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Regioselective diarylation of ketone enolates by homogeneous and heterogeneous catalysis: synthesis of triarylethanones☆

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Abstract—A novel, one-step approach to 1,2,2-triarylethanones is achieved by an efficient palladium-catalyzed α,α-diarylation of commercially available acetophenones. After assaying an array of experimental conditions, two convenient procedures, which avoid *ortho*-arylation side reactions, are chosen to perform the target regioselective diarylation. The former protocol is based on the use of such a simple homogeneous system as $Pd(OAc)_2/PPh_3/Cs_2CO_3$, and the latter one employs a commercially available polymer-anchored catalyst, FibreCat™ 1026.

The palladium-catalyzed multiple arylation of carbon nucleophiles has attracted much attention in the last few years, as this type of tandem processes implies valuable advantages in terms of economy, time and environmental concern.[1–3] In addition, it can constitute a direct access to complex systems otherwise difficult or tedious to prepare.[1b–d,2a,d,e,3d–g]

Although most of the palladium-catalyzed C–C bond forming reactions are homogeneously conducted, the use of heterogeneous palladium catalysts for liquid phase reactions is gradually transforming this already fundamental area of organic synthesis, presenting more efficient (in terms of chemical usage and energy) methodologies which allow efficient catalyst-product separation and catalyst recycle.[4] Among the variety of heterogeneous catalysts developed so far,[5] the application of polymer-supported palladium catalysts, where the homogeneous metal complexes are heterogenized by anchoring to a suitably functionalized polymer, must be underlined. On the basis of the fact that polymer-anchored ligands permit stabilization of catalytically active complexes without precipitous drops in induced reactivity, such polymer-bound catalysts do not contaminate the product solution and can be removed by simple filtration upon completion of the reaction.[6]

In fact, recent years have witnessed an increasing interest in the application of polymer-anchored palladium catalyst to Heck, Suzuki and Sonogashira coupling reactions.[4a,7] However, major drawbacks of the latter protocol involve high cost or difficult preparation of the catalysts as well as their relative instability under reaction conditions.[6,7c,8]

Following our investigations into the synthesis of 1,2,2-triarylethanones **1**,[9] structural analogs of the widely employed breast cancer therapy agent tamoxifen,[10] by means of a palladium-catalyzed arylation of deoxybenzoins, we envisaged that the use of acetophenones **2** as the carbonylic coupling partner could promote a double arylation process leading to the former target **1**. In addition, our aim was also at the comparative use of both homogeneous and polymer-anchored palladium catalysts. This paper discloses our most relevant results in this context.

Initially, in order to explore the double arylation of acetophenones, a range of experimental conditions summarized in Table 1 were assayed on acetophenone **2a** and bromoarenes **3a** and **3b** (R = H and R = OMe, respectively).

According to previous reports found in the literature, our own observations upon the arylation of deoxybenzoins,[9] and a range of preliminary assays, the main difficulties to be solved by our synthetic approach were related to (i) steric hindrance at the α-position for the consecutive insertion of a second aryl group[1a,b,3b,11] and (ii) poor regioselectivity that would allow the formation of *ortho*-arylation and other uncontrolled arylation

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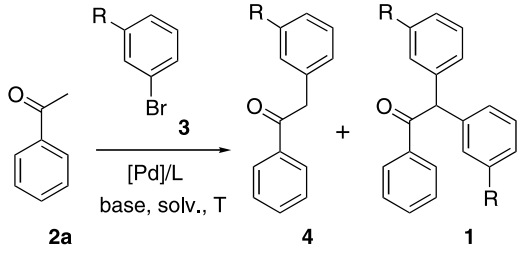
products such as **6** and **7**.[1e,g] Both initial problems were satisfactorily overcome and $Pd(OCOCF_3)_2/PPh_3$, $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ proved to be efficient catalytic systems to perform the target arylation with bromobenzene **3a** (Table 1, entries 3, 5, 6 and 7), but on applying to the methoxylated haloarene **3b**, only $Pd(OAc)_2/PPh_3$ provided triarylethanone **1b** in good yield (Table 1, entry 11).

Consequently, a series of acetophenones **2** were regioselectively diarylated by the latter procedure with the results shown in Table 2.

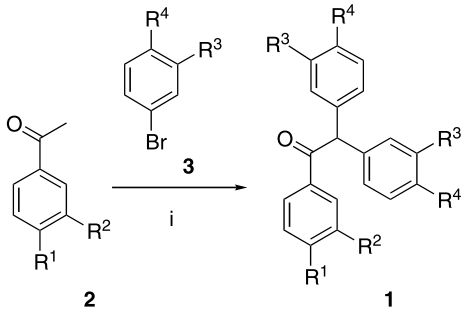
Table 1. Selected α,α-diarylation assays performed by homogeneous catalysis



Entry	Reaction conditions	Prod. (%)[a]
1	**3a**, $PdCl_2/PPh_3$, K_2CO_3, DMF, 130°C, 1.5 h[b,c,d]	**1a** (11) **2a** (79)
2	**5**, $PdCl_2/PPh_3$, Cs_2CO_3, DMF, 100°C, 6 h[e,f,g]	**1a** (49) **2a** (31)
3	**3a**, $Pd(OCOCF_3)_2/PPh_3$, Cs_2CO_3, DMF, 150°C, 1.5 h[b,e,h]	**1a** (82) **2a** (4) **4a** (4)
4	**3a**, Pd–C, Na_2CO_3, DMF, 150°C, 1.5 h[b,e,i]	**1a** (2) **2a** (89) **4a** (3)
5	**3a**, $Pd(PPh_3)_4$, Cs_2CO_3, *o*-xylene, 150°C, 5 h[b,e,j]	**1a** (71) **2a** (1) **4a** (2)
6	**3a**, $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 150°C, 2 h[b,e,k]	**1a** (68) **2a** (12) **4a** (1)
7	**3a**, $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 153°C, 1 h[b,e,h]	**1a** (94) **2a** (2) **4a** (2)
8	**3b**, $Pd(PPh_3)_4$, Cs_2CO_3, *o*-xylene, 150°C, 5 h[b,e,j]	**1b** (25) **2a** (59)
9	**3b**, $Pd(OCOCF_3)_2/PPh_3$, Cs_2CO_3, DMF, 150°C, 1.5 h[b,e,h]	**1b** (54) **2a** (8) **4b** (11)
10	**3b**, $Pd(OAc)_2/P^tBu_3$, NaO^{t}Bu, THF, 80°C, 6 h[b,c]	**1b** (5) **4b** (70)
11	**3b**, $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 153°C, 1.5 h[b,e,h]	**1b** (72) **2a** (2) **4b** (4)

[a] GC–MS yields measured on the basis of the starting amount of ketone **2a**. Propiophenone was used as the internal standard.
[b] 3.4 equiv. of **3a** were used.
[c] 2.5 equiv. of base were used.
[d] 0.03 equiv. of palladium catalyst and 0.12 equiv. of ligand were used.
[e] 3 equiv. of base were used.
[f] 2.2 equiv. of iodobenzene **5** were used instead of **3a**.
[g] 0.07 equiv. of palladium catalyst and 0.24 equiv. of ligand were used.
[h] 0.05 equiv. of palladium catalyst and 0.2 equiv. of ligand were used.
[i] 0.05 equiv. of palladium metal in a%5 Pd–C mixture were used. Since it was one of the preliminary assays, the experiment performed with the heterogeneous catalytic system Pd–C has been included in this table.
[j] 0.01 equiv. of palladium catalyst were used.
[k] 0.01 equiv. of palladium catalyst and 0.5 equiv. of ligand were used.

Table 2. Homogeneous and heterogeneous palladium-catalyzed α,α-diarylation of acetophenones **2**



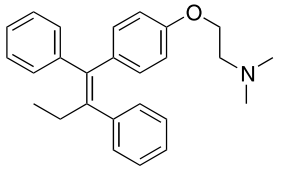
i: Method A: $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 153°C, 1-7h

Method B: FibreCat™ 1026, Cs_2CO_3, DMF, 153°C, 0.8-1h

Entry	R^1	R^2	R^3	R^4	**1** (%)[a]
1	H	H	H	H	**1a** (91) *89*
2	H	H	OMe	H	**1b** (71) *79*
3	H	H	OMe	OMe	**1c** (61) *80*
4	H	H	H	F	**1d** (63) *73*
5	Me	H	H	H	**1e** (87) *93*
6	Me	H	OMe	H	**1f** (69) *75*
7	Me	H	OMe	OMe	**1g** (60) *92*
8	Me	H	H	F	**1h** (68) *80*
9	OMe	OMe	H	H	**1i** (62) *90*
10	OMe	OMe	OMe	H	**1j** (57) *82*
11	OMe	OMe	OMe	OMe	**1k** (47) *64*
12	OMe	OMe	H	NO_2	**1l** (35) *20*
13	OMe	H	H	F	**1m** (52) *70*

[a] Isolated yields. Yields obtained from Method A are shown in parentheses and the yields derived from Method B are shown in italics.

It should be pointed out that only slight variations of the same protocol (the relative amount of the haloarene **3** and the base Cs_2CO_3) can provide monoarylation and diarylation reactions, when applied to deoxybenzoins[9] and acetophenones, respectively. In our opinion, the so-obtained results suggest that our method, based on the use of catalytic amounts of a relatively cheap palladium catalyst and such a simple phosphine ligand as triphenyl phosphine, can therefore constitute a general tool for the mono/multiple α-arylation of alkyl aryl ketones. In addition, it opens many synthetic possibilities for the synthesis of potentially bioactive analogs of the most widely used adjuvant drug therapy for the treatment of estrogen receptor breast cancer, tamoxifen.



Tamoxifen

However, unlike monoarylation of deoxybenzoins, the reported diarylation of acetophenones shows some drawbacks which cannot be ignored. Thus, in all cases, reaction with bromobenzene **3a** provided better results of the corresponding triaryl derivative **1** (Table 2, entries 1, 5 and 9) than with any other halobenzene **3**. In order to explain the latter behavior, a careful examination of the components of the reaction mixture obtained from the coupling partners methyl phenyl ketone **2a** and 3,4-dimethoxyphenyl bromide **3c** (Table 2, entry 3) was carried out, revealing a low but significant proportion (17%) of monophenylated product **1n**,[12] along with the target ketone **1c** (61%)[13]. Although the 'phenyl migration' or the phenyl–aryl exchange between the aryl halide/triflate and the phenyl group of PPh_3 ligand is well documented[14] and has even found synthetic applications,[15] such process, based in a palladium-mediated P–C bond cleavage and facilitated by electron-donating groups (i.e. methoxy),[14a,e–g] has not been reported in the arylation of ketone enolates. In an attempt to minimize its deleterious effects, other phosphine ligands (PEt_3, P^nBu_3, P^tBu_3, $P(o\text{-tolyl})_3$) were assayed instead of PPh_3, but only unreacted ketones **2** or monoarylation products **4** were obtained.[16]

With regard to the arylation with nitrophenyl bromide **3d**, the poor yields obtained (Table 2, entry 12) may be caused not only by the already mentioned phenyl–aryl exchange, but also by a reduction of the nitro group under the reaction conditions, since signals corresponding to phenyl moieties and free amino groups were detected from the crude mixture.[17,18]

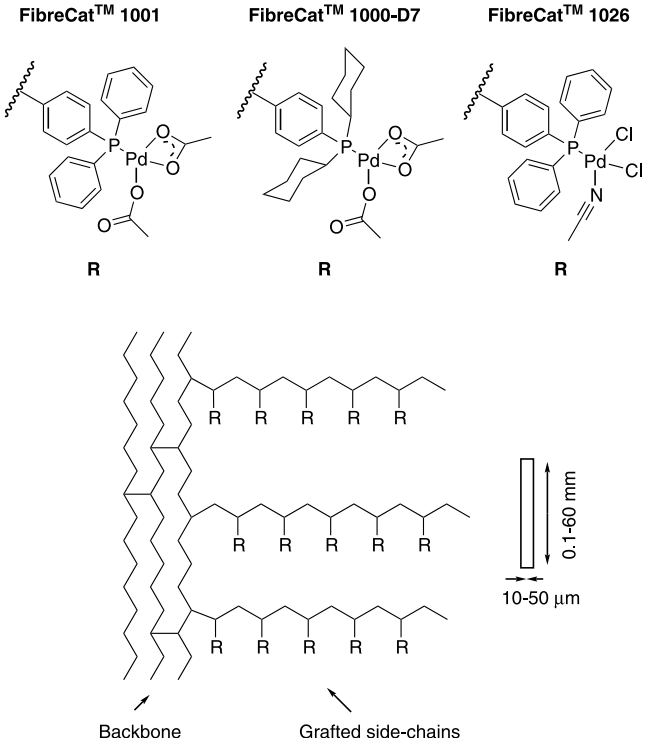
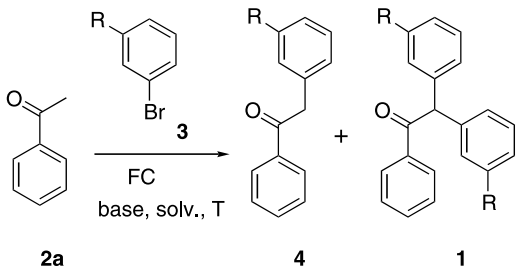


Figure 1. Example of FibreCat™ structure and different catalytic centers in FibreCat™ 1000 Series.

Table 3. Selected α,α-diarylation assays performed by heterogeneous catalysis

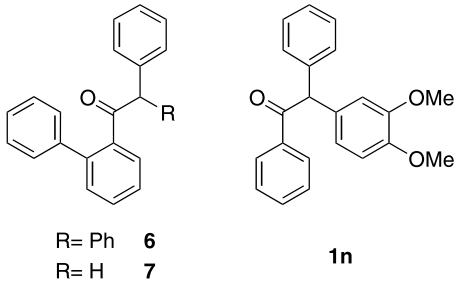


FC: FibreCat™ catalyst

Entry	Reaction conditions[a]	Prod. (%)[b]
1	**3a**, 5% FC 1001, K_2CO_3, toluene, 130°C, 10 h	**1a** (8) **2a** (40) **4a** (43)
2	**3a**, 1% FC 1000-D7, K_2CO_3, toluene, 130°C, 10 h	**1a** (45) **2a** (30) **4a** (16)
3	**3a**, 2% FC 1000-D7, K_2CO_3, xylene, 153°C, 6 h	**1a** (15) **2a** (32) **4a** (44)
4	**3a**, 2% FC 1000-D7, Cs_2CO_3, DMF, 153°C, 1 h	**2a** (87) **4a** (3)
5	**3a**, 2% FC 1026, Cs_2CO_3, DMF, 153°C, 3 h	**1a** (17) **2a** (41)
6	**3a**, 5% FC 1026, Cs_2CO_3, DMF, 153°C, 1 h	**1a** (93) **2a** (2) **4a** (2)
7	**3b**, 5% FC 1026, Cs_2CO_3, DMF, 153°C, 1 h	**1b** (85) **4b** (2)

[a] 3.3 equiv. of aryl bromide **3**, 3 equiv. of base and the indicated FibreCat™ catalyst (FC) were used. The disclosed proportion of FC (%) refers to the relative amount of Pd metal from the FC catalyst. The average content of Pd in the employed FC samples is 3%.

[b] GC–MS yields measured on the basis of the starting amount of ketone **2a**. Propiophenone was used as the internal standard.



The next step in our scheduled investigation into the arylation of aromatic ketones involved the use of polymer-supported catalysts. In order to perform a series of preliminary assays, we chose FibreCat™ 1001, FibreCat™ 1000-D7 and FibreCat™ 1026 palladium catalysts, since these polymer-anchored homogeneous catalyst provide, apart from their commercial availability, several advantages (ease of handling, good mechanical properties and high functional group accessibility) associated to their fibrous nature (Fig. 1).[19]

As shown in Table 3, although FibreCat™ 1001 and 1000-D7 catalysts afforded target diarylated derivative

1a in low to moderate yields, only when using FibreCat™ 1026 under optimized conditions (Table 3, entry 6) the latter ketone **1a** was detected as the main product. Moreover, this procedure showed a similar efficiency at the α,α-diarylation with 3-bromoanisole **3b** (Table 3, entry 7).

Accordingly, such optimized protocol was applied to the rest of acetophenones **2** and aryl bromides **3**, providing the corresponding triarylethanones **1** with the results summarized in Table 3.

It should be pointed out that the synthetic procedure shown above[20] constitutes the first example of polymer-anchored palladium catalysis applied to the α-arylation of ketone enolates so far.[21] Comparison of the results shown in Table 2 for both procedures suggests that the presented homogeneous and heterogeneous palladium catalytic systems provide alternative methodologies for the scarcely developed regioselective α,α-diarylation of ketone enolates,[22] although slightly better yields were obtained in most cases by using the polymer-bound catalyst. Such improvement is clearly related to a dramatic decrease in the proportion of phenyl–aryl exchange products caused by triphenyl phosphine ligand, thus suggesting that a tight binding of the phosphine to the polymer chain inhibits this inconvenient side-reaction. An additional advantage of the latter procedure involves the easy catalyst-product separation by simple filtration of the reaction mixture, and although additional experiments will be required to evaluate parameters as leaching or reusability, our contribution opens interesting perspectives towards a more environmentally benign chemistry[23] by appliance of polymer-supported catalysts to the arylation of ketone enolates.

Finally, the reported results clearly show the applicability of both homogeneous and heterogeneous catalytic systems to the diarylation with electron-rich bromoarenes (mono/polyalkoxylated), a feature that cannot be undervalued, above all considering that normally neutral or electron-deficient aryl halides have been used in previous reports on even monoarylation reactions.[1a,11b,c,22b,24]

In summary, a series of commercially available acetophenones have been regioselectively α,α-diarylated to provide the corresponding 1,2,2-triarylethanones, structural analogs of the most widely used adjuvant drug therapy for the treatment of estrogen receptor breast cancer, tamoxifen. The latter palladium-catalyzed double arylation process has been conducted using both homogeneous and, for the first time, polymer-anchored palladium catalysts, and a brief comparative study of the results obtained from each procedure is also presented. Although both approaches avoid *ortho*-arylation or dehalogenation side-reactions, the heterogeneous way eludes another unwanted process, aryl-phenyl exchange with PPh_3 ligand.

Encouraged by the advantageous use of polymer-bound catalysts in the diarylation of acetophenones, we are currently investigating not only the extension of the latter protocol to the monoarylation of other ketone enolates, but also suitable procedures for an efficient catalyst recycle.

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12. The structure of monophenylated product **1n** was assigned according to the ^{1}H NMR and GC–MS spectra of the crude reaction mixture and by comparison with a sample obtained from monoarylation of deoxybenzoin **4a** with 3,4-dimethoxyphenyl bromide **3c**.
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16. Traces of diarylation products **1** were detected. These results, along with a detailed mechanistic proposal, will be published elsewhere.
17. Kwong, F. Y.; Lai, C. W.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 10285–10289.
18. The palladium-catalyzed arsination of reducible *p*-nitrophenyl triflate with Ph_3As has been recently reported, see: Kwong, F. Y.; Lai, C. W.; Tian, Y.; Chan, K. S. *J. Am. Chem. Soc.* **2001**, *123*, 8864–8865. However, in our case, the use of the latter ligand instead of Ph_3P did not improve the yield of the diarylation product **1l**, and partial reduction of the nitro group to amino was also observed.
19. FibreCat™ 1000 Series is commercialized by Johnson Matthey Chemicals, Orchard Road, Royston, Herts, SG8 5HE, UK. Further information about FibreCat™ catalysts, including the catalyst site and structure schemes shown above, can be found at http://www.chemicals.matthey.com.
20. **General procedure B**. Dry degassed DMF (1 mL) was added to an oven-dried reaction flask charged with FibreCat™ 1026 (0.01 mmol of Pd), Cs_2CO_3 (0.6 mmol), ketone **2** (0.2 mmol), and aryl bromide **3** (0.68 mmol) under argon at room temperature. The resultant stirred suspension was heated to 153°C for 0.8–1 h. After cooling, the mixture was filtered, washed with CH_2Cl_2 and the filtrate was evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent.
21. To the best of our knowledge, the α-monoarylation of malonate enolates has been reported under heterogeneous conditions, but the corresponding heterogeneous catalyst was prepared by encapsulation of palladium in a porous material (zeolite), see: Djakovitch, L.; Köhler, K. *J. Organomet. Chem.* **2000**, *606*, 101–107.
22. For previous reports on one-pot α,α-diarylation reactions of ketones see Refs 1a,e and 6a,b. See also: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. A similar diarylation process performed with aryl chlorides has been recently published, see: (b) Ehrentraut, A.; Zapf, A. Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209–217.
23. The application of polymer-bound catalysts in synthetic ventures is a clear example of 'green' chemistry in which the waste streams and depletion of sources associated with transition metals is minimized. Consequently, this fact should be inspiration enough for further progress in next years. For a more detailed discussion on this subject, see Ref. 6a.
24. Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056.