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One-pot, two-step desymmetrization of symmetrical benzils catalyzed by the methylsulfinyl (Dimsyl) anion

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An operationally simple one-pot, two-step procedure for the desymmetrization of benzyls is herein described. This consists in the chemoselective cross-benzoin reaction of symmetrical benzils with aromatic aldehydes catalyzed by the methyl sulfinyl (dimsyl) anion, followed by microwave-assisted oxidation of the resulting benzoylated benzoins with nitrate, avoiding the costly isolation procedure. Both electron-withdrawing and electron-donating substituents may be accommodated on the aromatic rings of the final unsymmetrical benzil.

Introduction

Unsymmetrical benzils are attractive intermediates in organic synthesis and structural motifs of considerable importance in biologically active compounds.[1] They represent a direct access to valuable heterocyclic compounds such as quinoxalines, pyrazines, imidazoles,[1b,2] and exhibit potential as inhibitors of mammalian carboxylesterases (CE) involved in the metabolism of esterified drugs including cocaine, heroin, and xenobiotics.[3] In addition, they display photoresponsive activity in photoisomerization processes[4] and free radical photoinduced polymerizations.[5] Effective methods for the preparation of unsymmetrically substituted benzils are based on the oxidation of various precursors as alkynes,[6] alkenes,[7] α-hydroxyketones,[8] methylene aryl ketones,[9] benzotriazolyl ketones[10] (paths *a-e*, Scheme 1), on the oxidative coupling of acetophenones with unactivated arenes (path *f*),[11] on the oxidative C-C bond cleavage of 1,3-diketones[12] (path *g*), or on non-oxidative procedures from iminoethanones[2a,13] and β-ketoaldehydes[14] (paths *h-i*). Although some of the reported synthetic protocols are quite effective, the access to the above precursors is not without associate efficiency consideration as the need of multiple non-trivial steps in their synthesis,[15] the use of expensive starting materials, and/or metal catalysts.[16] Therefore, a simple, straightforward, and chemoselective general method to access unsymmetrically substituted benzils is highly desirable. Such a method should employ commercial or readily available starting materials, avoid the use of toxic reagents, and be easily adaptable to the preparation of a diversified library of benzils. Undoubtedly, the most direct and atom-efficient preparation of benzils is through the benzoin condensation of aromatic aldehydes under cyanide or *N*-heterocyclic carbene (NHC) catalysis to obtain α-hydroxyketones,[17] which in turn are conveniently oxidized to

benzils. While such a strategy is highly effective for the preparation of symmetrically substituted benzils, its extension to the synthesis of unsymmetrical benzils is complicated by the lack of regiochemical control in the cross-benzoin reaction of two different aldehydes.
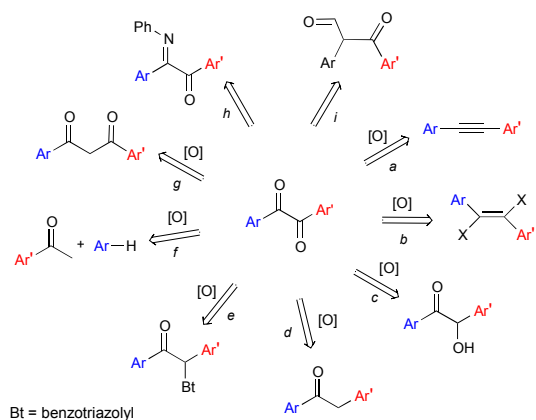
Scheme 1. Existing synthetic strategies to unsymmetrically substituted benzils

As previously pointed out, two crucial elements exercise control on the chemoselectivity of the process: the preference of the dimsyl anion for α-diketone over aldehyde addition, and the aptitude of the generated acyl anion equivalent **III** to intercept the aldehyde **2** (cross-coupling) rather than a second molecule of **1** (homo-coupling). By this strategy, the benzoylated benzoin products **3** are obtained with high efficiency in a fully atom-economic manner. Noteworthy, the

dimsyl anion belongs to the restricted class of organocatalysts capable of promoting umpolung transformations.[17]

With a ready access to benzoylated benzoins in hand, we envisaged the possibility of a direct elaboration of these compounds getting back to the α-diketone stage. Overall, the sequence is none other than the desymmetrization of a symmetrical benzil **1**, with the advantage that the aryl substituents of the final benzil **4** may be chosen independently.
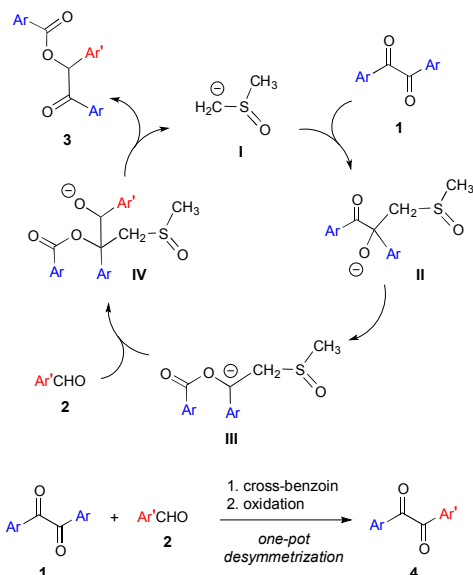
Scheme 2. Proposed mechanism for the cross-coupling of symmetrical benzils **1** with aromatic aldehydes **2** mediated by the dimsyl anion **I** and the designed two-step sequence towards unsymmetrical benzils **4**

Results and discussion

The planned strategy towards unsymmetrical benzils **4** required a preliminary study to find out the most suitable conditions for an efficient benzoylated benzoin-to-benzil conversion via initial benzoyl (Bz) group removal from **3** and subsequent *in situ* oxidation of the resulting benzoin intermediate. Aerobic basic conditions were first investigated due to their successful utilization in the oxidation of genuine benzoins to benzils and their suitability for the Bz deprotection step.[8,20] Hence, exposure of the model benzoylated benzoin **3a** to either NaOH,[20] NaH,[8b] or DBU,[8a] in different base/solvent combinations at different temperatures and in the presence of air led to a maximum 51% yield of isolated benzil **1a** (Table 1, entries 1-5; selected experiments). Also, no improvements were observed by replacing air with pure oxygen as the terminal oxidant (entry 6).[8b,c,20,21] Poor results were obtained under the above conditions mainly because of the instability of the intermediate benzoin in basic aqueous media (entries 1-2) and/or the only partial hydrolysis of the benzoate functionality in organic solvents (entries 3-6). Therefore, aerobic acidic conditions were next examined by treating **3a** with a 2:1 acetic acid (AcOH)-trifluoroacetic acid (TFA) mixture at 125 °C under air. Again, benzil **1a** was recovered in modest yield (22%, entry 7), but a good level of conversion of **3a** into benzoin was observed. This result and literature reports[22,23] prompted us to consider the utilization of the ammonium nitrate/acetic acid couple in virtue of its stronger oxidation ability. Accordingly, a solution of **3a** and NH$_4$NO$_3$ (10 equiv.) in acetic acid was warmed at 125 °C for 24 hours furnishing

benzil **1a** in 70% isolated yield (entry 8). Aiming at decreasing the reaction time, it was next evaluated the use of microwave (MW) dielectric heating (entries 9-13).[24] With a temperature control of 150 °C, the complete conversion of **3a** was achieved after 2 hours and benzil **1a** could be recovered in gratifying 88% yield (entry 9).

Table 1. Optimization of the oxidation reaction of the benzoylated benzoin **3a**.[a]

Entry	Prom.	Oxidant	Solv.	Temp. (°C)	Time (h)	Yield (%)[b]
1	NaOH[c]	air[d]	DMSO	25	16	28
2	NaOH[c]	air[d]	MeOH	25	16	41
3	NaH	air[d]	THF[e]	25	16	20
4	DBU	air[d]	DMSO	25	16	<5
5	DBU	air[d]	EtOAc	70	24	51
6	DBU	O$_2$[f]	EtOAc	70	24	50
7	TFA	air[d]	AcOH	70	24	22
8[g]	-	NH$_4$NO$_3$	AcOH	125	24	70
9[g,h]	-	NH$_4$NO$_3$	AcOH	150	2	88
10[g,h]	-	NH$_4$NO$_3$	AcOH	150	1	52
11[h,i]	-	NH$_4$NO$_3$	AcOH	150	2	53
12[h,j]	TFA	NH$_4$NO$_3$	AcOH	150	2	95
13[h,j,k]	TFA	NH$_4$NO$_3$	AcOH	150	2	92

[a]Reactions performed with 0.50 mmol of **3a**. [b]Isolated yield. [c]1 N aqueous solution. [d]Air-filled balloon. [e]Anhydrous solvent. [f]Oxygen-filled balloon. [g]NH$_4$NO$_3$: 10 equiv. [h]Microwave-assisted reaction performed with a single-mode cavity dedicated reactor (Biotage Initiator). [i]NH$_4$NO$_3$: 5 equiv. [j]NH$_4$NO$_3$: 3 equiv. [k]Degassed and performed under argon.

These conditions represented the better compromise between reaction time (entry 10) and oxidant loading (entry 11). Following the observation that a small excess of NH$_4$NO$_3$ (2 equiv.) was sufficient for the oxidation of a genuine sample of benzoin, benzil formation from benzoylated benzoin **3a** was finally optimized with three equivalents of oxidant in a more acidic reaction medium (2:1 AcOH-TFA), obtaining **1a** in 95% isolated yield (entry 12). The implication of NH$_4$NO$_3$ in **3a** oxidation, either or not in the presence of oxygen, was evident from an experiment performed under an argon atmosphere (entry 13). Two major reacting species have been proposed to form from ammonium nitrate in strong acidic media, that are nitronium (NO$_2^+$) and nitrosonium (NO$^+$) ions, both active in the oxidation of alcohols to carbonyl compounds.[25] It seems reasonable, therefore, to predict a mechanism that involves hydrolysis of the benzoyl group of **3a**, followed by addition of NO$_2^+$ and/or NO$^+$ to form the benzoin nitrate and/or benzoin nitrite esters, next converted into benzil. The recovery of equimolar benzoic acid, eventually containing the corresponding benzamide, further supported this hypothesis.

With the optimal conditions identified, the scope of the oxidation step was next explored. Accordingly, a set of benzoylated benzoins **3** (Table 2, entries 1-8) was initially prepared through cross-benzoin reactions (anhydrous DMSO, *t*-BuOK 10 mol%) of benzil **1a** and aryl aldehydes **2b-i** displaying halogen electron withdrawing groups, electron neutral, and electron donating substituents (-Me, -OMe).[19] In agreement with our previous findings, a moderate propensity of compounds **3** to rearrange into the isomeric benzoylated

Table 2. Substrate scope for the desymmetrization of symmetrical benzils **1**.

Entry	1	2	3 (%)[a]	7 (%)[a]	4 (%,[b] %[c])	Entry	1	2	3 (%)[a]	7 (%)[a]	4 (%,[b] %[c])
1	1a (Ar = Ph)	2b (Ar' = 2-ClC$_6$H$_4$)	3ab (95 %)	7ab (0 %)	4ab (85%, 78%)	9	1b (Ar =4-BrC$_6$H$_4$)	2f (Ar' =3-BrC$_6$H$_4$)	3bf (86 %)	7bf (5 %)	4bf (87%, 73%)
2	1a (Ar = Ph)	2c (Ar' = 2-BrC$_6$H$_4$)	3ac (87 %)	7ac (0 %)	4ac (74%, 65%)	10[d]	1b (Ar =4-BrC$_6$H$_4$)	2h (Ar' =2-MeC$_6$H$_4$)	3bh (71 %)	7bh (0 %)	4bh (61%, 36%)
3	1a (Ar = Ph)	2d (Ar' = 4-ClC$_6$H$_4$)	3ad (76 %)	7ad (19 %)	4ad (84%, 76%)	11[e]	1c (Ar =4-MeC$_6$H$_4$)	2f (Ar' =3-BrC$_6$H$_4$)	3cf (86 %)	7cf (5 %)	4cf (75%, 62%)
4	1a (Ar = Ph)	2e (Ar' = 4-BrC$_6$H$_4$)	3ae (46 %)	7ae (27 %)	4ae (79%, 61%)	12[d]	1c (Ar =4-MeC$_6$H$_4$)	2h (Ar' =2-MeC$_6$H$_4$)	3ch (52 %)	7ch (0 %)	4ch (73%, 35%)
5	1a (Ar = Ph)	2f (Ar' =3-BrC$_6$H$_4$)	3af (88 %)	7af (5 %)	4af (85%, 71%)	13	1a (Ar =Ph)	2j (Ar' =2-CF$_3$C$_6$H$_4$)	3aj (78 %)	7aj (0 %)	4aj (82%, 60%)
6[d]	1a (Ar = Ph)	2g (Ar' =1-naphthyl)	3ag (58 %)	7ag (0 %)	4ag (73%, 40%)	14[f]	1d (Ar =4-CF$_3$C$_6$H$_4$)	2c (Ar' = 2-BrC$_6$H$_4$)	3dc (79 %)	7dc (0 %)	4dc (77%, 51%)
7[d]	1a (Ar = Ph)	2h (Ar' =2-MeC$_6$H$_4$)	3ah (90 %)	7ah (0 %)	4ah (85%, 73%)	15	1a (Ar =Ph)	2m (Ar' =2-furyl)	3am (8 %)	7am (84 %)	4am (17%, 11%)
8[d]	1a (Ar = Ph)	2i (Ar' =2-OMeC$_6$H$_4$)	3ai (71 %)	7ai (0 %)	4ai (70%, 45%)	16[g]	1e (Ar = 2-pyridyl)	2b (Ar' = 2-ClC$_6$H$_4$)	3eb (95 %)	7eb (0 %)	4eb (25%, 21%)

[a]Isolated yield. [b] Yield of **4** starting from isolated **3** + **7**. [c] Yield of **4** strating from **1** by the one-pot two-step procedure. [d]First step performed at 50 °C with 3 equiv. of **2**. [e]First step performed with 2 equiv. of **1c**. [f]First step performed with 3 equiv. of **2**. [g]First step performed with Cs$_2$CO$_3$ (20 mol%) as the catalyst.

benzoins **7** was observed when starting from *para*-substituted (entries 3 and 4) and, to a much lower extent, from *meta*-substituted aldehydes (entry 5).[18f,26] The isomerization is supposed to proceed through intramolecular transesterification of the enolate intermediate **5** formed from **3** by deprotonation (Scheme 3). While this side reaction can be almost suppressed

by lowering the base loading (5 mol%) and the reaction temperature (0 °C) at the expense, however, of the reaction time and benzil conversion,[19] in this study it did not represent a limit of the whole procedure since both **3** and **7** concur to the formation of **4**. Therefore, conversion efficiency was privileged over selectivity in the formation of benzoylated benzoins **3** when staring from *meta*- and *para*-substituted aldehydes **2**.
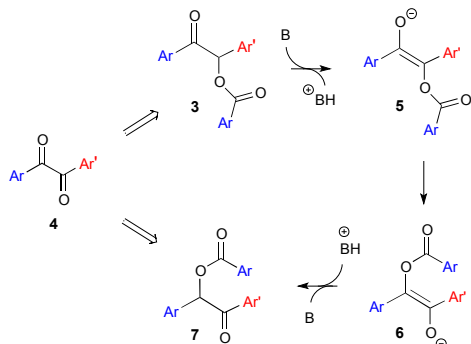
Scheme 3. Rearrangement of benzoylated benzoins **3** into the isomers **7**.

In a first protocol towards benzils **4**, intermediates **3** were isolated, eventually with the corresponding isomers **7**, and subjected to the optimized oxidation procedure using the NH$_4$NO$_3$/AcOH-TFA/MW system. Yields of unsymmetrical benzils **4** (entries 1-8) scored from acceptable to very good (70-85%, first yield value in bracket) irrespective of **3**/**7** isomeric composition, as proved by control experiments.[27] This promising result was the prerequisite for the development of a reliable one-pot process by simply interlocking the two reactivity steps. Accordingly, the symmetrical benzil **1a** and aryl aldehyde **2** were dissolved in DMSO and then *t*-BuOK (10 mol%) was added in one portion under an argon atmosphere. After completion of the reaction (TLC analysis), the resulting solution containing the benzoylated benzoin **3** (or the **3**/**7** mixture) was neutralized with a small amount of AcOH and freeze-dried. Subsequently, the residue was re-dissolved in AcOH-TFA and, after addition of NH$_4$NO$_3$, heated by MW irradiation. Finally, the unsymmetrical benzil **4** was recovered by aqueous work-up and chromatography. It is important to stress that quenching the first condensation reaction with acidic aqueous solutions promoted extensive decomposition of **3**.

The scope and limitations of the disclosed one-pot, two-step procedure were finally investigated by also considering the utilization of substituted benzils **1b-d** (Ar = 4-BrPh, 4-MePh, 4-CF$_3$Ph), 2,2'-pyridyl **1e**, and (hetero)aromatic aldehydes **2j-m** displaying common electron withdrawing substituents (-CF$_3$, -NO$_2$, -CN) and the electron rich furyl group. As far as the efficiency of the cross-benzoin is concerned, it resulted that the electronic feature of the aryl substituent on the acceptor aldehyde **2** was the most important factor determining the final yield of **4** (second value in bracket). More precisely, electron-deficient aromatic aldehydes afforded the best reaction outcomes (entries 1-5, 9, 13, and 16), whereas electron-donating groups on either α-diketone **1** or aldehyde **2** produced less remarkable results (entries 8, 10, and 12). Some particular comments have to be made about 4-nitro and 4-cyano benzaldehydes **2k,l** (not shown), and 2-furfuraldehyde **2m** as acceptors. The latter was highly reactive in the cross-benzoin reaction with benzil **1a** affording, however, the rearranged benzoylated benzoin **7am** as the major coupling product. By contrast, 4-nitrobenzaldehyde **2k** and 4-cyanobenzaldehyde **2l**

turned out to be unsuitable coupling partners because only trace amounts of the corresponding benzoylated benzoins **3**/**7** were obtained. Nevertheless, the low reactivity of nitro and cyano substituted aromatic aldehydes in benzoin condensations has been previously observed even using cyanide and NHCs catalysts.[18f,20]

Overall, a good tolerance to the quite harsh oxidation conditions was detected for the majority of functional groups investigated in this study (entries 1-14). Exceptions were the furyl and pyridyl substituents as reflected by the low yields of isolated unsymmetrical benzils **4am** and **4eb**, respectively (entries 15-16). While degradation to several by-products was observed in the oxidation of furfural-derived benzoin **7am**, conversion of pyridyl intermediate **3eb** into the target benzil **4eb** (25%) was accompanied by the formation of a major by-product tentatively assigned as the corresponding pyridyl *N*-oxide derivative.[28]

Conclusion

In summary, we have demonstrated that a practical two-step procedure for the desymmetrization of symmetrical benzils can be pursued using environmental benign conditions and low-cost reactants and catalyst. Indeed, the synthetic sequence relied on the chemoselective cross-benzoin reaction of symmetrical benzils with aromatic aldehydes catalyzed by the methyl sulfinyl (dimsyl) anion, and the subsequent microwave-assisted oxidation of the benzoylated benzoin intermediates with NH$_4$NO$_3$. The optimization of a one-pot procedure for the above sequence further increased the level of efficiency of the disclosed strategy by minimization of time-consuming and expensive isolation steps. Given the wide availability of symmetrical benzils and aromatic aldehydes, this methodology should permit access to a large number of unsymmetrical benzils with a broad range of structural elements of diversity for an extensive exploration of their properties in medicinal[1a,29] and synthetic chemistry.[30]

Experimental section

Potassium *tert*-butoxide was purified by sublimation (200-220 °C at 5 mmHg) using a Büchi glass oven B580 in the sublimation mode. Liquid aldehydes were freshly distilled before their utilization. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh). ^{1}H (400 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in CDCl$_3$ solutions at room temperature. Peaks assignments were aided by ^{1}H-^{1}H COSY and gradient-HMQC/HMBC experiments. ESI-MS analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1:1 MeCN/H$_2$O. For accurate mass measurements, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. The capillary source voltage was set at 1700V; the gas temperature and drying gas were kept at 350°C and 5 L/min, respectively. MS analyzer was externally calibrated with ESI-L low concentration tuning mix from m/z 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H$_2$O/ACN 0.1% TFA into the system at a flow rate of 0.4 □L/min. Elemental analyses were performed with FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). Microwave-assisted reactions were

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carried out using a single-mode cavity dedicated reactor (Biotage Initiator[TM]). Reactions were performed with temperature-controlled programs in glass vials (0.5-2 or 2-5 mL depending on the scale) sealed with a Teflon septum. Temperatures were measured externally by an IR sensor. The reaction time was counted when the reaction mixture reached the stated temperature. Pressure was measured by a non-invasive sensor integrated into the cavity lid. Residual water (% w/w) of commercially available (Sigma-Aldrich) anhydrous DMSO (0.016%) was determined by Fisher analysis with the 756 KF Coulometer (Metrohm). α-Diketones **1a-c,e** and aldehydes **2a-m** are commercially available (Sigma-Aldrich). α-Diketone **1d** was synthesized as described.[31] Benzoylated benzoins **3ab**,[19] **3ac**,[17f] **3ad**,[19] **7ad**,[19] 3ah,[19] **3am**,[18f] **7am**,[18f] and **3ae**[19] are known compounds. Benzils **4ab**,[7c] **4ac**,[9a] **4ad**,[7b,c,9a] **4ae**,[7b,c,9a] **4af**,[7b,12c] **4ag**,[6i,12c] **4ah**,[6e] **4ai**,[7c] **4cf**,[8d] **4aj**,[6j] and **4am**[10] are known compounds.

Optimization Study of the oxidation reaction of benzoylated benzoin 3a (Table 1).

Entries 1-2. A mixture of **3a** (158 mg, 0.50 mmol), 1 N NaOH (1 mL, 1 mmol), and the stated solvent (1 mL) was saturated with air (by an air-filled balloon) and stirred at room temperature for 16 hours. Then, the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a** as a yellow solid.

Entry 3. To a cooled (0°C), stirred solution of **3a** (158 mg, 0.50 mmol) in anhydrous THF (5 mL), was added NaH (60% dispersion in mineral oil, 40 mg, 1.00 mmol) in one portion. After the addition, the mixture was allowed to warm to room temperature, saturated with air (by an air-filled balloon), and stirred for 16 hours. Then, the mixture was diluted with 0.1 M $NaHCO_3$ (10 mL) and extracted with AcOEt (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entry 4. To a vigorously stirred solution of **3a** (158 mg, 0.50 mmol) in DMSO (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 149 μL, 1.00 mmol) in one portion. The mixture was saturated with air (by an air-filled balloon) and stirred at room temperature for 16 hours. Then, the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entry 5. To a vigorously stirred solution of **3a** (158 mg, 0.50 mmol) in AcOEt (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 149 μL, 1.00 mmol) in one portion. The mixture was saturated with air (by an air-filled balloon), warmed to 70°C, and stirred at that temperature for 24 hours. Then, the mixture was cooled to room temperature, diluted with H_2O (5 mL) and extracted with AcOEt (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entry 6. To a vigorously stirred solution of **3a** (158 mg, 0.50 mmol) in AcOEt (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 149 μL, 1.00 mmol) in one portion. The mixture was saturated with oxygen (by an oxygen-filled balloon), warmed to 70°C, and stirred at that temperature for 24 hours. Then, the mixture was cooled to room temperature, diluted with H_2O (5 mL) and extracted with

AcOEt (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entry 7. A vigorously stirred mixture of **3a** (158 mg, 0.50 mmol), AcOH (1 mL), and trifluoroacetic acid (TFA, 2 mL) was saturated with air (by an air-filled balloon) and refluxed for 24 h. Then, the mixture was cooled to room temperature, diluted with AcOEt (20 mL), and washed with cold (0 °C) saturated Na_2CO_3 solution (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entry 8. A vigorously stirred mixture of **3a** (158 mg, 0.50 mmol), AcOH (1 mL), and NH_4NO_3 (400 mg, 5.00 mmol) was refluxed for 24 h. Then, the mixture was cooled to room temperature, diluted with AcOEt (20 mL), and washed with cold (0 °C) saturated Na_2CO_3 solution (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entries 9-11. A 0.5-2.0 mL process vial was filled with **3a** (158 mg, 0.5 mmol), AcOH (1 mL), and the stated amount of NH_4NO_3 (5.00 or 2.50 mmol). The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation was performed at 150 °C for the stated reaction time. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was diluted with AcOEt (20 mL), and washed with cold (0 °C) saturated Na_2CO_3 solution (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**.

Entries 12-13. A 0.5-2.0 mL process vial was filled with **3a** (158 mg, 0.5 mmol), AcOH (0.66 mL), TFA (0.33 mL) and NH_4NO_3 (120 mg, 1.50 mmol). The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation was performed at 150 °C for the stated reaction time. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was diluted with AcOEt (20 mL), and washed with cold (0 °C) saturated Na_2CO_3 solution (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 30:1 cyclohexane-AcOEt to give **1a**. In entry 13, the mixture was degassed under vacuum and saturated with argon (by an argon-filled balloon) three times before irradiation.

General Procedure for the Cross-Benzoin Reactions of α-Diketones 1 with Aldehydes 2 (Table 2, columns 4-5 and 10-11).

To a vigorously stirred mixture of α-diketone **1** (1.00 mmol), aldehyde **2** (1.00 mmol), and anhydrous DMSO (2 mL), potassium *tert*-butoxide (11 mg, 0.10 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (by an argon-filled balloon) three times. The mixture was stirred at the stated temperature (Table 2) until complete disappearance or best conversion of the starting diketone was detected (TLC analysis, ca. 1-16 h). Then, the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (2 × 25 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the benzoylated benzoins **3** eventually containing isomers **7**.

1-(2-Chlorophenyl)-2-oxo-2-phenylethyl benzoate (3ab): Column chromatography with 20:1 cyclohexane-AcOEt afforded **3ab**[19] (332 mg, 95%) as a white foam. ^{1}H NMR: δ = 8.12-8.07 (m, 2 H, Ar), 8.02-7.98 (m, 2 H, Ar), 7.60-7.40 (m, 8 H, Ar), 7.44 (s, 1 H, H-1), 7.36-7.24 (m, 2 H, Ar); ^{13}C NMR: δ = 193.3, 165.8, 134.9, 134.4, 134.2, 133.8, 133.4,131.8, 130.8, 130.4, 130.2, 130.1, 130.0, 129.9, 129.5, 129.2,129.0, 128.8, 128.4, 127.6, 74.0.

1-(2-Bromophenyl)-2-oxo-2-phenylethyl benzoate (3ac): Column chromatography with 25:1 cyclohexane-AcOEt afforded **3ac**[17f] (344 mg, 87%) as a white amorphous solid. ^{1}H NMR: δ = 8.13-8.05 (m, 2 H, Ar), 8.05-7.96 (m, 2 H, Ar), 7.67 (dd, J = 7.9, 1.4 Hz, 1 H, Ar), 7.61-7.52 (m, 1 H, Ar), 7.54 (s, 1 H, H-1), 7.53-7.50 (m, 1 H, Ar), 7.49-7.39 (m, 5 H, Ar), 7.36-7.20 (m, 2 H, Ar); ^{13}C NMR δ = 193.4, 165.7, 133.8, 133.6, 133.5, 133.4, 131.0, 130.6, 130.6, 130.1, 129.1, 128.8, 128.7, 128.4, 128.2, 124.7, 76.6. Found: C, 63.71; H, 3.69. $C_{21}H_{15}BrO_3$ requires C, 63.81; H, 3.83%.

2-(4-Chlorophenyl)-2-oxo-1-phenylethyl benzoate (7ad): Column chromatography with 20:1 cyclohexane-AcOEt gave **7ad**[19] (66 mg, 19%) as first eluted compound. ^{1}H NMR: δ = 8.14-8.08 (m, 2 H, Ar), 7.94-7.90 (m, 2 H, Ar), 7.60-7.50 (m, 2 H, Ar), 7.48-7.32 (m, 8 H, Ar), 7.03 (s, 1 H, H-1); ^{13}C NMR: δ = 192.6, 166.0, 133.5, 130.2-128.5 (17 C), 77.9.

1-(4-Chlorophenyl)-2-oxo-2-phenylethyl benzoate (3ad): Column chromatography with 20:1 cyclohexane-AcOEt gave **3ad**[19] (266 mg, 76%) as second eluted compound. ^{1}H NMR: δ = 8.14-8.06 (m, 2 H, Ar), 8.00-7.94 (m, 2 H, Ar), 7.60-7.32 (m, 10 H, Ar), 7.06 (s, 1 H, H-1); ^{13}C NMR: δ = 193.4, 165.9, 135.4, 134.5, 133.7, 133.5, 130.0-128.4 (14 C), 77.3.

2-(4-Bromophenyl)-2-oxo-1-phenylethyl benzoate (7ae): Column chromatography with 20:1 cyclohexane-AcOEt gave **7ae** (106 mg, 27%) as first eluted compound. ^{1}H NMR: δ = 8.15-8.06 (m, 2 H, Ar), 7.89-7.82 (m, 2 H, Ar), 7.60-7.50 (m, 5 H, Ar), 7.48-7.34 (m, 5 H, Ar), 7.01 (s, 1 H, H-1); ^{13}C NMR: δ = 192.9, 166.1, 134.8, 133.5, 133.4, 132.1, 130.4, 130.0, 129.5, 129.3, 129.1, 128.8, 128.6, 128.5, 77.9. ESI-MS (395.2): 434.8 [M + K]$^+$. HRMS (ESI) m/z calcd for $C_{21}H_{16}BrO_3$ [M + H]$^+$ 395.0283, found 395.0240. Found: C, 63.55; H, 4.62. $C_{21}H_{15}BrO_3$ requires C, 63.81; H, 3.83%.

1-(4-Bromophenyl)-2-oxo-2-phenylethyl benzoate (3ae): Column chromatography with 20:1 cyclohexane-AcOEt gave **3ae** (182 mg, 46%) as second eluted compound. ^{1}H NMR: δ = 8.15-8.06 (m, 2 H, Ar), 8.02-7.93 (m, 2 H, Ar), 7.63-7.49 (m, 4 H, Ar), 7.49-7.35 (m, 6 H, Ar), 7.04 (s, 1 H, H-1); ^{13}C NMR: δ = 193.4, 165.9, 134.5, 133.8, 133.6, 132.8, 132.4, 130.3, 130.0, 129.7, 129.2, 128.8, 128.5, 123.7, 77.4. ESI-MS (395.2): 418.3 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{21}H_{15}BrO_3$ [M]$^+$ 394.0205, found 394.0227. Found: C, 63.99; H, 4.01. $C_{21}H_{15}BrO_3$ requires C, 63.81; H, 3.83%.

1-(3-Bromophenyl)-2-oxo-2-phenylethyl benzoate (3af): Column chromatography with 20:1 cyclohexane-AcOEt afforded **3af** (347 mg, 88%) as a white amorphous solid. ^{1}H NMR: δ = 8.16-8.07 (m, 2 H, Ar), 8.03-7.94 (m, 2 H, Ar), 7.76-7.69 (m, 1 H, Ar), 7.62-7.52 (m, 2 H, Ar), 7.51-7.38 (m, 6 H, Ar), 7.30-7.24 (m, 1 H, Ar), 7.04 (s, 1 H, H-1); ^{13}C NMR: δ =193.2, 165.8, 135.89, 134.4, 133.8, 133.5, 132.5, 131.5, 130.6, 130.0, 129.3, 129.1, 128.8, 128.5, 127.2, 123.1, 76.9. ESI-MS

(395.2): 396.5 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{21}H_{15}BrO_3$ [M]$^+$ 394.0205, found 394.0219. Found: C, 63.58; H, 3.61. $C_{21}H_{15}BrO_3$ requires C, 63.81; H, 3.83%.

1-(Naphthalen-1-yl)-2-oxo-2-phenylethyl benzoate (3ag): For the synthesis of **3ag** three equiv. of aldehyde **2g** were used and the reaction was performed at 50 °C. Column chromatography with 20:1 cyclohexane-AcOEt afforded **3ag** (212 mg, 58%) as a yellow amorphous solid. [1]H: δ = 8.34 (d, J = 8.5 Hz, 1 H, Ar), 8.13-8.07 (m, 1 H, Ar), 7.96-7.90 (m, 3 H, Ar), 7.85 (s, 1 H, H-1), 7.67-7.51 (m, 4 H, Ar), 7.50-7.39 (m, 4 H, Ar), 7.39-7.29 (m, 3 H, Ar); ^{13}C NMR: δ = 194.0, 166.1, 134.7, 134.2, 133.5, 133.4, 131.5, 130.4, 130.1, 129.9, 129.3, 129.1, 128.7, 128.6, 128.4, 127.4, 126.3, 125.4, 123.3, 75.6. ESI-MS (366.4): 367.7 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{25}H_{19}O_3$ [M]$^+$ 366.1256, found 366.1281. Found: C, 81.88; H, 4.68. $C_{25}H_{18}O_3$ requires C, 81.95; H, 4.95%.

2-Oxo-2-phenyl-1-(o-tolyl)ethyl benzoate (3ah): For the synthesis of **3ah** three equiv. of aldehyde **2h** were used and the reaction was performed at 50 °C. Column chromatography with 12:1 cyclohexane-AcOEt afforded **3ah**[19] (297 mg, 90%) as a white amorphous solid. ^{1}H NMR: δ = 8.14-8.08 (m, 2 H, Ar), 7.92-7.86 (m, 2 H, Ar), 7.60-7.37 (m, 8 H, Ar), 7.32-7.14 (m, 2 H, Ar), 7.29 (s, 1 H, H-1), 2.50 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 194.2, 166.1, 137.3, 135.0, 133.4, 133.3, 132.3, 131.3, 130.0-128.4 (11 C), 126.7, 75.6, 19.5. ESI-MS (330.4): 353.7 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{22}H_{19}O_3$ [M + H]$^+$ 331.1334, found 331.1358. Found: C, 79.65; H, 5.68. $C_{22}H_{18}O_3$ requires C, 79.98; H, 5.49%.

1-(2-Methoxyphenyl)-2-oxo-2-phenylethyl benzoate (3ai): For the synthesis of **3ai** three equiv. of aldehyde **2i** were used and the reaction was performed at 50 °C. Column chromatography with 20:1 cyclohexane-AcOEt afforded **3ai** (246 mg, 71%) as a white amorphous solid. ^{1}H NMR: δ = 8.15-8.07 (m, 2 H, Ar), 8.08-7.99 (m, 2 H, Ar), 7.59 (s, 1 H, H-1), 7.58-7.49 (m, 2 H, Ar), 7.49-7.38 (m, 5 H, Ar), 7.38-7.30 (m, 1 H, Ar), 7.01-6.90 (m, 2 H, Ar), 3.92 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 194.0, 166.2, 156.7, 134.7, 133.4, 133.2, 130.8, 130.0, 129.9, 129.7, 128.7, 128.5, 128.35, 122.3, 121.2, 111.3, 71.6, 55.8. ESI-MS (346.4): 347.7 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{22}H_{19}O_4$ [M + H]$^+$ 347.1283, found 347.1298. Found: C, 76.44; H, 5.12. $C_{22}H_{18}O_4$ requires C, 76.29; H, 5.24%.

1-(3-Bromophenyl)-2-(4-bromophenyl)-2-oxoethyl 4-bromobenzoate (3bf): For the synthesis of **3bf** 6 mL of solvent were used. Column chromatography with 30:1 cyclohexane-AcOEt afforded **3bf** (475 mg, 86%) as a white foam. ^{1}H NMR: δ 7.98-7.92 (m, 2 H, Ar), 7.85-7.80 (m, 2 H, Ar), 7.71-7.66 (m, 1 H, Ar), 7.63-7.55 (m, 4 H, Ar), 7.55-7.48 (m, 1 H, Ar), 7.49-7.43 (m, 1 H, Ar), 7.31-7.26 (m, 1 H, Ar), 6.94 (s, 1 H, H-1); ^{13}C NMR: δ = 191.8, 164.9, 135.0, 132.7, 132.6, 132.37, 132.0, 131.7, 131.3, 130.6, 130.0, 129.0, 128.7, 127.6, 127.0, 123.1, 76.8. ESI-MS (553.0): 576.5 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{21}H_{14}Br_3O_3$ [M + H]$^+$ 550.8493, found 550.8478. Found: C, 45.48; H, 2.50. $C_{21}H_{13}Br_3O_3$ requires C, 45.61; H, 2.37%.

2-(4-Bromophenyl)-2-oxo-1-(o-tolyl)ethyl 4-bromobenzoate (3bh): For the synthesis of **3bh** 6 mL of solvent and three equiv. of aldehyde **2h** were used; the reaction was performed at 50 °C. Column chromatography with 30:1 cyclohexane-AcOEt afforded **3bh** (341 mg, 71%) as a white amorphous solid. ^{1}H NMR: δ = 7.97-7.92 (m, 2 H, Ar), 7.75-7.69 (m, 2 H, Ar), 7.61-

7.50 (m, 4 H, Ar), 7.33-7.24 (m, 4 H, Ar), 7.19 (s, 1 H, H-1), 2.51 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 193.1, 165.3, 137.2, 134.6, 133.5, 132.0, 131.8, 131.7, 131.5, 130.1, 129.8, 129.5, 128.8, 128.65, 128.1, 126.8, 75.7, 19.4. ESI-MS (488.2): 489.6 [M + H]$^+$. HRMS (ESI) *m/z* calcd for C$_{22}$H$_{17}$Br$_2$O$_3$ [M + H]$^+$ 486.9544, found 486.9531. Found: C, 54.29; H, 3.45. C$_{22}$H$_{16}$Br$_2$O$_3$ requires C, 54.13; H, 3.30%.

1-(3-Bromophenyl)-2-oxo-2-(*p*-tolyl)ethyl 4-methylbenzoate (3cf): For the synthesis of **3cf** two equiv. of α-diketone **1c** were used. Column chromatography with 20:1 cyclohexane-AcOEt afforded **3cf** (364 mg, 86%) as a white amorphous solid. ^{1}H NMR: δ = 8.04-7.94 (m, 2 H, Ar), 7.95-7.85 (m, 2 H, Ar), 7.72 (t, *J* = 1.8 Hz, 1 H, Ar), 7.53-7.43 (m, 2 H, Ar), 7.29-7.18 (m, 5 H, Ar), 7.00 (s, 1 H, H-1), 2.41 (s, 3 H, CH$_3$), 2.38 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 192.7, 165.6, 144.5, 144.1, 136.1, 132.1, 131.7, 131.2, 130.3, 129.8, 129.3, 128.9, 128.8, 126.9, 126.2, 122.8, 76.8, 26.7, 21.5. ESI-MS (423.3): 446.5 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for C$_{23}$H$_{19}$BrO$_3$ [M]$^+$ 422.0518, found 422.0535. Found: C, 65.38; H, 4.41. C$_{23}$H$_{19}$BrO$_3$ requires C, 65.26; H, 4.52%.

2-Oxo-1-(*o*-tolyl)-2-(*p*-tolyl)ethyl 4-methylbenzoate (3ch): For the synthesis of **3ch** three equiv. of aldehyde **2h** were used and the reaction was performed at 50 °C. Column chromatography with 20:1 cyclohexane-AcOEt afforded **3ch** (186 mg, 52%) as a white amorphous solid. ^{1}H NMR: δ = 8.02-7.95 (m, 2 H, Ar), 7.82-7.76 (m, 2 H, Ar), 7.36 (d, *J* = 7.4 Hz, 1 H, Ar), 7.26-7.24 (m, 3 H, Ar), 7.23 (s, 1 H, H-1), 7.22-7.15 (m, 4 H, Ar), 2.52 (s, 3 H, CH$_3$), 2.40 (s, 3 H, CH$_3$), 2.35 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 193.7, 165.9, 144.1, 143.8, 137.0, 132.4, 132.2, 131.0, 129.8, 129.4, 129.3, 129.1, 128.6, 126.4, 126.4, 75.1, 21.5, 21.5, 19.3. ESI-MS (358.5): 397.8 [M + K]$^+$. HRMS (ESI) *m/z* calcd for C$_{24}$H$_{23}$O$_3$ [M + H]$^+$ 359.1647, found 359.1628. Found: C, 76.44; H, 5.12. C$_{24}$H$_{22}$O$_3$ requires C, 80.42; H, 6.19%.

2-Oxo-2-phenyl-1-(2-(trifluoromethyl)phenyl)ethyl benzoate (3aj): Column chromatography with 20:1 cyclohexane-AcOEt afforded **3aj** (299 mg, 78%) as a white amorphous solid. ^{1}H NMR: δ = 8.08-8.04 (m, 2 H, Ar), 7.96-7.92 (m, 2 H, Ar), 7.82-7.77 (m, 1 H, Ar), 7.60-7.52 (m, 4 H, Ar), 7.52 (s, 1 H, H-1), 7.46-7.38 (m, 4 H, Ar); ^{13}C NMR: δ = 193.4, 165.6, 134.5, 133.8, 133.5, 132.7, 132.2, 130.9, 130.1, 129.7, 129.5, 129.2, 128.9, 128.8, 128.5, 126.9, 126.8, 125.5, 73.1; ^{19}F NMR (376 MHz: δ = -58.6 (s, 3 F, CF$_3$). ESI-MS (384.3): 407.2 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for C$_{22}$H$_{15}$F$_3$O$_3$ [M]$^+$ 384.0973, found 384.0912. Found: C, 68.41; H, 3.70. C$_{22}$H$_{15}$F$_3$O$_3$ requires C, 68.75; H, 3.93%.

1-(2-Bromophenyl)-2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl 4-(trifluoromethyl)benzoate (3dc): For the synthesis of **3dc** three equiv. of aldehyde **2c** were used. Column chromatography with 30:1 cyclohexane-AcOEt afforded **3dc** (419 mg, 79%) as a white foam. ^{1}H NMR: δ = 8.24-8.18 (m, 2 H, Ar), 8.12-8.06 (m, 2 H, Ar), 7.74-7.68 (m, 5 H, Ar), 7.53 (s, 1 H, Ar), 7.46-7.41 (m, 1 H, Ar), 7.39-7.22 (m, 2 H, Ar); ^{13}C NMR: δ = 192.4, 164.7, 137.0, 135.7, 135.3, 135.2, 135.0, 134.9, 134.7, 134.0, 132.5, 132.3, 131.7, 130.7, 130.6, 129.2, 128.6, 127.5, 126.1, 126.0, 125.9, 125.8, 125.7, 125.6, 125.6, 125.4, 124.9, 124.8, 124.8, 122.3, 122.1, 76.8; ^{19}F NMR (376 MHz: δ = -63,2 (s, 3 F, CF$_3$), -63.3 (s, 3 F, CF$_3$). ESI-MS (531.2): 554.8 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for

C$_{23}$H$_{13}$BrF$_6$NaO$_3$ [M+ Na]$^+$ 552.9850, found 552.9821. Found: C, 52.67; H, 2.11. C$_{23}$H$_{13}$BrF$_6$O$_3$ requires C, 52.00; H, 2.47%.

1-(Furan-2-yl)-2-oxo-2-phenylethyl benzoate (3am): Column chromatography with 10:1 cyclohexane-AcOEt gave **3am**[18f] (25 mg, 8%) as first eluted compound. ^{1}H NMR: δ = 8.15-8.10 (m, 2 H, Ar), 8.02-7.96 (m, 2 H, Ar), 7.60-7.50 (m, 2 H, Ar), 7.48-7.40 (m, 5 H, Ar), 7.19 (s, 1 H, H-1), 6.55-6.50 (m, 1 H, Ar), 6.42-6.35 (m, 1 H, Ar); ^{13}C NMR: δ = 190.9, 165.9, 147.0, 144.4, 134.4, 133.8, 133.6, 130.2, 129.2, 128.8, 128.5, 112.2, 111.3, 71.3. ESI-MS (306.3): 399.2 [M + K]$^+$. HRMS (ESI) *m/z* calcd for C$_{19}$H$_{14}$O$_4$ [M]$^+$ 306.0892, found 306.0855. Found: C, 74.12; H, 4.87. C$_{19}$H$_{14}$O$_4$ requires C, 74.50; H, 4.61%.

2-(Furan-2-yl)-2-oxo-1-phenylethyl benzoate (7am): Column chromatography with 20:1 cyclohexane-AcOEt gave **7am**[18f] (257 mg, 84%) as second eluted compound. ^{1}H NMR: δ = 8.16-8.10 (m, 2 H, Ar), 7.66-7.52 (m, 4 H, Ar), 7.48-7.34 (m, 5 H, Ar), 7.32-7.28 (m, 1 H, Ar), 6.90 (s, 1 H, H-1), 6.48-6.40 (m, 1 H, Ar); ^{13}C NMR: δ = 182.6, 166.0, 150.7, 147.1, 133.6, 133.5, 130.1, 129.4, 129.4, 129.1, 128.7, 128.5, 119.1, 112.7, 77.4. ESI-MS (306.3): 418.3 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for C$_{19}$H$_{14}$O$_4$ [M]$^+$ 306.0892, found 306.0840. Found: C, 74.08; H, 4.20. C$_{19}$H$_{14}$O$_4$ requires C, 74.50; H, 4.61%.

1-(2-Chlorophenyl)-2-oxo-2-(pyridin-2-yl)ethyl picolinate (3eb): For the synthesis of **3eb** Cs$_2$CO$_3$ (20 mol%) was used as the catalyst. Column chromatography with 2:1 cyclohexane-AcOEt afforded **3eb**[19] (335 mg , 95%) as a white foam; ^{1}H NMR: δ = 8.79-8.74 (m, 1 H, Ar), 8.62-8.56 (m, 1 H, Ar), 8.20-8.14 (m, 1 H, Ar), 8.09-8.03 (m, 1 H, Ar), 8.08 (s, 1 H, H-1), 7.86-7.74 (m, 2 H, Ar), 7.49-7.36 (m, 4 H, Ar), 7.30-7.26 (m, 2 H, Ar); ^{13}C NMR: δ = 193.9, 164.3, 151.3, 150.1, 149.1, 147.5, 136.9, 136.8, 135.2, 131.9, 130.4, 130.3, 130.2, 127.6, 127.1, 127.0, 125.7, 122.8, 75.5.

General Procedure for the oxidation of benzoylated benzoins 3/7 to asymmetrical benzils 4 (Table 2). Method A.
A 0.5-2.0 mL process vial was filled with the benzoylated benzoin **3** or **3/7** isomers mixture (0.5 mmol), AcOH (0.66 mL), TFA (0.33 mL), and NH$_4$NO$_3$ (120 mg, 1.50 mmol). The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation was performed at 150 °C for 2 h. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was diluted with AcOEt (20 mL), and washed with cold (0 °C) saturated Na$_2$CO$_3$ solution (2 × 5 mL). The organic phase was dried (Na$_2$SO$_4$), concentrated, and eluted from a column of silica gel with the suitable elution system to give the benzil **4**. Final elution with 10:1 AcOEt-MeOH afforded the corresponding benzoic acid/benzamide mixture.

General Procedure for the one-pot, two step synthesis of benzils 4 (Table 2). Method B.
To a vigorously stirred mixture of α-diketone **1** (1.00 mmol), aldehyde **2** (1.00 mmol), and anhydrous DMSO (2 mL) in a 0.5-2.0 mL process vial, potassium *tert*-butoxide (11 mg, 0.10 mmol) was added in one portion. Then, the mixture was degassed under vacuum and saturated with argon (by an argon-filled balloon) three times. The mixture was stirred at the stated temperature (Table 2) until complete disappearance or best conversion of the starting diketone was detected (TLC analysis,

ca. 1-16 h). Then, the mixture was neutralized with AcOH and freeze-dried. The resulting residue containing the benzoylated benzoin **3** or **3/7** isomers mixture was dissolved in AcOH (1.3 mL mL) and TFA (0.7 mL), then NH_4NO_3 (240 mg, 3.00 mmol) was added in one portion. The vial was sealed with the Teflon septum and aluminium crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation was performed at 150 °C for 2 h. After the full irradiation sequence was completed, the vial was cooled to room temperature and then opened. The mixture was diluted with AcOEt (40 mL), and washed with cold (0 °C) saturated Na_2CO_3 solution (2 × 10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the benzil **4**. Final elution with 10:1 AcOEt-MeOH afforded the corresponding benzoic acid/benzamide mixture.

1-(2-Chlorophenyl)-2-phenylethane-1,2-dione (4ab): Method A. Column chromatography with 25:1 cyclohexane-AcOEt afforded **4ab**[7c] (103 mg, 85%) as a yellow amorphous solid. Method B: **4ab**[7c] (190 mg, 78%). ^{1}H NMR: δ = 8.07-8.00 (m, 2 H, Ar), 7.94-7.88 (m, 1 H, Ar), 7.70-7.63 (m, 1 H, Ar), 7.58-7.49 (m, 3 H, Ar), 7.47-7.40 (m, 2 H, Ar); ^{13}C NMR: δ = 193.7, 192.0, 134.6, 134.5, 134.0, 133.8, 132.4, 132.1, 130.5, 130.2, 128.9, 127.4. ESI-MS (244.0): 245.6 [M + H]$^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{10}ClO_2$ [M + H]$^+$ 245.0369, found 245.0355. Found: C, 68.90; H, 3.48. $C_{14}H_9ClO_2$ requires C, 68.72; H, 3.71%.

1-(2-Bromophenyl)-2-phenylethane-1,2-dione (4ac): Method A. Column chromatography with 40:1 cyclohexane-AcOEt afforded **4ac**[9a] (106 mg, 74%) as a yellow amorphous solid. Method B: column chromatography with 1.8:1 cyclohexane-CH_2Cl_2 afforded **4ac**[9a] (187 mg, 65%). ^{1}H NMR: δ = 8.10-8.03 (m, 2 H, Ar), 7.84-7.79 (m, 1 H, Ar), 7.70-7.61 (m, 2 H, Ar), 7.58-7.49 (m, 2 H, Ar), 7.49-7.43 (m, 2 H, Ar); ^{13}C: δ = 194.2, 191.5, 136.1, 134.5, 134.4, 133.8, 132.7, 132.6, 130.4, 128.9, 127.9, 121.8. ESI-MS (289.1): 312.4 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{10}BrO_2$ [M + H]$^+$ 288.9864, found 288.9835. Found: C, 58.28; H, 3.25. $C_{14}H_9BrO_2$ requires C, 58.16; H, 3.14%.

1-(4-Chlorophenyl)-2-phenylethane-1,2-dione (4ad): Method A. Column chromatography with 30:1 cyclohexane-AcOEt afforded **4ad**[9a] (102 mg, 84%) as a pale yellow solid (mp 71-73 °C). Method B: **4ad**[7b,c,9a] (185 mg, 76%). ^{1}H NMR: δ = 7.98-7.87 (m, 4 H, Ar), 7.71-7.62 (m, 1 H, Ar), 7.56-7.44 (m, 4 H, Ar); ^{13}C NMR: δ = 194.1, 193.3, 141.8, 135.3, 133.0, 131.5, 131.4, 130.2, 129.7, 129.3. ESI-MS (244.0): 267.3 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_9ClO_2$ [M]$^+$ 244.0291, found 244.0270. Found: C, 70.01; H, 3.45. $C_{14}H_9ClO_2$ requires C, 68.72; H, 3.71%.

1-(4-Bromophenyl)-2-phenylethane-1,2-dione (4ae): Method A. Column chromatography with 40:1 cyclohexane-AcOEt afforded **4ae**[7b,c,9a] (114 mg, 79%) as a pale yellow solid (mp 81-83 °C). Method B. Column chromatography with 1.3:1 cyclohexane-CH_2Cl_2 afforded **4ae**[7b,c,9a] (176 mg, 61%). ^{1}H NMR: δ = 7.99-7.92 (m, 2 H, Ar), 7.87-7.81 (m, 2 H, Ar), 7.71-7.62 (m, 3 H, Ar), 7.56-7.47 (m, 2 H, Ar); ^{13}C NMR: δ = 193.9, 193.3, 135.1, 132.8, 132.5, 131.8, 131.3, 130.6, 123.0, 129.1. ESI-MS (289.1): 290.1 [M + H]$^+$. HRMS (ESI) *m/z* calcd for

$C_{14}H_{10}BrO_2$ [M + H]$^+$ 288.9864, found 288.9811. Found: C, 58.45; H, 3.60. $C_{14}H_9BrO_2$ requires C, 58.16; H, 3.14%.

1-(3-bromophenyl)-2-phenylethane-1,2-dione (4af): Method A. Column chromatography with 1.5:1 cyclohexane-CH_2Cl_2 afforded **4af**[7b,12c] (123 mg, 85%) as a yellow amorphous solid. Method B: **4af**[7b,12c] (205 mg, 71%). ^{1}H NMR: δ = 8.12 (t, *J* = 1.7 Hz, 1 H, Ar), 8.00-7.92 (m, 2 H, Ar), 7.92-7.84 (m, 1 H, Ar), 7.82-7.74 (m, 1 H, Ar), 7.74-7.63 (m, 1 H, Ar), 7.59-7.46 (m, 2 H, Ar), 7.39 (t, *J* = 7.9 Hz, 1 H, Ar); ^{13}C NMR: δ = 193.5, 192.9, 137.7, 135.2, 134.6, 132.6, 132.5, 130.6, 130.0, 129.1, 128.6, 123.3. ESI-MS (289.1): 312.5 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{10}BrO_2$ [M + H]$^+$ 288.9864, found 288.9824. Found: C, 58.01; H, 3.75. $C_{14}H_9BrO_2$ requires C, 58.16; H, 3.14%.

1-(Naphthalen-1-yl)-2-phenylethane-1,2-dione (4ag): Method A. Column chromatography with 32:1 cyclohexane-AcOEt afforded **4ag**[6i,12c] (95 mg, 73%) slightly contaminated by uncharacterized by-products. Method B. For the synthesis of **4ag** three equiv. of aldehyde **2g** were used and the benzoin reaction was performed at 50 °C. Column chromatography with 1.7:1 cyclohexane-CH_2Cl_2 afforded **4ag**[6i,12c] (104 mg, 40%) slightly contaminated by uncharacterized by-products. ^{1}H NMR: δ = 9.30 (d, *J* = 8.5 Hz, 1 H, Ar), 8.13 (d, *J* = 8.5 Hz, 1 H, Ar), 8.07-7.98 (m, 2 H, Ar), 7.98-7.85 (m, 2 H, Ar), 7.81-7.70 (m, 1 H, Ar), 7.70-7.57 (m, 2 H, Ar), 7.57-7.47 (m, 3 H, Ar); ^{13}C NMR: δ = 197.2, 194.6, 136.0, 135.1, 134.7, 134.1, 133.3, 130.9, 130.0, 129.5, 129.0, 128.8, 127.2, 127.1, 125.9, 124.4. ESI-MS (260.3): 312.5 [M + K]$^+$.

1-Phenyl-2-(o-tolyl)ethane-1,2-dione (4ah): Method A. Column chromatography with 40:1 cyclohexane-AcOEt afforded **4ah**[6e] (95 mg, 85%) as a yellow solid (mp 56-57 °C). Method B. For the synthesis of **4ah** three equiv. of aldehyde **2h** were used and the benzoin reaction was performed at 50 °C. **4ah**[6e] (163 mg, 73%). ^{1}H NMR: δ = 8.01-7.93 (m, 2 H, Ar), 7.70-7.59 (m, 2 H, Ar), 7.55-7.45 (m, 3 H, Ar), 7.37-7.25 (m, 2 H, Ar), 2.70 (s, 3 H, CH_3); ^{13}C NMR: δ = 196.8, 194.9, 141.4, 134.7, 133.8, 133.12, 132.6, 131.8, 130.0, 129.1, 126.1, 22.0. ESI-MS (224.2): 225.6 [M + H]$^+$. HRMS (ESI) *m/z* calcd for $C_{15}H_{13}O_2$ [M + H]$^+$ 225.0916, found 225.0948. Found: C, 80.61; H, 5.90. $C_{15}H_{12}O_2$ requires C, 80.34; H, 5.39%.

1-(2-Methoxyphenyl)-2-phenylethane-1,2-dione (4ai): Method A. Column chromatography with 15:1 cyclohexane-AcOEt afforded **4ai**[7c] (84 mg, 70%) as a white amorphous solid. Method B. For the synthesis of **4ai** three equiv. of aldehyde **2i** were used and the benzoin reaction was performed at 50 °C. Column chromatography with 1.6:1 cyclohexane-CH_2Cl_2 afforded **4ai**[7c] (108 mg, 45%). ^{1}H NMR: δ = 8.06-7.99 (m, 1 H, Ar), 7.96-7.89 (m, 2 H, Ar), 7.65-7.54 (m, 2 H, Ar), 7.54-7.44 (m, 2 H, Ar), 7.16-7.08 (m, 1 H, Ar), 6.93 (d, *J* = 8.5 Hz, 1 H, Ar), 3.56 (s, 3 H, CH_3); ^{13}C NMR: δ = 194.6, 193.5, 160.4, 136.5, 133.8, 132.9, 130.5, 129.3, 128.7, 123.8, 121.5, 112.3, 55.7. ESI-MS (240.2): 263.8 [M + Na]$^+$. HRMS (ESI) *m/z* calcd for $C_{15}H_{12}O_3$ [M]$^+$ 240.0786, found 240.0711. Found: C, 74.77; H, 5.27. $C_{15}H_{12}O_3$ requires C, 74.99; H, 5.03%.

1-(3-Bromophenyl)-2-(4-bromophenyl)ethane-1,2-dione (4bf): Method A. Column chromatography with 1:1 cyclohexane-CH_2Cl_2 afforded **4bf** (158 mg, 87%) as a yellow amorphous solid. Method B. For the synthesis of **4bf** 6 mL of solvent were used in the benzoin reaction: **4bf** (269 mg, 73%).

^{1}H NMR: δ = 8.11 (t, J = 1.8 Hz, 1 H, Ar), 7.90-7.76 (m, 4 H, Ar), 7.71-7.63 (m, 2 H, Ar), 7.40 (t, J = 7.9 Hz, 1 H, Ar); ^{13}C NMR: δ = 192.1, 191.9, 137.7, 134.2, 132.31, 131.1, 130.6, 130.5, 130.4, 128.4, 123.2. ESI-MS (368.0): 391.5 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{14}H_9Br_2O_2$ [M + H]$^+$ 366.8969, found 366.8911. Found: C, 45.90; H, 2.55. $C_{14}H_8Br_2O_2$ requires C, 45.69; H, 2.19%.

1-(4-Bromophenyl)-2-(o-tolyl)ethane-1,2-dione (4bh): Method A. Column chromatography with 1.5:1 cyclohexane-CH$_2$Cl$_2$ afforded **4bh** (92 mg, 61%) as a yellow amorphous solid. Method B. For the synthesis of **4bh** 6 mL of solvent and three equiv. of aldehyde **2h** were used in the benzoin reaction that was performed at 50 °C: **4bh** (109 mg, 36%). ^{1}H NMR: δ = 7.88-7.80 (m, 2 H, Ar), 7.70-7.63 (m, 2 H, Ar), 7.63-7.56 (m, 1 H, Ar), 7.54-7.46 (m, 1 H, Ar), 7.37-7.26 (m, 2 H, Ar), 2.69 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 196.1, 193.6, 141.5, 134.0, 133.0, 132.6, 132.4, 131.8, 131.5, 131.3, 130.3, 126.1, 21.9. ESI-MS (303.1): 326.8 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{15}H_{11}BrNaO_2$ [M + Na]$^+$ 324.9840, found 324.9814. Found: C, 59.81; H, 3.12. $C_{15}H_{11}BrO_2$ requires C, 59.43; H, 3.66%.

1-(3-Bromophenyl)-2-(p-tolyl)ethane-1,2-dione (4cf): Method A. Column chromatography with 25:1 cyclohexane-AcOEt afforded **4cf**[8d] (113 mg, 75%) as a yellow amorphous solid. Method B. For the synthesis of **4cf** two equiv. of α-diketone **1c** were used. Column chromatography with 1.6:1 cyclohexane-CH$_2$Cl$_2$ afforded **4cf**[8d] (188 mg, 62%). ^{1}H NMR: δ = 8.11 (t, J = 1.7 Hz, 1 H, Ar), 7.90-7.82 (m, 3 H, Ar), 7.80-7.73 (m, 1 H, Ar), 7.42-7.34 (m, 1 H, Ar), 7.34-7.28 (m, 2 H, Ar), 2.44 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 193.1, 192.8, 146.3, 137.4, 134.6, 132.3, 130.3, 130.0, 129.9, 129.6, 128.3, 123.1, 21.8. ESI-MS (303.1): 304.4 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{15}H_{11}BrO_2$ [M]$^+$ 301.9942, found 301.9976. Found: C, 59.21; H, 3.88. $C_{15}H_{11}BrO_2$ requires C, 59.43; H, 3.66%.

1-(o-Tolyl)-2-(p-tolyl)ethane-1,2-dione (4ch): Method A. Column chromatography with 10:1 cyclohexane-AcOEt afforded **4ch** (87 mg, 73%) as a white amorphous solid. Method B. For the synthesis of **4ch** three equiv. of aldehyde **2h** were used in the benzoin reaction that was performed at 50 °C. Column chromatography with 1.3:1 cyclohexane-CH$_2$Cl$_2$ afforded **4ch** (83 mg, 35%). ^{1}H NMR: δ = 7.86 (d, J = 8.2 Hz, 2 H, Ar), 7.63 (dd, J = 7.8, 1.1 Hz, 1 H,Ar), 7.48 (dt, J = 7.6, 1.3 Hz, 1 H, Ar), 7.36-7.26 (m, 4 H, Ar), 2.70 (s, 3 H, CH$_3$), 2.44 (s, 3 H, CH$_3$); ^{13}C NMR: δ = 197.0, 194.7, 146.0, 141.4, 133.7, 133.1, 132.6, 131.9, 130.1, 129.8, 128.8, 126.0, 22.0. ESI-MS (238.28): 239.5 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{16}H_{15}O_2$ [M + H]$^+$ 239.1072, found 239.1080. Found: C, 80.41; H, 5.78. $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.92%.

1-Phenyl-2-(2-(trifluoromethyl)phenyl)ethane-1,2-dione (4aj): Method A. Column chromatography with 12:1 cyclohexane-AcOEt afforded **4aj**[6j] (114 mg, 82%) as a yellow amorphous solid. Method B: **4aj**[6j] (167 mg, 60%). ^{1}H NMR: δ = 8.12-8.06 (m, 2 H, Ar), 7.84-7.78 (m, 1 H, Ar), 7.76-7.62 (m, 4 H, Ar), 7.60-7.50 (m, 2 H, Ar); ^{13}C NMR: δ = 193.1, 191.0, 134.9, 134.6, 132.5, 132.1, 131.4, 130.9, 129.0, 128.6, 127.2, 127.2, 124.9, 122.1; ^{19}F NMR (376 MHz): δ = -57.9 (s, 3 F, CF$_3$). ESI-MS (278.2): 279.5 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{15}H_9F_3O_2$ [M]$^+$ 278.0555, found 278.0511. Found: C, 64.98; H, 3.12. $C_{15}H_9F_3O_2$ requires C, 64.75; H, 3.26%.

1-(2-Bromophenyl)-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (4dc): Method A. Column chromatography with 35:1 cyclohexane-AcOEt afforded **4dc** (179 mg, 77%) as a yellow foam. Method B. For the synthesis of **4dc** three equiv. of aldehyde **2c** were used in the benzoin reaction. Column chromatography with 1.3:1 cyclohexane-CH$_2$Cl$_2$ afforded **4dc** (182 mg, 51%). ^{1}H NMR: δ = 8.24-8.16 (m, 2 H, Ar), 7.84-7.76 (m, 3 H, Ar), 7.66-7.60 (m, 1 H, Ar), 7.55-7.44 (m, 1 H, Ar); ^{13}C NMR: δ = 193.7, 190.0, 136.0, 135.7, 135.0, 135.4, 134.8, 133.7, 133.6, 132.6, 132.7, 131.7, 130.8, 130.5, 129.2, 128.1, 128.0, 126.1, 126.0, 125.9, 125.8, 124.9, 122.2, 121.9 ; ^{19}F NMR (376 MHz): δ = -63.3 (s, 3 F, CF$_3$). ESI-MS (357.1): 380.4 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{15}H_8BrF_3NaO_2$ [M + Na]$^+$ 378.9557, found 378.9511. Found: C, 50.12; H, 2.66. $C_{15}H_8BrF_3O_2$ requires C, 50.45; H, 2.26%.

1-(Furan-2-yl)-2-phenylethane-1,2-dione (4am): Method A. Column chromatography with 12:1 cyclohexane-AcOEt afforded **4am**[10] (17 mg, 17%) as a yellow oil. Method B: **4am**[10] (22 mg, 11%). ^{1}H NMR: δ = 8.06-8.00 (m, 2 H, Ar), 7.78-7.75 (m, 1 H, Ar), 7.70-7.62 (m, 1 H, Ar), 7.55-7.46 (m, 2 H, Ar), 7.42-7.38 (m, 1 H, Ar), 6.65-6.58 (m, 1 H, Ar); ^{13}C NMR: δ = 191.7, 180.2, 149.8, 149.2, 134.5, 132.2, 130.0, 128.8, 123.1, 112.7; ESI-MS (200.2): 201.5 [M]$^+$. HRMS (ESI) m/z calcd for $C_{12}H_8O_3$ [M]$^+$ 200.0473, found 200.0412. Found: C, 69.78; H, 3.88. $C_{12}H_8O_3$ requires C, 72.00; H, 4.03%.

1-(2-Chlorophenyl)-2-(pyridin-2-yl)ethane-1,2-dione (4eb): Method A. Column chromatography with 4:1 cyclohexane-AcOEt afforded **4eb** (31 mg, 25%) as a yellow amorphous solid. Method B: **4eb** (51 mg, 21%). ^{1}H NMR: δ = 8.74-8.68 (m, 1 H, Ar), 8.24-8.18 (m, 1 H, Ar), 8.14-8.06 (m, 1 H, Ar), 8.00-7.90 (m, 1 H, Ar), 7.60-7.30 (m, 4 H, Ar); ^{13}C NMR: δ = 193.6, 191.7, 150.0, 149.3, 135.0, 132.6, 135.0, 130.3, 129.0, 123.5, 113.1 ESI-MS (245.7): 246.8 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{13}H_8ClNO_2$ [M]$^+$ 245.0244, found 245.0216. Found: C, 63.70; N, 5.12; H, 3.41. $C_{13}H_8ClNO_2$ requires C, 63.56; N, 5.70; H, 3.28%.

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Notes and references

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