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Highly diastereoselective synthesis of tetrahydrobenzofuranones by palladium-catalyzed reaction of propargylic carbonates with 2-substituted cyclohexane-1,3-diones

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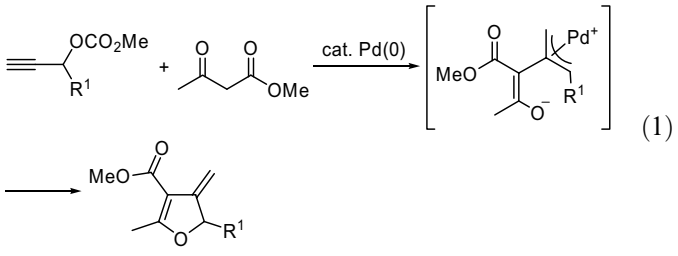
Abstract

The reaction of propargylic carbonates with 2-substituted cyclohexane-1,3-diones in the presence of palladium catalyst is described. Substituted tetrahydrobenzofuranones having a quaternary carbon stereocenter were synthesized in a highly diastereoselective manner.

Transition metal-catalyzed reactions of propargylic compounds have received considerable attention and have been extensively studied due to their versatile and specific reactivity.[1] The palladium-catalyzed reaction of propargylic compounds with soft nucleophiles is one of the most successful chemical processes developed to date.[2,3] For example, Tsuji et al. reported the reaction of propargylic carbonates with β-keto esters to produce substituted dihydrofurans (Eq. 1),[2b] in which propargylic carbonates react with β-keto esters via palladium catalysis to generate the π-allylpalladium complexes. These complexes further react with the resulting enolate intramolecularly to afford the cyclized dihydrofurans. In our studies on the reaction of propargylic compounds in the presence of palladium catalysts,[4] we focused on the nucleophilic activity of 2-substituted cyclohexane-1,3-diones. By introducing a substituent on the nucleophilic carbon, we thought that a quaternary carbon stereocenter could be constructed in the product. Herein, we describe the palladium-catalyzed reaction of propargylic carbonates with 2-substituted cyclohexane-1,3-diones producing tetrahydrobenzofuranones having a quaternary carbon stereocenter with high diastereoselectivity (Eq. 2).



The initial reactions were attempted using methyl 1-phenylprop-2-ynyl carbonate (**1a**) and 2-methylcyclohexane-1,3-dione (**2a**).[5] When **1a** and **2a** were subjected to the reaction in the presence of 10 mol % $Pd(PPh_3)_4$ in dioxane at 100 °C for 5 min, tetrahydrobenzofuranone **3aa** was obtained in 37% yield as a single diastereomer, along with the propargylic and allenic substitution compounds **4aa** and **5aa** (Table 1, entry 1). After experimenting with various reaction temperatures and solvents (entries 2–9), we found that the yield of **3aa** was improved to 66% when the reaction was carried out in DMSO at 120 °C (entry 8).

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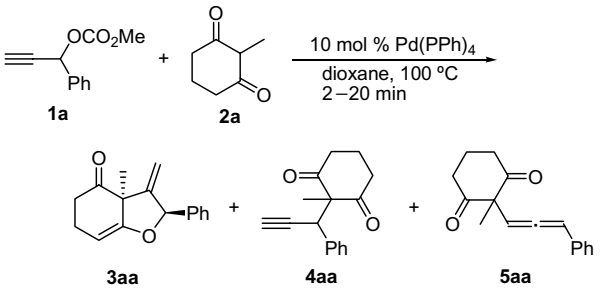
Table 1
Initial attempts using propargylic carbonate **1a** and 2-methyl-1,3-cyclohexanedione (**2a**)

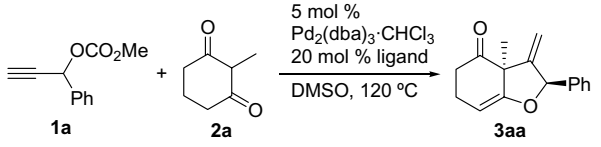


Entry	Solvent	Temp (°C)	Yields (%)		
			3aa	**4aa**	**5aa**
1	Dioxane	100	37	5	10
2	DMF	100	40	6	3
3	DMSO	100	51	4	4
4	NMP	100	51	2	1
5	Toluene	100	4	37	7
6	1,2-Dichloroethane	100	6	32	6
7	DMSO	80	39	8	3
8	DMSO	120	66	6	3
9	DMSO	140	55	5	4

The results of attempted reactions using various bidentate phosphine ligands[6] are summarized in Table 2. All of the reactions proceeded to afford tetrahydrobenzofuranone **3aa** (entries 1–7), the best results of which were obtained when dppf was used as the ligand (84% yield, entry 5).

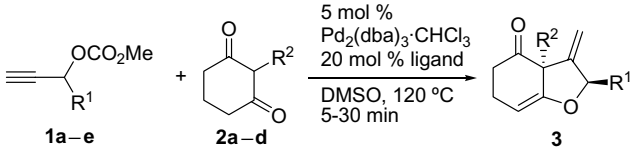
Having identified a useful set of reaction conditions, we then carried out a study of the substrate scope (Table 3). The propargylic carbonates **1b** and **1c** with a 1- and 2-naphthyl group at propargylic position successfully reacted with **2a** to produce tetrahydrobenzofuranones **3ba** and **3ca** in high yields, respectively (entries 1 and 2). Likewise the 3-furanyl- and pentyl-substituted substrates **1d** and **1e** also gave the corresponding products **3da** and **3ea** in moderate yields (entries 3 and 4). When 2-propylcyclohexane-1,3-dione (**2b**) was reacted with **1a**, the propyl-substituted tetrahydrobenzofuranone **3ab** was produced in 75% yield (entry 5). The benzyl- and 2-cyanoethyl-substituted substrates **2c** and **2d** uneventfully reacted with **1a** to deliver the corresponding products **3ac** and **3ad** in 76% and 82% yields, respectively (entries 6 and 7). The structure of tetrahydrobenzofuranone **3ca**, including the stereochemistry, was confirmed by an X-ray crystallographic analysis (Fig. 1),[7] and the stereochemistries of the other products were assigned by comparison of their NMR spectra with

Table 2
Effect of bidentate ligands



Entry	Ligand	Time (min)	Yield of **3aa** (%)
1	dppe	40	46
2	dppp	20	49
3	dppb	5	75
4	dpppentane	5	61
5	dppf	5	84
6	BINAP	10	57
7	Tol-BINAP	5	76

Table 3
Reactions using various substrates **1a–e** and **2a–e**



Entry	Substrates		Product **3**	Yield (%)
	R^1	R^2		
1[a]	1-Naphthyl (**1b**)	Me (**2a**)	**3ba**	83
2[b]	2-Naphthyl (**1c**)	Me (**2a**)	**3ca**	81
3[c]	3-Furanyl (**1d**)	Me (**2a**)	**3da**	55
4[d]	Pentyl (**1e**)	Me (**2a**)	**3ea**	43
5[a]	Ph (**1a**)	Pr (**2b**)	**3ab**	75
6[a]	Ph (**1a**)	Bn (**2c**)	**3ac**	76
7[d]	Ph (**1a**)	CN (**2d**)	**3ad**	82

[a] Dppf was used as a ligand.
[b] Dppp was used a ligand.
[c] Dpppentane was used a as a ligand.
[d] Dppb was used as a ligand.

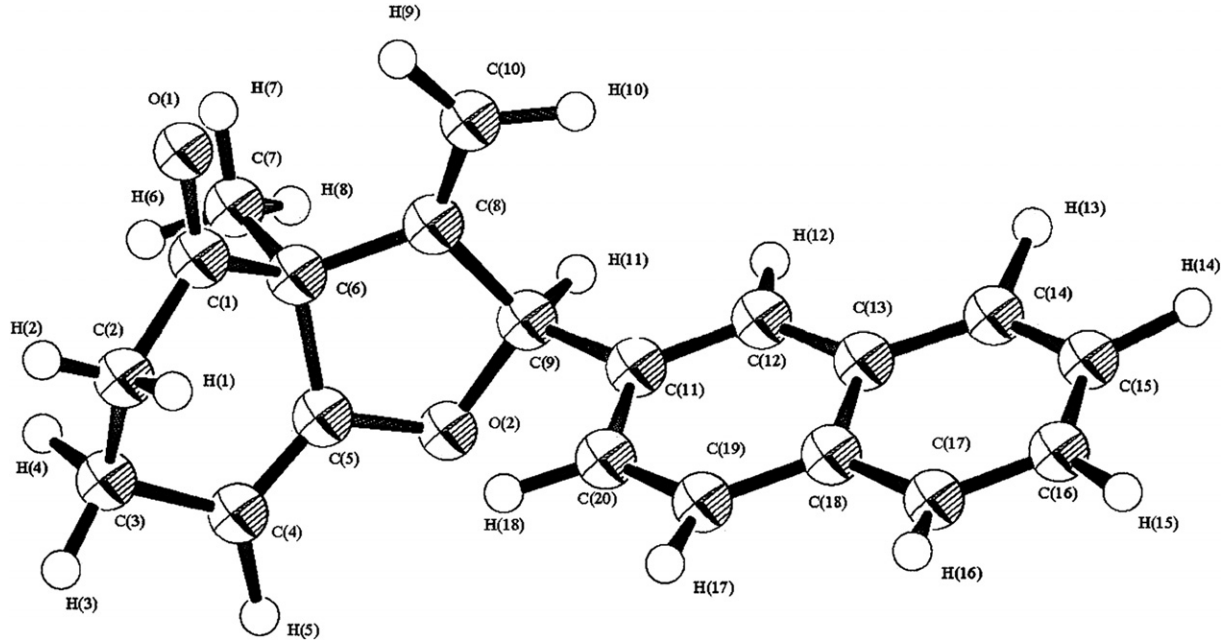
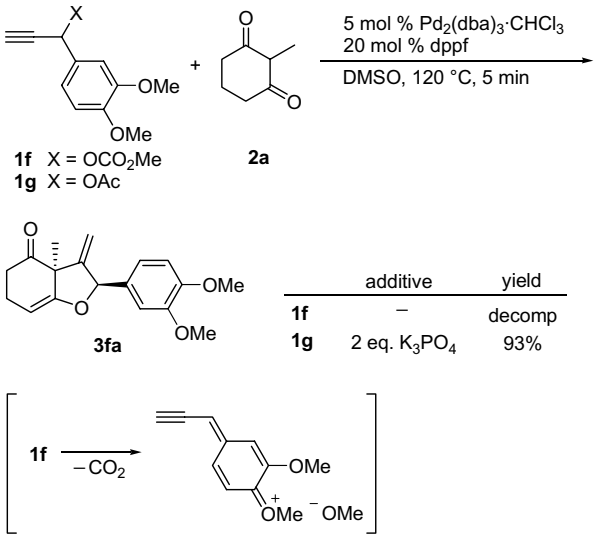


Fig. 1. ORTEP drawing of **3ca**.



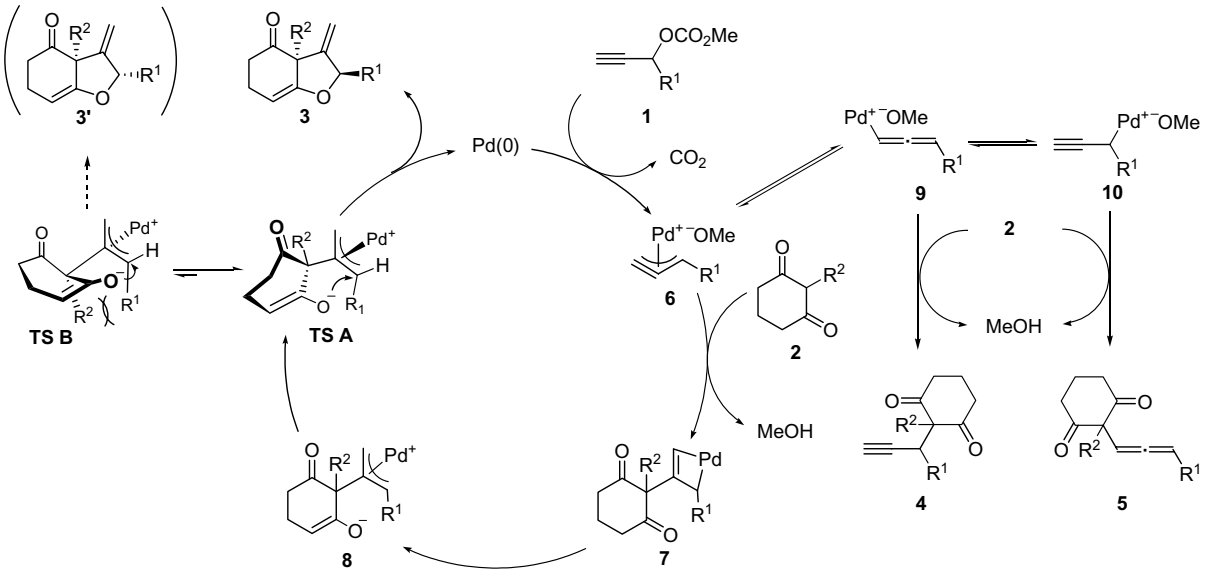
Scheme 1.

that of **3ca**. Since, in all cases, the resulting products **3aa**–**ea** and **3ab**–**ad** had been obtained as a single diastereomer, it was ascertained that this addition reaction had proceeded in a highly diastereoselective manner.

We next evaluated the reactivity of propargylic carbonate **1f**, which contained a 3,4-dimethoxyphenyl group at the propargylic position (Scheme 1). However, the reaction resulted in the decomposition of the substrate, presumably because of the instability of the carbonate moiety caused by the electron-donating effect of the methoxy groups. To overcome this problem, propargylic acetate **1g** having a less reactive leaving group was examined. As a result, the palladium-catalyzed reaction of **1g** and **2a** in the presence of 2 equiv of K_3PO_4 successfully proceeded to give the desired product **3fa** in 93% yield.

A plausible mechanism, which may account for the highly diastereoselective nature of this process, is shown in Scheme 2. On reacting with the palladium catalyst, the propargylic carbonate **1** undergoes decarboxylation to give the π-propargylpalladium complex **6**,[8] which further reacts with cyclohexane-1,3-dione **2** to lead to the π-allylpalladium intermediate **8**. Complex **8** is subjected to the intramolecular attack of the enolate to produce tetrahydrobenzofuranone **3**. The observed high diastereoselectivity is likely the result of steric factors, which influence the relative energies of the competing transition states **TS A** and **TS B**. It is expected that the transition state **TS A**, leading to product **3**, would have lower energy because of the absence of steric repulsion between the R^1 and R^2 groups that is present in **TS B**, which yields the diastereomer **3′**. The propargylic and allenic substitution byproducts **4** and **5** are produced via direct nucleophilic substitution from allenylpalladium **9** and propargylpalladium **10**,[3m] which are in equilibrium with π-propargylpalladium **6**.

In conclusion, the effort described above has led to the development of the palladium-catalyzed reaction of propargylic carbonates with 2-substituted cyclohexane-1,3-diones. The process yields tetrahydrobenzofuranones in a highly diastereoselective manner. Natural products having similar tetrahydrobenzofuranone structures have been reported,[9] and our methodology would provide a new and significant protocol for the synthesis of these high efficiency compounds.



Scheme 2. Proposed reaction mechanism.

Acknowledgments

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5. *General procedure for palladium-catalyzed reactions*: To a stirred solution of **1a** (30.0 mg, 158 μmol) in DMSO (2.0 mL) were added 2-methylcyclohexane-1,3-dione (**2a**) (26.3 mg, 189 μmol), $Pd_2(dba)_3 \cdot CHCl_3$ (8.2 mg, 7.9 μmol) and dppf (17.5 mg, 31.6 μmol) at rt under an argon atmosphere. The reaction mixture was allowed to heat to 120 °C, and stirred for 20 min. After filtration of the reaction mixture using a small amount of silica gel, the mass was concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (9:1 v/v) as eluent to give tetrahydrobenzofuranone **3aa** (32.0 mg, 133 μmol, 84%) as colorless needles; mp: 53.7–55.6 °C (from hexane); IR (neat): 1715, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.33–2.42 (m, 2H), 2.48–2.56 (m, 1H), 2.61–2.68 (m, 1H), 4.71 (d, $J = 2.4$ Hz, 1H), 5.19–5.21 (m, 1H), 5.67 (d, $J = 2.4$ Hz, 1H), 5.73 (t, $J = 2.4$ Hz, 1H), 7.22–7.27 (m, 2H), 7.31–7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_2), 25.4 (CH_3), 37.7 (CH_2), 53.2 (Cq), 83.6 (CH), 92.6 (CH), 110.3 (CH_2), 127.3 (CH × 2), 128.4 (CH), 128. 5 (CH × 2), 140.1 (Cq), 149.3 (Cq), 158.9 (Cq), 210.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O_2Na$ [M^++Na^+] 263.1048, found 263.1041.
6. In the previous studies, it has been known that bidentate ligands are suitable for the palladium-catalyzed reactions of propargylic compounds with soft nucleophiles, see Refs. 2–4.
7. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 665659. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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