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Synthesis of benzophenones from geminal biaryl ethenes using *m*-chloroperbenzoic acid

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ABSTRACT

The oxidation of geminal biaryl ethenes **3** and 1,3-enynes **5** using *m*-chloroperbenzoic acid in dichloromethane at room temperature presents a catalyst-free approach for the synthesis of functionalized benzophenones **4** and ynones **6**, respectively.

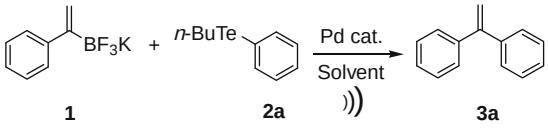
1. Introduction

Symmetrical and unsymmetrical benzophenones functionalized with electron-donating or -withdrawing groups are found in a large number of plants belonging to the Guttiferae family.[1–3] In the past few decades, numerous natural products bearing a benzophenone architecture, such as cariphenones A and B,[4] balanol,[5] Clusiaphenone,[6] and pestalone,[7] have been reported. Molecules built on these scaffolds are known to exhibit a wide range of biological and pharmacological activities, acting as antioxidants,[8] analgesics,[9] protein kinase inhibitors,[10] and antiviral agents.[11] Recently, several naturally occurring prenylated and isoprenylated benzophenones have been identified as potent cytotoxic and antimicrobial agents.[12] In addition, some synthetic benzophenones have been reported as a new class of non-nucleoside HIV reverse transcriptase inhibitors.[13]

While the chemistry of symmetrical and unsymmetrical benzophenones includes many synthetic methods, most of them fall into the categories of the oxidation of secondary alcohols in the presence of organometallic complexes, such as ruthenium(III) meso-tetraphenylporphyrin chloride,[14] 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/I_2O_5,[15] oxone,[16] palladium salts,[17] iron(III) nitrate,[18] Ag/HT,[19] and cuprous chloride.[20] Most of these approaches required inorganic oxidants that are not only relatively expensive but also produce large quantities of noxious heavy metal waste.[21] Over the last decade, Miyaura and his research group have reported the synthesis of unsymmetrical benzophenone compounds by palladium-catalyzed cross-coupling reactions of arylboronic acids with aryl halides in the presence of carbon monoxide.[22] Other research groups have reported the synthesis of benzophenones by palladium-catalyzed cross-coupling reactions of aromatic acyl chlorides with organoborons,[23] organostannanes,[24] or triarylbismuths.[25] In addition, acyl chlorides are commonly water-sensitive and corrosive, which would set limits on the industrial applications of this reaction. The other commonly used approaches for the synthesis of these compounds are bismuth(III) iodide-catalyzed deprotection of acetals[26] and copper-catalyzed benzoylation of *n*-butylphenylzinc (*n*-BuPhZn).[27] Recently, Shi and co-workers[28] reported the synthesis of benzophenones from geminal biaryl ethenes by oxidative cleavage using *tert*-butyl hydrogen peroxide (TBHP) as oxidant. This approach, however, requires neocuproine as ligand and an expensive catalyst, gold(I) chloride.[28]

When we encountered the need to convert 1,1-diarylethenes into benzophenones, we initially used $NaIO_4$ as an oxidant in the presence of ruthenium oxide,[29] but no reaction was observed. Although *m*-chloroperbenzoic acid (*m*-CPBA) is a well-known reagent for epoxidation, few reports exist in the literature in which *m*-CPBA promotes oxidative cleavage of specific endocyclic C=C

Table 1
Catalyst effects on the cross-coupling reaction of **1** and **2a** yielding **3a**



Entry	Catalyst[a]	Yield[b] (%)
1	$PdCl_2$	53
2	$Pd(Acac)_2$	34
3	$Pd_2(dba)_3$	46
4	$PdCl_2(BzCN)_2$	53
5	$Pd(AcO)_2$	49
6	$PdCl_2(dppf)\cdot CH_2Cl_2$	47
7	$Pd(PPh_3)_4$	68

[a] 10 mol % of catalyst.
[b] Isolated yields.

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Table 2
Effects of additive and base on the cross-coupling reaction of **1** and **2a**

Entry	Base	Additive	$Pd(PPh_3)_4$ (mol %)	Yield (%)[a]
1	K_2CO_3	Ag_2O	$Pd(PPh_3)_4$ (10)	60
2	Cs_2CO_3	Ag_2O	$Pd(PPh_3)_4$ (10)	64
3	Et_3N	Ag_2O	$Pd(PPh_3)_4$ (10)	61
4	—	Ag_2O	$Pd(PPh_3)_4$ (10)	45
5	Cs_2CO_3	—	$Pd(PPh_3)_4$ (10)	nr[a]
6	Cs_2CO_3	CuI	$Pd(PPh_3)_4$ (10)	17[a]
7	Cs_2CO_3	AgOAc	$Pd(PPh_3)_4$ (10)	81
8	Cs_2CO_3	AgOAc	$Pd(PPh_3)_4$ (5)	74
9	Cs_2CO_3	AgOAc	$Pd(PPh_3)_4$ (15)	77
10	Cs_2CO_3	AgOAc	$Pd(PPh_3)_4$ (20)	76
11	Et_3N	AgOAc	$Pd(PPh_3)_4$ (10)	84
12	Et_3N	AgOAc	$Pd(PPh_3)_4$ (10)	75[b]

[a] Isolated yields.

bonds into diketones.[30,31] We found no reports of the utility of *m*-CPBA to promote oxidative cleavage of terminal C=C bonds. We therefore envisaged that *m*-CPBA could be useful to convert 1,1-diaryl ethenes into benzophenones.

Herein, we report a general approach for the synthesis of benzophenones by the oxidations of 1,1-diarylethenes using *m*-CPBA under mild reaction conditions. The main advantage of this approach is that the oxidation occurs efficiently under mild conditions, requires no organometallic reagents or catalysts, and permits flexibility of introducing an electron-donating or -accepting functionality in the benzophenone architecture.

In order to prepare different 1,1-diarylethenes, we employed the Suzuki–Miyaura reaction of easily accessible aryl tellurides[32] **2a–j** with potassium 1-phenyl-1-trifluoroborate ethene salt **1**.

Initially, we determined optimal conditions for the reaction of **1** and the model phenylbutyltelluride **2a** (Tables 1 and 2). The reactions were monitored by either TLC or GC. First, we optimized the palladium catalyst using either Pd(II) or Pd(0) species. The best result was obtained with $Pd(PPh_3)_4$ (Table 1, entry 7). Using AgOAc as an additive, K_2CO_3 as a base, and methanol as the solvent, and irradiating the reaction for 20 min in an ultrasound bath, the product **3a** was obtained in 68% isolated yield.

In order to further investigate the effects of the additive, we performed the **1** + **2a** reaction using two different additives (CuI and AgOAc), and isolated the desired product in 17 and 81% yields, respectively (Table 2, entries 6 and 7). No product was observed in the absence of additives (Table 2, entry 5).

The catalyst loadings were also evaluated (Table 2, entries 7–10), and the best yield (81%) was obtained with 10 mol % of $Pd(PPh_3)_4$, (Table 2, entry 7). When triethylamine was employed, the final product was obtained in 84% isolated yield (Table 2, entry 11). Under 3 h of reflux with magnetic stirring, a lower yield (75%) was obtained (Table 2, entry 12).

From the optimization studies using the **1** + **2a**→**3a** reaction,[33] the best conditions used 1.1 mmol of **1**, 1.0 mmol of **2a**, 2.0 mmol of AgOAc, 2.0 mmol of triethylamine, and 10 mol % of $Pd(PPh_3)_4$ in methanol irradiated under ultrasonic waves for 20 min. This optimal condition was then used to prepare a series of 1,1-diarylethenes (**3a–j**) in 74–91% yields (Table 3). The course of the reaction was not affected by the presence of a methyl group at the *ortho*-position of **2i** and **2j**.

Our emphasis was then directed to the cleavage of the terminal C=C bonds of the geminal biaryl ethenes **3a–j** by *m*-CPBA. We used **3a** as a model in reactions performed in dichloromethane for 30 min at −78 °C and 60 min at room temperature[34] (Table 4).

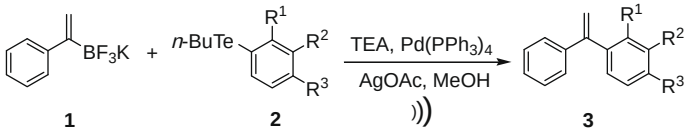
After the completion of reaction, the mixture was diluted with dichloromethane and washed with 10% NaOH solution. The resulting organic layer was evaporated under vacuum. The pure solid product **4a** was isolated by flash column chromatography using 20% chloroform in hexane as eluent.

The ^1H and ^{13}C NMR and IR spectroscopic data of the isolated compound **4a** matched perfectly with that of commercial benzophenone, which confirms the occurrence of the expected C=C oxidative cleavage. After confirming the structure of isolated

Table 4
Oxidative cleavage of terminal C=C bonds of 1,1-diarylethenes **3a–j** by *m*-CPBA, yielding **4a–j**

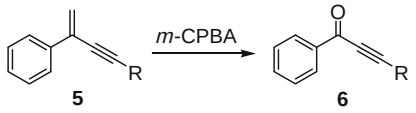
Entry	R^1	R^2	R^3	Time (min)	Yield (%)
4a	H	H	H	90	83
4b	H	H	Br	80	90
4c	H	H	Cl	80	83
4d	H	H	F	85	87
4e	H	CF_3	H	95	79
4f	H	H	Me	110	87
4g	H	H	OMe	120	91
4h	H	H	OH	90	89
4i	Me	H	H	170	67
4j	Me	H	F	180	49

Table 3
Suzuki–Miyaura reaction of **1** and the *n*-butylaryl tellurides **2a–j**, yielding **3a–j**



Entry	Product	R^1	R^2	R^3	Time (min)	Yield (%)
1	**3a**	H	H	H	20	80
2	**3b**	H	H	Br	20	91
3	**3c**	H	H	Cl	20	80
4	**3d**	H	H	F	20	79
5	**3e**	H	CF_3	H	20	85
6	**3f**	H	H	Me	20	82
7	**3g**	H	H	OMe	20	83
8	**3h**	H	H	OH	20	87
9	**3i**	Me	H	H	30	76
10	**3j**	Me	H	F	30	74

Table 5
Oxidative cleavage of the terminal C═C bond of 1,3-enynes **5a–d** by *m*-CPBA, yielding **6a–d**



5 6

Entry	R	Time (min)	Yield (%)
6a		75	87
6b	$-(CH_2)_4CH_3$	60	80
6c	$—(CH_2)_5CH_3$	60	84
6d		90	79

compound **4a**, we prepared a series of benzophenone compounds **4a–j** (see Table 4) by using the same reaction conditions employed to form **4a**. The C═C oxidation for these geminal biaryl ethenes proceeded smoothly, and the corresponding products were obtained in moderate to excellent yields. With either electron-donating or electron-withdrawing groups at the *para* and *meta* positions of one of the phenyl rings, the reaction ran efficiently in less than 2 h (entries **4a–h**, Table 4). The reaction was slightly slowed to 3 h for substrates bearing *ortho* Me groups (Table 4, entries **4i** and **4j**). The results for **4a–j** indicate that the electronic effects of the aryl groups in these geminal diaryl ethenes play only a minor role in affecting the rate of C═C oxidation, since various functional groups, including alkyl, alkoxy, halide, and hydroxy groups, were well tolerated (Table 4; entries **4b**–**j**). In contrast, steric hindrance seems to have a more pronounced effect on the reaction rate (Table 4, entries **4i** and **4j**).

As part of our continuing interest in exploring the utility of *m*-CPBA in forming ketonic compounds, we prepared the functionalized 1,3-enynes[35] **5a–d** by palladium-catalyzed cross-coupling reactions of potassium α-styryltrifluoroborate salts with acetylenic *n*-butyltellurides and attempted the oxidation reaction with *m*-CPBA under the optimized reaction conditions. The ynone-based compounds **6a–d** were isolated in 79–87% yields (Table 5).

To investigate the mechanism of C═C oxidative cleavage, we monitored the reaction of **4h** via direct infusion electrospray ionization mass and tandem mass spectrometry in the negative ion

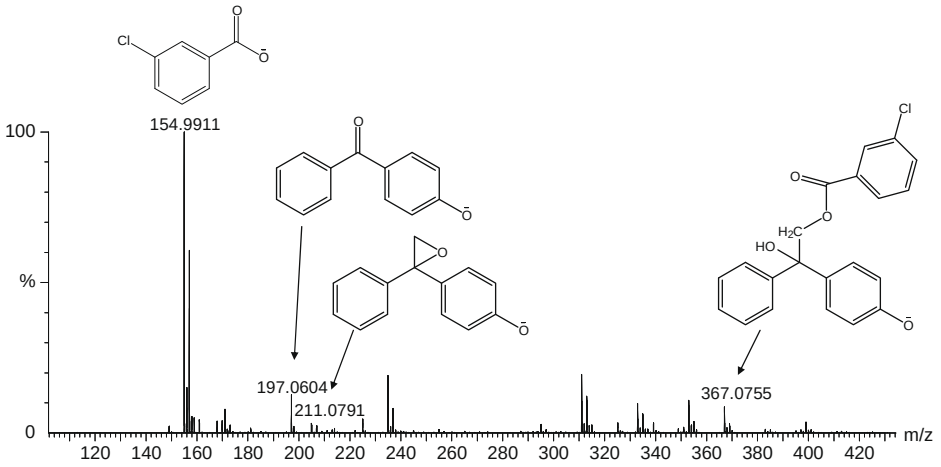


Figure 1. ESI-MS for the C═C oxidative cleavage of **4h** after 25 min of reaction.

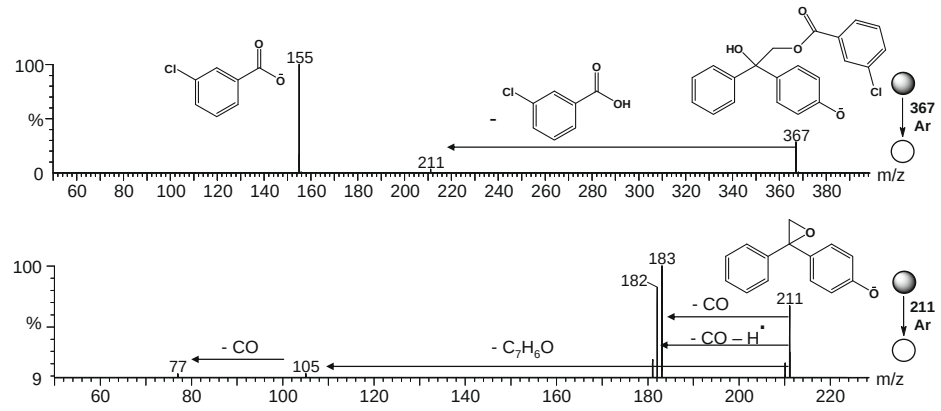


Figure 2. ESI-MS/MS for the key intermediates of *m*/*z* 367 and 211 after 25 min of C═C oxidative cleavage of **4h**.

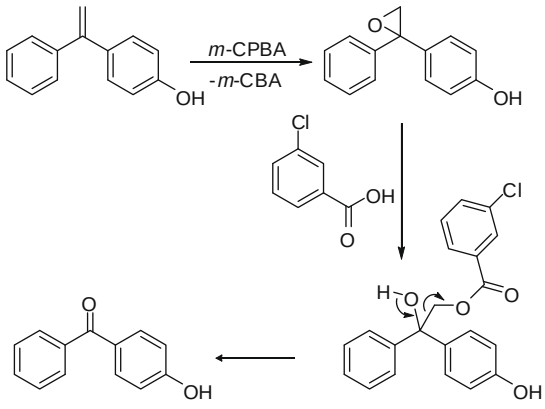


Figure 3. ESI-MS/MS-based possible mechanism for the conversion of terminal double bond into ketonic functionality.

mode: ESI(−)-MS(/MS).[36] Reagents, intermediates, and products in anionic forms were transferred directly from the reaction solution to the gas phase and then characterized. After 25 min of reaction, a characteristic ESI-MS (Fig. 1) was recorded.

In the spectrum of Figure 1, a series of anions were detected, and some anions were identified as key reaction species in their deprotonated forms: the reactant **4h** of *m/z* 197, *m*-CBA of *m/z* 155, and two intermediates of *m/z* 211 and *m/z* 367. The interception of these two key intermediates indicates that the mechanism involves epoxide formation (*m/z* 211), followed by epoxide opening via *m*-CPBA addition (*m/z* 367).

ESI-MS/MS (Fig. 2) was then used to characterize these important intermediates. The resulting spectra supported the structural assignments: the anion of *m/z* 367 undergoes retro-addition either by losing a neutral *m*-CPBA to yield the fragment ion of *m/z* 211 (the epoxide intermediate), or by losing the neutral epoxide to form deprotonated *m*-CPBA of *m/z* 155. The epoxide intermediate of *m/z* 211 loses mainly CO and then a H to yield the fragment ions of *m/z* 183 and *m/z* 182. Based on the above observations, we proposed a possible mechanism for the conversion of the terminal double bond into the ketonic functionality as shown in Figure 3.

2. Conclusion

In summary, we described a simple, fast, and catalyst-free approach to the synthesis of benzophenone and ynone systems by the oxidative cleavage of geminal biaryl ethenes and 1,3-enynes using *m*-CPBA under soft reaction conditions. This approach has the flexibility to introduce the functionalities to the benzophenone and ynone architectures.

Acknowledgments

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33. *General procedure for the synthesis of* **3a–j**: A suspension of 1-phenyl-1-trifluoroborate ethene salt (**1**) (0.105 g, 0.50 mmol), *n*-butylaryl telluride (**2**) (0.5 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.1 mmol), triethylamine (0.101 g, 1 mmol), and silver(I) acetate (0.167 g, 1 mmol) in 5 mL methanol was irradiated in a water bath of an ultrasonic cleaner for 20 min. Then, the reaction was diluted with ethyl acetate (30 mL). The organic layer was washed with a saturated solution of NH_4Cl (2 × 10 mL) and water (2 × 10 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash silica column chromatography using hexane as eluent. (**3a**) Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 2H, CH), 7.28–7.35 (m, 10H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 114.3, 127.7, 128.3, 141.5, 150.1; IR (neat) 1280, 1600, 1656 cm^{-1}; GC/MS: *m/z* (relative, %) 180 (100), 165 (92), 89 (62).
34. *General procedure for the synthesis of* **4a–j**: The solution of 1,1-diarylethene **3** (0.5 mmol) in dichloromethane (5 mL) was placed in a two-necked round-bottomed flask under nitrogen atmosphere. A solution of *m*-chloroperbenzoic acid (0.127 g, 0.75 mmol) in dichloromethane (5 mL) was added dropwise at −78 °C, and the solution was stirred for 30 min at the same temperature and for 60–180 min at room temperature. After the completion of the reaction, the mixture was diluted with chloroform and washed with brine and 10% NaOH solution, then dried with $MgSO_4$. The organic layer was evaporated under vacuum, and the crude product was purified by flash column chromatography using 20–40% chloroform in hexane.(**4a**) White solid; mp 50–52°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.2 Hz, 4H, ArH), 7.52 (t, *J* = 7.2 Hz, 2H, ArH), 7.74 (d, *J* = 7.2 Hz, 4H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 128.3, 130.1, 132.4, 137.6, 196.7; IR (KBr) 1659 (CO) cm^{-1}; GC–MS (%) 182 (52), 105 (100), 77 (64).
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