# Recent advances in transition metal-catalyzed or -mediated cyclization of 2,3-allenoic acids: New methodologies for the synthesis of butenolides*

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Abstract: The cyclization reactions of 2,3-allenoic acids or their salts with optically active bases affording butenolides are discussed. Two reaction pathways were observed: (1) intermolecular carbometallation-intramolecular allylation; (2) cyclic oxymetallation-reductive elimination. High efficiency of chirality transfer was realized with the latter case.

2,3-Allenoic acids are a class of interesting compounds with substituent-loading capability, chirality, and acidity; thus, they may be potential starting materials for the diverse synthesis of optically active molecules, providing that a high efficiency of chirality transfer can be realized. For the cyclizative coupling of 2,3-allenoic acids, there are, in principle, two pathways: (1) the intermolecular regioselective carbometallation [1] of the allene moiety forming π–allyl metal intermediates followed by intramolecular allylation and (2) oxymetallation followed by reductive elimination (Scheme 1).
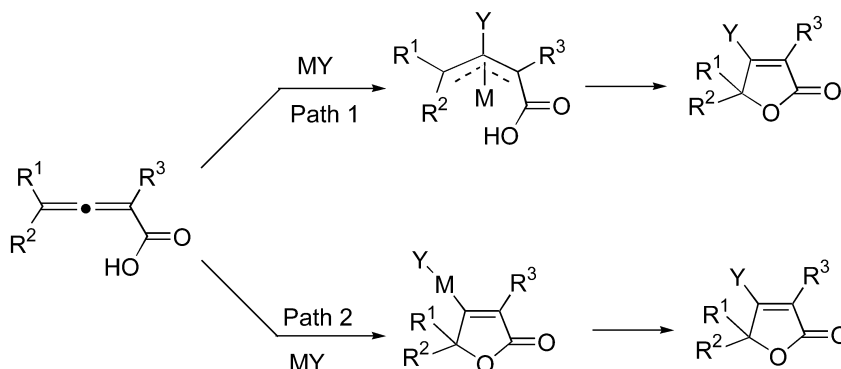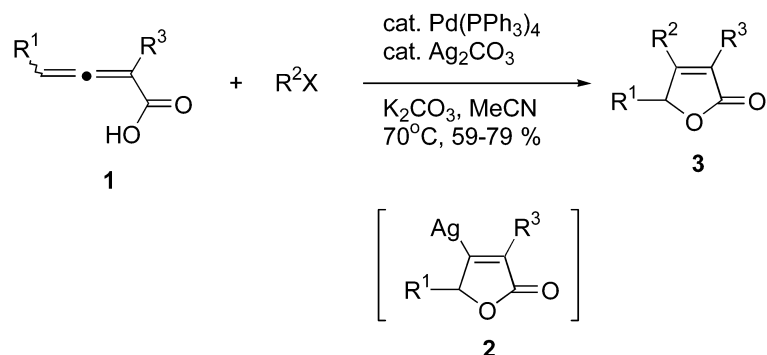

Scheme 1

Pd-CATALYZED COUPLING OF 2,3-ALLENOIC ACIDS WITH ORGANIC HALIDES

Pd(0)/Ag$^+$-cocatalyzed coupling-cyclization of aryl or 1-alkenyl halides and 2,3-allenoic acids forming β-aryl or -(1-alkenyl)butenolides were developed [2]. Here, the addition of a catalytic amount of Ag$^+$ is the key, which may be responsible for the formation of a cyclic silver intermediate **2** (Scheme 2) [3].
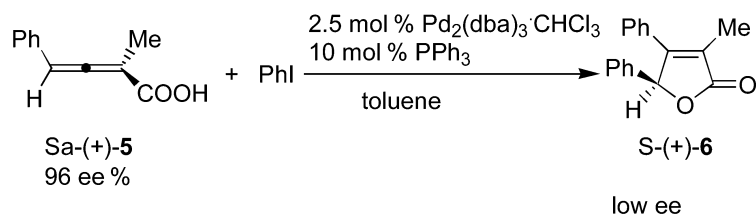
Scheme 2

Based on these results, we have succeeded in developing a solid-phase synthesis of butenolides [4]. Due to the relative stability of the C–O bond of the lactone ring as compared to that in the polymeric linkage, three protocols were developed for the selective removal of the polymer chain [5]: (1) The carboxyl linkage was cleaved with $AlCl_3$. (2) The ether linkage was cleaved with a combination of $ZnBr_2$ and CH_3COBr. With the benzylic ether linkage, the final product can be a butenolide with a benzylic bromide moiety, which is suitable for further elaboration. (3) The THP linkage was cleaved with TFA and MeOH.
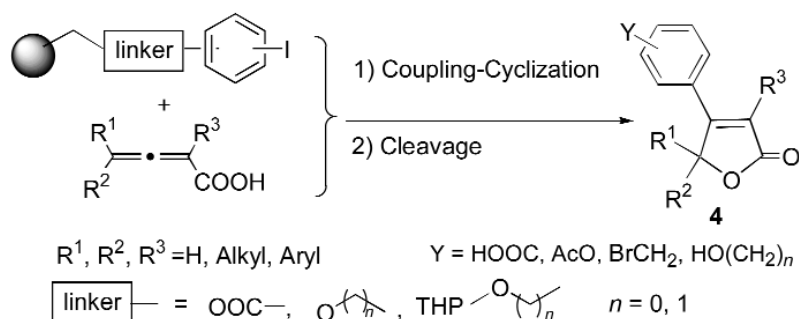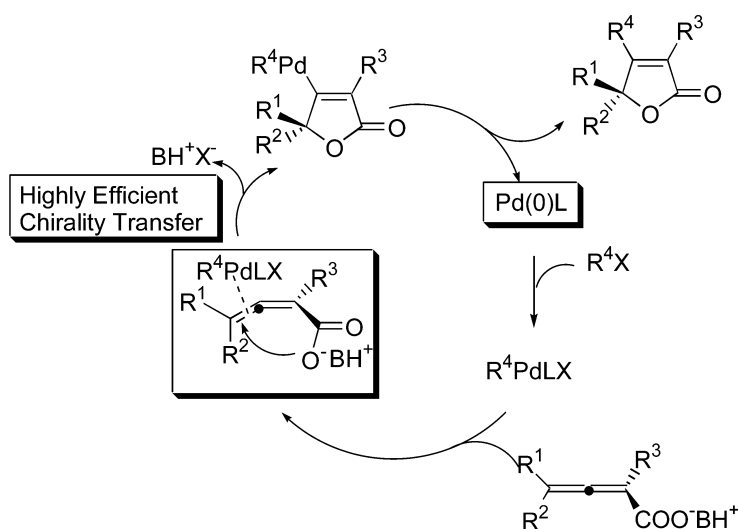

Scheme 3

It is interesting to observed that the results of Pd(0)-catalyzed reaction of Sa-(+)-2-methyl-4-phenyl-2,3-butadienoic acid Sa-(+)-**5** with PhI were rather disappointing with a highest ee of 60 % (Scheme 4) [6]. The chirality may be lost in the formation of the π–allyl palladium intermediate by the carbopalladation reaction (Scheme 1, Path 1).
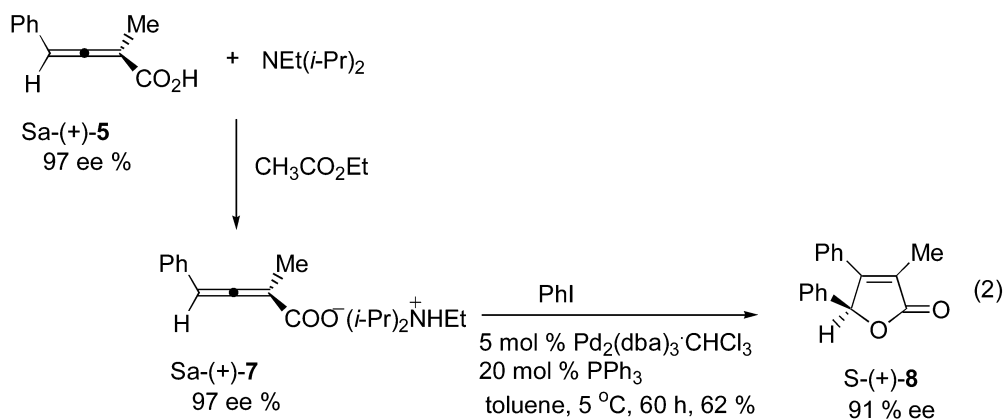

Scheme 4

A different mechanistic pathway that involves a R^4 PdX-coordination-directed oxypalladation-reductive elimination process may keep the chirality.
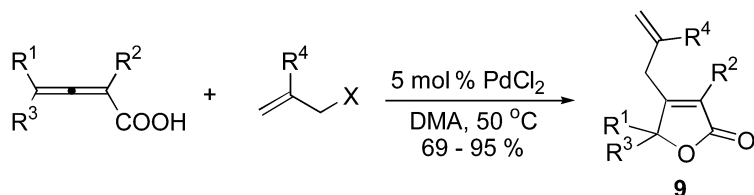
Scheme 5

Thus, the 1:1 salt of Sa-(+)-2-methyl-4-phenyl-2,3-butadienoic acid and *i*-Pr$_2$NEt Sa-(+)-**7** was prepared from their reaction in ethyl acetate at room temperature. Its corresponding Pd(0)-catalyzed reaction with PhI afforded (S)-(+)-**8** in 91 % ee, a dramatic improvement (Scheme 6) [6]. With the corresponding cinchonidine salt, the reaction should be carried out in the presence of TBAB as the phase-transfer catalyst. In this reaction, the preformed COO$^-$ in the salt may speed up the oxypalladation process.
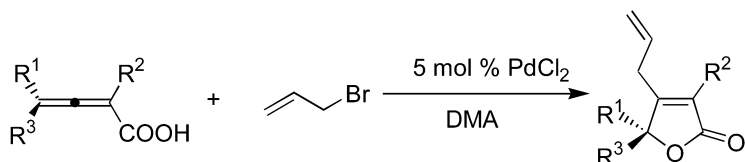

Scheme 6

Under the catalysis of PdCl$_2$, the reaction of 2,3-allenoic acids with allylic halides in DMA at 50 °C afforded β-allylic butenolides [7].
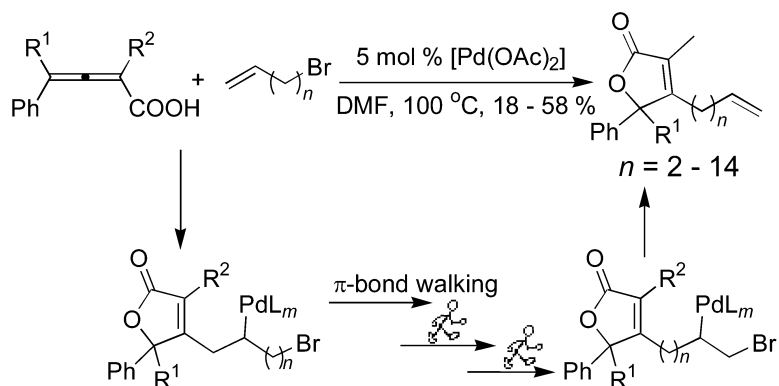

Scheme 7

With optically active 2,3-allenoic acids, the corresponding chiral β-allylic butenolides were obtained without the obvious lose of chirality, indicating that a Pd(II)-catalyzed oxypalladation mechanism may be more favorable [7].
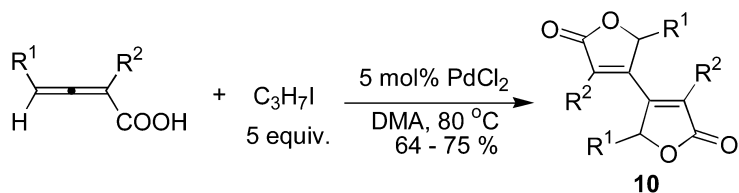
Scheme 8

With non-allylic (ω-1)-alkenylbromides, the reaction went through a π-bond walking process to afford β-(ω-1)alkenyl butenolides [8].
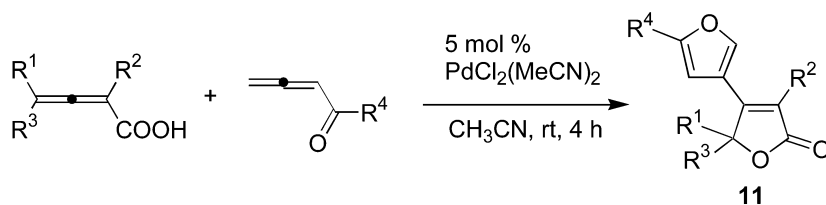
Scheme 9

Pd-CATALYZED SYNTHESIS OF BUTENOLIDES VIA BISALLENE APPROCHES

Furthermore, it is surprising that the reaction of 2,3-allenoic acids with alkyl iodide afforded bi-butenolides. The participation of alkyl iodide and the oxygen in air is crucial for the catalytic cycle [9].

Scheme 10

The matched cyclizative coupling reaction of 2,3-allenoic acids with 1,2-allenyl ketones afforded β-furanyl butenolides. Through a brief mechanistic study, it was believed that the reaction was catalyzed by a divalent palladium species, which may be regenerated via the cyclometallation of 1,2-allenyl ketones with the in situ generated Pd(0) followed by protonolysis with the HCl generated in the first oxypalladation step [10].

CuX$_2$-PROMOTED HALOLACTONIZATION OF 2,3-ALLENOIC ACIDS

We have developed iodo- and bromo-lactonization reactions using I_2 and NBS, respectively [11]. However, for the synthesis of the corresponding chlorides, NCS either does not work well or does not work at all. Thus, the halolactonization reaction (X = Cl or Br) was established, employing the reaction of CuX$_2$ with 2,3-allenoic acids in acetone/H$_2$O (2:1) at 65–70 °C. The reaction for bromides is usually faster and higher yielding than that for chlorides [12]. With a catalytic amount of CuCl, the reaction afforded the cycloisomerization product in fairly high yields [13].
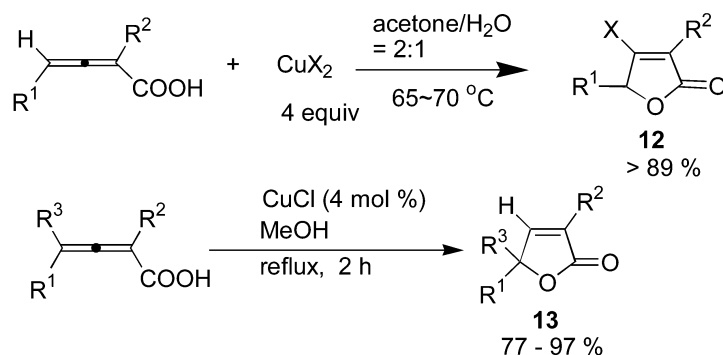
Scheme 12

The reaction of Sa-(+)-**5** with CuX$_2$ led to optically active β-halobutenolides **12** in high yields and ee's [14]. In addition, it is observed that when the corresponding salts with L-cinchonidine was treated with CuBr$_2$ in an aqueous solution of acetone, the reaction went smoothly to afford the optically active product **12** in high yields and ee's. From this reaction, we can conclude that (1) the efficiency of chirality transfer is high and (2) the steric information in cinchonidine has no influence on the stereochemistry of this halolactonization. Thus, α-methylbenzylamine can also be applied as the resolving agent for the synthesis of both (*R*)- and (*S*)-β-halobutenolides.

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