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Heterogeneous one-pot carbonylation and Mizoroki–Heck reactions in a parallel manner following the cleavage of cinnamaldehyde derivatives

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Abstract: Carbon monoxide (CO) and styrene derivatives, which can be both generated by a palladium on carbon (Pd/C)-catalyzed carbon-carbon (C-C) bond cleavage reaction of cinnamaldehyde derivatives, were effectively utilized in further palladium-catalyzed C-C bond forming reactions in a direct and practical way. CO derived from simple and affordable CO-carriers, such as cinnamaldehyde or terephthalaldehyde, was efficiently employed in the in-situ CO-fixation with various aromatic iodides through a palladium-catalyzed carbonylation followed by an inter- or intramolecular coupling reaction with alcohols to afford the corresponding esters or lactones, respectively. Styrene derivatives were also efficient substrates in an in-situ Mizoroki-Heck-type crosscoupling reaction with aryl iodides, leading to the effective formation of asymmetric stilbenes. The decarbonylation of cinnamaldehyde derivatives and the subsequent independent syntheses of both esters/lactones and 1,2-diarylethenes could be achieved in virtual one-pot and in-situ using a H-shaped pressure-tight glass sealed tube consisting of two independent but laterally connected reaction tubes in the gas space.

Introduction

[a]

The cleavage of a carbon-carbon (C-C) bond followed by the subsequent or simultaneous reconstruction of both carbon fragments by the formation of new C-C bonds could be used as a versatile and unique strategy for the synthesis of complex target compounds. To accomplish this strategy, the development of effective methods for both the cleavage of a specific C-C bond of a substrate and the generation of new C-C bonds is required. We have recently reported a Pd/C-catalyzed approach to two types of site-selective C-C bond cleavage of cinnamaldehyde derivatives based on the fine-tuning of the reaction conditions.^[1] The addition of Na₂CO₃ promoted the C–C bond cleavage between the alkene and aldehyde moieties of cinnamaldehyde to form styrene and carbon dioxide (CO). We have envisioned that the development of a successive C-C bond forming reaction of the in-situ generated CO and styrene derivatives could lead to a reconstructive method by exploiting these fragments as synthetic elements.

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Transition metal-catalyzed carbonylation of aryl halides using CO gas in the presence of nucleophiles is an important tool for the preparation of a wide range of aryl carbonyl compounds including esters, heterocyclic carbonyl compounds, etc.^[2] Significant efforts have been devoted to the use of Pd/C as heterogeneous catalyst^[3] in carbonylation reactions due to its universality, high stability, easy removal from the reaction mixture, and reusability properties. However, CO is a highly toxic gas, it requires a special gas cylinder and reaction equipment, such as an autoclave, in order to perform the synthetic procedure, and troublesome gas handling procedures. Therefore the development of a safe and stable CO synthon, which can readily generate CO within the reaction apparatus, avoiding the direct use of CO gas, has attracted great attention from synthetic chemists. The use of formic acid, formaldehyde, acyl chloride, or a metal carbonyl complex as CO surrogates has already been reported.^[4] Recently, Manabe and Kakiuchi have independently demonstrated some innovative methods for the homogeneous transition metal-catalyzed carbonylation of aryl halides to using N-formylsaccharin,^[5] prepare ester derivatives phenylformate,^[6] pentafluorobenzaldehyde,^[7] or formaldehyde^{[4|-} ^{n]} as CO carrier. We anticipated that the CO generated by the above mentioned Pd/C-catalyzed C-C bond cleavage of cinnamaldehyde derivatives could be easily used for the carbonylation reaction of haloarenes.

On the other hand, while palladium-catalyzed decarboxylative Mizoroki–Heck-type reactions between aryl carboxylic acids and olefins have been reported by Nilsson,^[8] Myers,^[9] Gooßen,^[10] and others,^[11] the decarbonylative Mizoroki–Heck-type reaction using cinnamaldehyde derivatives as alkene carriers has not been reported to date.

Herein, we demonstrate for the first time that terephthalaldehyde is an effective and readily available CO carrier besides cinnamaldehyde derivatives, and its use enables smooth Pd/Ccatalyzed carbonylations. Furthermore, the simultaneous carbonylation of aryl iodides and decarbonylative Mizoroki–Heck reaction with CO and styrene derivatives, respectively, both deriving from the C–C bond cleavage reaction of cinnamaldehyde derivatives, are also clarified (Scheme 1).



Scheme 1. This work: Effective utilization of cinnamaldehyde.

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Results and Discussion

Initially, we examined the capability of cinnamaldehyde, benzaldehyde, and terephthalaldehyde as CO donors (carriers), as shown in Table 1. The C–C cleavage reaction of these aldehydes was performed in *i*PrOH in the presence of 10% Pd/C (10 mol%) and Na₂CO₃ (2 equiv) at 120 °C, based on our previous research.^[1] After 24 h, a solution of 2-iodobenzylalcohol (1 equiv) and triphenylphosphine (PPh₃, 40 mol%) in *N*-methylpyrrolidone (NMP) was added to the reaction mixture, which was then stirred at 100 °C for further 24 h. The CO derived from each aldehyde underwent a cross-coupling reaction with the aryl iodide moiety of 2-iodobenzylalcohol and a subsequent intramolecular cyclization with the benzyl alcohol function to afford the corresponding phthalide. The use of 1 equiv of terephthalaldehyde was particularly effective, and the desired phthalide was obtained in 88% yield (Entry 3).



[a] Reactions were carried out on a 0.25 mmol scale. [b] Determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

OHC

In order to explore the scope of the in situ carbonylation using terephthalaldehyde as CO source, we next examined the synthesis of an isopropyl ester derivative starting from 4-iodoanisole and *I*PrOH. Since only a trace amount of isopropyl 4-methoxybenzoate was obtained in the absence of additives (Table 2, Entry 1), we investigated the effect of the addition of triethylamine or phosphine derivatives in view of their coordinating function as ligands. When triethylamine (40 mol%) was used as additive, the yield of the desired ester significantly increased (64%, Entry 2). The addition of PPh₃ was found to be the most effective among the examined potential ligands (Entries 2–7). The use of other solvents such as DMA, DMF, or toluene instead of NMP led to a significant decrease of the yield of the ester (Entries 8–10).



[a] Reactions were carried out on a 0.25 mmol scale. [b] Determined by $^1\mathrm{H}$ NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

DMA

DMF

Toluene

45

14

4

PPh₃

PPh₃

PPh₃

8

10

With these optimized conditions in hand (Table 2, Entry 7), we then investigated the substrate scope of aryl iodides and alcohols (Table 3). lodobenzene was effectively cross-coupled with the in situ generated CO and iPrOH to give the corresponding isopropyl benzoate in 88% yield (Entry 1). Aryl iodides possessing an electron-withdrawing or an electrondonating methoxy group on the benzene ring were also found to be good substrates for the carbonylation (Entries 2-4). A wide variety of normal and secondary alcohols could be used in the carbonylation of 4-iodoanisole to afford the corresponding alkyl 4-methoxybenzoates (Entries 5-8). Although only a trace amount of the desired methyl ester was obtained in the case of the reaction in MeOH (entry 9), this issue could be resolved by preactivating Pd/C with H₂ (1 atm) at rt for 1 h prior to the C-C cleavage reaction of terephthalaldehyde. Using this protocol, methyl 4-methoxybenzoate was obtained in 54% yield (Entry 10) Next, we investigated the syntheses of lactones and phthalimide starting from 2-iodobenzylalcohol and 2-iodobenzamide derivatives, respectively, through their carbonylation followed by intramolecular C-O and C-N coupling reactions. 2lodobenzylalcohol was converted to the corresponding lactone in 85% yield under the present reaction conditions (Entry 11). The reaction of 2-iodophenethylalcohol resulted in the generation of a six-membered benzolactone in 29% yield (Entry 12). Benzyl alcohol derivatives with a methyl group or two methoxy groups on the benzene ring were excellent substrates for the lactone synthesis (Entries 13-15). The carbonylation of diiodobenzene and 4-iodopyridine in *i*PrOH proceeded well to

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afford the corresponding diisopropyl terephthalate and isopropyl isonicotinate, respectively (Entries 16 and 17). Moreover, the use of 2-iodobenzamide as substrate in place of 2-iodobenzylalcohol led to the formation of phthalimide in good yield (Entry 18).





[a] Reactions were carried out on a 0.25 mmol. [b] Isolated yield. [c] 10% Pd/C (10 mol%) was stirred in the presence of Na₂CO₃ (2 equiv) in MeOH at rt under H₂ atmosphere for 1 h, then terephthalaldehyde was added.

The application of cinnamaldehyde derivatives in the decarbonylative Mizoroki-Heck cross-coupling reaction with iodoarenes was next investigated. When a solution of iodobenzene (1 equiv) and triethylamine (40 mol%) in NMP was added at 120 °C after the Pd/C-catalyzed CO cleavage reaction of 4-methoxycinnamaldehyde in *i*PrOH in the presence of Na₂CO₃ (2 equiv), the desired 4-methoxystilbene was produced in 48% yield (Table 4, Entry 1). The use of Na₂CO₃, diazabicyclo[2,2,2]octane (DABCO), or 2,2'-bipyridyl as additives in place of triethylamine was not effective to increase the yield of the product (Entries 2 and 3). It was reported that the addition of quaternary ammonium salts, such as tetrabutylammonium iodide (TBAI), was effective in the Mizoroki-Heck reaction possibly due to an acceleration of the reductive elimination step of the H-Pd-I species in the catalytic cycle.^[12] Such quaternary ammonium salts also facilitated the reaction progress in the present decarbonylative Mizoroki-Heck reaction, and TBAI was found to be the most effective additive among them (Entries 5-7).

 $\mbox{Table 4.}$ Optimization for the decarbonylative Mizoroki-Heck reaction of 4-methoxycinnamaldehyde with iodobenzene^{[a]}

Entry	Additive	Yield ^[b]
1	Et ₃ N	48
2	Na ₂ CO ₃	33
3	DABCO	49
4	2,2'-bipyridyl	45
5	Bu₄NI (TBAI)	61
6	Bu ₄ NBr (TBAB)	54
7	Bu₄NF (TBAF)	54

[a] Reactions were carried out on a 0.25 mmol. [b] Determined by $^1{\rm H}$ NMR using 1,1,2,2-tetrachloroethane as internal standard.

The above-mentioned results indicate that cinnamaldehyde derivatives could act as CO as well as styrene donors. Therefore, we envisioned that the carbonylation and Mizoroki–Heck cross-coupling reactions could proceed in a simultaneous and parallel manner in two sealed reaction tubes (one for the CO generation and Mizoroki–Heck reaction and the other for the carbonylation of aryl halides) connected through a double-ended needle for CO transfer. However, our initial trials were unsuccessful (55% yield at maximum), probably due to the inadequate diameter of the double-ended needle.

This issue could be solved by using a commercially available H-shaped pressure tight glass sealed tube consisting of two independent reaction tubes laterally connected by a glass tube with an adequate diameter in the gas space^[4h-k] (Table 5). In tube A, used for the generation of CO from cinnamaldehyde

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derivatives and their decarbonylative Mizoroki–Heck reaction, 4methoxycinnamaldehyde, 10% Pd/C (10 mol% of 4methoxycinnamaldehyde), Na₂CO₃ (2 equiv), and *i*PrOH were placed, while 2-iodobenzylalcohol (0.7 equiv), 10% Pd/C (10 mol% of 2-iodobenzylalcohol), PPh₃ (40 mol%), and NMP were placed in tube B, for the CO-mediated carbonylation of 2iodobenzylalcohol. The bottom of the H-tube was heated at 120 °C under a N₂ atmosphere. After the in situ generation of CO from 4-methoxycinnamaldehyde in tube A (6 h), a solution of iodobenzene (1 equiv) and TBAI (2 equiv) in NMP was added into tube A for the Mizoroki–Heck reaction. After 18 h (total 24 h) *E*-4-methoxystilbene and phthalide were obtained in 70% yield in tube A and in 82% yield in tube B, respectively (Table 5, Entry 1).

The Mizoroki-Heck reaction occurred more effectively in the Hshaped pressure tight tube compared to the same reaction conducted in a single test tube (Table 4, Entry 5), probably because the CO generated in tube A, which can act as a catalytic poison based on its cordinable properties decreasing the cross-coupling reaction rate, could effectively move to tube B and be consumed in the carbonylation. Various combinations of Mizoroki-Heck reaction and carbonylation worked well in a parallel manner (Table 5). Cinnamaldehyde derivatives bearing either an electron-donating methoxy group or an electronwithdrawing nitro group on the benzene ring could react with iodobenzene in Tube A to afford the corresponding stilbene in 70 and 63% yield, respectively (Entries 1-3). In the case of 4acetyl, nitro, and methoxyiodobenzene, the decarbonylative Mizoroki-Heck reaction could be easily achieved in Tube A (Entries 4-6). Furthermore, the carbonylation of aryl iodides also proceeded smoothly in Tube B by using the in situ generated CO in Tube A (Entries 1-6). It is noteworthy that not only phthalides but also a phthalimide could be obtained by the reaction with 2-iodobenzamide in place of 2-iodobenzylalcohol (Entry 3). 10% Pd/C could be recovered from both tubes, but the recovered Pd/C could not be reused for both carbonylation and Mizoroki-Heck reactions.^[13]



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[a] Isolated Yield.

The proposed mechanism for the reactions in Tube A and Tube B is illustrated in Scheme 2. Vinyl Pd(II) hydride complex **C** and CO are generated in Tube A through the oxidative insertion of the C(O)-H bond of a cinnamaldehyde derivative into Pd(0)/C followed by the migration of Pd. Subsequently, Pd(II) complex **C** can undergo the oxidative addition of an aryl iodide to give the corresponding Pd(IV) complex **D**. Coexisting Na₂CO₃ might help the reductive elimination of **D** to produce the desired stilbene derivative **1** together with regenerated Pd(0)/C.^[14,15] CO moves Tube A

freely back and forth between Tube A and Tube B, where it is consumed in the Pd-catalyzed carbonylation. The aryl iodide bearing a benzylalcohol or a carboxyamide at the *ortho*-position of the iodine within the molecule is oxidatively added to Pd(0)/C to give the corresponding aryl Pd(II) complex **E**. The insertion of CO into the aryl-Pd bond of **E** and subsequent cyclization by intramolecular nucleophilic attack of the *ortho*-substituent gives the corresponding phthalide or phthalimide **2**.



Conclusions

In conclusion, we have demonstrated that terephthalaldehyde is a readily available, easy to handle, inexpensive, and quite practical CO-carrier. Furthermore, we have developed a Pd/Ccatalyzed simultaneously-proceeding efficient Mizoroki–Heck and carbonylation reaction protocol using the in situ generated styrene derivatives and CO derived from the corresponding cinnamaldehyde derivatives through a virtual one-pot three reactions system (decarbonylation, carbonylation, and Mizoroki– Heck reactions).

Experimental Section

General procedure for ester synthesis (Table 3)

A mixture of 10% Pd/C (26.6 mg, 25.0 µmol), terephthalaldehyde (33.5 mg, 250 µmol), Na₂CO₃ (53.0 mg, 500 µmol) in *i*PrOH (1 mL) in a 17-mL test tube was stirred using a personal organic synthesizer ChemistationTM (EYELA, Tokyo) or ChemistPlazaTM (Shibata Scientific Technology, Ltd., Tokyo) at 120 °C under an N₂ atmosphere. After 24 h, a solution of iodoarene (250 µmol), PPh3 (26.2 mg, 100 µmol) in *N*-methylpyrrolidone (NMP, 1 mL) was added to the reaction mixture at 100 °C under a N₂ atmosphere. After 24 h, the mixture was passed through a membrane filter (Millipore Corp., Billerica, MA; Millex-LH, 0.45 µm) to remove the insoluble catalyst, and the filtered residue was washed with EtOAc (30 mL). The combined filtrate was washed with H₂O (3 × 20 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 20:1) or preparative TLC (hexane) to afford the corresponding ester.

General procedure for the decarbonylative Mizoroki–Heck reaction (Table 4)

A mixture of 10% Pd/C (26.6 mg, 25.0 µmol), 4-methoxycinnamaldehyde (40.5 mg, 250 µmol), Na₂CO₃ (53.0 mg, 500 µmol) in *i*PrOH (1 mL) in a 17-mL test tube was stirred using a personal organic synthesizer ChemistationTM (EYELA, Tokyo, Japan) or ChemistPlazaTM (Shibata Scientific Technology, Ltd., Tokyo, Japan) at 120 °C under a N₂ atmosphere. After 24 h, a solution of iodobenzene (51.0 mg, 250 µmol) the additive (500 µmol) in NMP (1 mL) was added to the reaction mixture at 120 °C under a N₂ atmosphere. After 24 h, the mixture was passed through a membrane filter (Millipore Corp., Billerica, MA; Millex-LH, 0.45 µm) to remove the insoluble catalyst, and the filtered residue was washed with EtOAc (30 mL). The combined filtrate was washed with H₂O (3 × 20 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 20:1) or preparative TLC (hexane) to afford the 4-methoxystilbene.

General procedure for simultaneous synthesis of diarylethene and ester in a virtual one-pot manner (Table 5) 10% Pd/C (59.9 mg, 37.5 μ mol), the cinnamaldehyde derivative (375 μ mol), Na₂CO₃ (79.5 mg, 750 μ mol), and *i*PrOH (1 mL) were placed in Tube A of the H-shaped pressure tight glass sealed tube, while 10% Pd/C (26.6 mg, 25.0 μ mol), 2-iodobenzylalcohol or 2-iodobenzamide (250 μ mol), PPh₃ (26.2 mg, 100 μ mol), and *i*PrOH/NMP (0.5 mL/0.5 mL) were in Tube B of the H-shaped tube. Both tubes were sealed with a screwcap fitted with a Teflon[®] seal. The both tubes were heated at 120 °C. After 6 h, a solution of the iodoarene (750 μ mol), and tetrabutylammonium iodide (139 mg, 375 μ mol) in NMP (1 mL) was

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added to the reaction mixture at 120 °C under a N₂ atmosphere. After 18 h, the mixture in both tubes was separately worked up. For Tube A, the mixture was passed through a membrane filter (Millipore Corp., Billerica, MA; Millex-LH, 0.45 μ m) to remove the insoluble catalyst, and the filtered residue was washed with EtOAc (30 mL). The combined filtrate was washed with H₂O (3 × 20 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 20:1) or preparative TLC (hexane) to afford the corresponding stilbenes. For Tube B, the mixture was treated as described for Tube A to afford the corresponding phthalide or phthalimide.

Reuse test of 10% Pd/C for the simultaneous synthesis of 4methoxystilbene and phthalide in a virtual one-pot manner

10% Pd/C (59.9 mg, 37.5 µmol), 4-methoxycinnamaldehyde (60.8 mg, 375 µmol), Na₂CO₃ (79.5 mg, 750 µmol), and *I*PrOH (1 mL) were placed in Tube A of H-shaped pressure tight glass sealed tubes, and 10% Pd/C (26.6 mg, 25.0 $\mu mol),$ 2-iodobenzylalcohol (58.5 mg, 250 $\mu mol),$ PPh_3 (26.2 mg, 100 µmol), and iPrOH/NMP (0.5 mL/0.5 mL) were placed in Tube B of the H-shaped tubes. Each tube was sealed with a screwcap fitted with a Teflon[®] seal. Both tubes were heated under N₂ atmosphere at 120 °C for 6 h. A solution of the iodobenzene (153 mg, 750 µmol) and tetrabutylammonium iodide (139 mg, 375 µmol) in NMP (1 mL) was added to the Tube A at 120 °C under N2 atmosphere. Each reaction mixture was stirred for further 18 h, and then the reaction mixture in Tube A was filtered using a Kiriyama funnel (1 µm filter paper). The catalyst on the filter paper was sequentially washed with EtOAc (20 mL), H_2O (20 mL), and MeOH (20 mL), and the filtrate and wash EtOAc were combined and concentrated in vacuo to give 4-methoxystilbene (57.5 mg, 0.274 mmol, 73%). The recovered catalyst was dried at room temperature under reduced pressure for 24 h, then weighed [66.5 mg, 111%, 66.5 ÷ 59.9 × 100]. The reaction mixture in Tube B was worked up in the same manner. Phthalide was obtained in 81% yield (27.2 mg, 0.203 mmol), and the catalyst (28.7 mg) was recovered [108%, 28.7 \div 26.6 × 100]. The reaction for the second run was carried out using recovered catalyst in the same manner as the first run. 4-Methoxystilbene was not obtained, and the catalyst (57.5 mg) was recovered [96%, 57.5 ÷ 59.9 × 100]. The formation of only a trace amount of phthalide in Tube B was observed, and the catalyst (26.1 mg) was recovered [98%, 26.1 ÷ 26.6 × 100].

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Keywords: Carbonylation • Cleavage reactions • Heck reaction • Heterogeneous catalysis • Palladium

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- [13] The CO generation in Tube A was detectable during the second run of the reuse test by the use of a CO detector tube (Gastec Corporation, 1H). Therefore, the carbonylation and Mizoroki-Heck reactions might be time-dependently prevented by the relatively potent coordination effect of CO.
- [14] The cross-coupling reaction between 4-methoxystyrene and iodobenzene under present reaction conditions using 10% Pd/C, Na₂CO₃, TBAI, *i*PrOH, and NMP gave 4-methoxystilbene in only 38% yield, which was much lower than 61% yield for the present decarbonylative coupling of 4-methoxycinnamaldehyde with iodobenzene (Table 4 Entry 5). We therefore proposed the reductive elimination mechanism from the intermediate **D** leading to the formation of stilbene (1) rather than the β -hydride elimination mechanism for the typical Mizoroki–Heck reaction, although the latter mechanism should not be thoroughly omitted.
- [15] For the Pd(IV)-mediated C(sp²)-C(sp²) cross-coupling reactions: a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330-7331; b) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047-14049; c) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142-15143; d) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142-15143; d) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234-11241; e) A. J. Hickman, M. S. Sanford, *ACS Catal.* **2011**, *1*, 170-174; f) J. J. Topczewski, M. S. Sanford, *Chem. Sci.*

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Heterogeneous one-pot carbonylation and Mizoroki–Heck reactions in a parallel manner following the cleavage of cinnamaldehyde derivatives

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