

Novel synthesis of 4-oxo-1-isoquinolone derivatives utilizing inter- and intramolecular tandem carbopalladation-heterocyclic ring expansion

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Abstract

The palladium(0)-catalyzed inter- and intramolecular carbopalladation-heterocyclic ring expansion employing allenic alcohols and aryl iodides provides a novel and facile route to 4-oxo-1-isoquinolone derivatives in reasonable to high yields. © 1998 Elsevier Science Ltd. All rights reserved.

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The palladium(0)-catalyzed coupling of haloarenes and haloalkenes with olefins, known as the Heck reaction, has proved to be an efficient reaction for the carbon-carbon bond formation. The application of this reaction in both inter- and intramolecular modes for the synthesis of carbo- and heterocyclic systems is well documented.¹ In view of increasing interest in the elegant utility of this methodology, inter- and intramolecular cyclic carbopalladation of allenes has attracted attention, which has been focused, in part, on the carbo- and heterocyclic compounds.² Generally, when aryl halides are used in Heck reactions, a frequent problem is the formation of

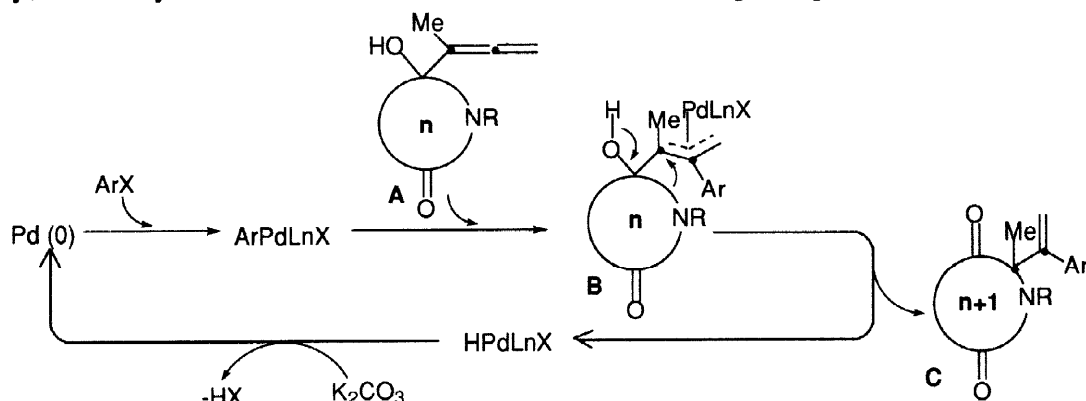
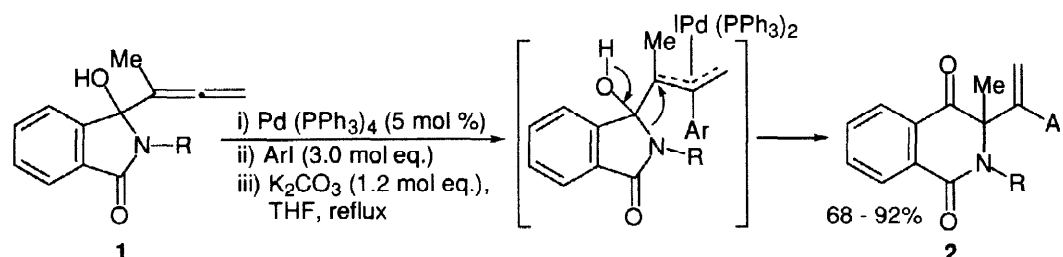


Figure 1

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stable π -allylpalladium intermediates, which serve to remove the metal catalyst and then terminate the catalytic cycle.³ In conjunction with this phenomenon, we expected that if a nucleophilic attack of amide anion formed by cleavage of the C-N bond in a π -allylpalladium intermediate **B** was involved, a ring expansion reaction induced by the coupling of allenic alcohols **A** with aryl halides (ArX) could be catalytically promoted by use of Pd(0), yielding one-carbon ring-expanded heterocyclic compounds **C** as illustrated in Fig. 1.

Recently, Nemoto et al. reported an excellent carbocyclic carbopalladation of allenylcyclobutanols followed by ring expansion giving the corresponding cyclopentanones.⁴ We now describe a novel, efficient construction method of 4-oxo-1-isoquinolones **2** starting from γ -lactam precursors **1** bearing an allenic alcohol moiety based on the inter- and intramolecular tandem carbopalladation-heterocyclic ring expansion (Schemes 1 and 2). Compounds **1** were successfully prepared by treatment of a mixture of *N*-alkylphthalimides, magnesium flakes, and catalytic HgCl₂ with a solution of 1-bromo-2-butyne in THF.⁵ A variety of reaction conditions were examined for the initial feasibility studies of the compounds **1**, that is, exposure of allenic alcohols **1**, excess of aryl iodides (ArI), and 1.2 mol eq. of K₂CO₃ to 5 mol % of Pd(PPh₃)₄ using DMF as a solvent. These conditions gave substituted 4-oxo-1-isoquinolones **2**, but only in poor yields (<34%). Although variation of the amounts of K₂CO₃ (>1.2 mol eq.) and employment of other base (e.g., Et₃N) were investigated to elevate the chemical yields relevant to this heterocyclic carbopalladation-ring expansion reaction, all tentative reactions resulted in yields less than 38% along with the decomposition of the compounds **1**. Lautens and Ren⁶ reported that the addition of molecular sieves to a similar cyclization could be participated in improvement of the yields; however, in our case such addition proved inadequate. After various experiments for the conversion of **1** to **2**, we reached optimized reaction conditions with 5 mol % of Pd(PPh₃)₄, using THF as the solvent (shown in Scheme 1).⁷ Thus, the desired reaction proceeded smoothly at reflux when a THF solution of all-



Scheme 1. Intermolecular tandem carbopalladation-heterocyclic ring expansion mode

enic alcohols **1**, 3 mol eq. of aryl iodides, and 5 mol % of Pd(PPh₃)₄ are mixed in the presence of 1.2 mol eq. of K₂CO₃ under an N₂ atmosphere. All results of the intermolecular carbopalladation-ring expansion are listed in Table 1. In our system, the reactions proceeded to give exclusively the nonconjugated exomethylene products **2** (entries 1-12) without producing a mixture with the α , β -unsaturated ketones, because the methyl-substituted allenes such as **1** were used.⁴ In these reactions, the cases using the aryl iodides bearing an electron-donating substituent gave better yields and had shorter reaction times (entries 2, 3, 5, 6, 8, 9, 11, and 12) than those using phenyl iodides (entries 1, 4, 7, and 10), respectively.⁴ When the *N*-benzyl derivative **1** (R

= Bn) was employed (entries 10-12), the reactions showed a decreased tendency of the chemical yields in comparison with the tendencies shown by corresponding other *N*-alkyl derivatives **1** (R = Et, *n*-Pr, and *i*-Pr). The use of excess K_2CO_3 as the base was unnecessary to promote the re-

Table 1. Conversion of **1** to **2**

entry	1 R	Ar	time (h)	yield (%) ^{a)} 2	entry	1 R	Ar	time (h)	yield (%) ^{a)} 2
1	Et	Ph	30	81	7	<i>i</i> -Pr	Ph	31	84
2	"	<i>p</i> -MePh	26	90	8	"	<i>p</i> -MePh	28	90
3	"	<i>p</i> -MeOPh	25	90	9	"	<i>p</i> -MeOPh	26	88
4	<i>n</i> -Pr	Ph	40	86	10	Bn	Ph	23	68
5	"	<i>p</i> -MePh	24	92	11	"	<i>p</i> -MePh	22	70
6	"	<i>p</i> -MeOPh	36	91	12	"	<i>p</i> -MeOPh	15	74

^{a)} Isolation yield

action. In the absence of aryl iodides, $PdCl_2$ was tentatively used for the ring expansion reaction. However, no reaction occurred (94% recovery of the starting material). The structures of products **2** were determined by their characteristic spectroscopic data [IR ($CHCl_3$) 1692 - 1690 (ketone) and 1647-1645 (amide carbonyl) cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 5.52 - 5.63 (s, 1H, exomethylene) and 5.55 - 5.82 (s, 1H, exomethylene)] and X-ray crystallographic analysis⁸ (**2**: R = Bn, Ar = *p*-MePh) as shown in Fig. 2. We have also attempted an intramolecular carbopalladation-ring expansion reaction of allenic alcohol **3**. Namely, subjecting allenic alcohol **3** to the reaction conditions identical to those which were successful in the intermolecu-

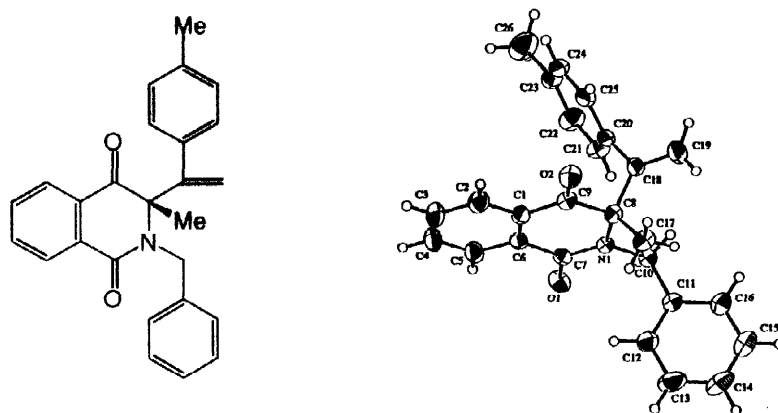
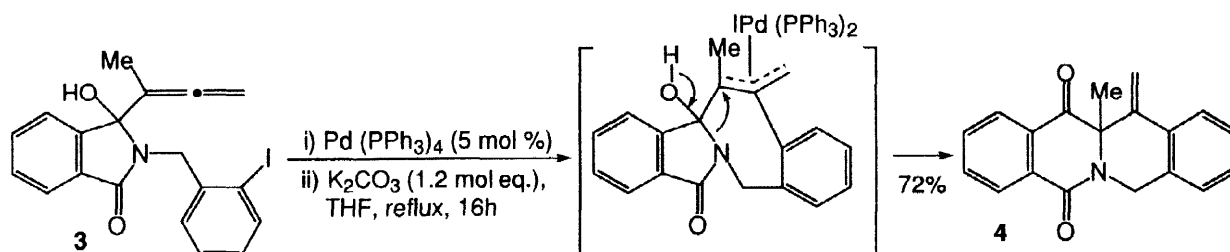


Figure 2. ORTEP plot of the molecular structure of **2** (R = Bn, Ar = *p*-MePh)



Scheme 2. Intramolecular tandem carbopalladation-heterocyclic ring expansion mode

lar reactions afforded 4-oxo-1-isoquinolone derivative **4** [colorless prisms (Et_2O -hexane-

CH_2Cl_2), mp 130-131°C^p involving the fused tetracyclic system in 72% yield (Scheme 2). As described above, formation of six-membered rings *via* inter- and intramolecular carbopalladation-ring expansion using allenic alcohols and aryl iodides appears to be quite general.

In conclusion, the results described here demonstrate that inter- and intramolecular tandem carbopalladation-heterocyclic ring expansion reactions based on the three-component combination of allenic alcohols, aryl iodides, and $\text{Pd}(\text{PPh}_3)_4$ are profoundly influenced by incorporating THF solvent into the reaction. Applications to the syntheses of natural products and other heterocyclic compounds will be pursued in future work.

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- [7] A typical procedure of intermolecular reaction (entry 2 in Table 1): A mixture of *N*-ethyl-3-hydroxy-3-allenylindan-1-one (0.15 g, 0.66 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.04 g, 5 mol %), 4-iodotoluene (0.43 g, 1.98 mmol), and K_2CO_3 (0.11 g, 0.66 mmol) in anhydrous THF (5 mL) was refluxed under an N_2 atmosphere for 26 h. The reaction mixture was quenched with sat. NH_4Cl and then extracted with ether. The organic layer was washed with brine, dried over MgSO_4 , and filtered. The filtrate was evaporated *in vacuo* to afford the crude product, which was purified by flash column chromatography on silica gel with ether-hexane (1:3) to give 4-oxo-1-isoquinolone **2** (R = Et, Ar = *p*-MePh) (0.19 g, 90 % yield) as a pale yellow oil.
- [8] X-ray data for **2** (R = Bn, Ar = *p*-MePh): $\text{C}_{26}\text{H}_{23}\text{NO}_2$; fw = 381.47; colorless prism; primitive triclinic; space group $\text{P}\bar{1}$ (#2); a = 10.154 (2) Å, b = 11.462 (2) Å, c = 8.949 (1) Å; V = 1030.7 (3) Å³; α = 91.64 (1)°, β = 96.59 (1)°, γ = 85.09 (1)°; Z = 2; R = 0.069, R_w = 0.085, GOF = 1.76
- [9] Compound **4**: IR (CHCl_3) 1689, 1645 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.87 (s, 3H), 4.39 (d, J = 17.57 Hz, 1H), 5.03 (s, 1H), 5.60 (s, 1H), 6.03 (d, J = 17.57 Hz, 1H), 7.29 (brs, 3H), 7.74 (m, 3H), 8.19 (d, J = 7.57 Hz, 1H), 8.31 (d, J = 7.57 Hz, 1H); HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{NO}_2$ MW 289.1103, found m/z 289.1094 (M^+).