Transition Metal-Catalyzed/Mediated Reaction of Allenes with a Nucleophilic Functionality Connected to the α-Carbon Atom

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ABSTRACT

Allenes with a nucleophilic functionality connected to the α-carbon atom have been shown to be versatile building blocks for the synthesis of γ-butenolides, γ-lactams, γ-iminolactones, vinylic epoxides, 4-amino-2-alkenols, 2-amino-3-alkenols, 2,5-dihydrofurans, furans, vinylic cyclopropanes, and cyclopentenes, depending on the nature of the nucleophilic centers. The reaction may proceed via the carbometalation-nucleophilic attack mechanism or nucleometallation-reductive elimination. The stereochemical outcomes by these two pathways are different.

I. Introduction

The report on the first synthetic allene can be dated back to as early as 1887,[1] and its structure was confirmed in 1954.[2] Allenes can also be found in many natural sources.[3] Due to the notion that these compounds would be thermally unstable, for a long period of time, their chemistry and synthetic routes had not been well established. However, due to the presence of the unique cumulated diene structual unit, allenes are a class of compounds with the following interesting properties:[4] (1) with up to four substituents, methodologies starting from allenes provide synthetic diversity; (2) the electron density and the reactivity of each carbon atom of the allene unit can be tuned by the substituent effect; (3) the inherent axial chirality provides a challenge for the highly stereoselective synthesis of optically active allenes and the transfer of the chirality of the allenes into final products (Scheme 1). Thus, the chemistry of allenes has been catching the attention of chemists[5] and some nice reviews have appeared.[6] In this Account, we will present some of our own recent results involving allenes with a nucleophilic functionality connected to the α-carbon atom.

Shengming Ma is originally from Zhejiang Province, China. He received his B.S. degree in Chemistry from Hangzhou University (1986) and M.S. degree (1998) and a Ph.D. degree (1990) from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. After the postdoctoral research experience at ETH of Switzerland and Purdue University, he joined the faculty of Shanghai Institute of Organic Chemistry (1997), where currently he is Professor of Chemistry and the Director of State Key Laboratory of Organomeatllic Chemistry.

Scheme 1

(1) establishment of two cumulated C-C bonds
(2) establishment of chirality

(1) control of reactivity
(2) control of regioselectivity
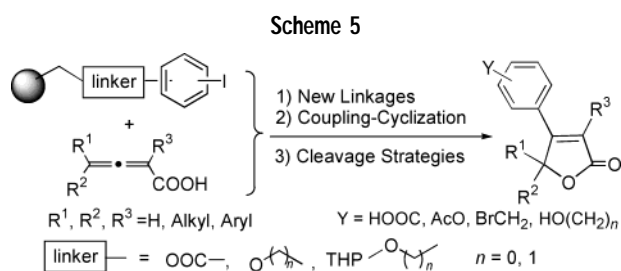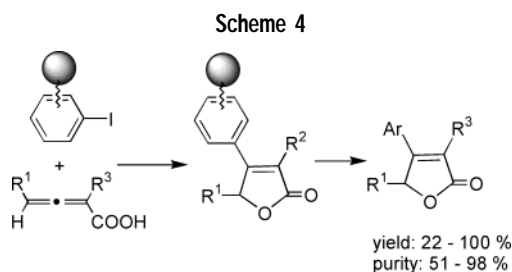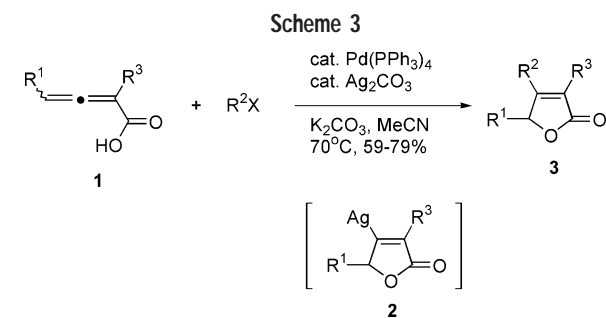(2) transfer of chirality
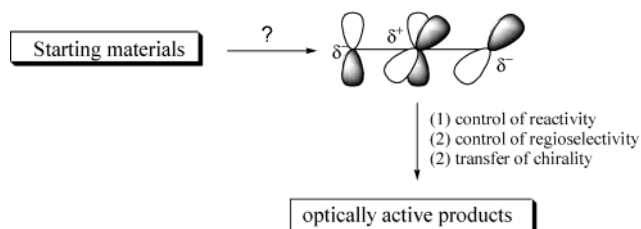
Scheme 2
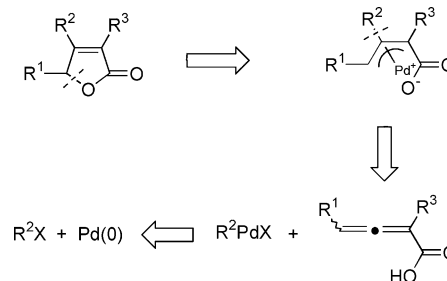
II. Cyclization of 2,3-Allenoic Acids

Besides the chirality and substituent-loading capability, the acidity of 2,3-allenoic acids provides the possibility of getting both enantiomers by a simple recrystallization of salts formed by their reaction with optically active bases, which are usually cheap and easily available. Butenolides are a class of compounds with a broad range of interesting biological activities, which have attracted much attention.[7] However, in all the procedures published, there are three problems remaining to be tackled (1) Lengthy procedure; (2) Transition metal does not participate in the formation of the chiral center; (3) Diversity (the possibility of facile solid-phase synthesis). Thus, cyclization reactions starting from 2,3-allenoic acids would address some of these issues leading to a library of butenolides[7] of high enantiopurities with diverse structures.

A. Pd-Catalyzed Coupling Cyclization of Organic Halides with 2,3-Allenoic Acids. On the basis of the carbopalladation of the allene moiety[8] of 2,3-allenoic acids followed by intramolecular trapping to construct a C−O bond, butenolides may be constructed by a one-pot reaction of R^2X with 2,3-allenoic acids with the possible introduction of chirality in the prospective enantioselective C−O bond formation step (Scheme 2).

On the basis of this concept, a Pd(0)/Ag$^+$-cocatalyzed coupling−cyclization of organic halides and 2,3-allenoic acids was developed.[7,9] 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 3).[10]

Recently, much attention has been paid to the combinatorial synthesis of libraries of compounds with interesting properties.[11] We have succeeded in attaching an organic halide to a polymeric chain; upon its treatment

Scheme 3

Scheme 4

yield: 22 - 100 %
purity: 51 - 98 %

Scheme 5

R^1, R^2, R^3 =H, Alkyl, Aryl   Y = HOOC, AcO, BrCH$_2$, HO(CH$_2$)$_n$

linker — = OOC—, O⟋⟍$_m$, THP ⟋O⟍$_n$ n = 0, 1

Scheme 6

coupling reaction

Scheme 7

Scheme 8

R' = TMS, CH$_2$OH, alkyl, phenyl

R" = aryl, 1-alkenyl, alkyl

Scheme 9

2aa, X = Cl, 24 h, 83%
          92% (with the addition of 4 equiv of LiCl)

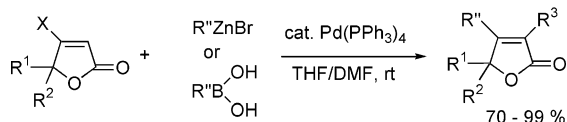**2ab**, X = Br, 12 h, 70% (with the addition of 4 equiv of LiBr)
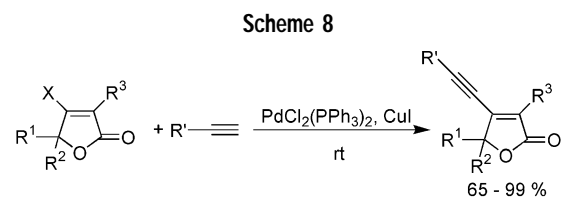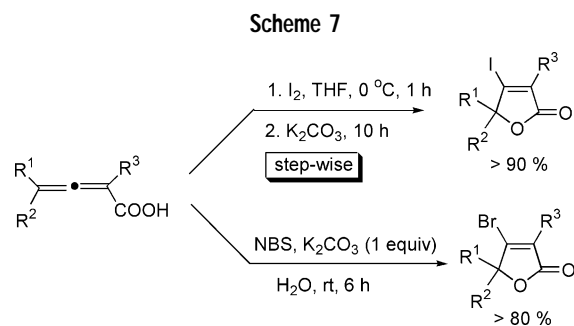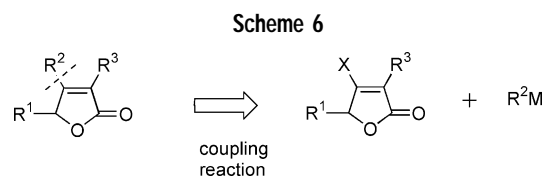   84%

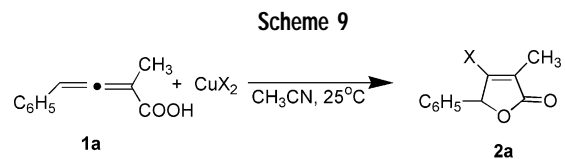with an excess amount of 2,3-allenoic acids, the reaction afforded the polymer-supported butenolides.

The cleavage was troublesome at the beginning due to the relative stability of the C–O bond of the lactone ring as compared to that in the linkage.[12] With subtle adjustments, three protocols were developed for the removal of the polymer chain (Scheme 5):[13] (1) the carboxyl linkage was cleaved with AlCl$_3$; (2) the ether linkage was cleaved with a combination of ZnBr$_2$ and CH$_3$COBr, and with the benzylic ether linkerage, 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.

B. CuX$_2$-Promoted Halolactonization of 2,3-Allenoic Acids. Cross-coupling reactions, such as Kumada, Suzuki, Stille, Negishi couplings, have been proven to be a very powerful tool for the construction of C–C bonds and C–X bonds.[14] Due to the intrinsic problem of oxidative addition reaction of sp^3 C–X bond and the failure experienced with acetylenic halides, we started to consider the coupling reaction of organometallic reagents with β-halobutenolides as a complementary method for the synthesis of β-alkyl- or β-alkynyl-substituted butenolides (Scheme 6).

We have developed iodo- and bromo-lactonization reactions using I$_2$ and NBS, respectively (Scheme 7).[15] For the iodolactonization reaction, the stepwise addition of I$_2$ and K$_2$CO$_3$ is important to ensure a high yield of the product due to the possible conversion of 2,3-allenoic acids to 2,4-alkadienoic acids under the basic conditions.
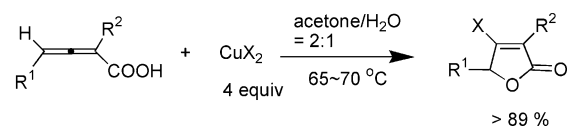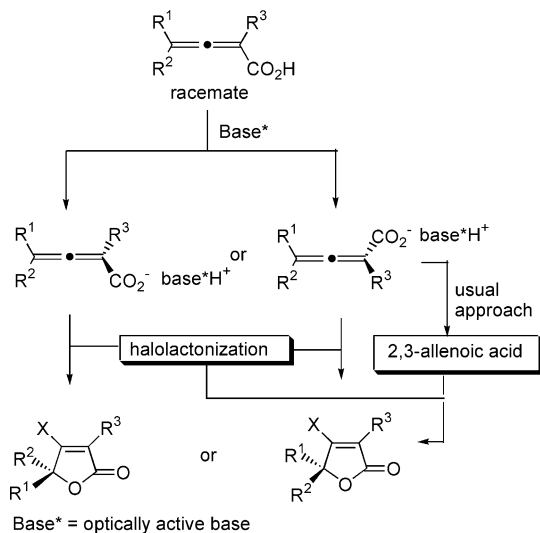
The Pd(0)-catalyzed coupling reaction with terminal alkynes and organic zincs underwent smoothly to afford β-differently substituted butenolides.[16,17] Using this method, sp-C-, sp^2-C-, and sp^3-C-centered substituents can be introduced to the β-position, and a formal synthesis of cis-whisky lactone was realized (Scheme 8).[16]

But for the synthesis of the corresponding chlorides, NCS either does not work well or does not work at all. Thus, the chlorolactonization reaction was established employing the reaction of CuCl$_2$ with 2,3-allenoic acids (Scheme 9). For 4-aryl-substituted 2,3-allenoic acids, the reaction with CuX$_2$ (X = Cl, Br) in MeCN at room temperature afforded the corresponding β-halobuteno-lides in good yields. However, the reaction of 4-alkyl-

Scheme 10

$n\text{-}C_7H_{15}$ ... H / H ... COOH + CuX_2 $\xrightarrow[\text{acetone / H}_2O]{65\text{-}70\,^\circ C}$ $n\text{-}C_7H_{15}$ ... furanone X = H or Cl

2 equiv

R^1 ... R^3 / R^2 ... COOH $\xrightarrow[\text{reflux, 2 h}]{\substack{\text{CuCl (4 mol\%)} \\ \text{MeOH}}}$ butenolide

77 - 97%

Scheme 11

R^1 ... R^3 / R^2 ... CO_2H

racemate

Base*

R^1 ... R^3 / R^2 ... CO_2^- base*H$^+$ or R^1 ... CO_2^- base*H$^+$ / R^2 ... R^3

usual approach

halolactonization   2,3-allenoic acid

X ... R^3 / R^2 ... R^1 ... O   or   X ... R^3 / R^1 ... R^2 ... O

Base* = optically active base

Scheme 12

Ph ... Me / H racemate CO_2H + (L)-cinchonidine $\longrightarrow$ Ph ... Me / H Sa-(+)-**5a** CO_2^- (L)-cinchonidine-H$^+$

dil. H_2SO_4

Ph ... Me / H Sa-(+)-**6a** CO_2H

Scheme 13

Ph ... Me / H Sa-(+)-**5a** CO_2^- (L)-cinchonidine-H$^+$ $\longrightarrow$ Br ... Me / H ... Ph (S)-(+)-**7a**

| reagent	reaction time (h)	yield of (S)-(+)-**7a** (ee)
NBS/H$_2$O/rt	6	21% (94% ee)
NBS/H$_2$O/rt	24	50% (64% ee)
CuBr$_2$/acetone-H$_2$O(2:1)/60-65°C	3	95% (98% ee)

substituted 2,3-allenoic acids did not occur smoothly. Thus, a new set of reaction conditions, i.e., acetone/H$_2$O (2:1) and 65−70 °C, was established (Scheme 10). This set of aqueous conditions is general for all the substrates. The reaction for bromides is usually faster and higher yielding than that for chlorides.[18]

Four equivalents of CuX$_2$ were required in order to avoid the formation of a cycloisomerization product. Actually when only a catalytic amount of CuCl was applied in MeOH or EtOH, the cycloisomerization product can be formed as the only product in fairly high yields, indicating that the in situ formed Cu(I) is responsible for the formation of the cycloisomerization product (Scheme 10).[10,18,19]

As previously discussed, the reaction of racemic 2,3-allenoic acids with optically active bases would afford optically active 1:1 acid−base salts, which may be easily enriched by recrystallization (Scheme 12).[20,21] Upon treatment with dilute aqueous H$_2$SO$_4$ solution, 2,3-allenoic acid was released, which may be halolactonized. Another possibility is to use the optically active 1:1 salt directly as the starting point for the halolactonization. However, attention should be paid to the influence of the steric information of the resolving optically active base on the stereochemical outcome of the halolactonization (Scheme 11).

Indeed, the reacion of racemic 2-methyl-4-phenyl-2,3-butadienoic acid with L-(−)-cinchonidine afforded the salt Sa-(+)-**5a**, which upon treatment with dilute H$_2$SO$_4$ afforded Sa-(+)-2-methyl-4-phenyl-2,3-butadienoic acid Sa-(+)-**6a**. The absolute configuration of the allene moiety
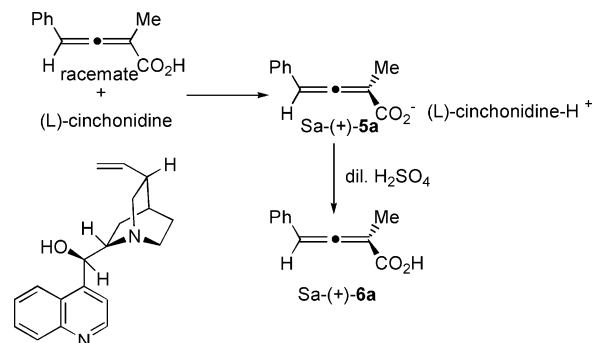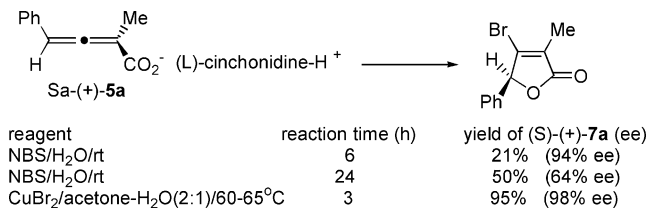
was established by an X-ray diffraction study of a single crystal of (+)-**5a**, which contains a water molecule (Scheme 12).

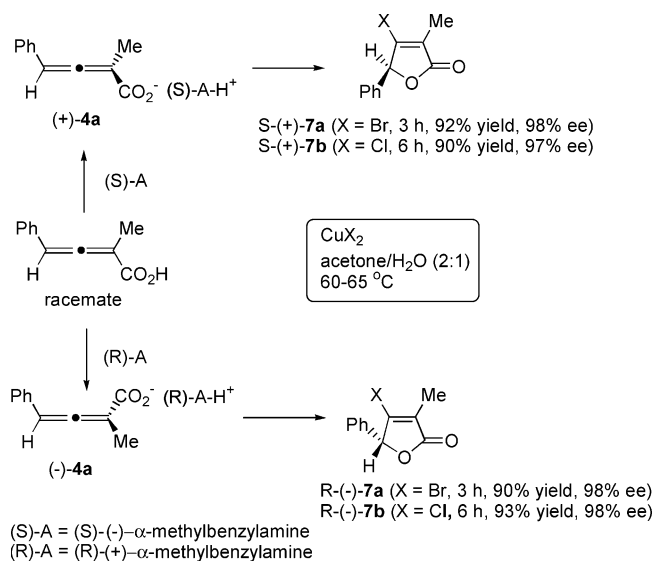Its reaction with CuX$_2$ led to the synthesis of optically active β-halobutenolides **7** in high yields and ees.[21] Furthermore, it is interesting to note that the direct reaction of the salt Sa-(+)-**5a** with NBS in H$_2$O afforded 21% of (S)-(+)-**7a** with 94% ee within 6 h. With prolonged reaction, the yield was improved to 50%. However, the enantiopurity of the β-bromobutenolide dropped to 64% ee (Scheme 13).

Luckily, when Sa-(+)-**5a** was treated with CuBr$_2$ in an aqueous solution of acetone, the reaction went smoothly to afford the product (S)-(+)-**7a** in 95% yield and 98% ee (Scheme 13). From this reaction, we can concluded 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.[21]
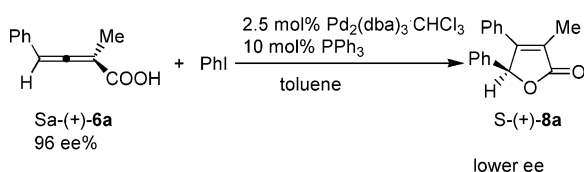
Since the steric information of the optically active base has no influence on the stereochemical outcome of the halolactonization reaction, we applied α-methylbenzyl-amine as the resolving agent. Two advantages for this compound are that (1) both R and S isomers are easily and cheaply available and (2) its molecular weight is low, which makes the reaction more atom economic. For the synthesis of (S)-β-halobutenolides, (R)-α-methylbenzyl-amine should be applied, while with (S)-α-methylben-zylamine, (R)-β-halobutenolides can be prepared (Scheme 14).

However, when we ran the corresponding coupling reaction of optically active β-halobutenolides with orga-nometallic reagents,[15−17] the β-substituted butenolides were formed in good yields but with obvious loss of the enantiopurity. Therefore, for the propose of getting opti-cally active β-aryl butenolides directly, the Pd(0)-catalyzed reaction of Sa-(+)-2-methyl-4-phenyl-2,3-butadienoic acid Sa-(+)-**6a** with PhI was studied. The results were rather disappointing with a highest ee of 60% (Scheme 15).[22]
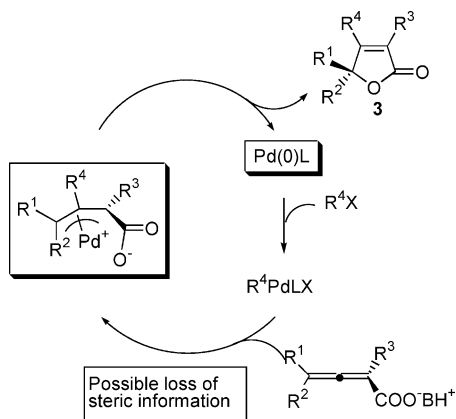
Scheme 14

S-(+)-**7a** (X = Br, 3 h, 92% yield, 98% ee)
S-(+)-**7b** (X = Cl, 6 h, 90% yield, 97% ee)

CuX$_2$
acetone/H$_2$O (2:1)
60–65 °C

R-(-)-**7a** (X = Br, 3 h, 90% yield, 98% ee)
R-(-)-**7b** (X = Cl, 6 h, 93% yield, 98% ee)

(S)-A = (S)-(-)-α-methylbenzylamine
(R)-A = (R)-(+)-α-methylbenzylamine

Scheme 15

2.5 mol% Pd$_2$(dba)$_3$·CHCl$_3$
10 mol% PPh$_3$
toluene

Sa-(+)-**6a**
96 ee%

S-(+)-**8a**

lower ee

Scheme 16

The chirality may be lost in formation of the π-allyl palladium intermediate by the carbopalladation reaction (Scheme 16).

This prompted us to try a different mechanistic pathway which involves a R^{4}PdX-coordination-directed oxypalladation-reductive elimination process, through which the chirality may be reasonably kept (Schme 17).[22]

Thus, the 1:1 salt of Sa-(+)-2-methyl-4-phenyl-2,3-butadienoic acid and *i*-Pr$_2$NEt Sa-(+)-**9a** was prepared from their reaction in ethyl acetate at room temperature. Its corresponding Pd(0)-catalyzed reaction with PhI afforded (S)-(+)-**8a** in 91% ee, a dramatic improvement (Scheme 18).[22] With the cinchonidine salt Sa-(+)-**5a**, the reaction should be carried out in the presence of TBAB as the phase transfer catalyst.[22] The preformed COO$^-$ in the salt may speed up the oxypalladation process.

Scheme 17
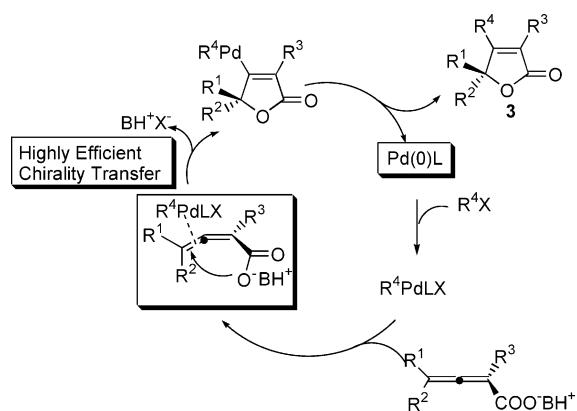
The stereochemistry of this reaction was established by the X-ray diffraction study of Sa-2-(*n*-propyl)-4-(*p*-bromophenyl)-2,3-butadienoic acid and (S)-(+)-**8f** and the related study of (S)-(+)-**8g**, which provides further evidence for the plausible mechanism shown in Scheme 17 (Scheme 19).[22]

III. CuX$_2$-Promoted Cyclization of 2,3-Allenoates

Usually 2,3-allenoic acids were prepared by the hydrolysis of 2,3-allenoates. In some cases, a mixture of 2,3-allenoic acids and 3-alkynoic acids can be obtained. Furthermore, it is more convenient to synthesize the optically active 2,3-allenoates. Thus, it is desirable to develop methodologies starting from 2,3-allenoates (Scheme 20).

As a first try, the direct reaction of 2,3-allenoates with CuBr$_2$ at 80−85 °C in equeous ethanol was developed, indicating that the carbonyl oxygen atom is nucleophilic enough to paticipate the cyclization reaction (Scheme 21).[23]

In some difficult cases, the benzyl ester is a better choice (Scheme 22).[23]

IV. Cyclization of 2,3-Allenamides-Synthesis of γ-Lactams or γ-Iminolactones

Ag$^+$-catalyzed cycloisomerization of 2,3-allenylamines and Pd(0)-catalyzed coupling cyclization of 2,3-allenylamines with organic halides have been studied by Claesson[24] and Ibuka,[25] respectively. No reports had been disclosed for the cyclization of 2,3-allenamides. On the other hand, 5-hydroxypyrrol-2(5H)-ones exhibit interesting biological activities.[26] Typical examples are **10**, **11**, and **12** (Scheme 23). Compared to other known methodologies,[27] due to the easy availability of starting materials, the methods described here are efficient, and the products were formed in high yields with high stereoselectivity and diversity.

It is interesting to observe that the CuX$_2$-promoted cyclization reaction of 2,3-allenamides afforded 5-hydroxypyrrol-2(5H)-ones directly in high yields. Here, the 4-halopyrrol-2(5H)-one formed during the reaction was oxidized by the oxygen in air. This process may also be mediated by Cu(II) (Scheme 24).[27]
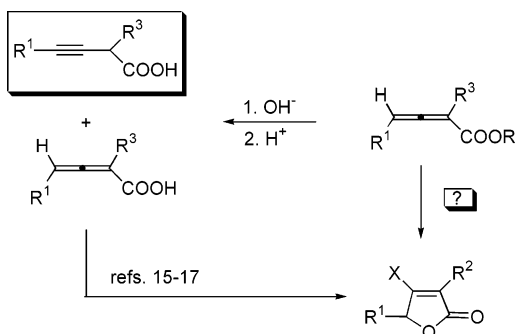
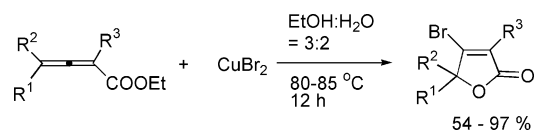**Scheme 18**
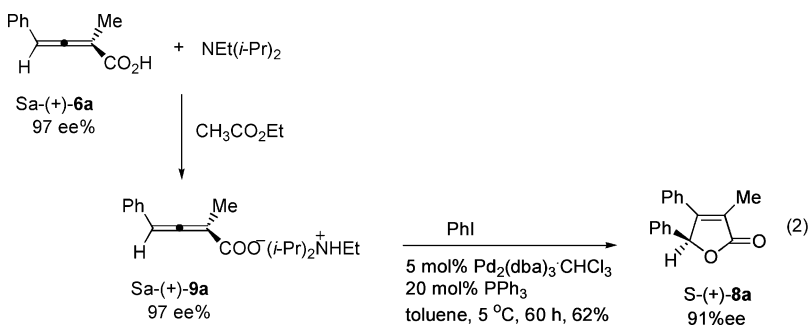
Scheme 19
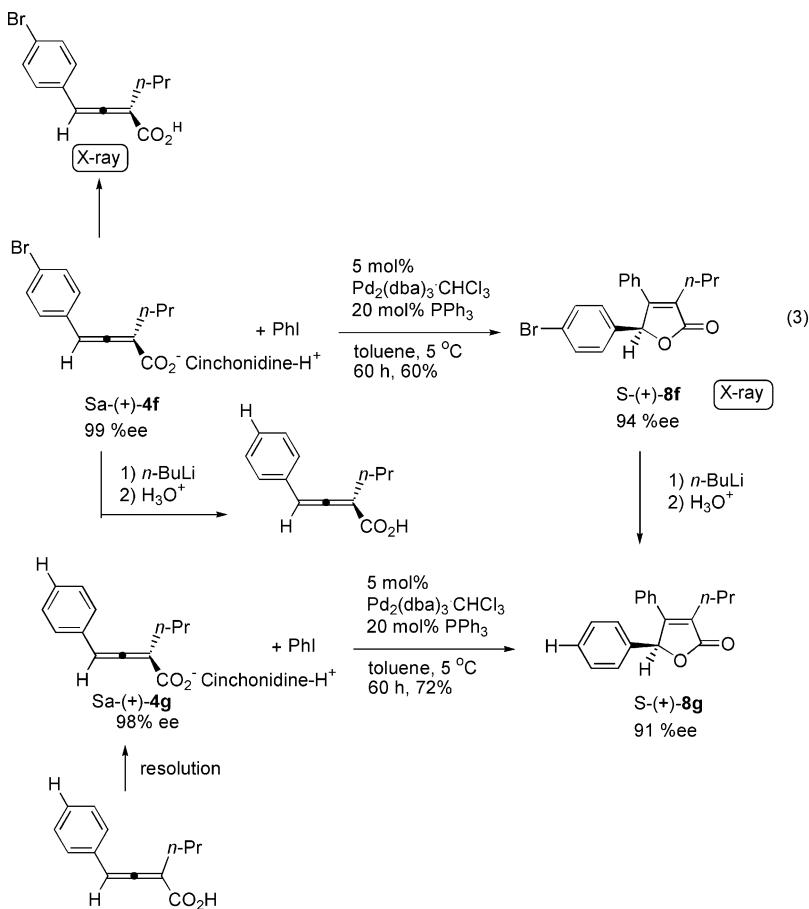
Scheme 20

The Pd(0)-catalyzed reaction of organic halides with 2,3-allenamides afforded 5-hydroxypyrrol-2(5H)-ones or iminolactones, depending on the steric effect of the substitutent(s) at the 4-position of 2,3-allenamides: with
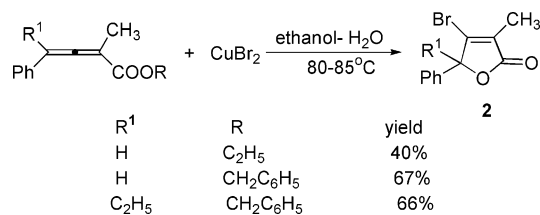
Scheme 21

4-monosubstituted 2,3-allenamides, the N-atom attacks the carbon terminal connected with R^1 group, while with 4,4-disubstituted 2,3-allenamides, the less hindered carbonyl oxygen acts as the nucleophile leading to iminolactones.[28]
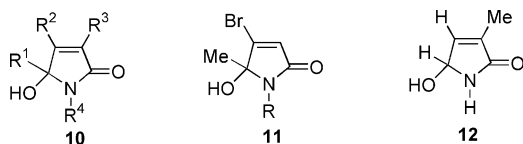
V. Pd-Catalyzed Reaction of 2,3-Allenols with Organic Halides

Ag^{+}-catalyzed cycloisomerizations of 2,3-allenols were reported by Claesson[29] and Marshall (Scheme 26).[30]
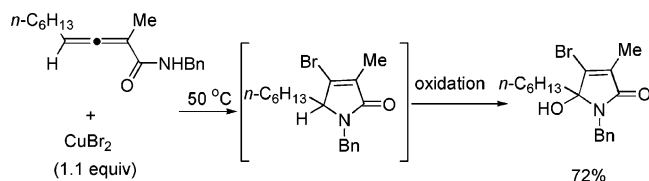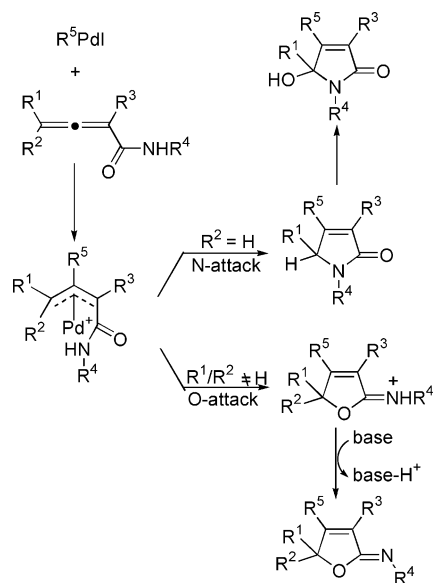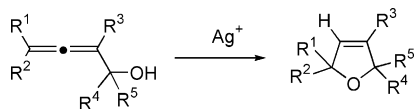
Scheme 22

R[1]	R	yield
H	C_2H_5	40%
H	$CH_2C_6H_5$	67%
C_2H_5	$CH_2C_6H_5$	66%

Scheme 23

10 11 12

Scheme 24

72%

Scheme 25

Scheme 26

Scheme 27

Scheme 28

46 - 95 %
d.r. 92:8 ~ 100:0

Scheme 29

52%

98 % ee
R,R

85%

96% ee
R,R

In this reaction,[32,33] we found that Ag_2CO_3 is not required, the best solvent is DMF, and the reaction afforded trans-three-membered vinylic epoxides exclusively and highly stereoselectively (Scheme 28).

Under these conditions, optically active trans-vinylic epoxides can be prepared by starting from the optically active 2,3-allenols. The absolute configuration of the chiral center adjacent to the sp^2C center was controlled by the steric information of the chiral center of 2,3-allenol[34] due to the high diastereoselectivity of this reaction (Scheme 29).

Furthermore, it is interesting to note that even with the increased hindrance by the introduction of R^2 group, the reaction still afforded three-membered products exclusively (Scheme 30).[34]

Pursuing the chemistry for the formation of five-membered 2,5-dihydrofunans from 2,3-allenols, a Pd(II)-catalyzed reaction was designed, in which a dehalopalladation reaction was used to regenerate the catalytically active Pd(II) species (Scheme 33). Indeed, a $PdCl_2$-catalyzed coupling reaction of allylic bromide with 2,3-allenols leading to the formation of 2,5-dihydrofurans in DMA occurred smoothly.[35] The reaction is efficient for primary, secondary, and tertiary alcohols.
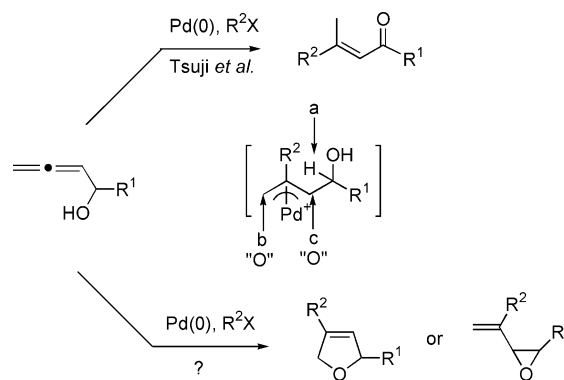
The Pd(0)-catalyzed reaction of organic halides with 2,3-allenols was first studied by Tsuji et al. in Japan,[31] in which, due to the involvement of β-H elimination, α,β-unsaturated enone was formed (Scheme 29). Although it is well-known that there should be a big difference in terms of reactivity between 2,3-allenoic acids and 2,3-allenols, we utilized the same reaction conditions for the corresponding coupling-cyclization reaction of 2,3-allenoic acid with organic halide[7] to see the possibility of forming either 4-substituted-2,5-dihydrofurans or vinylic epoxides from 2,3-allenols (Scheme 27).
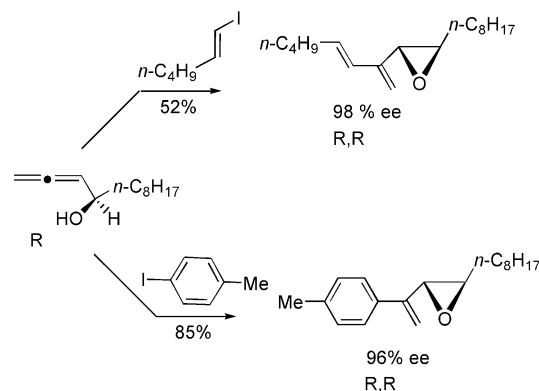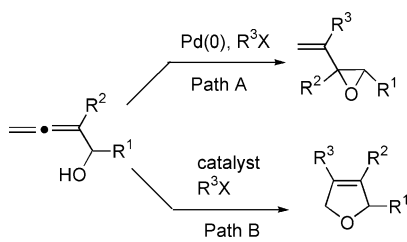
Scheme 30

Scheme 31

76 %

Scheme 32

5 equiv.	4 h	4%	65%
0.25 equiv.	10 h	trace	73%
0 equiv.	48 h	-	24%

Scheme 33

regioselectivity control

stereoselectivity control

The substituent(s) of the allene moiety was found to play a very important role in this reaction. With unsubstituted allenols, dimerization was observed even in the presence of allyl bromide. This can be rationalized by the relatively higher reactivity of unsubstituted allene moiety, as compared to that of the C–C double bond in allyl bromide (Scheme 32).[36]

In the presence of an external nucleophile, i.e., amine, the three-component reaction with 2,3-allenols and or-

Scheme 34

Scheme 35

a: stereoelectronic effect control
b: steric effect control

Scheme 36

catalyst = Ag$^+$, (PPh$_3$)$_3$RhCl

Scheme 37

ganic halides would provide a convenient entry to amino alcohols, providing that the issues of regio- and stereo-selectivity can be addressed (Scheme 33).

Through trial and error, it was observed that both issues can be controlled by the substituent adjacent to the hydroxyl group: with R^1 being the aryl group, the reaction afforded α-amino homoallyl alcohol; with R^1 being alkyl, alkenyl, and prefluoroalkyl groups, the reaction produced γ-amino allylic alcohols with a Z-selectivity for the C=C bond (Scheme 34).[37] Et$_3$N is the best solvent for this reaction.

Scheme 38

PhX + *n*-C$_{12}$H$_{25}$ (allene) → 5 mol% Pd(PPh$_3$)$_4$, PhMe, 12 h → Ph-furan *n*-C$_{12}$H$_{25}$—Me **14** + H,H-furan *n*-C$_{12}$H$_{25}$—Me **15**

NEt$_3$ (1.5 equiv.), 100 °C   53%   42%
Ag$_2$CO$_3$ (10 mol%), NEt$_3$ (2 equiv.), 80 °C   88%   9%

Scheme 39

C$_7$H$_{15}$ ... **16** + aryl iodide (R) → Pd(Ph$_3$P)$_4$ (5 mol %), Ag$_2$CO$_3$ (10 mol%), Et$_3$N, toluene, 80 °C, 18 h → C$_7$H$_{15}$—furan—*t*-Bu **17**

R = H, 74%
R = CO$_2$Me, 68%

Scheme 40

R^4, R^2 allene + R^1 ketone + allyl Br → cat. Pd → furan (R^2, R^4, CH$_2$R^1, allyl) 50 - 79 %

Scheme 41

allene (Me) ketone + Ph—CH=CH—CH$_2$Br → 5 mol% PdCl$_2$(PhCN)$_2$, K$_2$CO$_3$ (1 equiv), CH$_3$CN, 25 °C → Ph—furan (H, Me) 20 h, 50%

(II)Pd ... Me **18**, Ph—CH=CH—Br

furan (Ph, allyl) not formed

Scheme 42

R^1, R^2, R^3, COOH allene + R^4 allenyl ketone → 5 mol% PdCl$_2$(MeCN)$_2$, CH$_3$CN, rt, 4 h → bicyclic (R^4, R^2, R^1, R^3) **19** 69 - 92 %

The stereoelectronic effect of the two aryl groups in intermediate **13** may be responsible for the α-regioselectivity, and the steric effects of the two terminal substituents are the determining factor for the γ-regioselectivity, respectively (Scheme 35).[37]

VI. Pd(0)-Catalyzed Coupling Cyclization of 1,2-Allenyl Ketones

Transition metal-catalyzed cycloisomerization of 1,2-allenyl ketones leading to furan derivatives has been extensively studied by Marshall[30b,38] and Hashmi[39] (Scheme 36).

Hashmi also demonstrated the AuCl$_3$-[39c] or Pd(II)-catalyzed[39b,40] dimeric cyclization of 1,2-allenyl ketones (Scheme 37).

When we applied the coupling−cyclization concept to the synthesis of polysubstituted furans, a mixture of coupling-cyclization product **14** and cycloisomerization product **15** was formed. Here again, a catalytic amount of Ag$^+$, i.e., Ag$_2$CO$_3$, is essential for the selective formation of coupling−cyclization product. Otherwise, the cycloisomerization product was formed in significant amounts (Scheme 38).[41] Compared with the cycloisomerization protocol, an extra substituent may be easily introduced into the 3-position of furans.

The reaction of *tert*-butyl-substituted 1,2-allenyl ketone **16** also afforded the corresponding products **17** in good yields, indicating that the carbonyl oxygen atom is nucleophilic enough to participate the coupling cyclization reaction (Scheme 39).

With the above-discussed protocol, only arylic and vinylic halides can be applied. For the synthesis of 3-allyl furans, the Pd-catalyzed coupling−cyclization reactions of 1,2-allenyl ketone with allylic bromides were also developed (Scheme 40).[42]

It is interesting to observe that the reaction with 3-phenyl-2(*E*)-propenyl bromide afforded 2,3-dimethyl-4-(3′-phenyl-2′(*E*)-propenyl)furan as the only product. The formation of 2,3-dimethyl-4-(1′-phenyl-2′-propenyl)furan was not observed, indicating a direct replacement of
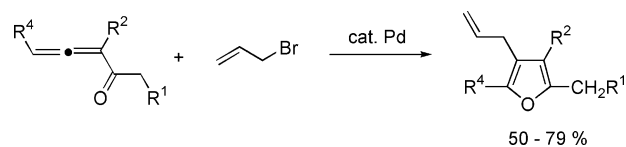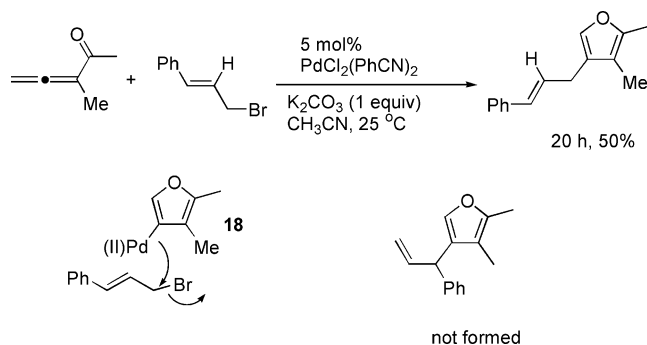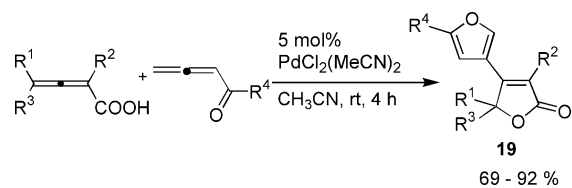
bromide by the sp^2 C−Pd species **18** or an oxidative addition−reductive elimination process (Scheme 41).[42]
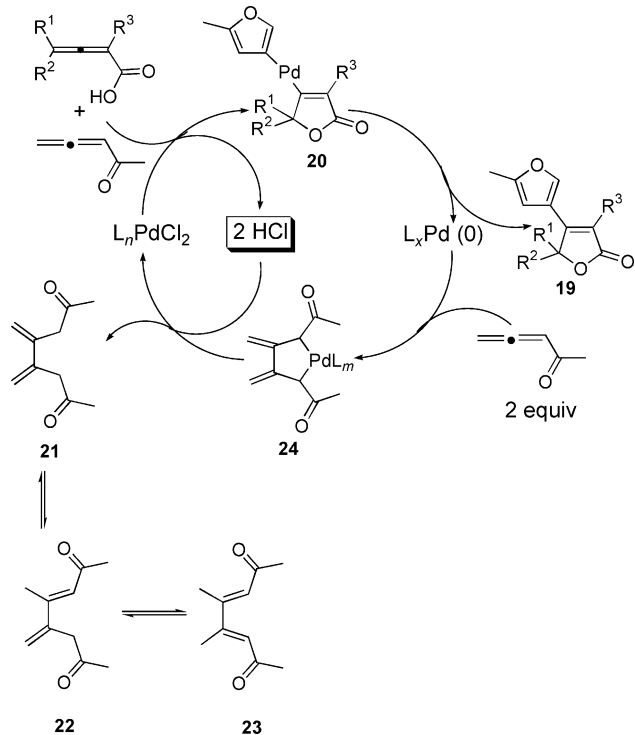
1,2-Allenyl ketone can also be applied as a partner in the Pd(II)-catalyzed biallene approach for the synthesis of dumbbell-type bicyclic compounds **19** (Scheme 42).[43]

Here an excess of 1,2-allenyl ketone was required not only for the bicyclization reaction itself but also for the regeneration of the catalytically active species. This was proved by the isolation of three 1,6-diketones **21**, **22**, and **23**, which were formed by the protonolysis of cyclometalated intermediate **24**. The HCl formed in situ in the first step is also crucial for the catalytic cycle. The matched reactivities of 2,3-allenoic acids and 1,2-allenyl ketone are the key for the formation of intermediate **20** (Scheme 43).[39a,43]
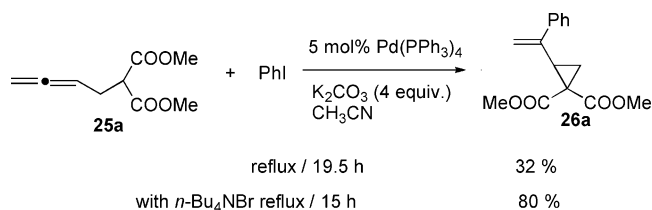
VII. Pd(0)-Catalyzed Coupling-Cyclization of 2′-(2′,3′-Butadienyl)malonates with Organic Halides—Tuning the Regioselectivity

Cazes reported the Pd(0)-catalyzed coupling-cyclization of 2-(2′,3′-butadienyl)malonates and organic halides.[44] Except in a few limited cases, the reaction afforded five-

Scheme 43

Scheme 44

reflux / 19.5 h	32 %
with *n*-Bu$_4$NBr reflux / 15 h	80 %

Scheme 45

E = COOMe

Scheme 46

Conditions A = 5 mol % Pd(PPh$_3$)$_4$, K$_2$CO$_3$ (4 equiv.), 10 mol % of n-Bu$_4$NBr, CH$_3$CN, reflux

Conditions B = 5 mol % Pd(PPh$_3$)$_4$, K$_2$CO$_3$ (4 equiv.), THF, reflux

Scheme 47

Conditions		
2 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 4 mol % dppe, K$_2$CO$_3$ (4.0 equiv.), 10 mol % of *n*-Bu$_4$NBr, and DMSO, 85 °C, 24 h	49%	13%
2 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 4 mol % dppe, NaH (1.1 equiv.), DMSO, 85 °C 12.5 h	14%	58%
Conditions C, (5 mol % Pd(PPh$_3$)$_4$, NaH (1.1 equiv.), DMSO, 85 °C) 12 h	0	**88%**

membered products highly selectively. We have observed that under the catalysis of Pd(PPh$_3$)$_4$ (5 mol %), the reaction of dimethyl 2-(2′,3′-butadienyl)malonate and PhI in the presence of K$_2$CO$_3$ (4 equiv) produced the three-membered vinylic cyclopropane derivative in CH$_3$CN exclusively, albeit in a low yield. With the addition of *n*-Bu$_4$NBr, the three-membered product was formed in 80% yield as the only product (Scheme 44).[45]
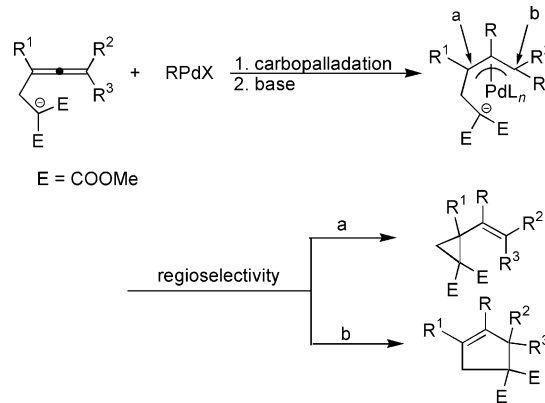
Thus, we attempted to develop different reaction conditions for the control of regioselectivity of this reaction (Scheme 45).[46]

The same reaction in THF afforded the three-membered product exclusively even in the absence of *n*-Bu$_4$NBr. Under conditions A, even with dimethyl 2-(2′-benzyl-2′,3′-butadienyl)malonate, the reaction afforded the cyclopropane derivative highly selectively. The formation of cyclopentene derivative was limited to 2−3% (Scheme 46).[46]
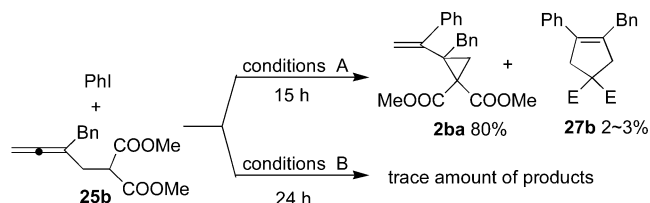
By tuning the solvent and base, reaction conditions (conditions C) for the highly selective formation of cyclopentene derivatives were also found (Scheme 47). However, conditions C can only be perfectly applied to the 2′-substituted malonate.[46]

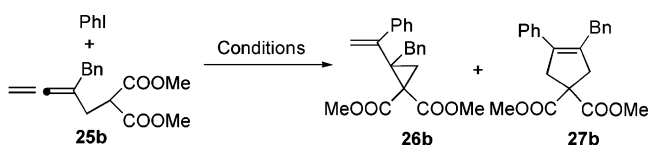The reactions with 2-(2′-unsubstituted-2,3-butadienyl)malonates under conditions C afforded a mixture of three-membered and five-membered products. Conditions D then were developed, under which the reaction produced cyclopentene derivatives exclusively. With this set of reaction conditions, the selectivity problem under conditions C was also addressed nicely (Scheme 48).[46]

Furthermore, it is interesting to observe that the steric effect of organic halides also has an obvious impact on the regioselectivity. Under conditions A, the reaction of dimethyl (2′-benzyl-2′,3′-butadienyl)malonate with PhI afforded three-membered product **26b**, while the same reaction except that *o*-methylphenyl iodide was used instead of PhI afforded five-membered product **27c** exclusively (Scheme 49).

It is proposed that the cyclopropane derivative may be formed via the intermediate *syn*-**28** while the five-

Scheme 48

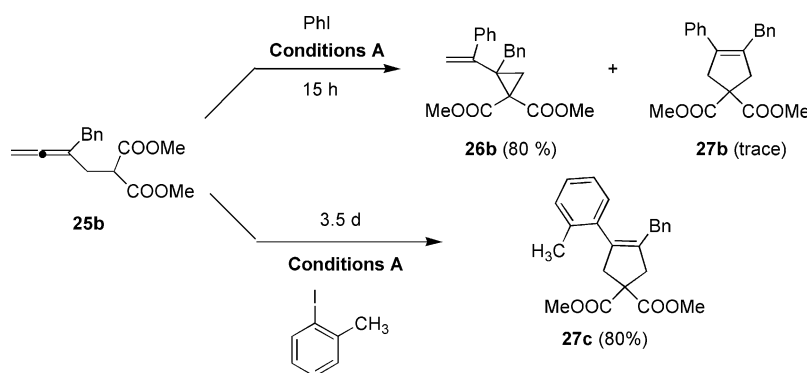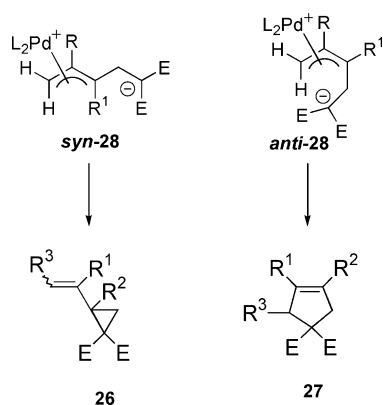| entry	R^1	R^2	Conditions D		Conditions C	
			26 (%)	27 (%)	26 (%)	27 (%)
1	H	*p*-MeC$_6$H$_4$	0	63	-	-
2	H	*p*-MeOC$_6$H$_4$	0	57	-	-
3	*n*-Pr	*p*-MeOC$_6$H$_4$	0	51	7	47
4^a	*n*-Pr	*p*-MeOC$_6$H$_4$	0	70	-	-
5	*n*-Pr	*p*-MeO$_2$CC$_6$H$_4$	0	52	8	54
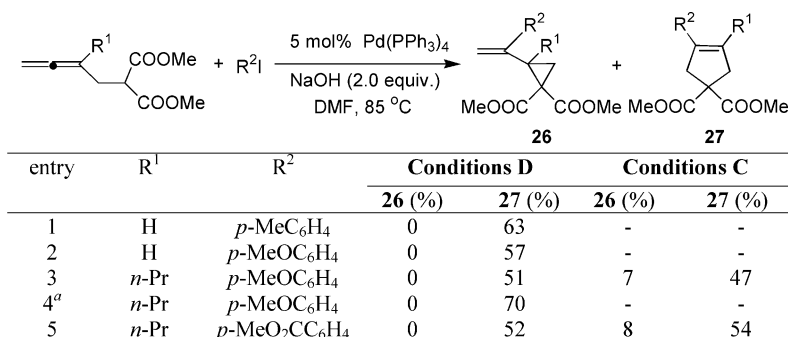
^{a} NaH (1.1 equiv.) was used instead of NaOH as the base.

Scheme 49

Scheme 50

membered product was formed via the intermediate *anti-***28** (Scheme 50).

According to this assumption, it is believed that the syn-intermediate **28** is thermally more stable than the anti-intermediate **28**.[47] Thus, if enough time is allowed, the latter will convert to the former. This was proved by the experimental data. When a mixture of PhI and 2-(2′-benzyl-2′,3′-butadienyl)malonate was treated with 20 mol % Pd(PPh$_3$)$_4$ in DMSO at 85 °C for 6 h first, followed by the addition of NaH (1.1 equiv), this process afforded the three-membered product **26b** in 29% yield, a result in contrast to the same reaction, except that Pd(PPh$_3$)$_4$ and NaH were added simutaneously (Scheme 51).

VIII. Concluding Remarks and Perspectives

We have demonstrated that allenes with a nucleophilic functionality connected to the α-carbon atom are versatile

Scheme 51
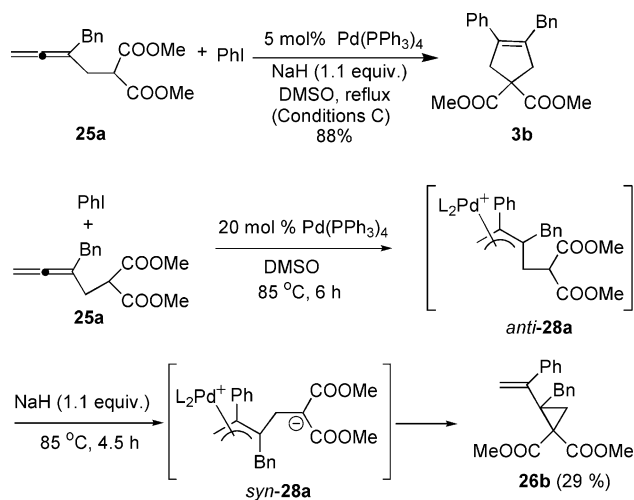
starting materials for some cyclic and acyclic compounds of synthetic and biological importance. Due to the substituent-loading capability and diversity of the functionalities, these methodologies are efficient, selectivity tunable, and diverse. Due to the chirality of the allene moiety and any chiral elements in the starting compounds, synthesis of compounds with optical activity is possible, depending on the availability of the optically active starting materials and the efficiency of chirality transfer. Future attention must be focused on the enantioselective synthesis of optically active allenes with a functionality.[34,48] Attention should also be directed to the influence of the nature of the tether between the allene moiety and the functionality on tuning the reactivity and selectivity,

polycomponent coupling cyclization reaction, new reaction patterns with different metal catalysts, etc. More research will be carried out to demonstrate the potentials of allenes.

Note Added after ASAP Posting

This paper first appeared on the Web with an error in Scheme 14. The correct version was published 6/25/2003.

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