DOI: 10.1002/adsc.200600547

# Palladium-Catalyzed Synthesis of Functional Tetralins *via* Benzylic Activation

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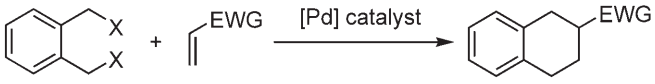
Received: October 23, 2006

**Abstract:** 2-Monosubstituted, 2,2- and 2,3-disubstituted tetralin derivatives have been synthesized from α,α′-dihalo-*o*-xylenes and activated olefins using a palladium catalyst under basic conditions. The effects of temperature, base, palladium precursor and solvent have been fully explored, and this new catalytic reaction has been extended to a variety of substrates.

**Keywords:** benzylic activation; homogeneous catalysis; palladium; tetralin synthesis

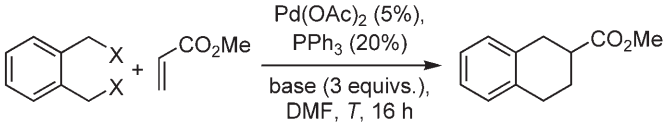
Tetralins, or tetrahydronaphthalene derivatives are substituted aromatic nuclei fused onto a [4.4.0] carbocyclic system that may contain stereogenic centers. The tetralin moiety is found in materials[1] and polymer chemistry,[2] and functional tetralin derivatives are also useful intermediates to access biologically active natural compounds and analogues. Thus, such a structure is present in hamigeran B, a strong antiviral and low cytotoxic compound,[3] a lavendustin A analogue, which exhibits tubulin polymerization inhibition,[4] the σ-receptor (+)-pentazoine,[5] the highly potent and selective IP agonist FK 788,[6] inhibitors of human placental aromatase,[7] and prolyl endopeptidase (PEP).[8]




**Scheme 1.**

Several methods are used for the preparation of the tetralin motif. Thus, the Bergman cycloaromatization of 3-ene-1,5-diynes[9] and the hydrogenation reaction of naphthalene[10] or dihydronaphthalene derivatives[11] lead to tetralins. Polycyclic compounds are also synthesized by ring expansion of 1-alkenyl-2-benzyl-1-cyclopentanol mediated by thallium trifluoroacetate[12] or ring opening of cyclopropyl silyl ethers upon oxidative photo-induced electron transfer.[13] So far, the most popular way to prepare tetralin derivatives is the [4+2] cycloaddition reaction between a dienophile and an *in situ* generated *o*-quinodimethane (oQDM).[14] There are several established methods for generating oQDMs including elimination of small molecules ($SO_2$, $CO_2$, $N_2$, CO),[15] thermal benzocyclo-

**Table 1.** Palladium-catalyzed tetralin ester formation.




| Entry[a] | X | Base | *T* [°C] | Yield [%][b] |
|---|---|---|---|---|
| 1 | Br | *t*-BuOK | 100 | 0 |
| 2 | Br | $K_2CO_3$ | 100 | 4 |
| 3 | Br | $NBu_3$ | 100 | 32 |
| 4 | Br | $NEt_3$ | 100 | 44 |
| 5 | Cl | $NBu_3$ | 100 | 24 |
| 6 | Cl | $NEt_3$ | 100 | 28 |
| 7 | Br | $NBu_3$ | 80 | 15 |
| 8 | Br | $NBu_3$ | 90 | 30 |
| 9 | Br | $NBu_3$ | 110 | 30 |
| 10 | Br | $NEt_3$ | 90 | 30 |
| 11 | Br | $NEt_3$ | 110 | 44 |
| 12 | Cl | $NBu_3$ | 110 | 43 |
| 13 | Cl | $NEt_3$ | 110 | 40 |
| 14 | Br | $NBu_3$ | 120 | 25 |
| 15 | Br | $NEt_3$ | 120 | 22 |
| 16 | Cl | $NBu_3$ | 120 | 35 |
| 17 | Cl | $NEt_3$ | 120 | 33 |
| 18[c] | Cl | $NEt_3$ | 110 | 55 |
| 19[d] | Cl | $NEt_3$ | 110 | 62 |

[a] *Reaction conditions:* 2 mmol of dihaloxylene, 4 mmol of methyl acrylate, 0.1 mmol of $Pd(OAc)_2$, 0.4 mmol of $PPh_3$, 6 mmol of base in DMF (10 mL, 0.2 M).
[b] Isolated yields.
[c] Addition of the dihaloxylene in 11 h.
[d] Addition of the dihaloxylene in 22 h.

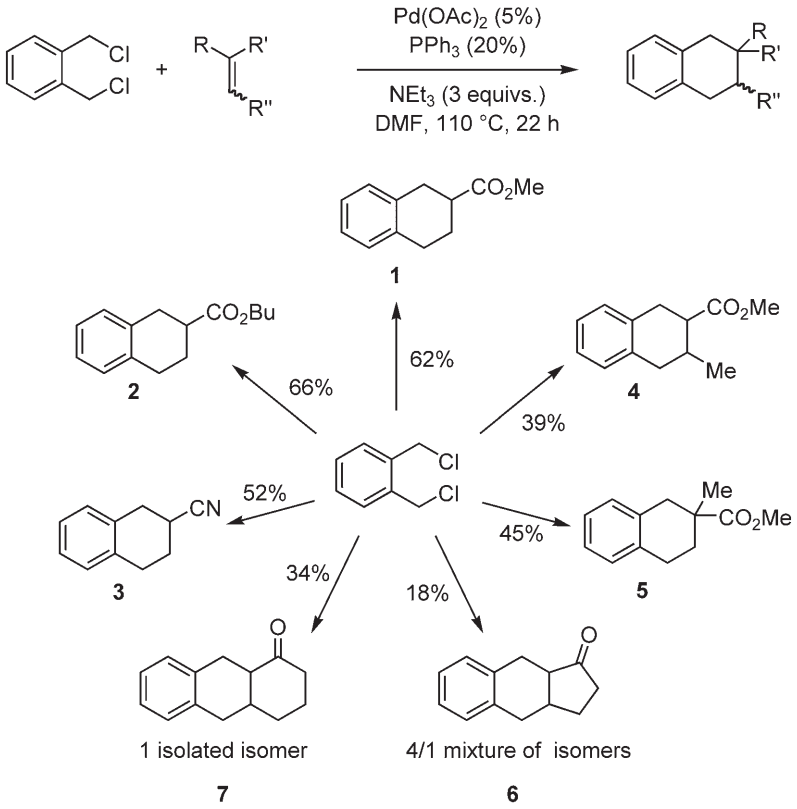
butene ring opening,[16] electrochemical and UV activation,[17] and reductive dehalogenation of α,α′-dihalo-1,2-dialkylbenzene halides.[18] However, all of these methodologies suffer from drawbacks, such as low yields, by-product formation, multi-step reactions or not easily accessible precursors.

While significant advances in the palladium-catalyzed reactions of aryl halides and activated alkenes have been made,[19] very few examples of catalytic transformations of benzylic halides have been reported.[20] In this communication, we report a new catalytic reaction based on the coupling of commercially available α,α′-dihalo-1,2-xylenes with olefins in the presence of palladium precursors (Scheme 1).

We initially studied the reaction of α,α′-dibromo- and α,α′-dichloroxylenes with methyl acrylate as a benchmark reaction in the presence of 5 mol% of palladium acetate, 20 mol% of triphenylphosphine and a base in DMF at 100°C for 16 h (Table 1). The use of a base appeared to be necessary and an organic tertiary amine gave better yields than *t*-BuOK or $K_2CO_3$ (entries 1–4). Decreasing the temperature below 90°C or increasing it above 110°C provided lower yields, whatever the dihalide derivative (entries 7–9, 11 *vs.* 15, 12 *vs.* 16, 13 *vs.* 17). It is worth mentioning that, at 110°C, the less expensive dichloroxylene gave similar or better results than the dibromo precursor (entries 10–13).

Other solvents were also screened (toluene, dioxane, DMSO; 12%, 14% and 15% yields, respectively), but the yields were lower. Electron-rich ligands [$PCy_3$, bis(mesityl)imidazolylidene] did not provide any bicyclic compound and diphosphines led to very poor results. In order to improve the efficiency of this catalytic reaction, we turned our investigation to the addition rate of dichloroxylene. Indeed, at elevated temperatures, dihaloxylenes can undergo dimerization and polymerization.[17b,21] Thus, upon slow addition of the dihalide, side reactions were limited and the yield was increased from 40% to 62% (entries 13, 18 and 19, Table 1).

Having determined the optimal reaction conditions [5 mol% of $Pd(OAc)_2$, 20 mol% of $PPh_3$, 3 equivalents of $Et_3N$ in DMF and slow addition of the xylene derivative over 22 h], we extended this process to various electrophiles (Scheme 2). With acrylate type derivatives, compounds **1**–**3** were isolated in 52–66% yields. Such yields are comparable or higher than those previously described in the literature.[20b,c,e] This new procedure was highlighted by its application to other substrates. With methyl crotonate and methyl methacrylate, 2,3- and 2,2-disubstituted tetralins **4** and **5** were obtained in lower but reasonable yields (39–45%); still better than the overall yields resulting from multi-step syntheses.[18b,c,22] This procedure also gave access to polycyclic compounds (**6**–**7**) from α,α′-




**Scheme 2.**

dichloro-1,2-xylene and the corresponding conjugated cycloenones. The compound **6** was isolated in only 18% yield as a mixture of *trans* and *cis* isomers.[23] Compound **7** was also obtained as a mixture of isomers. The pure, isolated, major isomer (34% yield) was identified as the *cis*-isomer by comparison with literature data.[13] The *trans*-isomer was formed along with an unknown compound in an inseparable mixture. To the best of our knowledge, this methodology provides the first one-step access to compounds **6** and **7**.[12,13,17b,24]

Either a Diels–Alder-type reaction or a Heck-type reaction with an internal trapping of the second halide might explain the formation of the tetralin derivatives. Based on the yield improvement upon slow addition of the α,α′-dichloro-1,2-xylenes, a Diels–Alder reaction, *via* an *o*-quinodimethane (oQDM), could be proposed. The transient oQDM could be produced by a double oxidative addition of the C–X bonds to the palladium species, followed by reductive elimination.[18d,25] However, some relevant observations could rule out this mechanism. Good dienophiles, such as maleic anhydride, dimethyl maleate or dimethyl fumarate, did not give any tetralin product. Moreover, starting from cyclohexenone or cyclopentenone, we obtained a mixture of stereoisomers (compounds **6** and **7**), which is in contradiction with the Alder/Stein rules.

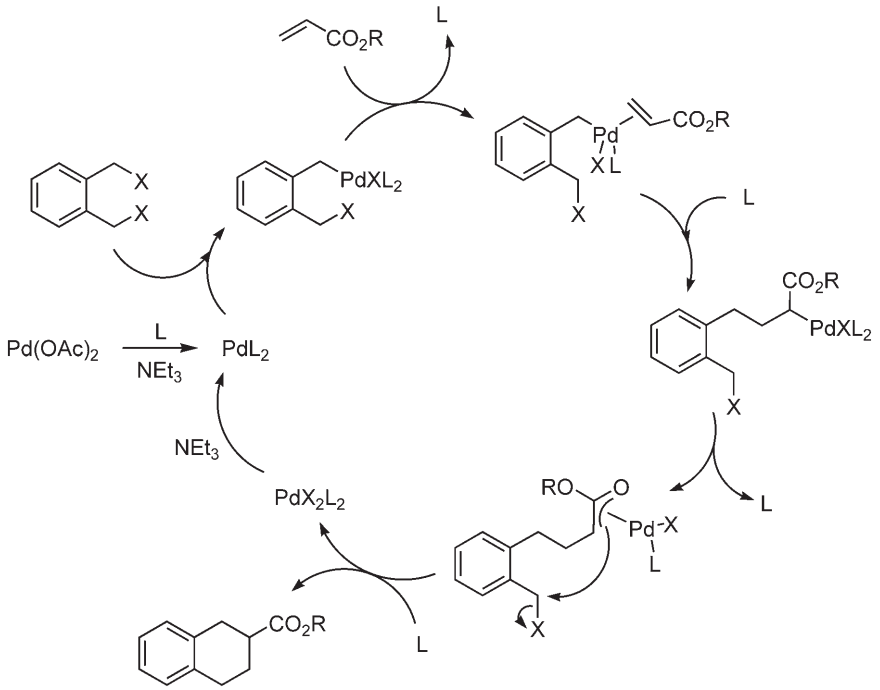
Alternatively, the second plausible mechanism would follow the first elementary steps of the Heck reaction (Scheme 3). It could be initiated by oxidative addition of one C–X bond to a palladium(0) species, followed by carbopalladation of the alkene. Then, instead of the usual β-H elimination, which takes place in a Heck reaction, a palladium enolate[26] could be involved and react with the second electrophile ($CH_2$–X) leading to the tetralin derivative.

In conclusion, we have developed a straightforward, new synthesis of 2-monosubstituted, 2,2- and 2,3-disubstituted tetralin derivatives catalyzed by palladium complexes. Although some yields are still moderate, most of them compete with results from the literature, especially with respect to the ease of performance from commercially available starting compounds. This transformation thus appears very attractive and useful for organic synthesis.

## Experimental Section

### Typical Procedure for the Synthesis of Tetralin Derivatives

α,α′-Dichloro-1,2-xylene (350 mg, 2 mmol) in DMF (5 mL) was added over 22 h to a solution of $Pd(OAc)_2$ (22 mg, 0.1 mmol, 0.05 equivs.), $PPh_3$ (105 mg, 0.4 mmol, 0.2 equivs.), $NEt_3$ (840 μL, 6 mmol, 3 equivs.) and olefin (4 mmol, 2 equivs.) in DMF (5 mL) at 110 °C. After 2 more hours at 110 °C, the mixture was cooled to room temperature and hydrolyzed with a saturated aqueous solution of $NH_4Cl$. After extraction with $CH_2Cl_2$, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (heptane/$Et_2O$) to give the tetralin.




**Scheme 3.**

**Methyl 1,2,3,4-tetrahydronaphthalene-2-carboxylate (1):** $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–$7.10$ (m, 4H), 3.77 (s, 3H), 3.06 (d, $J = 8.2$ Hz, 2H), 2.90 (m, 2H), 2.77 (m, 1H), 2.24 (m, 1H), 1.90 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 176.3$ (s), 136.1 (s) 135.2 (s), 129.5 (d), 129.3 (d), 126.4 (d), 126.3 (d), 52.2 (q), 40.4 (d), 32.1 (t), 29.0 (t), 26.3 (t); HR-MS (EI): $m/z = 190.0980$, calcd. for $C_{12}H_{14}O_2$ [$M^+$]: 190.09938.

## Acknowledgements

*The authors thank Oril Industrie for a PhD grant for B.L.*

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