A new entry to *o,o'*-dihalogenated deoxybenzoins by palladium-catalyzed α-arylation of 2'-chloroacetophenones

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Dedicated to Professor Joan Bosch on the occasion of his 60th birthday

Abstract

The palladium-catalyzed arylation reaction is a valid, advantageous tool for the construction of *o,o'*-dihalo-1,2-diarylethanones. After an exhaustive range of assays the arylation of 2'-chloroacetophenones is performed in good yields, thus overcoming the handicap imposed by the presence of the *ortho*-chloro substituent and controlling the regioselective monoarylation with dibromoarenes.

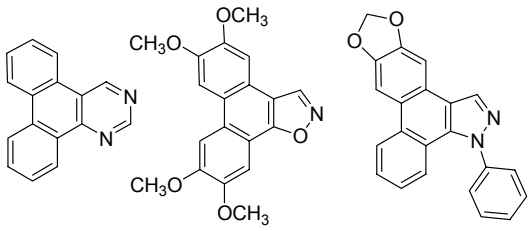
Keywords: α-Arylation, palladium catalysts, homogeneous catalysis, deoxybenzoins

Introduction

The extensive use of 1,2-diarylethanones or deoxybenzoins over the last decades as versatile building blocks of a whole range of compounds[1] has promoted a search for efficient ways for their preparation. Led by the classical Friedel-Crafts arylation of arylacetic acid derivatives, several methodologies have been developed for this purpose, providing a good amount of alternatives available to the synthetic chemist. However, when the nature of the functional groups attached to the aromatic moieties of deoxybenzoins is labile or sensitive to the reaction conditions, or when specific functionalization of *ortho* and/or *ortho'* positions is required, most of the above procedures fail.[2]

Our group has contributed to the development of new protocols for the generation of 1,2-diarylethanones, especially in the field of palladium-catalyzed arylation of ketone enolates, providing simple, highly efficient approaches based on both homogeneous and heterogeneous catalysis that avoid the use of usually harmful transmetallating agents and allow in some cases catalyst recycling and reuse.[3] Nevertheless, the latter protocols had never been tested in the synthesis of *o,o'*-dihalogenated deoxybenzoins, an appealing kind of difunctionalized

diarylethanones as they are key starting materials to access complex heterocyclic systems, like the phenanthro[9,10]pyrimidines, isoxazoles and pyrazoles shown below.[4]

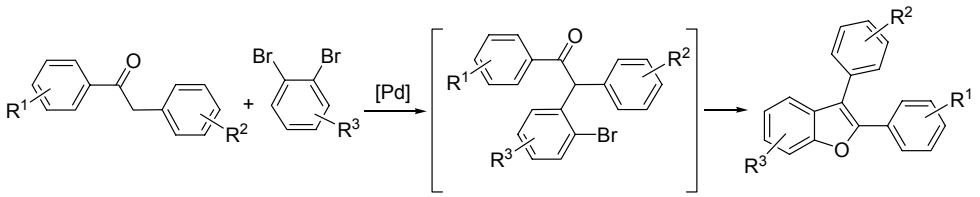


This paper deals with our efforts towards a reliable, straightforward method to prepare such *o,o*-dihalo-1,2-diarylethanones employing a palladium-catalyzed arylation of acetophenones.

Results and Discussion

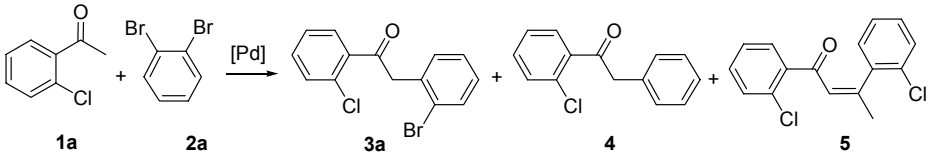
Before starting to evaluate different procedures to accomplish our aim, a reflexive thought about the most convenient substrates was required, as the use of polyhalogenated coupling partners could lead to a lack of regioselectivity.[5] Following the initial work of Miura,[6] our experience in the synthesis of 2,3-diarylbenzofurans[7] had revealed that upon certain reaction conditions α-arylation with 1,2-dibromoarenes can be stopped at the *C*-arylation stage to provide α-*ortho*-bromoaryl moieties (Scheme 1). With regard to the *ortho*-haloacetophenone coupling partner, the choice of the halide was mainly determined from the comparison of the dissociation energies C-I<C-Br<C-Cl, which are closely related to the oxidative addition, key step of the catalytic cycle proposed as the mechanism to explain arylation of ketone enolates. Thus, iodo derivatives were discarded due to their high reactivity which makes them less selective. In the same context, *ortho*-bromoacetophenones could also competitively act as arylating agents instead of as sources of enolate.[8]

Accordingly, 2'-chloroacetophenones **1** were chosen as suitable starting materials along with dibromoarenes **2**, taking phenyl methyl ketone **1a** and dibromobenzene **2a** as model substrates in order to perform a range of assays resumed in Table 1.



Scheme 1

Table 1. Palladium-catalyzed α-arylation assays of acetophenone **1a**



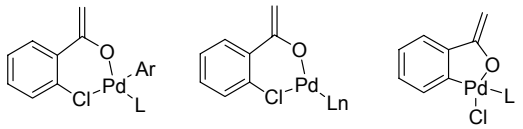
1a **2a** **3a** **4** **5**

Entry	Reaction conditions[a]	**1a:2a**	Products (%)[b]
1	3.3% $Pd(OAc)_2$, 13% PPh_3, 1. 6 eq. Cs_2CO_3, *o*-xylene, 100°C, 22.5 h	1:1.2	-[c]
2	1.3% $Pd(OAc)_2$, 8.3% PPh_3, 1.5 eq. K_2CO_3, *o*-xylene, 100°C, 22.5 h	1:1.1	-[d]
3	5% $Pd(OAc)_2$, 21% PPh_3, 2 eq. Cs_2CO_3, *o*-xylene, 130°C, 4h	1:1.2	**3a** (46)
4	6.3% $Pd(OAc)_2$, 21% PPh_3, 2.3 eq. Cs_2CO_3, *o*-xylene, 140°C, 4.5 h	1:1.2	**3a** (17)
5	11% $Pd(OAc)_2$, 42% $P(^tBu)_3$, 2 eq. Cs_2CO_3, *o*-xylene, 100°C, 19 h.	1:1	**3a** (0)
6	1% $Pd(PPh_3)_4$, 1.5 eq. Cs_2CO_3, *o*-xylene, 130°C, 7 h.	1:1.1	**3a** (8)
7	5% $PdCl_2$, 10.5% PPh_3, 1.2 eq. K_2CO_3, DMF, 100°C, 24 h.	1:1.2	-[d]
8[e]	1.3% $Pd(OAc)_2$, 3% L, 2.5 eq. NaO^tBu, toluene, r.t., 23.5 h	1.2:1	-[c]
9[e,f]	2% $Pd(OAc)_2$, 7% L, 2.3 eq. K_3PO_4, THF, 50°C, 32.5 h	1.2:1	-[d]
10[f]	1.7% $Pd(OAc)_2$, 1.4 eq. NaO^tBu, toluene, 85°C, 3.5 h	1.2:1	-[c]
11	10.5% $PdCl_2(PPh_3)_2$, 30% PPh_3, 2 eq. Cs_2CO_3, toluene, 130°C, 3h	1:1	-[c]
12	2.5% $Pd(dba)_2$, 6% $P(^tBu)_3$, 2 eq. Cs_2CO_3, toluene, 120°C, 3.5 h	1:1.2	-[c]
13	1.2% Pd_2dba_3, 3.4% BINAP, 1 eq. NaO^tBu, THF, 70°C, 22 h.	1:1.2	**3a** (16), **4** (1)
14	1.3% Pd_2dba_3, 3.3% BINAP, 1.4 eq. NaO^tBu, THF, 80°C, 22 h.	1:1.1	**3a** (41), **4** (1)
15	1.5% Pd_2dba_3, 1.5% IPr·HCl, 1.5 eq. KO^tBu, 1,4-dioxane, 80°C, 17 h.	1:1.2	-[c]
16	1.5% Pd_2dba_3, 3% IMes·HCl, 2 eq. Cs_2CO_3, 1,4-dioxane, 80°C, 22 h.	1:1.2	-[c]
17	4% $Pd(OAc)_2$, 8.5% IMes·HCl, 2 eq. Cs_2CO_3, DMF, 120°C, 42 h.	1:1.2	-[c]
18	1.3% Pd_2dba_3, 3% IPr·HCl, 1.4 eq. NaO^tBu, THF, 80°C, 6.5 h	1:1.2	-[c]
19	1.5% $Pd(dba)_2$, 2.5% IMes·HCl, 2.5 eq. NaO^tBu, pyridine, 90°C, 40 h.	1.2:1	-[c]
20	3.5% (IPr)Pd(allyl)Cl, 1.1 eq. NaO^tBu, THF, 90°C, 25 h.	1:1.1	-[c]
21	4.5% $Pd(OAc)_2$, 6% IMes·HCl, 0.45 eq. NaI, 2 eq. NaO^tBu, 1,4-dioxane, 90°C, 21 h.	1.2:1	-[d]
22	8% $PdCl_2$, 6% IPr·HCl, 0.15eq. LiCl, 1.4eq. NaO^tBu, THF, 50°C, 23 h.	1:1.1	-[d]
23	4% $Pd(OAc)_2$, 6.5% IPr·HCl, 0.5 eq. TBAI 2eq. Cs_2CO_3, DMF, 130°C, 48 h.	1.2:1	-[c]
24	1.5% Pd_2dba_3, 1.5% BINAP, 3% IMes·HCl, 1.4eq. NaO^tBu, THF, 90°C, 26 h.	1.2:1	**3a** (37)
25	2.2% $PdCl_2(PPh_3)_2$, 5% PPh_3, 6% IMes·HCl, 0.25eq. LiCl, 1.4eq. NaO^tBu, THF, 90°C, 31 h	1.2:1	-[d]
26	7% $Pd(OAc)_2$, 20% PPh_3, 11% IPr·HCl, 0.3 eq. LiCl, 1.4eq. NaO^tBu, THF, 70°C, 25 h	1:1.1	-[d]
27	1.3% Pd_2dba_3, 3.3% BINAP, 1.4 eq. NaO^tBu, 1,4-dioxane, 80°C, 23 h	1:1.2	-[c]
28	1.5% Pd_2dba_3, 3.3% BINAP, 1.4 eq. KO^tBu, THF, 90°C, 28 h	1:1.2	**3a** (6)
29	1.5% Pd_2dba_3, 3.3% BINAP, 1.4 eq. NaO^tBu, toluene, 90°C, 28 h	1:1.2	**3a** (20)
30	1.5% Pd_2dba_3, 3.3% BINAP, 1.4 eq. NaO^tBu, THF, 90°C, 28 h	1.2:1	**3a** (92), **4** (3)
31	1.5% Pd_2dba_3, 3.3% BINAP, 1.4 eq. NaO^tBu, MS4A, THF, 90°C, 27 h	1.2:1	**3a** (52), **4** (1)
32	0.25% Pd_2dba_3, 0.7% BINAP,1.4 eq. NaO^tBu, THF, 90°C, 27 h	1.2:1	**3a** (19), **5** (42)
33	0.25% Pd_2dba_3, 0.7% BINAP,1.4 eq. NaO^tBu, THF, 90°C, 27 h	1.2:1	**5a** (4), **5** (24)

[a] The amounts of palladium catalyst and ligand are indicated in mol%. [b] GC-MS yields using tetrabutylammonium bromide as internal standard. [c] Both starting materials were recovered unreacted. [d] Complex mixture in which **3a** was not detected [e] L= 2-(di-*tert*-butylphosphino)diphenyl. [f] Sealed tube [g] The dilution employed was twice the one of the previous assay (entry 32).

It was clear from the beginning that slight variations of temperature, relative amounts of palladium sources and ligands or even the metal counterion of the base provoke important variations in the reaction results. Another remarkable feature was that the conditions optimized for the isolation of 2-bromoaryl intermediates depicted in Scheme 1 (Table 1, entries 1-2)[6,7] provided complex mixtures in this case, and it was necessary to increase the temperature and the amount of base to detect the target ethanone **3a** (Table 1, entries 3-4), though with relatively low yields (46%) and the occurrence of several side-products which made the purification task difficult. Then, a variety of procedures and variations based on previous work of the group of Hartwig,[9] Buchwald,[10] and Nolan[11] involving ligands or catalytic systems that had proven useful in other α-arylation reactions (P^tBu_3, 2-(di-*tert*-butylphosphino)diphenyl, absence of ligands, $Pd(PPh_3)_4$, BINAP, *N*-Heterocyclic Carbene [NHC] ligands like IPr and IMes) were investigated, affording in most cases negligible results. Only a combination of Pd_2dba_3 and BINAP, NaO^tBu and THF (Table 1, entries 13-14) provided a yield similar to that of the initial assay shown in entry 3. It is particularly surprising to notice the lack of ketone **3a** when the complex (IPr)Pd(allyl)Cl (entry 20) was employed as this system had been specifically designed for the α-arylation of acetophenones.[11a]

In most of the performed assays, the reaction mixture turned red after 0.5 h of reaction. The structures **6-8** depicted below were tentatively proposed as possible complexes that would explain such coloration[12] and also to some extent the hindrance to reach target ethanone **3**.



6 **7** **8**

Several aspects can seriously prevent the formation of 3, such as a) the formation of palladacycle **6**, formed after the expected oxidative addition can attack the enolate and coordinate to the *o*-chloride, b) the formation of complex **7**, generated by an initial coordination to the bidentate enolate, or even c) the formation of organometallic compound **8**, the product of an oxidative addition of C-Cl bond instead of C-Br, which could be stable enough to influence the reaction path. Accordingly, in order to avoid such deleterious side-processes, it was decided to increase the amount of ligand or to add a halide salt (NaI, LiCl, Bu_4NI) in the hope that this would lead to an improved coordination to Pd. Both strategies failed (Table 1, entries 21-23).

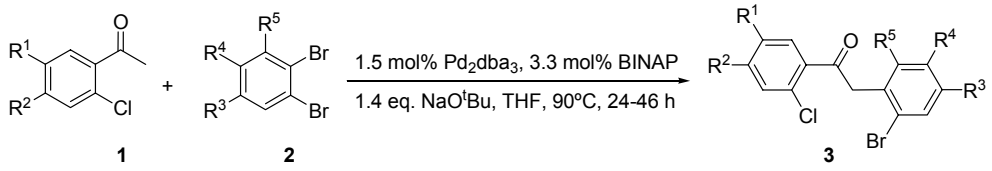
In view of the moderate results obtained when using Pd_2dba_3/BINAP (Table 1, entries 13-14), the effect of little variations in this system could not be discarded. Those variations performed in entries 27-33 featured an optimized procedure (Table 1, entry 30) where finally target ethanone **3a** was obtained with good yield, in the presence of traces of monohalogenated deoxybenzoin **4**, probably generated by a phenyl migration[13] or a dehalogenation process.[14] Attemps to reduce the amount of the catalyst led to the enone **5**, generated by an aldol condensation of reagent **1a**. This

side-reaction could not be avoided even when a higher dilution was used (Table 1, entries 32-33).

The optimized protocol for the preparation of **3a** was applied accordingly to a range of commercially or readily available 2-chloroaryl methyl ketones **1** and dibromoarenes **2**, as shown in Table 2.

With regard to the acetophenones, the best yields were afforded by **1a**, probably due to the relative instability of the trifluoromethylated ketone **1b** under these reaction conditions and due to a greater hindrance of the dimethylated ketone **1c** to generate the corresponding enolate.[15] Moreover, and in accordance with previous reports on aryl monohalides and theoretical studies about oxidative addition,[3] electronically neutral and poor dibromoarenes **2a**,**d** couple more efficiently than methylated or alkoxylated derivatives **2b-c**.

Table 2. Synthesis of *o,o'*-dihalodeoxybenzoins **3**



1 **2** **3**

Entry	R^1	R^2	**1**	R^3	R^4	R^5	**2**	**3** (%)[a]
1	H	H	**1a**	H	H	H	**2a**	**3a** *92* (70)
2	H	H	**1a**	CH_3	CH_3	H	**2b**	**3b** *71* (62)
3	H	H	**1a**	OCH_2O		H	**2c**	**3c** *47* (39)
4	H	H	**1a**	F	H	F	**2d**	**3d** *88* (53)
5	CF_3	H	**1b**	H	H	H	**2a**	**3e** *45* (30)
6	CH_3	CH_3	**1c**	H	H	H	**2a**	**3f** *77* (55)
7	CH_3	CH_3	**1c**	CH_3	CH_3	H	**2b**	**3g** *45* (42)

[a] GC-MS yields using tetrabutylammonium bromide as internal standard are featured in italics. Isolated yields are shown in parentheses.

Due to the presence of structurally similar by-products and starting acetophenones, a decrease to moderate to good yields obtained after purification, considerably lower than the GC-MS yields, has been noticed. However, the advance achieved in this context should be pointed out, particularly taking into account that the only existing general route to *o,o'*-dihalodeoxybenzoins implies a long (three-, four- and even five-step) sequence with overall yields around 20-60% and with obvious disadvantages in terms of atom-economy and sustainability.[4]

In summary, a new, straightforward synthesis of structurally challenging *ortho,ortho'*-dihalodeoxybenzoins has been carried out by means of a palladium-catalyzed arylation of 2-chloroaryl methyl ketones with dibromoarenes. The promising potential of the presented protocol

is firmly established by the series of so-obtained diarylethanones and the mild reaction conditions required.

Experimental Section

General Procedures. For general experimental details, see ref. 4.

2-(2-Bromophenyl)-1-(2-chlorophenyl)ethanone (3a).[16] **Typical procedure**
A suspension of 2'-chloroacetophenone **1a** (0.13 ml, 0.97 mmol), 1,2-dibromobenzene **3a** (0.09 ml, 0.73 mmol), NaO^{t}Bu (101 mg, 1.02 mmol), Pd_2dba_3 (10 mg, 0.011 mmol) and BINAP (15 mg, 0.024 mmol) in 4.2 ml of THF was heated to 90°C for 27 hours under argon. After cooling, HCl (5 ml of a 5% solution in water) was added to neutralize the mixture, and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using hexane/CH_2Cl_2 as eluent, providing target deoxybenzoin **3a** (157.9 mg, 70%) as a yellow oil; IR (film, cm^{-1}) 1682; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.43 (2H, s), 7.12-7.19 (1H, m), 7.26-7.46 (5H, m), 7.55-7.59 (2H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 49.9, 125.0, 126.8, 127.5, 128.8, 129.1, 130.4, 130.7, 131.8, 131.9, 132.7), 134.3, 138.9, 199.1; EI-MS (*m/z*, %) 231 (3), 229 (8), 141 (33), 139 (100), 113 (6), 111 (19); HRMS calcd for $C_{14}H_{10}BrClO$ 307.9604, found 307.9615.
2-(2-Bromo-4,5-dimethylphenyl)-1-(2-chlorophenyl)ethanone (3b). When the above procedure (using a sealed tube) was applied to 2'-chloroacetophenone **1a** (0.13 ml, 0.97 mmol) and 1,2-dibromo-4,5-dimethylbenzene **2b** (190.6 mg, 0.70 mmol), deoxybenzoin **3b** (146.9 mg, 62%) was obtained as yellow oil; IR (film, cm^{-1}) 1685; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.22 (3H, s), 4.35 (2H, s), 7.07 (1H, s), 7.29-7.45 (4H, m), 7.54-7.57 (1H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 19.1, 49.5, 121.6, 126.9, 129.2, 130.4, 130.4, 131.3, 131.7, 132.9, 133.4, 136.1, 137.8, 139.3, 199.7; EI-MS (*m/z*, %) 259 (7), 257 (20), 141 (32), 139 (100), 113 (5), 111 (13); HRMS calcd for $C_{16}H_{14}BrClO$ 335.9917, found 335.9920.
2-(2-Bromo-4,5-methylendioxiphenyl)-1-(2-chlorophenyl)ethanone (3c). When the above procedure was applied to 2'-chloroacetophenone **1a** (0.19 ml, 1.42 mmol) and 1,2-dibromo-4,5-methylendioxibenzene **2c** (204.5 mg, 0.72 mmol), deoxybenzoin **3c** (98.4 mg, 39%) was obtained as yellow oil; IR (film, cm^{-1}) 1693; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.32 (2H, s, 5.97 (2H, s,), 6.79 (1H, s), 7.01 (1H, s), 7.29-7.44 (3H, m), 7.52-7.55 (1H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 49.7, 101.8, 111.3, 112.7, 115.5, 126.9, 127.0, 129.1, 130.4, 130.7, 131.8, 139.1, 147.4, 147.7, 199.5; EI-MS (*m/z*, %) 275 (7), 273 (26), 141 (32), 139 (100), 113 (7), 111 (17); HRMS calcd for $C_{15}H_{10}BrClO_3$ 351.9502, found 351.9500.
2-(2-Bromo-4,6-difluorophenyl)-1-(2-chlorophenyl)ethanone (3d). When the above procedure was applied to 2'-chloroacetophenone **1a** (0.11 ml, 0.82 mmol) and 1,2-dibromo-3,5-difluorobenzene **2d** (192.7 mg, 0.70 mmol), deoxybenzoin **3d** (128.4 mg, 53%) was obtained as

yellow oil; IR (film, cm^{-1}) 1697; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.46 (2H, s), 6.81-6.93 (2H, m), 7.32-7.47 (3H, m), 7.57-7.59 (1H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 49.5, 103.9 (d, *J* = 26.9 Hz), 107.0 (d, *J* = 21.5, Hz), 114.6 (dd, *J* = 3.6, 23.3 Hz), 127.1, 129.3, 130.7, 131.0, 138.1 (d, *J* = 8.9 Hz), 159.4 (dd, *J* = 12.6, 247.7 Hz), 161.5 (dd, *J* = 12.6, 249.5 Hz), 197.8; EI-MS (*m/z*, %) 141 (32), 139 (100), 113 (6), 111 (22); HRMS calcd for $C_{14}H_8BrClF_2O$ 343.9415, found 343.9418.

2-(2-Bromophenyl)-1-(2-chloro-5-trifluoromethylphenyl)ethanone (3e). When the above procedure was applied to 2'-chloro-5'-trifluoromethylacetophenone **1b** (0.15 ml, 0.91 mmol) and 1,2-dibromobenzene **2a** (0.09 ml, 0.73 mmol), deoxybenzoin **3e** (82.2 mg, 30%) was obtained as yellow oil; IR (film, cm^{-1}) 1691; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.44 (2H, s), 7.14-7.21 (1H, m), 7.30-7.32 (2H, m), 7.55-7.67 (3H, m), 7.78-7.79 (1H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 49.9, 125.1, 126.2 (q, *J* = 3.59 Hz), 127.5 (q, *J* = 266 Hz), 127.6, 128.3 (q, *J* = 3.59 Hz), 128.9 (q, *J* = 30.5 Hz), 129.2, 131.1, 131.9, 132.8, 134.6, 133.7, 139.6, 197.9; EI-MS (*m/z*, %) 299 (5), 297 (16), 209 (34), 207 (100), 181 (6), 179 (20); HRMS calcd for $C_{15}H_9BrClF_3O$ 375.9477, found 375.9476.

2-(2-Bromophenyl)-1-(2-chloro-4,5-dimethylphenyl)ethanone (3f). When the above procedure was applied to 2'-chloro-4',5'-dimethylacetophenone **1c**[17] (234 mg, 1.28 mmol) and 1,2-dibromobenzene **2a** (0.09 ml, 0.73 mmol), deoxybenzoin **3f** (134.8 mg, 55%) was obtained as yellow oil; IR (film, cm^{-1}) 1686; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.26 (6H, s), 4.44 (2H, s), 7.11-7.31 (4H, m), 7.41 (1H, s), 7.55-7.58 (2H, m); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 19.1, 19.5, 49.7, 125.1, 127.4, 128.2, 128.7, 130.6, 131.3, 131.9, 132.6, 134.8, 135.6, 135.8, 141.7, 198.6; EI-MS (*m/z*, %) 257 (2), 169 (31), 167 (100), 141 (2), 139 (7), 103 (14); HRMS calcd for $C_{16}H_{14}BrClO$ 335.9917, found 335.9917.

2-(2-Bromo-4,5-dimethylphehyl)-1-(2-chloro-4,5-dimethylphenyl)ethanone (3g). When the above procedure was applied to 2'-chloro-4',5'-dimethylacetophenone **1c**[17] (199.2 mg, 1.09 mmol) and 1,2-dibromo-4,5-dimethylbenzene **2b** (190.6 mg, 0.70 mmol), deoxybenzoin **3g** (107.3 mg, 42%) was obtained as yellow oil; IR (film, cm^{-1}) 1691; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.22 (3H, s), 2.25 (3H, s), 2.26 (3H, s), 4.36 (2H, s), 7.06 (1H, s), 7.19 (1H, s), 7.34 (1H, s), 7.40 (1H, s); ^{13}C-NMR (63 MHz, $CDCl_3$) δ 19.1, 19.2, 19.5, 49.3, 121.6, 128.2, 130.6, 131.3, 131.7, 132.9, 133.3, 135.5, 135.9, 136.0, 137.6, 141.5, 199.1; EI-MS (*m/z*, %) 287 (3), 285 (8), 169 (35), 167 (100), 141 (2), 139 (5), 103 (12); HRMS calcd for $C_{18}H_{18}BrClO$ 364.0230, found 364.0229.

Supplementary Information Available

^{1}H-NMR and ^{13}C-NMR spectra of deoxybenzoins **3a-g**.

Acknowledgements

This research was supported by the University of the Basque Country (Project UPV 41.310-13656) and the Spanish Ministry of Education and Science (MEC CTQ2004-03706/BQU). M.C. also thanks the Ministry of Education and Science (MEC) for a predoctoral scholarship.

References and Footnotes

1. See, for example: (a) Kim, Y. W.; Hackett, J. C.; Brueggemeier, R. W. *J. Med. Chem.* **2004**, *47*, 4032. (b) Walter, G.; Liebl, R.; Von Angerer, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4659. (c) Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. *Tetrahedron* **2003**, *59*, 3283.
2. (a) Smyth, T. P.; Corby, B. W. *J. Org. Chem.* **1998**, *63*, 8946. (b) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458. (c) Mitchell, L. H.; Barvin, N. C. *Tetrahedron Lett.* **2004**, *45*, 5669. (d) Justik, M. W.; Koser, G. F.; *Tetrahedron Lett.* **2004**, *45*, 6459. (e) Moreno, I.; Tellitu, I.; Domínguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126. (f) Babudri, F.; Fiandanese, V.; Musio, R.; Naso, F.; Sciavovelli, O.; Scilimati, A. *Synthesis* **1991**, 225.
3. (a) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2002**, *4*, 2393. (b) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron Lett.* **2003**, *44*, 5925. (c) Churruca, F.; SanMartin, R.; Carril, M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2004**, *60*, 2393.
4. In this case, deoxybenzoins were prepared by a relatively long sequence that involved benzylation of α-aminonitriles followed by acidic hydrolysis of the so-formed enamine intermediates. See: Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398.
5. In fact, uncontrolled *ortho*- and polyarylation processes are the main side-reactions observed in even well-established α-arylations of ketones. For a more detailed discussion on this subject, see ref. 3a.
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7. Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Eur. J. Org. Chem.* **2005**, 2481.
8. Furthermore, the presence of an ortho-acetyl moiety would accelerate the oxidative addition at the C-Br position thus facilitating processes like homocoupling. Heck-type arylations of arenes , for example, occurs more readily in *ortho*-acylated haloarene moieties. See: Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237. In fact, preliminary assays with 2'-bromoacetophenones provided negligible results.
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12. It is known that similar metallic complexes give coloured solutions. See: Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371.
13. Phenyl-aryl exchange between aryl halides and the phenyl group of the ligand (BINAP in this case) is well documented, and based on a palladium-mediated P-C bond cleavage. See ref. 3b. See also: Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. However, the absence of such a by-product when other dibromoarenes were used (Table 2) might point to an alternative process.
14. Such dehalogenations are usually associated to β-elimination or traces of moisture. See: (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) Satoh, T.; Inoh, J. I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. The former was not possible in our case, and although molecular sieves were added (Table 1, entry 31) the yield of target dihaloderivate **3a** decreased notably (51%) without avoiding the residual formation of dehalogenated **4**.
15. Steric and electronic factors must be combined in order to explain why the presence of 3,4-dimethyl substituents can modify so markedly the behaviour of ketone **1c** in comparison to **1a**. See ref. 3c for a related example.
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