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Synthesis of unsymmetrical benzils via palladium-catalysed \( \alpha \)-arylation–oxidation of 2-hydroxyacetophenones with aryl bromides

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A diverse set of unsymmetrically substituted benzils were facilely synthesised by a cross-coupling reaction between 2-hydroxyacetophenones and aryl bromides in the presence of a palladium catalyst. Experimental studies suggested a reaction mechanism involving a one-pot tandem palladium-catalysed \( \alpha \)-arylation and oxidation, where aryl bromides play a dual role as mild oxidants as well as arylating agents.

Introduction

1,2-Diketones are members of an important class of molecules with diverse application potential in various fields. They are useful building blocks for the synthesis of a range of carbonyl and heterocyclic compounds, and 1,2-diketone-derived compounds have been utilised as ligands for transition metals. Among these 1,2-diketones, benzils (diphenylethanediones) are recognised as privileged scaffolds that have distinct properties, and they can be converted into compounds with vicinal diphenyl groups. Benzils are generally synthesised via oxidation of the corresponding benzoins, diarylacetylenes, or other 1,2-diphenyl derivatives. Thus, the traditional synthesis of unsymmetrical benzils necessitates the preparation of unsymmetrical starting materials, which can complicate the process considerably. In this context, significant advances have recently been made, whereby coupling strategies offer a viable and effective procedure for the synthesis of unsymmetrical benzoins. In particular, a reaction employing an aryl halide as the aryl source would be advantageous, as a large number of unsymmetrical benzils necessitates the preparation of unsymmetrical starting materials, which can complicate the process considerably. In this context, significant advances have recently been made, whereby coupling strategies offer a viable and effective procedure for the synthesis of unsymmetrical benzoins. In particular, a reaction employing an aryl halide as the aryl source would be advantageous, as a large number of unsymmetrical benzils necessitates the preparation of unsymmetrical starting materials, which can complicate the process considerably.

Palladium-catalysed \( \alpha \)-arylation of ketones with aryl halides, enabling cross-coupling between an electrophilic aryl group and a nucleophilic ketone enolate, represents a versatile and robust method for the synthesis of \( \alpha \)-aryl ketones. Although the \( \alpha \)-arylation of other carbonyl compounds, such as esters and aldehydes, as well as nitriles, and nitroalkanes has been well established, to date, there have been no reports on a reaction utilizing \( \alpha \)-hydroxy ketones as nucleophiles. In this paper, we report that palladium(0)-catalysed \( \alpha \)-arylation of 2-hydroxyacetophenones with aryl bromides produces benzoins, which are subsequently oxidised to benzils through the action of aryl bromides as mild oxidants, under catalytic conditions. In reactions of \( \alpha \)-hydroxy ketones with two nucleophilic sites, \( \alpha \)-arylation is particularly favoured over O-arylation. Moreover, a control experiment revealed that 2-hydroxyacetophenones are more prone to \( \alpha \)-arylation than acetophenone.

Results and discussion

2-Hydroxyacetophenone (1a) and 4-bromotoluene (2a, 2 equiv) were heated in toluene at 100 °C in the presence of 10 mol% \( \text{Pd(PPh}_3\text{)}_2 \) as the catalyst and \( \text{NaO}_t\text{-Bu} \) as a base for 24 h (Table 1, entry 1). The reaction primarily resulted in a reductive homocoupling to afford a biaryl, and no cross-coupling was observed. In contrast, when \([\text{PdCl(allyl)}]_2\) was employed as the catalyst, cross-coupling between 1a and 2a occurred, but the benzil product 3aa was isolated in only 9% yield (entry 2). The anticipated \( \alpha \)-arylation product, benzoin, was not detected in the reaction mixture, indicating that oxidation had occurred concomitantly during the reaction. To increase the product yield, we examined various phosphine ligands and found that XPhos was the most effective (36% yield) among those examined (entries 3–8). As for the palladium complexes, \([\text{PdCl(allyl)}]_2\) was found to be the complex of choice for this reaction (entries 8–11).

Table 1. Screening of palladium complexes and phosphine ligands for the palladium-catalysed coupling of 2-hydroxyacetophenone (1a) with 4-bromotoluene (2a)

| Ligand  | Yield (%) |
|---------|-----------|
| 1          | 9%        |
| 2          | 36%       |
| 3–8        | 36%       |
| 8–11       | 36%       |

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As the decomposition of benzil 3aa was observed with longer reaction times under the conditions employing NaOt-Bu, further optimisation was performed (Table 2). An extensive investigation into the choice of base (entries 1–6) indicated that the use of K$_2$PO$_4$ resulted in a cleaner reaction, furnishing 3aa in 62% yield within 6 h; the yield was further improved to 80% when the reaction time was 18 h (entry 7). Notably, the reaction proceeded smoothly without the need for stronger bases, such as alkoxides. Solvent screening confirmed that t-BuOH was the optimal solvent, giving superior results in terms of the prevention of decomposition of α-hydroxy ketone 1a (entries 7–13). Finally, the use of 2.5 equiv of both the aryl bromide 2a and the base afforded 3aa in 90% yield (entry 14). The reaction with 5 mol% catalyst loading provided a comparable yield, while the yield deteriorated with further catalyst loading reduction to 2 mol% (entries 15 and 16). The coupling was successfully performed on a gram scale to furnish 1.2 g of 3aa in 91% yield (entry 17).

### Table 2. Screening of bases and solvents

| Entry | Base | Solvent | Time (h) | Yield (%) |
|-------|------|---------|----------|-----------|
| 1     | NaOt-Bu | toluene | 6        | 65        |
| 2     | KOT-Bu  | toluene | 6        | 62        |
| 3     | NaN(SiMe$_3$)$_2$ | toluene | 6        | 32        |
| 4     | Cs$_2$CO$_3$ | toluene | 6        | 33        |
| 5     | K$_2$CO$_3$ | toluene | 6        | 35        |
| 6     | K$_3$PO$_4$ | toluene | 6        | 62        |
| 7     | K$_3$PO$_4$ | t-BuOH  | 18       | 80        |
| 8     | K$_3$PO$_4$ | 1,4-dioxane | 18 | 72        |
| 9     | K$_3$PO$_4$ | THF     | 18       | 70        |
| 10    | K$_3$PO$_4$ | CICH$_2$CH$_2$Cl | 18 | 33        |
| 11    | K$_3$PO$_4$ | DMF     | 18       | 25        |
| 12    | K$_3$PO$_4$ | t-BuOH  | 18       | 33        |
| 13    | K$_3$PO$_4$ | t-BuOH  | 18       | 83        |
| 14    | K$_3$PO$_4$ | t-BuOH  | 18       | 83        |
| 15    | K$_3$PO$_4$ | t-BuOH  | 18       | 25        |
| 16    | K$_3$PO$_4$ | t-BuOH  | 18       | 91        |

The reaction proved efficient using an aryl triflate, providing 3aa in 98% yield (Scheme 1). A slight decrease in yield was observed for aryl chlorides. In the case of an aryl iodide, however, the yield was reduced to 52% due to the competing biaryl homocoupling.

With the optimised conditions in hand, we investigated the scope of the coupling reaction and found that a diverse array of unsymmetrical benzils, as well as the parent benzil could be effectively synthesised (Table 3). Coupling of 1a with bromobenzenes 2c–g bearing electron-donating and electron-withdrawing substituents at the meta- or para-positions afforded the corresponding benzils 3ac–ag in 61–98% yields (entries 2–6). Moreover, it was established that the reaction was effective in the presence of heteroatom substituents (entries 7–10). The reaction using 2- and 1-naphthyl bromides 2l and 2m delivered 1,2-diketones 3al and 3am in 79% and 58% yields, respectively, (entries 11 and 12). However, the yields of 3 declined considerably when ortho-substituted bromobenzenes 2n and 2o were used (entries 13 and 14). The attempted reaction with 4-bromophenol afforded only a trace amount of the desired product, and the formation of complex product mixtures was observed with 1-bromo-3-nitrobenzene and 3′-bromoacetophenone. Further, a variety of α-hydroxy ketones 1b–k, including naphthyl and heteroaryl...
ketones, also underwent the coupling reaction with 2a to deliver 3ba–ka (entries 15–24). Finally, it was demonstrated that additional unsymmetrical benizls, including highly electronically biased 3ee, could be obtained by the coupling protocol (entries 25–31).

**Table 3. Scope of palladium-catalysed α-arylation—oxidation of 1 with 2**

| Entry | [Ar⁺] | [Ar⁺] | Yield [%] |
|-------|--------|--------|-----------|
| 1     | 1a (Ph) | 2b (Ph) | 3ab 88    |
| 2     | 1a (Ph) | 2c (4-t-BuOEt) | 3ac 86 |
| 3     | 1a (Ph) | 2d (3-MeOCH₃) | 3ad 78 |
| 4     | 1a (Ph) | 2e (4-MeOCH₃) | 3ae 78 |
| 5     | 1a (Ph) | 2f (4-FCC₆H₄) | 3af 70 |
| 6     | 1a (Ph) | 2g (3-MeO₂CC₆H₄) | 3ag 61 |
| 7     | 1a (Ph) | 2h (4-FCC₆H₄) | 3ah 89 |
| 8     | 1a (Ph) | 2i (4-FC₆H₄H) | 3ai 98 |
| 9     | 1a (Ph) | 2j (3-MeSCH₃) | 3aj 76 |
| 10    | 1a (Ph) | 2k (3-danBC₆H₄) | 3ak 49 |
| 11    | 1a (Ph) | 2l (2-naphthyl) | 3al 79 |
| 12    | 1a (Ph) | 2m (1-naphthyl) | 3am 58 |
| 13    | 1a (Ph) | 2n (2-MeCH₃) | 3an 45 |
| 14    | 1a (Ph) | 2o (3-MeCH₃) | 3ao 44 |
| 15    | 1b (4-MeC₆H₄) | 2a (4-MeC₆H₄) | 3ba 92 |
| 16    | 1c (3-MeC₆H₄) | 2a (4-MeC₆H₄) | 3ca 95 |
| 17    | 1d (3-MeOCH₃) | 2a (4-MeC₆H₄) | 3da 78 |
| 18    | 1e (4-FCC₆H₄) | 2a (4-MeC₆H₄) | 3ea 64 |
| 19    | 1f (4-FC₆H₄) | 2a (4-MeC₆H₄) | 3fa 79 |
| 20    | 1g (4-MeC₆H₄) | 2a (4-MeC₆H₄) | 3ga 71 |
| 21    | 1h (2-naphthyl) | 2a (4-MeC₆H₄) | 3ha 74 |
| 22    | 1i (1-naphthyl) | 2a (4-MeC₆H₄) | 3ia 72 |
| 23    | 1j (2-furyl) | 2a (4-MeC₆H₄) | 3ja 55 |
| 24    | 1k (2-thienyl) | 2a (4-MeC₆H₄) | 3ka 76 |
| 25    | 1d (3-MeOCH₃) | 2e (4-MeOCH₃) | 3de 71 |
| 26    | 1e (4-FCC₆H₄) | 2e (4-MeOCH₃) | 3ee 59 |
| 27    | 1g (4-MeC₆H₄) | 2f (4-FCC₆H₄) | 3gf 65 |
| 28    | 1g (4-MeC₆H₄) | 2g (2-naphthyl) | 3gl 70 |
| 29    | 1h (2-naphthyl) | 2f (4-FCC₆H₄) | 3hf 62 |
| 30    | 1i (1-naphthyl) | 2f (4-FCC₆H₄) | 3if 61 |
| 31    | 1k (2-thienyl) | 2f (2-naphthyl) | 3kl 82 |

* Reaction conditions: 1 (0.200 mmol), 2 (0.500 mmol), [PdCl₂(allyl)]₂ (0.010 mmol, 10 mol% Pd), K₂PO₄ (0.040 mmol, 20 mol%), t-BuOH (0.5 mL) at 100 °C for 18 h. † Isolated yield. ‡ B(dan) = naphtho[1,8-de][1,3,2]diazaborinin-2-yl.

Several control experiments were conducted to elucidate the mechanistic aspects of the coupling reaction (Scheme 2). When the reaction was terminated after 1 h, benzil 3aa was isolated in 49% yield in addition to benzil 3aa (37%), suggesting that 4aa is the initial product, and that 3aa is subsequently formed by the oxidation of 4aa (Scheme 2A). The preference of α-arylation of α-hydroxy ketone 1a over acetophenone (5) was confirmed by a competition experiment with equimolar amounts of 1a and 5 under the standard conditions. After 1 h, 3aa and 4aa were isolated in 85% combined yield while 5, lacking the hydroxyl group, remained intact (Scheme 2B).

Palladium-catalysed oxidation of alcohols using aryl halides as oxidants has been reported. Indeed, oxidation of benzil (4ab) with 2a in the presence of the Pd–XPhos catalyst and K₂PO₄ in t-BuOH furnished benzil (3aa) in a high yield, whereas the oxidation of 4ab failed to occur in the absence of 2a (Scheme 2C). In the case of the reaction with 1-bromo-4-(tert-butyl)benzene (2c), the formation of tert-butylbenzene (42%) was detected by GC along with the quantitative formation of benzil 3ac (Scheme 2D). Another possible scenario involving an initial oxidation of an α-hydroxy ketone to a glyoxal, which is subsequently arylated, was excluded, and no arylation of phenylglyoxal (6) was observed under our conditions (Scheme 2E).

**Scheme 3. Control experiments (conditions: 5 mol% [PdCl₂(allyl)]₂, 20 mol% XPhos, 2.5 equiv K₂PO₄, t-BuOH, 100 °C)**

Based on these experimental observations, we conclude that the present reaction involves an initial α-arylation of 2-hydroxyacetophenone (1a) followed by oxidation of the resulting benzil 4 to benzil 3, both of which are catalysed by a palladium complex equipped with XPhos; two equivalents of ary bromide are consumed during the process (Scheme 3).

**Conclusions**

In summary, we have developed a novel synthetic method for accessing unsymmetrical benizls starting from 2-hydroxyacetophenones, achieved by a tandem α-arylation–
oxidation sequence, both of which are catalysed by a palladium–XPhos system. Readily available aryl bromides initially function as arylating agents to form C–C bonds, and then subsequently oxidise the resulting benzoins to benzils, with concomitant hydrodestruction. The widely applicable transformation can be conducted under mild and virtually redox-neutral conditions.18

Conflicts of interest
There are no conflicts to declare.

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