

# Development of a Robust and Practical Process for the Darzens Condensation and $\alpha,\beta$ -Epoxide Rearrangement: Scope and Limitations of the Methodology

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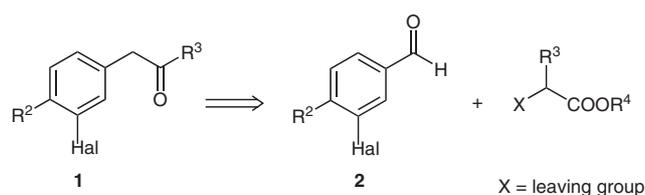
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Received 19 December 2007

**Abstract:** A practical and robust process for the Darzens condensation of substituted benzaldehydes and subsequent  $\alpha,\beta$ -epoxy rearrangement is reported. The process developed is both amenable to large scale and parallel synthesis. While electron-poor benzaldehydes gave mixtures of aryl ketones and 2-substituted aryl ketones in mediocre to low yields, electron-rich benzaldehydes were found to react in high yields with complete regioselectivity to form 2-substituted aryl ketones.

**Key words:** condensation, rearrangement, regioselectivity, homologation, decarboxylation

In the course of one of our development program, we became interested in the well-documented Darzens condensation.<sup>2</sup> Since the seminal work of Erlenmeyer and Darzens, the methodology has been extensively used for aromatic aldehydes as well as for aromatic and aliphatic ketones.<sup>3</sup> During the reaction, a carbonyl is reacted with an  $\alpha$ -halo ester in the presence of a base to give an epoxide. Of particular interest for us was the opening of the latter and decarboxylation upon thermolysis, to afford the corresponding one-carbon homologue of the starting aldehyde or ketone.<sup>3,4</sup> Development of a practical and robust metal-free one-carbon homologation process for access to ketone **1** from substituted and readily available benzaldehydes **2** (Scheme 1) was our initial objective. The stereochemistry of the Darzens condensation was of no relevance in this process.

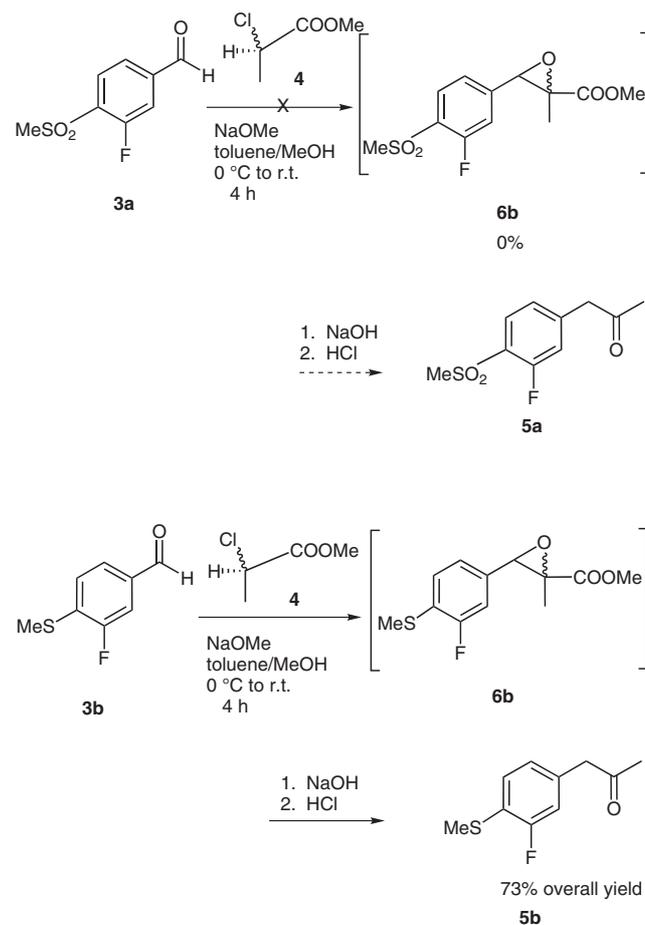


**Scheme 1** Retrosynthetic analysis

A series of potent candidates containing a sulfone moiety was first brought to our attention ( $R^2 = \text{CH}_3\text{SO}_2$  in Scheme 1). Under classical conditions, we found that the desired product **5a** did not form from the benzaldehyde **3a**. Interestingly, the 4-methylsulfanyl-substituted benzaldehyde **3b** reacted smoothly under identical conditions

and afforded the desired ketone **5b** in 73% isolated yield at the first attempt (Scheme 2). Careful investigation revealed that the Darzens condensation was not proceeding at all in the case of the sulfone **3a**. A thorough literature search revealed that only sparse results suggesting an electronic bias in the Darzens reaction of aromatic aldehydes were reported.<sup>5</sup> Our project was a perfect opportunity to probe the substrate scope of the reaction while streamlining our process. Particular attention was paid to the practicality and robustness of the overall process to illustrate the importance of the methodology in process development.

In the case of aldehyde **3b**, the reaction was found to proceed well with the inexpensive ( $\pm$ )-2-chloropropionic acid methyl ester **4** and sodium methoxide at 0 °C in a toluene–



**Scheme 2** Influence of electronic configuration of the aromatic ring in the Darzens epoxide rearrangement

SYNTHESIS 2008, No. 8, pp 1221–1226

Advanced online publication: 27.03.2008

DOI: 10.1055/s-2008-1067002; Art ID: Z29207SS

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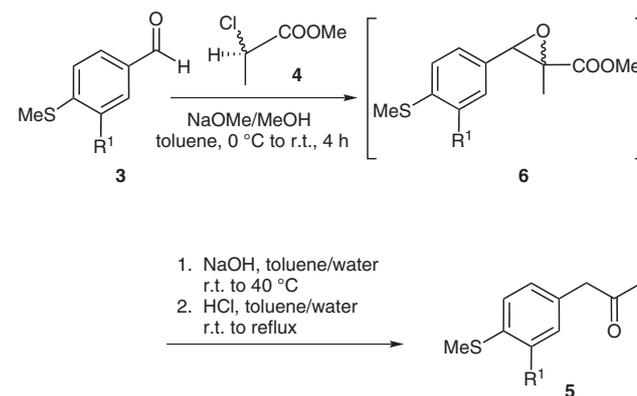
methanol solvent system. A solvent screen had shown that the presence of methanol as a polar co-solvent greatly enhanced the rate of the condensation. A base screening had also revealed that sodium methoxide was a suitable base for the reaction. Eventually, a commercially available 25% solution of sodium methoxide in methanol was used directly and gave optimal results for the condensation step. The subsequent hydrolysis proceeded smoothly with sodium hydroxide and the carboxylate could be recovered in high purity directly from the water phase. The epoxide opening and decarboxylation was carried out in the same pot under thermal and acidic conditions. This streamlined three-step one-pot process led to material of high purity, which could be used without further purification (purity typically higher than 98%). Careful quantitative analyses by both  $^1\text{H}$  NMR and HPLC showed that the hydrolysis and epoxide opening–decarboxylation steps proceeded in almost quantitative yields, indicating that the yield observed at the end of the sequence was representative of the Darzens condensation.

The methylsulfonyl benzaldehyde series was of particular interest to us and the sequence described above was used to elaborate the various substrates depicted in Table 1. The electron-rich aromatic aldehydes notably displayed the best reactivity. The initial condensation proceeded in moderate to good yield for all benzaldehydes carrying electron-donating substituents in a position *meta* to the aldehyde (yields ranging from 50–83%) while the yield dropped to below 45% for electron-withdrawing groups. Monitoring by NMR showed that the reaction proceeded in all cases with high selectivity in the epoxide formation (>95:5) and with minimal side-reaction. Only the  $\alpha$ -chloro ester **4** was found to decompose over time when the aldehyde was not reactive enough. The streamlined protocol allowed for removal of unreacted starting material and by-products from  $\alpha$ -chloro ester by simple extraction. The epoxide opening and subsequent rearrangement proceeded also smoothly and selectively to the methyl ketone for electron-rich aromatic rings in almost quantitative yields.

This strategy provided a valuable entry into the alkylated aryl derivatives (entry 3), and the halogenated aryls (entries 1, 7, 8), precursors to more functionalized products after  $\text{S}_{\text{N}}\text{Ar}$  or a metal-mediated cross-coupling reaction.

These encouraging results prompted a study of more general substrates (Table 2). In the case of monosubstituted benzaldehydes, the presence of electron-donating groups was again found to favor the condensation and gave the desired final methyl ketones in moderate to good yield (from 51–79%). On the other hand, electron-poor aromatic rings were found not only to be poorly reactive under our conditions, but also to display an opposite selectivity in the epoxide opening. Indeed, the aryl ethyl ketone **9j'** was isolated in ca. 15% yield as the major product along with ca. 5% yield of **9j**. The same trend was observed in the nitrile series (13% aryl ethyl ketone **9k'** and 3% **9k**). Similar results were observed by Kagan and Singh who reported that the decarboxylation of  $\alpha$ -aryl- $\beta$ -dimethyl glycidate in acid medium involved the formation of a mix-

**Table 1** Preparation of Functionalized 3-Substituted (4-Methylsulfonylphenyl)propan-2-ones

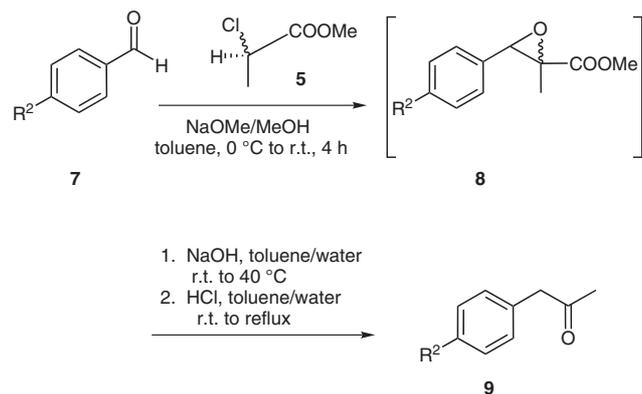


Entry	R <sup>1</sup>	Substrate	Product	Yield (%)
1	F	<b>3b</b>	<b>5b</b>	83
2	H	<b>3c</b>	<b>5c</b>	58
3	Me	<b>3d</b>	<b>5d</b>	55
4	NO <sub>2</sub>	<b>3e</b>	<b>5e</b>	35
5	CN	<b>3f</b>	<b>5f</b>	42
6	CF <sub>3</sub>	<b>3g</b>	<b>5g</b>	6
7	Cl	<b>3h</b>	<b>5h</b>	59
8	Br	<b>3i</b>	<b>5i</b>	50
9	OMe	<b>3j</b>	<b>5j</b>	58

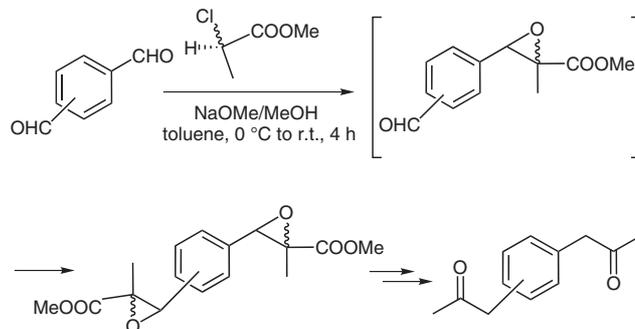
ture of two products. The first one corresponds to the simple decarboxylation and is referred to as ‘normal’. The other product where the decarboxylation is followed by a migration of the substituent from the  $\alpha$ - to the  $\beta$ -position is referred to as ‘abnormal’. The importance of the aromatic substituent R<sup>1</sup> during the rearrangement step and in particular during the formation of the carbocation is also illustrated here.<sup>6</sup>

The bisaldehydes **7g** and **7h**, although electronically poor, displayed remarkable and unexpected reactivity (Scheme 3). When 2 equivalents of  $\alpha$ -chloro ester **4** were used, they were found to afford the methyl ketone products **9g** and **9h** in 34% and 44% isolated yield, respectively. The low reactivity of the electron-poor benzaldehydes could apparently be overcome by the change in the electronic configuration after initiation of the reaction.

The stereoelectronic contribution of the position of the substituent was then evaluated in more details with various methoxybenzaldehydes **10**. As expected, a methoxy substituent in the *para*-position (Table 3, entry 3) led to improved results (79% isolated yield of methyl ketone) compared to a methoxy substituent in the *ortho*-position (entry 1, 63% isolated yield of methyl ketone), presumably due to steric constraint. It also performed better compared to a methoxy substituent in the *meta*-position (entry 2, 54% isolated yield of methyl ketone), presumably due

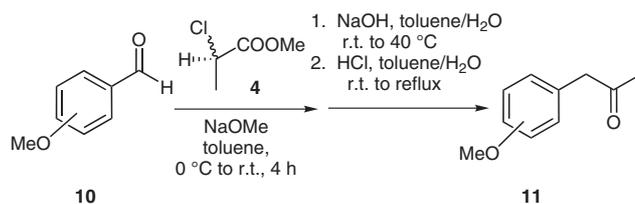
**Table 2** Preparation of Functionalized 4-Substituted Phenylpropan-2-ones

Entry	R <sup>2</sup>	Substrate	Product	Yield (%)
1	OMe	<b>7a</b>	<b>9a</b>	79
2	H	<b>7b</b>	<b>9b</b>	36
3	Me	<b>7c</b>	<b>9c</b>	51
4	F	<b>7d</b>	<b>9d</b>	64
5	SO <sub>2</sub> Me	<b>7e</b>	<b>9e</b>	no reaction
6	Ph	<b>7f</b>	<b>9f</b>	50
7	CHO	<b>7g</b>	<b>9g</b>	34
8		<b>7h</b>	<b>9h</b>	44
9	CF <sub>3</sub>	<b>7i</b>	<b>9i</b>	trace
10	NO <sub>2</sub>	<b>7j</b>	<b>9j</b>	5 ( <b>9j</b> ) 15 ( <b>9j'</b> )
		<b>7j'</b>	<b>9j'</b>	
11	CN	<b>7k</b>	<b>9k</b>	3 ( <b>9k</b> ) 13 ( <b>9k'</b> )
		<b>7k'</b>	<b>9k'</b>	

**Scheme 3** Proposed rationale for reactivity of bis-aldehydes

to poorer electron-donating ability. The latter could be overcome when a second methoxy substituent was introduced in the *ortho*- or *para*-position (entries 4 and 5), which increased the overall yield to almost 80% isolated yield.

Finally, a series of experiments were carried out in order to better understand this remarkable difference in reactivity between electron-rich and electron-poor aromatic benzaldehydes. One possible explanation for such differences is the formation of a poorly reactive ketal or hemiketal. The Darzens condensation of *p*-cyano-substituted benzaldehyde with ( $\pm$ )-2-chloropropionic acid methyl ester was therefore conducted under a variety of dehydrating conditions (molecular sieves, potassium carbonate, sodium sulfate, etc.). None of the attempts resulted in an improved yield of the required product. In all cases, only about 20% carbon-carbon bond-forming event was observed. Additional spectroscopic analyses (<sup>1</sup>H and <sup>13</sup>C NMR) did not reveal any change in the starting material under these treatments. The described preliminary experiments do not allow to draw definitive conclusions and further work to better understand the trend illustrated in this paper are currently ongoing in our laboratory.

**Table 3** Stereoelectronic Influence of the Substitution Pattern on the Darzens Epoxide Rearrangement

Entry	Position of OMe	Substrate	Product	Yield (%)
1	<i>ortho</i>	<b>10a</b>	<b>11a</b>	63
2	<i>meta</i>	<b>10b</b>	<b>11b</b>	54
3	<i>para</i>	<b>7a</b>	<b>11a</b>	79
4	<i>ortho</i> + <i>meta</i>	<b>10c</b>	<b>11c</b>	77
5	<i>meta</i> + <i>para</i>	<b>10d</b>	<b>11d</b>	80

In conclusion, we have developed a rapid, practical and robust process for the Darzens condensation of substituted benzaldehydes and subsequent  $\alpha,\beta$ -epoxy rearrangement. The process developed is amenable to both large scale and parallel synthesis. In the course of our investigation, we have demonstrated the remarkable regioselectivity in the epoxide opening and the limitations of the condensation to electron-rich benzaldehydes.

NMR spectra were recorded using a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm and referenced to  $\text{CDCl}_3$  on the  $\delta$  scale; coupling constants are given in Hz. Column chromatography was carried out using silica gel (70–230 mesh, E. Merck). High-resolution mass spectra were recorded using a Bruker FT ITR MS 4.7T Bio Apex II spectrometer. All solvents, and reagents used were of technical grade and readily available from multiple suppliers. All reactions were carried out under  $\text{N}_2$ .

#### Darzens Condensation/ $\alpha,\beta$ -Epoxide Rearrangement of Benzaldehydes **3**, **7**, **10** with Methyl 2-Chloropropionate; General Procedure

To a solution of the respective aldehyde **3**, **7**, or **10** (10 mmol, 1 equiv) in toluene (10 mL) at r.t. was added ( $\pm$ )-2-chloropropionic acid methyl ester (**4**; 1.2 equiv) over 10 min. The solution was cooled to 0–5 °C and a solution of NaOMe in MeOH (1.15 equiv) was added over 20 min at a rate such that the temperature remained below 10 °C (mild exotherm). The resulting suspension was stirred for an additional 30 min at 0–5 °C, and then warmed to r.t. and stirred until completion of the reaction (3–6 h). The mixture was diluted with toluene (5 mL) and warmed to 35–40 °C. Aq 30% NaOH (1.15 equiv) was added over 45 min to hydrolyze the ester and the suspension was allowed to stir for 1 h. At completion of the hydrolysis,  $\text{H}_2\text{O}$  (10 mL) was added, the mixture was cooled to r.t., and the two phases were separated. The by-products derived from ( $\pm$ )-2-chloropropionic acid methyl ester (**4**) and possible remaining aldehyde **3**, **7**, or **10** were removed by extraction with toluene (2  $\times$  10 mL). Additional toluene (20 mL) was added and the resulting mixture was heated to 60 °C. Conc'd HCl (1.2 equiv) was added over 30 min to reach pH 2.5 (exothermic;  $\text{CO}_2$  evolution). The mixture was stirred for 1 h at 60 °C and for an additional 4 h at 95 °C. The biphasic mixture was then cooled to r.t. and the phases were separated. The organic phase was washed with  $\text{H}_2\text{O}$  (10 mL), and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (eluent: EtOAc–hexanes).

#### 1-(3-Fluoro-4-methylsulfonylphenyl)propan-2-one (**5b**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.16 (t,  $J$  = 8.0 Hz, 1 H), 6.87 (dd,  $J$  = 8.0, 2.1 Hz, 1 H), 6.83 (dd,  $J$  = 10.3, 1.8 Hz, 1 H), 3.60 (s, 2 H), 2.39 (s, 3 H), 2.11 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 205.5, 159.1–161.5, 134.0, 129.0, 125.6, 124.0, 116.4, 50.0, 29.5, 15.7.

HRMS:  $m/z$  calcd (M + H): 199.05146; found: 199.05874.

#### 1-(4-Methylsulfonylphenyl)propan-2-one (**5c**)<sup>7</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.22 (d,  $J$  = 1.8 Hz, 1 H), 7.15 (d,  $J$  = 8.0 Hz, 1 H), 7.09 (dd,  $J$  = 8.0, 1.8 Hz, 1 H), 3.66 (s, 2 H), 2.48 (s, 3 H), 2.19 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 205.5, 136.5, 132.0, 131.7, 130.3, 128.3, 125.8, 49.7, 29.4, 15.2.

HRMS:  $m/z$  calcd (M + H): 181.06088; found: 181.06816.

#### 1-(3-Methyl-4-methylsulfonylphenyl)propan-2-one (**5d**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.28–7.01 (m, 5 H), 3.65 (s, 2 H), 2.50 (s, 3 H), 2.39 (s, 3 H), 2.11 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 206.2, 136.1, 135.9, 130.5, 130.2, 127.1, 124.8, 50.0, 28.9, 19.3, 15.0.

HRMS:  $m/z$  calcd for (M + H): 195.07654; found: 195.09464.

#### 1-(4-Methylsulfonyl-3-nitrophenyl)propan-2-one (**5e**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.13 (d,  $J$  = 2.0 Hz, 1 H), 7.45 (dd,  $J$  = 8.3, 2.0 Hz, 1 H), 7.37 (d,  $J$  = 8.5 Hz, 1 H), 3.82 (s, 2 H), 2.52 (s, 3 H), 2.27 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 203.0, 142.0, 136.7, 133.6, 129.2, 125.6, 124.6, 47.7, 28.4, 14.6.

HRMS:  $m/z$  calcd for (M + H): 226.04596; found: 226.05324.

#### 2-Methylsulfonyl-5-(2-oxopropyl)benzonitrile (**5f**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.44 (d,  $J$  = 1.7 Hz, 1 H), 7.37 (dd,  $J$  = 8.3, 2.0 Hz, 1 H), 7.31 (d,  $J$  = 8.3 Hz, 1 H), 3.74 (s, 2 H), 2.58 (s, 3 H), 2.24 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 204.6, 142.3, 134.3, 134.2, 131.4, 126.7, 116.8, 112.0, 49.1, 29.8, 15.9.

HRMS:  $m/z$  calcd for (M + H): 206.05613; found: 206.06341.

#### 1-(4-Methylsulfonyl-3-trifluoromethylphenyl)propan-2-one (**5g**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.46 (d,  $J$  = 1.8 Hz, 1 H), 7.37 (d,  $J$  = 8.3 Hz, 1 H), 7.34 (dd,  $J$  = 8.3, 1.8 Hz, 1 H), 3.74 (s, 2 H), 2.58 (s, 3 H), 2.24 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 190.1, 153.1, 135.7, 133.8, 133.7, 125.6, 116.7, 112.0, 30.7, 15.9.

HRMS:  $m/z$  calcd for (M + H): 249.04827; found: 249.05555.

#### 1-(3-Chloro-4-methylsulfonylphenyl)propan-2-one (**5h**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.22 (d,  $J$  = 1.8 Hz, 1 H), 7.15 (d,  $J$  = 8.0 Hz, 1 H), 7.09 (dd,  $J$  = 8.0, 1.8 Hz, 1 H), 3.66 (s, 2 H), 2.48 (s, 3 H), 2.19 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 205.5, 136.5, 132.0, 131.7, 130.3, 128.3, 125.8, 49.7, 29.4, 15.2.

HRMS:  $m/z$  calcd for (M + H): 215.02191; found: 215.02919.

#### 1-(3-Bromo-4-methylsulfonylphenyl)propan-2-one (**5i**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.40 (d,  $J$  = 1.8 Hz, 1 H), 7.15 (dd,  $J$  = 8.3, 1.8 Hz, 1 H), 7.11 (d,  $J$  = 8.3 Hz, 1 H), 3.66 (s, 2 H), 2.48 (s, 3 H), 2.2 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 205.6, 138.5, 133.5, 131.7, 128.9, 125.6, 121.9, 49.7, 29.4, 15.8.

HRMS:  $m/z$  calcd for (M + H): 258.97140; found: 258.97867.

#### 1-(3-Methoxy-4-methylsulfonylphenyl)propan-2-one (**5j**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.14 (d,  $J$  = 8.0 Hz, 1 H), 6.82 (dd,  $J$  = 8.0, 1.8 Hz, 1 H), 6.69 (d,  $J$  = 1.8 Hz, 1 H), 3.90 (s, 3 H), 3.68 (s, 2 H), 2.44 (s, 3 H), 2.17 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 206.4, 156.5, 132.2, 126.5, 125.7, 122.2, 111.1, 55.8, 50.8, 29.2, 14.8.

HRMS:  $m/z$  calcd for (M + H): 211.07145; found: 211.07873.

#### 1-(4-Methoxyphenyl)propan-2-one (**9a**)<sup>8</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.14 (dd,  $J$  = 6.8, 2.0 Hz, 2 H), 6.90 (dd,  $J$  = 6.8, 2.0 Hz, 2 H), 3.82 (s, 3 H), 3.66 (s, 2 H), 2.16 (s, 3 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 207.0, 158.7, 130.4, 129.0, 128.2, 126.3, 114.2, 52.3, 50.1, 29.1.

HRMS:  $m/z$  calcd (M + H): 165.08373; found: 165.09101.

**1-Phenylpropan-2-one (9b)<sup>9</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.22–7.29 (m, 5 H), 3.72 (s, 2 H), 2.18 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.5, 134.2, 129.4, 128.8, 127.1, 50.1, 29.3.

HRMS: *m/z* calcd (M + H): 135.07317; found: 135.08044.

**1-*p*-Tolylpropan-2-one (9c)<sup>9</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.14 (dd, *J* = 8.0, 2.0 Hz, 2 H), 7.08 (dd, *J* = 8.0, 2.0 Hz, 2 H), 3.68 (s, 2 H), 2.36 (s, 3 H), 2.16 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 207.0, 136.7, 129.5, 129.3, 128.2, 50.7, 29.2, 21.1.

HRMS: *m/z* calcd for (M + H): 149.08881; found: 149.08021.

**1-(4-Fluorophenyl)propan-2-one (9d)<sup>10</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.18–7.04 (m, 4 H), 3.70 (s, 2 H), 2.19 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.1, 160.8, 131.0, 130.9, 129.9, 115.7, 115.5, 52.3, 50.0, 29.3.

HRMS: *m/z* calcd for (M): 152.06374; found: 152.05982.

**1-Biphenyl-4-ylpropan-2-one (9f)<sup>11</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.64–7.56 (m, 4 H), 7.50–7.42 (m, 2 H), 7.40–7.34 (m, 1 H), 7.33–7.26 (m, 2 H), 3.77 (s, 2 H), 2.22 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.3, 140.7, 140.1, 133.2, 129.9, 128.8, 127.5, 127.3, 127.1, 50.6, 29.4.

HRMS: *m/z* calcd for (M + H): 210.10447; found: 211.11174.

**1-[4-(2-Oxopropyl)phenyl]propan-2-one (9g)<sup>12</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.19 (s, 4 H), 3.70 (s, 4 H), 2.18 (s, 6 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.3, 133.0, 129.8, 50.1, 29.4.

HRMS: *m/z* calcd for (M + H): 191.09938; found: 191.10666.

**1-[3-(2-Oxopropyl)phenyl]propan-2-one (9h)<sup>13</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.19 (s, 4 H), 3.70 (s, 4 H), 2.18 (s, 6 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.3, 133.0, 129.8, 50.1, 29.4.

HRMS: *m/z* calcd for (M + H): 191.09938; found: 191.10666.

**1-(3-Methoxyphenyl)propan-2-one (9i)<sup>9</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.69 (d, *J* = 8.3 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 3.86 (s, 2 H), 2.23 (s, 3 H).

**1-(4-Trifluoromethylphenyl)propan-1-one (9i')<sup>14</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (d, *J* = 8.3 Hz, 2 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 3.06 (q, *J* = 7.3 Hz, 2 H), 1.27 (t, *J* = 7.3 Hz, 3 H).

**1-(4-Nitrophenyl)propan-2-one (9j)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.61 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 3.98 (s, 2 H), 2.19 (s, 3 H).

HRMS: *m/z* calcd for (M + H): 180.05824; found: 180.06552.

**1-(4-Nitrophenyl)propan-1-one (9j')**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.34 (d, *J* = 8.0 Hz, 2 H), 8.18 (d, *J* = 8.0 Hz, 2 H), 3.13 (q, *J* = 7.3 Hz, 2 H), 1.10 (t, *J* = 7.3 Hz, 3 H).

HRMS: *m/z* calcd for (M + H): 180.05824; found: 180.06552.

**4-(2-Oxopropyl)benzotrile (9k)<sup>15</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.64 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 3.96 (s, 2 H), 2.24 (s, 3 H).

HRMS: *m/z* calcd for (M – H): 158.06841; found: 158.06114.

**4-Propionylbenzotrile (9k')**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.06 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H), 3.04 (q, *J* = 7.3 Hz, 2 H), 1.26 (t, *J* = 7.3 Hz, 3 H).

HRMS: *m/z* calcd for (M – H): 158.06841; found: 158.06114.

**1-(2-Methoxyphenyl)propan-2-one (11a)<sup>16</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.29 (td, *J* = 8.0, 1.8 Hz, 1 H), 7.14 (dd, *J* = 7.3, 1.8 Hz, 1 H), 6.95 (td, *J* = 7.3, 1.8 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 3.84 (s, 3 H), 3.70 (s, 2 H), 2.16 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 207.0, 157.3, 131.0, 128.6, 123.7, 120.3, 110.2, 55.3, 45.8, 29.3.

HRMS: *m/z* calcd for (M + H): 165.20594; found: 165.09101.

**1-(3-Methoxyphenyl)propan-2-one (11b)<sup>17</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.14 (t, *J* = 7.78 Hz, 1 H), 6.85–6.77 (m, 3 H), 3.82 (s, 3 H), 3.69 (s, 2 H), 3.18 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.3, 159.7, 135.4, 129.5, 121.5, 114.8, 112.3, 55.0, 50.1, 29.1.

HRMS: *m/z* calcd for (M + H): 165.20594; found: 165.09101.

**1-(2,3-Dimethoxyphenyl)propan-2-one (11c)<sup>18</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.02 (t, *J* = 7.9 Hz, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 2.18 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 206.7, 152.7, 147.1, 128.8, 124.1, 122.7, 111.6, 60.4, 55.7, 45.3, 29.4.

HRMS: *m/z* calcd for (M + H): 195.09429; found: 195.00356.

**1-(3,4-Dimethoxyphenyl)propan-2-one (11d)<sup>19</sup>**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.74 (dd, *J* = 8.1, 1.9 Hz, 2 H), 6.66 (d, *J* = 1.9 Hz, 1 H), 3.81 (s, 6 H), 3.58 (s, 2 H), 2.09 (s, 3 H).

HRMS: *m/z* calcd for (M + H): 195.09429; found: 195.01002.

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