

Palladium-Catalyzed Sequential Carbon–Carbon Bond Cleavage/Formation Producing Arylated Benzolactones

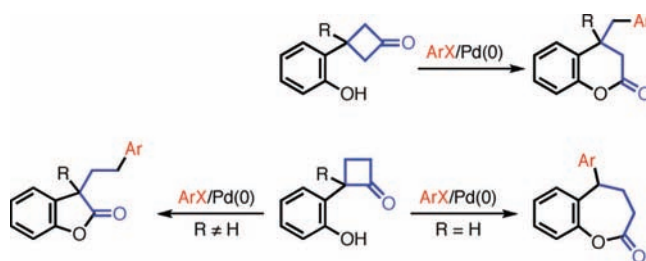
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ABSTRACT



3-(2-Hydroxyphenyl)cyclobutanones react with aryl bromides in the presence of palladium catalysts to afford 4-arylmethyl-3,4-dihydrocoumarins in high yields through a sequence involving carbon–carbon bond cleavage and formation. In the case of the reaction with 2-(2-hydroxyphenyl)cyclobutanones, five- or seven-membered lactones were produced depending on the presence of an additional substituent at the 2-position.

We recently developed a rhodium-catalyzed reaction of 3-(2-hydroxyphenyl)cyclobutanones forming 3,4-dihydroxycoumarins.¹ The intermediate rhodium cyclobutanolate underwent ring opening by β -carbon elimination.² With the resulting organorhodium species,³ a rhodium shift immediately followed to place a methyl substituent at the 4-position (Scheme 1, path a). Nishimura and Uemura reported a palladium-catalyzed reaction of cyclobutanols with aryl halides producing arylated ring-opened ketones.⁴ The

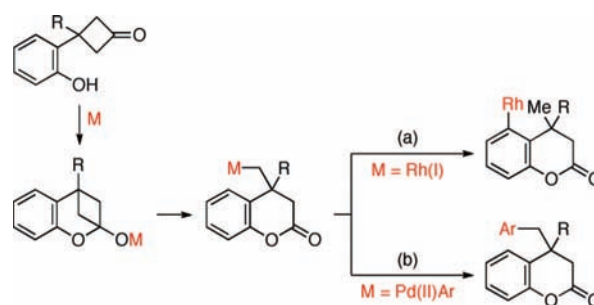
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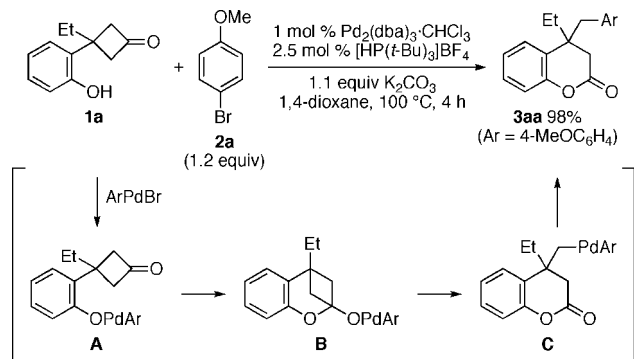
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Scheme 1



facile β -carbon elimination occurring with a palladium cyclobutanolate led us to examine a similar reaction system with 3-(2-hydroxyphenyl)cyclobutanone substrates (Scheme 1, path b). Herein, we report the palladium-catalyzed reaction

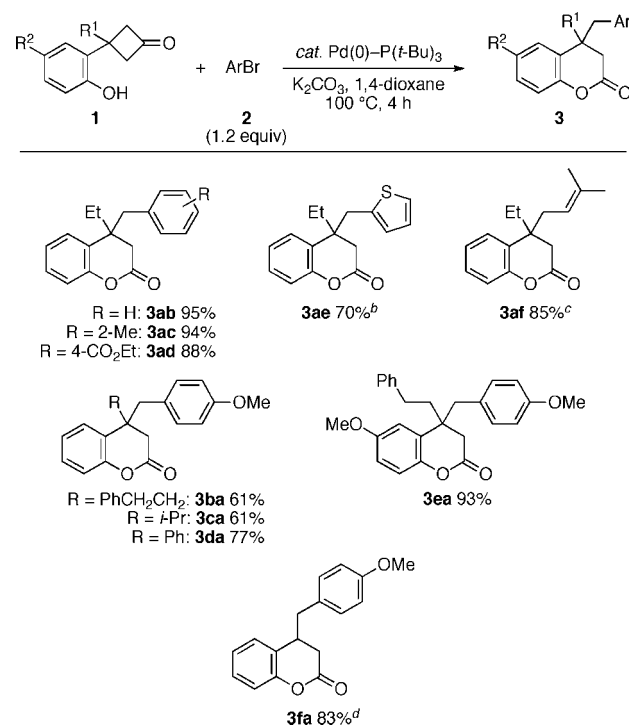
Scheme 2



of cyclobutanones having a pendant phenol moiety with aryl halides, which produces arylated five- to seven-membered benzolactones.

Initially, the reaction of 3-ethyl-3-(2-hydroxyphenyl)cyclobutanone (**1a**) and 4-bromoanisole (**2a**) was examined in the presence of various palladium catalysts. As shown in Scheme 2, when tri-*tert*-butylphosphine was used as a ligand in combination with K₂CO₃ as a base, 4-ethyl-4-(4-methoxybenzyl)-3,4-dihydrocoumarin (**3aa**) was obtained in 98% yield. We assume the reaction proceeds via (i) oxidative addition of **2a** to palladium(0), (ii) replacement of a bromide ion with a phenoxide forming arylpalladium(II) aryloxy **A**, (iii) addition of the Pd–O bond to the C=O bond generating arylpalladium(II) cyclobutanolate **B**, (iii) ring opening by β -carbon elimination from **B**, giving (aryl)-(alkyl)palladium(II) intermediate **C**, and (iv) reductive elimination affording the product and palladium(0).⁵ On the basis of reports that show alkene insertion into a Pd–O bond of arylpalladium(II) alkoxide⁶ and aldehyde insertion into a Rh–O bond of rhodium(I) alkoxide,⁷ we suppose that analogous carbonyl insertion to the Pd–O bond might occur in the present catalytic cycle. Although the asymmetric variant of the reaction was examined with various chiral phosphines, barely 15% ee was achieved with BINAP.⁸

Results with other 3-(2-hydroxyphenyl)cyclobutanones are shown in Scheme 3. The reaction of cyclobutanone **1a** and aryl bromides **2b–d** occurred in 1,4-dioxane at 100 °C to give 4,4-disubstituted 3,4-dihydrocoumarins **3ab–3ad** in good yields. 2-Bromothiophene (**2e**) underwent the reaction with **1a** to give the corresponding product **3ae** in 70% yield, while 2-bromopyridine failed to couple with **1a** under identical reaction conditions. Alkenylation could also be carried out with isobutenyl bromide **2f**. The reaction of cyclobutanones **1b–e** bearing several substituents at the

Scheme 3. Palladium-Catalyzed Arylation of Cyclobutanones 1 Forming Six-Membered Lactones 3^a

^a Conditions: 1 mol % Pd₂(dba)₃·CHCl₃, 2.5 mol % [HP(*t*-Bu)₃]BF₄ (1.25 equiv to Pd), 1.1 equiv K₂CO₃, 1,4-dioxane, 100 °C, 4 h. ^b 17 h. ^c 3 equiv **2f**, 3 mol % Pd₂(dba)₃·CHCl₃, 7.5 mol % [HP(*t*-Bu)₃]BF₄, 90 °C, 14 h. ^d 1.5 equiv **2a**, 5 mol % Pd₂(dba)₃·CHCl₃, 12.5 mol % [HP(*t*-Bu)₃]BF₄, 1.3 equiv Cs₂CO₃, toluene, 50 °C, 24 h.

3-positions afforded the corresponding arylated lactones **3ba–3ea**.⁹ Arylation of 3-monosubstituted cyclobutanone, 3-(2-hydroxyphenyl)cyclobutanone (**1f**), with **2a** proceeded in a similar manner to afford 4-monosubstituted 3,4-dihydrocoumarin **3fa** in 83% yield.

An analogous reaction of the regioisomers of **1**, i.e., 2-(2-hydroxyphenyl)cyclobutanones **4**, was then examined. Use of iodoarenes **2'** were found to be effective for the reaction with cyclobutanones **4a** and **4b** lacking an additional substituent at the 2-position (Table 1). In the presence of the Pd(0)–P(*t*-Bu)₃ catalyst, the reaction of **4a** and **2'd** gave seven-membered benzolactone **5ad** in 79% yield via ring expansion by selective cleavage of the more sterically congested carbon–carbon (C1–C2) bond (entry 1).¹⁰ A proper choice of the base is crucial for attaining good yield of **5**. Whereas methyl-substituted **4b** yielded slightly better results than **4a**, use of the corresponding bromide **2d** led to poor results (entry 2). The reaction with iodobenzene (**2'b**) that lacks electron-withdrawing substituents led to a complex mixture of products (entry 4). The reaction of sterically demanding **2'h** was inefficient (entry 5).

In contrast, cleavage of the less substituted carbon–carbon (C1–C4) bond took place selectively to give five-membered

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(5) Because ¹H NMR spectrum of cyclobutanone **1a** suggested that it equilibrated with the corresponding hemiketal (cyclobutanone:hemiketal = 89:11), **B** might also be formed from the hemiketal.

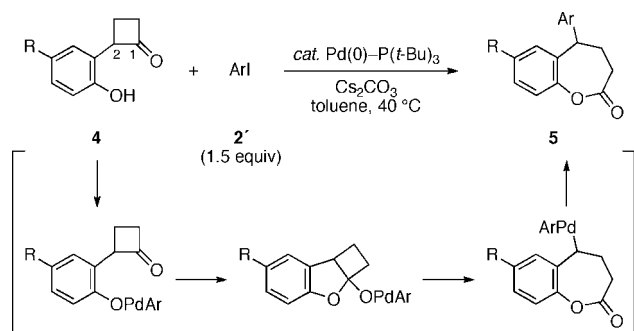
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(8) Result with 4-bromotoluene (3 equiv) and Cs₂CO₃ (1 equiv) in the presence of the Pd catalyst (10 mol % Pd).

(9) The lower yield of the product **3ba** was due to the formation of protonation product (ca. 30%).

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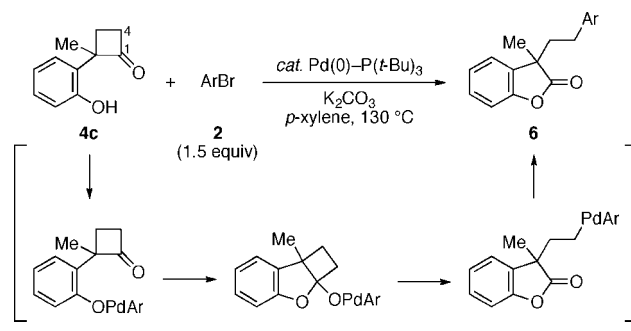
Table 1. Palladium-Catalyzed Arylation of Cyclobutanones **4** Forming Seven-Membered Lactones **5**^a

entry	4	R	2'	Ar	5	yield
1	4a	H	2'd	4-EtO ₂ CC ₆ H ₄	5ad	79% (35% ^b)
2	4b	Me	2'd		5bd	84% (60% ^c)
3	4b	Me	2'g	4-NCC ₆ H ₄	5bg	75%
4	4b	Me	2'h	Ph	5bb	— ^d
5	4b	Me	2'h		5bh	35%

^a 5 mol % Pd₂(dba)₃·CHCl₃, 12.5 mol % [HP(*t*-Bu)₃]BF₄, 1.3 equiv Cs₂CO₃, toluene, 40 °C, 15–25 h. ^b The reaction was carried out with K₂CO₃ in 1,4-dioxane. ^c The reaction was carried out with the corresponding bromide **2d**. ^d A complex mixture of products was obtained.

benzolactones **6** when 2,2-disubstituted cyclobutanone **4c** was used as the substrate (Table 2). Migration of the palladium to the tertiary carbon atom would be difficult due to steric reasons, thereby resulting in the cleavage of another carbon–carbon bond. Good yields were attained irrespectively to the electronic nature of the aryl bromides.

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Table 2. Palladium-Catalyzed Arylation of Cyclobutanone **4c** Forming Five-Membered Lactones **6**^a

entry	2	Ar	6	yield (%)
1	2a	4-MeOC ₆ H ₄	6a	86
2	2b	Ph	6b	93 (35 ^b)
3	2d	4-EtO ₂ CC ₆ H ₄	6d	86
4	2g	4-NCC ₆ H ₄	6g	83

^a 5 mol % Pd₂(dba)₃·CHCl₃, 12.5 mol % [HP(*t*-Bu)₃]BF₄, 1.3 equiv K₂CO₃, *p*-xylene, 130 °C, 10–16 h. ^b The reaction was carried out with Cs₂CO₃.

In summary, we have developed a palladium-catalyzed arylation reaction producing five- to seven-membered benzolactones via a sequential carbon–carbon bond cleavage/formation process. This reaction provides an access to 2,4-, 3,4-, and 4,4-diarylbutyric acid derivatives, which are intermediates in the synthesis of natural products and pharmaceuticals.¹¹

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Supporting Information Available: Experimental procedures and NMR spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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