Review

Pd⁰- and Pdᴵᴵ-catalyzed oxaheterocyclization of substrates having both an allylic leaving group and a hydroxylated tether

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ABSTRACT

This review surveys the different asymmetric and non-asymmetric Pd-catalyzed heterocyclizations of allylic alcohols, esters, ethers, carbonates, amines or silanes and vinyl epoxides, which bear a hydroxylated tether. Lactones or carbonates have been obtained from reactions carried out under carbon oxide or carbon dioxide atmosphere, respectively. The dichotomy between the mechanisms of the Pd⁰ and Pdᴵᴵ processes is emphasized.

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Contents

1. Introduction

Through the different synthetic processes of oxaheterocycles, Pd^0- and Pd^{II}-catalyzed reactions of substrates having both an allylic leaving group and a hydroxylated tether represent interesting possibilities and have led to a number of reports. Schemes 1 and 2, which summarize the different possibilities from such substrates, emphasize the mechanicodivergence between the Pd^0- and Pd^{II}-catalyzed reactions. In the presence of a Pd^0 catalyst, the cyclization occurs via the intramolecular nucleophilic addition of the hydroxy group to the *in situ* produced η^3-allyl palladium complex (paths *a*). In contrast, the Pd^{II}-catalyzed reaction involves a η^2-complex and a Wacker-type reaction. The resulting σ-complex undergoes a β-elimination of either the leaving group (paths *b*) or a hydrogen (paths *c*) to give the product. Moreover, reactions performed in the presence of CO_2 or CO can provide carbonates (paths *d*) or lactones (paths *e*), respectively. A few Pd-catalyzed heterocyclizations have also been carried out from substrates having an amino group or a silane unit as the leaving group. A limited number of the above types of heterocyclization, some of them being enantio- or diastereoselectives, have been included in reviews [1–4]. Given the development of these efficient reactions over the recent years and the crucial role of the unsaturated oxygenated heterocycles in synthesis, we here present a review especially devoted to these Pd-catalyzed cyclizations [5]. For each section, we will try to follow a chronological order of the reports to highlight the progress of the procedures and their use.
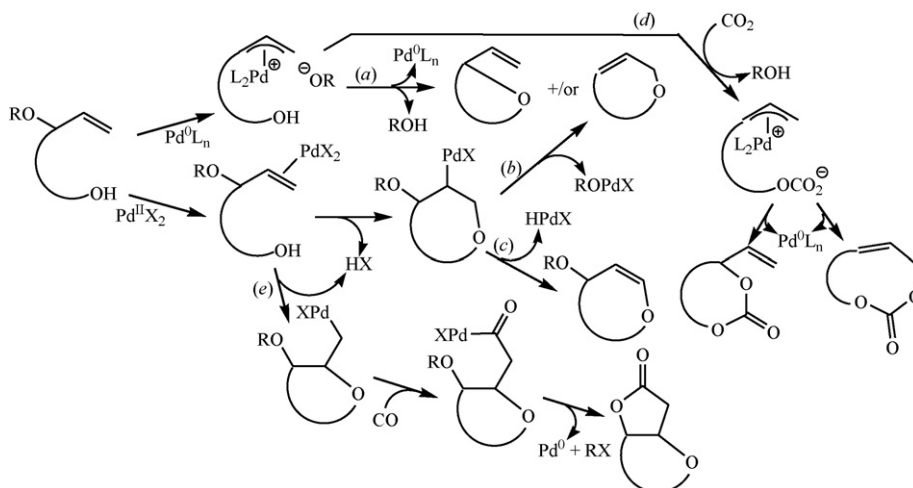
Scheme 1. Pd^0- and Pd^{II}-catalyzed reactions of substrates having both an allylic leaving group and a hydroxylated tether.
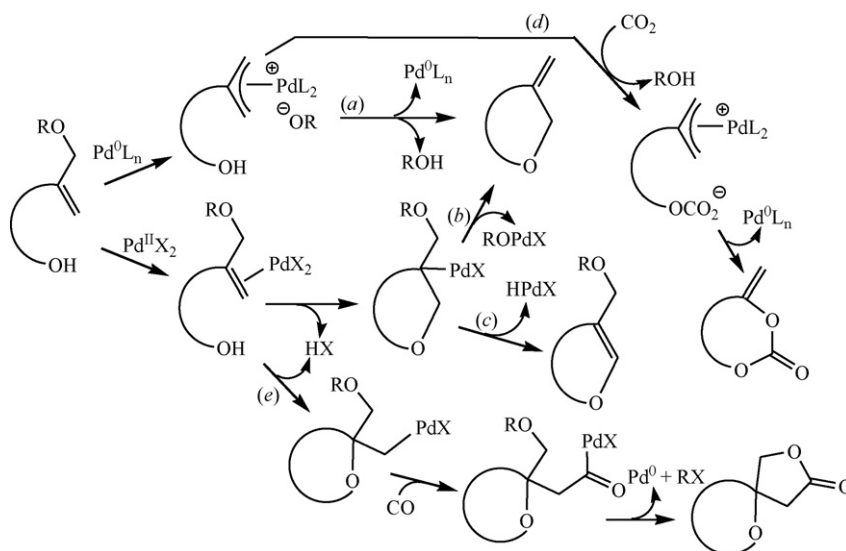
Scheme 2. Pd^0- and Pd^{II}-catalyzed reactions of substrates having both an allylic leaving group and a hydroxylated tether.
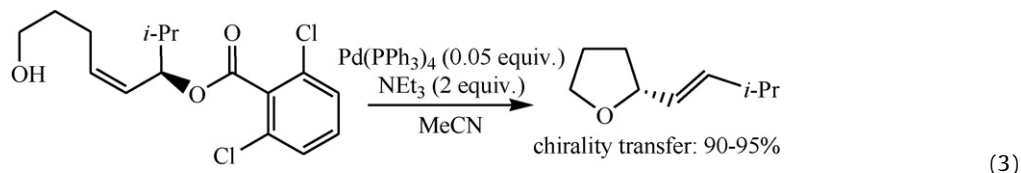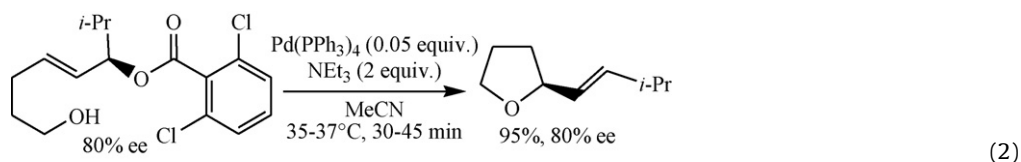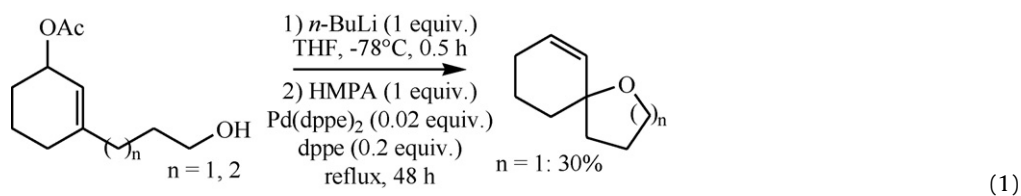
2. Pd⁰-catalyzed cyclizations

This section concerns the intramolecular additions of hydroxy groups to η^3-allylpalladium intermediates obtained from the catalytic reaction of Pd⁰ species with an allylic ester, carbonate or alcohol, or with a vinyl epoxide. The substrates are achiral or chiral (racemic or optically active), and the cyclizations can be carried out in the presence of unichiral ligands [6].

2.1. In the absence of chiral ligands

2.1.1. Ester as the leaving group

In 1983, two teams published, independently, the Pd⁰-catalyzed synthesis of 2-alkenyltetrahydrofurans(pyrans) from the intramolecular substitution of a η^3-allylpalladium complex, *in situ*-formed from an allylic ester. Godleski's team synthesized, in low yields, spiro-compounds via the addition of a preformed alcoholate (Eq. (1)) [7], while Stork and Poirier fulfilled the efficient synthesis of (*R*)- and (*S*)-2-alkenyltetrahydrofurans, with high to complete chirality transfer, from optically active substrates having 2,6-dichlorobenzoate as the leaving group (Eqs. (2) and (3)) [8]. Interestingly, the configuration of the new chiral center depended on the stereochemistry of the C=C bond of the substrate.

(1)

(2)

(3)

Two years later, Trost and Bonk described the synthesis of various 4-methylenetetrahydrofurans using an *in situ* prepared Pd⁰ catalyst and DBU as the base (Eq. (4)) [9]. While the previous cyclizations concerned only the reaction of primary alcohols, these compounds were obtained from secondary and tertiary alcohols.

(4)
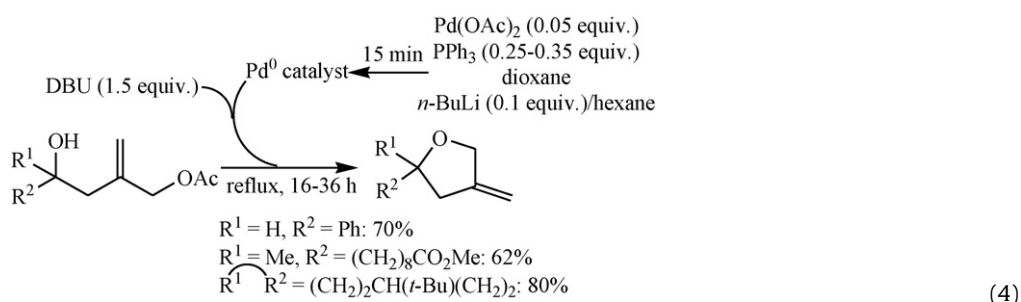
Vinylmorpholines have been obtained, at 40 °C, with a good diastereoselectivity from the Pd-catalyzed 6-*exo-trig* cyclization of (−)-ephedrine derivative using triethylamine as the base (Eq. (5)) [10]. The same base has been used, at room temperature, for the cyclization of the polyhydroxylated substrate shown in Eq. (6) [11]. Some substrates require stringent conditions, as noted by Smith et al. for the reaction shown in Eq. (7), which necessitated heating to 150 °C [12]. We suspect that the corresponding low yields are due to the concurrent elimination reaction from the allylpalladium intermediate, which leads to the corresponding 1,3-diene [13].

(5)

Pd(PPh$_3$)$_4$ (0.18 equiv.)
NEt$_3$ (2 equiv.)
PhMe, rt, 5 h

E/Z = ~ 5:1

90%, dr = >20:1

(6)

PdCl$_2$(PPh$_3$)$_2$ (0.2 equiv.)
EtN(i-Pr)$_2$ (1 equiv.)
DMF, 150 °C, 12 h

30–40%, dr = 1.5:1

(7)
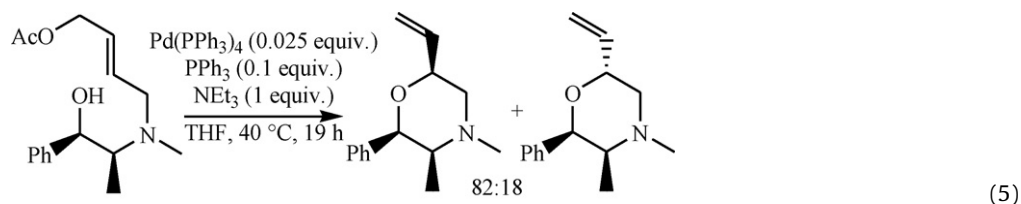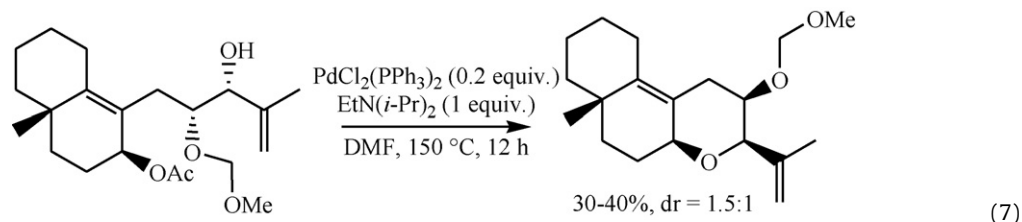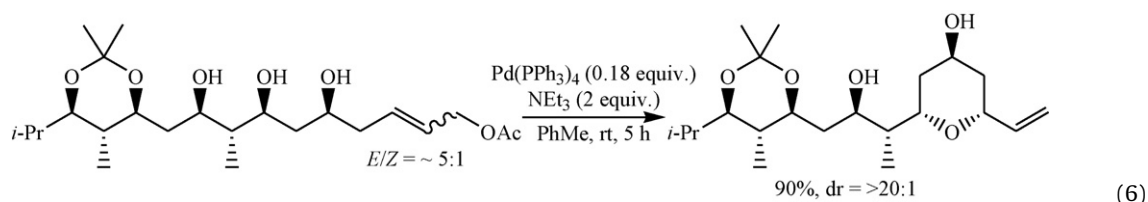
In fact, the presence of a base is not always required, even at room temperature, as subsequently exemplified by the teams of Keinan (Eq. (8)) [14], Trost (Eqs. (9)–(11)) [15] and Hara (Eq. (12)) [16]. As depicted in Eqs. (8), (11) and (12), the chirality of the hydroxy nucleophile is preserved in the course of the cyclization. For the reactions shown in Eq. (12) with L = PPh$_3$, the reverse of diastereoselectivity with the nature of the OR substituent leads to envisage some coordination of the terminal hydroxy at the level of transition states. Base-free conditions have also been used for double cyclizations (Eq. (13)) [17] and, recently, for the heterocyclization at 40–55 °C of polyfunctionalized substrates (Eqs. (14) and (15)) [18,19].

Pd(PPh$_3$)$_4$
(0.032 equiv.)
THF, rt, 20 h

dr = 1

35%   +   59%

(8)

(9)

Pd$_2$(dba)$_3$·CHCl$_3$ (0.04 equiv.)
PPh$_3$ (0.16-0.32 equiv.)
THF, rt

n = 0
2-3 h

95%, dr = 91:9

n = 1, 3.5 h
n = 2, 6 h
n = 3, 24 h

n = 1: 86%, dr = 1:1
n = 2: 95%, dr = 1:1
n = 3: 25%, dr = 3:1

(10)

Pd$_2$(dba)$_3$·CHCl$_3$ (0.04 equiv.)
PPh$_3$ (0.16-0.32 equiv.)
THF, rt, 3 h

93%

(11)

Pd(dba)$_2$ (0.04 equiv.)
L (0.05- 0.2 equiv.)
THF, rt, 12-24 h

R = H
L = PPh$_3$: 74%, cis/trans = 34:66
L = (R)-(S)-PPFA: 72%, cis/trans = 40:60
L = (S)-(R)-PPFA: 74%, cis/trans = 29:71
L = (R) or (S)-BINAP: 0%
L = (+)-DPPIO: 48%, cis/trans = 52:48
L = (-)-DPPIO: 83%, cis/trans = 23:77

R = SiPh$_2$t-Bu
L = PPh$_3$: 85%, cis/trans = 63:37
L = (+)-DPPIO: 96%, cis/trans = 81:19
L = (-)-DPPIO: 98%, cis/trans = 45:55

PPFA = N,N-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
DPPIO = 2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline

(12)

$$(13)$$

95%, 1:2:1

$$(14)$$

95%, 2:1

$$(15)$$

$\begin{cases} PPh_3, 3.75 \text{ h: } 98\%, 88:12 \\ P(C_6H_4\text{-}p\text{-OMe})_3, 4 \text{ h: } 99\%, 96:4 \\ P(2\text{-furyl})_3, 0.5 \text{ h: } 93\%, 83:17 \end{cases}$

L (0.1 equiv.), 40 °C

L (0.05 equiv.) $\begin{cases} L^*_1, 45 \text{ °C, } 0.67 \text{ h: } 100\%, 40:60 \\ L^*_2, 55 \text{ °C, } 20 \text{ h: } 60\%, 91:6 \end{cases}$

L^*_1 and L^*_2: see Scheme 6

$E/Z = 95:5$

MPM = p-MeOC$_6$H$_4$CH$_2$
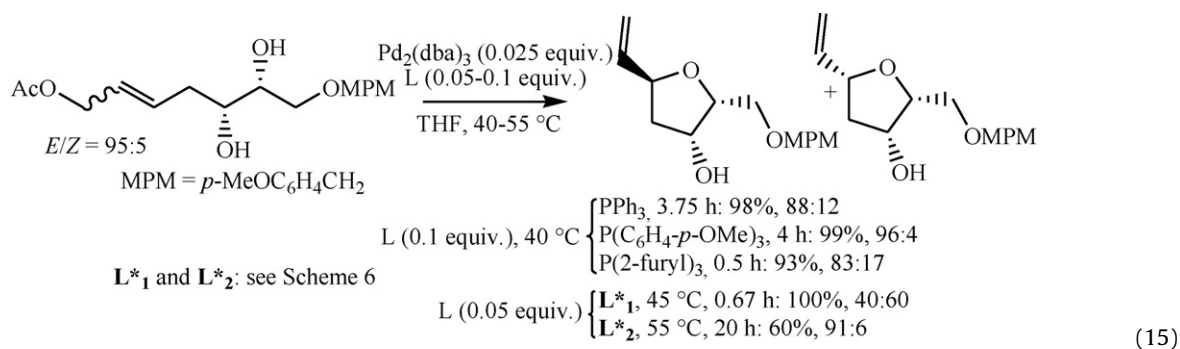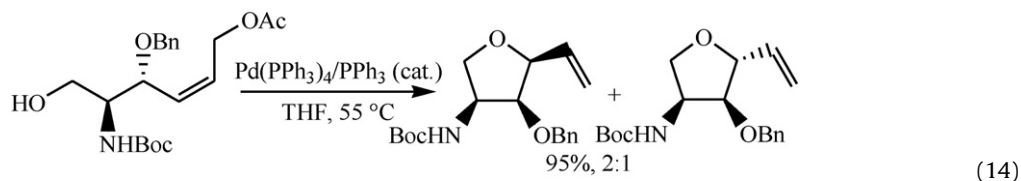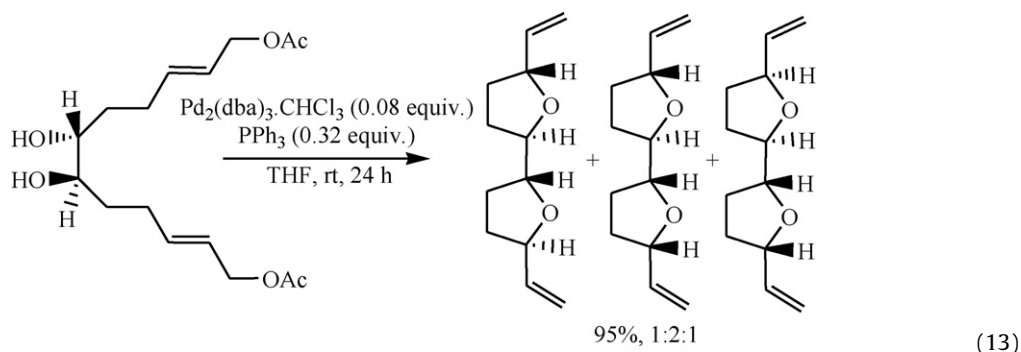
Using neocuproine as a ligand, Uenishi and Ohmi observed a surprising selectivity between the two isomeric allylic benzoates shown in Eq. (16) [20]. Indeed, one of them was unreactive under the reaction conditions and, according to the authors, even under harsher conditions [20]. This contrasts with the reactivity of the corresponding carbonate under similar Pd^0 catalysis (see below Eq. (25)) and alcohol under Pd^{II} catalysis (see below Eq. (87)).
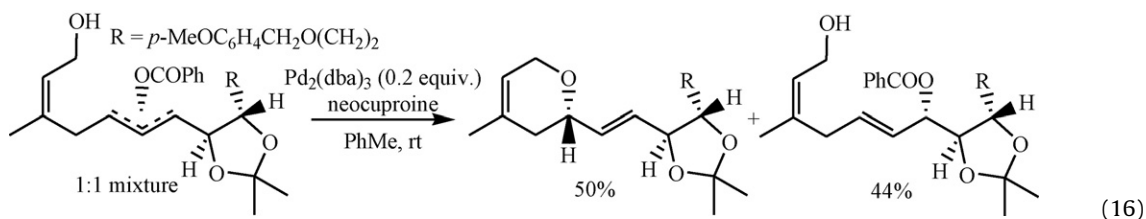
R = p-MeOC$_6$H$_4$CH$_2$O(CH$_2$)$_2$

1:1 mixture

50%   44%

$$(16)$$

In studying the intermolecular etherification of allylic acetates with alcohols under Pd^0 catalysis, Kim and Lee observed the promotion of the reaction by zinc alkoxides. Thus, they have used the procedure for intramolecular etherifications (Eq. (17)) [21]. With Pd(OAc)$_2$/PPh$_3$ as the catalytic system, another efficient promoter is Ti(Oi-Pr)$_4$ as shown by Harrity and co-workers (Eq. (18)) [22]. For these procedures, the authors presume the formation, as nucleophiles, of Zn- and Ti-alkoxides, respectively.

n = 1, 2

92-94%, dr = 1:1

$$(17)$$

$$\tag{18}$$
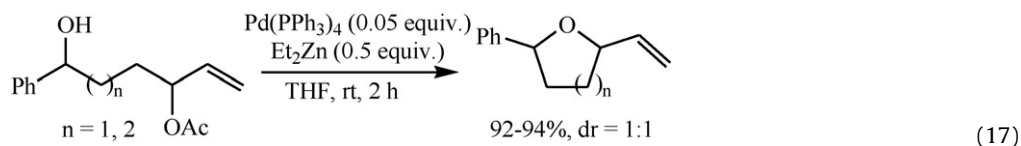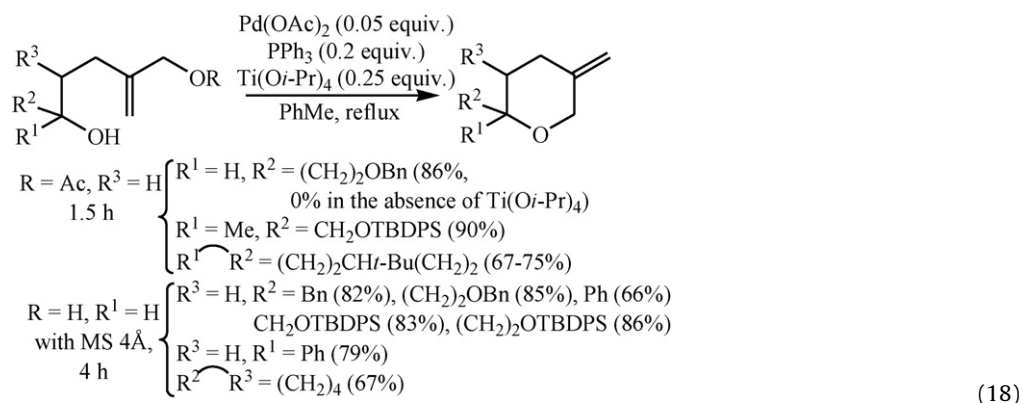
2.1.2. Carbonate as the leaving group

The formation of the η^3-allylpalladium intermediates from allylic carbonates delivers $MeOCO_2{}^-$, which leads to MeO^- and CO_2. Therefore, these substrates provide an internal source of base which can react with the tethered hydroxy, leading to the corresponding alcoholate.

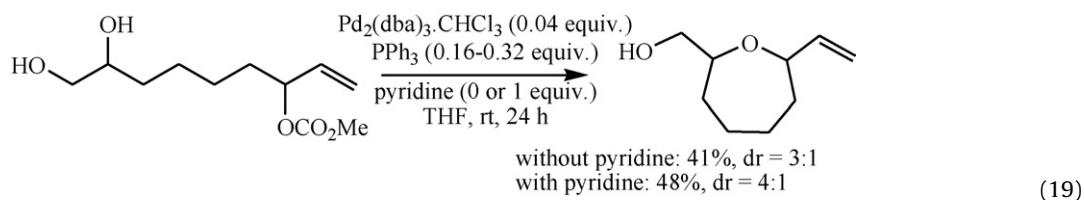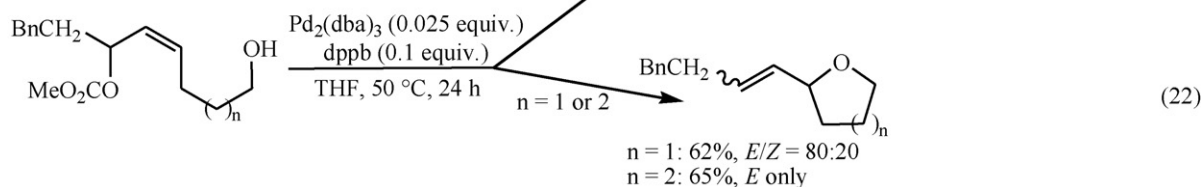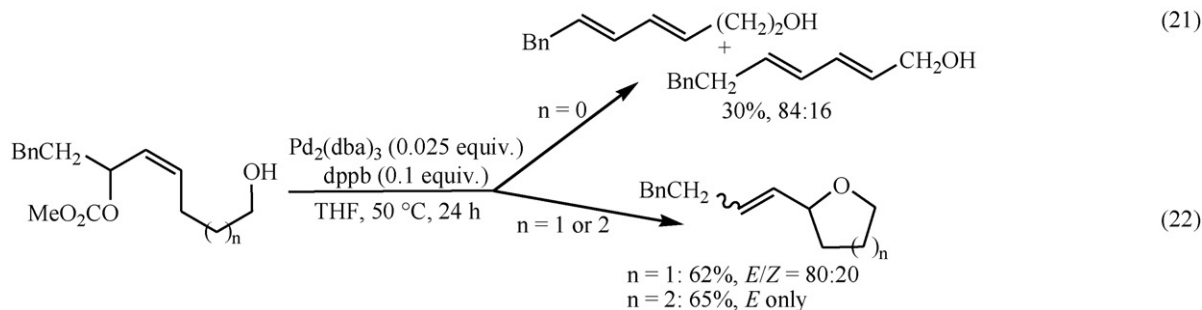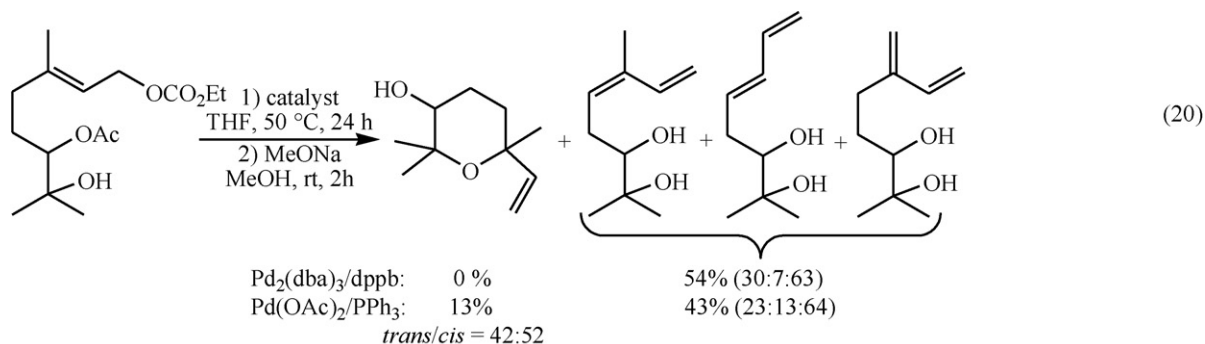In 1988, Trost and Tenaglia disclosed the synthesis of a seven-membered cyclic ether from an intramolecular nucleophilic addition to a η^3-allylpalladium formed from an allylic carbonate (Eq. (19)) [15]. The yield and the stereoselectivity were slightly improved in the presence of pyridine.

$$\tag{19}$$

Using ethyl (E)-6,7-dihydroxy-3,7-dimethyloct-2-enyl carbonate and methyl (Z)-6,7-dihydroxy-3,7-dimethyloct-2-enyl carbonate as substrates, Sinou and co-workers have shown that the *trans/cis* ratio of the 5-*exo-trig* cyclization is almost independent on the double bond geometry, but can be highly influenced by the nature of the phosphine (Scheme 3) [23]. Inversion of the diastereoselectivity, which was observed only with P(o-tolyl)$_3$ as the ligand, corresponds however to an heterocyclization occurring in a low yield due to the concurrent formation of 1,3-dienes arising from a β-H elimination at the level of Pd intermediates. According to the authors, this secondary reaction could change the *trans/cis* ratio. Attempts to obtain 6-*exo-trig* cyclization from the above terpenes having masked the secondary hydroxy group afford, at the best, a low yield of the expected tetrahydropyran (Eq. (20)) [23]. Apparently, the efficiency of the cyclization using Sinou's procedure depends on the length of the hydroxy tether (Eqs. (21) and (22)) [24].

$$\tag{20}$$

$$\tag{21}$$

$$\tag{22}$$

E. C.: Pd$_2$(dba)$_3$ (0.025 equiv.), L (0.05 equiv.), THF, 50 °C, 24 h

L: yield, *trans:cis*
PPh$_3$: 70%, *81:19*; dppe: 53%, *84:16*; dppp: 64%, *80:20*
dppb: 52%, *80:20*; dpppe: 52%, *84:16*
P(2-furyl)$_3$: 65%, *82:18*; P(*m*-tolyl)$_3$: 52%, *75:25*
P(*o*-tolyl)$_3$: 35%, *35:65*

L: yield, *trans:cis*
PPh$_3$: 50%, *86:14*;
dppb: 59%, *83:17*;
P(2-furyl)$_3$: 60%, *85:15*;
P(*o*-tolyl)$_3$: 31%, *27:73*
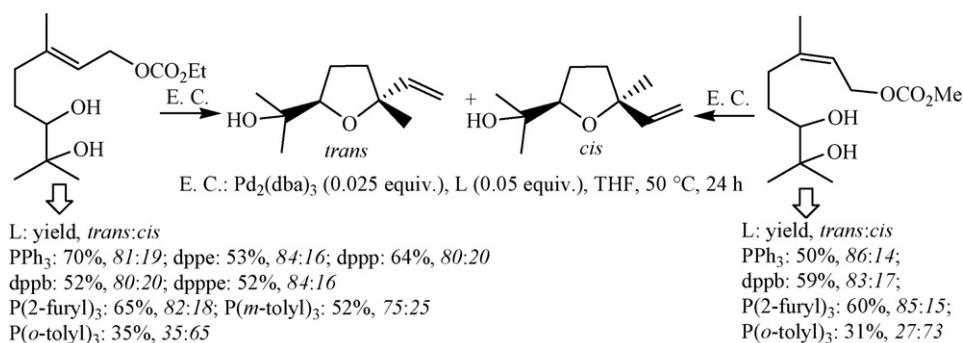
Scheme 3. Dependence of the stereoselectivity on the ligand.

Using enantioenriched substrates, Hansen and Lee have synthesized a range of 2-alkenyl-4-methylene tetrahydropyrans with an excellent transfer of the stereochemistry as shown from Eqs. (23) and (24) [25]. The 6-*exo-trig* cyclization with 1,3-chirality transfer has also been used by Uenishi and Ohmi to prepare a substituted 3,6-dihydro[*2H*]pyran unit leading to the total synthesis of (−)-laulimalide (Eq. (25)) [20]. The modest yields in cyclic ethers are due to the concurrent formation of trienes. It is, however, worth mentioning that the allylic benzoate corresponding to the allylic carbonate depicted in Eq. (25) did not convert into the dihydropyran (see above and Eq. (16)) [20]. Recently, Spilling and co-workers have used the methodology for the cyclization of nonracemic hydroxy phosphono allylic carbonates: the reaction occurred with complete chirality transfer but was limited to the formation of five- and six-membered cyclic ethers (Eq. (26)) [26]. Interestingly, tertiary alcohols were also viable nucleophiles (Eq. (27)) [26]. It should be noted that, in the presence of trimethyl borate, the 5-*exo-trig* cyclization of ethyl (*E*)-6-hydroxydec-2-enyl carbonate is preferred to the expected methoxylation of the transient η^3-allylpalladium (Eq. (28)) [27]. In fact, the borate could enhance the nucleophilicity of the hydroxy group via the formation of an "ate" complex [3].

(23)

(24)

(25)
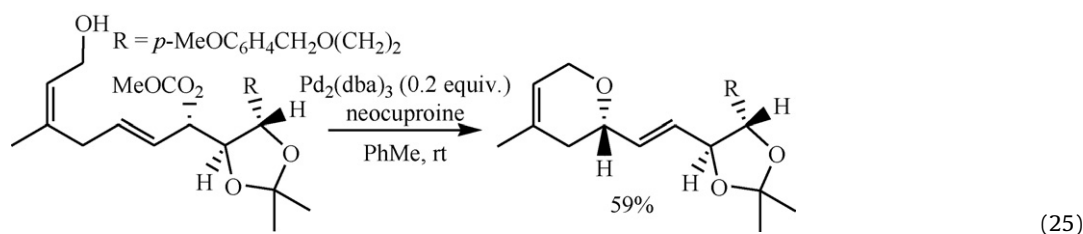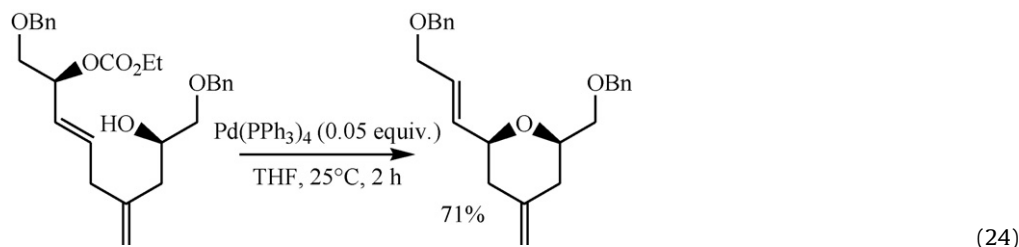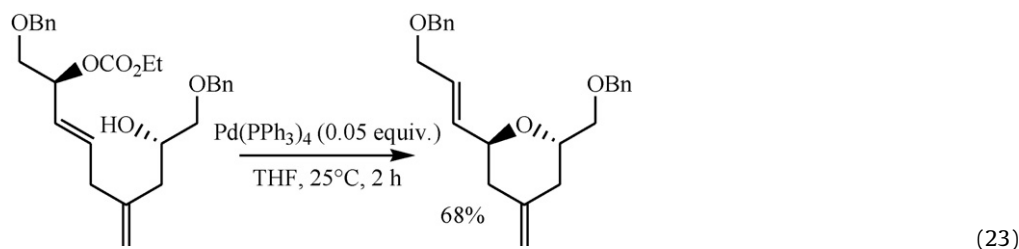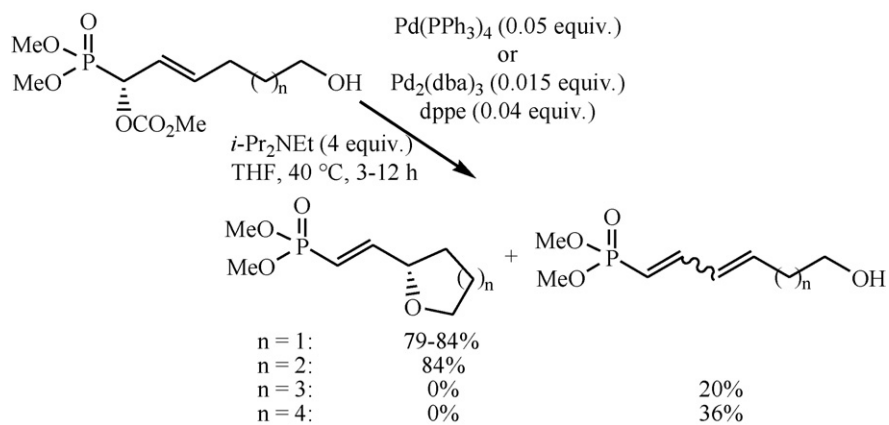
$$ (26) $$
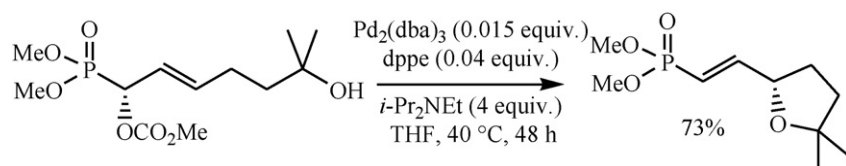
$$ (27) $$

$$ (28) $$

An erythromycin-derived macrolide has been synthesized by Wang et al. from the selective intramolecular addition of a secondary hydroxy group to an allylic *t*-butyl carbonate moiety (Eq. (29)) [28].
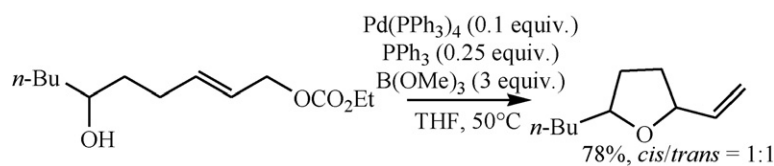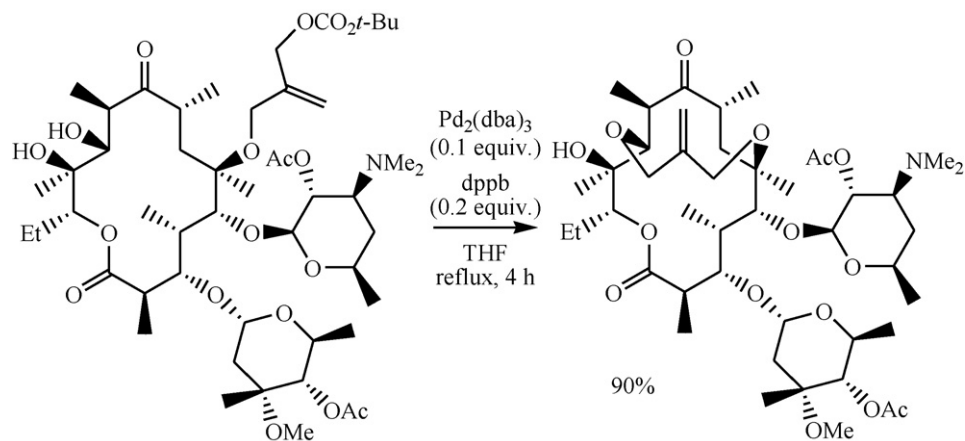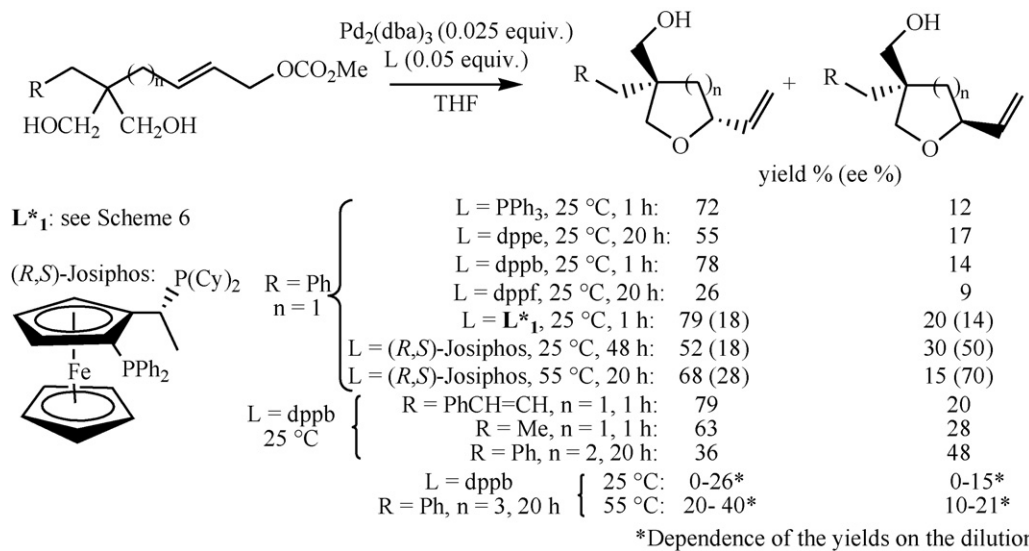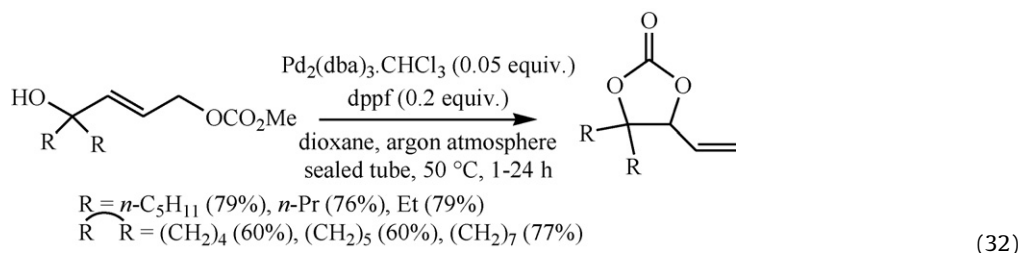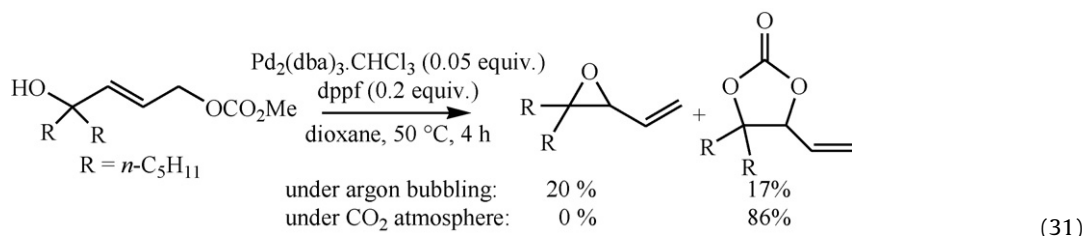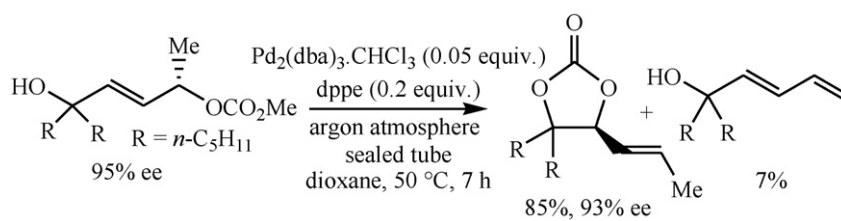

$$ (29) $$

Given studies, from Sinou and co-workers, of the cyclization of the methylcarbonates of ω,ω-bis(hydroxymethyl)-α,β-unsaturated alcohols (Eq. (30)), the stereoselectivity and the efficiency can depend on the nature of the catalytic system [29].

	yield % (ee %)	
L = PPh$_3$, 25 °C, 1 h:	72	12
L = dppe, 25 °C, 20 h:	55	17
L = dppb, 25 °C, 1 h:	78	14
L = dppf, 25 °C, 20 h:	26	9
L = L*$_1$, 25 °C, 1 h:	79 (18)	20 (14)
L = (R,S)-Josiphos, 25 °C, 48 h:	52 (18)	30 (50)
L = (R,S)-Josiphos, 55 °C, 20 h:	68 (28)	15 (70)
R = PhCH=CH, n = 1, 1 h:	79	20
R = Me, n = 1, 1 h:	63	28
R = Ph, n = 2, 20 h:	36	48
L = dppb, R = Ph, n = 3, 20 h, 25 °C:	0-26*	0-15*
L = dppb, R = Ph, n = 3, 20 h, 55 °C:	20- 40*	10-21*

*Dependence of the yields on the dilution   (30)

A vinylic epoxide has been isolated in a low yield, by Yoshida et al., from (E)-4-hydroxy-4-penthylnon-2-enyl methyl carbonate, the concurrent reaction being the production of an allylic carbonate (Eq. (31)) [30]. The efficiency of the carbon dioxide elimination-fixation process from 1,1-disubstituted-4-methoxycarbonyloxy-2-buten-1-ols increases for reactions performed in a sealed tube (Eq. (32)) or under carbon dioxide atmosphere (Eq. (31)) [30]. Reactions under these latter conditions will be reviewed in Section 2.3 [31].

under argon bubbling:	20 %	17%
under CO$_2$ atmosphere:	0 %	86%

(31)

R = n-C$_5$H$_{11}$ (79%), n-Pr (76%), Et (79%)
R R = (CH$_2$)$_4$ (60%), (CH$_2$)$_5$ (60%), (CH$_2$)$_7$ (77%)

(32)

These cascade elimination-fixation reactions can also occur with chirality transfer (Eq. (33)) [30] and from dienic substrates, with a selectivity depending on both the reaction temperature and the nature of the ligand (Eq. (34)) [32]. The crossover experiment using the 1:1 mixture of the carbonate and the benzoate shown in Eq. (35) has demonstrated the in situ generation of carbon dioxide [32]. These reactions may be explained following the mechanism depicted in Scheme 4 which involves isomerizations of η^3-allylpalladium intermediates [32]. Garcia and co-workers have disclosed that the carbon dioxide elimination-fixation process is not limited to tertiary alcohols, and can efficiently occur at room temperature in methylene chloride (Eq. (36)) [33].

(33)

Pd$_2$(dba)$_3$.CHCl$_3$ (0.05 equiv.)
L (0.2-0.4 equiv.)

dioxane, argon atmosphere
sealed tube, 50-100 °C, 4 h

R = n-C$_5$H$_{11}$

L = PPh$_3$ (0.4 equiv.), 50 °C: 4%   56%
L = dppm (0.2 equiv.), 50 °C: 7%   60%
L = dppe (0.2 equiv.), 50 °C: 57%
L = dppv (0.2 equiv.), 50 °C: 58%   27%
L = dppv (0.2 equiv.), 100 °C: 22%   74%

(34)

Pd$_2$(dba)$_3$.CHCl$_3$ (0.05 equiv.)
dppv (0.2 equiv.)
BSA (1.5 equiv.)

dioxane, argon atmosphere
sealed tube, 50 °C, 4 h

R = n-C$_5$H$_{11}$ + 1:1
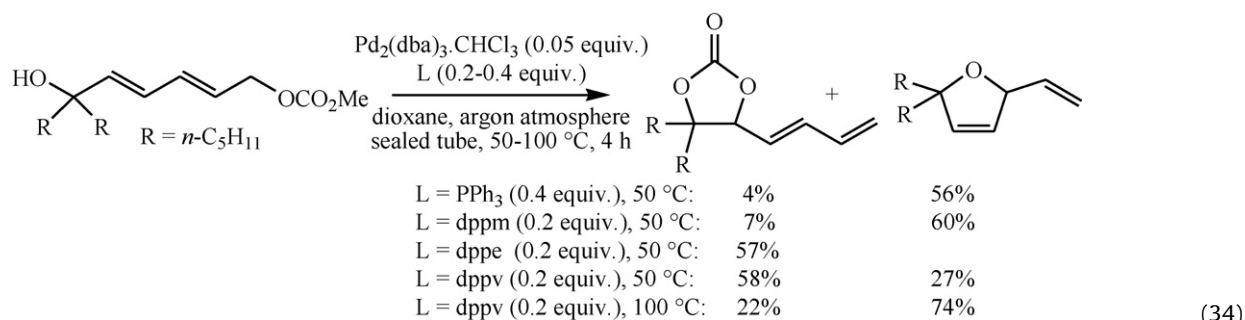
23%   31%   14%
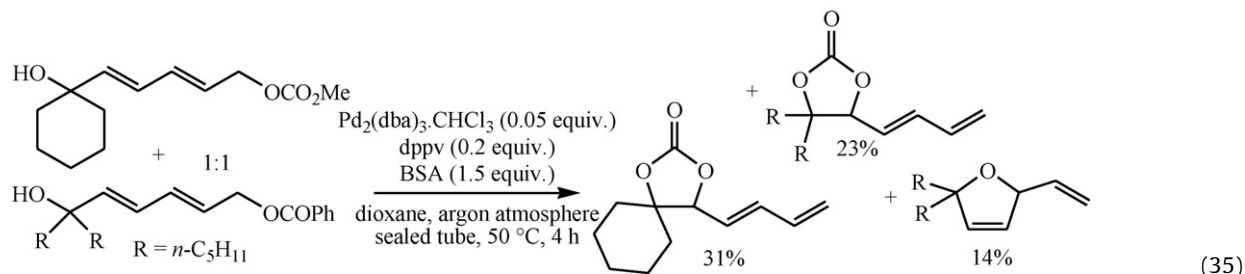
(35)

Scheme 4. Cascade elimination–fixation reaction of carbon dioxide.
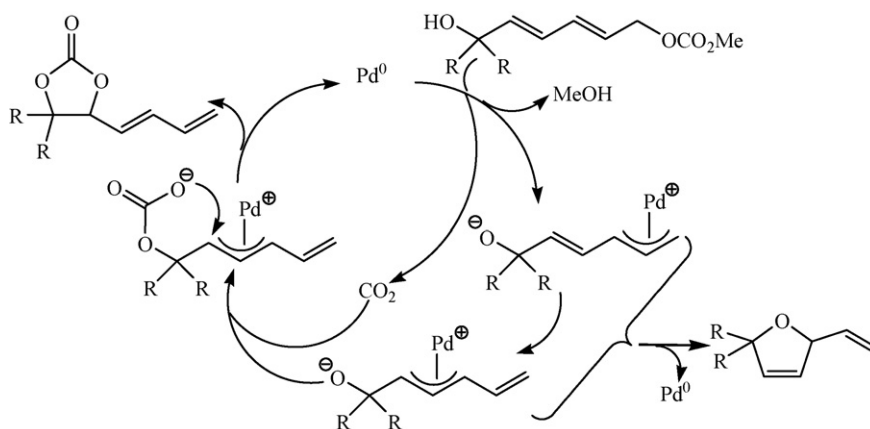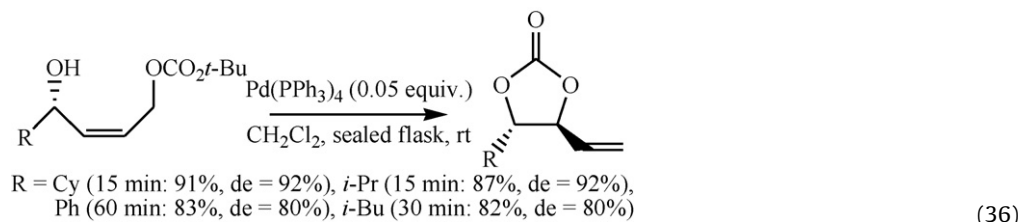
Pd(PPh$_3$)$_4$ (0.05 equiv.)

CH$_2$Cl$_2$, sealed flask, rt

R = Cy (15 min: 91%, de = 92%), i-Pr (15 min: 87%, de = 92%),
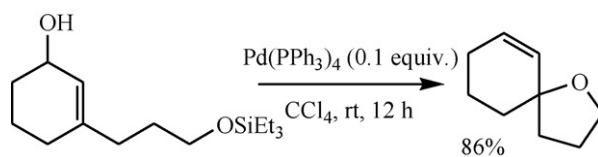Ph (60 min: 83%, de = 80%), i-Bu (30 min: 82%, de = 80%)
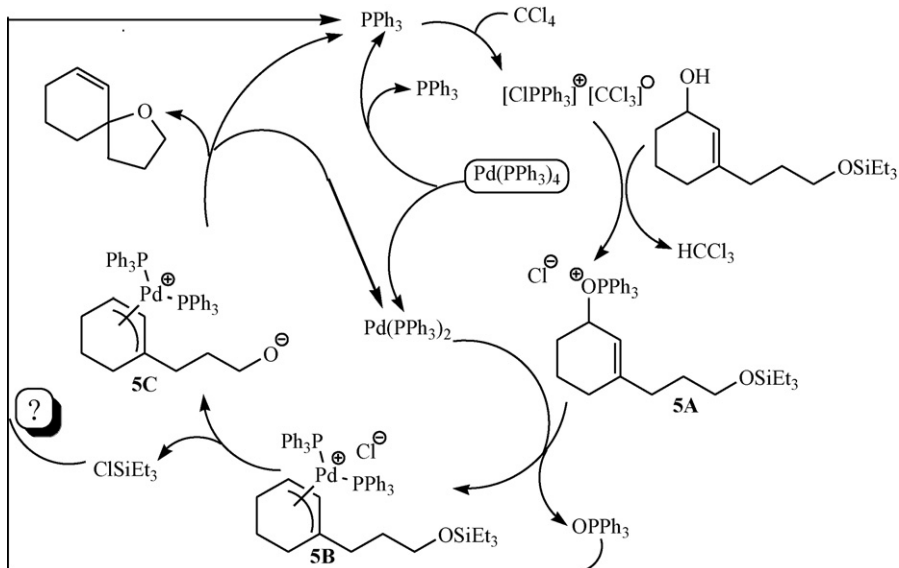
(36)

2.1.3. Hydroxy as the leaving group

According to Harrity and co-workers, the Pd^0-catalyzed cyclization of 2-(hydroxyalkyl)-prop-2-en-1-ols shown in Eq. (18) (R=H) was very sluggish even in refluxing toluene. This cyclization has however been promoted by the addition of titanium^{IV} isopropoxide [22,34]. It is known that Ti(Oi-Pr)$_4$ promotes the formation of η^3-allylpalladium complexes from allylic alcohols [35] but, given the experiments carried out by Harrity's team [22], it appears that this additive has also a significant role in the cyclization step, presumably via the formation of the Ti-alkoxide of the tethered hydroxy.

Another heterocyclization method, that would also involve a nucleophilic alkoxide, has previously been disclosed by Godleski and co-workers [7]. This concerns the synthesis of furan rings, in particular spirotetrahydrofurans, by the exposure to catalytic Pd(PPh$_3$)$_4$ of carbon tetrachloride solutions of allylic alcohols substituted in the β-position by a triethylsilyloxyalkyl chain (Eq. (37)). The authors proposed the mechanism shown in Scheme 5: PPh$_3$ liberated from Pd(PPh$_3$)$_4$ would react with CCl$_4$ to form the known PPh$_3$Cl$^+$CCl$_3$$^-$ salt, which would be trapped by the hydroxy group of the substrate to provide HCCl$_3$ and oxyphosphonium ion 5A. The reaction of 5A with Pd^0 would give the η^3-allylpalladium complex 5B. Deprotection of the triethylsilyl ether with Cl$^-$ would afford 5C, thus enabling the cyclization step. The reduction of OPPh$_3$ by Et$_3$SiCl to regenerate PPh$_3$ was suspected, but control experiments showed too slow a reaction at room temperature to be operative.
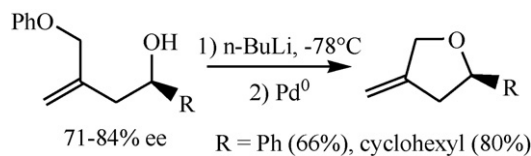
$$(37)$$

Scheme 5. Suggested mechanism for the formation of spirotetrahydrofurans from allylic alcohols β-substituted by a triethylsilyloxyalkyl chain.

2.1.4. Aryloxy as the leaving group

In 1993, Klumpp and co-workers reported briefly the cyclization of chiral homoallylic alcohols β-substituted by a phenoxymethyl group (Eq. (38)) [36].

$$(38)$$

71–84% ee   R = Ph (66%), cyclohexyl (80%)

For the synthesis of pyran and furan derivatives shown in Eqs. (39) and (40), Trost et al. have chosen a *p*-nitrophenyloxy as the leaving group because its stability towards the ruthenium complexes used to prepare the substrates [37–39].

$$(39)$$

base = Bu₄NF (42%), tetramethylguanidine (61%)

Ar = *p*-O₂NC₆H₄

$$(40)$$

yield, *cis/trans*

$R^1 = Me_3Si$, $R^2 = Ph(CH_2)_2$: 47%, 4:1
$R^1 = Me_2PhSi$, $R^2 = Cy$: 45%, 5:1

Ar = *p*-O₂NC₆H₄

2.1.5. Amino as the leaving group

Chalk et al. have isolated vinyltetrahydrofurans(pyrans) as side products of the Pd-catalyzed deamination of allylic amines bearing a 4-hydroxyalkyl sub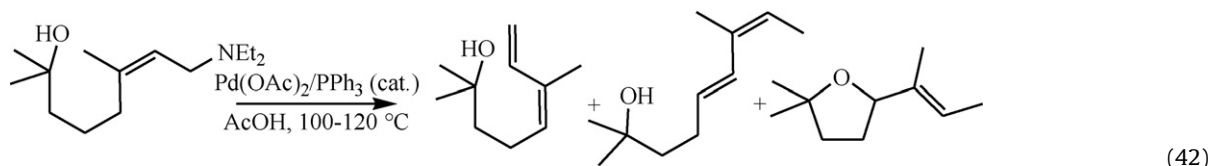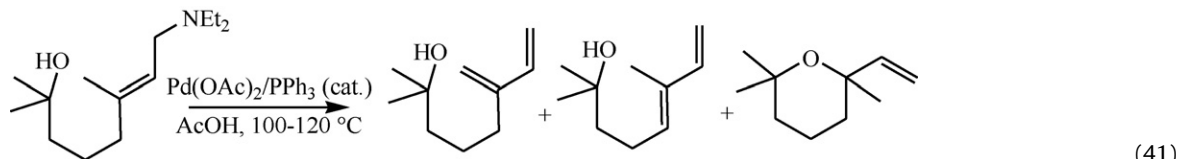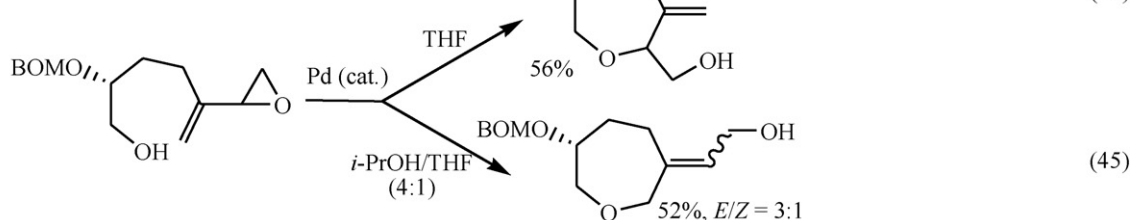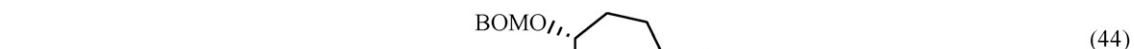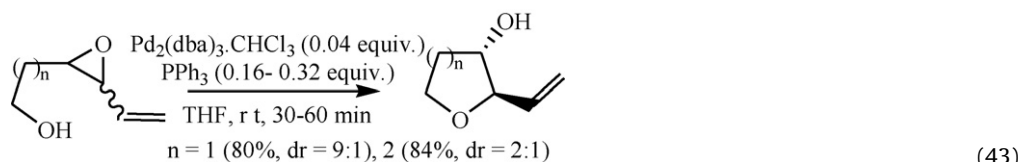stituent in the β-position (Eqs. (41) and (42)) [40]. The formation of the furan derivative from the Z-isomer could imply isomerization of the initially formed η³-allylpalladium intermediate.
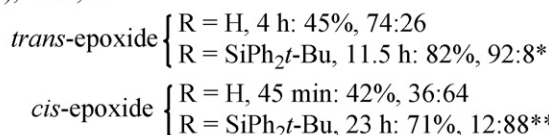
$$(41)$$

$$(42)$$

2.1.6. From vinylepoxides

In 1988, Trost and Tenaglia disclosed the synthesis of 2-vinyl-3-hydroxytetrahydrofuran(pyran)s from vinyl epoxides substituted with a hydroxyalkyl chain (Eq. (43)) [15]. Subsequently, an interesting dichotomy in terms of regioselectivity has been observed in the course of the synthesis of (+)-zoapatanol (Eqs. (44) and (45)): the attack of the hydroxy nucleophile is proximal in THF, and distal in a mixture of i-PrOH and THF. It was presumed that the regioselective proximal attack results from intramolecular hydrogen bonding between the hydroxy and the departing oxygen of the epoxide, such interaction being interrupted by addition of an exogeneous alcohol [41].

$$(43)$$

$$(44)$$

$$(45)$$

Hirama and co-workers, who have synthesized cis- and trans-2-alkenyl-3-hydroxytetrahydropyrans, have revealed the dependence of the stereoselectivity with the stereochemistry of the epoxide (Eq. (46)) [42]. These authors succeeded in the increase of the stereoselectivity in using a silyl ether as potential nucleophile and its in situ deprotection with tetrabutylammonium fluoride (Eq. (46)). Under these conditions, they assumed that the nucleophilic species is the corresponding ammonium alkoxide [42]. The method has been subsequently applied to the synthesis of the IJ ring of ciguatoxin (Eq. (47)) [43]. The cyclizations shown in Eqs. (48) and (49) exemplify that the stereoselectivity can be, moreover, dependent on the stereochemistry of the C=C bond [44].

$$(46)$$

$$(47)$$

$$(48)$$

$$(49)$$

2.2. In the presence of chiral ligands

Through the various chiral ligands described in the literature, those discovered by Trost and co-workers, and named pocket ligands [45], have emerged as to be, in most cases, the best in terms of enantioselection and chemical yield; some of them are shown in Scheme 6.

Scheme 6. Trost's pocket ligands.

2.2.1. Ester as the leaving group

Hara et al. have observed a strong dependence on the diastereoselectivity and efficiency of the cyclization of (S,E)-6,7-dihydroxyhept-2-enyl acetate with the nature of the chiral ligand, leading to "matched" and "mismatched" effects (Eq. (12)) [16,46]. Burke's team has used Trost's pocket ligands to prepare either tetrahydrofuran (Eqs. (50) and (51)) [47] or bis-tetrahydrofuran (Eqs. (52) and (53)) [17,48] cores from diol bis(allylic acetates), and bis-oxanes from *meso*-tetraol bis-(allylic acetates) (Eq. (54)) [49]. Such efficient enantioselective heterocyclizations afford intermediates for the synthesis of uvaricin [17], halichondrin B [47], phorboxazoles [49] and annonaceous acetogenins [48]. It is worth mentioning that (i) Eqs. (50) and (54) concern desymmetrizations reactions, and (ii) the use of PPh_3 instead of L_1^* or L_2^* with the substrate shown in Eqs. (52) and (53) afforded a statistical mixture of the bis-tetrahydrofurans (see Eq. (13)) [17].

$$(50)$$

$$(51)$$

(52)

(53)

(54)

Trost et al. have thoroughly examined the influence of the substituents of the pocket ligands, the nature of the leaving group and experimental conditions on the efficiency of the heterocyclization of different substrates, and used optimized conditions for the synthesis of (+) hippospongic acid A (Eqs. (55) and (56)) [50].

$$R = CO_2Me \begin{cases} L^*_1, CH_2Cl_2, 0\ °C: 50\%\ conversion, 55\%\ ee \\ L^*_3, CH_2Cl_2, 0\ °C: 75\%\ conversion, 64\%\ ee \\ L^*_3, CH_2Cl_2, 25\ °C: 100\%\ conversion, 68\%\ ee \\ L^*_3, dioxane, 25\ °C: 53\%\ conversion, 95\%\ ee \\ L^*_3, dioxane, 80\ °C: 100\%\ conversion, 83\%\ ee \end{cases}$$

$$R = CN \begin{cases} L^*_1, PhMe, 60\ °C: 100\%\ conversion, 91\%\ ee \\ L^*_3, PhMe, 80\ °C: 100\%\ conversion, 81\%\ ee \\ L^*_3, MeCN, 80\ °C: 100\%\ conversion, 67\%\ ee \\ L^*_3, dioxane, 80\ °C: 100\%\ conversion, 68\%\ ee \\ L^*_3, dioxane, 25\ °C: 52\%\ conversion, 98\%\ ee \end{cases}$$

(55)

R = Ac, 25 °C: 45% conversion, 94% ee
R = Ac, 80 °C: 55% conversion, 50% yield, 91% ee
R = Ac, 100 °C: 100% conversion, 65% ee
R = CO$_2$CH$_2$CCl$_3$, 25 °C: 47% conversion, 87% ee
R = CO$_2$t-Bu, 25 °C: 53% conversion, 23% ee

(56)

Wilkinson has synthesized optically active vinylmorpholines via the Pd^0-catalyzed double allylic substitution of Z-1,4-diacetoxy-2-butene by achiral amino alcohols [51]. Among the range of chiral ligands tested, the best enantioselectivity has been provided with L^*_1 (Eq. (57)). This synthesis is included in the present review because the intermediate formation of an allylic acetate substituted with a hydroxylated tether is involved (see Eq. (5)).

(57)

Pocket ligands have also been used for diastereoselective oxaheterocyclizations (Eq. (58)) [52], leading possibly to match and mismatch effects (Eq. (15)) [19].

(58)

2.2.2. Carbonate as the leaving group

To the best of our knowledge, Sinou's team has been the first to study enantioselective Pd^0-catalyzed heterocyclizations of allylic compounds bearing a hydroxylated tether. The reactions, carried out using allylic carbonates as substrates and unichiral ligands such as (R)-BINAP, (S,S)-CHIRAPHOS, (S,S)-DIOP or (S,S)-BDPP, provided however low enantioselectivities [24]. This team has also studied diasteroisomeric reactions in the presence of chiral ligand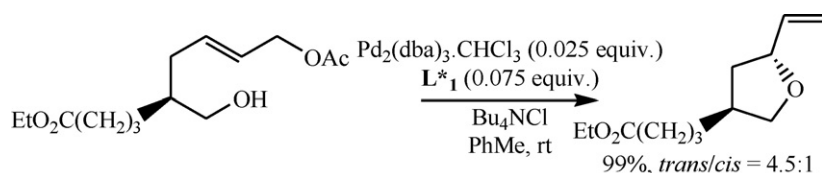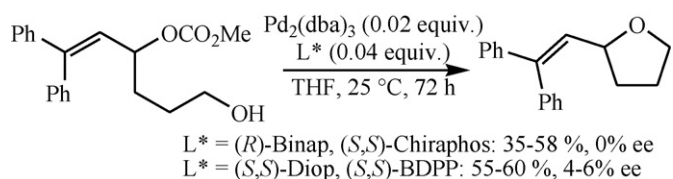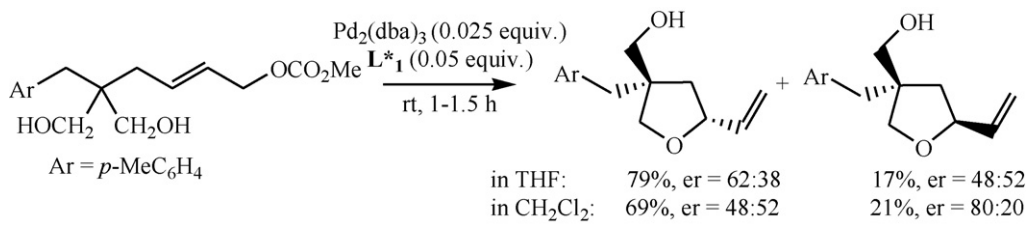s, but with only low or moderate selectivities even with the chiral pocket ligands (Eq. (59)). Nevertheless, a strong influence of the nature of the solvent was observed as shown in Eq. (60) [29]. Subsequently, Hansen and Lee reported large match and mismatch effects induced by Trost's ligands (Eq. (61)) [25].

(59)

(60)

(61)

It has been briefly noted that the use of a substrate with a carbonate instead of an acetate as the leaving group is less effective in terms of enantioselectivity for the synthesis of (+) hippospongic acid A (Eq. (56)) [50].

2.2.3. Aryloxy as the leaving group

Trost et al. have carried out enantio-and diastereoselective synthesis of heterocycles via the intramolecular addition of alcohols to η^3-allylpalladium complexes obtained from p-nitrophenyl allyl ethers. In terms of yield and selectivity, the authors have observed that $Pd_2(dba)_3 \cdot CHCl_3$ as the catalyst and NEt_3 as the base have to be preferred to (η^3-$C_3H_5PdCl)_2$ and DBU, respectively (Eq. (62)) [37,38]. In a recent report, another base, $NEt(i\text{-Pr})_2$, has been used successfully (Eq. (63)) [53]. As depicted in Eq. (64), pocket ligands can induce high matched effects and, moreover, in some cases an increase in the chemical yield [37].

Pd-dimer (0.02 equiv.)
L*$_1$ (0.06 equiv.)
NEt$_3$ (1 equiv.)
solvent, -35 to 60 °C, 2 h

Ar = p-O$_2$NC$_6$H$_4$

	°C	yield %	ee %
n = 1, CH$_2$Cl$_2$, Pd$_2$(dba)$_3$·CHCl$_3$:	0	84	76
n = 2, THF, Pd$_2$(dba)$_3$·CHCl$_3$:	-35	27	89
	0	83	82
	25	86	77
	60	73	72
n = 2, CH$_2$Cl$_2$ Pd$_2$(dba)$_3$·CHCl$_3$:	0	80	94
n = 2, CH$_2$Cl$_2$ [(η^3-allyl)PdCl]$_2$:	0	71	92
n = 3, CH$_2$Cl$_2$, Pd$_2$(dba)$_3$·CHCl$_3$:	0	0	

(62)

Ar = p-O$_2$NC$_6$H$_4$

Pd$_2$(dba)$_3$.CHCl$_3$ (0.02 equiv.)
L*$_2$ (0.055 equiv.)
NEt(i-Pr)$_2$ (1.1 equiv.)
CH$_2$Cl$_2$, rt, 1 h

[?]$_D$ = -1.4

[?]$_D$ = -68.5
97%
cis:trans = 15:1

(63)

Pd$_2$(dba)$_3$.CHCl$_3$ (0.02 equiv.)
ligand (0.06 equiv.)
NEt$_3$ (1 equiv.)
CH$_2$Cl$_2$, 0 °C, 2 h

Ar = p-O$_2$NC$_6$H$_4$

ligand, yield, cis:trans ratio

n = 0, R = Cy
- dppp, 45%, 5:1
- L*$_1$, 53%, 1:4.5
- L*$_2$, 57%, 23:1

n = 1, R = CH$_2$OCOn-Pr
- (1:1 L*$_1$ + L*$_2$) 54%, 3.6:1
- L*$_1$, 60%, <3:>97
- L*$_2$, 58%, >97:<1

(64)

2.3. In the presence of carbon dioxide

Yoshida et al., reacting 1,1-dipentyl-4-benzoyloxy-2-buten-1-ol with CO_2 in a basic medium containing a Pd^0 catalyst, have obtained the corresponding cyclic carbonate with a fair yield (Eq. (65)) via the possible mechanism illustrated in Scheme 7 [30]. An atmosphere of CO_2 has even been used for the reaction of dienylic carbonates when the elimination/fixation sequence of CO_2 has a low efficiency. (Eq. (66)) [32].

Scheme 7. Carbonatation reaction.

$$
(65)
$$

$$
(66)
$$

The Pd⁰-catalyzed synthesis of 1,3-dioxolan-2-one from (*S,Z*)-4-hydroxynon-2-enyl benzoate did not occur with CO_2 but succeeded with potassium *t*-butyl carbonate as source of CO_2 (Eq. (67)) [33]. This reaction is very sensitive to the nature of the substituents since the procedure was ineffective from a substrate having a phenyl instead of a pentyl substituent.

$$
(67)
$$

3. Pd^II-catalyzed cyclizations

The Pd^II-catalyzed cyclizations of substrates having both an allylic OR group and a hydroxylated tether involve, in most cases, an intramolecular Wacker-type reaction and the regeneration of the Pd^II catalyst via the cleavage of the C-OR bond, or by addition of oxidants. These observations lead to divide the present section in two main parts.

3.1. With elimination of the leaving group

3.1.1. Ester as the leaving group

Makabe and co-workers have recently reported the diastereoselective cyclizations shown in Eq. (68) [54,55]. According to the authors, the key intermediate involves a chair-like transition state, for which, both the C=C bond and the hydroxy are coordinated to Pd^II (Scheme 8) [55]. The reaction did not occur with $PdCl_2(PPh_3)_2$ as the catalyst, and its efficiency depended highly on the nature of the ester group (Eq. (68)).

$$
(68)
$$

Scheme 8. Chair-like transition states leading to 2-vinyl-tetrahydropyrans.

3.1.2. Hydroxy as the leaving group

In 1992, Saito et al. disclosed the synthesis of optically active dihydrofurans and small quantities of furans via, apparently, the *5-endo-trig* cyclization of unichiral (*E*)-3-ene-1,2-diols induced with catalytic amounts of both PdCl$_2$(MeCN)$_2$ and *t*-BuOOH (Eq. (69)), the presence of *t*-BuOOH increasing the initial rate [56]. Rather than a Wacker-type mechanism, the authors proposed a chloropalladation of the double bond occurring from nucleophilic *anti*-attack of the η^2-Pd–alkene complex 9A by a chloride anion (Scheme 9). The intramolecular S$_{N2}$ displacement of the chloride substituent of 9B by the homoallylic hydroxy group provides 9C which evolves towards the dihydrofuran. This proposal agrees with the observation that the addition of NEt$_3$, or the use of Pd(OAc)$_2$ as the catalyst, disabled completely the process. HOPdCl, that is liberated, via a *syn*-elimination, from 9C, may promote the reaction by itself or regenerates PdCl$_2$ by its react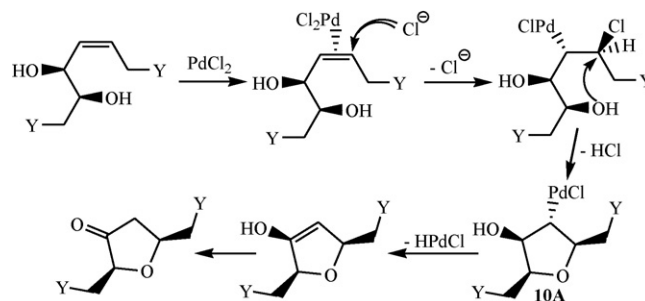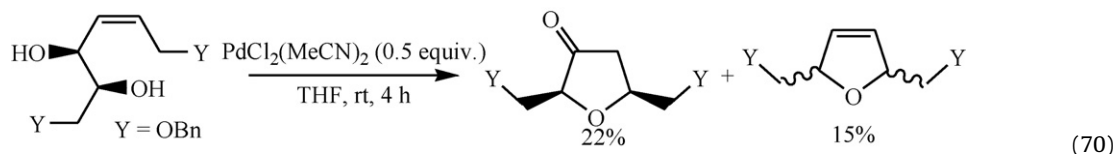ion with HCl [57]. The use of a substrate with a *Z* double bond affords a significant amount of a furanone (Eq. (70)). The authors suggest that this compound is obtained via the elimination of HPdCl from intermediate 10A which has PdCl and the vicinal OH arranged *anti* to each other (Scheme 10). It is worth noting that, according to these mechanistic schemes, the allylic hydroxy substituent has no great influence on the stereoselectivity of the Pd^{II} coordination, but determine the regioselectivity of the chloride attack.
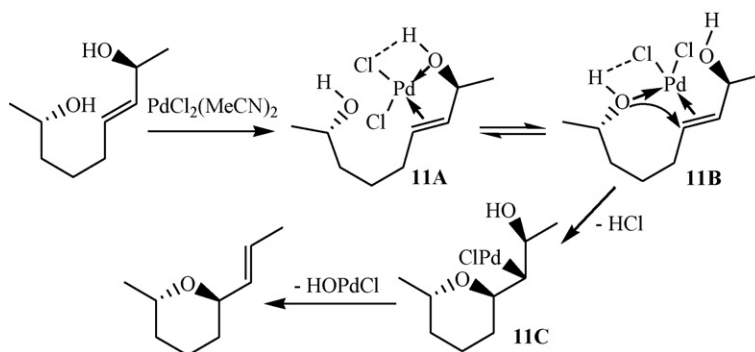

$$\tag{69}$$

Scheme 9. The intermediate chloropalladation.

$$\tag{70}$$

Scheme 10. The furanone formation.

From 2005, Uenishi's team has intensively reported diastereoselective cyclizations of unsaturated diols. The intramolecular oxypalladation of unichiral 2-ene-1,7-diols and 4-ene-1,3-diols gave stereospecifically tetrahydro- and 3,6-dihydro[2*H*]pyran rings, respectively (Eqs. (71) and (72)) [58]. In the case of the 6-*exo-trig* cyclization (Eq. (71)), the authors suggested that the 1,3-chirality transfer occurs via a Wacker-type reaction (Scheme 11) [57,58], rather than via the chloropalladation of the double bond. It was proposed that the allylic hydroxy group controls, by coordination, the stereoselectivity of the formation of the η^2-Pd–alkene complex. The complex thus obtained (11A) is in equilibrium with 11B, which has the hydroxy nucleophile coordinated to palladium. *Syn*-attack of this hydroxy ligand to the activated C=C bond affords 11C. Elimination of HOPdCl from 11C leads to the corresponding *trans*-pyran with an exocyclic (*E*)-C=C bond. As for the 6-*endo-trig* cyclization (Eq. (72)), the di-coordination of the allylic alcohol unit to palladium followed by the *syn*-attack of the remote hydroxy has been proposed (Scheme 12) [20]. The decisive role of the allylic hydroxy on the stereoselectivity is exemplified in Eq. (73). Indeed, a substrate with a nucleophilic (*S*)-hydroxy and a primary allylic alcohol yielded a 1:1 mixture of the two isomeric tetrahydropyrans [59]. Cyclizations were possibly performed in the presence of a substoichiometric amount of benzoquinone (Eq. (74)) [20].

Scheme 11. 6-*Exo-trig* cyclization via a Wacker-type reaction.

Scheme 12. 6-*Endo-trig* cyclization via a Wacker-type reaction.

$$(71)$$

$$(72)$$

$$(73)$$

$$(74)$$

A selectively depending on the stereochemistry of the C=C bond, the reaction temperature and traces of moisture has been observed. At 0 °C in THF, (*E*,2*S*,8*S*)-non-3-ene-2,8-diol afforded selectively the corresponding (*E*)-*trans*-tetrahydropyran (Eq. (71)) while a 1:1 mixture of (*Z*)-*cis*- and (*E*)-*trans*-isomers was obtained from (*Z*,2*R*,8*S*)-non-3-ene-2,8-diol (Scheme 13). In contrast, (*E*)-*cis*-isomer was selectively produced from (*Z*,2*S*,8*S*)-non-3-ene-2,8-diol (Eq. (75)) [57]. At −40 °C in the same solvent, the (*Z*,2*R*,8*S*)-substrate yielded exclusively the (*Z*)-*cis*-isomer but, unexpectedly, the presence of 0.1 equiv. of H$_2$O resulted in the formation of only the (*E*)-*trans*-isomer. The mechanism proposed by the authors for the (*Z*)-substrates is more complicated than the one depicted in Scheme 11 for the (*E*)-substrate, and the water effect remains unclear [57].

Scheme 13. Selectivity dependence on the experimental conditions.

(75)

In the absence of any chiral hydroxy, the introduction of a sterically hindered substituent, such as *t*-butyldiphenylsilylether, in homoal-lylic position can lead to a diastereoselective cyclisation (Eq. (76)) [59,60]. Nevertheless, when the allylic alcohol is secondary, the selectivity depends only on its configuration (Eqs. (77 and 78)) [59]. The induction of the chirality by the allylic hydroxy is also observed in the formation of bis-heterocycles (Eqs. (79) and (80)), leading to the synthesis of aspergillidines [61].

(76)

(77)

(78)

(79)

(80)

Tetrahydropyrans containing tetrasubstituted chiral carbons have been stereospecifically produced from 3-substituted-2-ene-1,7-diols (Eqs. (81)–(84)) [62].

(81)

(82)

(83)

(84)

Similar observations concerning the chirality transfer have been made for the diastereoselective synthesis of tetrahydrofurans and oxepans from 2-ene-1,6-diols and 2-ene-1,8-diols (Eqs. (85) and (86)). The synthesis, in high yields, of oxepans has however required the use of PhMe instead of THF as solvent, and the increase of the catalyst loading [59].

(85)

(86)

In the course of the synthesis of (−)-laulimalide, Uenishi and Ohmi have carried out the Pd^{II}-catalyzed diastereoselective 6-*exo-trig* cyclization shown in Eq. (87) [20]. The substrate being a 2,5-diene,1,7-diol, two different 6-*exo-trig* cyclizations could occur. According to the experimental result, only that involving the addition of the primary alcohol was observed. Since the substitution of the two C=C bonds of the substrate are different, it remains not obvious to determine the origin of the selectivity: preference in the Pd/C=C coordination, or higher reactivity of the primary alcohol? On whatever reason, it has to be noted that these experimental conditions were more effective than those using the corresponding allylic carbonate as the substrate under Pd^0 catalysis (Eq. (25)).

(87)

The total synthesis of (−)-diospongins A and B has required the use of 2-ene-1,5,7-triols having secondary the three hydroxy. As shown from the results depicted in Eqs. (88)–(90), the allylic hydroxy is, once more, responsible of the diastereoselection [63].

(88)

(89)

(90)

Sinou and co-workers have also studied the Pd^{II}-catalyzed cyclization of unsaturated triols but their substrates were achirals with two hydroxymethyl substituents on the same carbon and the third hydroxy also primary (Eq. (91)) [29,64]. In accordance with Uenishi's proposal, these cyclizations would occur from Wacker-type reactions of π-complexes 14A and 14B, which are in equilibrium (Scheme 14). These intermediates undergo concurrent *exo-trig* and *endo-trig* cyclizations leading to σ-complexes 14C and 14D, respectively. Elimination of HOPdCl from 14C provides the monoheterocycle. Successive β-H elimination/addition of HPdCl/β-H elimination from 14D afford 14E, the acidity of the reactive mixture mediating its cyclisation into the dioxabicyclo compound. In agreement with this proposal, this latter compound was not obtained when the reaction was performed in the presence of 2 equiv. of NEt_3 per palladium. It has also been noted that switching to $Pd(OAc)_2$ as the catalyst instead of $PdCl_2(MeCN)_2$ gave a very low yield.

	n = 1, THF, %:	29	3	68
	n = 1, MeOH, %:	33	30	30
R = Bn	n = 1, MeCN, %:	40	46	13
	n = 2, THF, %:	31	41	23
	n = 3, THF, %:	39	50	0
R = PhCH=CHCH₂, n = 1, THF, %:		60	15	19
R = Et, n = 1, THF, %:		37	14	46

(91)

3.1.3. Silane as the leaving group

Mascári and Szabó have reported cyclizations of hydroxyalkyl-tethered allylic silanes, which in contrast to the above Pd^{II}-catalyzed reactions, occur through η^3-allylpalladium complexes, and, moreover, require reoxidants (Eq. (92) and Scheme 15) [65,66]. These reactions were carried out using either $PdCl_2$ and $CuCl_2$ in *i*-PrOH, or $Pd(OAc)_2$, benzoquinone and H_3PO_4 in CH_2Cl_2/MeOH [67], the latter conditions raising the reaction time and decreasing the yield. The alcoholic solvent facilitates the palladadesilylation step, in leading to alkylsiloxanes. The reoxidants have a dual role since i) the rate of the formation of the allylpalladium complex depends on the chloride ion concentration, and ii) both $CuCl_2$ and benzoquinone [68] can be activating agents of the allylpalladium towards nucleophilic attack [65]. It seems interesting to point out that the nucleophilic attack by the internal hydroxyl was much faster than that by the external alcohol.

$R^1 = R^2 = R^4 = H, R^3 = CH_2OH$; 25 °C, 1.5 h: 86%
$R^1 = Ph, R^2 = R^3 = R^4 = H$; 40 °C, 1.5 h: 69%
$R^1 = R^2 = Ph, R^3 = R^4 = H$; 40 °C, 2.5 h: 60%
$R^1 = R^2 = Ph, R^3 = H, R^4 = C_5H_{11}$; 40 °C, 2.5 h: 81%

(92)

Scheme 14. Competition between *exo-trig* and *endo-trig* cyclizations.

Scheme 15. Intermediate η^3-allylpalladium complexes from hydroxyalkyl-tethered allylic silanes.

3.2. Without cleavage of the leaving group

The Pd^{II}-catalyzed cyclization without cleavage of the leaving group requires the presence of oxidants to regenerate active catalytic species.

3.2.1. In the presence of oxidants

In 2005, Gracza and co-workers reported the synthesis of the enantiomerically pure 1,4:2,5-dianhydro-3-*O*-benzyl-D-lyxitol from the Pd^{II}-catalyzed cyclization of a 1:1 diastereoisomeric mixture of the diol depicted in Eq. (93). The configuration of the new stereocentre is governed by that of the homoallylic hydroxyl group (Scheme 16), while the C$_2$-symmetry of the obtained bicyclic leads to the degeneration of the initial allylic stereogenic center [69]. The reaction proceeds at room temperature, in AcOH with AcONa as a buffer, via the intramolecular nucleophilic attack of the terminal hydroxy to the π-complex 16A, leading to 16B. According to the authors, 16B evolves to the oxapalladacycle 16C. Reductive elimination from 16C delivers the bicyclic compound and Pd^0 which is reoxidized with CuCl$_2$. The replacement of CuCl$_2$ for benzoquinone has a detrimental effect [70]. This type of cyclization has been then carried out using a range of polyols (Eq. (94)) [70] and for the synthesis of (+)-varitriol from dimethyl L-tartrate [71].

$$PdCl_2 \text{ (0.075 equiv.)}$$
$$CuCl_2 \text{ (3 equiv.)}$$
$$AcONa \text{ (3 equiv.)}$$
$$\xrightarrow{\quad AcOH, \text{ rt, } 12 \text{ h} \quad}$$

dr = 1:1   79%

(93)

Scheme 16. Degeneration of the initial allylic stereogenic center.

$$PdCl_2 \text{ (0.1 equiv.)}$$
$$CuCl_2 \text{ (3 equiv.)}$$
$$AcONa \text{ (3 equiv.)}$$
$$\xrightarrow{\quad AcOH \quad rt, 44 \text{ h} \quad}$$

43%

(94)

In the presence of copper chloride, oxygen, water and catalytic amounts of palladium chloride, Sharma et al. obtained ketals from γ,δ-olefinic alcohols having an allylic OR group (Eqs. (95) and (96)) [72]. Given the experimental conditions and the results, two Wacker reactions, the first one being intramolecular and the second intermolecular, would be involved. As shown in Scheme 17, the reoxidation system plays a part only in the intramolecular reaction. Under rather similar conditions, Kadouri-Puchot and co-workers have recently synthesized the unichiral bicyclic oxazolidines shown in Eqs. (97) and (98) [73]. The epimerization observed from the substrate having a *cis* relationship of the Ph and OMe substituents (Eq. (98)) could be due to a first cyclization through an aza-Wacker reaction with a reversible β-H elimination involving the hydrogen geminated to the OMe group. The second cyclization could occur through a Wacker reaction, an imminium ion as intermediate has been however postulated [73].

$$PdCl_2 \text{ (0.1 equiv.)}$$
$$CuCl \text{ (1 equiv.)}$$
$$O_2 \text{ bubbling}$$
$$MeCN/H_2O \text{ (7:1)}$$
$$rt, 0.5\text{-}2 \text{ h}$$

R = H, Me, C_5H_{11} >75%

(95)

$$PdCl_2 \text{ (0.1 equiv.)}$$
$$CuCl \text{ (1 equiv.)}$$
$$O_2 \text{ bubbling}$$
$$MeCN/H_2O \text{ (7:1)}$$
$$rt, 0.5\text{-}2 \text{ h}$$
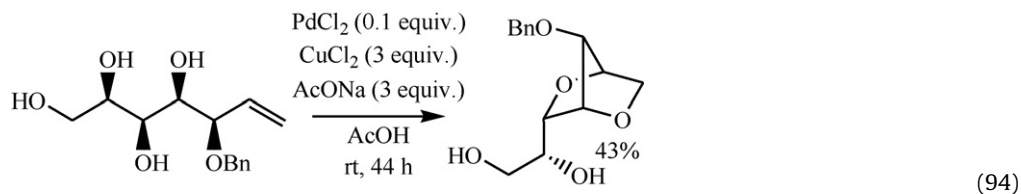
>75%

(96)
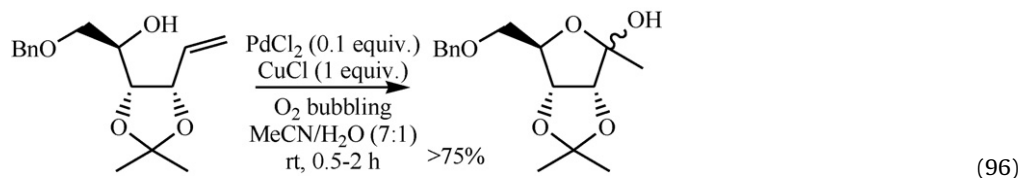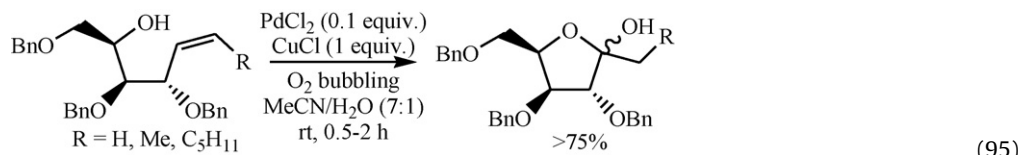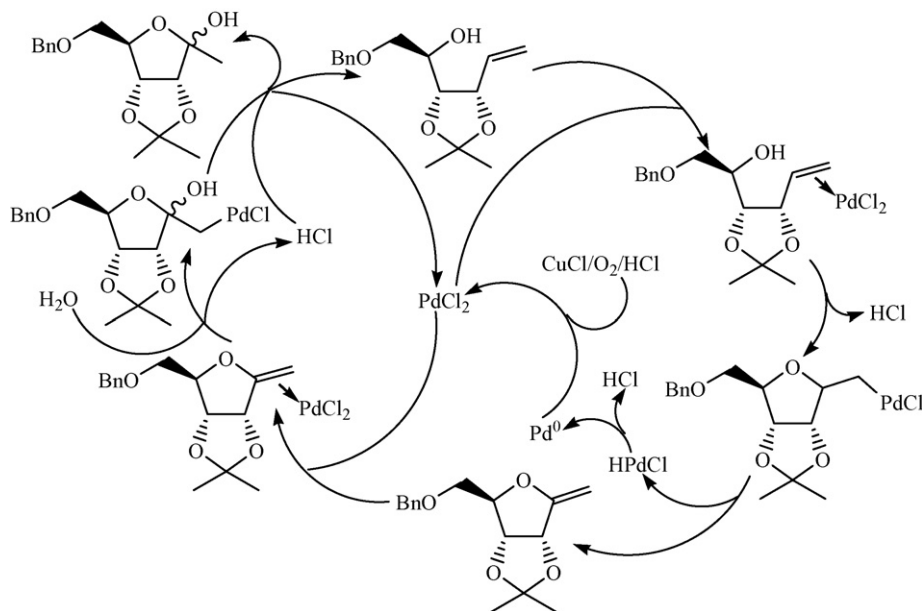
Scheme 17. The successive intra- and intermolecular Wacker reactions.

(97)

(98)
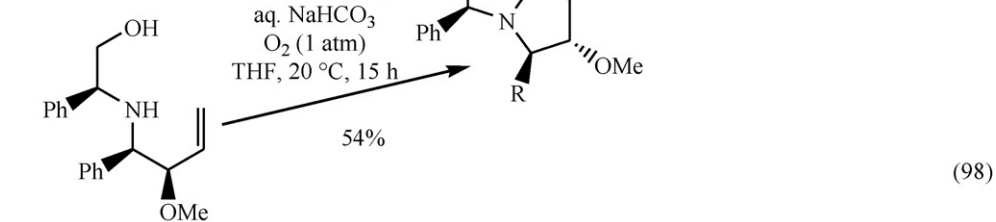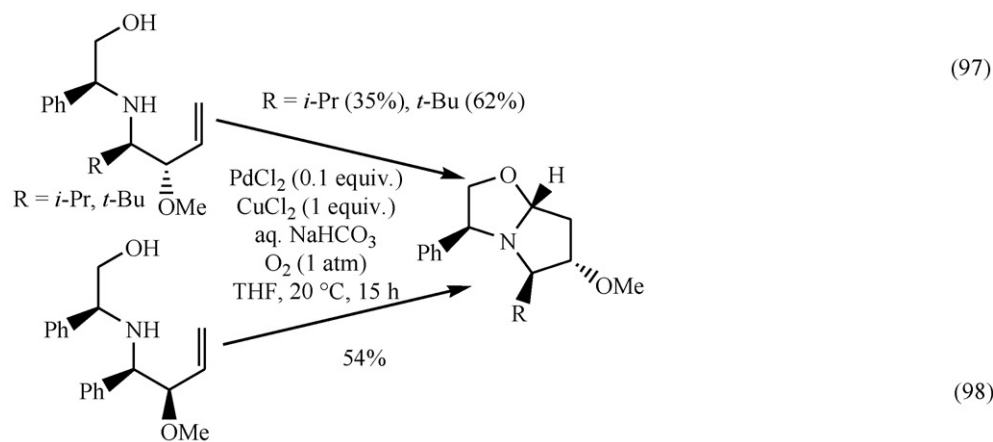
3.2.2. In the presence of oxidants and carbon oxide

The Pd intermediate produced from the Wacker addition of a hydroxyl to a C=C bond can react with carbon oxide to afford an acyl-palladium complex (Schemes 1 and 2, paths e), intramolecular trapping of this latter by an oxygenated species leading to the lactone. The literature contains a plethora of such reactions from allylic alcohols substituted with a hydroxylated tether. The present review is limited to the recent reports [74].

Gracza and co-workers have disclosed further oxycarbonylative annulations in AcOH, either diastereoselective [70,75] or enantioselective [75], using CuCl$_2$ (Eq. (99)) or benzoquinone (Eq. (100)) as reoxidant. The method has been investigated for the kinetic resolution of pent-4-ene-1,3-diol through its asymmetric oxycarbonylative bicyclization and a conversion controlled by the amount of benzoquinone. Besides the chiral ligand, the efficiency depends on the anionic part of the catalyst and the solvent. Under optimum conditions, the lactone was isolated in 29% yield and 62% ee (Eq. (101)) [76]. It should be noted that, contrary to CuCl$_2$, the regeneration of the active Pd^{II} species with benzoquinone are carried out in the absence of AcONa [75,76].

(99)

Pd(OCOCF$_3$)$_2$
(0.05 equiv.)
(0.15 equiv.)
i-Pr   i-Pr

benzoquinone (4 equiv.)
CO (balloon)
AcOH/CH$_2$Cl$_2$ (1:8), 20 °C, 4 d

79%, 7% ee OBn

(100)

Pd(OAc)$_2$
(0.025 equiv.)

(0.075 equiv.)

benzoquinone (0.5 equiv.)
CO (balloon)   50% conversion   29% yield
AcOH, 18 °C, 30 h   62% ee

(101)
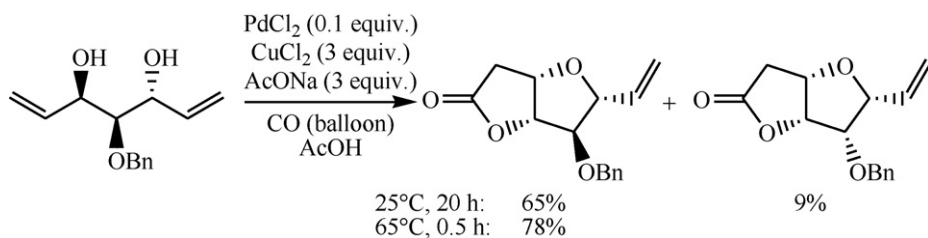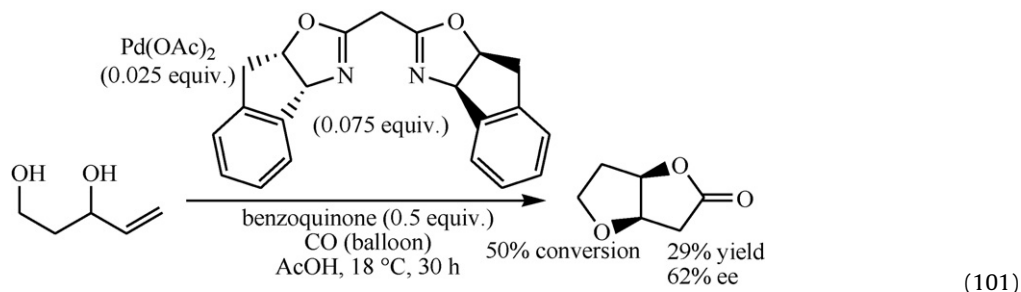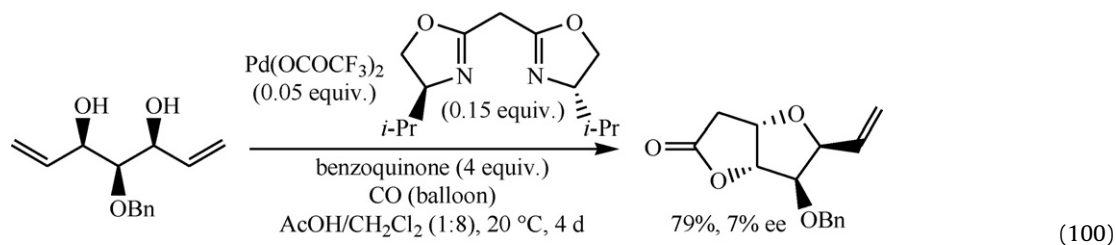
Semmelhack's team, who has firstly reported an approach to the synthesis of plakortones using stoichiometric amounts of Pd(OAc)$_2$ [77], has established the corresponding viable synthetic route under catalytic conditions (Eq. (102)) [78]. Recently, the procedure has been adopted by Nesbitt and McErlean to prepare intermediates leading to 2,5-disubstituted-3-oxygenated tetrahydrofurans [79] and (+)-kumausallene [80].

PdCl$_2$ (0.1 equiv.)
CuCl$_2$ (3 equiv.)
AcONa (3 equiv.)
CO (1 atm)
AcOH, 23 °C, 24 h   75%

(102)
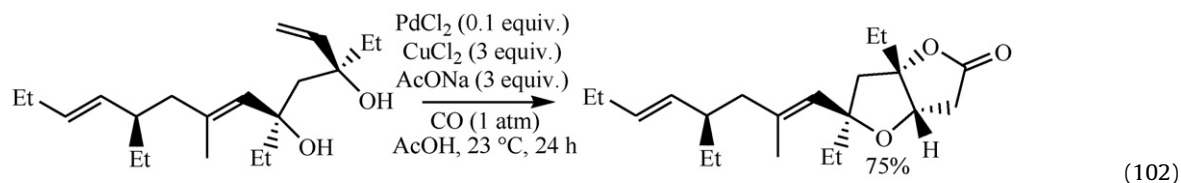
Approaching the synthesis of micrandilactone A, Yang and co-workers have used thiourea as ligand for the Pd-catalyzed alkoxycarbonylative annulation of the highly functionalized substrate depicted in Eq. (103) [81]. The unexpected formation of the chloro adduct shown in Eq. (104) was observed as the main product when the substrate contains an intracyclic C=C bond instead of the epoxide.

Pd(OAc)$_2$ (0.3 equiv.)
thiourea A (0.3 equiv.)
CuCl$_2$ (3 equiv.)
CO (1 atm)
THF, 70 °C, 8 h   95%

thiourea A:

(103)

Pd(OAc)$_2$ (0.1 equiv.)
thiourea A (0.1 equiv.)
CuCl$_2$ (2.5 equiv.)
CO (1 atm)
THF, 50 °C, 18 h

25%   +   30%

(104)
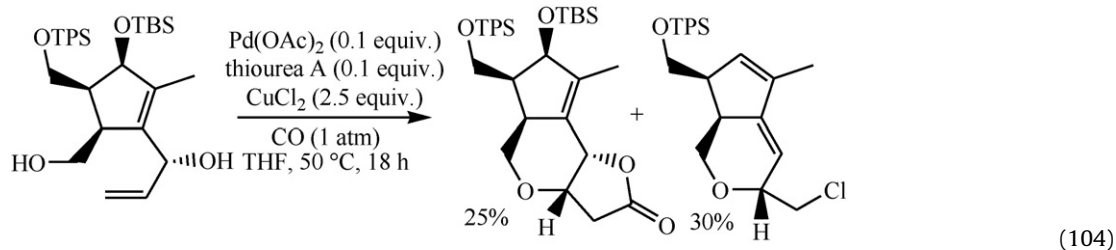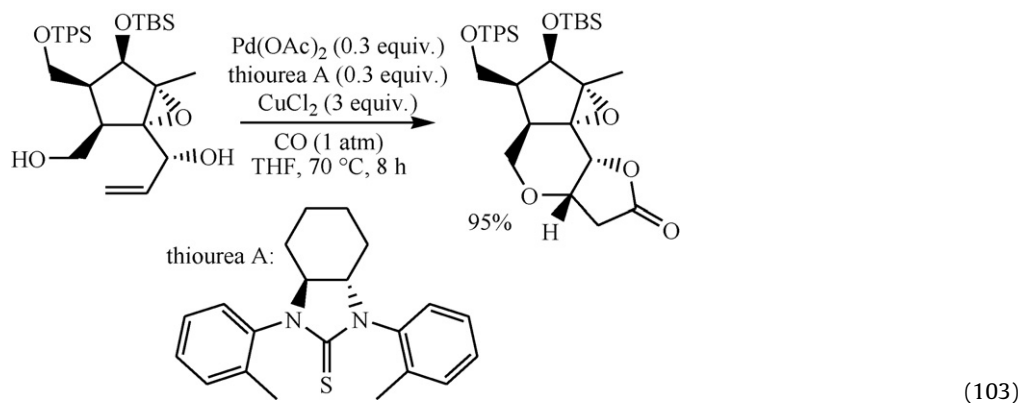
Yang's team has also investigated various experimental conditions to improve the bis-annulation, catalyzed by the Pd(OAc)$_2$/1,1,3,3-tetramethylthiourea system, of 1-(2-(hydroxymethyl)phenyl)prop-2-en-1-ol; efficient process was achieved with both propylene oxide and ammonium acetate as additives (Eq. (105)) [82]. Switching from Pd(OAc)$_2$ to PdCl$_2$, PdI$_2$, [ClPd(η^3-allyl)]$_2$ or, in particular, PdCl$_2$(PPh$_3$)$_2$ to carry out this reaction decreased the yields [83]. The formation of the different products can be explained as shown in Scheme 18 which is inspired from the one published by Yang and co-workers [82]. The key step is the generation of complex 18A which can lead to the allylic chloride via an intra or intermolecular reaction (paths a and b respectively). The absence of such a compound in the presence of propylene oxide suggests, in fact, an intermolecular reaction. The formation of the bicyclic and tricyclic compounds has been explained via

intermediate 18C. Carbonylation of 18C would lead to 18D, reductive elimination of PdL$_n$ from which would deliver the lactone. It should be noted that the proposal of 18C is reminiscent of intermediate 16C (Scheme 16). According to Scheme 1, path *e*, carbonylation of 18B is, however, also a possible reactive pathway [84]. As for the bicyclic product, instead of the 18C → 18E step, a β-H elimination from 18B could lead to HPdClL$_n$ and an allylic alcohol, the isomerization of which giving the carbonyl unit [85,86]. The method has been used for the synthesis of a wide range of fused pyran-γ-lactones in fair to high yields (Eq. (106)) [83]. It is worth mentioning that no oxidation of the benzylic hydroxy groups was observed [87], the favorite reaction of these substrates being the intramolecular Wacker process.

(105)

Scheme 18. Possible evolutions of 1-(2-(hydroxymethyl)phenyl)prop-2-en-1-ol.

R^1 = R^2 = H, R^3 = Et:	70%	23%
R^1 = R^2 = H, R^3 = Me:	69%	21%
R^1 = Me, R^2 = R^3 = H:	62%	9%
R^1 = CH=CH$_2$, R^2 = R^3 = H:	30%	16%
R^1 = R^2 = R^3 = Me:	48%	34%

(106)
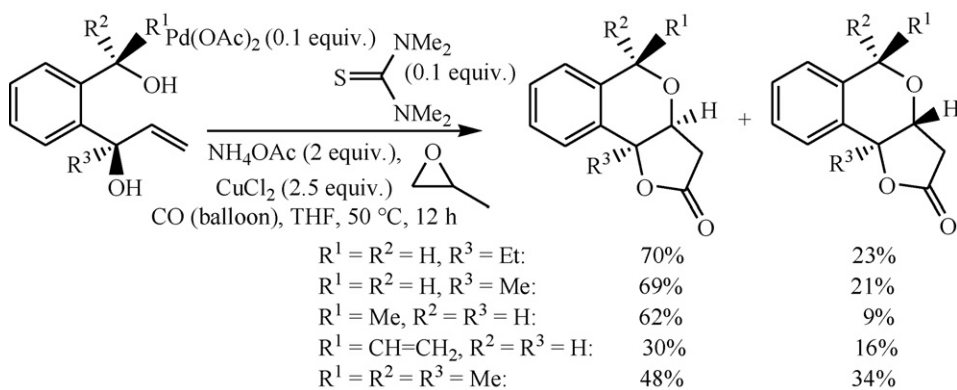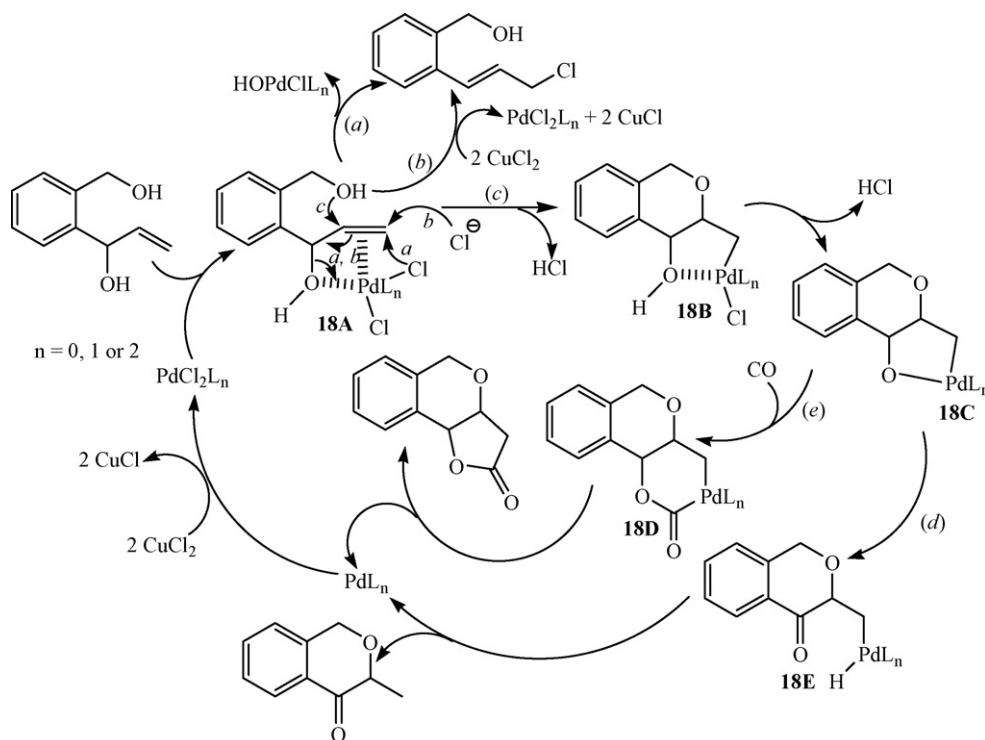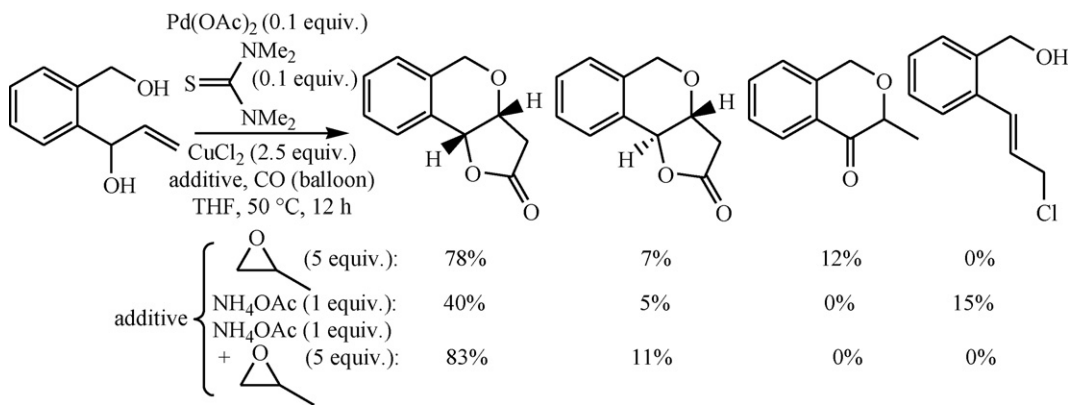
4. Conclusions

Since the discovery in 1983 of the formation, under Pd^0 catalysis, of 2-alkenyltetrahydrofurans(pyrans) from allylic esters substituted with a hydroxyalkyl chain [7,8], a variety of oxaheterocycles has been synthesized using procedures inspired by the original publications. These reactions involving η^3-allylpalladium complexes as intermediates, their application to the synthesis of natural compounds has benefited from the emergence of efficient chiral ligands. The potential of substrates having both an allylic OR group (mainly those with an allylic hydroxy) and a hydroxylated tether has been increased with the report, in 1992 [56], of their possible diastereoselective heterocyclizations in the presence of Pd^{II} catalysts, these reaction occurring with or without cleavage of the OR substituent. Moreover, the above substrates can react under carbon dioxide or carbon oxide, leading to another range of synthetic possibilities.

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