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Review

Heterocyclic synthesis by the use of the oxidizing potential of palladium(II)

Yoshinao Tamaru* and Zen-ichi Yoshida

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606 (Japan)

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Abstract

This is a review of the palladium(II)-catalyzed cyclization of unsaturated alcohols, amines, and carboxylic acids, and comprises the intramolecular oxycarbonylation of 4-penten-1,3-diols (giving *cis*-3-hydroxytetrahydrofuran-2-acetic acid lactones), carboxycarbonylation of 3-hydroxy-4-pentenoic acids (giving *cis*-3-hydroxy-γ-butyrolactone-4-acetic acid lactones), aminocarbonylation of 3-hydroxy-4-pentenylamines (giving *cis*-3-hydroxypyrrolidine-2-acetic acid lactones), intramolecular di-carbonylation of homoallyl alcohols (giving γ-butyrolactone-2-acetic acid esters), 1,1-aryletherification of unsaturated alcohols (giving 2-aryl substituted 5-, 6-, 7-, and 8-membered oxygen heterocycles), and 1,1-arylamination of unsaturated amines (giving 2-aryl substituted 5- and 6-membered nitrogen heterocycles).

Introduction

From a synthetic viewpoint, palladium has been recognized as one of the most important and useful transition metals. Of the Pd-catalyzed reactions, mostly the Pd^0 catalyzed reactions have been developed in recent years and those catalyzed by Pd^{II} seem to have fallen behind. Pd^{II}-catalyzed molecular rearrangement is one of the important examples of newly developed methodologies [1]. In these Pd^0- and Pd^{II}- catalyzed reactions, the catalysts are usually regenerated after completion of the reactions, and hence these reactions are not accompanied by a change in oxidation level of substrates. As typified by the Wacker reaction, Pd^{II} is able to oxidize substrates by its own reduction to Pd^0. This type of reaction is stoichiometric with respect to palladium and so it is necessary to reoxidize Pd^0 to Pd^{II} with suitable oxidants to maintain the catalytic cycle. Despite its high inherent potential for multifunctionalization of substrates, this type of Pd^{II}-catalyzed reaction has not received much attention [2], probably owing to the anticipated incompatibility of functionalized substrates and/or products with the re-oxidation conditions and the small turn-over number of the catalytic cycles.

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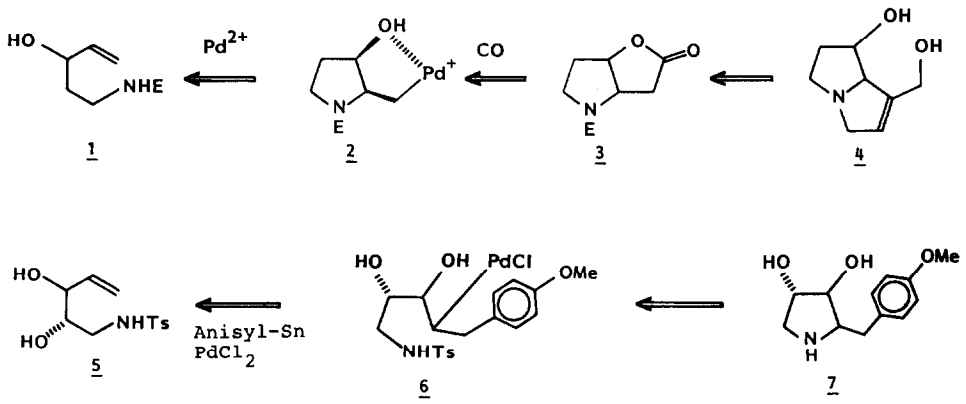
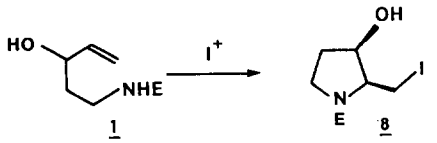


Scheme 1

In this review, our work for the past 3 years, which was focused on developing new methodologies utilizing the oxidizing potential of Pd^{II} (Scheme 1) is described. Our main concern was to find out how we could functionalize the Pd–C bonds formed in the Wacker (or Hegedus) aminopalladation, and Heck arylpalladation reactions. If the Pd–C bond of **2** could be carbonylated, and if the Pd of **6** could be displaced with amine, these reactions could open a very facile route to pyrrolidine alkaloid syntheses (e.g., retronecine **4**, anisomycin **7**).

Carbonylation of Wacker intermediates

Before beginning the study outlined in Scheme 1, we knew that 3-hydroxy-4-pentenylamines **1**, by treatment with I_2, stereoselectively cyclize to give *cis*-3-hydroxy-2-iodomethylpyrrolidines (**8**) (eq. 1) [3]. The stereoselective cyclization is general for other substrates. For example, 3-hydroxy-4-pentenoylamides [4] and 3-hydroxy-4-pentenols [5] were converted to *cis*-3-hydroxy-4-iodomethyl-γ-butyrolactones and *cis*-2-iodomethyl-3-hydroxytetrahydrofurans, respectively. The *cis* selectivity is generally more than 95%. The Pd^{II}-assisted or -catalyzed intramolecular amination of olefin has been developed by Hegedus [2] (eq. 2). However, the Pd–C bond (e.g., **9**) has the propensity for undergoing a dehydropalladation to give **10** and/or its double bond regioisomers. Hence, to achieve carbonylation, very specific conditions seem to be required [6]. Thus the expected reaction sequence starting with **1** and leading to **3** is: (i) Pd^{II} serves as an electrophile for the cyclization of **1** and selectively provides *cis*-2-pallado-methyl-3-hydroxypyrrolidine (**2**) just like the iodonium ion does in eq. 1, (ii) the 3-hydroxy group coordinates to Pd^{II} and prevents a dehydropalladation by forming a five-membered ring [7], and (iii) the *cis* configuration of the 2-palladomethyl and 3-hydroxyl groups in the pyrrolidine ring probably facilitates the carbonylation and also the intramolecular esterification to give the γ-lactone **3**. This mechanism was confirmed and the intramolecular double cyclization of **1** proceeded smoothly to give the expected product **3** in respectable yield (90% isolated) under very mild conditions and by a convenient procedure (0.1 equiv. of $PdCl_2$, 1 atm of CO in acetic acid containing 3 equiv. of NaOAc and 3 equiv. of $CuCl_2$, at room temperature for 1 d) [8]. The reaction was best when



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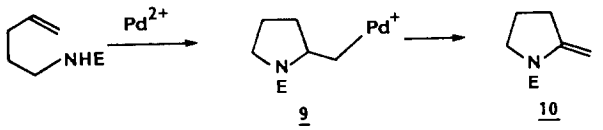
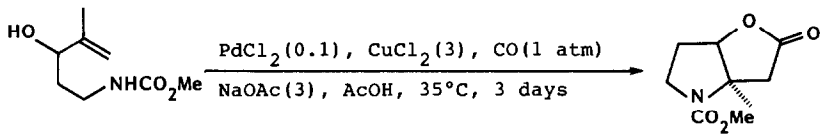
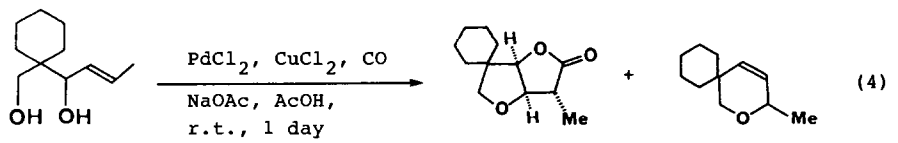


9 10 (2)



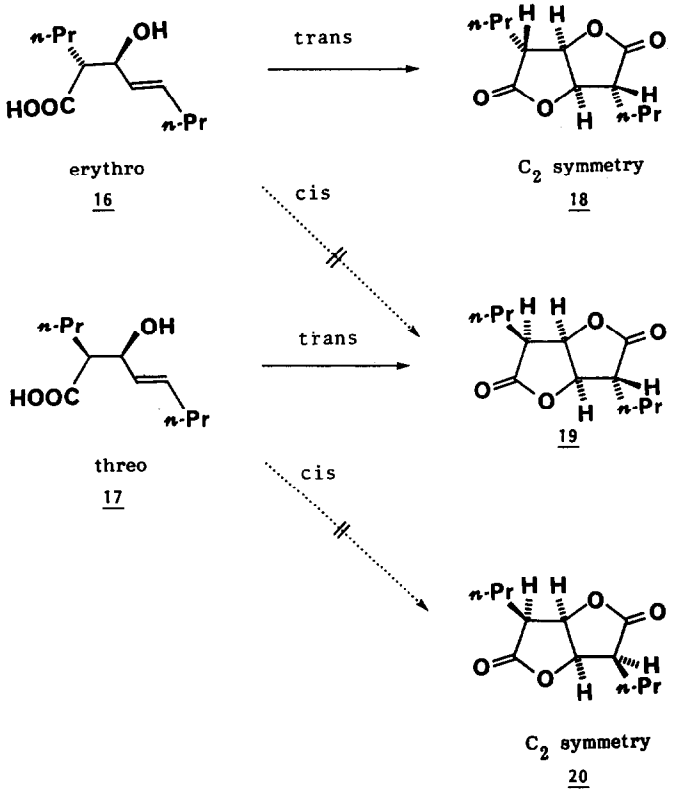
11 12 (80%, 35% conv) (3)



13 14 (24%) 15 (37%) (4)

conducted in acetic acid. When carried out in methanol, *N*-*p*-toluenesulfonyltetrahydropyridine was produced in addition to **3** in almost equal amounts. It should be noted that the Pd–C bond of **2** is not affected by protonolysis with acetic acid or by oxidation with $CuCl_2$.

Under similar conditions, 3-hydroxy-4-pentenols and 3-hydroxy-4-pentenoic acids undergo similar intramolecular double cyclizations, to give *cis*-3 hydroxytetrahydrofuran-2-acetic acid lactones (e.g., **14**, eq. 4) [9] and bis-lactones (e.g., **18** and **19**, Scheme 2) [10], respectively. All these reactions tolerate substitution on the sp^3 carbons (C(1)–C(3)), though slight differences in reactivity between the two diastereomeric pairs have been noted. However, as is normal for Pd^{II}-catalyzed reactions, they are subject to some restrictions on the cyclization of the substrates with substituents on the olefinic carbons (C(4) and C(5)). General trends are summarized in Table 1. The amine nucleophile is restricted the most. For C(4)-substituted substrates an amine nucleophile, when protected as a urethane, barely undergoes the cyclization (eq. 3), whereas the corresponding tosylamide does not undergo cyclization at all. The C(5) substituted derivatives are totally unreactive, irrespective of the type of protecting groups and reaction conditions. The carboxyl nucleophile, on the other hand, enjoys the widest applicability and undergoes



Scheme 2

cyclization both for the C(4) and C(5) substituted derivatives (Scheme 2). The reactivity of the hydroxyl nucleophile lies between that of the amine and that of the carboxyl nucleophiles. Thus the C(5) substituted diol **13** does give the expected lactone **14** in low yield, however, dihydropyran **15** is the main product (eq. 4). In accordance with the trend shown in Table 1, the cyclization of hydroxyl and carboxyl nucleophiles attains completion when reduced amounts of $PdCl_2$ are used (0.01 equiv. to substrates).

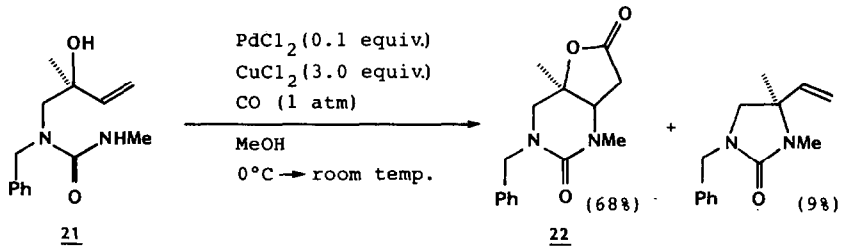
The present cyclization consists of two stereospecific processes. One is the stereospecific cyclization which yields *cis*-fused bicyclo[3.3.0] systems and the other

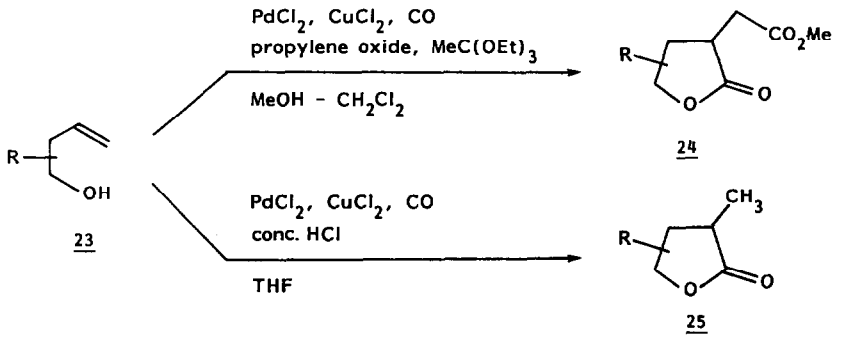
Table 1

Reactivity of heteronucleophiles toward the C(4)- and C(5)-substituted 3-hydroxy-4-pentenyl system

Nucleophile	Substituent	
	C(4)	C(5)
NH	○ [a] (as urethane)	× [b]
OH	○	△ [c]
CO_2H	○	○

[a] ○ reactive. [b] × unreactive. [c] △ intermediate.





is a stereospecific addition of nucleophile and CO at the double bond. The latter was verified by the stereospecific transformation of *erythro*- (**16**) and *threo-trans*-2-n-propyl-3-hydoxy-4-noneic acids (**17**) to the bis-lactone (**18**) with C_2-symmetry and the bis-lactone (**19**) with C_1-symmetry, respectively (Scheme II).

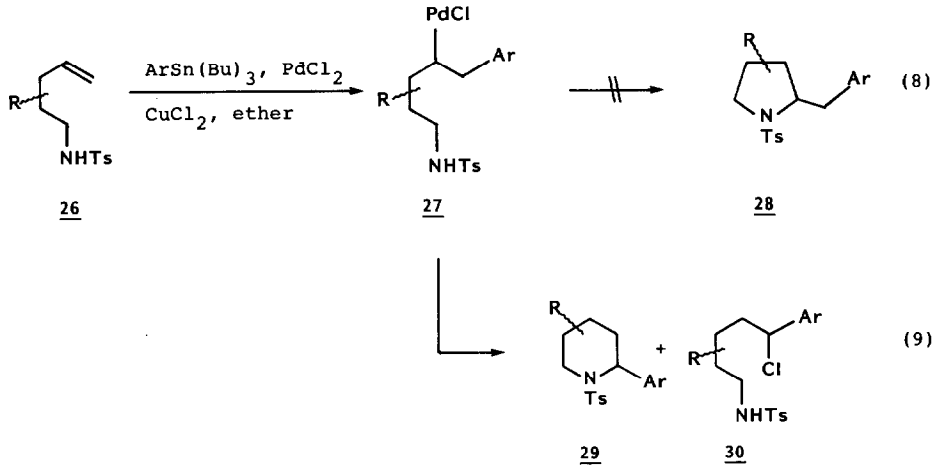
Variations of these cyclizations, typified by the reactions shown in eqs. 5 [11] and 6 [12] have been developed. Reaction 5 is of interest because of the following points:
(1) Urea serves as an *N*-nucleophile. This is the first example which shows that urea can be used for the Pd^{II} catalyzed amination of olefins. Urea is an ambident nucleophile and generally serves as an oxygen nucleophile toward alkylation agents to form *O*-alkyl isoureas [13].
(2) Even for the construction of a bicyclo[4.3.0] system, the high *cis* cyclization selectivity holds.
(3) *N*-allylureas undergo similar aminocarbonylation and lead to five-membered ureas.

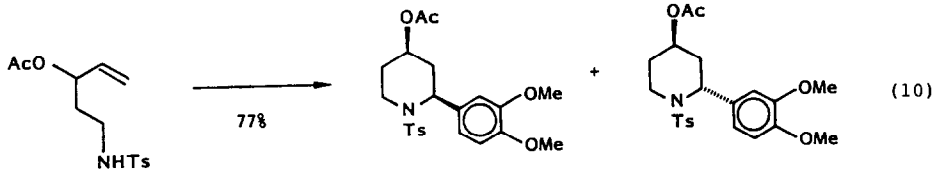
Intramolecular oxycarbonylation of 4-pentenols and 5-hexanols proceeds as shown in eq. 4, reported by Semmelhack [14] and yields tetrahydrofuran-2-acetic acid esters and tetrahydropyran-2-acetic acid esters, respectively. 3-Butenols (**23**), however, do not undergo this cyclization, instead they give the di-carbonylation products, γ-butyrolacetone-2-acetic acid esters (**24**) in good yields [12] (eq. 6). This reaction is similar to the hydrocarbonylation of 3-butenols (reported by Alper [15] (eq. 7) and also to the intermolecular di-carbonylation of olefins reported by Stille [16]. Although the reaction mechanism of Alper's or our reaction is not clear at present, comparison of the optimized conditions is quite interesting. For Alper's reaction, conc. HCl is essential, Stille's di-carbonylation proceeds best under basic conditions, on the other hand, our reaction requires neutral conditions, which are

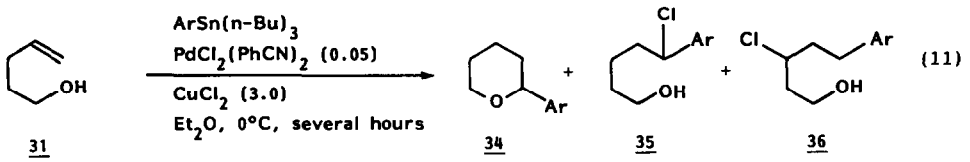
maintained by the use of 3–5 equiv. of propylene oxide. Yields of **24** are greatly improved when the reaction is carried out in the presence of ethyl orthoacetate, which presumably works as a drying agent. Thus γ-butyrolactone-2-acetic acid methyl ester was isolated in 72% yield by treatment of 3-butenol with 0.01 equiv. of $PdCl_2$, 3.0 equiv. of $CuCl_2$, 4 equiv. of propylene oxide, and 0.2 equiv. of ethyl orthoacetate in a methanol/CH_2Cl_2 solvent mixture under 1 atm of CO at room temperature for 6 d.

Nucleophilic substitution of Heck's intermediates

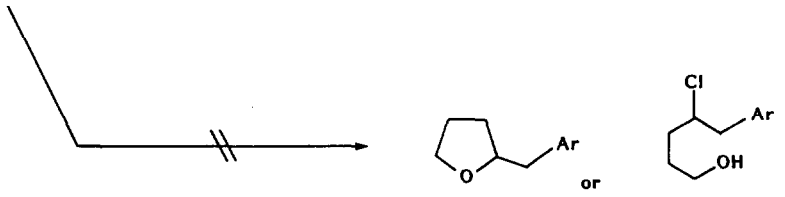
That intramolecular displacement of Pd in Heck's intermediates by heteroatoms could be a useful route to heterocyclic complexes (Scheme 1), has been demonstrated by Horino [17] and Larock [18] for the synthesis of oxygen heterocycles via vicinal oxyarylation of olefins. However, the displacement reaction (**6** → **7**) did not proceed in the expected manner. In our system, no 2-arylmethylpyrrolidines (**28**) were obtained (eq. 8). Instead, only 2-arylpirperidines (**29**) were obtained in ca. 70% yields when arylation was carried out with aryltins with electron-donating substituents on the aromatic ring (e.g., tri-n-butyl(4-methoxyphenyl)tin and tri-n-butyl(3,4-dimethoxyphenyl)tin) (eq. 9). Arylation with tri-n-butyl(phenyl)tin, on the





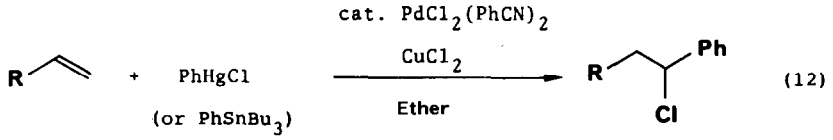


31 34 35 36

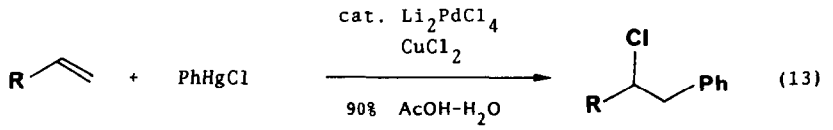


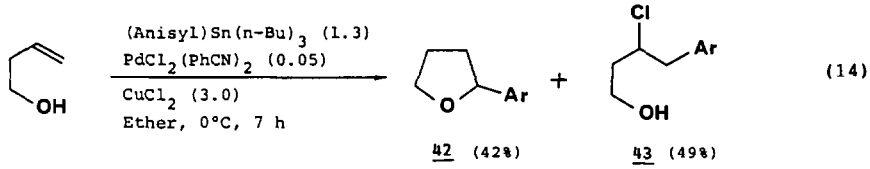
32 33

1,1-Arylchlorination

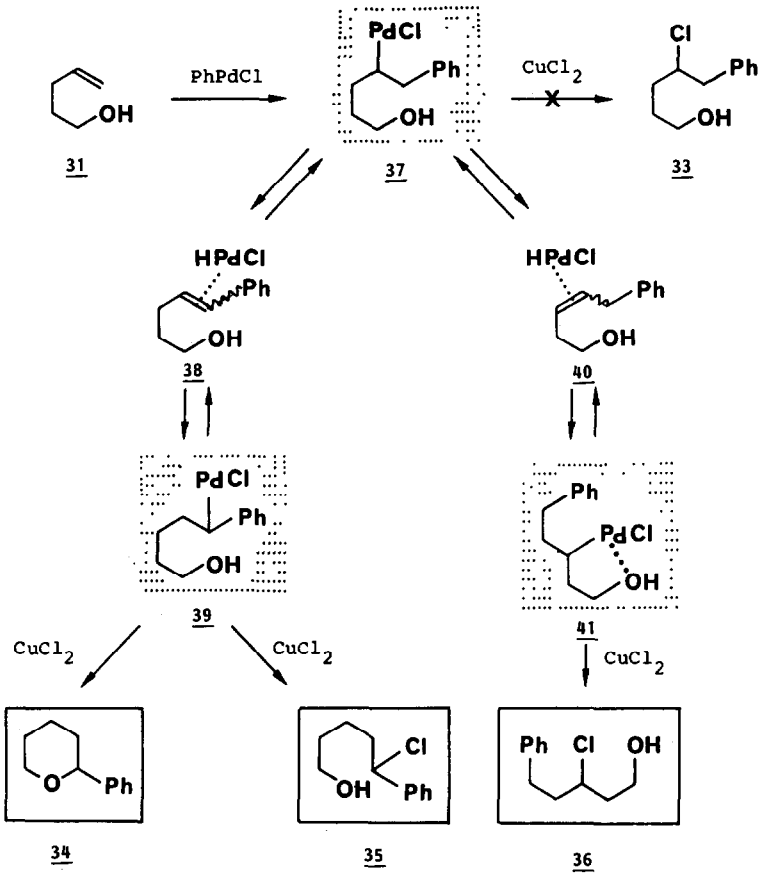


1,2-Arylchlorination (Heck Reaction)





42 (42%) 43 (49%)

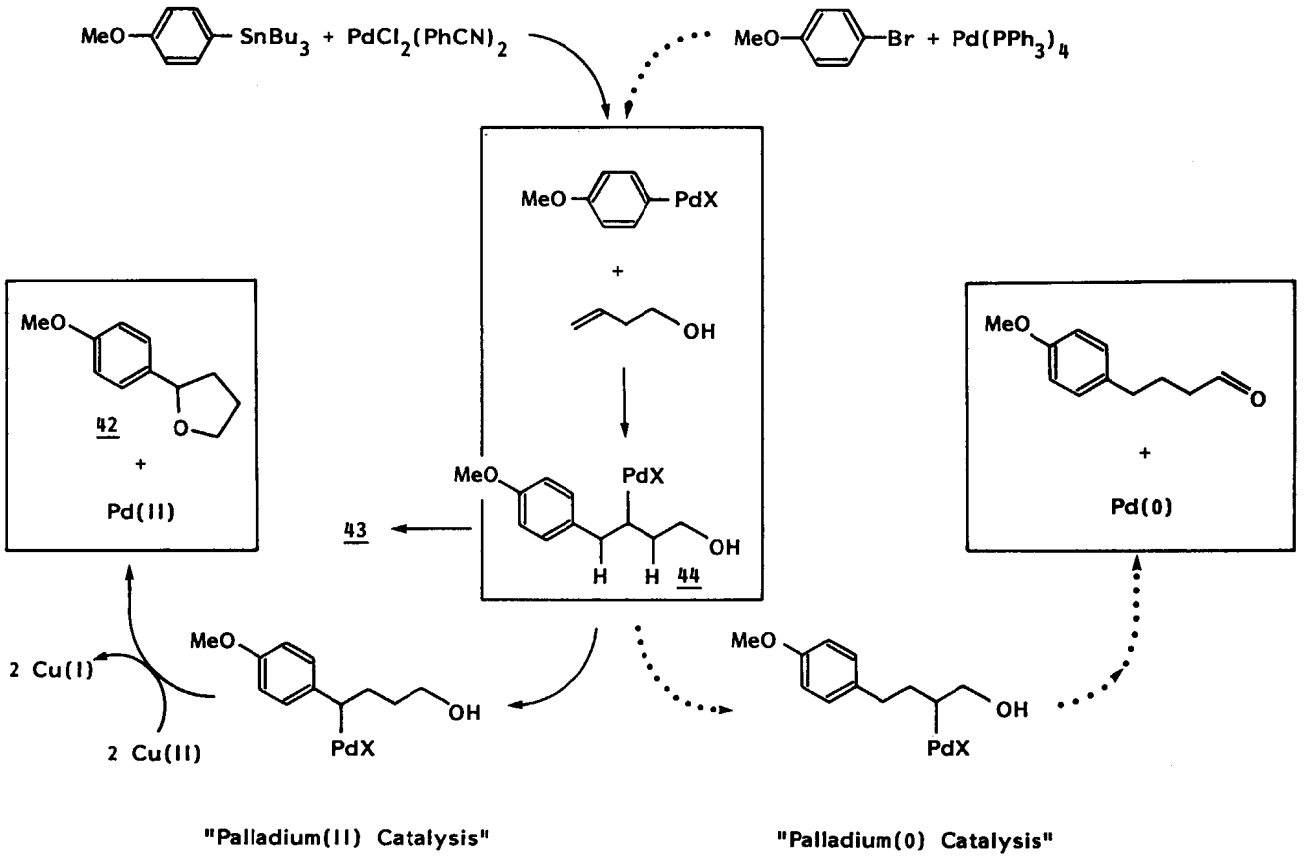


Scheme 3

other hand, selectively gives 5-phenyl-5-chloropentylamines (**30**) in ca. 70% yields [19]. 3-Butenylamines were similarly arylaminated at the terminal position, providing 2-arylpyrrolidines in 60–80% yields. Substituents at C(1)–C(3) do not affect the regioselectivity (e.g., eq. 10).

Similar behaviour is found in the arylation of unsaturated alcohols [20]. 4-Pentenols, upon arylation with tri-n-butyl(4-methoxyphenyl)tin, were selectively converted to 1,1-aryletherification products **34** (eq. 11). Upon arylation with tri-n-butyl(phenyl)tin, 1,1- (**35**) and 1,3-arylchlorination products (**36**) were isolated as the major products together with **34**. Furthermore, in these cases neither 1,2-aryletherification **32** nor 1,2-arylchlorination products **33** were detected. These results can be summarized as the 1,1- and 1,3-regioselective difunctionalization of olefin, and are in marked contrast to Heck's 1,2-arylchlorination [21] (eq. 13) and Horino and Larock's 1,2-oxyarylation [22*]. The unique regioselectivity is not confined to unsaturated amines and alcohols, but seems to be general for terminal olefins. For example, 1-octene was cleanly converted to 1-phenyl-1-chlorooctane by

* This and other references marked with an asterisk indicates a note occurring in the list of references.


MeO
SnBu3 + PdCl2(PhCN)2
MeO
Br + Pd(PPh3)4
MeO
PdX
+
OH
MeO
42
O
+
Pd(II)
43
MeO
PdX
OH
H H 44
MeO
O
+
Pd(0)
2 Cu(I)
2 Cu(II)
MeO
OH
PdX
MeO
OH
PdX
"Palladium(II) Catalysis"
"Palladium(0) Catalysis"

Scheme 4

arylchlorination either with tri-n-butyl(phenyl)tin or with phenylmercuric chloride (eq. 12). The essential difference between the reaction conditions specified by Heck and those specified by us, (eqs. 12 and 13) lies in the reaction media employed, 90% acetic acid compared to diethyl ether.

The mechanism of the Pd–C bond cleavage is still controversial [2]; however, on the assumption that the Pd–C bond dissociates heterolytically leaving a carbocation [17], then the above 1,1-, 1,2- and 1,3-difunctionalization could follow Scheme 3. The primary intermediate **37** equilibrates with intermediates **39** and **41** via a series of elimination-additions by HPdX. Further equilibria forming intermediates where Pd is closer than the γ-position to the hydroxy group might be restricted, because in the cyclic intermediate **41**, the endo methylene carbon β to Pd does not bear the hydrogen *syn* to the Pd–C bond. In intermediate **39**, intramolecular nucleophilic displacement of Pd by hydroxyl group provides tetrahydropyran **34**, whereas cleavage of the Pd–C bond of **39** and **41** with $CuCl_2$ gives **35** and **36**, respectively. When diethyl ether is used as solvent, the intermediate, **37**, is stable enough not to undergo heterolytic cleavage at the Pd–C bond, hence no **33** is formed. However, this cleavage does occur in protic dipolar solvents such as 90% AcOH. Judging from the similar natures of the Pd–C bonds of **41** and those of **37** (a non-benzylic secondary carbon–Pd bond), the transition from **41** to **36** may also be slow; however, high concentrations of **41** seem to be responsible for the generation of **36**. This seems to be supported by the exceptional formation of 1,2-arylchlorination product **43**, as observed for the reaction of 3-butenol (eq. 14). For this special case, addition of ArPdX to 3-butenol directly forms a palladocyclopentane (like **41**) and results in the formation of 1,2-regioisomer **43**, even when the arylation is carried out with anisyltin (vide supra). The present 1,1-aryletherification of unsaturated alcohols seems to be applicable to the higher homologues. To date we have been successful in forming cyclic ethers with up to 8 members.

The present Pd^{II}-catalyzed cyclization reaction is interesting in the light of the Pd^0 catalyzed arylation of unsaturated alcohols [23]. The arylation of 3-butenol is shown as an example in Scheme 4. Both the Pd^{II}-catalyzed (solid line) and the Pd^0-catalyzed (dotted line) reactions presumably involve a common intermediate, **44**. Under oxidative conditions ($CuCl_2$), the Pd atom intermediate **44** may be more positively charged, and hence (i) Pd is expected to form a discrete palladocycle (like **41**; see Scheme 3) to give **43**, and (ii) Pd requires a hydrogen with high hydride character for the dehydropalladation process. High hydride character seems to be very important in realizing the present high 1,1-regioselectivity. Dehydropalladation toward the benzylic position becomes more favorable than toward the hydroxyl moiety by virtue of the formation of a stable benzylic cation (see also the equilibria between **37** and **38**, and **37** and **40** in Scheme 3). For the Pd^0 catalyzed reaction, on the other hand, no such electronic bias is expected this means that the palladium can move in both directions with equal likelihood with the elimination-addition sequence of HPdX to give an aldehyde [24].

Acknowledgements

We are deeply indebted to our present and past coworkers, whose names appear in the references, for their enthusiastic and creative contributions which made this study possible.

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