

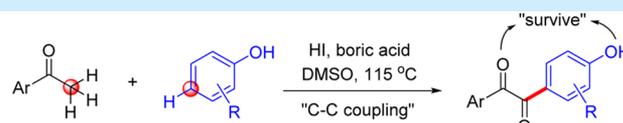
Direct Construction of 4-Hydroxybenzils via *Para*-Selective C–C Bond Coupling of Phenols and Aryl Methyl Ketones

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S Supporting Information

ABSTRACT: A highly *para*-selective C–C bond coupling is presented between phenols C(sp²) and aryl methyl ketones C(sp³), which enables the direct construction of 4-hydroxybenzil derivatives. This practical method exhibits a broad substrate scope and large-scale applicability and represents a general gateway to the hydroxybenzil natural product family. Mechanistic investigations indicated that the combination of HI with DMSO realized the oxidative carbonylation of aryl methyl ketones, while boric acid acted as a dual-functional relay reagent to promote this transformation.



- High regio & chemoselectivity
- >30 examples, scalable
- New mechanism
- Access to the first total syntheses of: Sophodibenzoside F; Sophodibenzoside I; 2-hydroxy-4,5,6-trimethoxybenzil

The 4-hydroxybenzil motif is a prominent structural feature in natural products,¹ drug candidates,² and organic synthons.³ Common though this structure is, its synthetic pathways are few and indirect.⁴ In this context, a methodology capable of using a protecting group-free process, readily available substrates, and a one-pot setup would be highly desirable. We envisioned that building a linkage between phenol and acetophenone derivatives under an oxidative coupling strategy,⁵ which has been well-defined for bond formation between two nucleophiles,^{5a} would be an accessible pathway. However, two chemical limitations outweigh the challenge of synthesizing (Figure 1). First, the oxidative medium needs to be carefully chosen because strong oxidizing agents may lead one or both of the nucleophilic coupling partners to undergo homocoupling⁶ or even overoxidation of the desired products. Second, but more importantly, this coupling reaction must be carried out set-selectively, particularly for phenols. As demonstrated by Jiao et

al., reactions between aryl methyl ketones and phenols may undergo a selective O–H insertion, which results in esters^{7a} or α -ketoesters^{7b} under oxidative conditions. Alternatively, a coupling reaction with competitive selectivity at the *ortho*-position of phenols has been demonstrated in several studies. The cooperative catalytic effect induced by the hydroxyl group, along with the subsequent involvement of O–H in the cyclization step, leads to high specificity for the *ortho*-selective reaction.⁸ This method can be found in Li's FeCl₃·6(H₂O)-(t-BuO)₂-catalyzed oxidative coupling/annulation synthesis of benzofurans.^{8a} In addition, *ortho*-dominated selectivity also exists in Friedel–Crafts-type conversions⁹ and metal-catalyzed arylations.¹⁰ *Para*-selective coupling reactions of phenols, achieved by the control of electronic factors, are surprisingly rare, especially for unprotected phenols. Representative but limited examples¹¹ were achieved by Gaunt^{11a} and Zhang^{11b} in their arylation and C–H functionalization reactions, respectively. To the best of our knowledge, a selective coupling reaction that achieves our synthetic goal as mentioned above is still unrevealed. This paper presents a *para*-selective C–C coupling reaction to forge 4-hydroxybenzil motifs from acetophenone and phenol derivatives under mild HI combined with a DMSO catalyst system. The discovery, extension, and preliminary mechanistic insights of this transformation are detailed, culminating in the first total syntheses of sophodibenzoside F, I, and 2-hydroxy-4,5,6-trimethoxybenzil.

Our investigation started with the optimization of the reaction conditions between acetophenone (1a), *o*-cresol (2a), and the green oxidant I₂ in DMSO. Representative results are shown in Table 1. Several predicted (M1–8) and detected (M1–6) byproducts/intermediates are listed as contrasts and guides for

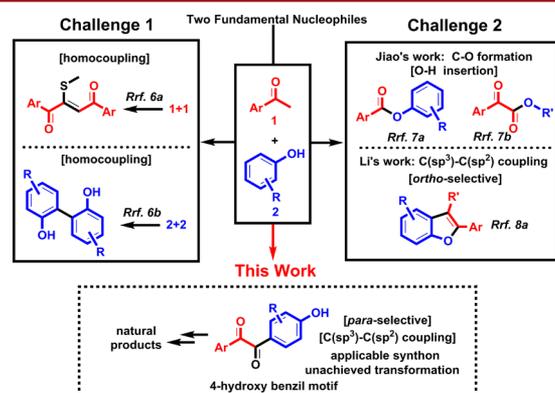
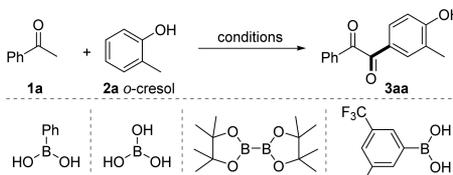
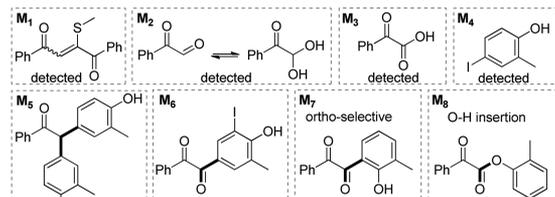


Figure 1. Selectivity trends in the reaction of aryl methyl ketones and phenols.

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Table 1. Reaction Optimization^a


entry	I ₂ (equiv)	acid (equiv)	additive (equiv)	temp (°C)	yield ^b (%)
1	1.5	-	-	100	trace
2	1.5	-	A (1.0)	100	<10
3	1.5	CuBr ₂ (0.2)	A (1.0)	100	32
4	1.5	CuBr ₂ (0.2)	B (1.0)	100	40
5	1.5	CuBr ₂ (0.2)	C (1.0)	100	trace
6	1.5	CuBr ₂ (0.2)	D (1.0)	100	43
7	1.5	InBr ₃ (0.2)	B (1.0)	100	38
8	1.5	TfOH (0.2)	B (1.0)	100	37
9	1.5	TFA (0.2)	B (1.0)	100	30
10 ^c	1.5	HI (0.2)	B (1.0)	100	42
11 ^c	-	HI (0.2)	B (2.0)	115	25
12 ^c	-	HI (0.5)	B (2.0)	115	71
13 ^c	-	HI (1.0)	B (2.0)	115	65
14 ^d	-	HBr (0.5)	B (2.0)	115	0

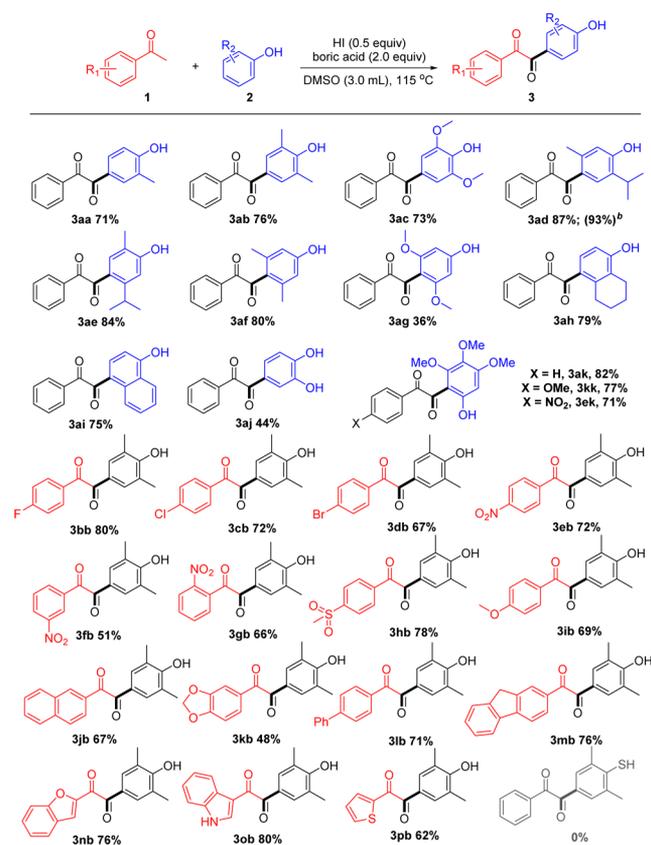


^aReaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), additive, solvent (DMSO 3.0 mL) for 6 h. ^bIsolated yields based on **1a**. Reactions were carried out in a pressure vessel. ^cUsing hydriodic acid, 57 wt % solution in H₂O. ^dUsing hydrobromic acid, 47 wt % solution in H₂O.

our optimization (Table 1, dashed box). Initially, a low yield of the desired product was obtained when I₂ was used as a single additive (entry 1). The homocoupling product **M1** and several other products (**M2**–**M4**) were found instead. After various additives were scanned, we found that the use of phenylboronic acid (**A**) was beneficial (entry 2). Then, when an extra Lewis acid (CuBr₂) was added, the yield of **3aa** was further improved (entry 3). Boric acid (**B**) was found to be a better reagent than its derivatives (**A**, **C**, and **D**) (entry 4). The strong Lewis acid (3,5-bis(trifluoromethyl)phenyl)boronic acid (**D**)¹² gave a yield equal to that of **B** but impeded the separation of the product. Subsequent scanning focused on the species of the additional acid, including selected Brønsted acids (entries 8–10). However, the yields were still unsatisfactory, as two persistent byproducts (**M5** and **M6**) hindered the reaction process. Reducing the dose of I₂ produced disappointing results. The overiodination byproduct **M5** could not be avoided when I₂ was used as the oxidant. A breakthrough occurred when we added HI instead of I₂: the reaction still proceeded, and almost no **M5** was formed (entry 11). However, the use of HBr provided no trace of the product (entry 14). After further investigation, the optimal

conditions were determined to be 0.5 equiv of HI and 2.0 equiv of boric acid at 115 °C for 6 h (entry 12). Under these conditions, neither *ortho*-selective (**M7**) nor O–H insertion product (**M8**) was isolated.

With the optimized conditions in hand, we proceeded to investigate the scope of the reaction (Scheme 1). Several phenols

Scheme 1. Scope of Substrates^a

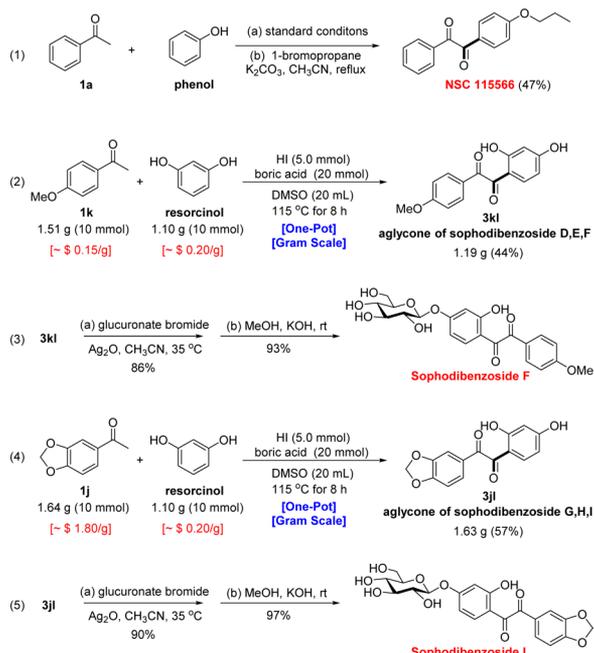
^aReaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), HI (0.5 mmol), boric acid (2.0 mmol), DMSO (3.0 mL), 115 °C for 6 h. Isolated yields. Reactions were carried out in a pressure vessel. ^bYield as calculated by ¹H NMR analysis.

were tested, and all reacted smoothly under the optimized conditions. Notably, **2c**, bearing two methoxy groups in the *ortho*-positions as competitive substituents, was coupled with acetophenone exclusively at the hydroxy *para*-position. Thymol (**2d**) and carvacrol (**2e**), two small naturally occurring phenols, gave relatively high reaction efficiencies. Quantitative NMR demonstrated that the yield of **3ad** was 93%. *Ortho*-free substrates, 3,5-dimethylphenol (**2f**) and 3,5-dimethoxyphenol (**2g**),¹³ could afford the desired products **3af** and **3ag**. Meanwhile, naphthalen-1-ol (**2i**) was also compatible in this reaction to give the O–H *para*-coupling product (**3ai**, 75%); this selectivity is almost identical to that of its hydrogenated derivative **2h** (**3ah**, 79%). The reaction tolerated dihydroxy group substrates such as catechol (**2j**), which resulted in a moderate yield (**3aj**, 44%). When the *para*-positions of phenols were blocked by alkyl or alkoxy groups, no target molecule was formed: neither the *ortho*-coupling nor the O–H insertion products. Notably, when using the highly electrophilically substituted aromatic 3,4,5-trimethoxyphenol (**2k**), *ortho*-selective coupling occurred to afford 2-hydroxy-4,5,6-trimethoxyben-

zil (**3ak**) in one pot, which is a natural product isolated from *Fissistigma latifolium*. To confirm this selectivity, congeners **3kk** and **3ek** were also prepared in moderate to good yields. Next, we turned our attention to the scope and tolerance for aryl methyl ketones. Aromatic rings bearing halogen substituents ($-F$, $-Cl$, $-Br$) were all well tolerated in this mild transformation. Nitro groups located at all positions of the aromatic ring also afforded the desired products, as expected. 1-(4-nitrophenyl)ethanone (**1e**) gave the best efficiency, followed by 1-(2-nitrophenyl)ethanone. Bearing an electron-withdrawing methylsulfonyl substituent, **1h** gave a relatively high yield. Compounds **3ib** and **3kb**, containing alkoxy groups, could also be obtained without any demethylation byproducts being isolated.¹⁴ Substitution with sterically bulky substituents showed no detrimental effects on the yields of **1j**, **1l**, and **1m**. Therefore, the desired products could be obtained in good yields (**3jb**, **3lb**, and **3mb**, respectively). Heteroatomic (O, N, S) aromatic ketones, such as 2-benzofuranyl, 3-indolyl, and 2-thienyl substrates, all submitted to the transformation. This diversity broadens the horizon of the reaction's applicability. Unfortunately, thiophenols were unable to realize the corresponding transformation.

As a testament to the utility of this method, target-oriented compounds were specified. The pharmaceutical candidate NSC 115566, which is considered difficult to synthesize,¹⁵ can be obtained from the reaction between simple acetophenone and phenol under our conditions, followed by an alkylation reaction, in 47% overall yield (Scheme 2). Moreover, this coupling

Scheme 2. Pharmaceutical Compounds and Natural Product Applications

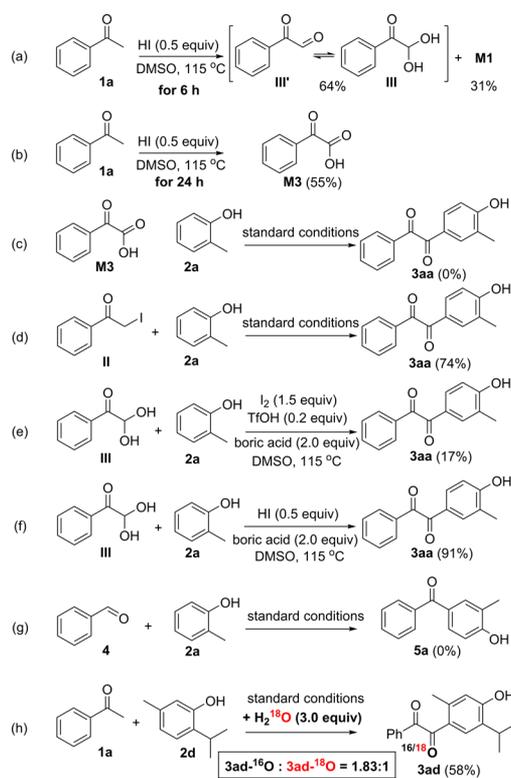


reaction has definite potential to open up new vistas in the total synthesis of 4-hydroxybenzil natural products. The sophodibenzoside family,¹⁶ isolated from *Sophora flavescens* in 2013, shares similar hydroxybenzil aglycone structures, which are suitable as our synthetic targets. Conducted on the gram scale, our method allows facile access to aglycones of the sophodibenzoside D-I under favorable conditions from cheap starting materials in one pot (**3kl**, 1.19 g, 44% yield; **3jl**, 1.63 g, 57% yield). In particular,

we took sophodibenzosides F and I as examples to furnish their first total syntheses, in which we employed glucuronate bromide as a glycosyl donor and KOH/MeOH hydrolysis conditions to ensure enantioselectivity.¹⁷ With the advantages of efficiency, scalability, and easy accessibility, we hope this coupling reaction will reshape the retrosynthetic analysis of other relevant congener families.^{18,19}

We then investigated the mechanism experimentally (Scheme 3). Treating **1a** under standard conditions for 6 h without boric

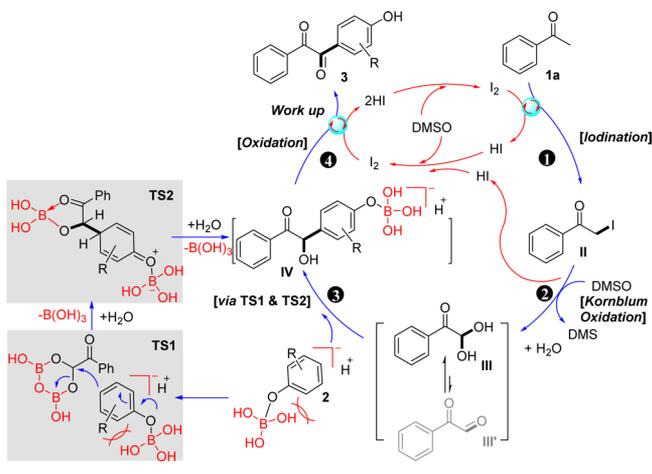
Scheme 3. Control Experiments



acid and phenols gave **III** and **III'** in 64% yield, accompanied by homocoupling products **M1**. Extension of the reaction time led to the formation of overoxidative product **M3**, which was proven not to be our intermediate (equation c). Treating α -iodoketone (**II**) under standard conditions afforded **3aa** in 74% yield. Further experiments determined that HI is crucial to the subsequent transformation. However, treating **4** with **2a** could not produce the coupling product **5a**, which means that the keto carbonyl group of **III** or **III'** has a role in the transformation. An isotope labeling experiment was also undertaken; adding 3.0 equiv of $H_2^{18}O$ to the reaction mixture led to **3ad** with 58% yield, and the ratio of ^{16}O and ^{18}O -labeled product was 1.83:1, which indicated H_2O was involved in the reaction and phenylglyoxal monohydrate can be seen as the intermediate.

Next, we explored the coordination of phenylglyoxal monohydrate with boric acid (see the Supporting Information for details). On the basis of the results and previous studies,²⁰ a probable mechanism is depicted in Scheme 4. Initially, HI acted as a reducing agent to react with DMSO²¹ and deliver I_2 . Acetophenone **1a** underwent iodination to form α -iodoketone **II**, which was smoothly converted to the phenylglyoxal **III'** via a Kornblum-type oxidation. Because the hydroiodic acid reagent is in aqueous solution, water cannot be ignored in the reaction system. Compound **III'** presumably transformed into its

Scheme 4. Probable Mechanisms



monohydrate form **III**, and then its hydrides were abstracted by boric acid to form **TS1**, incompletely and with rapid reversibility. This six-membered boric complex ring activated the phenylglyoxal monohydrate in situ. Meanwhile, boric acid coordinated with phenolic hydroxyl to prevent the O–H insertion reaction and acted as a steric agent to prevent *ortho*-selective attack. The observed *para*-selective attack led to the creation of a C–C bond in the acid medium, accompanied by the formation of a five-membered boric complex ring (**TS2**). Hydrolyzed by water, intermediate **IV** was furnished. It was then oxidized by the terminal oxidant I_2 , which was provided by the combination of HI with DMSO. As another product, HI was released to close the catalytic cycle. The desired product 4-hydroxybenzyl derivatives **3** could be obtained after workup.

In summary, we demonstrated the first example of constructing 4-hydroxybenzyl derivatives through a *para*-selective C–C bond coupling reaction between phenols and acetophenones. With the advantages of good substrate tolerance and operational simplicity, this method led to the first total syntheses of sophodibenzosides **F** and **I** and 2-hydroxy-4,5,6-trimethoxybenzyl and holds promise to become a general laboratory solution for the collective synthesis of the hydroxybenzyl natural product family. We envisage that this highly selective bond formation strategy will be applicable to other valuable transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02118.

Experimental procedures, product characterizations, crystallographic data, and 1H , ^{13}C , and ^{19}F NMR spectra (PDF)

X-ray data for compound **3aa** (CIF)

X-ray data for compound **3jb** (CIF)

X-ray data for compound **3kb** (CIF)

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Notes

The authors declare no competing financial interest.

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