PALLADIUM-CATALYZED RING EXPANSION OF HYDROXY METHOXYALLENYLPHTHALANS AS A NOVEL SYNTHETIC METHOD FOR HIGHLY SUBSTITUTED 4-ISOCHROMANONE DERIVATIVES[†]

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Abstract - The palladium(0)-catalyzed ring expansion reaction using hydroxy methoxyallenylphthalans (**3**) proceeded smoothly to give highly substituted 4-isochromanone derivatives (**4**), and treatment of commercially available phthalide (**5**) with lithium methoxyallene furnished two atom ring-expanded *endo*-benzoxepin-5-one (**8**).

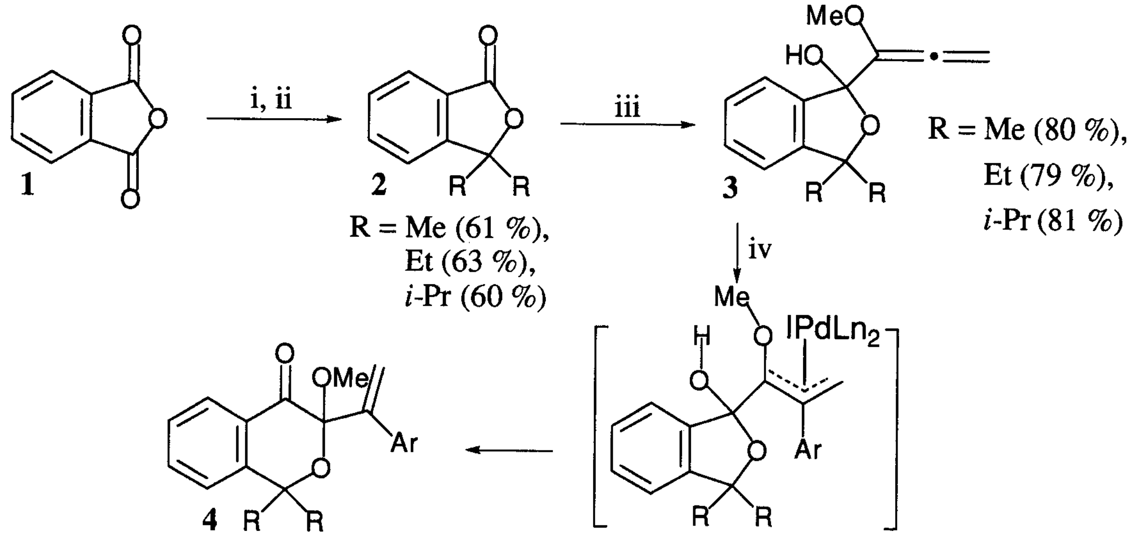
Recent efforts in our laboratory have focussed on the synthesis of palladium-catalyzed (or base-mediated) 6- and 7-membered heterocycles such as benzazepine-1,5-diones and 4-oxo-1-isoquinolones.[1,2] For the synthesis of cyclic ethers, the rearrangement of oxonium ylides constitutes one of several versatile approaches.[3] Further, recent studies have reported a novel synthetic route *via* rearrangement of the oxonium ylides derived from chiral copper carbenoids[4] and Friedel-Crafts acylation of the ketenes prepared from photochemically activated chromium-carbene-complex in the synthesis of 4-isochromanones,[5] and two-atom ring expansion of a vinyl-substituted cyclic ketene acetal (or aminal) *via* Claisen rearrangement[6] yielding the corresponding cyclic ethers. Among these rearrangements, however, photolytic methodology using ketenes as acylating groups seems to give generally low yields in the synthesis of cyclic ethers.[7] We report here a novel hetrocyclic ring enlargement reaction based on the palladium-catalyzed intermolecular cascade carbopalladation, leading to 4-isochromanone derivatives in high yields.

In previous ring expansion reactions we have conducted, propargylic and methylallenic alcohols have been employed as the starting compounds. Thus, in order to perform further application of this methodology, we intended to prepare 1-hydroxy-1-(1-methoxyallenyl)-3,3-dialkylphthalan analogues (**3**). The compounds (**3**), precursors of ring expansion, were accessible by a two-step reaction pathway from commercially available phthalic anhydride (**1**), as shown in Scheme 1.

Compound **1** was allowed to react with Grignard reagents[8] followed by the addition reaction of the resultant dialkylated phthalides (**2**) with lithio methoxyallene[9] in THF at -30 ℃ to give **3**[‡] in high yields. The structures of **3** were confirmed by their characteristic spectroscopic data [^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52-3.53 (s, 3H, OMe), 3.76-3.80 (s, 1H, OH), and 5.54-5.57 (s, 2H, terminal olefin of allene); IR ($CHCl_3$) 3555-3556 (OH) and 1962-1963 (allenyl) cm^{-1}; high resolution MS (M^+)] and elemental analyses. The ring expansion reaction commenced with the Pd(0)-promoted conditions we had previously established.[2] Namely, treatment of **3** with 5 mol % of $Pd(PPh_3)_4$, excess ArI, and K_2CO_3 in THF at 80 ℃

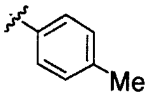
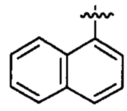
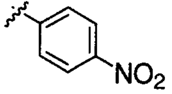
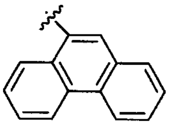
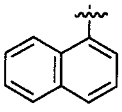
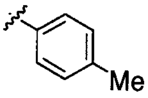
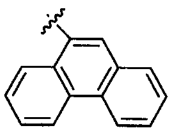
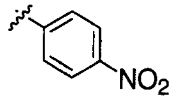
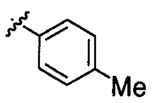
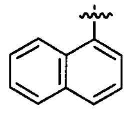
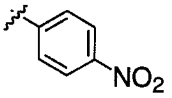
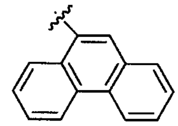
[†] Dedicated to Prof. Teruaki Mukaiyama on the occation of his 73rd birthday.

readily afforded the desirable 4-isochromanone derivatives (**4**)[¶] in 55-94% yields. All experimental results are summarized in Scheme 1 and Table 1. The reactions with aryl iodides such as 1-iodonaphthalene and 9-iodophenanthrene seem to demonstrate reactivity lower than those with other aryl iodides. These aspects of the reaction may be due to steric hindrance between the methoxy group on the allenic moiety and the bulky aryl group during the approach of the arylpalladium complex to the allene center to form the π-allylpalladium complex intermediate. In the case of the reactions of **3** (R = Me, Et, and *i*-Pr) with 1-iodo-4-



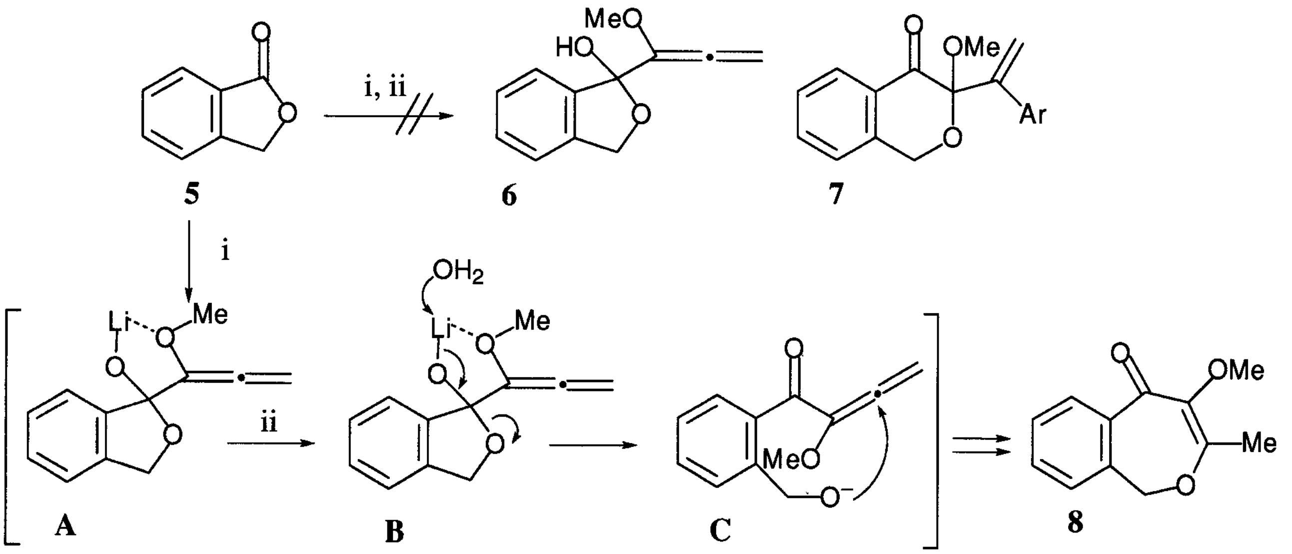
Scheme 1. *Reagents and conditions*: i, RMgBr (2.2 mol eq.), THF, 0 °C; ii, 10 % HCl; iii, Methoxyallene (2.0 mol eq.), BuLi (1.2 mol eq.), THF, -30 °C; iv, $Pd(PPh_3)_4$ (5 mol %), ArI (3.0 mol eq.), K_2CO_3 (1.2 mol eq.), THF, reflux

Table 1. Intermolecular Cascade Carbopalladation-Hetrocyclic Ring Expansion Reaction Using **3** and Aryl Iodides (ArI)

R	Ar	time (h)	yield of **4** (%)[a)]	R	Ar	time (h)	yield of **4** (%)[a)]
Me		9	94	Et		38	84
"		6	61	"		52	82
"		35	80	*i*-Pr		12	86
"		45	85	"		7	55
Et		11	89	"		36	82
"		5	57	"		46	83

[a)] Isolation yield after purification by neutral silica gel column chromatography.

nitrobenzene, which has an electron-withdrawing group, reaction times were shorter but yields were lower than those of other aryl iodides. Excellent results were obtained by the reactions of **3** (R = Me, Et, and *i*-Pr) with ArI (Ar = *p*-MePh) under the same reaction conditions. The reactions of **3** (R = Me) with 4-iodotoluene in solvents other than THF, such as DMF, DMSO, and benzene, resulted in low yields (<30%) of **4** (R = Me, Ar = *p*-MePh). The structures of 4-isochromanones (**4**) were determined by their characteristic spectroscopic data^{2} [^{1}H NMR (200 MHz, $CDCl_3$)δ 5.35-5.72 (s, 1H, exomethylene) and 5.70-6.11 ppm (s, 1H, exomethylene); IR ($CHCl_3$) 1697-1703 cm^{-1} (ketone); MS (M^+)] and X-Ray crystallographic analysis§ (**4**: R = Et, Ar = *p*-NO_2Ph) (Figure 1). Furthermore, we attempted to prepare an unsubstituted allenic alcohol (**6**) as another precursor to the formation of a 6-membered ring (**7**) (Scheme 2). However, the treatment of **5** with lithio methoxyallene, the same treatment with water as that of **2** gave immediatly a 7-membered ring (**8**) in 90% yield without producing a detectable amount of allenic alcohol (**6**). This outcome may be explained as follows. In the reaction of **5**, initially formed lithiate (**A**) seemes to be converted to ring-opened alkoxide (**C**) *via* **B** involving abstraction of lithium with water. Then, the transient alkoxide (**C**) can be converted rapidly *via* an intramolecular Michael-type cyclization (*endo*-mode cyclization)^{1} to thermodynamically stable *endo*-benzoxepine (**8**). In the reaction of dialkylated phthalides (**2**), **A**-type lithiate is, however, not easy in its conversion to **C**-type alkoxide because of steric repulsion between dialkyl groups and a phenyl *peri*-proton without any driving force (*e.g.*, heating etc.). In the both ^{1}H NMR and IR spectrum of **8**, there appeared a methyl signal (3H) at 2.30, methoxy (3H) at 3.70, and methylene (2H) at 5.07 ppm as each singlet and α,β-unsaturated carbonyl peaked at 1627cm^{-1}, respectively. The structure was explicitly confirmed by X-Ray crystallographic analysis§ of **8** (Figure 1).



Scheme 2. *Reagents and conditions*: i, Methoxyallene (2.0 mol eq.), BuLi (1.2 mol eq.), THF, -30 °C; ii, H_2O

In summary, we assume for the good formation of 4-isochromanones (**4**) that the electron-donating effect of methoxy substituent on the allenic moiety should stabilize a π-allylpalladium intermediate formed by coordination of **3** with the arylpalladium complex. Hereafter, the introduction of a methoxy substituent may be utilized for its capacity as a versatile leaving group in the synthetic application to natural products.

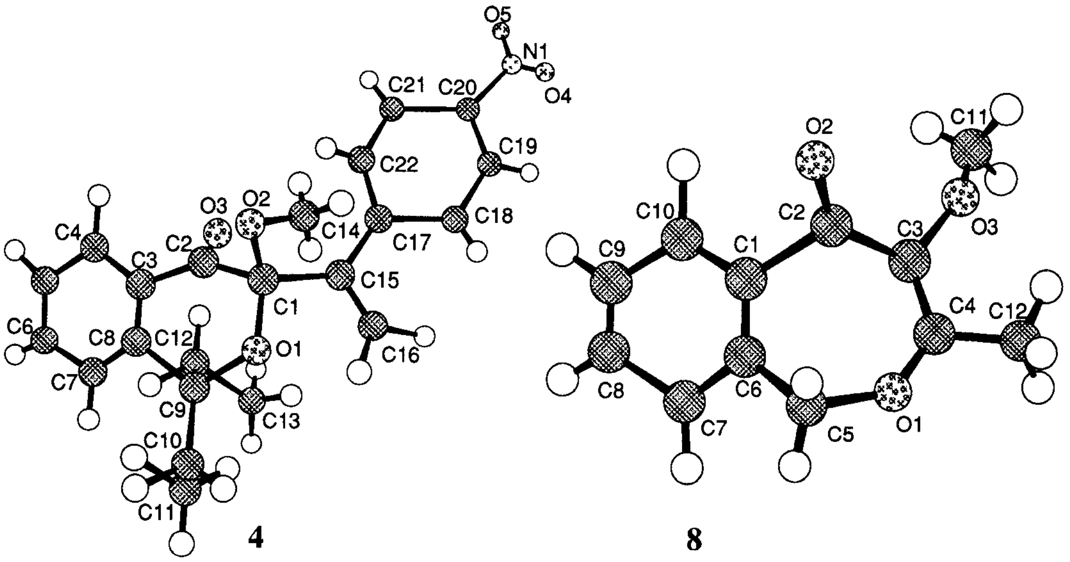


Figure 1. Computer-generated drawing of **4** (R = Et, Ar = p-NO_2Ph) and **8** derived from the X-Ray coordinates

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‡ *A typical procedure and selected spectroscopic data* for **3** (R = Et): A solution of methoxyallene (1.32 g, 18.8 mmol) in anhydrous THF (10 mL) was treated with 1.61 M BuLi (7.0 mL, 11.3 mmol) in hexane under N_2 atmosphere at -30 °C and stirred for 30 min. Then, 3,3-diethylphthalide (1.79 g, 9.4 mmol) was added within 5 min. After being stirred for 10 min, the reaction mixture was submitted to the usual workup to give 1-hydroxy-1-methoxyallenyl-3,3-diethylphthalan (**3**) (1.93 g, 79%) as a yellow oil: IR ($CHCl_3$) 3555, 1962 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.79 (m, 6H), 1.88 (m, 4H), 3.52 (s, 3H), 3.77 (s, 1H), 5.54 (s, 2H), 7.06 (d, J = 7.3 Hz, 1H), 7.33 (m, 3H); HRMS calcd for $C_{16}H_{20}O_3$ MW 272.1412, found *m/z* 272.1453 (M^+); Anal. Calcd for $C_{16}H_{20}O_3$: C, 74.97; H, 7.4. Found: C, 75.32; H, 7.65.

¶ *A typical procedure and selected spectroscopic data* for **4** (R = Et, Ar = *p*-MePh): A mixture of 3,3-diethyl-1-hydroxy-1-methoxyallenylphthalan (**3**) (0.26 g, 0.98 mmol), $Pd(PPh_3)_4$ (0.05 g, 5 mol %), 4-iodotoluene (0.64 g, 2.94 mmol), and K_2CO_3 (0.16 g, 1.18 mmol) in anhydrous THF (10 mL) was refluxed under N_2 for 11 h. The reaction mixture was submitted to the usual workup to give 1,1-diethyl-3-methoxy-3-(4-methylstyrenyl)-4-isochromanone (**4**) (0.31 g, 89 %) as a colorless oil: IR ($CHCl_3$) 1702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.68 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 2.06 (m, 4H), 2.31 (s, 3H), 3.38 (s, 3H), 5.69 (s, 1H), 5.72 (s, 1H), 7.29 (m, 7H), 7.94 (d, J = 6.6 Hz, 1H); HRMS calcd for $C_{23}H_{26}O_3$ MW 350.1881, found *m/z* 350.1893 (M^+); Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.65; H, 7.60.

§ *Crystal data for* **4** (R = Et, Ar = *p*-NO_2Ph): $C_{22}H_{23}NO_5$, F.w = 381.43, colorless prism (Et_2O-hexane-CH_2Cl_2) , primitive orthorhombic, space group Pb_{ca} (#61), a = 28.598(8) Å, b = 17.464(3) Å, c = 7.807(2) Å, V = 3899(2) $Å^3$, Z = 8, GOF = 1.63, R = 0.052, R_w = 0.082; *Crystal Data for* **8**: $C_{12}H_{12}O_3$, F.w = 204.22, colorless prism (Et_2O-hexane-CH_2Cl_2), primitive monoclinic, space group $P2_1/c$(#14), a = 13.544(2) Å, b = 19.044(3) Å, c = 8.489(1) Å, V = 2074.0(5) $Å^3$, β = 108.70(1)°, Z = 8, GOF = 1.39, R = 0.047, R_w = 0.074.

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