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Multicomponent Reactions

Scalable Multicomponent Synthesis of (Hetero)aryl-Substituted Phenyls: Focus on Metal-Free Halogenated Biaryls, 3-Arylindoles, and Isourolithine A Synthesis

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Dedicated to Professor Lucio Minuti on occasion of his retirement.

Abstract: In the context of the growing interest of the scientific community for the development of sustainable synthetic strategies to access aromatic structures, we present a practical and metal-free approach to (hetero)biaryls which exploits the advantages of multicomponent reactions in sustainable solvents. *In situ* acid-catalysed generation of (hetero)aryl acetoxy dienes from the corresponding (hetero)arylidene acetones in a metal vessel, followed by Diels-Alder reaction using an electron-poor alkyne as dienophile, delivers the expected aromatic products after final oxidation of the cycloadduct. This protocol has been demonstrated as a convenient alternative to the previously reported synthetic strategies, considering its scalability and environmental sustainability and the low cost of substrates and equipment. Moreover, it has been successfully applied to the metal-free regioselective synthesis of (hetero)aryl-substituted-phenyls, 2-unsubstituted-3-aryl-indoles, and to the total synthesis of isourolithine A.

Introduction

In current organic chemistry, the synthetic routes to aromatic targets mostly rely on the use of transition metal catalysts.[1–4] However, the ever-growing concerns about the transition metals exhaustibility[5] and toxicity[6] encouraged the exploration of efficient metal-free alternatives[7] which are able to meet the current standards for residual metal traces in pharmaceutical[8] and electronic[9] industry.

In particular, great attention has been given to the development of metal-free approaches to biaryls[7,10] and heterobiaryls, considering the importance of these scaffolds in several fields, ranging from their use as ligands in organic synthesis[11–13] to their predominance in pharmacologically active natural[14–16] and synthetic compounds.[17–20] Moreover, thanks to their electronic properties, (hetero)biaryls play a key role in current research on electronic materials[21,22] and liquid crystals[23] (Figure 1).

There is no doubt that the most common strategies to construct a biaryl scaffold involve transition metal-catalysed reactions.[24] However, beyond the above mentioned general considerations on the use of these catalysts, the limited substituents tolerance, with specific reference to the presence of extra halogens, strongly contributes to incentive the development of alternative methods to prepare halogenated biaryls, although some sporadic transition metal-catalysed[25–30] and metal free[7,31] strategies with limited scope have already been reported.

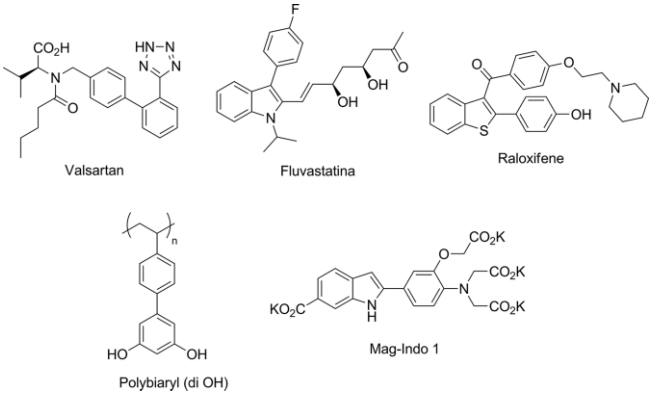

Figure 1. Examples of (hetero)biaryl-containing drugs and functional materials.

Our research group has recently identified high pressure-promoted Diels-Alder reaction as a key step to accomplish metal-free synthesis of biaryls, even achieving the total synthesis of biaryl-containing biologically active natural compounds in a few steps.[32,33] Coupling this strategy with the advantages of multicomponent reactions to generate in situ an electron-rich diene, a palette of functionalised aromatics has been prepared under hyperbaric conditions.[34,35]

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Unfortunately, the expensive high-pressure apparatus is not so common in organic chemistry laboratories and it requires properly trained users. In addition, hyperbaric reactions do not match the growing interest of the scientific community towards scalable procedures, which are potentially relevant to industrial applications when enabling the economical, environmentally benign, and safe manufacturing of large amounts of compounds.

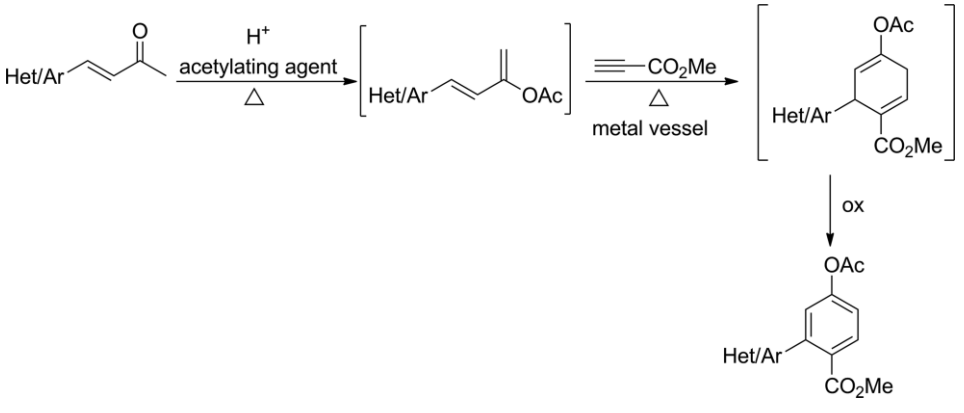
Therefore, we planned a novel synthetic strategy, identifying an alternative metal-free activation method for the Diels-Alder reaction in order to avoid the use of a high-pressure apparatus. Considering that metal-free thermal activation of electron-poor alkynes in Diels-Alder reactions for biaryls synthesis has already been demonstrated to be an achievable target,[36–41]a cheap metal vessel seemed to be a convenient option to export the advantages of a hyperbaric multicomponent protocol to industrial plants and less equipped laboratories. In contrast with other systems requiring glass vessels, like microwave and Q-tube,[42] metal vessels can bear higher pressures and they are usually equipped with a safety gauge. Indeed, a wide range of metal vessels with different capability, pressure and temperature rating, corrosion resistance, and design features are commercially available and in-house construction of pressure vessels for laboratory use is also possible.

We also planned to address the solvent choice concerns to satisfy the updated green chemistry standards.[43] Balancing the requirements of polarity and solubility with hazard parameters and toxicological risks is not always easy but, in general, the substitution of chlorinated solvents with an environmental sensitive alternative is always considered a wise choice.[44]

Consequently, a systematic screening of the best reaction conditions to perform a multicomponent acid-catalysed enol-acetylation of (hetero)arylidene acetones followed by Diels-Alder reaction with an electron-poor alkyne was performed in a metal vessel. This involved the in situ generation of an electron-rich acetoxy diene which was then reacted with methyl propiolate in a thermal Diels-Alder reaction. Oxidation of the resulting cycloadduct allowed to obtain the corresponding aromatic products (Scheme 1).Excepting the reports involving dimethyl acetylenedicarboxylate,[45–47] which deliver products with two identical substituents, the use of methyl propiolate as dienophile in metal-free Diels-Alder reactions is still a fertile field of research under hyperbaric, thermal and microwave activation,[48–50] due to the scarce reactivity of this compound with consequently unsatisfying yields.[51]

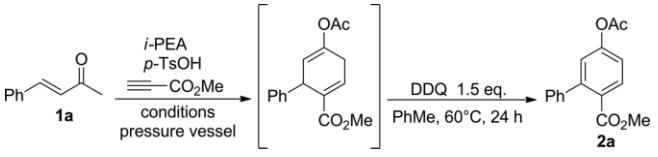
Results and Discussion

A mixture of commercially available (3*E*)-4-phenyl-but-3-en-2-one **1a**, *p*-toluenesulfonic acid (*p*TsOH), isopropenyl acetate (*i*PEA), and methyl propiolate was chosen as a model system to test the efficiency of our synthetic idea. First of all, the reaction mixture was refluxed in dichloromethane (DCM) using a standard glassware apparatus for 48 h (Table 1, Entry 1). GC–MS analysis of the crude mixture showed the presence of unreacted **1a** and the corresponding enol acetate intermediate in 1:1 ratio, as well as traces of **2a**. Next, the reaction was carried out under hyperbaric conditions in a DCM filled Teflon vial (Entry 2) following a previously reported procedure.[34] The substrate was regioselectively converted into the corresponding 2,5-substituted cycloadduct which was quickly filtered through a silica pad and oxidised with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[52] to give biaryl **2a** in good yield. Then, the reaction was performed at 110 °C in a metal vessel using *i*PEA as solvent with slightly better results (Entry 3) but decreasing the amount of alkyne to 1.2 equiv. to improve the reaction atom economy halved the final yield (Entry 4). Using a combination of DCM and *i*PEA (6 equiv.) as co-solvents reported the average yield of the previous experiments (Entry 5), confirming the possibility to obtain good results using just a slightly over stoichiometric amount of alkyne in the right solvent. An attempt to reduce reaction times did not allow the multicomponent reaction completion even if 1.5 equiv. of alkyne and 10 equiv. di *i*PEA were used (Entry 6). In order to induce the full conversion of the substrate, the temperature was raised to 145 °C (oil bath temperature) for 48 h, yielding **2a** in good yield after oxidation with no trace of unreacted **1a** (Entry 7). Using 1 equiv. of *p*TsOH did not allow the reaction completion in 24 h, as unreacted **1a** and enol acetate intermediate were detected in 1:1 ratio (Entry 8). This result confirmed that the Diels-Alder reaction is effectively the limiting step of the synthetic sequence. Next, we looked for an alternative solvent, in order to replace toxic DCM. PhMe did not allow the substrate conversion (Entry 9), possibly due to the scarce solubility of *p*TsOH in this



Scheme 1. Thermal activation of alkynes in multicomponent metal-free synthesis of (hetero)aryl-substituted phenyls in metal vessel.

Table 1. Optimisation of the multicomponent enolacetylation-cycloaddition sequence in metal vessel. Conditions: **1a**, 1 equiv., 0.33 M; *p*TsOH 0.04 equiv.



Entry	Solvent	*i*PEA[equiv.]	Methyl propiolate [equiv.]	Oil bath [°C]	t [h]	**2a** isolated yield [%][a]
1	DCM	5	3	85	48	Traces[b,c]
2	DCM	5	3	40	68	45[d]
3	*i*PEA	–	3	110	24	53
4	*i*PEA	–	1.2	110	36	25
5	DCM	6	1.2	110	24	48
6	DCM	10	1.5	110	36	48[e]
7	DCM	10	1.5	145	48	56
8	DCM	10	1.5	145	48	Traces[c,f]
9	PhMe	10	1.5	145	48	0
10	Me_2CO_3	10	1.5	145	48	60[g]
11	EtOAc	10	1.5	145	48	54
12	EtOAc	10	1.5	145	24	67[h,i]
13	EtOAc	10	1.5	40	68	42[d,h,i]
14	Ac_2O	–	1.5	145	68	50[e,h,i,j]
15	EtOAc	10	1.5	145	6	20[k]

[a] Enolisation-cycloaddition-aromatisation overall yield. [b] Refluxing glassware apparatus. [c] Unreacted **1a** and enolacetate intermediate were detected in 1:1 ratio. [d] Teflon vial, 9 kbar. [e] Unreacted **1a** was recovered. [f] 1 equiv. of *p*TsOH was employed. [g] 4:1 Mixture of **2a** and its methoxycarbonyl analogue. [h] **1a**Concentration 0.2 M. [i] EtOAc was used as oxidation solvent. [j] Diels-Alder cycloadduct yield calculated by GC–MS. [k] Microwave irradiation 260 watts in a 10 mL glass vial.

solvent. Me_2CO_3, instead, delivered an inseparable 4:1 mixture of **2a** and its corresponding methoxycarbonyl analogue in 60 % overall yield (Entry 10). Good results were achieved using EtOAc as solvent (Entry 11) and further improvement of the reaction yield was achieved decreasing **1a** concentration from 0.33 M to 0.2 M and using EtOAc as solvent also in the oxidation step (Entry 12). To disprove any influence of metal particles leakage from the metal vessel walls, a Teflon chamber was charged with the reaction mixture and placed inside the metal vessel, thus avoiding any contact between the reaction mixture and the metal walls of the vessel. Interestingly, no substantial change in **2a** yield was observed (65 % isolated yield, results not shown). EtOAc under hyperbaric conditions (Entry 13) did not deliver better results compared to the same reaction in metal vessel (Entry 12) and the hyperbaric reaction in DCM (Entry 2). Performing the reaction in acetic anhydride as both acylating agent and solvent only lead to 50 % conversion of **1a** into the corresponding cycloadduct calculated by GC–MS (Entry 14). In order to compare autoclave and microwave activation, the reaction was also carried out in a glass vial under microwave irradiation (260 watts for 6 h) (Entry 15). GC–MS analysis of the crude mixture showed the massive presence of a cyclohexene by-product derived by Diels-Alder reaction between the enol acetate intermediate and **1a**. Moreover, unreacted **1a,** enol acetate intermediate, and the expected cycloadduct **2a** (20 % global yield) were also detected.

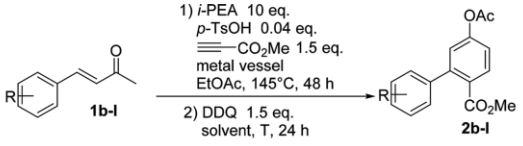
Hypothesising a dual contribution to the reaction activation, combining thermal and hyperbaric factors due to the heating of a solution in a closed vessel, another experiment using the reaction conditions described in Table 1, Entry 12 was carried out in a metal vessel equipped with a pressure gauge. In this way it was possible to assess that the pressure inside the vessel ranged between 3 and 5 bar during the reaction, thus confirming the potential dual activation theory but suggesting a scarce contribution from the pressure generated inside the vessel.

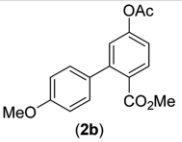
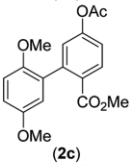
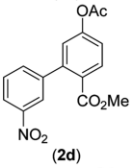
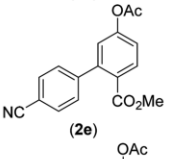
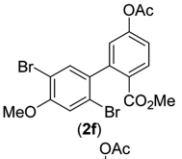
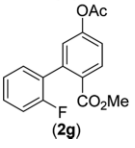
Unfortunately, any attempt to extend the protocol to disubstituted alkynes was not successful. Substrate **1a** and methyl pentynoate did not react at all under hyperbaric conditions described in Table 1, Entry 1. The reaction conditions reported in Table 1, Entry 12 using a metal vessel only lead to the formation of the enol acetate intermediate and its Diels-Alder reaction with the alkene moiety of **1a** to give the cyclohexene by-product, without any participation of the alkyne. In order to promote the Diels-Alder reaction, the mixture was heated to 195 °C but complete decomposition of the substrate was observed.

After the reaction conditions screening, we tested the versatility of our protocol using variously functionalised benzylidene acetones **1** under the conditions reported in (Table 1, Entry 12). Appreciable results were obtained when electron-donating (Table 2, Entries1–2) or electron-withdrawing **(**Entries 3–4) substituents or both (Entry5) were present on the aromatic ring of the arylidene acetone. Unfortunately, the presence of electron-withdrawing substituents did not allow the oxidation reaction to being complete in 24 h in EtOAc but a simple switch to PhMe allowed to achieve this goal in the desired time. It is worthy to note that this protocol allowed the synthesis of biaryls bearing every kind of halogens (Entries 6–9) and even multiple halogen atoms (Entry 10) or a combination of different halogens (Entry 11). This objective is not easy to achieve using common metal-free synthetic strategies, not to mention the

chemoselectivity issues arising when using transition-metal mediated reactions.

Table 2. Substrate scope exploration.



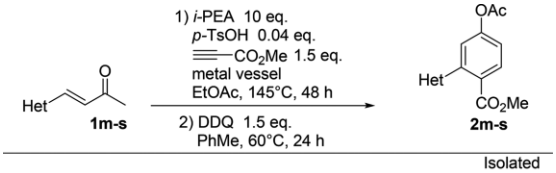
Entry	Butenone (-R)	Oxidation solvent	Oil bath oxidation T (°C)	Biaryl **2**	Isolated yield (%)[a]
1	4-OMe (**1b**)	EtOAc	60	 (**2b**)	60
2	2,5-OMe (**1c**)	EtOAc	80	 (**2c**)	30
3	3-NO_2 (**1d**)	PhMe	70	 (**2d**)	51
4	4-CN (**1e**)	PhMe	60	 (**2e**)	50
5	2,5-Br, 4-OMe (**1f**)	PhMe	60	 (**2f**)	40
6	2-F (**1g**)	PhMe	60	 (**2g**)	54

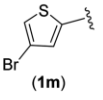
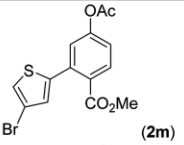
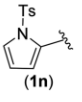
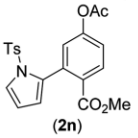
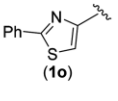
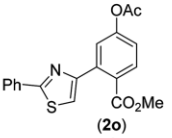
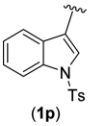
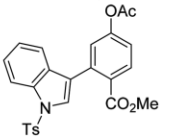
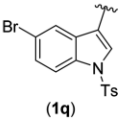
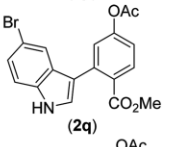
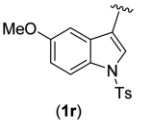
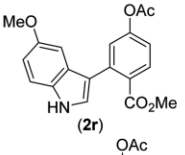
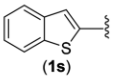
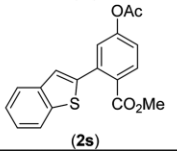
[a] Enolisation-cycloaddition-aromatisation overall yield. [b] Oxidation was completed in 45 h.

Moreover, the multigram scale-up of this protocol has been easily achieved using 15 mmol (2.7 g) of **1h** as the substrate in a 50 mL metal vessel. The expected product **2h** was obtained in 55 % overall isolated yield, thus demonstrating the scalability of the presented strategy.

The use of heteroarylidene acetones as substrates also gave satisfying results (Table 3). Firstly, five-membered aromatic rings bearing a sulfur (Entry 1) or a nitrogen (Entry 2) atom or both (Entry 3) were tested to replace the phenyl group of **1a**. All these substrates gave the expected products with total regioselectivity in good yields, although no complete conversion of substrate **1n** was achieved under the optimised reaction conditions. Secondly, the protocol was extended to benzo-fused five-membered heterocyles. Interestingly, 2-unsubstituted-3-aryl indoles were easily prepared with this strategy (Entries 4–6), delivering a scaffold of interest for medicinal chemists due to its pharmacological potential.[53–56] Bearing in mind the similar importance of 2-aryl benzothiophenes in medicinal chemistry,[57] also heterobiaryl **2s** has been prepared under the optimised reaction conditions in good yield and total regioselectivity (Entry 7).

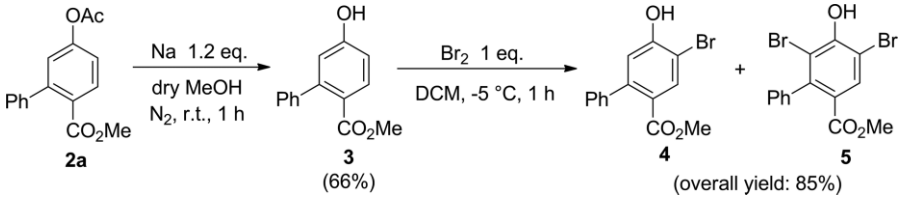
Table 3. Application of the protocol to heterobiaryls synthesis in metal vessel.



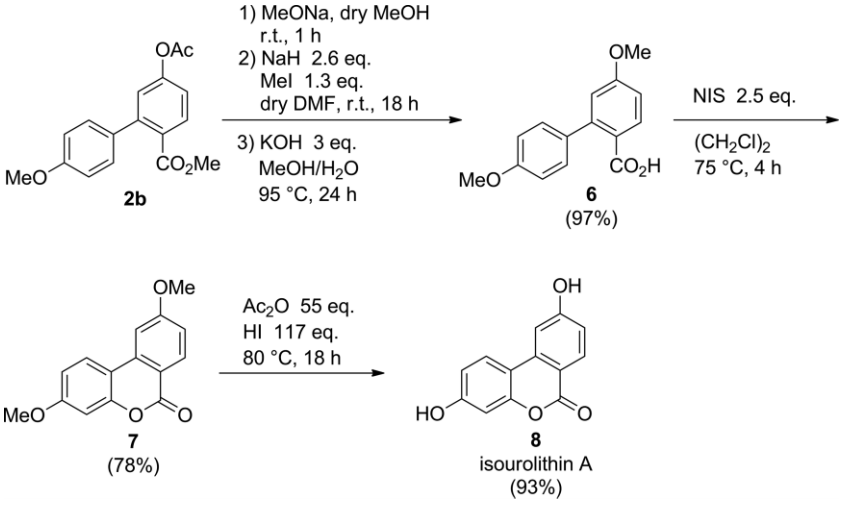
Entry	Het-	Heterobiaryl**2**	Isolated yield (%)[a]
1	 (**1m**)	 (**2m**)	72
2	 (**1n**)	 (**2n**)	43[b]
3	 (**1o**)	 (**2o**)	67
4	 (**1p**)	 (**2p**)	64
5	 (**1q**)	 (**2q**)	61
6	 (**1r**)	 (**2r**)	63[c]
7	 (**1s**)	 (**2s**)	59[c]

[a] Enolacetylation-cycloaddition-aromatisation overall yield. [b] Calculated on converted substrate. [c] Multicomponent reaction completed in 72 h.

Further functionalisation of the obtained scaffold can also be planned. As proof of concept, we decided to introduce an extra halogen on the newly constructed ring.[58] To do so, we deprotected the phenolic moiety of **2a** with sodium in dry MeOH. The resulting phenol **3** was then treated with Br_2 solution in DCM to give a mixture of mono- and di-brominated phenols **4** and **5** in 3:1 ratio (Scheme 2). Regioselective iodination of phenol **3** was attempted by treatment with *N*-iodosuccinimide



Scheme 2. Further functionalisation of the biaryl scaffold via phenol halogenation.



Scheme 3. Metal-free total synthesis of isourolithin A.

(NIS) and trifluoroacetic acid (TFA) but an inseparable 1:1 mixture of the two possible mono-*ortho*-iodinated regioisomers was obtained.

Next, we foresaw the opportunity to exploit the presented method to achieve the metal-free total synthesis of a biaryl-containing natural product. In particular, we focused on dibenzo-α-pyrone, which is a common structural motif in biologically active natural compounds.[59–62]Among all the possibilities, we were particularly intrigued by the potential use of biaryl **2b** as starting material for the synthesis of isourolithin A (Scheme 3).

Firstly, removal of the acetoxy protecting group was achieved, followed by methoxylation of the phenolic moiety and basic hydrolysis of the carbomethoxy group without isolation of the intermediates.[52] The resulting biaryl carboxylic acid **6** was converted into dimethyl isourolithin A**7** by treatment with NIS in dichloroethane.[63] Deprotection of the phenolic substituents[33] delivered the expected natural product **8** in excellent yield.

Conclusions

We have demonstrated that (hetero)aryl-substituted phenyls synthesis via thermal multicomponent enolacetylation-cycloaddition reaction, followed by cycloadducts oxidation, is possible using a simple metal vessel. The use of more sustainable reaction solvents as ethyl acetate and toluene, as well as the rational use of recyclable reagents like *i*PEA and DDQ,[64] strongly contribute to making this scalable protocol very attractive, in addition to the ready availability of equipment and starting materials. The synthetic path tolerates both electron-withdrawing and electron-donating substituents on the aromatic ring of the benzylidene acetone and it can be considered as a convenient strategy for the synthesis of halogenated biaryls as it is compatible with the presence of halogens on the starting material or their subsequent introduction on the newly built ring.

Moreover, its compatibility with heteroarylidene acetones opens the lead for the efficient metal-free synthesis of heterobiaryls with potential applications in pharmaceuticals and electronics, as highlighted by the selected substrates. The versatility of this strategy has also allowed accessing the natural compound isourolithin A in a few, high-yielding, metal-free passages.

Further exploration of other positions to create tetra- and penta-substitution pattern on the newly built ring is currently ongoing in our laboratories.

Experimental Section

Compounds purification by column chromatography was performed on silica gel (Merck 60, 70–230 mesh), and analytical TLC was carried out on pre-coated silica gel plates (Merck 60 F254, 0.25 mm) using UV light and 0.5 % w/v $KMnO_4$ aqueous solution (followed by gentle heating) for visualisation. Melting points were measured on a hot plate apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were recorded at 200 and 400 MHz. Carbon magnetic resonance (^{13}C-NMR) spectra were recorded at 50.3 and 100.6 MHz. Chemical shifts (δ) are reported in

parts per million (ppm). The NMR spectra were calibrated using the proton or carbon signals of residual non-deuterated solvent peaks: δ_H = 7.27 and δ_C7 = 7.0 for $CDCl_3$, δ_H = 2.54 and δ_C = 40.4 for $(CD_3)_2SO$. Infrared (IR) spectra were recorded with a FT-IR instrument, using a diffuse reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). GC–MS analysis were obtained with a gas chromatograph (HP-5MS capillary column 29.0 m, ID 0.25, film 0.25 μm) equipped with a mass selective detector at an ionising voltage of 70 eV. Combustion analyses were carried out on an elemental analyser. Hyperbaric experiments were conducted with a Unipress LV30/16 apparatus while metal vessel experiments were carried out in a home-made pressure vessel (stainless steel AISI 304). IUPAC names of compounds were generated with ACD/Name.

Benzylidene acetones **1a**, **1g–h** and **1k** are commercially available. Benzylidene acetones **1b-d** and **1j** were prepared by base-catalysed aldol condensation with acetone from the corresponding aldehydes.[34] (Hetero)arylidene acetones **1e–f** and **1l–s** were prepared by Wittig reaction with 1-(triphenylphosphoranylidene)propan-2-one from the corresponding aldehydes.[34] Characterisation data for (hetero)arylidene acetones **1b**,[65] **1c–e**,[34] **1i–j**,[34] **1m**,[34] **1n**,[66] and **1o**[34] matched the ones previously reported in literature for these compounds.

(3E)-4-(3,5-Dibromo-4-methoxyphenyl)but-3-en-2-one (1f): Eluent EtOAc/Hex, 30:70; light yellow solid (98 % isolated yield), m.p. 99–103 °C. IR (KBr): $\tilde{\nu}$ = 2930, 1692, 1665, 1609, 1475, 1261, 979, 741 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.68 (s, 2H, ArH); 7.32 (d, 1H, *J* = 16.2 Hz, =CH); 6.62 (d, 1H, *J* = 16.2 Hz, =CH); 3.90 (s, 3H, OCH_3); 2.37 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 197.5, 155.5, 139.5, 133.1, 132.1 (2C), 128.2, 118.8 (2C), 60.8, 27.9 ppm. MS: *m/z* (%) = 334 (53) $[M]^+$, 319 (81), 353 (26), 238 (71), 195 (15), 167 (30), 116 (38), 101 (22), 88 (33), 74 (29), 62 (35), 43 (100). $C_{11}H_{10}Br_2O_2$ (334): calcd. C 39.56, H 3.02; found C 39.29, H 3.13.

(3*E*)-4-(2-Bromo-4-chlorophenyl)but-3-en-2-one (1l): Eluent Et_2O/Hex, 20:80; colorless oil (89 % isolated yield). IR (KBr): $\tilde{\nu}$ = 3089, 2927, 1690, 1466, 1259, 1101, 864, 733 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.82 (d, 1H,*J* = 16.3 Hz, =CH); 7.64 (d, 1H, *J* = 2.2 Hz, ArH); 7.56 (d, 1H, *J* = 8.3 Hz, ArH); 7.34 (dd, 1H, *J* = 8.3, 2.2 Hz, ArH); 6.61 (d, 1H,*J* = 16.3 Hz, =CH); 2.43 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 198.0, 140.5, 136.5, 133.0, 132.9, 129.9, 128.3, 128.2, 125.7, 27.3 ppm. MS: *m/z* (%) = 260 (4) $[M]^+$, 258 (3), 245 (10), 181 (34), 179 (100), 138 (13), 136 (38), 99 (15), 75 (16). $C_{10}H_8BrClO$ (259): calcd. C 46.28, H 3.11; found C 46.50, H 3.34.

(3*E*)-4-{1-[(4-Methylphenyl)Sulfonyl]-1*H*-indol-3-yl}but-3-en-2-one (1p):[67] IR (KBr): $\tilde{\nu}$ = 3113, 3054, 1688, 1605, 1444, 1373, 1174, 1127, 966, 809, 752 cm^{-1}. ^{13}C-NMR (50.3 MHz, $CDCl_3$):δ = 198.2, 145.6, 135.5, 134.5, 130.1 (2C), 128.8, 127.9, 127.1, 126.9 (2C), 125.5, 124.1, 120.6, 118.1, 113.8, 27.5, 21.6 ppm.

(3*E*)-4-{5-Bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}but-3-en-2-one (1q): Eluent EtOAc/Hex, 30:70; light yellow oil (63 % isolated yield). IR (KBr): $\tilde{\nu}$ = 3136, 3067, 1656, 1435, 1374, 1158, 972, 821, 798, 706 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.97–7.85 (m, 3H, ArH); 7.79 (d, 2H,*J* = 8.4 Hz, ArH); 7.57 (d, 1H, *J* = 16.4 Hz, =CH); 7.48 (dd, 1H, *J* = 8.8, 1.8 Hz, ArH); 7.28 (d, 2H, *J* = 8.4 Hz, ArH); 6.76 (d, 1H,*J* = 16.4 Hz, =CH); 2.37 (s, 3H, CH_3); 2.33 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 198.0, 145.9, 134.2, 134.1, 133.6, 130.2 (2C), 129.6, 129.5, 128.5, 127.3, 126.9 (2C), 123.4, 117.7, 117.3, 115.1, 27.6, 21.6 ppm. MS: *m/z* (%) = 419 (49) $[M]^+$, 417 (48), 281 (12), 264 (39), 262 (36), 183 (39), 155 (62), 91 (100). $C_{19}H_{16}BrNO_3S$ (418): calcd. C 54.55, H 3.86, N 3.35; found C 54.69, H 4.03, N 3.30.

(3*E*)-4-{5-Methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}but-3-en-2-one (1r): Eluent EtOAc/Hex, 20:80; white solid (82 % isolated yield). M.p.58–60 °C. IR (KBr): $\tilde{\nu}$ = 3116, 2954, 2837, 1661, 1602, 1438, 1377, 1173, 978, 887, 809 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, 1H,*J* = 9.1 Hz, ArH); 7.86 (s, 1H, ArH); 7.78 (d, 2H,*J* = 8.4 Hz, ArH); 7.62 (d, 1H, *J* = 16.3 Hz, =CH); 7.32–7.16 (m, 3H, ArH); 7.01 (dd, 1H, *J* = 9.1, 2.5 Hz, ArH); 6.77 (d, 1H,*J* = 16.3 Hz, = CH); 3.86 (s, 3H, OCH_3); 2.41 (s, 3H, CH_3); 2.36 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 198.2, 156.9, 145.5, 134.5, 134.4, 130.1, 130.0 (2C), 129.1, 129.0, 126.8 (2C), 126.7, 118.0,114.6, 114.3, 103.2, 55.7, 27.5, 21.1ppm.MS: *m/z* (%) = 369 (64) $[M]^+$, 341 (17), 281 (15), 214 (100), 207 (74), 199 (20), 171 (55), 156 (13), 143 (10), 91 (37), 73 (31). $C_{20}H_{19}NO_4S$ (369): calcd. C 65.02, H 5.18, N 3.79; found C 64.90, H 5.01, N 3.66.

(3*E*)-4-(1-Benzothien-2-yl)but-3-en-2-one (1s):[68] Eluent Et_2O/Hex, 20:80; light yellow oil (66 % isolated yield). IR (KBr): $\tilde{\nu}$ = 3056, 2927, 2867, 1666, 1638, 1612, 1360, 1263, 1144, 955, 818, 751, 727 cm^{-1}. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 197.5, 140.1, 139.6, 139.4, 136.1, 129.3, 127.7, 126.3, 124.8, 124.3, 122.4, 27.8 ppm. MS: *m/z* (%) = 202 (68) $[M]^+$, 187 (100), 159 (24), 115 (57), 89 (10). $C_{12}H_{10}OS$ (202): calcd. C 71.25, H 4.98; found C 71.47, H 5.19.

General Procedure for Multicomponent Reaction in Metal Vessel and Oxidation Reaction: A solution of (hetero)arylidene acetone **1** (1 mmol, 1 equiv.), *i*PEA (10 mmol, 10 equiv.), *p*TsOH (0.04 mmol, 0.04 equiv.) and methyl propiolate (1.5 mmol, 1.5 equiv.) in 4 mL of EtOAc was placed in an 8 mL metal vessel. The vessel was closed, placed in an oil bath and stirred at 145 °C for 48 h. The cooled mixture was filtered through a silica pad and the solvent was evaporated. The crude residue was dissolved in 10 mL of EtOAc or PhMe (see Table 2 and Table 3) and 1.5 mmol of DDQ (1.5 equiv.) were added. The mixture was stirred under the conditions reported in Table 2 and Table 3 for the appropriate reaction time. The mixture was poured into a saturated aqueous solution of Na_2HCO_3 and extracted twice with EtOAc. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel to give pure product **2**. Characterisations data for compounds **2c–e**, **2h–j**, **2m** and **2o** matched the ones previously reported in literature for these compounds.[34]

Methyl 5-(Acetyloxy)biphenyl-2-carboxylate (2a): Eluent EtOAc/Hex, 20:80; yellow oil (64 %overall isolated yield). IR (KBr): $\tilde{\nu}$ = 3029, 2950, 1765, 1730, 1601, 1286, 1206, 928, 766 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 7.89 (d, 1H, *J* = 8.4 Hz, ArH); 7.43–7.28 (m, 5H, ArH); 7.17 (dd, 1H, *J* = 8.4, 2.4 Hz, ArH); 7.13 (d, 1H, *J* = 2.4 Hz); 3.62 (s, 3H, OCH_3); 2.31 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.9, 168.1, 152.5, 144.5, 140.4, 131.4, 128.2 (2C), 128.1, 128.0 (2C), 127.5, 123.8, 120.3, 51.9, 21.1 ppm. MS: *m/z* (%) = 270 (29) $[M]^+$, 228 (63), 197 (100), 168 (15), 139 (29), 115 (15). $C_{16}H_{14}O_4$ (270): calcd. C 71.10, H 5.22; found C 71.37, H 5.04.

Methyl 5-(Acetyloxy)-4′-methoxybiphenyl-2-carboxylate (2b): EluentEtOAc/Hex, 30:70; yellow oil (60 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 2948, 1765, 1726, 1605, 1434, 1246, 1179, 927, 726 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.85 (d, 1H, *J* = 8.9 Hz, ArH); 7.24 (d, 2H, *J* = 8.8 Hz, ArH); 7.16 (dd, 1H, *J* = 8.9, 2.4 Hz, ArH); 7.11 (d, 1H, *J* = 2.4 Hz, ArH); 6.96 (d, 2H, *J* = 8.8 Hz, ArH); 3.85 (s, 3H, OCH_3); 3.68 (s, 3H, OCH_3); 2.34 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.9, 168.4, 159.1, 152.5, 144.1, 132.7, 131.4, 129.4 (2C), 128.1, 123.8, 119.9, 113.5 (2C), 55.2, 52.0, 21.1 ppm. MS: *m/z* (%) = 300 (69) $[M]^+$, 258 (100), 227 (97), 184 (16), 155 (11), 128 (10). $C_{17}H_{16}O_5$ (300):calcd. C 67.99, H 5.37; found C 67.80, H 5.51.

Methyl 5-(Acetyloxy)-3′,5′-dibromo-4′-methoxybiphenyl-2-carboxylate (2f): Eluent EtOAc/Hex, 20:80; yellow oil (40 % overall iso-

lated yield). IR (KBr): $\tilde{\nu}$ = 2947, 1734, 1652, 1472, 1205, 1001, 880, 741 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.76 (d, 1H, *J* = 8.5 Hz, ArH); 7.35–7.25 (m, 2H, ArH); 7.03 (dd, 1H, *J* = 8.5, 2.3 Hz); 6.90 (d, 1H, *J* = 2.3 Hz, ArH); 3.78 (s, 3H, OCH_3); 3.58 (s, 3H, OCH_3); 2.16 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.7, 167.1, 153.4, 152.7, 141.2, 138.8, 132.4 (2C), 132.0, 127.4, 123.9, 121.1, 117.5 (2C), 60.7, 52.2, 21.0 ppm. MS: *m/z* (%) = 458 (40) $[M]^+$, 416 (100), 385 (28), 306 (28). $C_{17}H_{14}Br_2O_5$ (458): calcd. C 44.57, H 3.08; found C 44.33, H 3.32.

Methyl 5-(Acetyloxy)-2′-fluorobiphenyl-2-carboxylate (2g): Eluent EtOAc/Hex, 30:70; yellow oil (54 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 2952, 1764, 1731, 1435, 1290, 1202, 930, 762 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.1 (d, 1H, *J* = 8.5 Hz, ArH); 7.41–7.11 (m, 6H, ArH); 3.69 (s, 3H, OCH_3); 2.30 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.7, 166.9, 159.1 (d, J_{C-F} = 266.2 Hz), 152.9, 138.4, 131.7, 130.25 (d, J_{C-F} = 3.1 Hz), 129.5 (d, J_{C-F} = 7.8 Hz), 128.4, 128.0, 124.5, 123.95 (d, J_{C-F}= 3.4 Hz), 120.9, 114.9 (d, J_{C-F} = 22.2 Hz), 51.9, 21.0 ppm. MS: *m/z* (%) = 288 (13) $[M]^+$, 246 (76), 227 (15), 215 (100), 186 (9), 157 (19), 133 (9). $C_{16}H_{13}FO_4$ (288): calcd. C 66.66, H 4.55; found C 66.46, H 4.71.

Methyl 5-(Acetyloxy)-2′,4′-dichlorobiphenyl-2-carboxylate (2k): EluentEtOAc/Hex, 20:80; yellow oil (45 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 2951, 1772, 1733, 1370, 1287, 1202, 929, 780 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, 1H, *J* = 8.6 Hz, ArH); 7.47 (d, 1H, *J* = 2.4 Hz, ArH); 7.36–7.17 (m, 3H, ArH); 7.02 (d, 1H, *J* = 2.4 Hz, ArH); 3.72 (s, 3H, OCH_3); 2.33 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 183.6, 181.1, 168.0, 156.1, 153.2, 148.8, 148.3, 146.9, 144.7, 143.8, 142.3, 141.8, 139.1, 136.2, 67.1, 36.1 ppm. MS: *m/z* (%) = 303 (69) $[M - Cl]^+$, 261 (100), 246 (28), 230 (9), 202 (12), 173 (13), 139 (9). $C_{16}H_{12}Cl_2O_4$ (339): calcd. C 56.66, H 3.57; found C 56.89, H 3.42.

Methyl 5-(Acetyloxy)-2′-bromo-4′-chlorobiphenyl-2-carboxylate (2l): Eluent EtOAc/Hex, 20:80; yellow oil (57 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 2951, 1765, 1726, 1469, 1369, 1201, 927, 774 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.10 (d, 1H, *J* = 8.6 Hz, ArH); 7.65 (d, 1H, *J* = 2.1 Hz, ArH); 7.36 (dd, 1H, *J* = 8.2, 2.1 Hz, ArH); 7.27 (dd, 1H, *J* = 8.6, 2.3 Hz, ArH); 7.19 (d, 1H, *J* = 8.2 Hz, ArH); 7.00 (d, 1H, *J* = 2.3 Hz, ArH); 3.71 (s, 3H, OCH_3); 2.36 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.6, 166.0, 153.0, 142.9, 140.3, 133.8, 131.9, 131.8, 130.5, 127.3, 127.1, 124.1, 123.0, 121.3 ppm. MS: *m/z* (%) = 384 (9) $[M]^+$, 342 (100), 311 (49), 202 (20) 173 (13), 139 (13). $C_{16}H_{12}BrClO_4$ (383.6): calcd. C 50.09, H 3.15; found C 50.38, H 2.92.

Methyl 4-(Acetyloxy)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}benzoate (2n): Eluent EtOAc/Hex, 30:70; yellow oil (43 % overall isolated yield, a 10 % of the starting heteroarylidene acetone was also recovered). IR (KBr): $\tilde{\nu}$ = 2954, 1766, 1723, 1369, 1291, 1188, 921, 724 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, 1H, *J* = 8.6 Hz, ArH); 7.44 (dd, 1H, *J* = 3.3, 1.7 Hz, ArH); 7.25–7.10 (m, 5H, ArH); 6.79 (d, 1H, *J* = 2.4 Hz, ArH); 7.34 (t, 1H, *J* = 3.3 Hz, ArH); 6.15 (dd, 1H, *J* = 3.3, 1.7 Hz, ArH); 3.66 (s, 3H, OCH_3); 2.37 (s, 3H, CH_3); 2.32 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 168.5, 165.9, 152.0, 144.6, 135.5, 133.7, 132.4, 131.3, 129.8, 129.5 (2C),127.2 (2C), 126.0, 122.8, 121.7, 114.9, 11.6, 52.0, 21.5, 20.0 ppm. MS: *m/z* (%) = 413 (89) $[M]^+$, 371 (18), 258 (11), 242 (36), 216 (100), 185 (39), 156 (12), 91 (43). $C_{21}H_{19}NO_6S$ (413): calcd. C 61.01, H 4.63, N 3.39; found C 61.22, H 4.80, N 3.25.

Methyl 4-(Acetyloxy)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}benzoate (2p): Eluent EtOAc/Hex, 30:70; light yellow solid (64 % overall isolated yield), m.p.58–60 °C. IR (KBr): $\tilde{\nu}$ = 2948, 1771, 1721, 1602, 1448, 1368, 1175, 1010, 963, 915, 748 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.07–7.93 (m, 2H, ArH); 7.82 (d, 2H, *J* = 8.3 Hz, ArH); 7.64 (s, 1H, ArH); 7.40–7.19 (m, 7H, ArH); 3.36 (s, 3H, OCH_3); 2.37 (s, 3H, CH_3); 2.34 (s, 3H, CH_3) ppm. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 168.9, 167.6, 152.9, 145.0, 135.1, 134.7, 134.6, 132.0, 130.2, 129.9 (2C), 128.9, 126.9 (2C), 124.9, 124.5, 124.0, 123.6, 122.7, 121.0, 119.7, 113.8, 51.9, 21.6, 21.1ppm. HRMS *m/z*: $[M + Na]^+$, ($C_{25}H_{21}NO_6SNa$) 486.09818, found 486.1000.

Methyl 4-(Acetyloxy)-2-{5-bromo-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}benzoate (2q): Eluent EtOAc/Hex, 30:70; light yellow solid (61 % overall isolated yield), m.p.145–148 °C. IR (KBr): $\tilde{\nu}$ = 3103, 2949, 1765, 1729, 1586, 1463, 1370, 1188, 1115, 965, 803, 751 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, 1H, *J* = 8.5 Hz, ArH); 7.95–7.87 (m, 1H, ArH); 7.80 (d, 2H, *J* = 8.4 Hz, ArH); 7.63 (s, 1H, ArH); 7.47–7.38 (m, 2H, ArH); 7.33–7.24 (m, 2H, ArH); 7.22 (d, 1H, *J* = 2.4 Hz, ArH); 7.17 (d, 1H, *J* = 2.4 Hz, ArH); 3.49 (s, 3H, OCH_3); 2.38 (s, 3H, CH_3); 2.35 (s, 3H, CH_3) ppm. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 168.8, 167.1, 152.9, 145.3, 134.8, 133.9, 133.3, 132.1, 131.9,130.0 (2C), 128.6, 127.8, 126.8 (2C), 125.2, 124.5, 122.5, 121.7, 121.3, 117.1, 115.2, 52.0, 21.6, 21.1 ppm. HRMS *m/z*: $[M + Na]^+$, ($C_{25}H_{20}BrNO_6SNa$) 564.00869, found 564.0099.

Methyl 4-(Acetyloxy)-2-{5-methoxy-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-3-yl}benzoate (2r): Eluent EtOAc/Hex, 30:70; yellow oil (63 % overall isolated yield), m.p. 55–57 °C. IR (KBr): $\tilde{\nu}$ = 2950, 1758, 1717, 1471, 1370, 1175, 1128, 925, 811, 751 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.99–7.88 (m, 2H, ArH); 7.78 (d, 2H, *J* = 8.3 Hz, ArH); 7.59 (s, 1H, ArH); 7.32–7.14 (m, 4H, ArH); 6.94 (dd, 1H, *J* = 9.0, 2.5 Hz, ArH); 6.75 (d, 1H, *J* = 2.5 Hz, ArH); 3.74 (s, 3H, OCH_3); 3.35 (s, 3H, OCH_3); 2.35 (s, 3H, CH_3); 2.34 (s, 3H, CH_3) ppm. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 168.9, 167.8, 156.7, 152.9, 144.8, 135.1, 134.5, 132.0, 131.2, 129.8 (2C), 129.3, 128.8, 126.8 (2C), 124.7, 124.4, 122.8, 120.9, 114.7, 114.3, 55.5, 51.2, 21.5, 21.1ppm. HRMS *m/z*: $[M + Na]^+$, ($C_{26}H_{23}BrNO_7SNa$) 516.1087, found 516.1099.

Methyl 4-(Acetyloxy)-2-(1-benzothien-2-yl)benzoate (2s): Eluent EtOAc/Hex, 30:70; yellow oil (59 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 2950, 1762, 1727, 1601, 1251, 1204, 1013, 838, 726 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.91–7.77(m, 3H, ArH); 7.44–7.27 (m, 4H, ArH); 7.23 (dd, 1H, *J* = 8.4, 2.3 Hz, ArH); 3.74 (s, 3H, OCH_3); 2.35 (s, 3H, CH_3) ppm. ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 168.8, 167.9,152.3, 141.3, 140.3, 139.8, 136.3, 131.3, 129.1,124.5, 124.1, 123.8, 123.2, 122.1, 121.5, 52.4, 21.1ppm.MS: *m/z* (%) = 326 (76) $[M]^+$, 284 (100), 253 (82), 224 (14), 195 (16), 181 (12), 152 (15). $C_{18}H_{14}O_4S$ (326): calcd. C 66.24, H 4.32; found C 66.09, H 4.47.

Synthesis of Phenol 3: To a solution of **2a** (2.4 mmol, 1 equiv.) in 20 mL of dry MeOH 2.8 mmol (1.2 equiv.) of sodium were added at r.t. under N_2 flow. After 1 h the reaction was quenched with a saturated NH_4Cl aqueous solution and extracted twice with EtOAc.The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel to give pure **3**.

Methyl 5-Hydroxybiphenyl-2-carboxylate (3): Eluent EtOAc/Hex, 20:80; yellow oil (66 % overall isolated yield). IR (KBr): $\tilde{\nu}$ = 3387, 2952, 1670, 1436, 1294, 1204, 877, 764 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 7.79 (dd, 1H, *J* = 7.2, 1.9 Hz, ArH); 7.38–7.18 (m, 6H, ArH and ArOH); 6.80–6.73 (m, 2H, ArH); 3.63 (s, 3H, OCH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 169.4, 158.9, 145.6, 141.2, 132.6, 128.1 (2C), 127.9 (2C), 127.2, 121.6, 117.9, 114.2, 52.0ppm. MS: *m/z* (%) = 228 (60) $[M]^+$, 197 (100), 141 (18), 115 (15). $C_{14}H_{12}O_3$ (228): calcd. C 73.67, H 5.30; found C 73.50, H 5.53.

Synthesis of Brominated Phenols 4 and 5: To a cooled (–5 °C) solution of **3** (0.4 mmol, 1 equiv.) in DCM (4.5 mL) a solution of Br_2 (0.4 mmol, 1 equiv.) in DCM (2 mL) was added dropwise over 30 min. After stirring for an extra hour, the mixture was diluted with EtOAc and the organic layer was washed with water and brine,

dried with $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography allowed to isolate **4** and **5** in 85 % overall isolated yield.

Methyl 4-Bromo-5-hydroxybiphenyl-2-carboxylate (4): Eluent Et_2O/Hex, 30:70; yellow oil (21 % yield). IR (KBr): $\tilde{\nu}$ = 3350, 2952, 1700, 1591, 1437, 1308, 1253, 1104, 905, 766 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.09 (s, 1H, ArH); 7.41–7.25 (m, 5H, ArH); 6.99 (s, 1H, ArH); 6.05 (br s, 1H, ArOH); 3.65 (s, 3H, OCH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 166.8, 154.5, 145.0, 140.1, 134.4, 128.0, 127.9 (2C), 127.5 (2C), 123.6, 118.1, 108.6, 51.9 ppm. MS: *m/z* (%) = 308 (77) $[M]^+$, 306 (76), 277 (99), 275 (100), 196 (75), 168 (37), 139 (52). $C_{14}H_{11}BrO_3$ (307): calcd. C 54.75, H 3.61; found C 54.49, H 3.90.

Methyl 4,6-Dibromo-5-hydroxybiphenyl-2-carboxylate (5): Eluent Et_2O/Hex, 30:70; yellow oil (64 % yield). IR (KBr): $\tilde{\nu}$ = 3355, 2950, 1717, 1432, 1292, 1244, 976, 786 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.15 (s, 1H, ArH); 7.46–7.43 (m, 3H, ArH); 7.19–7.14 (m, 2H, ArH); 6.45 (br s, 1H, ArOH); 3.58 (s, 3H, OCH_3) ppm. ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 165.4, 152.1, 144.1, 139.6, 133.7, 128.3 (2C), 127.9 (2C), 127.8, 125.1, 113.8, 108.0, 52.1 ppm. MS: *m/z* (%) = 308 (77) $[M - Br]^+$, 306 (76), 277 (99), 275 (100), 196 (75), 168 (37), 139 (52). $C_{14}H_{10}Br_2O_3$ (386): calcd. C 43.56, H 2.61; found C 43.40, H 2.87.

Metal-Free Total Synthesis of Isourolithin A (8): To a solution of **2b** (1.5 mmol, 1 equiv.) in dry MeOH (20 mL) 1.8 mmol (1.2 equiv.) of sodium methoxide were added at r.t. under N_2 flow. After 1 h the reaction was quenched with 10 % HCl aqueous solution and extracted twice with EtOAc. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The crude residue was dissolved in dry DMF (15 mL) under N_2 atmosphere before adding NaH (1.9 mmol, 1.3 equiv.) and stirring for 1 h at r.t. Then, MeI (1.9 mmol, 1.3 equiv.) was added and the reaction mixture was stirred overnight. The reaction was quenched with 10 % HCl aqueous solution and extracted three times with Et_2O. The organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The crude residue was dissolved in MeOH (10 mL) and a solution of KOH (4.5 mmol, 3 equiv.) in 10 mL of water was slowly added. After stirring for 24 h at 95 °C, the solution was acidified with 10 % HCl aqueous solution and extracted three times with DCM. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give pure acid **6**.

4′,5-Dimethoxybiphenyl-2-carboxylic Acid (6): Yellow solid (97 % overall isolated yield), m.p.158–160 °C; IR (KBr): $\tilde{\nu}$ = 3275, 2921, 1678, 1465, 1281, 1031, 828, 714 cm^{-1}. ^{1}H-NMR (200 MHz, $DMSOd_6$): δ = 12.40 (s, 1H, COOH); 7.67 (d, 1H, *J* = 8.7 Hz, ArH); 7.17 (d, 1H, *J* = 8.4 Hz, ArH); 6.93–6.82 (m, 3H, ArH); 6.74 (d, 1H, *J* = 2.7Hz, ArH); 3.81 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 2.34 (s, 3H, CH_3) ppm. ^{13}C-NMR (50.3 MHz, $DMSOd_6$): δ = 169.2, 161.2, 158.9, 143.9, 133.7, 132.1, 129.8 (2C), 124.0, 116.1, 113.7 (2C), 112.5, 55.7, 55.4 ppm. MS: *m/z* (%) = 300 (69) $[M]^+$, 258 (100), 227 (97), 184 (16), 155 (11), 128 (10). $C_{15}H_{14}O_4$ (300): calcd. C 67.99, H 5.37; found C 67.50, H 5.71.

NIS (2.2 mmol, 2.5 equiv.) was added to a solution of **6** (0.9 mmol, 1 equiv.) in dichloroethane (6 mL). The mixture was stirred for 4 h at 75 °C before adding a saturated aqueous solution of Na_2SO_3. Extraction with EtOAc (three times) delivered an organic phase which was washed with brine and dried with Na_2SO_4. Evaporation of the organic solvent afforded the crude residue which was purified by column chromatography on silica gel.

3,9-Dimethoxy-6*H*-benzo[*c*]chromen-6-one(7):[69] Eluent EtOAc/Hex, 20:80; yellow solid (78 % yield), m.p. 190–191 °C.

Deprotection of the phenol groups was achieved heating to 80 °C a solution of **7** (0.5 mmol, 1 equiv.) and acetic anhydride (27.5 mmol, 55 equiv.) to which hydrogen iodide (58.8 mmol, 117 equiv.) was added dropwise. Reaction quenching was achieved after 18 h simply adding water and washing the mixture with a saturated aqueous solution of Na_2SO_3. After extracting with EtOAc (three times) the organic phase was washed with brine and dried with Na_2SO_4. After evaporation of the organic solvent, the solid residue was triturated with Et_2O to give pure **8** without any further purification.

Isourolithin A (8):[70] white solid (93 % yield), m.p. 289–290 °C.

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Keywords: Biaryls · Cycloaddition · Cyclization · Enones · Multicomponent reactions · Synthetic methods

[1] C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043.
[2] A. Piontek, E. Bisz, M. Szostak, *Angew. Chem. Int. Ed.* **2018**, *57*, 11116–11128; *Angew. Chem.* **2018**, *130*, 11284.
[3] S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang, D. Ma, *Angew. Chem. Int. Ed.* **2017**, *56*, 16136–16179; *Angew. Chem.* **2017**, *129*, 16352.
[4] G. J. P. Perry, I. Larrosa, *Eur. J. Org. Chem.* **2017**, *2017*, 3517–3527.
[5] E. Daviers, *Chem. World* **2011**, 50–54.
[6] K. S. Egorova, V. P. Ananikov, *Organometallics* **2017**, *36*, 4071–4090.
[7] F. Piazzolla, F. Colognese, A. Temperini, *Curr. Org. Chem.* **2018**, *22*, 2537–2554.
[8] *European Medicines Agency Committee for Medicinal Products for Human Use*, **2008**.
[9] F. C. Krebs, R. B. Nyberg, M. Jørgensen, *Chem. Mater.* **2004**, *16*, 1313–118.
[10] J. Lee, B. Hong, A. Lee, *J. Org. Chem.* **2019**, *84*, 9297–9306.
[11] M. McCarthy, P. J. Guiry, *Tetrahedron* **2001**, *57*, 3809–3844.
[12] G. Li, O. V. Zatolochnaya, X.-J. Wang, S. Rodríguez, B. Qu, J.-N. Desrosiers, H. P. R. Mangunuru, S. Biswas, D. Rivalti, S. D. Karyakarte, J. D. Sieber, N. Grinberg, L. Wu, H. Lee, N. Haddad, D. R. Fandrick, N. K. Yee, J. J. Song, C. H. Senanayake, *Org. Lett.* **2018**, *20*, 1725–1729.
[13] J.-J. Pi, X.-Y. Lu, J.-H. Liu, X. Lu, B. Xiao, Y. Fu, N. Guimond, *J. Org. Chem.* **2018**, *83*, 5791–5800.
[14] R. Barnett, P. Stallforth, *Chem. Eur. J.* **2018**, *24*, 4202–4214.
[15] T. Esumi, G. Makado, H. Zhai, Y. Shimizu, Y. Mitsumoto, Y. Fukuyama, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2621–2625.
[16] J. Xu, M. H. Lacoske, E. A. Theodorakis, *Angew. Chem. Int. Ed.* **2014**, *53*, 956–987; *Angew. Chem.* **2014**, *126*, 972.
[17] Z. J. Jain, P. G. Gide, R. S. Kankate, *Arab. J. Chem.* **2017**, *10*, S2051–S2066.
[18] X.-W. Xie, R.-Z. Wan, Z.-P. Liu, *ChemMedChem* **2017**, *12*, 1157–1168.
[19] M. S. Malamas, J. Sredy, C. Moxham, A. Katz, W. Xu, R. McDevitt, F. O. Adebayo, D. R. Sawicki, L. Seestaller, D. Sullivan, J. R. Taylor, *J. Med. Chem.* **2000**, *43*, 1293–1310.
[20] P. A. Smith, M. F. T. Koehler, H. S. Girgis, D. Yan, Y. Chen, Y. Chen, J. J. Crawford, M. R. Durk, R. I. Higuchi, J. Kang, J. Murray, P. Paraselli, S. Park, W. Phung, J. G. Quinn, T. C. Roberts, L. Rougé, J. B. Schwarz, E. Skippington, J. Wai, M. Xu, Z. Yu, H. Zhang, M.-W. Tan, C. E. Heise, *Nature* **2018**, *561*, 189–194.
[21] L. V. Ivanova, T. S. Navale, D. Wang, S. Lindeman, M. V. Ivanov, R. Rathore, *Chem. Commun.* **2018**, *54*, 5851–5854.
[22] C. Nagamani, J. Guo, S. Thayumanavan, *J. Polym. Sci., Part A J. Polym. Sci., Part A Polym. Chem.* **2012**, *50*, 1187–1196.
[23] K.-S. Jang, J. C. Johnson, T. Hegmann, E. Hegmann, L. T. J. Korley, *Liq. Cryst.* **2014**, *41*, 1473–1482.
[24] S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263–303.
[25] Z.-J. Luo, H.-Y. Zhao, X. Zhang, *Org. Lett.* **2018**, *20*, 2543–2546.
[26] C.-G. Dong, Q.-S. Hu, *J. Am. Chem. Soc.* **2005**, *127*, 10006–10007.
[27] A. K. Danodia, R. K. Saunthwal, M. Patel, R. K. Tiwari, A. K. Verma, *Org. Biomol. Chem.* **2016**, *14*, 6487–6496.

[28] H. Li, A. Sasmal, X. Shi, J.-F. Soulé, H. Doucet, *Org. Biomol. Chem.* **2018**, *16*, 4399–4423.
[29] K.-X. Sun, Q.-W. He, B.-B. Xu, X.-T. Wu, J.-M. Lu, *Asian J. Org. Chem.* **2018**, *7*, 781–878.
[30] S. T. Keaveney, G. Kundu, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 12573–12577; *Angew. Chem.* **2018**, *130*, 12753.
[31] T. Saied, C. Demangeat, A. Panossian, F. R. Leroux, Y. Fort, C. Comoy, *Eur. J. Org. Chem.* **2019**, 5275–5284.
[32] L. Minuti, E. Ballerini, A. Barattucci, P. M. Bonaccorsi, M. L. Di Gioia, A. Leggio, C. Siciliano, A. Temperini, *Tetrahedron* **2015**, *71*, 3253–3262.
[33] L. Minuti, A. Temperini, E. Ballerini, *J. Org. Chem.* **2012**, *77*, 7923–7931.
[34] L. Minuti, F. Piazzolla, A. Temperini, *Eur. J. Org. Chem.* **2017**, *36*, 5370–5377.
[35] F. Piazzolla, L. Minuti, A. Temperini, *Polycycl. Aromat. Compd.* **2018**, DOI https://doi.org/10.1080/10406638.2019.1647255.
[36] Y. Yamamoto, K. Nunokawa, M. Ohno, S. Eguchi, *Synthesis* **1996**, *8*, 949–953.
[37] Y. Liu, K. Lu, M. Dai, K. Wang, W. Wu, J. Chen, J. Quan, Z. Yang, *Org. Lett.* **2007**, *9*, 805–808.
[38] J. A. Reed, C. L. Schilling, R. F. Tarvin, T. A. Rettig, J. K. Stille, *J. Org. Chem.* **1968**, *34*, 2188–2192.
[39] B. O. Ashburn, R. G. Carter, L. N. Zakharov, *J. Am. Chem. Soc.* **2007**, *129*, 9109–9116.
[40] B. O. Ashburn, L. K. Rathbone, E. H. Camp, R. G. Carter, *Tetrahedron* **2008**, *64*, 856–865.
[41] B. O. Ashburn, R. G. Carter, *Angew. Chem. Int. Ed.* **2006**, *45*, 6737–6741; *Angew. Chem.* **2006**, *118*, 6889.
[42] C. O. Kappe, *Chem. Rec.* **2019**, *19*, 15–39.
[43] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2016**, *18*, 288–296.
[44] K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem.* **2008**, *10*, 31–36.
[45] K. Alder, H. F. Rickert, *Ber. Dtsch. Chem. Ges. B* **1937**, *70*, 1354–1363.
[46] J. Wolinsky, R. B. Login, *J. Org. Chem.* **1970**, *35*, 3205–3207.
[47] S. C. Philkhana, D. S. Reddy, *Tetrahedron Lett.* **2017**, *58*, 1262–1264.
[48] J. Gaitzsch, V. Rogachev, M. Zahel, P. Metz, *Synthesis* **2014**, *46*, 531–536.
[49] A. Fuentes, R. Martínez-Palou, H. A. Jiménez-Vázquez, F. Delgado, A. Reyes, J. Tamariz, *Monatsh. Chem.* **2005**, *136*, 177–192.
[50] E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, A. Fernández, R. Alvarez-Manzaneda, A. Haidour, J. M. Ramos, A. Akhaouzan, *Chem. Commun.* **2012**, *48*, 606–608.
[51] N. Yasukawa, H. Yokoyama, M. Masuda, Y. Monguchi, H. Sajiki, Y. Sawama, *Green Chem.* **2018**, *20*, 1213–1217.
[52] F. Piazzolla, C. Siciliano, L. Minuti, A. Temperini, *Tetrahedron* **2018**, *74*, 6534–6543.
[53] M. S. C. Pedras, M. Hossain, *Bioorg. Med. Chem.* **2007**, *15*, 5981–5996.
[54] T. I. Richardson, C. A. Clarke, K.-L. Yu, Y. K. Yee, T. J. Bleisch, J. E. Lopez, S. A. Jones, N. E. Hughes, B. S. Muehl, C. W. Lugar, T. L. Moore, P. K. Shetler, R. W. Zink, J. J. Osborne, C. Montrose-Rafizadeh, N. Patel, A. G. Geiser, R. J. Sells Galvin, J. A. Dodge, *ACS Med. Chem. Lett.* **2011**, *2*, 148–153.
[55] T. C. Leboho, J. P. Michael, W. A. L. van Otterlo, S. F. van Vuuren, C. B. de Koning, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948–4951.
[56] K. N. Kaushik, N. Kaushik, P. Attri, N. Kumar, H. C. Kim, K. A. Verma, H. E. Choi, *Molecules* **2013**, *18*, 6620–6662.
[57] R. S. Keri, K. Chand, S. Budagumpi, S. Balappa Somappa, S. A. Patil, B. M. Nagaraja, *Eur. J. Med. Chem.* **2017**, *138*, 1002–1033.
[58] F. Lo Monte, T. Kramer, J. Gu, M. Brodrecht, J. Pilakowski, A. Fuertes, J. M. Dominguez, B. Plotkin, H. Eldar-Finkelman, B. Schmidt, *Eur. J. Med. Chem.* **2013**, *61*, 26–40.
[59] Z. Mao, W. Sun, L. Fu, H. Luo, D. Lai, L. Zhou, *Molecules* **2014**, *19*, 5088–5108.
[60] Z. Mao, D. Lai, X. Liu, X. Fu, J. Meng, A. Wang, X. Wang, W. Sun, Z. L. Liu, L. Zhou, Y. Liu, *Pest. Manag. Sci.* **2017**, *73*, 1478–1485.
[61] J. Tian, L. Fu, Z. Zhang, X. Dong, D. Xu, Z. Mao, Y. Liu, D. Lai, L. Zhou, *Nat. Prod. Res.* **2017**, *31*, 387–396.
[62] M. Á. Ávila-Gálvez, J. C. Espín, A. González-Sarrías, *J. Agric. Food Chem.* **2018**, *66*, 8547–8555.
[63] P. Gao, Y. Wei, *Synthesis* **2014**, *46*, 343–347.
[64] A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638–14658; *Angew. Chem.* **2015**, *127*, 14848.
[65] N. Solin, L. Han, S. Che, O. Terasaki, *Catal. Commun.* **2009**, *10*, 1386–1389.
[66] N. Karousis, J. Liebscher, G. Varvounis, *Synthesis* **2006**, *9*, 1494–1498.
[67] X. Guo, W. Hu, S. Cheng, L. Wang, J. Chang, *Synth. Commun.* **2006**, *36*, 781–788.
[68] K. R. Buszek, N. Brown, *Org. Lett.* **2007**, *9*, 707–710.
[69] D. J. Hart, A. Kim, R. Krishnamurthy, G. H. Merriman, A.-M. Waltos, *Tetrahedron* **1992**, *48*, 8179–8188.
[70] W. Auamcharoen, A. Chandrapatya, A. Kijjoa, A. M. S. Silva, W. Herz, *Biochem. Syst. Ecol.* **2009**, *37*, 535–537.

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Multicomponent Reactions

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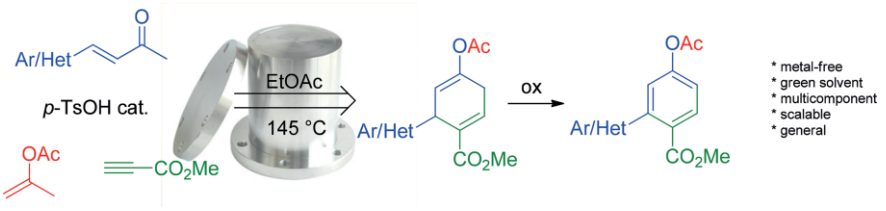
Scalable Multicomponent Synthesis of (Hetero)aryl-Substituted Phenyls: Focus on Metal-Free Halogenated Biaryls, 3-Arylindoles, and Isourolithine A Synthesis



A simple, scalable and metal-free multicomponent enol acetylation of (hetero)arylidene acetones followed by a thermal Diels-Alder reaction with methyl propiolate was accomplished in a pressure metal vessel. Aromatization of the cycloadduct intermediates yielded the corresponding functionalised (hetero)biaryls.

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