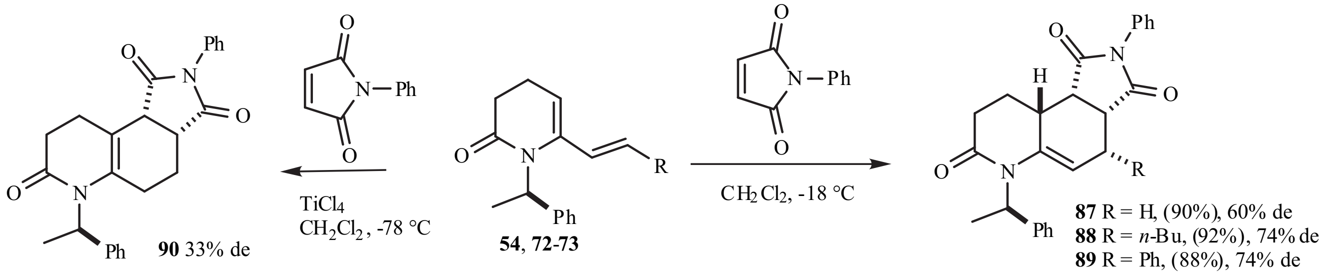
The introduction of an alkynyl moiety on lactams by Pd(0)-catalyzed coupling with terminal alkynes (Sonogashira coupling) was the first of such reactions to be reported for lactam-derived vinyl triflates **1** [1]. The coupling is best carried out in the presence of CuI as a co-catalyst in an organic solvent with a large excess of organic base (usually



Scheme 13.

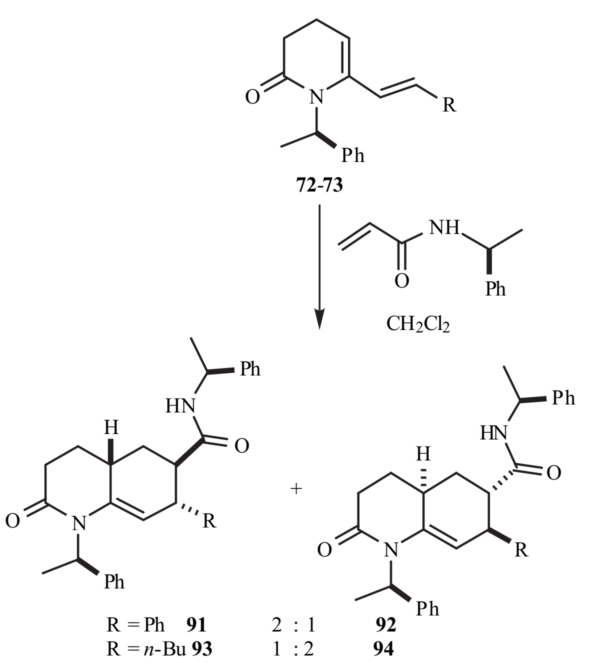


Scheme 14.



Scheme 15.

Et$_2$NH or Et$_3$N) [12,17]. Together with carbonylation reactions, this coupling has been more often applied to the synthesis of natural compounds than the other types of coupling described herein. As depicted in (Scheme **18**), this coupling has been exploited for the synthesis of functionalized enantiopure piperidines such as **115** (eq. **1**) [15], analogues of tobacco alkaloids such as **117** (eq. **2**) [36], and clavepictines A and B (**119-121**) (eq. **3**) [19, 37].

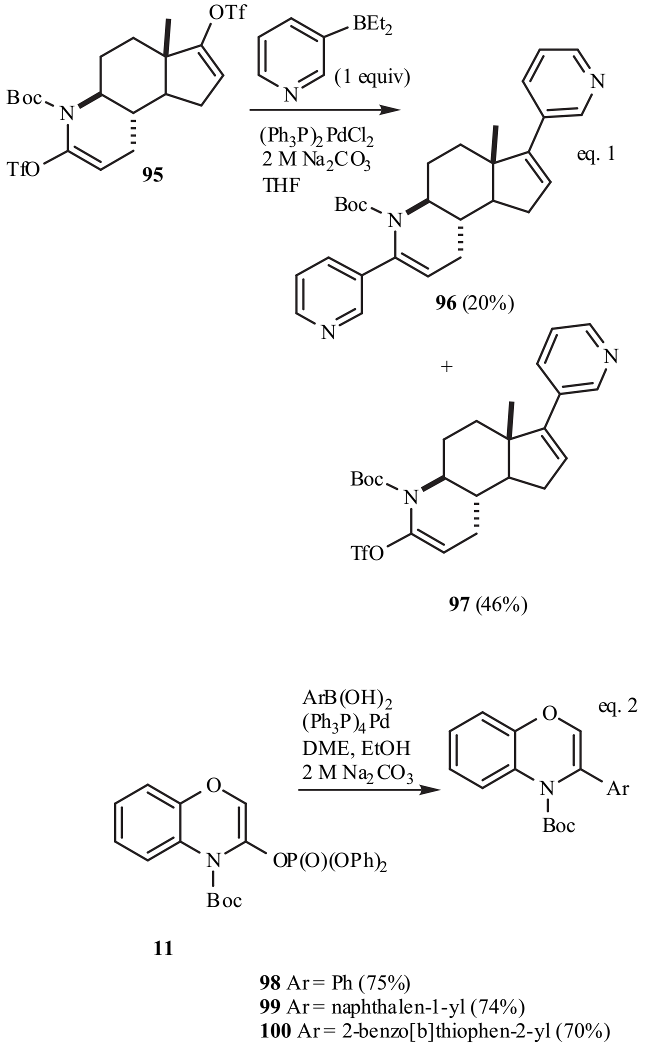


Scheme 16.

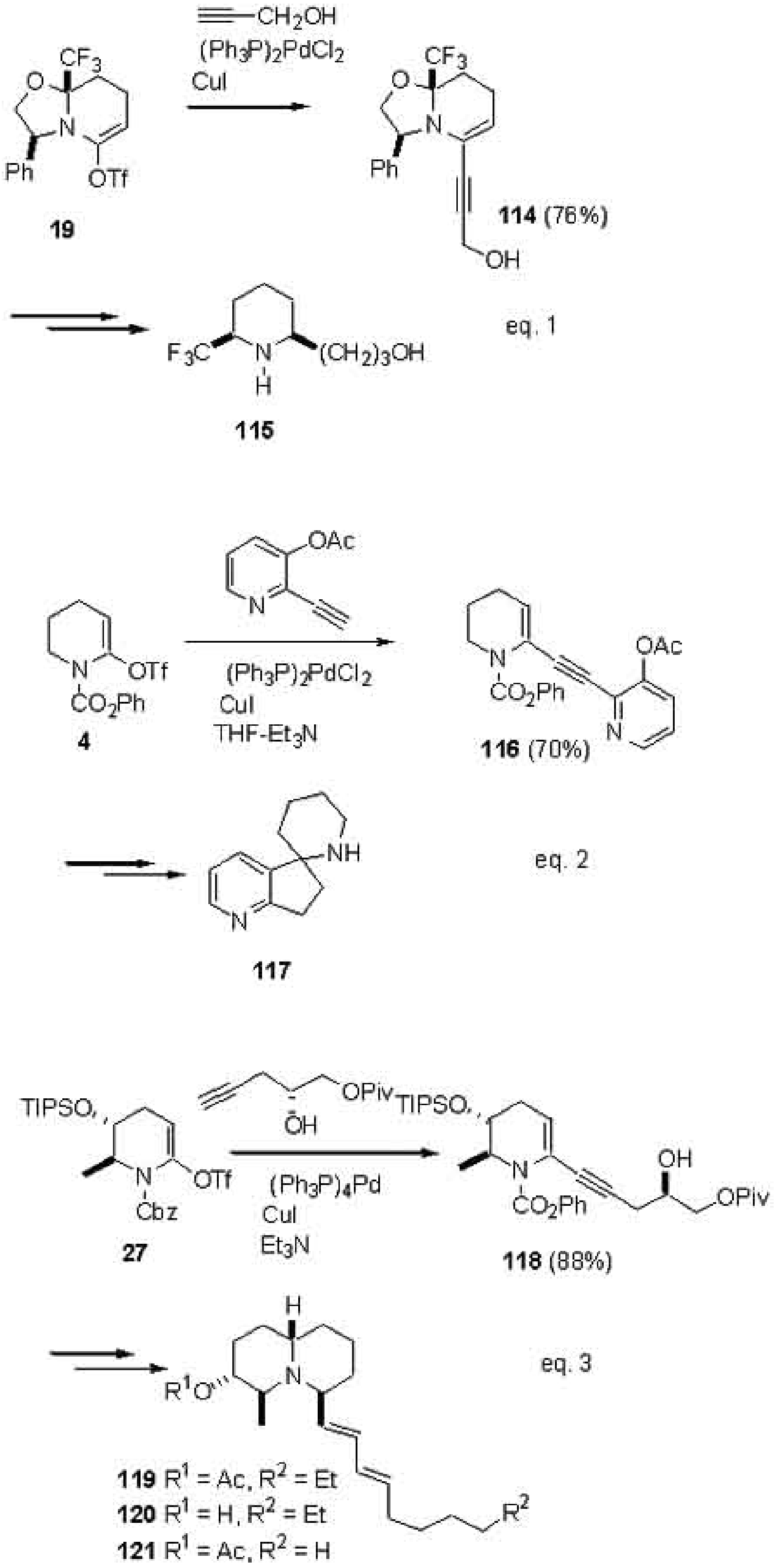
HECK COUPLING

Despite its enormous potential in C-C bond formation, the Heck reaction has never been attempted on triflates **1** and phosphates **2**, with a single exception being that of the intramolecular Heck reaction carried out under standard conditions on glutarimide-derived vinyl phosphate **24** in the synthesis of racemic cytisine **123** (Scheme **19**) [18].

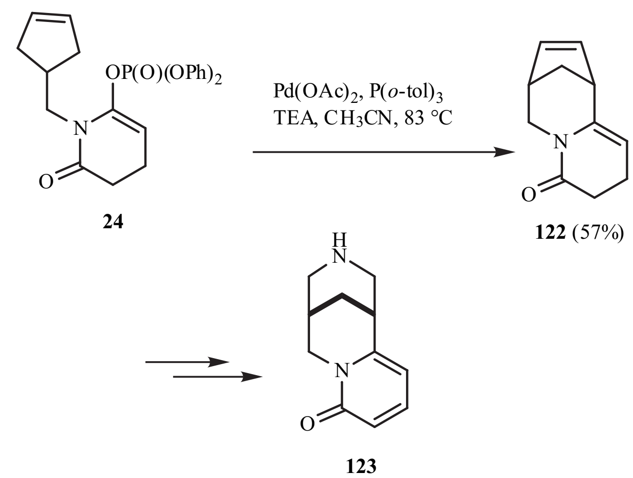
Preliminary studies on the influence of chiral ligands in the cyclization event have been performed, too, although low enantioselectivity has been achieved [18].



Scheme 17.


CF3
O
N
Ph
OTf
19
CH2OH
(Ph3P)2PdCl2
CuI
114 (76%)
OH
eq. 1
F3C
N
H
(CH2)3OH
115
OAc
N
OTf
CO2Ph
4
(Ph3P)2PdCl2
CuI
THF-Et3N
116 (70%)
NH
117
eq. 2
TIPSO
Cbz
27
OPiv
OH
(Ph3P)4Pd
CuI
Et3N
118 (88%)
H
R1O
R2
eq. 3
119 R1 = Ac, R2 = Et
120 R1 = H, R2 = Et
121 R1 = Ac, R2 = H

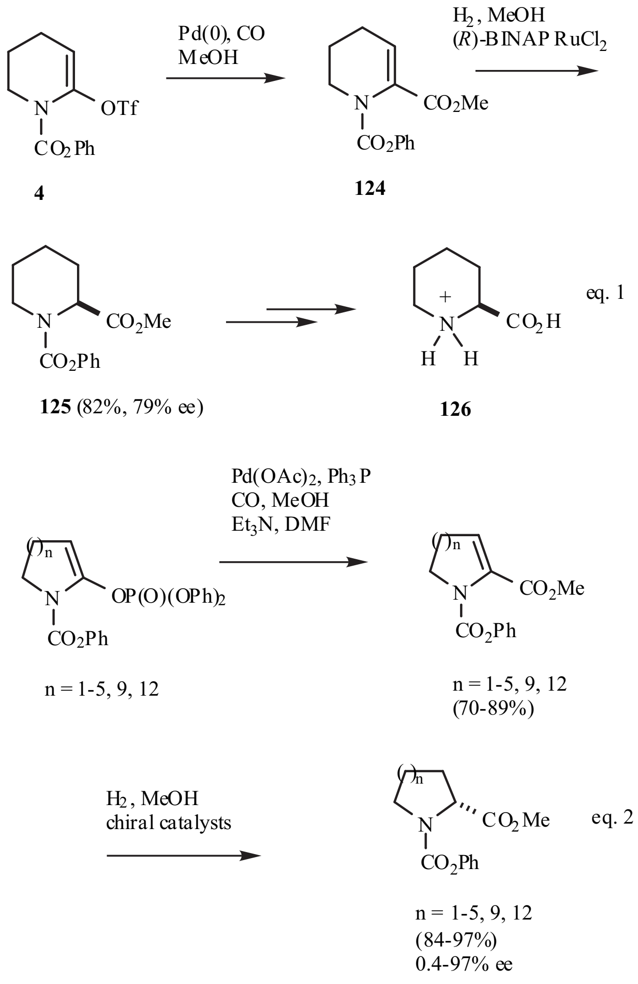
Scheme 18.



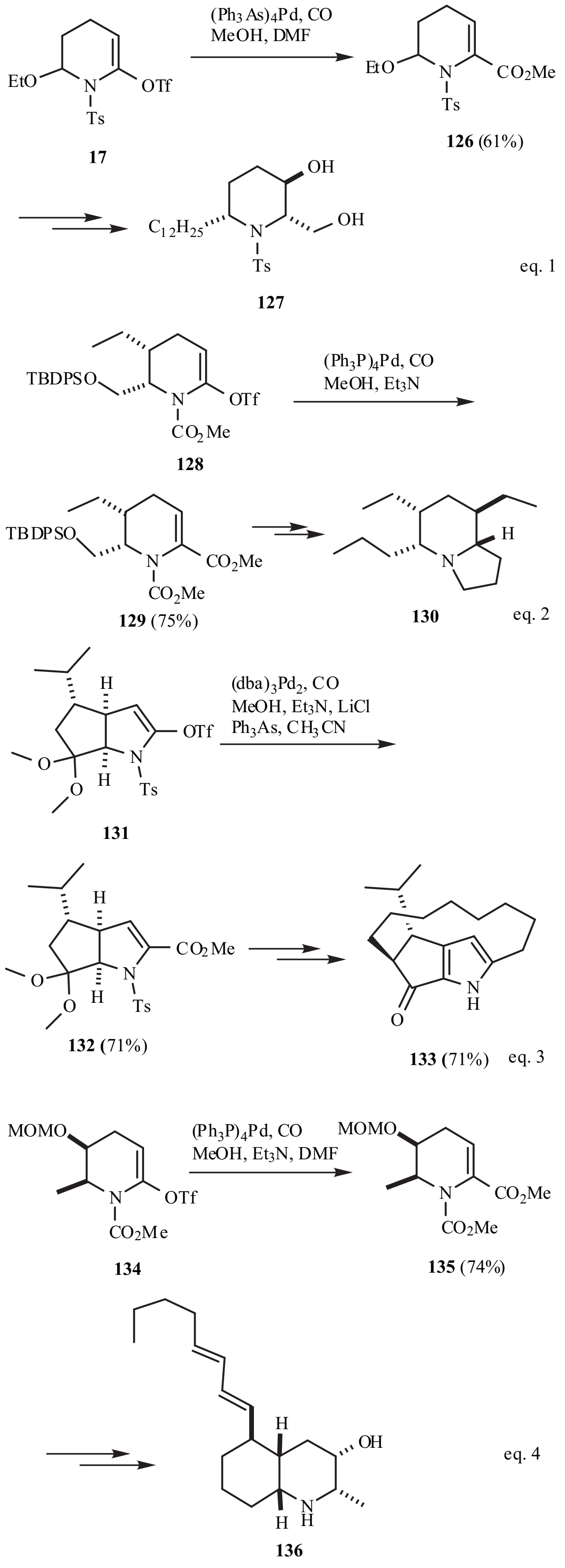
Scheme 19.

CARBONYLATION REACTIONS

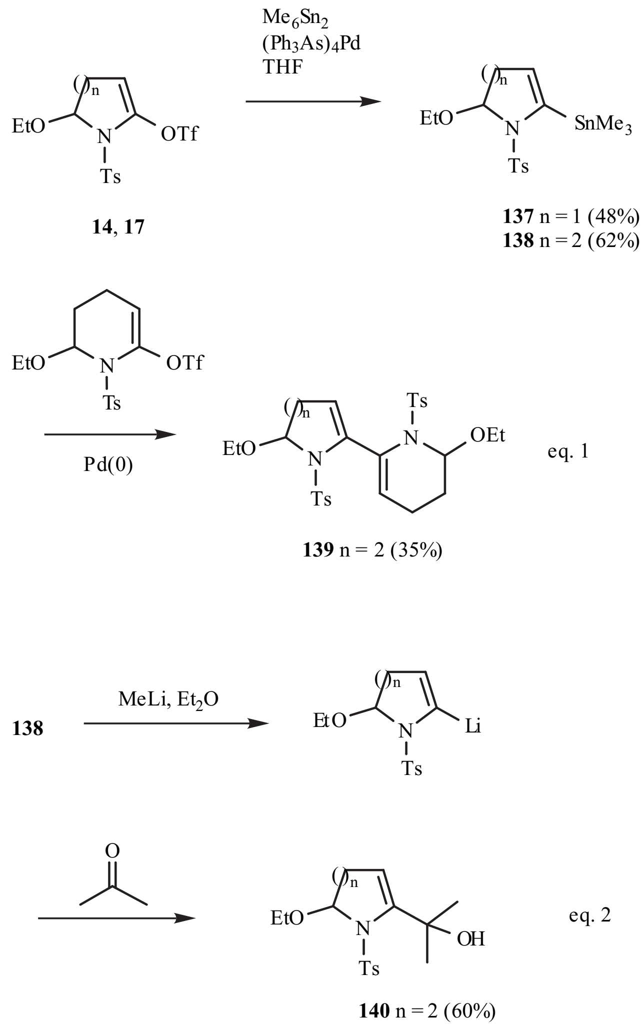
A carbonylation reaction was first reported by Comins for lactam-derived vinyl triflates **1** [3] and by Nicolaou for vinyl phosphates **2** [12]. In both cases (Scheme **20**, eqs **1** and **2**) the coupling products were obtained in good yield by Pd(0)-catalyzed carbonylation in the presence of MeOH. Their subsequent reduction via catalytic asymmetric



Scheme 20.



Scheme 21.



Scheme 22.

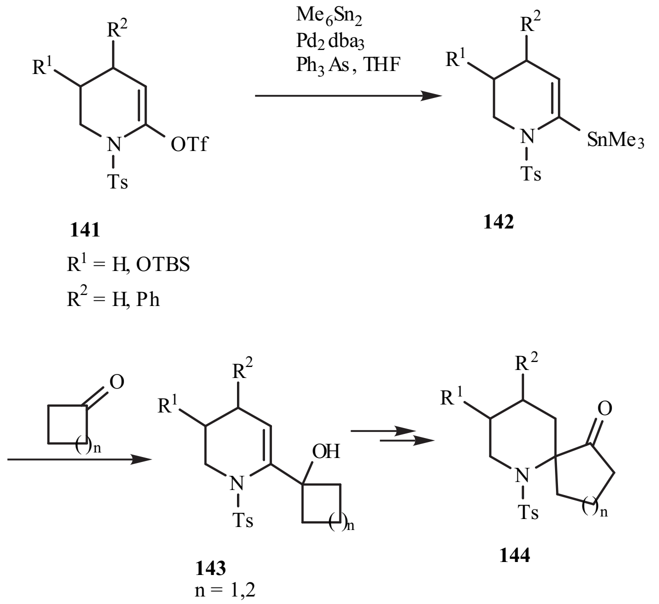
hydrogenation provided enantiomerically enriched (0.4-97% e.e.) piperidine derivatives, such as (*S*)-pipecolic acid **126** [3]. Noyori's ruthenium catalyst (*R*)-BINAP $RuCl_2$ and [Rh(COD)-(-)-(*R*,*R*)-EtDuPHOS)]OTf were used in the hydrogenation step. The carbonylation reaction of triflates **1** has been employed in the synthesis of various natural products such as desoxoprosophylline **127** [38], alkaloid 223A **130** [39], a synthetic intermediate (**133**) of roseophilin [40], and lepadin B **136** [41-42] (Scheme **21**).

UMPOLUNG PROCEDURES

Whereas vinyl triflates **1** and phosphates **2** are formally considered electrophiles, conversion to the corresponding vinylstannanes results in an umpolung [8,12]. Such stannanes can be easily converted to vinyllithium derivatives via transmetalation and both species used as nucleophiles. This procedure, first reported by Hiemstra and Speckamp (Scheme **22**) [8], was successfully applied to the synthesis of azaspirocyclic ketones **144** (Scheme **23**) [43].

CONCLUDING REMARKS

Since the original work on lactam-derived vinyl triflates was published, their number, and that of the corresponding vinyl phosphates, has greatly increased as did the understanding of the factors affecting their stability and the range of reactions that can be carried out on them. All this has found conclusion in the synthesis of some natural compounds. Concerning the issues of the stability, based on the current knowledge, statements about the rather unstable, difficult-to-isolate nature of the lactam-derived vinyl triflates are no more justified unless referred to specific compounds. On the other hand, the phosphate counterparts prove to be generally more stable than the triflates and, moreover, are economically convenient.



Scheme 23.

Much remains to be done with these classes of chemical intermediates. Perhaps, not only the chemistry of these lactam derivatives has been not yet fully explored but also it has been scarcely used for the synthesis of target N-heterocycles. Just to mention some important (and obvious, considering the case) C-C bond forming reactions that have found several applications in organic synthesis, Heck and Nozaki-Hiyama-Kishi reactions have been practically not experimented with vinyl triflates **1** and phosphates **2**. Also, an exhaustive study on the *B*-alkyl Suzuki-Miyaura coupling, despite its enormous potential, has perhaps not been yet performed with the purpose of suppressing the prevailing β-H elimination process. Use of non conventional solvents, reaction conditions, and Pd catalysts also could provide suitable solutions where standard conditions fail. Certainly none of the triflates (and phosphates) mentioned herein is currently commercially available, but several of them, besides being easily prepared, are stable and crystalline compounds, being thus suitable starting material for developing new chemistry. For the same reasons, they should also enter into the range of those triflates that are normally employed for testing novel catalysts and coupling reactions.

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REFERENCES

[1] Okita, T.; Isobe, M. *Synlett* **1994**, 589.
[2] Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737.
[3] Foti, C. J.; Comins, D. L. *J. Org. Chem*. **1995**, *60*, 2656.
[4] Tsushima, K.; Hirade, T.; Hasegawa, H.; Murai, A. *Chem. Lett*. **1995**, *9*, 801.
[5] Bernabé, P.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett*. **1996**, *37*, 3561.
[6] Comins, D. L.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299.
[7] Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett*. **1996**, *37*, 8257.
[8] Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 8131.
[9] Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459.
[10] Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem*. **2002**, *67*, 7144.
[11] Du, Y.; Wiemer, D. F. *J. Org. Chem*. **2002**, *67*, 5709.
[12] Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun*. **1998**, 1757.
[13] Buon, C.; Chacun-Lefèvre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605.
[14] Buon, C.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 701.
[15] Jiang, J.; De Vita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593.
[16] Sudau, A.; Winfried, M.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem*. **2002**, 3315.
[17] Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem*. **2003**, *68*, 6360.
[18] Coe, J. W. *Org. Lett*. **2000**, *2*, 4205.
[19] Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc*. **1999**, *121*, 10012.
[20] Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett*. **1986**, *27*, 6369.
[21] Chemler, S. R.; Traumer, D.; Danishefsky, S. *Angew. Chem. Int. Ed*. **2001**, *40*, 4544.
[22] Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem. Int. Ed*. **2001**, *40*, 1090.
[23] Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett*. **1998**, *39*, 9027.
[24] Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett*. **1999**, *1*, 1075.
[25] Sasaki, M.; Noguchi, K; Fuwa, H.; Tachibana, K. *Tetrahedron Lett*. **2000**, *41*, 1425.
[26] Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett*. **2000**, *41*, 8371.
[27] Chen, H.; Deng, M.-Z. *Org. Lett*. **2000**, *2*, 1649.
[28] Occhiato, E. G.; Trabocchi, A.; Guarna, A. *Org. Lett.* **2000**, *2*, 1241.
[29] Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett*. **1993**, *34*, 3599.
[30] Stewart, S. K.; Whiting, A. *Organomet. Chem*. **1994**, *482*, 293.
[31] Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem*. **1998**, *63*, 3810.
[32] Guarna, A.; Occhiato, E. G.; Machetti, F.; Giacomelli, V. *J. Org. Chem*. **1999**, *64*, 4985.
[33] Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969.
[34] Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett*. **1999**, *40*, 6373.
[35] Xu, Z.; Kozlowski, M. C. *J. Org. Chem*. **2002**, *67*, 3072.
[36] Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett*. **2000**, *2*, 2291.
[37] Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem*. **1997**, *62*, 4550.
[38] Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3592.
[39] Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Martin Garraffo, H.; Kaneko, T. *Org. Lett*. **2002**, *4*, 1715.
[40] Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett*. **2000**, *2*, 1157.
[41] Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem*. **1999**, *64*, 2182.
[42] Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673.
[43] Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett*. **2001**, *3*, 2109.

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