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Transition-metal-catalyzed reactions of allenes*

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Abstract: Pathways for carbometallation of simple allenes and allenes bearing a nucleophilic functionality with RMX have been discussed. The bisallene approaches for the efficient synthesis of carbocycles and heterocycles have been developed.

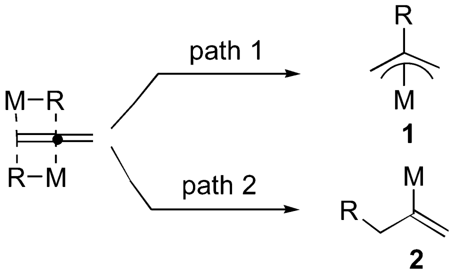
Keywords: allenes; carbopalladation; transition-metal-catalyzed; bisallene; carbometallation.

INTRODUCTION

Although the correct structure of allenes was predicted by van't Hoff in 1874, this class of compounds was considered as "highly unstable" for a long period of time, which may have induced a negative impact on the development of the chemistry of allenes [1]. However, due to the efforts of many chemists, the reactions of allenes are making an increasingly indispensable contribution to modern synthetic chemistry [2]. In this paper, we will discuss some of the transition-metal-catalyzed reactions of allenes developed in our group.

INTERMOLECULAR CARBOPALLADATION OF ALLENES

In principle, two different metallic species, i.e., π-allyl metallic species **1** and *sp*^{2} C-M species **2** may be formed via the carbometallation of allenes depending on the regioselectivity of the insertion reaction (Scheme 1) [3].



Scheme 1

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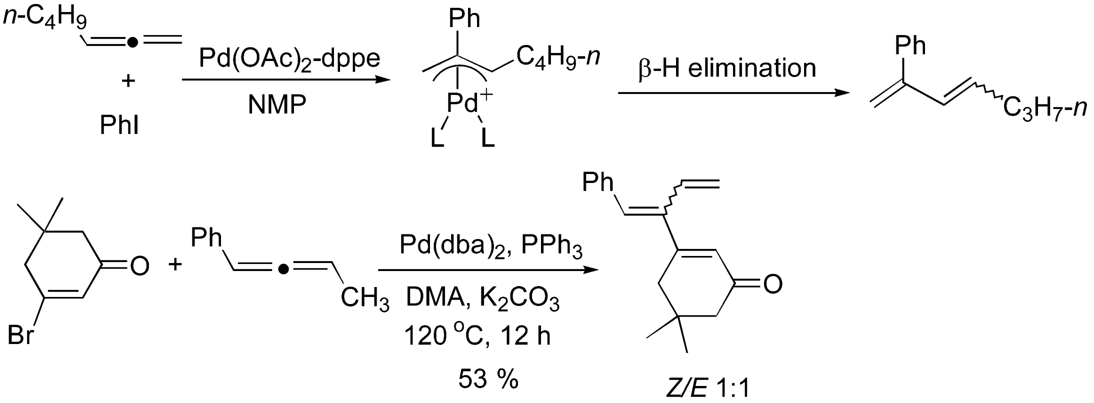
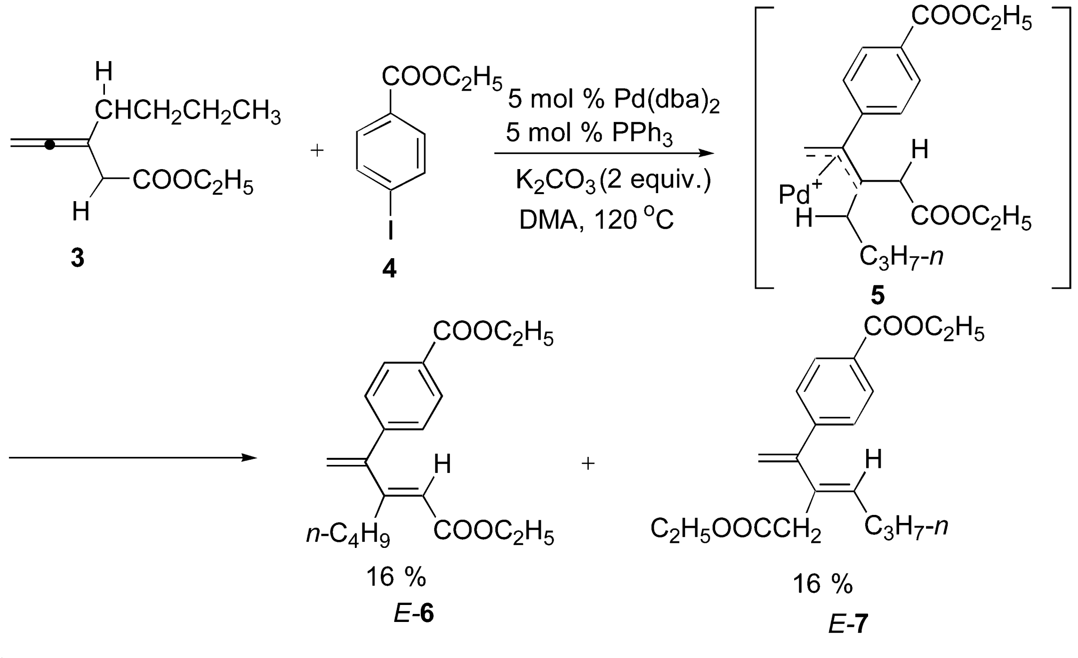
The π-allyl metallic species-forming pathway was observed by Schultz in 1964 [4] and van Helden in 1968 [5]. In 1984, Tsuji et al. reported the Pd-catalyzed intermolecular carbometallation of allenes affording 1,3-dienes with low stereoselectivity [6]. In 2000, Cheng et al. developed $Pd(dba)_2/PPh_3$-catalyzed reaction of organic halides with allenes affording 1,3-dienes with a poor stereoselectivity (Scheme 2) [7].



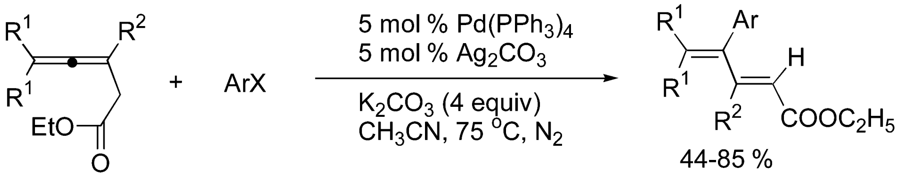
Scheme 2

During the course of our study on the chemistry of allenes, we applied Cheng's conditions to the reaction of 3,4-alkadienoate **3** and *p*-ethoxycarbonylphenyl iodide **4** for the synthesis of 4-aryl-2,4-alkadienoate *E*-**6**. However, a 16 % yield of *E*-4-(*p*-ethoxycarbonylphenyl)-3-butylidene-4-pentenoate *E*-**7** was also formed, indicating the low regioselectivity of the β-H elimination of π-allylic intermediate **5** (Scheme 3) [8].



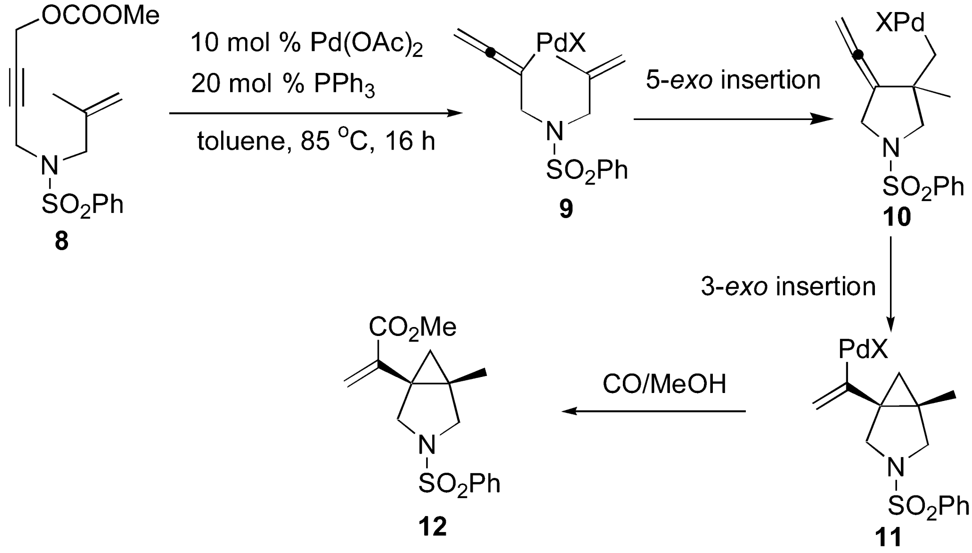
Scheme 3

After some screening, we observed that the $Pd(PPh_3)_4$ and Ag_2CO_3-cocatalyzed reaction of aryl halides and 3,4-alkadienoates in MeCN using K_2CO_3 as the base afforded 4-aryl-2,4-alkadienates in 44–85 % yields highly regio- and stereoselectively (Scheme 4) [8].



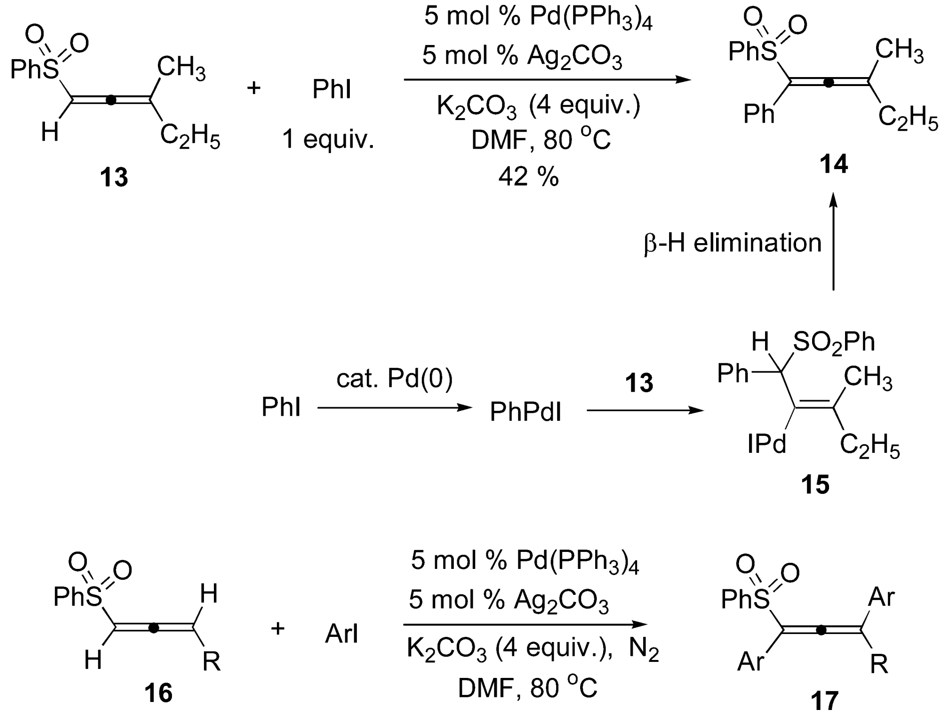
Scheme 4

There is one example in the literature reported by Grigg et al. for the formation of **2**-type vinylic palladium intermediate [9]. The Pd-catalyzed reaction of *N*-(2-methylallyl)-*N*-(4-methoxycarbonyloxy-2-butynyl) benzenesulfonamide **8** in the presence of CO and MeOH afforded 2-bicyclic propenoate **12** via the intermediacy of **2**-type vinylic palladium intermediate **11**. However, the Heck-type of carbopalladation-β–H elimination had not been reported (Scheme 5).



Scheme 5

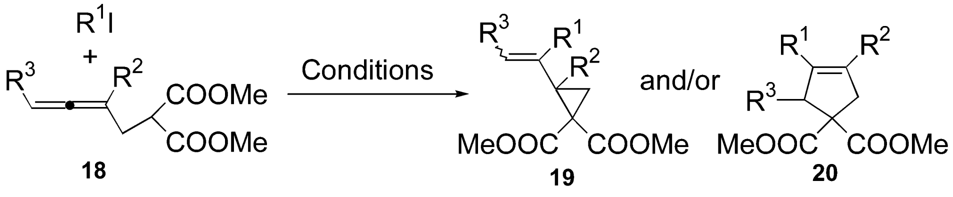
Recently, we observed that the Pd-catalyzed Heck-type reaction of 3-methyl-1,2-pentadienyl phenyl sulfone **13** with PhI afforded the phenyl-substituted 1,2-allenyl sulfone **14**. The reaction may proceed via the β-H elimination of **2**-type vinylic palladium intermediate **15**. For 1,3-monosubstituted allenes, **16** bisarylation was observed (Scheme 6) [10].



Scheme 6

INTERMOLECULAR CARBOPALLADATION OF ALLENES WITH A NUCLEOPHILIC FUNCTIONALITY WITH RPDX

For the carbometallation of allenes with a nucleophilic functionality, due to the presence of the nucleophilic center, there are more possibilities. The most notable one would be nucleometallation [2b,11]. The $Pd(PPh_3)_4$-catalyzed reaction of organic halides and 2-(2',3'-allenyl)malonates **18** afforded vinylic cyclopropanes **19** under conditions A or B and cyclopentenes **20** under conditions C or D highly selectively (Scheme 7) [12].

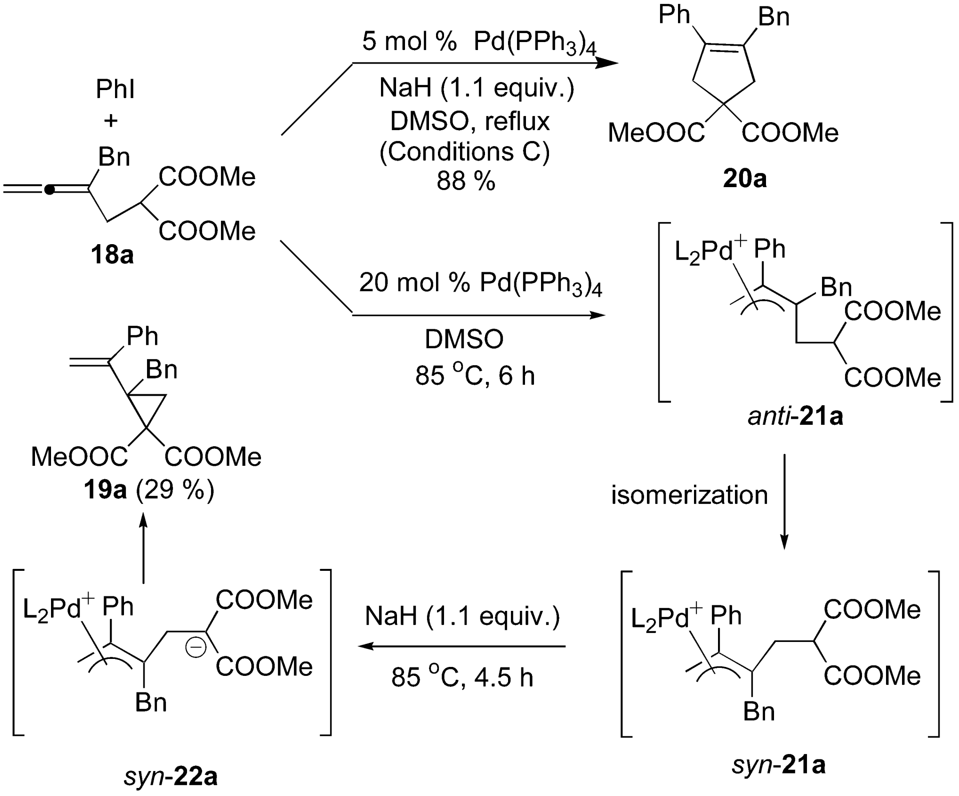


Conditions A = 5 mol % $Pd(PPh_3)_4$, K_2CO_3 (4 equiv), 10 mol % *n*-Bu_4NBr, MeCN
Conditions B = 5 mol % $Pd(PPh_3)_4$, K_2CO_3 (4 equiv), THF
Conditions C = 5 mol % $Pd(PPh_3)_4$, NaH (1.1 equiv), DMSO
Conditions D = 5 mol % $Pd(PPh_3)_4$, NaOH (1.1 equiv), DMF

Scheme 7

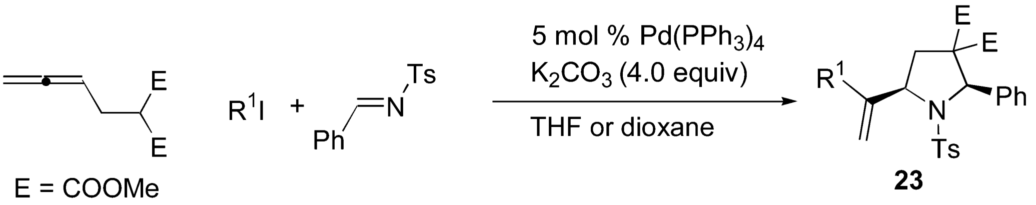
Under conditions C, the reaction of **18a** with phenyl iodide afforded cyclopentene derivative **20a** in 88 % yield with highly selectivity. However, it is interesting to observe that if the same reaction mixture was treated with 20 mol % of $Pd(PPh_3)_4$ alone for 6 h first, which was followed by the addition of

NaH, the reaction afforded vinylic cyclopropane product **19a** as the only product! We reasoned that π-allyl metallic intermediate *anti*-**21a** was formed in the first place. Due to the absence of a nucleophilic center, intramolecular allylation is not possible. Subsequent isomerization of *anti*-**21a** to *syn*-**21a**, deprotonation, and cyclic allylation afforded **19a** (Scheme 8) [12].



Scheme 8

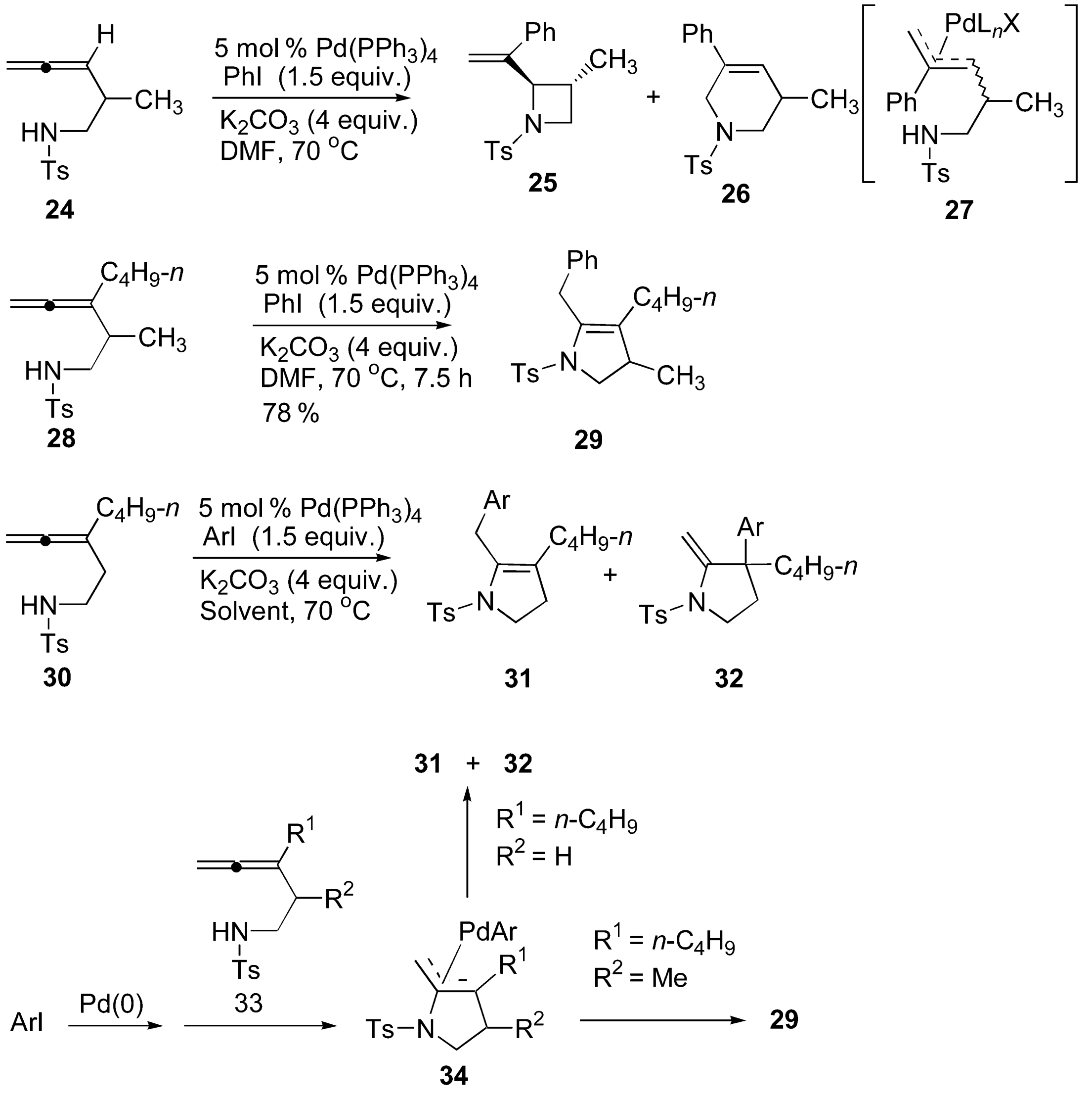
Actually, *syn*-**22a**-type intermediate may further undergo 1,2-addition reaction with an imine to form a new nucleophilic nitrogen atom, which would be followed by intramolecular amination to produce 2,5-*cis* pyrrolidines **23** highly stereoselectively (Scheme 9) [13].



Scheme 9

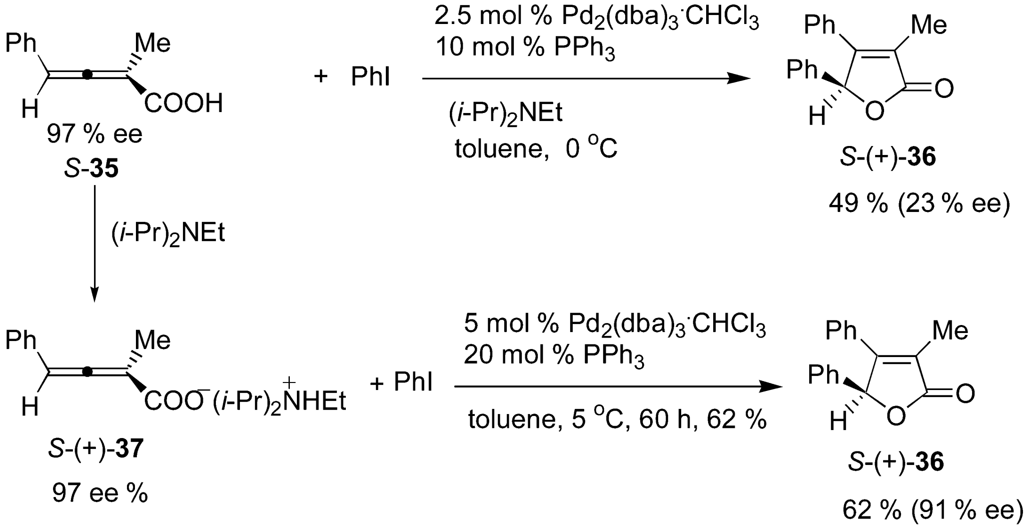
A similar reaction pathway has also been observed with $Pd(PPh_3)_4$-catalyzed coupling cyclization of 2-methyl-3,4-pentadienyl toluenesulfonamide **24** with PhI [14,15]. Azetidine **25** and tetrahydropyridine **26** were formed via the cyclic amination of the π-allyl palladium intermediate **27**.

However, when the same reaction conditions were applied to *N*-(2-methyl-3-butyl-3,4-pentadienyl)toluenesulfonamide **28**, 5-membered 2,3-dihydropyrrole **29** was formed as the only product in 78 % yield. The coupling-cyclization reaction of **30** (compared with **28**, the 2-methyl group is removed) with different ArI afforded a mixture of 2,3-dihydropyrroles **31** and 2-methylenetetrahedropyrroles **32** (Scheme 10). The reaction may proceed via the reductive elimination of the π-allyl palladium intermediate **34**, which was formed via the nucleometallation of ArPdI with 3,4-alkadienyl toluenesulforamide **33** (Scheme 10) [14].



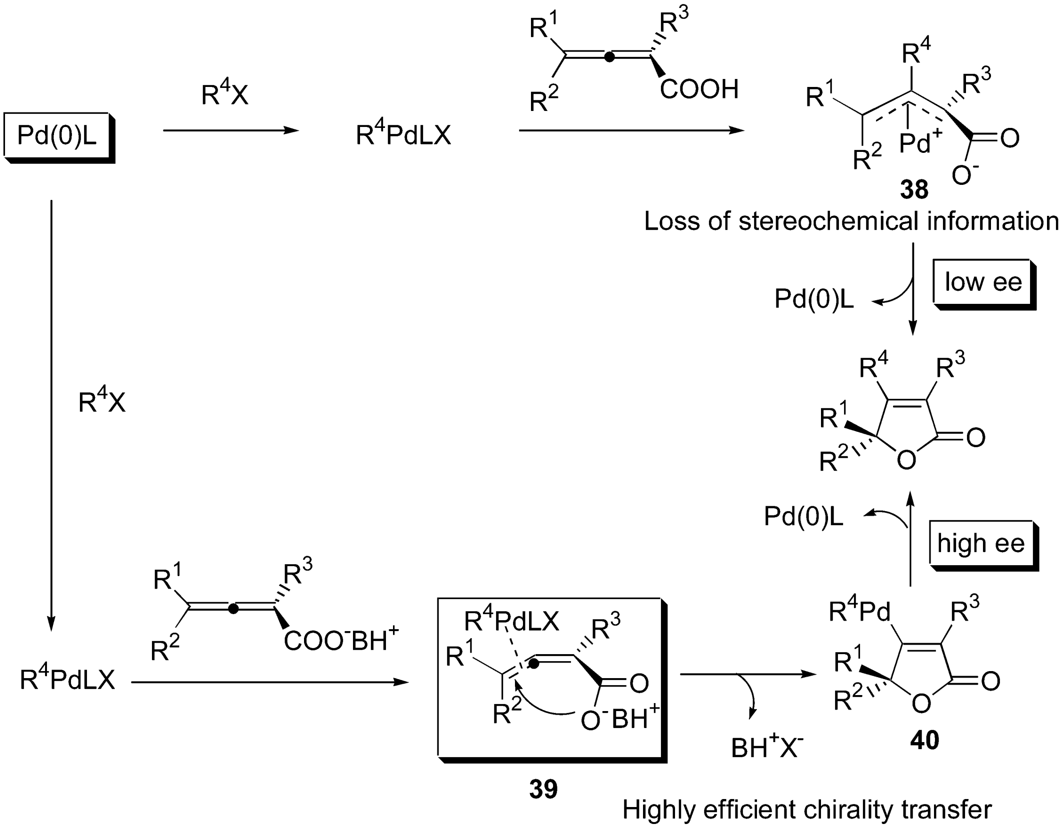
Scheme 10

Similarly, the $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$-catalyzed reaction of optically active 2-methyl-4-phenyl-2,3-butadienoic acid (*S*-**35**) with PhI afforded optically active butenolide *S*-(+)-**36** in 49 % yield with only 23 % ee, indicating the serious loss of the chirality. However, when *S*-**35** was converted to its 1:1 salt with $(i\text{-}Pr)_2NEt$ *S*-(+)-**37** first, the reaction of *S*-(+)-**37** with PhI under the same reaction conditions afforded *S*-(+)-**36** in 62 % yield with 91 % ee (Scheme 11) [16].



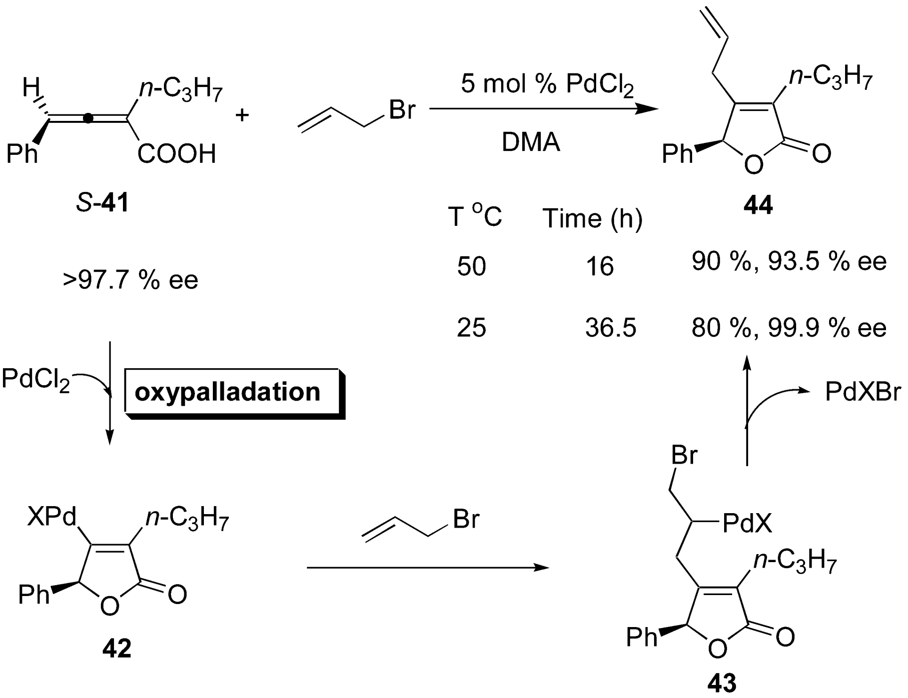
Scheme 11

The stereochemical information in the starting optically active 2,3-allenic acid may be lost due to the isomerization of π-allyl palladium intermediate **38**. In the case of the 1:1 optically active salt, the reaction may proceed via the high stereoselective oxypalladation forming 2(5*H*)-furanonyl palladium intermediate **40** (Scheme 12).



Scheme 12

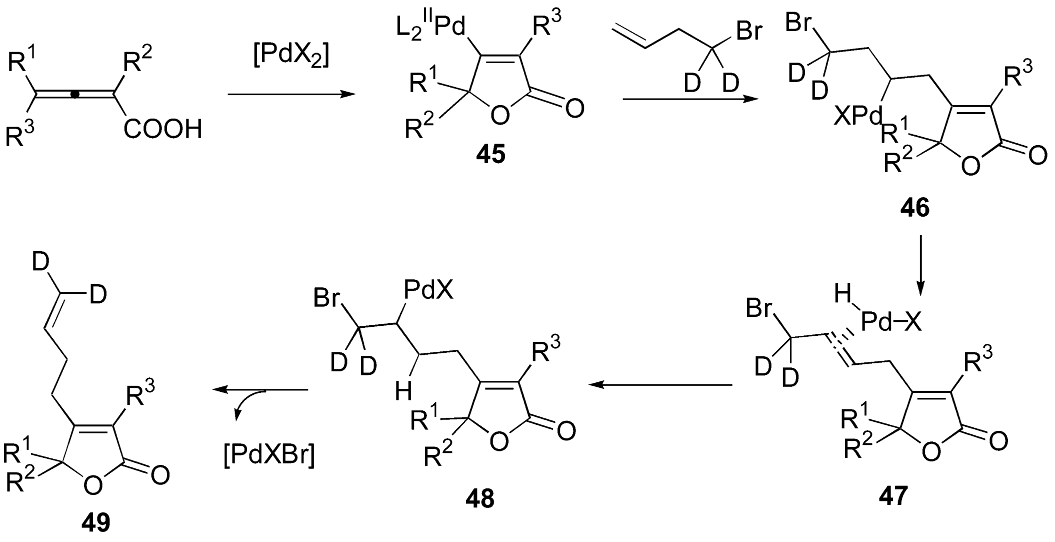
The high efficiency of chirality transfer was also observed in the $PdCl_2$-catalyzed coupling-cyclization reaction of *S*-**41** with allyl bromide [17]. Again, oxypalladation of 2,3-alkadienic acid *S*-**41** forming 2(5*H*)-furanonyl palladium intermediate **42** may be responsible for the high efficiency of the chirality transfer (Scheme 13).



T °C	Time (h)	
50	16	90 %, 93.5 % ee
25	36.5	80 %, 99.9 % ee

Scheme 13

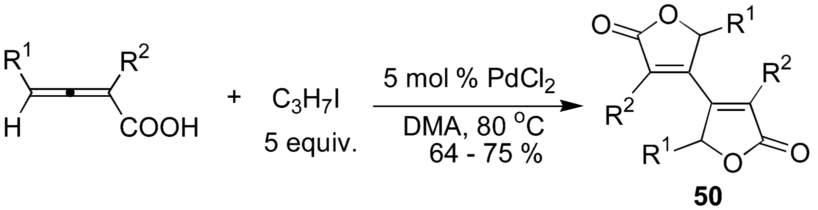
This type of oxypalladation has also been observed in the Pd(II)-catalyzed coupling cyclization of 2,3-allenoic acids with ϖ-alkenyl halides. The product **49** was formed via the insertion of the C=C bond of the organic bromide with the C–Pd bond in **45**, the subsequent repeated dehydropalladation/hydropalladation of **46**, and dehalopalladation of **48** (Scheme 14) [18].



Scheme 14

TRANSITION-METAL-CATALYZED REACTIONS OF TWO ALLENE MOIETIES

With these results in hand, we started to study the Pd(II)-catalyzed reaction of 2,3-allenoic acid in the presence of an alkyl iodide. To our surprise, the reaction afforded bisbutenolides **50** via double oxypalladation (Scheme 15) [17]. After further study, it is believed that the I_2 in situ generated by the reaction of I^- released by the alkyl iodide with the O_2 in air may act as the oxidant to oxidize the in situ generated Pd(0) to the catalytically active Pd(II) species. Based on these, we also developed the protocols using KI or benzoquinone as the oxidant [19]. In terms of generality, the alkyl iodide-protocol is the best while the benzoquinone protocol provides the bisbutenolides in the highest yields.



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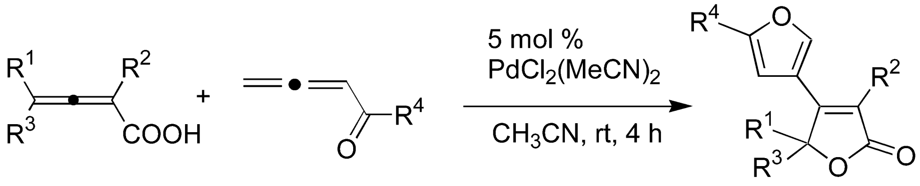
Scheme 15

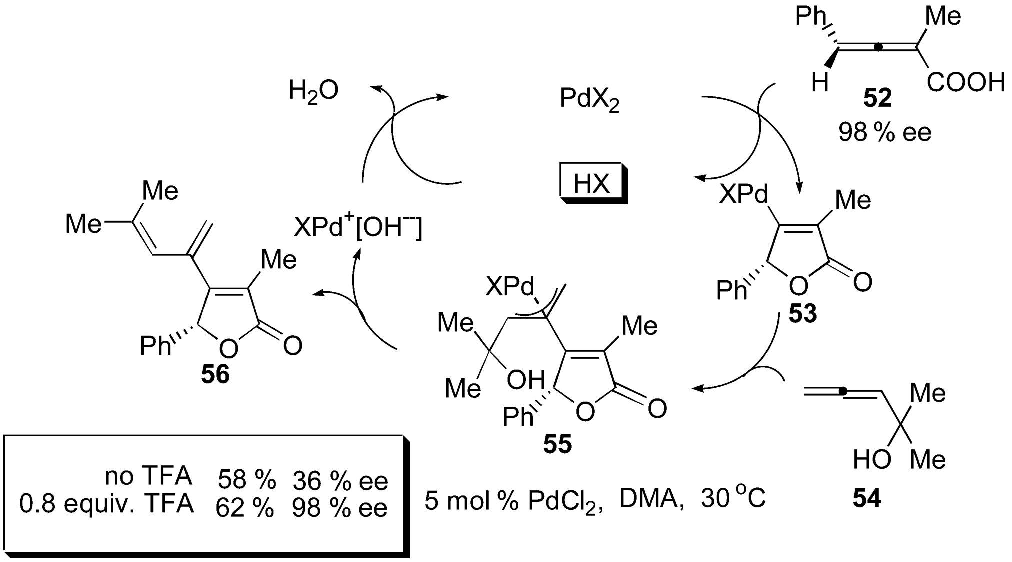


51

Scheme 16

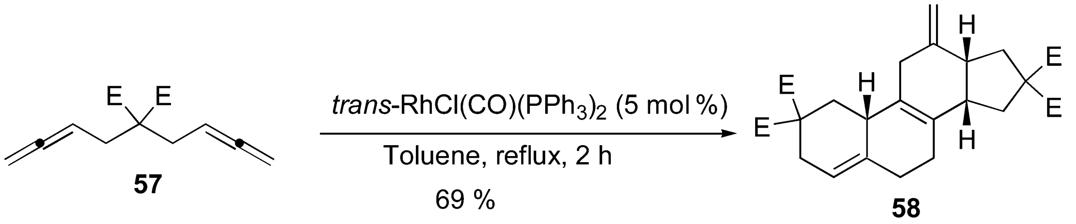
We have also developed the double cyclization reaction of 2,3-allenoic acids with 5 equiv of 1,2-allenyl ketones affording β-furanyl butenolides **51** (Scheme 16). By using the optically active starting 2,3-allenoic acids as the probe, X-ray diffraction studies revealed a double oxypalladation mechanism [20].

Recently, we observed the Pd(II)-catalyzed cyclization reaction of 2,3-allenoic acids with 2,3-allenols producing β-(1,3-dien-2-yl)butenolide **54**. Obviously, instead of biscyclization, the hydroxyl group in 2,3-allenols was β-eliminated, which may induce the low-efficiency of chirality transfer observed in the reaction of **52** with **54**. When the same reaction was conducted in the presence of 0.8 equiv of trifluoroacetic acid (TFA), which was used to neutralize the in situ generated OH^-, the chirality was transferred highly efficiently (Scheme 17) [21].



Scheme 17

When we combined the two allene moieties into one molecule, such as **57**, *trans*-$RhCl(CO)(PPh_3)_2$ can catalyze its bimolecular cyclization reaction to afford steroid motif **58** in 69 % in one step (Scheme 18). Although the mechanism is far away from being clear, two cyclometallation–carbometallation forming a π-allyl metallic species-reductive elimination-intramolecular Diels–Alder reaction of a 1,3-diene moiety with an allene moiety pathways have been proposed [22].



Scheme 18

In conclusion, we have observed some interesting reactions of allenes. Due to the relatively unexplored nature of the chemistry of allenes, more reactions of allenes with high synthetic potential will be developed.

ACKNOWLEDGMENTS

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