HETEROCYCLES, Vol. 87, No. 9, 2013, pp. 1835 - 1864. © The Japan Institute of Heterocyclic Chemistry
Received, 18th June, 2013, Accepted, 4th July, 2013, Published online, 16th July, 2013
DOI: 10.3987/REV-13-776

SYNTHESES OF FUNCTIONALIZED CYCLIC MOLECULES BY PALLADIUM-CATALYZED CYCLIZATION OF PROPARGYLIC ESTERS WITH BIS-NUCLEOPHILES

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Abstract – It is known that propargylic esters react with palladium complex leading to π-propargylpalladium complexes, which further cause various transformations in the presence of soft nucleophiles to produce the corresponding products. Among them, palladium-catalyzed cyclization of propargylic esters with bis-nucleophiles is one of the useful methodologies for the construction of functionalized cyclic molecules in one step. Since the pioneering work reported by Tsuji in 1985, a considerable number of reactions have been reported by the use of various bis-nucleophiles. In this review, a comprehensive overview of the studies on palladium-catalyzed reactions of propargylic esters with bis-nucleophiles is described, in which various functionalized cyclic molecules can be synthesized in a regio- and stereoselective manner.

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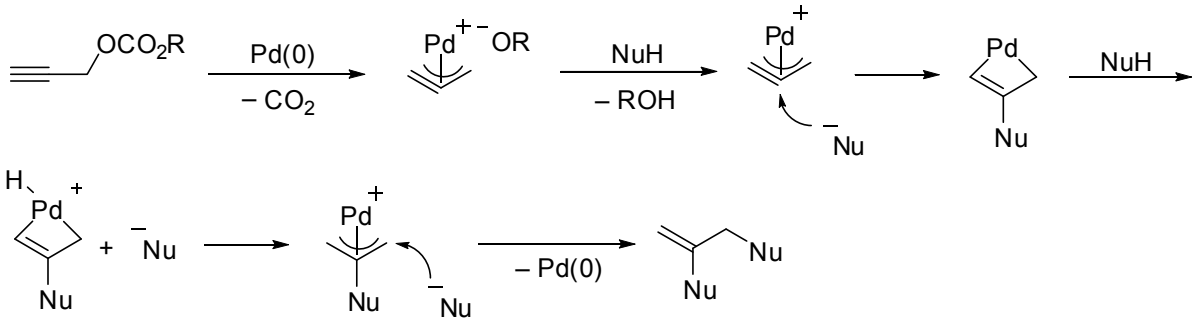
1. INTRODUCTION

Propargylic compounds containing an ester or a halide at the propargylic positions are known as useful intermediates in organic synthesis, and a number of reactions utilizing the properties of propargylic compounds have been reported.[1–3] For example, propargylic carbonates react with palladium complex leading to π-propargylpalladium complexes, which further cause various transformations in the presence of soft nucleophiles to produce the 1,2-disubstituted allylic compounds along with the regenerated palladium complexes (Scheme 1).[2,3] In the reaction, a nucleophile initially attacks to the central carbon of π-propargylpalladium to transform the π-allylpalladium complex via the palladacyclobutene,[4,5] which further reacts with another nucleophile to afford the disubstituted products. Various transformations including cyclization reactions have been developed by the design of propargylic substrates and nucleophiles.

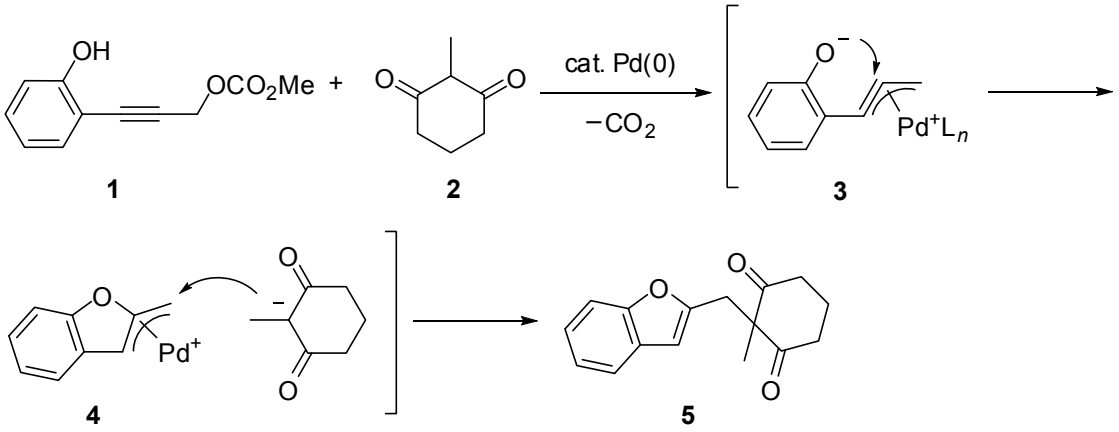


Scheme 1

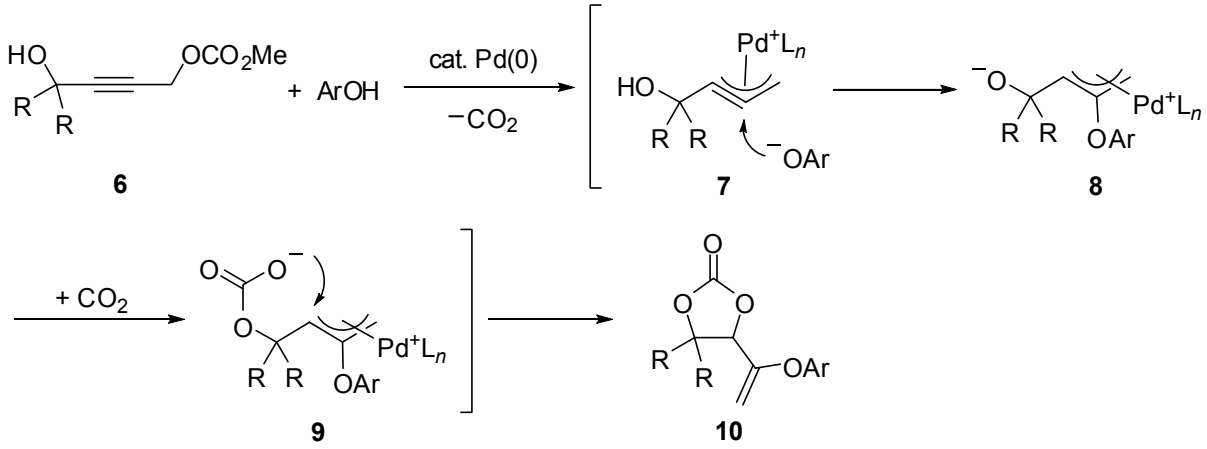
As an example of the reaction, we have reported the synthesis of 2-substituted benzofurans by the reaction of 2-phenoxy-substituted propargylic carbonate **1** with 2-methyl-1,3-cyclohexanedione (**2**) (Scheme 2).[6] In the reaction, the intramolecular nucleophilic attack of the phenolic oxygen to the π-propargylpalladium **3** gave the π-allylpalladium intermediate **4**, which was subjected to the intermolecular nucleophilic attack by **2** to afford the product **5**.

We also found the formation of substituted cyclic carbonates by the "CO_2-recycling" reaction of propargylic carbonates **6** having a hydroxyl group with phenols (Scheme 3).[7] In the reaction, decarboxylation of **6** triggered by palladium initially occurred to form the π-propargylpalladium **7**, which

caused the nucleophilic attack by phenoxide leading to the π-allylpalladium **8**. The intermediate **8** then trapped the liberated CO_2 in situ to afford the carbonate species **9**, which was transformed to the phenoxy-substituted cyclic carbonate **10** by intramolecular cyclization. In these reactions, a variety of cyclic molecules can be synthesized by introducing the nucleophilic moiety within the propargylic esters.

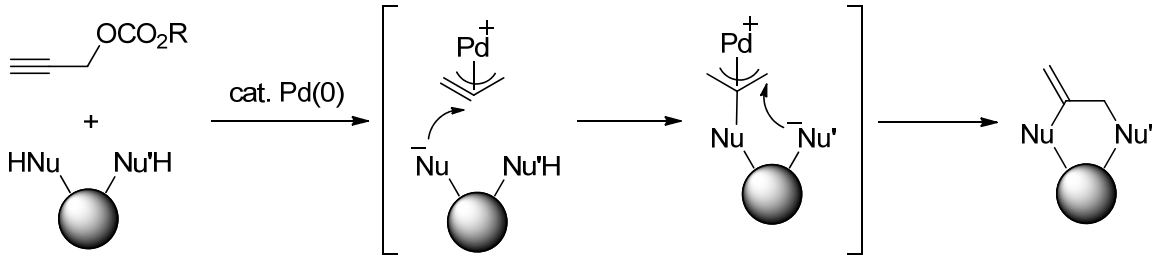


Scheme 2



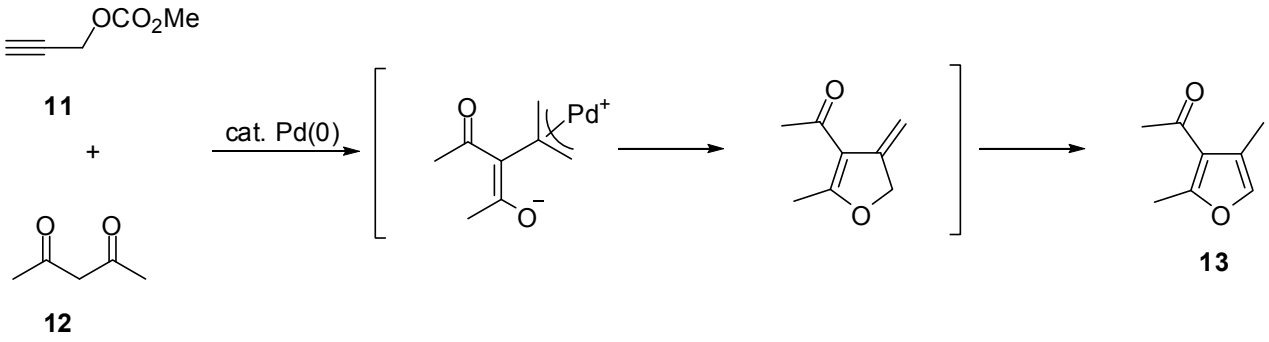
Scheme 3

As another type of the palladium-catalyzed cyclization of propargylic compounds with nucleophiles, it is known that the use of bis-nucleophiles, which contain two nucleophilic parts within the molecules. In this reaction, the initially formed π-propargylpalladium intermediate is subjected to consecutive nucleophilic attacks by the bis-nucleophilic part to give the cyclized product (Scheme 4).



Scheme 4

As this pioneering work, Tsuji reported propargylic carbonates **11** reacted with 1,3-diketone **12** to produce substituted furans **13** (Scheme 5).[8] In this reaction, the π-propargylpalladium complex, which derived from propargylic carbonates and a palladium catalyst, reacted with 1,3-diketone to give the π-allylpalladium complex. Then the complex caused the intramolecular nucleophilic attack of the enolate oxygen followed by the isomerization of the olefin to produce the cyclized product **13**. This type of cyclization is useful for the synthesis of various heterocyclic compounds in one step, and extensive studies about this process have been examined in recent years. In this review, a comprehensive overview of the studies on palladium-catalyzed reactions of propargylic esters with bis-nucleophiles is described, in which various functionalized cyclic molecules can be synthesized in a regio- and stereoselective manner.



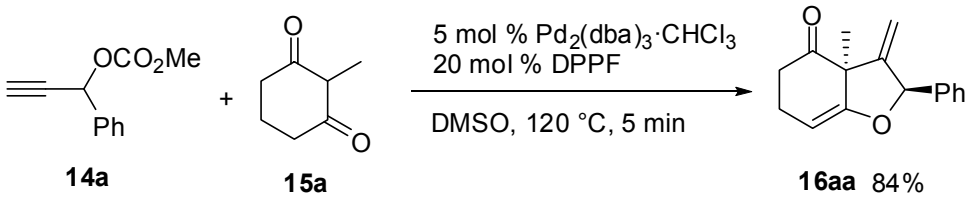
Scheme 5

2. USE OF β-DICARBONYL COMPOUNDS AS A NUCLEOPHILE

2-1. 2-Substituted 1,3-Diketones

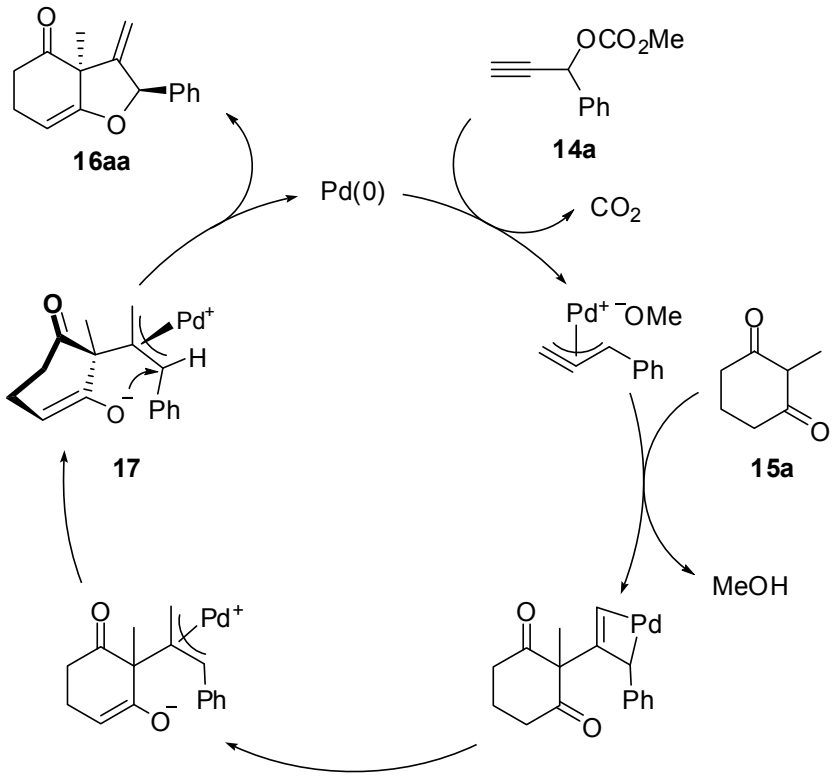
Although the use of 1,3-diketones as a bis-nucleophile in the palladium-catalyzed cyclization of propargylic esters have been reported by Tsuji as shown in Scheme 5, the stereochemistry of the reaction has not been well examined. During the course of our early studies about palladium-catalyzed reactions of propargylic compounds,[6,7,9] we decided to use 2-substituted 1,3-diketones with propargylic esters in the diastereoselective synthesis of cyclic molecules. When propargylic carbonate **14a** and

2-methylcyclohexane-1,3-dione (**15a**) were treated with 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % DPPF in DMSO at 120 °C for 5 min, tetrahydrobenzofuranone **16aa** having *trans*-stereochemistry was produced in 84% yield as a single diastereomer (Scheme 6).[10]



Scheme 6

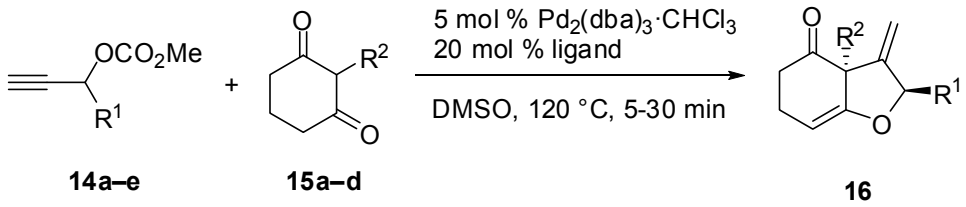
A proposed mechanism for the production of **16aa** is shown in Scheme 7. The propargylic carbonate **14a** reacts with palladium to form the π-propargylpalladium complex, which causes the nucleophilic attack of 1,3-diketone **15a** to give the π-allylpalladium intermediate via the palladacyclobutene.[4] The π-allylpalladium intermediate is further subjected to the intramolecular attack of the enolate oxygen to give the cyclized product **16aa**. The observed *trans*-diastereoselectivity would be explained via the transition state **17**, which has lower energy because of the absence of steric repulsion between the phenyl and methyl groups.



Scheme 7

Table 1 shows the examinations using various substrates. When the reaction of 2-propylcyclohexane-1,3-dione (**15b**) with **14a** was attempted, the propyl-substituted product **16ab** was produced in 75% yield (entry 1). The benzyl- and 2-cyanoethyl-substituted substrates **15c** and **15d** uneventfully reacted with **14a** to afford the corresponding products **16ac** and **16ad** in 76% and 82% yields, respectively (entries 2 and 3). The reactions of propargylic carbonates **14b** and **14c** containing a 1- and 2-naphthyl group at the propargylic position with **15a** also proceeded to produce the corresponding products **16ba** and **16ca**, respectively (entries 4 and 5). Reactions using the 3-furanyl- and *n*-pentyl-substituted substrates **14d** and **14e** gave the corresponding products **16da** and **16ea** in moderate yields (entries 6 and 7).

Table 1. Reactions using various substrates **14a–e** and **15a–d**



14a–e **15a–d** **16**

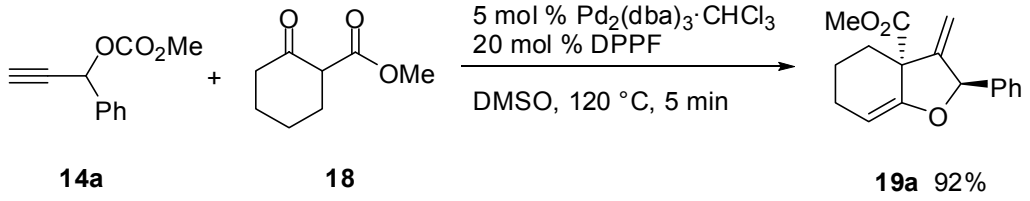
Entry	Substrates		Product	Yield (%)
	R^1	R^2		
1[a]	phenyl (**14a**)	*n*-propyl (**15b**)	**16ab**	75
2[a]	phenyl (**14a**)	benzyl (**15c**)	**16ac**	76
3[b]	phenyl (**14a**)	2-cyanoethyl (**15d**)	**16ad**	82
4[a]	1-naphthyl (**14b**)	methyl (**15a**)	**16ba**	83
5[c]	2-naphthyl (**14c**)	methyl (**15a**)	**16ca**	81
6[d]	3-furanyl (**14d**)	methyl (**15a**)	**16da**	55
7[b]	*n*-pentyl (**14e**)	methyl (**15a**)	**16ea**	43

[a]DPPF was used as a ligand. [b]DPPB was used as a ligand. [c]DPPP was used as a ligand. [d]DPPPentane was used as a ligand.

2-2. Cyclic β-Keto Esters

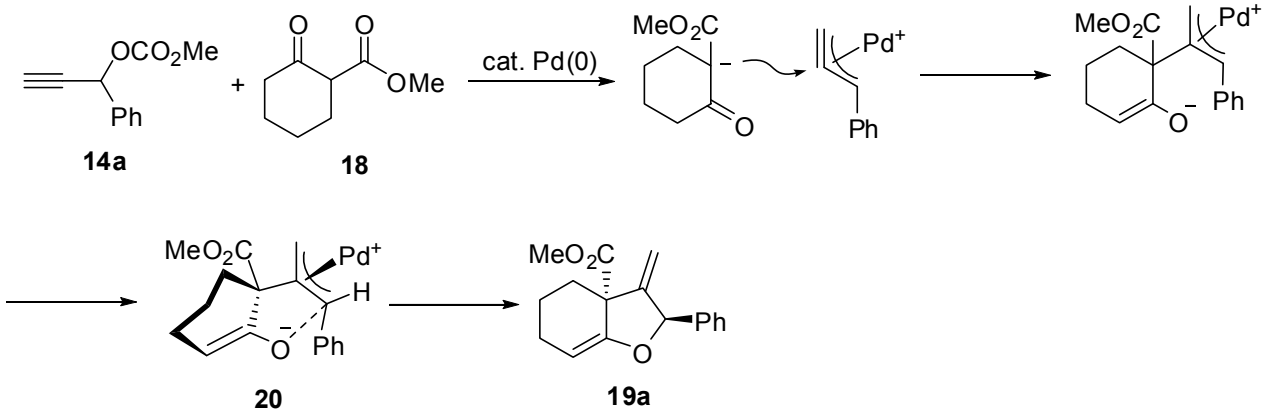
We next examined the reaction of propargylic carbonates with the cyclic β-keto ester. When propargylic carbonate **14a** and methyl 2-oxocyclohexanecarboxylate (**18**) were subjected to the reaction with 5 mol %

$Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % DPPF in DMSO at 120 °C for 5 min, *trans*-substituted hexahydrobenzofuran **19a** was obtained in 92% yield as a single diastereomer (Scheme 8).[10,11]



Scheme 8

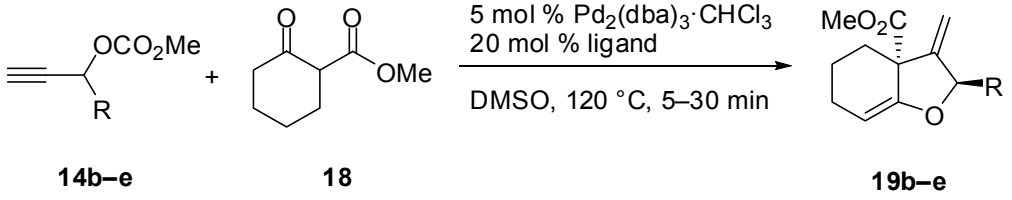
As the proposed mechanism, initially formed π-propargylpalladium complex from the propargylic carbonate **14a** reacts with the β-keto ester **18** to give to the π-allylpalladium intermediate. Then intramolecular nucleophilic attack via the favorable transition state **20** occurs to afford the cyclized product **19a** (Scheme 9).



Scheme 9

The reactions using various propargylic carbonates **14b–e** with **18** are summarized in Table 2. The reactions of the naphthyl-substituted substrates **14b** and **14c** proceeded to produce the cyclized products **19b** and **19c** in 66% and 76% yields, respectively (entries 1 and 2). The substrates **14d** and **14e** having a 3-furanyl and a *n*-pentyl group also reacted to afford the corresponding products **19d** and **19e** in 51% and 56% yields, respectively (entries 3 and 4). It was clear that these reactions proceed in a highly diastereoselective manner since the resulting hexahydrobenzofurans **19a–e** were produced as a single diastereomer.

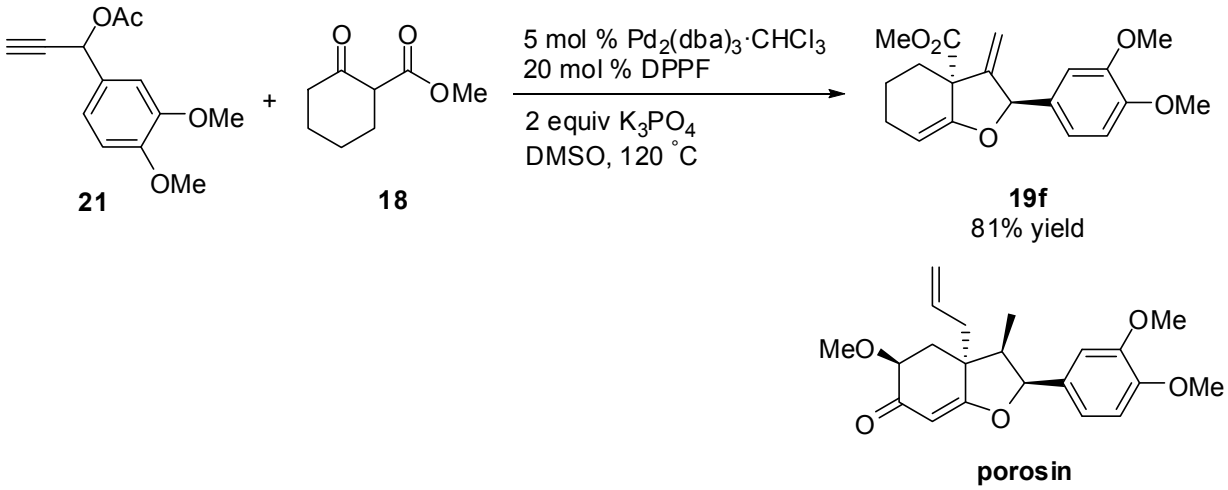
Table 2. Reactions of propargylic carbonates **14b–e** with β-keto ester **18**



14b–e **18** **19b–e**

Entry	R	ligand	product	yield (%)
1	1-naphthyl (**14b**)	DPPF	**19b**	66
2	2-naphthyl (**14c**)	DPPF	**19c**	76
3	3-furanyl (**14d**)	DPPPentane	**19d**	51
4	*n*-pentyl (**14e**)	DPPB	**19e**	56

The reaction of the 3,4-dimethoxyphenyl-substituted propargylic acetate **21** with the 2-oxocyclohexanecarboxylic ester **18** in the presence of K_3PO_4 afforded the corresponding hexahydrobenzofuran **19f** in 81% yield (Scheme 10). The resulting product **19f** contains a core structure of porosin, a neolignan from *Ocotea porosa* and *Urbanodendron verrucosum*,[12] and this cyclization reaction could be synthetically useful for the synthesis of this kind of natural products.

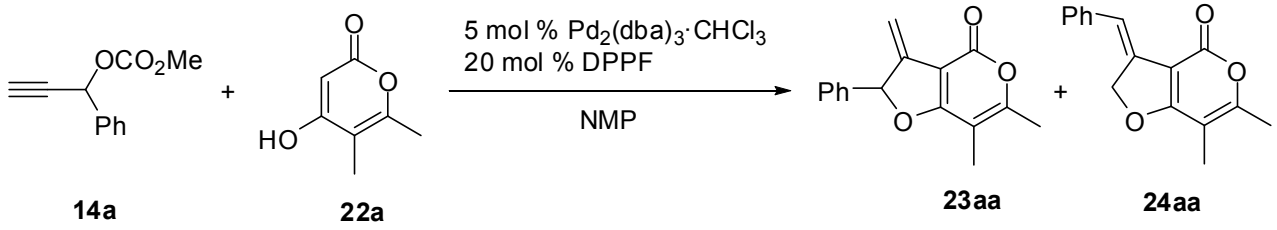


Scheme 10

2-3. β-Hydroxy-α-pyrones

Furo[3,2-*c*]pyran-4-ones are one of the important class of heteroaromatic molecules which are components in a variety of biologically active natural products.[13] We focused on the nucleophilic activity

of 4-hydroxy-2-pyrones as a bis-nucleophile, which is expected to construct the furo[3,2-*c*]pyran-4-ones by the palladium-catalyzed cyclization with propargylic esters. When propargylic carbonate **14a** and 4-hydroxy-2-pyrone **22a** were treated with 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPF in NMP at 25 ºC, the reaction proceeded to afford the 2-phenyl-substituted furopyranone **23aa** in 89% yield as a sole product (Scheme 11).[14] Interestingly, the 3-benzylidene-subsituted furopyranone **24aa** was also obtained as the reaction temperature was increased. Thus, the regioisomer **24aa** was produced together with **23aa** when the reaction was carried out at 100 ºC (**23aa**:**24aa** = 1:1.9, 86% yield), and **24aa** was exclusively obtained in 79% yield in the reaction at 120 ºC. From these results, it has been found that the regioselectivity of the reaction can be controlled depending on the reaction temperature.

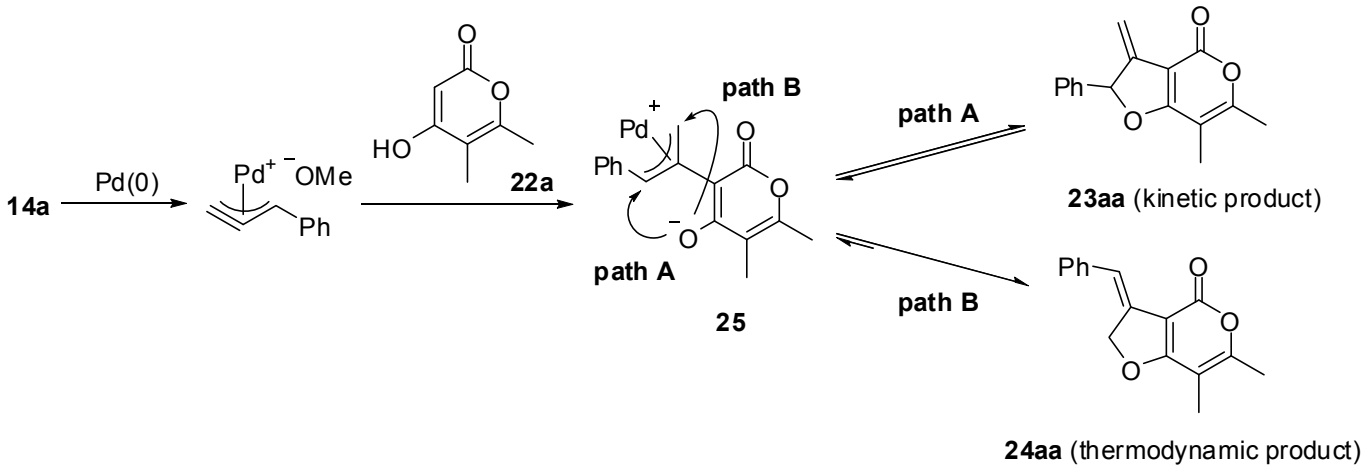


14a **22a** **23aa** **24aa**

Temp.	Product	Total Yield
25 ºC	**23aa** only	89%
100 ºC	**23aa**:**24aa** = 1:1.9	86%
120 ºC	**24aa** only	79%

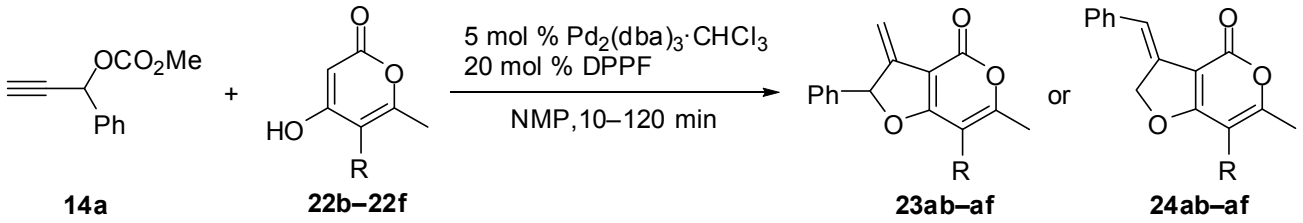
Scheme 11

A proposed mechanism for the formation of the furopyranones **23aa** and **24aa** is shown in Scheme 12. The π-propargylpalladium complex, resulting from the propargylic carbonate **14a** with palladium, reacts with the 4-hydroxy-2-pyrone **22a** to form the π-allylpalladium intermediate **25**. The intermediate **25** is further subjected to intramolecular attack of the hydroxy anion to produce the cyclized product **23aa** or **24aa**. The observed regioselectivity depending on the reaction temperature would be the result of kinetic and thermodynamic control in the cyclization process. In the low reaction temperature, it is expected that the cyclization occurs via path A to provide **23aa** as the kinetic product. On the other hand, there could be equilibrium between the products and π-allylpalladium intermediate **25** at the high temperature. As a result, the thermodynamically more stable **24aa** would be selectively formed via path B.



Scheme 12

Table 3. Reactions using substituted 4-hydroxy-2-pyrones **22b–f** with **14a**



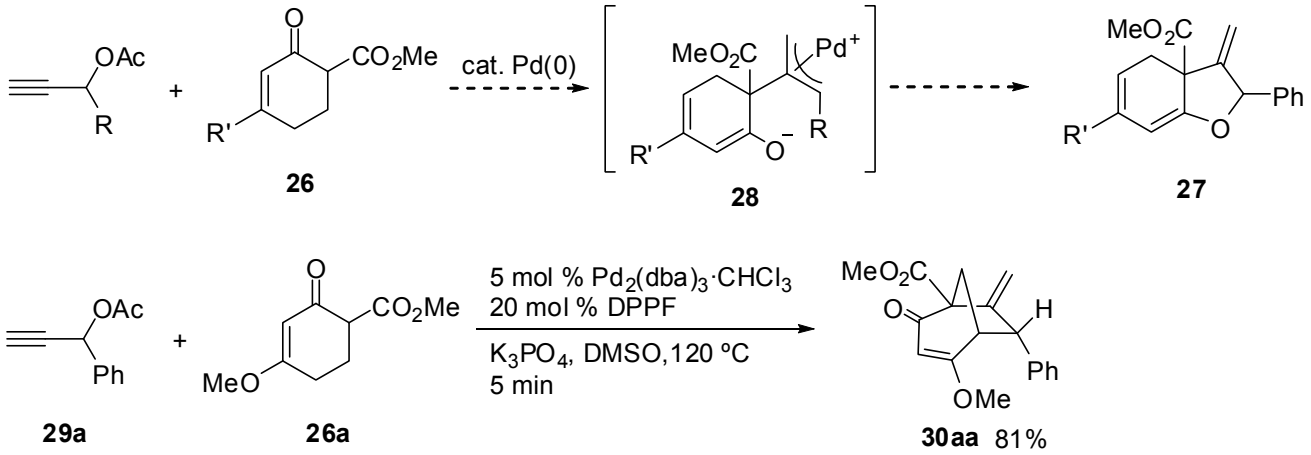
Entry	R	Temp. (ºC)	Product	Yield (%)
1	H (**22b**)	25	**23ab**	47
2	Et (**22c**)	25	**23ac**	78
3	heptyl (**22d**)	25	**23ad**	64
4	allyl (**22e**)	25	**23ae**	47
5	Bn (**22f**)	25	**23af**	70
6	H (**22b**)	120	**24ab**	69
7	Et (**22c**)	120	**24ac**	71
8	heptyl (**22d**)	120	**24ad**	61
9	allyl (**22e**)	120	**24ae**	68
10	Bn (**22f**)	120	**24af**	64

Table 3 shows the examinations using various 4-hydroxy-2-pyrones **22b**–**f**[15] with **14a**. When the substrate

22b having no substituent on the 3-position of the pyrone ring was subjected to the reaction at 25 ºC, the 2-phenyl-substituted furopyranone **23ab** was produced in 47% yield (entry 1). Similarly, the substrates **22c**–**f** containing an ethyl, a heptyl, an allyl and a benzyl group were transformed to the corresponding kinetic products **23ac**–**af** in moderate yields, respectively (entries 2–5). On the other hand, the corresponding 3-benzylidene-subsituted furopyranones **24ab**–**af** were solely produced as the thermodynamic products in each cases when the 4-hydroxy-2-pyrones **22b**–**f** were subjected to the reaction at 120 ºC (entries 6–10).

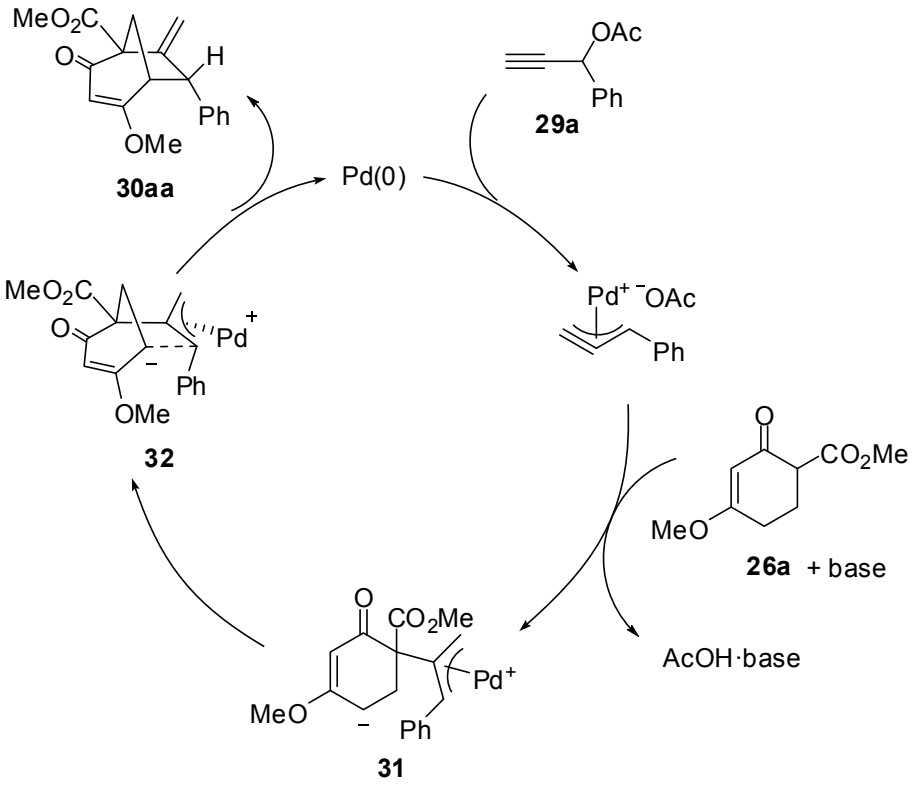
2-4. 2-Oxocyclohex-3-enecarboxylates

As an application of the use of β-keto esters in the palladium-catalyzed reaction with propargylic esters, we focused on the nucleophilic activity of 2-oxocyclohex-3-enecarboxylates **26**. We initially expected that the tetrahydrobenzofuran **27** could be obtained via the π-allylpalladium-dienolate intermediate **28** (Scheme 13). As the result, the unexpected bicyclo[3.2.1]octenone **30aa** was produced in 81% yield as a single stereoisomer when 1-phenyl-2-propynyl acetate (**29a**) and 2-oxocyclohex-3-enecarboxylate **26a** were treated with 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPF and K_3PO_4 in DMSO at 120 ºC for 5 min.[16]



Scheme 13

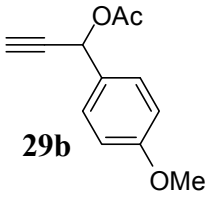
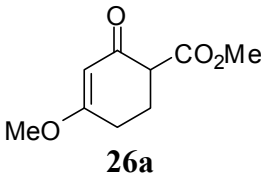
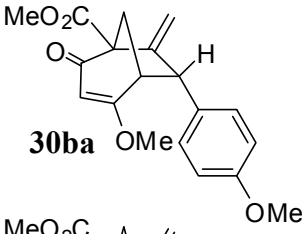
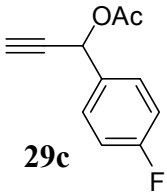
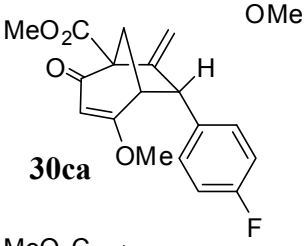
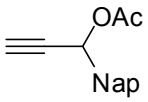
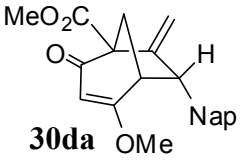
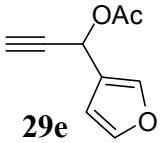
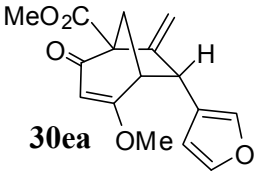
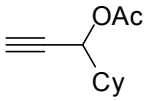
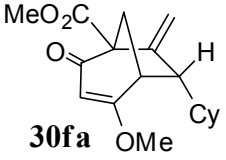
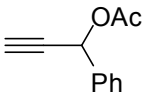
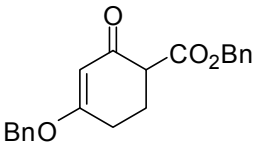
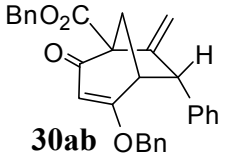
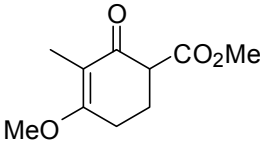
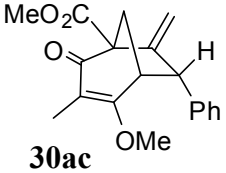
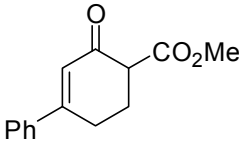
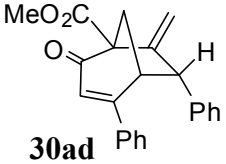
A proposed mechanism for the production of the bicyclo[3.2.1]octenone **30aa** is shown in Scheme 14. After the formation of the π-propargylpalladium complex from **29a** with palladium, the nucleophilic attack of the α-carbon of the 2-oxocyclohex-3-enecarboxylate **26a** gave the π-allylpalladium intermediate **31**. The complex **31** is then subjected to intramolecular attack of the γ-carbon of the enone moiety via the transition state **32** to produce the bicyclo[3.2.1]octenone **30aa**.



Scheme 14

Examinations using various substituted substrates are summarized in Table 4. When the reactions of the propargylic acetates **29b** and **29c** having a *p*-methoxyphenyl and a *p*-fluorophenyl group with **26a** were carried out, the bicyclo[3.2.1]octenones **30ba** and **30ca** were produced in 69% and 80% yield, respectively (entries 1 and 2). The substrates **29d–f** containing a 2-naphthyl, a 3-furanyl and a cyclohexyl group also reacted to produce the corresponding products **30da–fa** in good yields (entries 3–5). When the reaction of the 2-oxocyclohex-3-enecarboxylate **26b** containing a benzyl ester moiety with **29a** was carried out, the bicyclo[3.2.1]octenone **30ab** was produced in 82% yield (entry 6). The reactions of **26c** having a methyl group on the α-position of the enone system also proceeded to give the corresponding product **30ac** in 64% yield (entry 7). The substrate **26d**, which has a phenyl group at the β-position, was successfully transformed to the bicyclo[3.2.1]octenone **30ad** in 75% yield (entry 8). The process produces substituted bicyclo[3.2.1]octenones in a highly stereoselective manner. Since various natural products having a bicyclo[3.2.1]octane structure have been reported,[17] our methodology would provide a new protocol for the synthesis of these compounds with high efficiency.

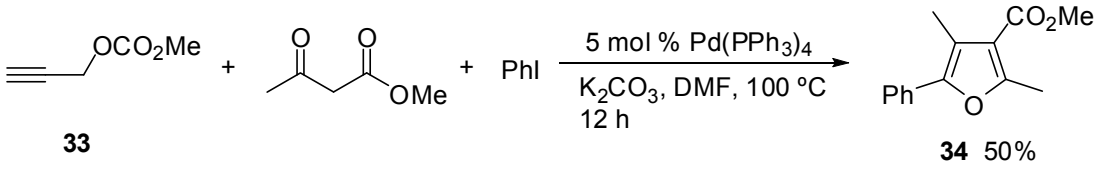
Table 4. Reactions using various substrates **29a–f** and **26a–d**[a]

Entry	Propargylic acetate	β-Keto ester	Product	Yield (%)
1	 **29b**	 **26a**	 **30ba**	69
2	 **29c**	**26a**	 **30ca**	80
3[b]	 **29d**	**26a**	 **30da**	82
4	 **29e**	**26a**	 **30ea**	80
5[c]	 **29f**	**26a**	 **30fa**	78[d]
6	 **29a**	 **26b**	 **30ab**	82
7	**29a**	 **26c**	 **30ac**	64[d,e]
8	**29a**	 **26d**	 **30ad**	75

[a]The reactions were carried out in the presence of **26** and **29**, 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPF and 2 equiv K_3PO_4 in DMSO at 120 ºC for 5 min. [b]Nap = 2-naphthyl. [c]Cy = cyclohexyl. [d]BINAP was used as the ligand. [e]The reaction was carried out at 80 ºC.

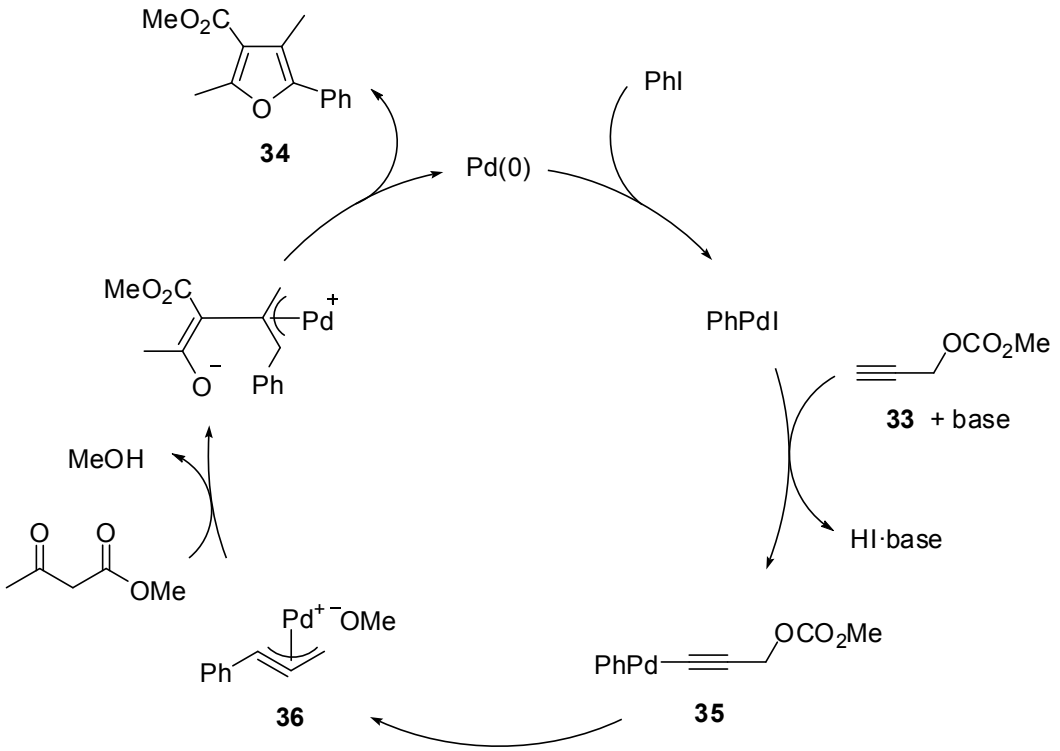
2-5. β-Keto Esters with Aryl Halides

As an application of the synthesis of substituted furans by palladium-catalyzed reaction of propargylic carbonates with β-dicarbonyl compounds, Liang reported that one-pot synthesis of tetrasubstituted furans by a three-component coupling–cyclization reaction (Scheme 15).[18] When propargylcarbonate **33**, acetoacetic acid methyl ester and iodobenzene were treated with 5 mol % $Pd(PPh_3)_4$ and K_2CO_3 in DMF at 100 ºC, the tetrasubstituted furan **34** was produced in 50% yield.



33 **34** 50%

Scheme 15



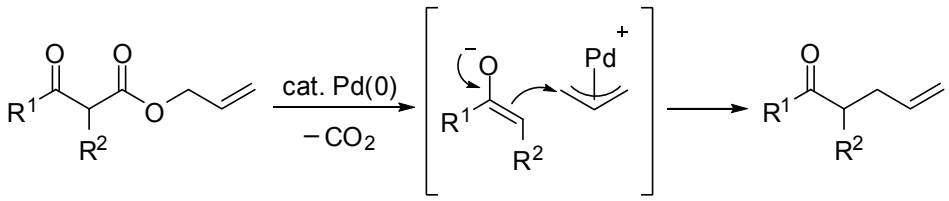
Scheme 16

A tentative mechanism for the production of **34** was shown in Scheme 16. Oxidative addition of iodobenzene to the palladium initially generates the phenylpalladium iodide, which would coordinate

with the propargylcarbonate **33** to transform to the phenylalkynylpalladium **35** in the presence of base. The complex then undergoes decarboxylation to afford the π-propargylpalladium **36**, which would further react with acetoacetic acid methyl ester to afford the tetrasubstituted furan **34**.

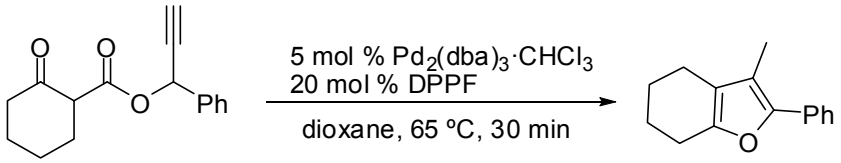
2-6. Propargyl β-Keto Esters

Palladium-catalyzed allylic substitutions with nucleophiles have been extensively studied due to their versatile and specific reactivities,[19] in which soft carbanions derived from β-dicarbonyl compounds are suitable as nucleophiles. On the other hand, examples of the reaction with non-stabilized carbanions such as monoketone enolates are limited.[20] A solution to this problem highlights a decarboxylative allylation of allyl β-keto esters, in which the non-stabilized monoketone enolate is effectively formed in situ to afford an allylated product (Scheme 17).[21]



Scheme 17

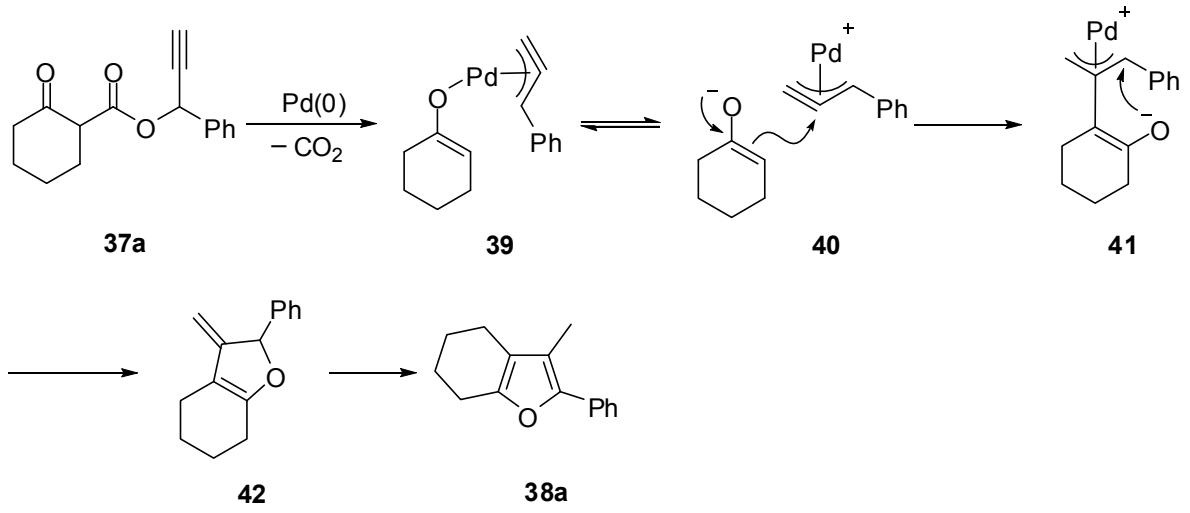
In planning our application about the reaction of propargylic esters with bis-nucleophiles, we focused on the reactivity of propargyl β-keto esters. In contrast to the extensive studies on the reaction of allyl β-keto esters, no examples have been reported on the reactivity of propargyl β-keto esters with palladium. When propargyl β-keto ester **37a** was treated with 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % DPPF in dioxane at 65 ºC, the reaction proceeded to afford the cyclized tetrahydrobenzofuran **38a** in 76% yield (Sceheme 18).[22]



37a **38a** 76%

Scheme 18

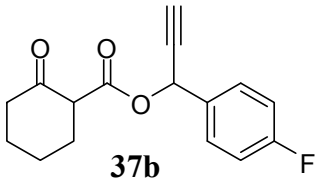
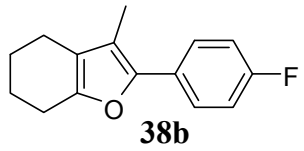
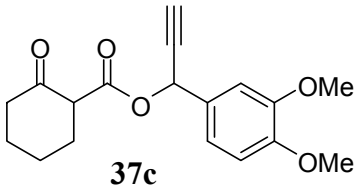
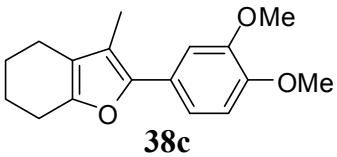
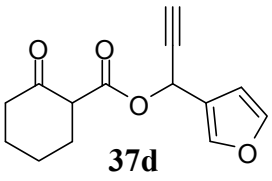
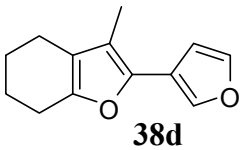
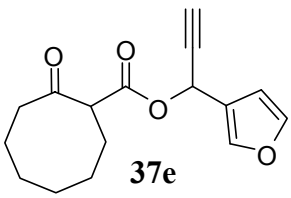
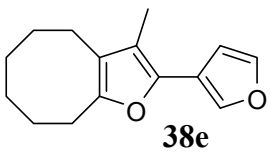
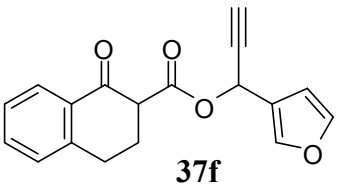
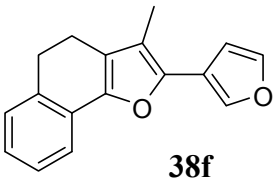
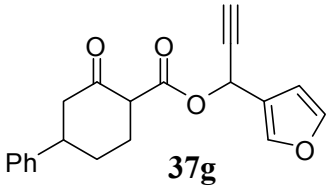
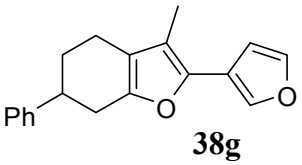
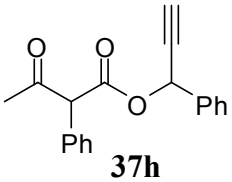
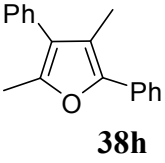
A proposed mechanism for the formation of the tetrasubstituted furans **38a** is shown in Scheme 19. The propargyl β-keto ester **37a** undergoes decarboxylation by palladium to form the π-propargylpalladium enolate **39**, which is in equilibrium with the ion pair **40**. Then nucleophilic attack of the enolate on the π-propargylpalladium undergoes to lead to the π-allylpalladium intermediate **41**. The intermediate **41** is subjected to an intramolecular attack by the enolate oxygen to produce the dihydrofuran **42**, which further isomerizes to afford the substituted furan **38a**.



Scheme 19

The reactions using various propargyl β-keto esters **37b–h** are summarized in Table 5. When the reactions of the substrates **37b** and **37c** having a 4-fluorophenyl and a 3,4-dimethoxyphenyl group were carried out, the tetrahydrobenzofurans **38b** and **38c** were obtained in moderate yields (entries 1 and 2). The reaction of the substrate **37d**, which have a 3-furyl group, also proceeded to afford the tetrahydrobenzofuran **38d** in 79% yield (entry 3). The reactions of the substrates **37e** having a cyclooctanone ring successfully proceeded to give the cycloocta[*b*]furan **38e** in 74% yield (entry 4). The substrate **37f**, which have a 1-tetralone moiety, was also converted to the corresponding product **38f** in 70% yield (entry 5). When the reaction of **37g** having a phenyl group at the 4-position of the cyclohexane ring was carried out, the corresponding substituted tetrahydrobenzofuran **38g** was obtained as the sole product (entry 6). This result indicates that the reaction proceeds via the regioselective formation of the corresponding enolate. The acyclic propargyl β-keto ester **37h** also reacted with the palladium catalyst to produce the substituted furan **38h**, but the yield was decreased to 21% (entry 7).

Table 5. Reactions using various propargyl β-keto esters **37b-h**.[a]

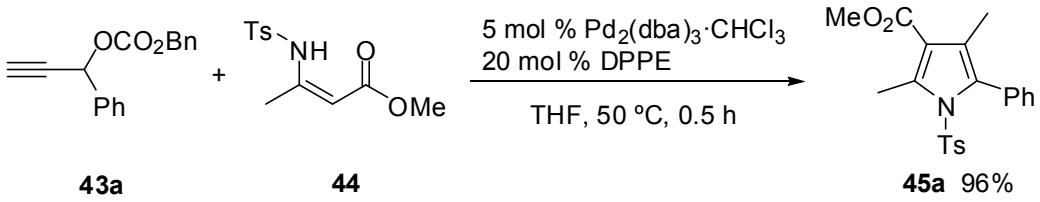
Entry	Substrate **37**	Product **38**	Yield (%)
1	 **37b**	 **38b**	68
2	 **37c**	 **38c**	63
3	 **37d**	 **38d**	79
4	 **37e**	 **38e**	74
5	 **37f**	 **38f**	70
6	 **37g**	 **38g**	76
7[b]	 **37h**	 **38h**	21

[a]The reactions were carried out in the presence of 2.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 10 mol% DPPF in dioxane at 65 °C for 20-60 min. [b]The reaction was carried out at 100 °C.

3. USE OF β-ENAMINO ESTERS AS A NUCLEOPHILE

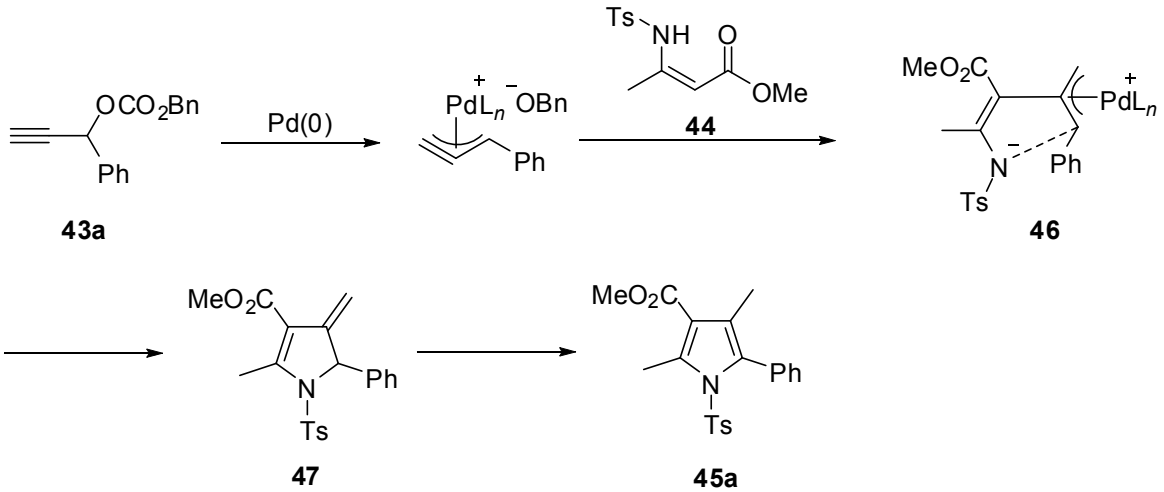
Pyrroles are important components as a structural fragment of many biologically active natural products, pharmaceutical agents and electronic and magnetic materials.[23] During the course of our study for the

construction of various cyclic molecules, we took notice of the nucleophilic activity of β-enamino esters, which could be converted to the substituted pyrroles by the reaction with propargylic esters in the presence of palladium. When propargylic carbonate **43a** and tosyl-substituted β-enamino ester **44** were treated with 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPE in THF at 50 ºC, tetrasubstituted pyrroles **45a** was obtained in 96% yield (Scheme 20).[24]



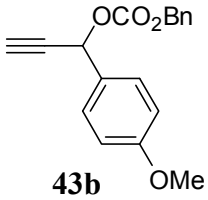
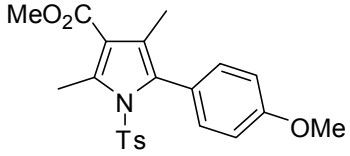
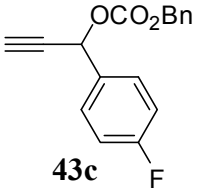
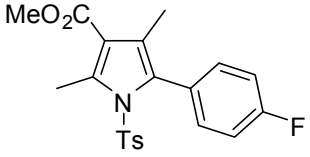
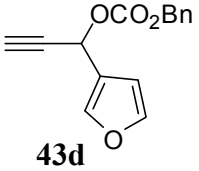
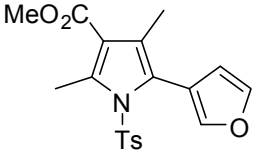
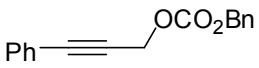
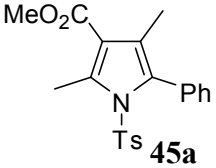
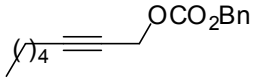
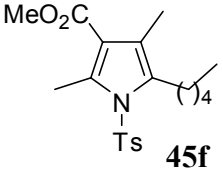
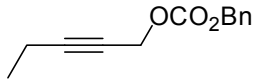
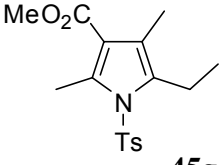
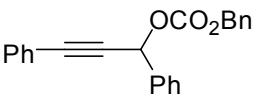
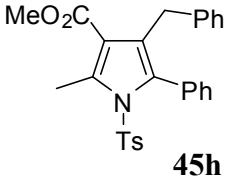
Scheme 20

A plausible mechanism for the production of the pyrrole is shown in Scheme 21. The propargylic carbonate **43a** reacts with palladium to transform to the π-propargylpalladium complex, which causes nucleophilic attack of the α-carbon of the β-enamino ester **44** followed by proton transfer affording the π-allylpalladium intermediate **46**. Then the intramolecular nucleophilic attack of the sulfonamide anion to the π-allylpalladium followed by isomerization of the resulting **47** proceeds to give the tetrasubstituted pyrrole **45a**.



Scheme 21

Table 6. Reactions using various propargylic carbonates **43b-h** with **44**[a]

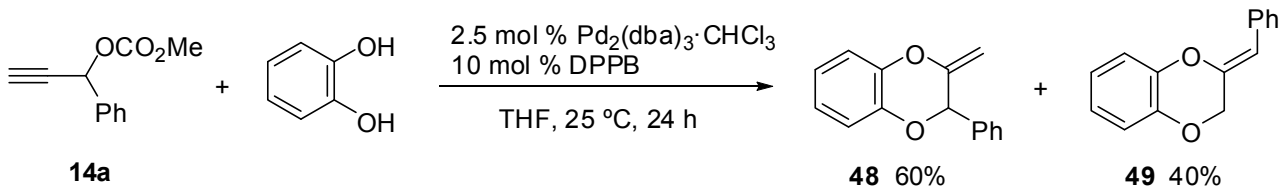
Entry	Substrate **43**	Product **45**	Yield (%)
1	 **43b**	 **45b**	91
2	 **43c**	 **45c**	90
3	 **43d**	 **45d**	76
4	 **43e**	 **45a**	92
5	 **43f**	 **45f**	91
6	 **43g**	 **45g**	94
7	 **43h**	 **45h**	82

[a]The reactions were carried out in the presence of **43** and **44**, 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPE in THF at 50 ºC for 3 h.

The reactions of various propargylic carbonates **43b–h** with β-enamino ester **44** are summarized in Table 6. When the reactions of the substrates **43b** and **43c** containing a *p*-methoxyphenyl and a *p*-fluorophenyl group at the propargylic position were attempted, tetrasubstituted pyrroles **45b** and **45c** were produced in 91% and 90% yield, respectively (entries 1 and 2). The substrate **43d** having a 3-furyl a group also reacted with **44** to give the product **45d** in 76% yield (entry 3). When the propargylic carbonate **43e** containing a phenyl group on the alkynyl moiety was subjected to the reaction, the tetrasubstituted pyrrole **45a**, which was the same product from the reaction of **43a**, was obtained in 92% yield (entry 4). The result indicates that the reaction proceeds via the formation of a common π-allylpalladium intermediate **46** in Scheme 21. Similarly, the corresponding products **45f** and **45g** were obtained in high yields from the reactions using pentyl- and ethyl-substituted substrates **43f** and **43g** (entries 5 and 6). The diphenyl-substituted substrate **43h** uneventfully reacted with **44** to deliver the corresponding product **45h** in 82% yield (entry 7).

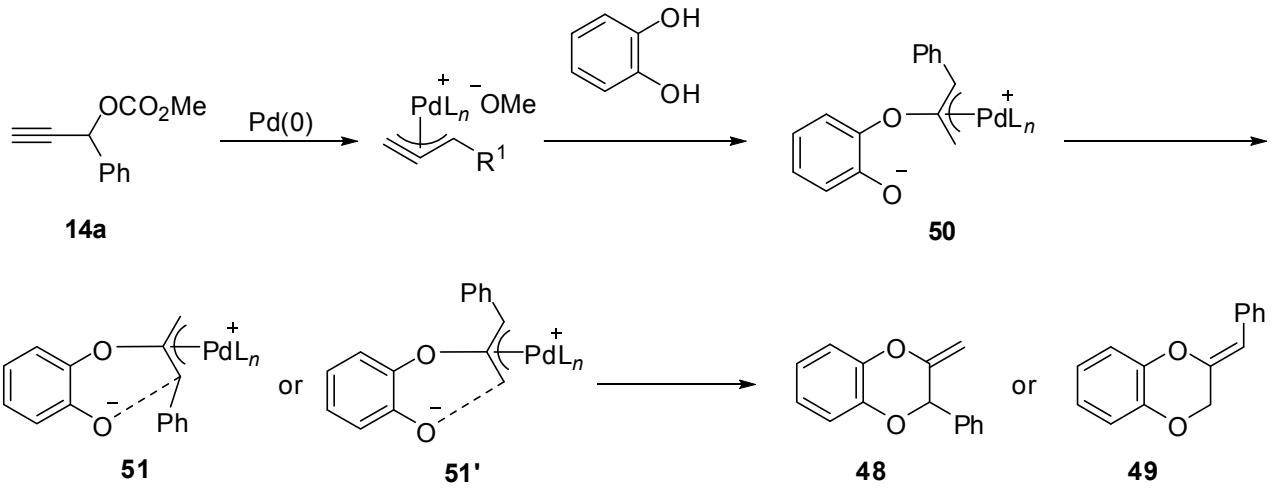
4. USE OF CATECHOLS AS A NUCLEOPHILE

Synthesis of 1,4-benzodioxanes have attracted considerable attention because of their interesting biological activities.[25] Sinou reported the synthesis of 2-alkylidene-1,4-benzodioxanes by utilizing a catechol as a bis-nucleophile in the palladium-catalyzed cyclization with propargylic carbonates. When propargylic carbonate **14a** and catechol were treated with 2.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % DPPB in THF at 25 °C for 24 h, 3-phenyl-2-methylene-1,4-benzodiozane **48** and 2-benzylidene-1,4-benzodiozane **49** were produced in 60% and 40% yields, respectively (Scheme 22).[26]



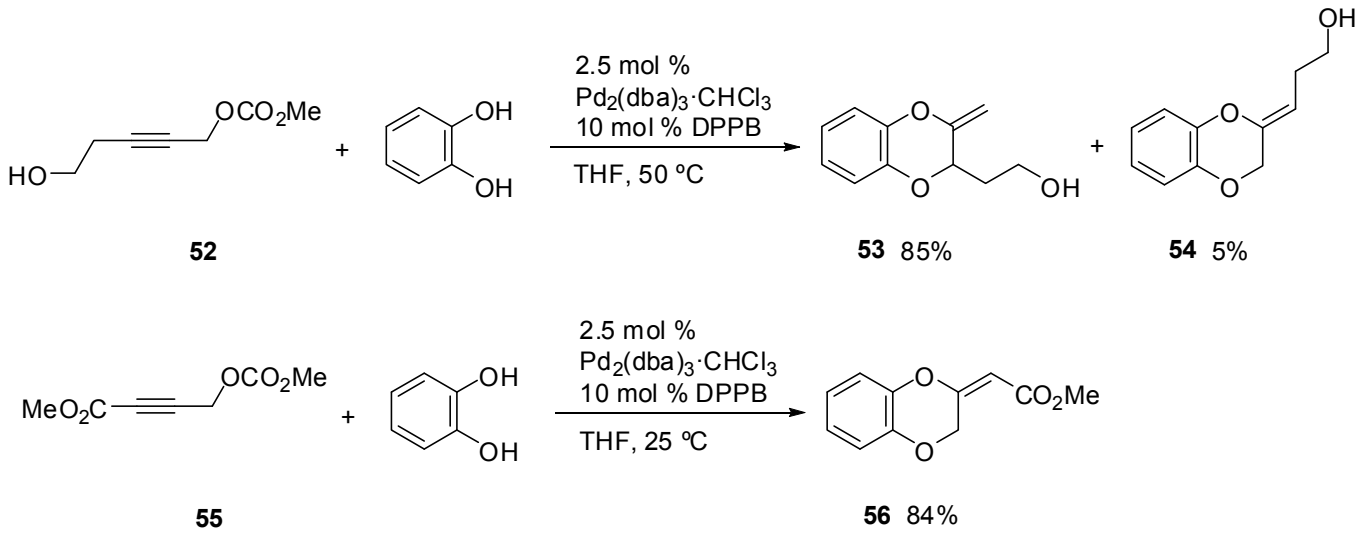
Scheme 22

Scheme 23 shows a predicted mechanism for the formation of **48** and **49**. The π-propargylpalladium complex, resulting from propargylic carbonate **14a** with palladium, would cause the nucleophilic attack of the phenolic oxygen of a catechol to afford the π-allylpalladium intermediate **50**. Then, intramolecular nucleophilic attack of the another phenolic oxygen via **51** or **51'** would occur to afford the 1,4-benzodioxanes **48** and **49**.



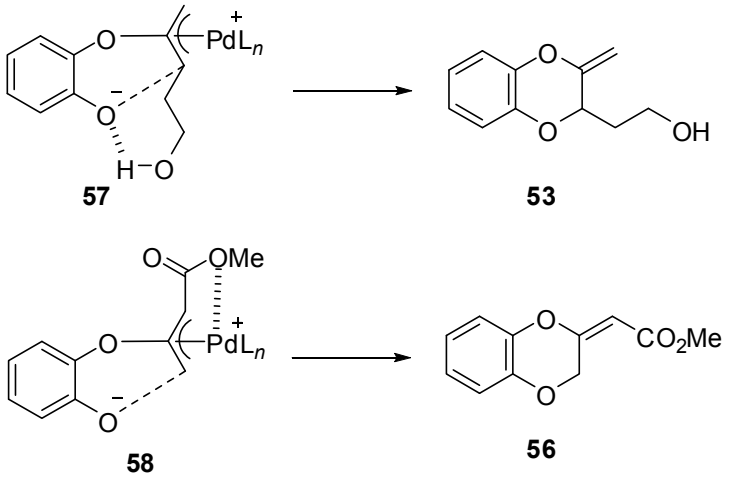
Scheme 23

Although the regioselectivity of this reaction was not high, Sinou reported the regiocontrolled synthesis of substituted 1,4-benzodioxanes by the use of substituted propargylic carbonates (Scheme 24).[27] Thus, when the reaction of a propargylic carbonate **52** containing a hydroxyethyl group with catechol was carried out, 3-substituted-2-methylene-1,4-benzodioxane **53** was selectively produced in 85% yield in accordance with its regioisomer **54** in 5% yield. Furthermore, the 2-methoxycarbonyl-methylidene-1,4-benzodioxane **56** was produced in 84% yield as a sole product when the substrate **55** having an ester moiety at the alkynyl position was subjected to the reaction.



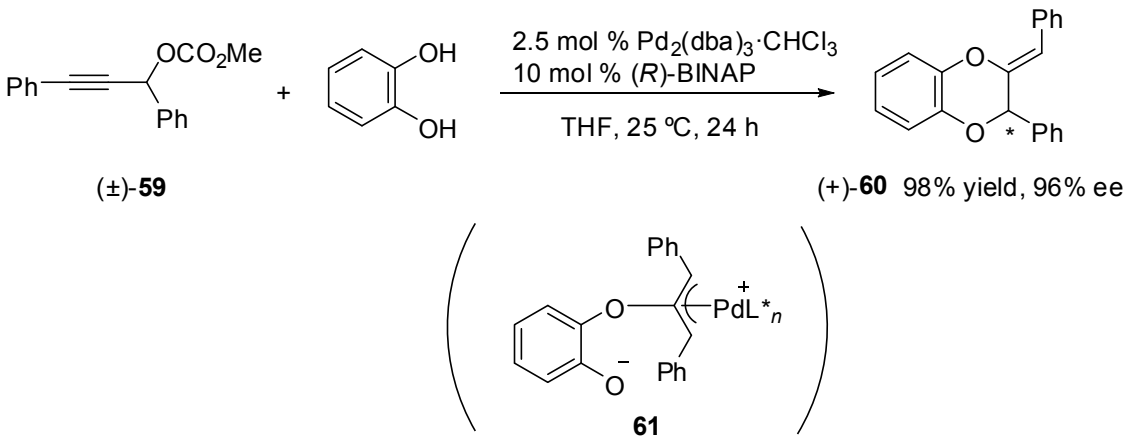
Scheme 24

As a reason for the observed regioselectivity depending on the functional group on the propargylic substrate, Sinou proposed directing effects of the substituents on the propargylic carbonates (Scheme 25). In case of the hydroxyethyl-substituted substrate **52**, it is expected that the cyclization occurs via the intermediate **57**, which forms a hydrogen bond with the hydroxyl function, to provide **53** as a major product. On the other hand, there could be complexation of the ester to the palladium in the reaction of **55**. As a result, the 1,4-benzodioxane **56** would be regioselectively formed via the intermediate **58**.



57 **53** **58** **56**

Scheme 25



(±)-**59** (+)-**60** 98% yield, 96% ee

61

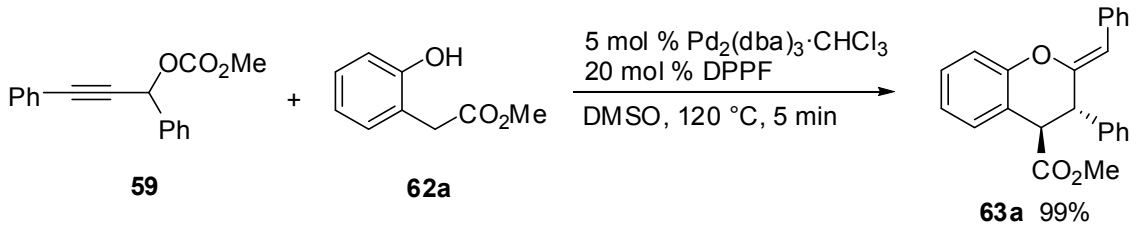
Scheme 26

As an application of this cyclization process, Sinou examined to synthesize optically active 1,4-benzodioxanes in the presence of chiral palladium catalyst. As a result, when the reaction of (±)-**59** with catechol was carried out in the presence of 2.5 mol % $Pd_2(dba)_3·CHCl_3$ and 10 mol % (*R*)-BINAP in

THF at 25 °C for 24 h, the optically active 3-phenyl-2-benzylidene-1,4-benzodioxane (+)-**60** was obtained in 98% yield with 96% ee (Scheme 26).[28] In this reaction, the achiral π-allylpalladium intermediate **61** would be formed from the racemic substrate **59**, and it is presumed that the enantioselective cyclization from **61** would occur in the presence of chiral phosphine ligand.

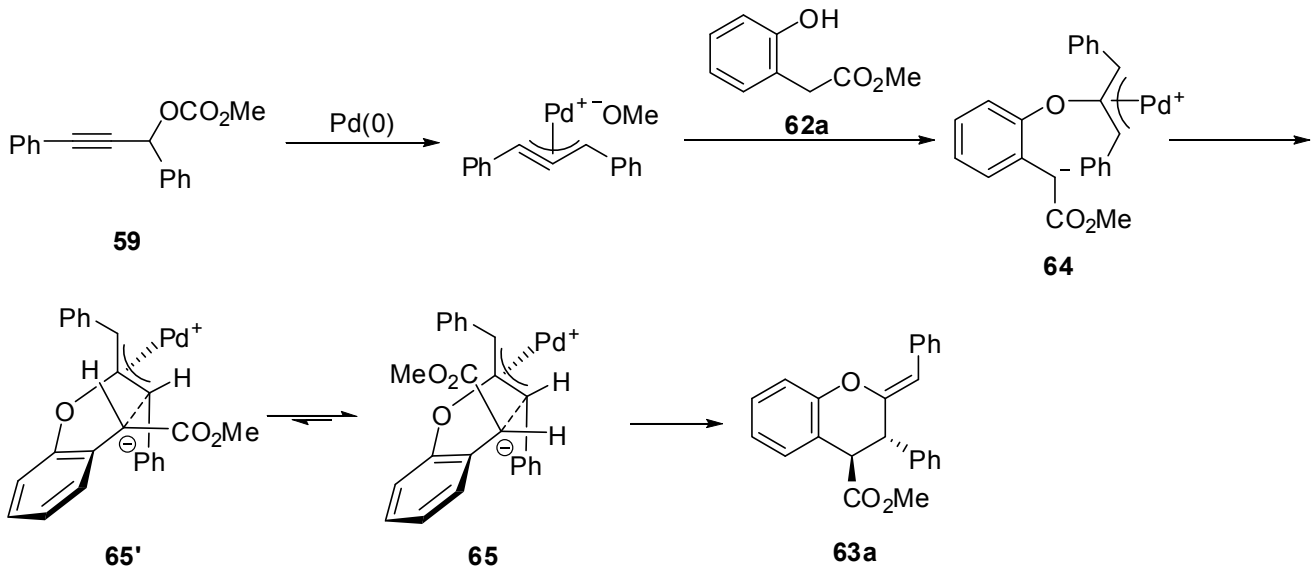
5. USE OF 2-HYDROXYPHENYLACETIC ACID ESTERS AS A NUCLEOPHILE

We next focused on the reactivity of 2-(2-hydroxyphenyl)acetates as a bis-nucleophile. By introducing phenolic oxygen and an α-carbon of ester moiety as the nucleophilic part within the substrate, we expected that substituted chromans, common structures in many pharmaceutical and agricultural compounds,[29] could be synthesized. When propargylic carbonate **59** and 2-(2-hydroxyphenyl)acetate (**62a**) were subjected to the reaction in the presence of 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % DPPF in DMSO at 120 °C for 5 min, the reaction successfully proceeded to afford the substituted chroman **63a** having the *Z*-alkenyl moiety with *trans*-stereochemistry in 99% yield as a single stereoisomer (Scheme 27).[30]



Scheme 27

A plausible mechanism for this diastereoselective cyclization is shown in Scheme 28. The π-propargylpalladium complex, derived from the propargylic carbonate **59** with palladium, is subjected to the nucleophilic attack of the 2-(2-hydroxyphenyl)acetate **62a** leading to the π-allylpalladium intermediate **64**. The complex **64** further causes the intramolecular attack of the α-carbon of the ester moiety to produce the chroman **63a**. In the cyclization step, it is expected that there are two transition states, **65** and **65'**. The desired *trans*-product **63a** would be produced via **65**, which would have lower energy because of the absence of steric repulsion between the ester and aryl groups that is present in **65'**. As another possibility, the epimerization of the initially produced *cis*-product to the thermodynamically stable *trans*-product could occur during the reaction.

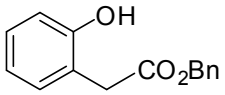
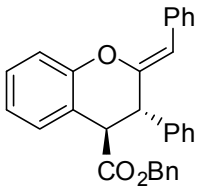
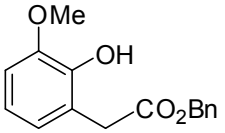
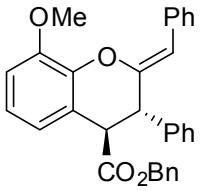
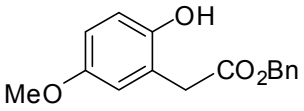
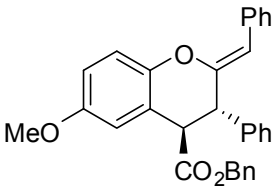
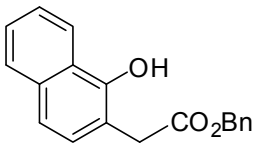
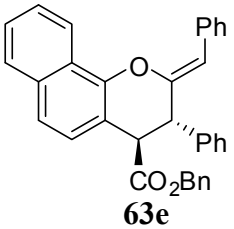


Scheme 28

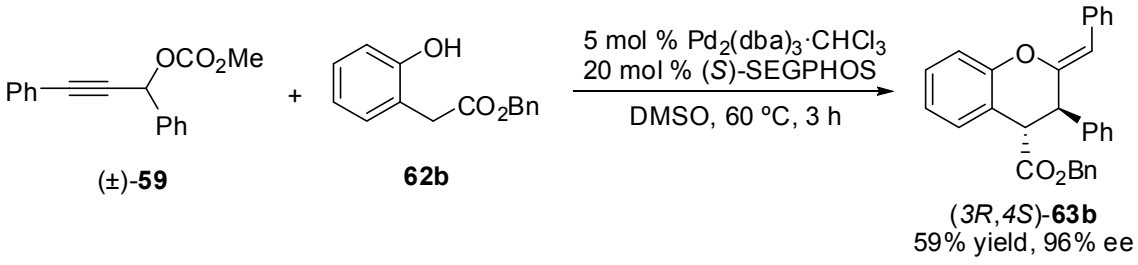
Attempts using various 2-(2-hydroxyphenyl)acetates **62b–e** are summarized in Table 7. The reaction of benzyl 2-(2-hydroxyphenyl)acetate (**62b**) with **59** proceeded to afford the substituted chroman **63b** in 99% yield (entry 1). The substrates **62c** and **62d** having a methoxy group at the 2- and 4-position on the benzene ring also reacted to give the corresponding products **63c** and **63d** in 80% and 88% yields, respectively (entries 2 and 3). When the naphthyl-substituted substrate **62e** was subjected to the reaction, the corresponding product **63e** was produced in 51% yield (entry 4). Since the resulting products **63a–e** had been obtained as a single stereoisomer in all cases, it was clear that the reaction proceeded in a highly stereoselective manner.

We attempted applying this process to an enantioselective reaction. In the synthesis of chromans, an asymmetric center is formed via the achiral π-allylpalladium intermediate **64** as shown in Scheme 28, and it is presumed that the absolute configuration of the newly formed stereogenic center could be controlled by chiral palladium catalysts. After several attempts using various chiral phosphine ligands, we found that the optically active chroman (3*R*,4*S*)-**63b** was produced in 59% yield with 96% ee when (*S*)-SEGPHOS was employed at 60 ºC in the reaction of (±)-**59** with **62b** (Scheme 29).

Table 7. Reactions using various phenols **62b–e** with **59**[a]

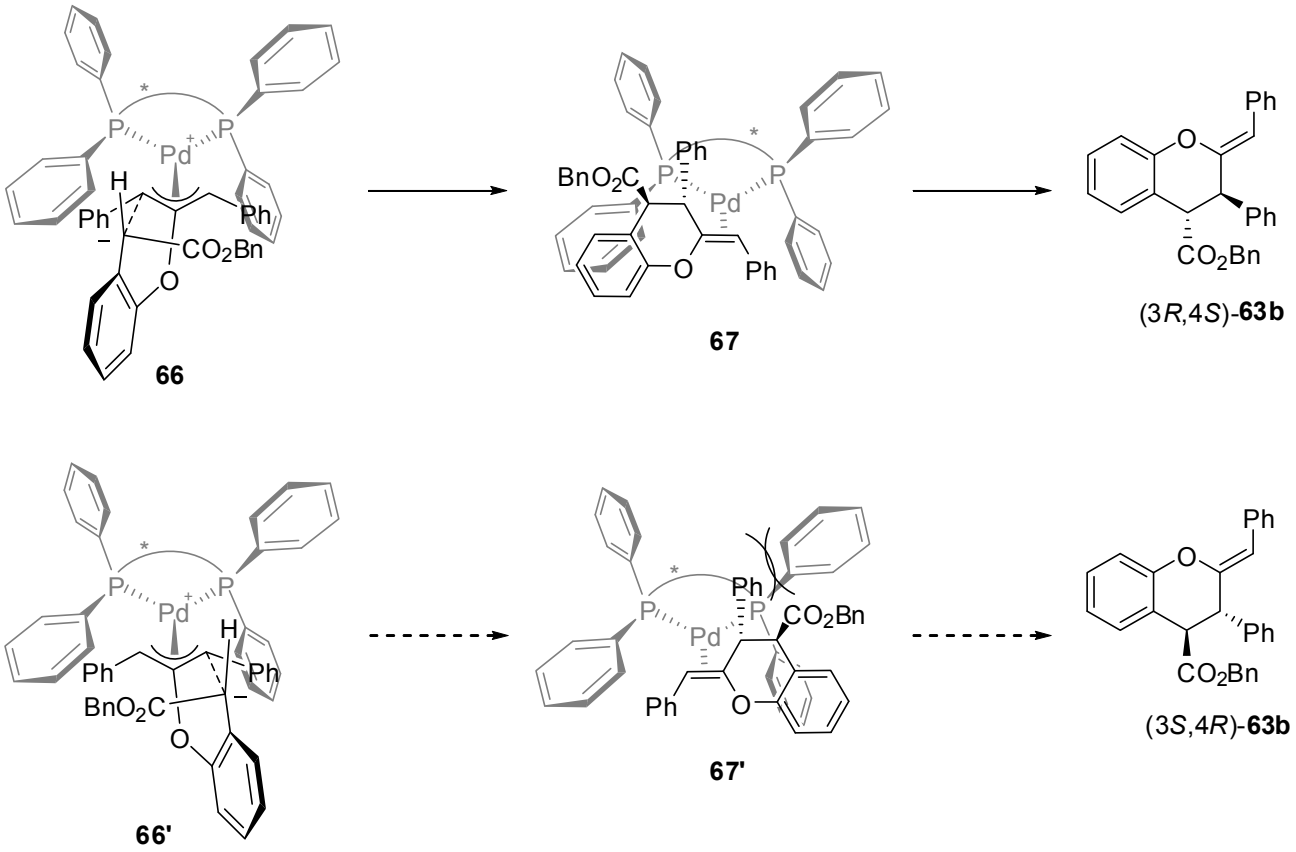
Entry	Phenol	Product	Yield (%)
1	 **62b**	 **63b**	99
2	 **62c**	 **63c**	80
3	 **62d**	 **63d**	88
4	 **62e**	 **63e**	51

[a]The reactions were carried out in the presence of **59** and **62**, 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPF in DMSO at 120 ºC for 5 min.



Scheme 29

A plausible mechanism for the appearance of enantioselectivity is shown in Scheme 30. The enantioselectivity is determined during the cyclization of the corresponding π-allylpalladium intermediate, and there are two possible transition states **66** and **66'**. It is presumed that the observed selectivity is related to the thermodynamic stability of the resulting Pd(olefin) complexes which are postulated as primary products.[31] Assuming a pseudo-square planar coordination geometry, the palladium complex **67** is expected to be more stable than **67'**, based on steric considerations. Therefore, it is plausible that the reaction would take place via the favored transition state **67** to provide (3*R*,4*S*)-**63b**.



Scheme 30

6. CONCLUSION

Examples about the palladium-catalyzed cyclization of propargylic compounds with bis-nucleophiles were presented, in which various functionalized molecules were synthesized depending on the type of bis-nucleophiles. By using 2-substituted cyclic 1,3-diketones as bis-nucleophiles, we have developed a diastereoselective synthesis of tetrahydrobenzofuranones by a palladium-catalyzed reaction of propargylic carbonates. The reaction using cyclic β-keto esters has also proceeded to produce the substituted tetrahydrobenzofuran having the *trans*-stereochemistry in a highly stereoselective manner. The

regioselective synthesis of substituted furo[3,2-*c*]pyran-4-one derivatives have been achieved by a cyclization of propargylic carbonates with 4-hydroxy-2-pyrones. The regioselectivity of the reaction can be controlled depending on the reaction temperature. We also observed the palladium-catalyzed reaction of propargylic acetates with 2-oxocyclohex-3-enecarboxylates. The process produces substituted bicyclo[3.2.1]octenones in a highly stereoselective manner. One-pot synthesis of tetrasubstituted furans has been developed by a three-component coupling–cyclization reaction of propargylic carbonate, β-keto esters and aryl halide. We have established a palladium-catalyzed reaction of propargyl β-keto esters, in which tetrasubstituted furans having a variety of substituents were produced via a decarboxylative [3+2] cyclization pathway. By using β-enamino esters as bis-nucleophiles, we have developed a synthesis of tetrasubstituted pyrroles by a palladium-catalyzed reaction of propargylic carbonates. This process regioselectively produces tetrasubstituted pyrroles having a variety of substituents via a successive nucleophilic cyclization. Substituted 1,4-benzodioxanes were produced by the reaction of a catechol with propargylic carbonates. In this reaction, the regiocontrolled synthesis of substituted 1,4-benzodioxanes have been accomplished by the use of substituted propargylic carbonates. Optically active 1,4-benzodioxanes were obtained by carrying out the reaction in the presence of chiral ligand. The palladium-catalyzed reaction of propargylic carbonates with 2-(2-hydroxyphenyl)acetates has been achieved. The process produces substituted chromans having the *trans*-stereochemistry with the *Z*-alkenyl moiety in a highly stereoselective manner. Enantioselective reactions proceeded successfully in the presence of chiral ligand to give the optically active chromans with high enantioselectivity. We believe that these reactions could provide useful methodologies in the field of synthetic organic chemistry.

ACKNOWLEDGEMENTS

I am very grateful to Professor Emeritus Kozo Shishido of The University of Tokushima for valuable advice on this research. I would like to express my sincere appreciation to all students whose names are acknowledged on our publications cited in this review for their dedication and excellent creativity. This study was supported in part by a Grant-in-Aid for the Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS).

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