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Palladium- and platinum-catalyzed cyclocarbonylation reactions of substituted allyl acetates *

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Abstract

The scope and limitation of novel palladium- and platinum-catalyzed cyclocarbonylation reactions of 3-arylallyl and 2,4-pentadienyl acetates are described. The detailed mechanism of these reactions is also discussed.

Introduction

Cyclocarbonylation is among the most synthetically versatile reactions because both one carbon elongation by carbonylation and cyclization can be achieved at one time. Particularly, the cyclocarbonylation of aromatic compounds is interesting in that aromatic C–H bonds can be directly and catalytically transformed into C–C bonds. However, the synthetic versatility of cyclocarbonylation has not widely been explored, because reactions of this type so far reported require drastic reaction conditions and are only applicable to limited types of compounds [1]. From these points of view, we have embarked on developing a novel catalytic cyclocarbonylation which has high general utility as a synthetic reaction. Here we wish to summarize our recent results on the cyclocarbonylation of substituted allyl acetates.

Results and discussion

Cyclocarbonylation of cinnamyl acetates

It is well known that cinnamyl compounds undergo carbonylation in the presence of a nucleophile such as an alcohol and a palladium catalyst to give the corresponding esters [2]. Considering the electrophilic reactivity of aromatic groups,

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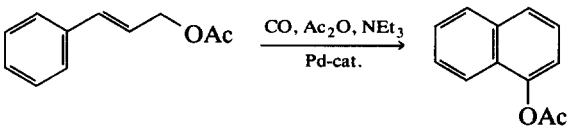
* Dedicated to Professor Akio Yamamoto upon his retirement from Tokyo Institute of Technology and in honor of his contributions to organometallic chemistry.

we expected that carbonylation of cinnamyl compounds in the absence of an external nucleophile would lead to a novel type of cyclocarbonylation. In fact, when cinnamyl acetate was allowed to react with CO (60 atm) in the presence of NEt_3, Ac_2O and a catalytic amount of $PdCl_2(PPh_3)_2$ in benzene at 160°C, 1-naphthyl acetate was obtained in 74% yield (eq. 1) [3].

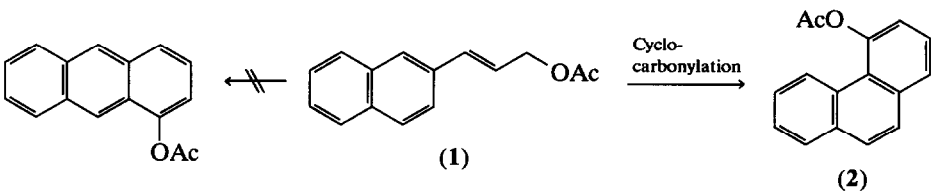


(1)

Addition of both NEt_3 and Ac_2O was essential to obtain the product in a high yield. Some other palladium monophosphine complexes and $PtCl_2(PPh_3)_2$ were also effective catalysts, while $PdCl_2$(dpe) and $Pd(OAc)_2$ showed no catalytic activity. Other group 8 metal complexes were much less effective.

Substituted cinnamyl compounds were also smoothly carbonylated to afford the corresponding substituted 1-naphthyl acetates in high yields (Table 1). In the reaction of *meta*-substituted cinnamyl acetates, both of the two possible products were obtained, the *para*-cyclization products being predominant probably for steric reasons.

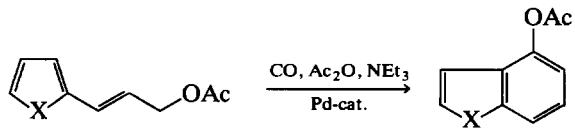
Cyclocarbonylation is also applicable to the construction of tricyclic systems; 1-phenanthryl acetate and 4-phenanthryl acetate (**2**) were obtained from 3-(1-naphthyl)allyl acetate and 3-(2-naphthyl)allyl acetate (**1**), respectively [4]. Interestingly, in the reaction of **1**, **2** was the only cyclocarbonylation product and no 1-anthryl acetate was detected by GC, although the latter seems to be sterically the more favored product (eq. 2). This selectivity was not affected by the catalysts used.



(2)

Synthesis of fused heteroaromatic systems

Although fused heterocyclic compounds are among the most desirable targets in organic synthesis because of their wide occurrence in natural products, cyclocarbonylation has never been applied to their synthesis. With a view to developing a novel synthetic method for fused heterocyclic systems, cyclocarbonylation of 3-heteroarylallyl acetates was examined [5]. As expected, carbonylation of various 3-furylallyl, 3-thienylallyl and 3-pyrrolylallyl acetates afforded the corresponding benzofurans, benzothiophenes, and indoles, respectively, in good yields (eq. 3)

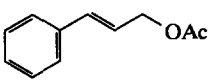
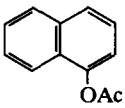
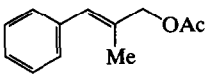
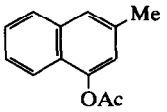
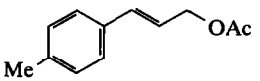
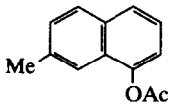
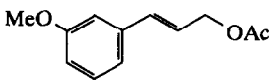
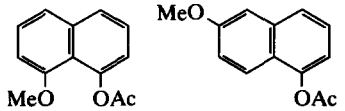
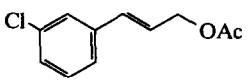
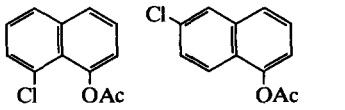
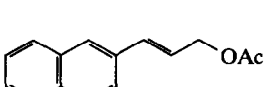
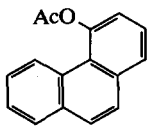
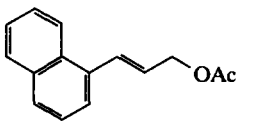
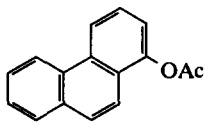


(3)

X = O, S, N-MOM
(MOM = CH_3OCH_2)

Table 1

Synthesis of naphthyl and phenanthryl acetates [a]

Substrate	Product	Conversion (%)	Yield (%)
		92	74 [b]
		69	59 [b]
		90	76 [b]
		77	77 [b] (22:78)
		91	88 [b] (26:74)
		100	73 [c]
		100	50 [c]

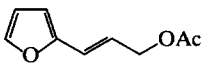
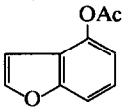
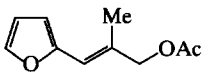
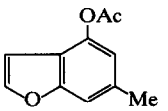
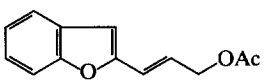
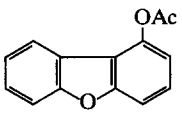
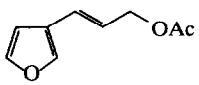
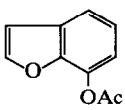
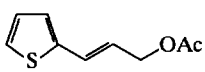
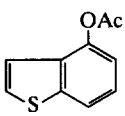
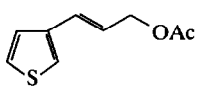
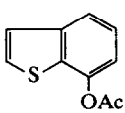
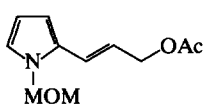
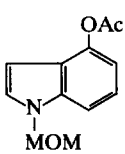
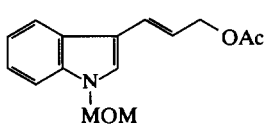
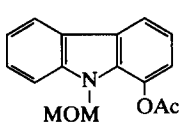
[a] Reaction conditions: substrate, 10 mmol; $PdCl_2(PPh_3)_2$, 0.07 mmol; Ac_2O, 20 mmol; NEt_3, 20 mmol; benzene, 8 ml; CO, 60 atm; 160°C, 1 h. [b] GC yield. [c] $PdCl_2(PPh_3)_2$, 0.5 mmol; CO, 70 atm; 170°C, 1.5 h, isolated yield.

(Table 2). Dibenzofuran and carbazole skeletons were also obtained. It should be noted that 3-(3-furyl)allyl and 3-(3-thienyl)allyl acetates cyclized selectively at the 2-position to form 7-acetoxybenzofuran and 7-acetoxybenzothiophene, respectively, as the sole products.

The present cyclocarbonylation is considered to be particularly useful as a synthetic method of multi-substituted fused-ring aromatics with functional groups at specific positions. Synthetic applicability of the present reaction was exemplified by a facile synthesis of cannabifuran (**3**) [6], a naturally occurring tetrasubstituted dibenzofuran in *Cannabis sativa* L. (eq. 4). Cyclocarbonylation of benzofuran **4**, which was prepared from isothymol by several steps, smoothly proceeded and acetate **5** was obtained in 74%. Hydrolysis of **5** by KOH/MeOH and acidification afforded **3** in 94%. It should be noted that there is no possibility of regioisomer

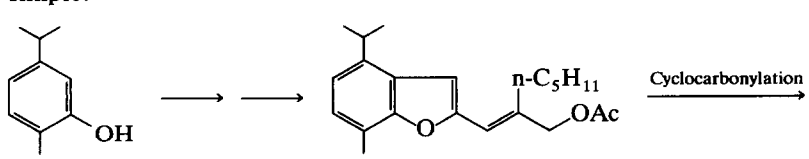
Table 2

Synthesis of fused heteroaromatic compounds [a]

Substrate	Product	Isolated yield (%)
		85
		78
		70
		89
		79
		86
		52 [b]
		53 [b]

[a] Reaction conditions: substrate, 10 mmol; $PdCl_2(PPh_3)_2$, 0.5 mmol; Ac_2O, 20 mmol; NEt_3, 20 mmol; benzene, 10 ml; CO 70 atm; 170°C, 1.5 h. [b] 130°C.

formation during the cyclization, and this makes the work-up procedure quite simple.



(4)

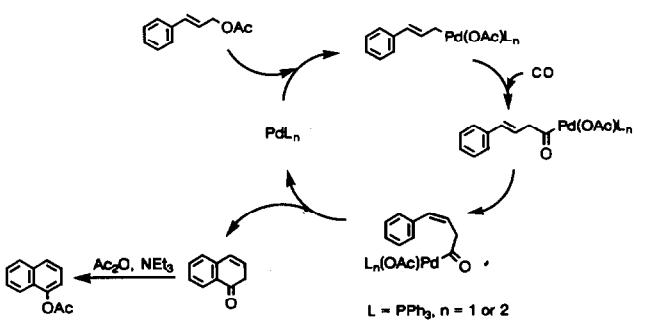
(4)

(5) (3)

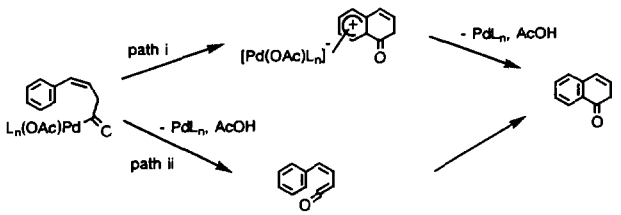
In order to compare the reactivities of heteroaromatic and benzene rings, the temperature effect on the cyclocarbonylation was examined. Both cinnamyl and 3-(2-furyl)allyl acetates gave the cyclocarbonylation products in high yields at 170°C. However, at 100°C the former gave essentially no 1-naphthyl acetate, while the latter still gave 4-acetoxybenzofuran in 48% yield. In contrast, no isolable cyclocarbonylation product was obtained in the reactions of 3-(3-pyridyl)allyl and 3-(2-pyridyl)allyl acetate. Thus the order of the reactivity in the cyclocarbonylation is estimated to be furan > benzene > pyridine ring.

Mechanism of cyclocarbonylation

In order to elucidate the mechanism of the cyclocarbonylation, the reaction of $Pd(CO)(PPh_3)_3$ with cinnamyl bromide was examined in detail [7]. At room temperature under 20 atm of CO, oxidative addition and CO insertion proceeded smoothly to afford an acyl complex, $PdBr(COCH_2CH{=}CHPh)(PPh_3)_2$ (**6**), which was shown to be in equilibrium with $PdBr(COCH{=}CHCH_2Ph)(PPh_3)_2$ in solution. Further, **6** was transformed into 1-naphthyl acetate in 54% yield under catalytic cyclocarbonylation conditions. The platinum analogue $PtBr(COCH_2CH{=}CHPh)(PPh_3)_2$ also reacted to give 1-naphthyl acetate in 40% yield under similar conditions. Therefore, it is reasonable to conclude that 4-arylbutenoyl complexes such as $Pd(OAc)(COCH_2CH{=}CHAr)(PPh_3)_n$ and $Pd(OAc)(COCH{=}CHCH_2Ar)(PPh_3)_n$ ($n = 1$ or 2), which could be formed by oxidative addition of an allylic acetate to a Pd^0 species followed by CO insertion, are the intermediates in the cyclocarbonylation. These acyl complexes would undergo double bond *E–Z* isomerization in the course of the double bond migration, although it is not clear how such double bond isomerization and migration occur. Subsequent intramolecular cyclization of the *Z*-4-arylbutenoyl complexes would produce naphthalenone and acetic acid, and the latter is neutralized by NEt_3. Tautomerization of the naphthalenone to 1-naphthol and acetylation by Ac_2O/NEt_3 yield 1-naphthyl acetate as the final product (Scheme 1). The acetylation of the naphthol effectively



Scheme 1.

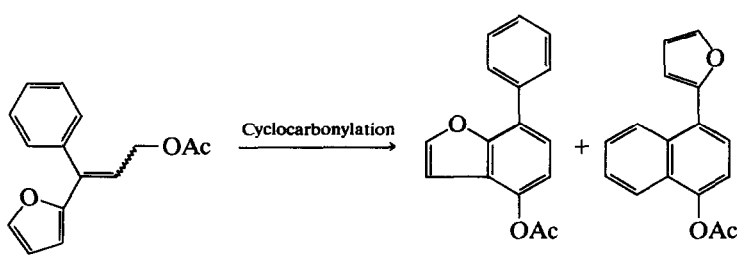


Scheme 2.

prevents the undesirable reactions between the naphthol (or naphthoxide anion) and the acyl complexes.

Although the detailed mechanism of the ring closure of the acyl complexes remains unclear, several facts useful in elaborating it have been obtained. As described above, cyclization of 3-(2-naphthyl)-, 3-(3-furyl)-, and 3-(3-thienyl)allyl acetate occurred selectively at the 1-, 2-, and 2-position of the aromatic nuclei, respectively, and the order of the reactivity of the aromatic rings in the cyclocarbonylation is in agreement with that of their electrophilic reactivity. These findings strongly suggest that the ring closure step is an electrophilic reaction on the aromatic ring, which may involve either direct electrophilic attack of the acyl moiety on the aromatic ring (path i) or, alternatively, cyclization of an alkenylketene intermediate formed from the acylpalladium complex (path ii) (Scheme 2). A reaction mechanism involving an alkenylketene intermediate has been proposed for the benzannulation of chromium-arylcarbene complexes [8].

In order to obtain further information on the ring closure mechanism, cyclocarbonylation of 3,3-diarylallyl acetates was investigated [9]. For example, cyclocarbonylation of 3-(2-furyl)-3-phenylallyl acetate (7) predominantly occurred at the more electron-rich furan ring in spite of high E/Z ratio of the starting compound 7 (eq. 5). This selectivity is opposite to that reported for the benzannulation of



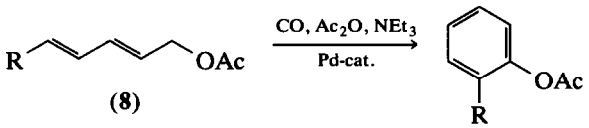
(7, $E/Z = 91/9$) (55%) (23%) (5)

chromium-diarylcarbene complexes [10], and therefore the ring closure mechanism including direct electrophilic attack of the acyl group (path i) seems to be more favored.

Synthesis of phenol derivatives by cyclocarbonylation of 2,4-pentadienyl acetates

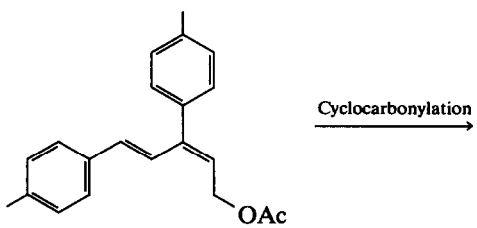
When 2,4-pentadienyl acetates were used instead of cinnamyl acetates as a starting material, we found that the palladium-catalyzed cyclocarbonylation provides an effective synthetic route to phenyl acetates [11]. Thus, in the presence of NEt_3, Ac_2O, and a catalytic amount of $PdCl_2(PPh_3)_2$, 5-phenyl-2,4-pentadienyl

acetate (**8**) (R = Ph) was smoothly cyclocarbonylated to give 2-acetoxybiphenyl (**9**) (eq. 6). $PtCl_2(PPh_3)_2$ was also found to be an effective catalyst, while other group 8 metal complexes were inactive.

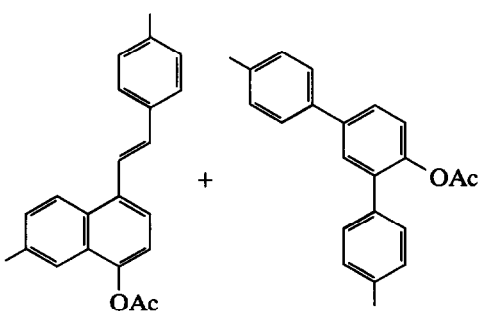


(8) (9) (6)

As shown in Table 3, various substituted phenyl esters were obtained in moderate to high yields by this unique cyclocarbonylation. In particular, 5-aryl-2,4-pentadienyl acetates are good substrates for this reaction and introduction of substituents at the 2- or 4-position of the substrates seems to lower the yields of the products. In the reaction of *E,E,E*-2,4,6-undecatrienyl acetate, the six-membered ring formation again exclusively occurred to give *o*-(1-hexenyl)phenyl acetate, but the product was a mixture of the *E* and *Z* isomers in a ratio of 79:21. It is noteworthy that the present carbonylation is applicable to the synthesis of 3,5- and 2,3-disubstituted phenyl acetates, which are difficult to prepare by conventional electrophilic substitution reactions of phenol. This exemplifies the effectiveness of our cyclocarbonylation as a synthetic method for substituted phenols. However, when (2*E*,4*E*)-3,5-di(*p*-tolyl)-2,4-pentadienyl acetate (**10**) was carbonylated under similar reaction conditions, cyclization toward the tolyl group at the 3-position competed with the phenyl acetate formation to give naphthyl acetate (**11**) (17%) concurrent with the expected 2,4-di(*p*-tolyl)phenyl acetate (**12**) (38%) in spite of the *E* configuration of the substrate.



(10)

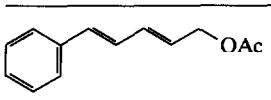
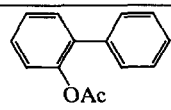
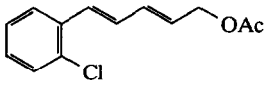
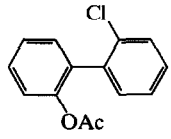
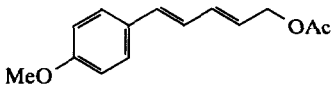
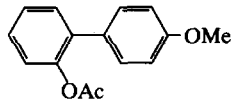
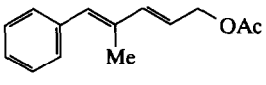
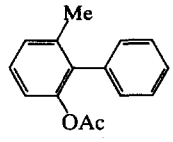
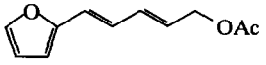
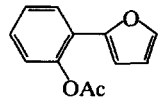
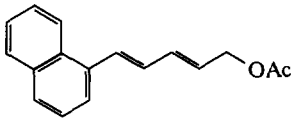
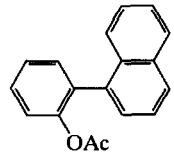
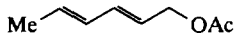
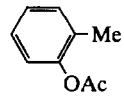
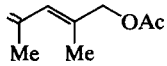
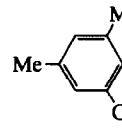
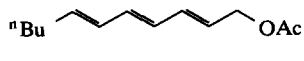
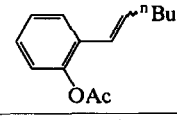


(11, 17%) (12, 38%) (7)

Previously, Negishi reported that palladium-catalyzed cyclocarbonylation of *cis*-2,4-pentadienyl chlorides in the presence of MeOH and NEt_3 yields cyclopen-

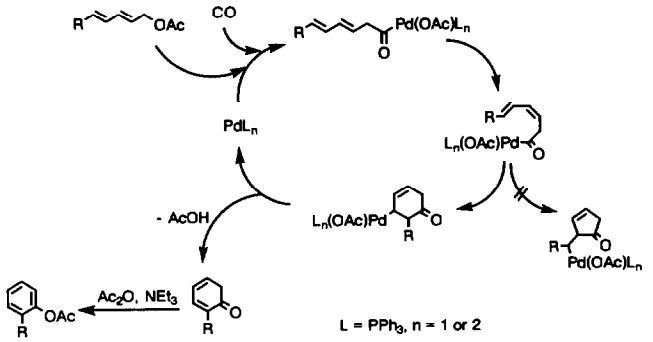
Table 3

Synthesis of phenyl acetates [a]

Substrate	Product	Isolated yield (%)
		69 (74) [b]
		84
		73
		57
		57
		79
		51 [c]
		40
		52 [d]

[a] Reaction conditions: substrate, 3 mmol; $PdCl_2(PPh_3)_2$, 0.09 mmol; Ac_2O, 6 mmol; NEt_3, 6.6 mmol; benzene, 5 ml; CO, 50 atm; 140°C, 3 h. [b] GC yield in parentheses. [c] Benzene (2 ml) was used as a solvent. [d] $E/Z = 79:21$.

tenone derivatives, and that the cis configuration of the substrates is required for the cyclization [12]. Although the catalytic systems are closely related to each other, the cyclocarbonylation described here is in sharp contrast to Negishi's reaction in that only the six-membered products are selectively obtained and



Scheme 3.

substrates of the *trans* configuration smoothly undergo the cyclization. The latter point is especially advantageous from a synthetic point of view. As expected, carbonylation of **8** (R = Ph) under Negishi's conditions resulted in the formation of methyl (3*E*,5*E*)-6-phenyl-3,5-hexadienoate (60%) and methyl (2*E*,4*E*)-6-phenyl-2,4-hexadienoate (13%).

The present reaction is considered to proceed via a hexadienoylpalladium complex such as $Pd(OAc)(COCH_2CH{=}CHCH{=}CHR)(PPh_3)_n$ (n = 1 or 2), which is generated by successive oxidative addition of a pentadienyl acetate and CO insertion (Scheme 3). In the absence of an external nucleophile, the hexadienoylpalladium complex would undergo *E*–*Z* isomerization of the internal double bond and intramolecular insertion of the terminal C=C double bond into the Pd–C bond. Subsequent β-elimination gives a cyclohexadienone, which tautomerizes to afford the corresponding phenol and is finally acetylated by Ac_2O. We must await further investigation to elucidate the reason why the hexadienoyl palladium species selectively cyclizes to form a six-membered ring but not a five-membered one under the present reaction conditions.

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