Synthesis M. Chiarini et al. Feature

Synthesis of 3-Substituted 2,1-Benzisoxazoles by the Oxidative Cyclization of 2-Aminoacylbenzenes with Oxone

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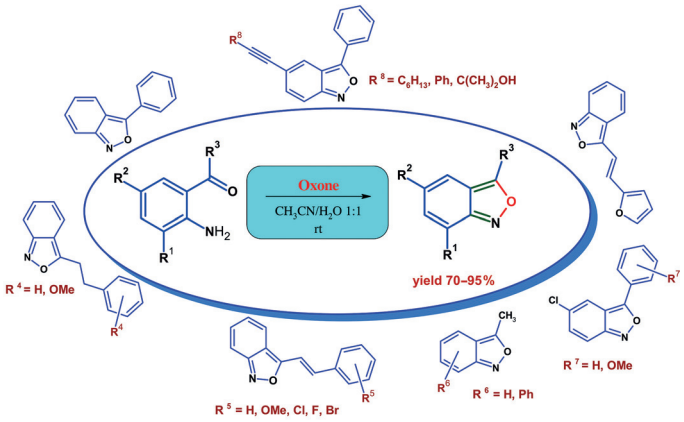

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Abstract An efficient approach to the synthesis of 2,1-benzisoxazoles through direct construction of the N–O bond by the chemoselective oxidation of 2-aminoacylbenzenes with Oxone is described. This alternative methodology is characterized by its simple and transition-metal-free conditions and good functional group compatibility utilizing Oxone as a green oxidant instead of hypervalent iodine compounds. Moreover, this new procedure simplifies the number of steps compared to the previously reported procedure by circumventing the use of 2-azido-substituted aryl ketones.

Key words Oxone, 2,1-benzisoxazoles, 2-aminoacylbenzenes, oxidative cyclization, transition-metal-free

The direct construction of the N–O bond to form the corresponding heterocyclic derivatives is a long-standing challenge in organic synthesis.[1] Despite the relevance of N–O bonds in biologically active heterocycles, only a few methods that form this bond have been reported. Benzisoxazole scaffolds are among the most highly recognized pharmacophores because of their extensive biological activities.[2] In particular, 2,1-benzisoxazoles (anthranils) are key intermediates in the synthesis of various drugs,[3] in addition to their direct application as pharmacologically active compounds.[4] Classically, these compounds are prepared from starting materials with a pre-existing N–O bond. The reactions of 1,3-diketones with hydroxylamine results in 2,1-benzisoxazoles.[4a] A variety of methods for the synthesis of 2,1-benzisoxazoles consist of the condensation of nitroarenes and arylacetonitriles.[5] The $BF_3{\cdot}OEt_2$-catalyzed reaction of glyoxylate esters with nitrosoarenes provided a convergent route to this class of compounds.[6] Reductive heterocyclization of 2-nitroacylbenzenes has also been frequently used to build-up the 2,1-benzisoxazole nucleus.[7] Conversely, an approach to the synthesis of 2,1-benzisoxazoles involving formation of the N–O bond was previously accomplished by the reaction of 2-azido-substituted aryl ketones **2** promoted by iron salts (Scheme 1a).[8] These latter derivatives are obtained in one-step from the 2-aminoacylbenzenes **1**. Moreover, the direct hypervalent iodine oxidation of suitable 2-aminoacylbenzenes **1** to give the corresponding products **3** enabled an efficient synthesis of 3-(β-styryl)-2,1-benzisoxazoles (Scheme 1b).[9]

With the aim to simplify the number of steps by circumventing the use of 2-azido-substituted aryl ketones as the starting materials and to develop a simple, safer and sustainable strategy for the selective oxidative cyclization of the 2-aminoacylbenzenes, herein we report the results of our investigation on the transformation of these latter substrates into the corresponding 2,1-benzisoxazoles by using Oxone as the oxidant (Scheme 1c). Current efforts are devoted to circumvent the use of stoichiometric hypervalent iodine compounds which generate equimolar amounts of organic waste.[10]

Oxone is a non-toxic, cheap, and stable white solid, is easy-to-handle, and is soluble in water. Applications of Oxone in synthetic chemistry represent an attractive area of research.[11] Even though the ability of Oxone to oxidize a broad spectrum of functional groups has been demonstrated,[12] no studies have been reported to date for promoting chemoselective oxidative cyclizations of 2-aminoacylbenzenes. Recently, Oxone was employed as a green oxidant (in water) of nitrogen-rich heterocyclic amines to give the corresponding nitroaromatics via the production of a hydroxylamine intermediate.[13] Oxone over silica gel or alumina was also found to oxidize primary and secondary amines into the corresponding hydroxylamines.[14] Hence, we envisaged that the in situ generation of the hydroxylamine function by the oxidation of the starting 2-aminoacylbenzenes **1** would allow the selective attack on the carbonyl in a subse-

Biographical Sketches

Marco Chiarini received his 'Laurea' degree in chemistry from the University of Camerino in 1994, and his Ph.D. degree in chemistry from the University of Roma 'Tor Vergata' in 2000. Presently he is a full-time Researcher in Organic Chemistry at the Department of Food Chemistry at the University of Teramo. His research interests are focused on supramolecular and organometallic chemistry. In this field, particular attention was directed toward the synthesis of conjugate polymers and on applied colloid and surfaces chemistry. He has worked in the field of surfactant-catalyzed reactions, both from the point of view of possible synthetic applications and of basic knowledge of micellar structure and reactivity, and has acquired skills in magnetic resonance techniques (multinuclear NMR and EPR) applied to organic and food chemistry. In the field of organometallic chemistry, he has acquired expertise on the synthesis of organic conductive π-conjugated polymers.

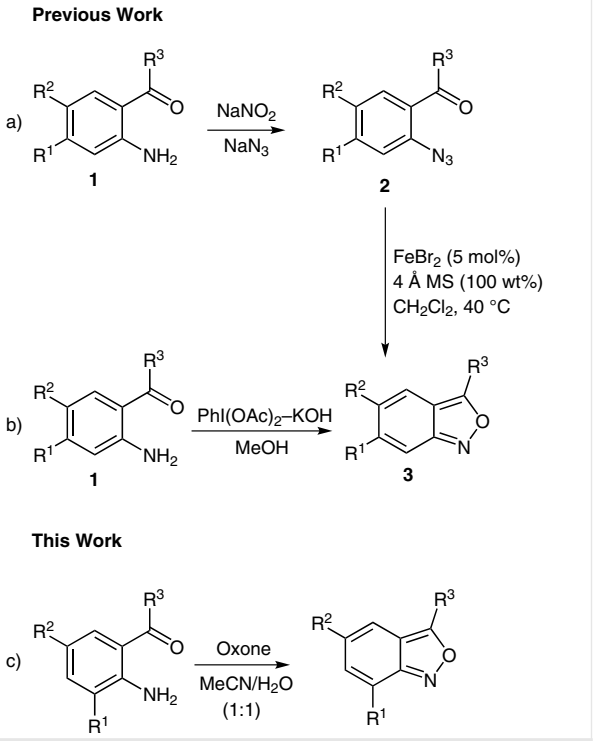
Luana Del Vecchio received he her 'Laurea' degree from 'G. D'Annunzio' University in Chieti in 2014. In the same year, she moved to L'Aquila to begin her Ph.D. in organic chemistry in the group of Professor Antonio Arcadi. Her research is centered on the synthesis of heterocycles.

Fabio Marinelli obtained his 'Laurea' degree in chemistry at the University of Rome 'La Sapienza' in 1980. In 1983, he became Organic Chemistry Researcher at the University of L'Aquila. Since 2001, he has been Associate Professor of Organic Chemistry at the same University. His research interests are centered on the application of organometallic complexes as catalysts in organic synthesis. The main topics of his scientific activity include the synthesis of heterocyclic compounds from alkynes bearing proximate nucleophiles in the presence of Pd and Au salts, or by means of in situ generated organopalladium(II) intermediates, and hydroarylation/hydrovinylation of internal alkynes with aryl halides and organoboron derivatives catalyzed by Pd and Rh complexes.

Leucio Rossi obtained his 'Laurea' degree in chemistry in 1991, and his Ph.D. in chemistry at the University of Rome 'La Sapienza'. In 1995, he became Assistant Professor of Chemistry at the University of L'Aquila, and since 2002, he has been Associate Professor of Chemistry at the same University. His research activity is mainly focused on green chemistry, organic electrosynthesis, and carbon dioxide recycling and reuse.

Antonio Arcadi obtained his 'Laurea' degree in medicinal chemistry and technology at the University of Rome 'La Sapienza' in 1978 under the guidance of Professor S. Cacchi. In 1979, he joined the Institute of Chemistry at the University of L'Aquila to undertake a teaching fellowship and research activities on organometallic chemistry directed toward organic synthesis. He was appointed Associate Professor of Organic Chemistry in 1992 at the university of Urbino, and as Full Professor of Organic Chemistry in 2002 at the University of L'Aquila. His current research interests lie in the area of developing new synthetic methodologies through transition-metal catalysis. More recently, he has focused on the development of gold catalysis in organic synthesis. His other achievements have been obtained in the field of domino reactions as useful tools in 'green chemistry'.

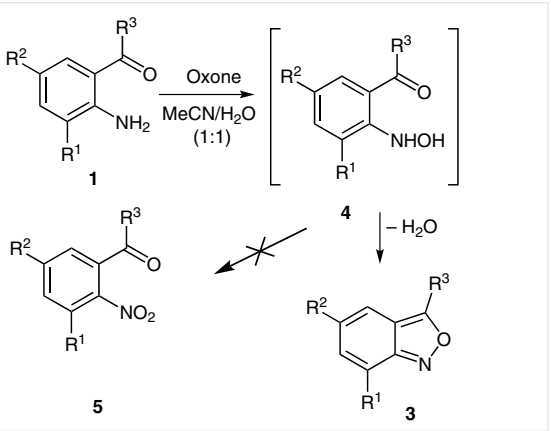
quent heterocyclization–dehydration reaction, overriding further oxidation of the primary amino group into the corresponding nitroaromatic derivatives **5**.[15]



Scheme 1 The previous and our present study on the oxidative cyclization of 2-aminoacylbenzenes **1** to give 2,1-benzisoxazoles **3**

As a part of our ongoing research on the development of efficient, mild, and benign protocols for oxidative cyclizations to access useful heterocycles, herein, we report that Oxone can promote the selective oxidative cyclization of various aminoacylbenzenes **1** to achieve an effective alternative entry into the target 3-substituted 2,1-benzisoxazoles **3** (Scheme 2).

We began our investigation by using commercially available 2-aminobenzophenone (**1a**) in a model reaction and the results are summarized in Table 1. According to our previous studies on the silver-catalyzed oxidative cyclization of unprotected 2-alkynylanilines with Oxone,[16] we carried out the oxidation of **1a** with Oxone in MeCN/H_2O in the presence of a catalytic amount of $AgNO_3$. The desired product **3a** was isolated in 93% yield when the reaction was carried out at 60 °C for 0.5 hours with an excess of Oxone (2 equiv) in the presence of $AgNO_3$ (0.1 equiv) (Table 1, entry 1). A comparable yield of **3a** was observed by omitting the silver catalyst (Table 1, entry 2). Gratifyingly, by lowering the amount of Oxone to one equivalent and omitting the catalyst, product **3a** was isolated in 90% yield at room temperature in a longer time (Table 1, entry 3). The use of other oxidants resulted in unsatisfactory transformations (Table 1, entries 4–12).

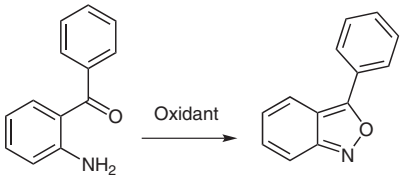


Scheme 2 Proposed reaction pathway

Potassium peroxydisulfate ($K_2S_2O_8$) gave a low conversion of **1a** with no formation of **3a** (Table 1, entry 4).[17] Complete degradation of **1a** into benzoic acid occurred in the presence of Selectfluor (Table 1, entry 5). Similarly, the conversion of **1a** into **3a** was not observed by carrying out the reaction in MeCN at room temperature by using both a slight excess of urea hydrogen peroxide (1.5 equiv) or a larger quantity (10 equiv) of 50% H_2O_2 as the oxidant (Table 1, entries 6 and 7). The 2,1-benzisoxazole **3a** was isolated in 6% yield when the reaction of **1a** with 50% H_2O_2 was carried out at 60 °C (Table 1, entry 8). A lack of selectivity occurred when adding $AgNO_3$ (0.1 equiv) as the catalyst in the hydrogen peroxide mediated oxidation of **1a**. Under these latter conditions, the complete conversion of **1a** led to the formation of **3a** (30% yield) and 1,2-bis(2-benzoylphenyl)diazene-1-oxide (**5a**) (22% yield) (Table 1, entry 9). According to the literature, the further oxidation of the hydroxylamine intermediate **4a** into 1,2-bis(2-benzoylphenyl)diazene-1-oxide (**5a**) could be accelerated by metal catalysts.[18] Although methyltrioxorhenium–hydrogen peroxide systems,[19] iron(III)-salen–H_2O_2[20] as well as mesoporous titania microspheres,[21] and simple TiO_2 in ionic liquid[22] have been used to promote selective aniline oxidative coupling to give the corresponding azoxybenzenes, challenges remain to afford high selectivities, and the study of the effects of silver catalysis toward this aim deserves in-depth analysis.

The formation of a variable amount of the derivative **5a** was also detected both in the presence of $AgNO_3$ and under metal-free conditions when *m*-CPBA was used as the oxidant instead of hydrogen peroxide (Table 1, entries 10–12).[23] The oxidation of **1a** to give the nitro derivative **6a** prevailed by using excess *m*-CPBA (Scheme 3).

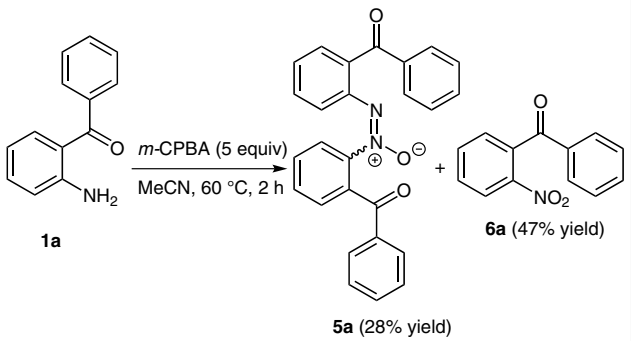
Table 1 Optimization of the Reaction Conditions



1a **3a**

Entry	Oxidant (equiv)	Temp (°C)	Time (h)	Yield of **3a** (%)[a,b]
1	Oxone (2)[c]	60	0.5	93
2	Oxone (2)	60	0.5	92
3	Oxone (1)	r.t.	22	90
4	$K_2S_2O_8$ (1)	r.t.	24	– (90)[d,e]
5	Selectfluor (3)[d]	r.t.	1	–
6	$H_2NCONH_2{\cdot}H_2O_2$ (1.5)[d]	r.t.	48	– (83)[e]
7	50% H_2O_2 (10)[f]	r.t.	24	– (84)[e]
8	50% H_2O_2 (10)[f]	60	24	6 (84)[e]
9	50% H_2O_2 (10)[g]	60	24	30[h]
10	*m*-CPBA (1.5)[d]	r.t.	48	2 (45)[e,i]
11	*m*-CPBA (1.5)[d]	60	24	3 (40)[e,j]
12	*m*-CPBA (1.5)[d]	60	24	3 (41)[e,k]

[a] Yield of isolated product.
[b] Unless otherwise noted, all reactions were performed with 1.0 mmol of **1a** in MeCN/H_2O (2.5 mL/2.5 mL).
[c] Reaction was carried out in the presence of 0.1 equiv of $AgNO_3$.
[d] Reaction was carried out in MeCN.
[e] Figures in parentheses refer to the recovered yield of **1a**.
[f] Reaction was performed with 1.8 mmol of **1a** in MeCN/H_2O_2 50 wt% in H_2O (4.0 mL/1.0 mL).
[g] Reaction was performed with 1.8 mmol of **1a** in MeCN/H_2O_2 50 wt% in H_2O (4.0 mL/1.0 mL) in the presence of 0.1 equiv of $AgNO_3$.
[h] Compound **5a** was isolated in 22% yield.
[i] Compound **5a** was isolated in 21% yield.
[j] Compound **5a** was isolated in 47% yield.
[k] Compound **5a** was isolated in 35% yield.

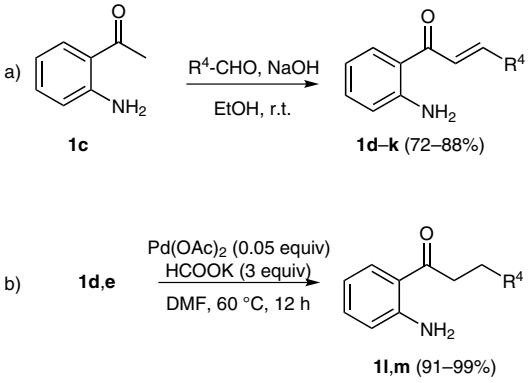


1a **6a** (47% yield)

5a (28% yield)

Scheme 3 *m*-CPBA-mediated oxidative coupling of 2-aminobenzophenone (**1a**)

Our results clearly highlight that the oxidation of the amino group of **1a** may result in the formation of multiple products and that the lack of selectivity can represent a strong shortcoming. Interestingly, in the case of Oxone, the exclusive formation of **3a** was achieved in high yield avoiding harsh conditions and expensive catalysts. Thus, we finalized the reaction conditions by employing a 1:1 mixture of MeCN/H_2O as the reaction medium with Oxone (1 equiv) at room temperature. These conditions were utilized to explore the substrate scope of the oxidative cyclization of 2-aminoacylbenzenes **1**. The 2-aminochalcones **1d**–**k** were easily prepared by means of aldol condensation reactions (Scheme 4a).[24]



1c **1d–k** (72–88%)

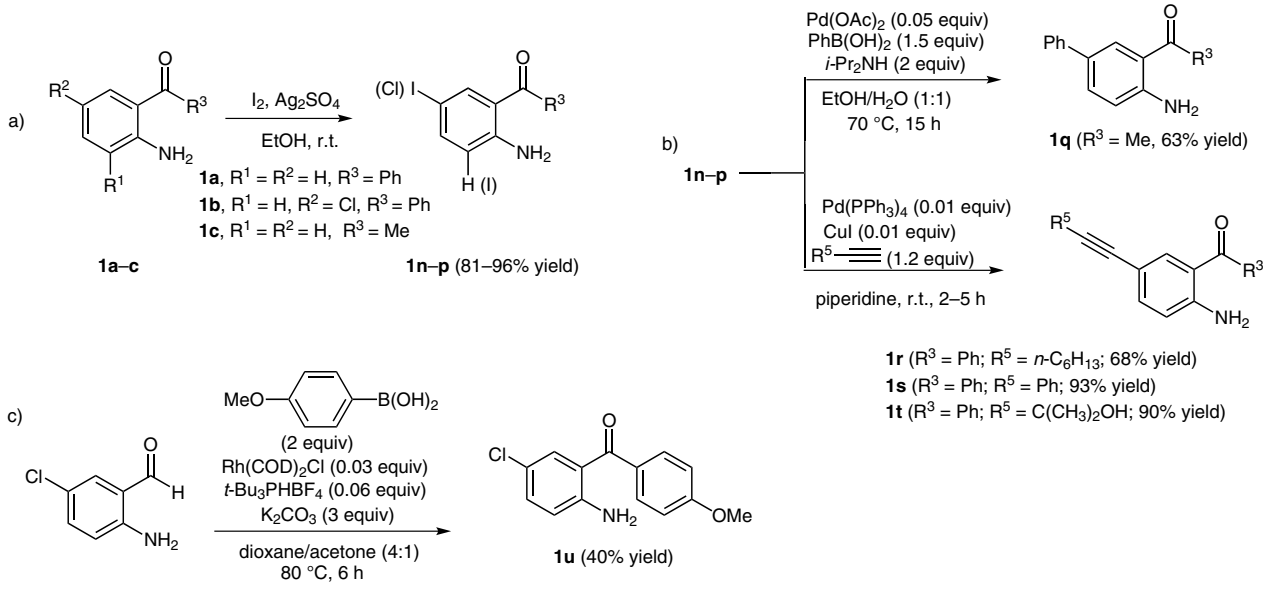
1d,e **1l,m** (91–99%)

Scheme 4 Synthesis of 2-aminochalcones **1d**–**k** and the palladium-catalyzed conjugate reduction of 2-aminochalcones **1d,e**

The palladium-catalyzed selective reduction reactions of **1d,e** with potassium formate led to the isolation of the corresponding alkyl derivatives **1l,m** in 99% and 91% yield, respectively (Scheme 4b).[25]

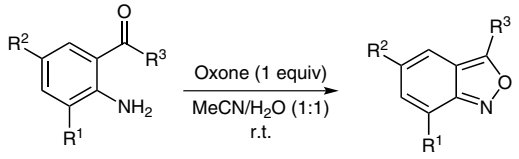
The iodination of **1a**–**c** led selectively in high yields to the corresponding iodo derivatives **1n**–**p** (Scheme 5a),[26] which in turn underwent palladium-catalyzed cross-couplings to give 1-(4-amino-[1,1'-biphenyl]-3-yl)ethan-1-one (**1q**)[27] and the alkynyl derivatives **1r**–**t** (Scheme 5b).[28] The direct access to 2-aminoacyl derivative **1u** was achieved from the corresponding 2-amino-5-chlorobenzaldehyde via rhodium-catalyzed cross-coupling with (4-methoxyphenyl)boronic acid (Scheme 5c).[29]

The results of our investigations on the substrate scope of the Oxone-mediated oxidative cyclization of 2-aminoacylbenzenes are summarized in Table 2.



Scheme 5 Functionalization reactions of 2-aminoacylbenzenes

Table 2 Scope of the Oxone-Promoted Oxidative Cyclization of 2-Aminoacylbenzenes into 2,1-Benzisoxazoles



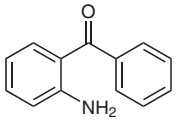
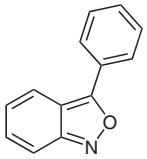
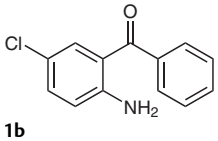
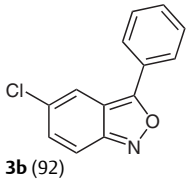
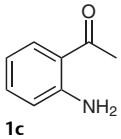
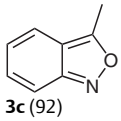
Entry	Substrate	Time (h)	Product/yield (%)[a]
1	 **1a**	20	 **3a** (90)
2	 **1b**	16	 **3b** (92)
3	 **1c**	8	 **3c** (92)

Table 2 (continued)

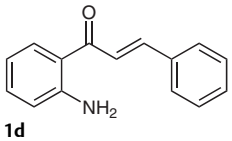
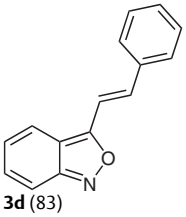
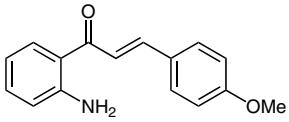
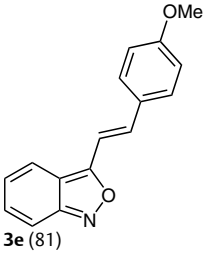
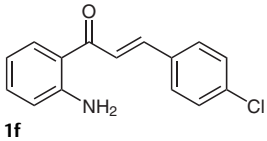
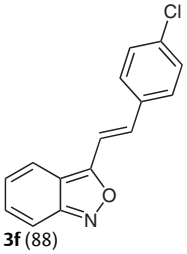
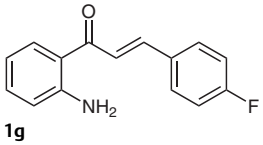
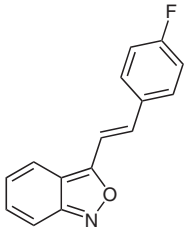
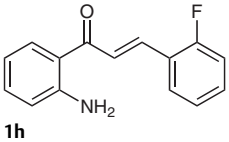
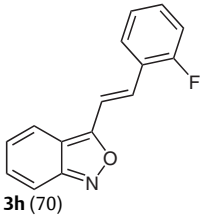
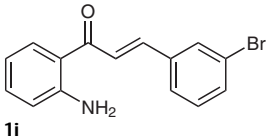
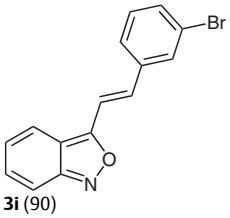
Entry	Substrate	Time (h)	Product/yield (%)[a]
4	 **1d**	12	 **3d** (83)
5	 **1e**	12	 **3e** (81)
6	 **1f**	12	 **3f** (88)
7	 **1g**	24	 **3g** (72)
8	 **1h**	12	 **3h** (70)
9	 **1i**	6	 **3i** (90)

Table 2 (continued)

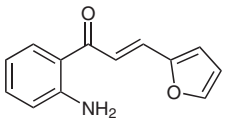
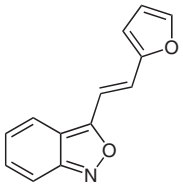
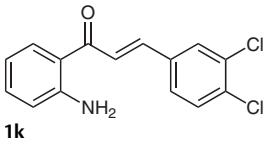
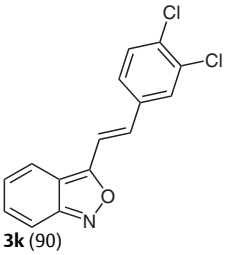
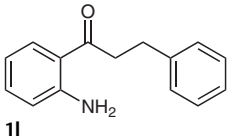
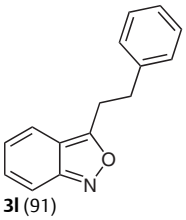
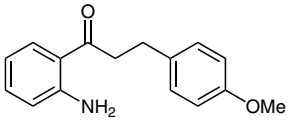
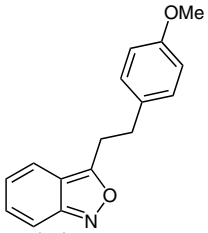
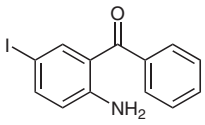
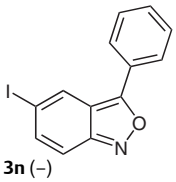
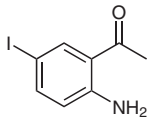
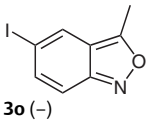
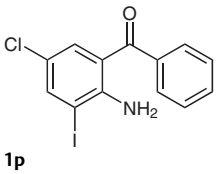
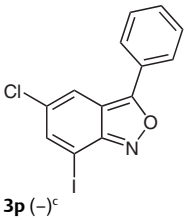
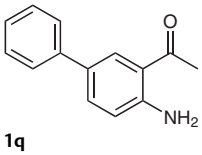
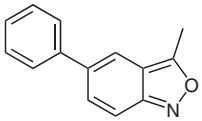
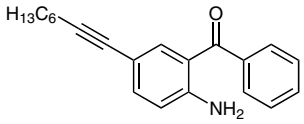
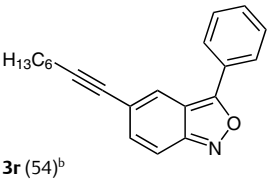
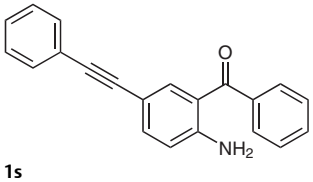
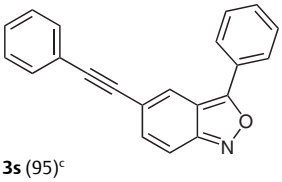
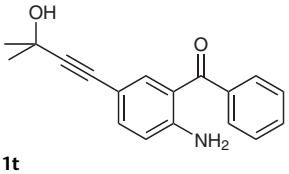
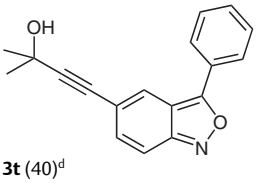
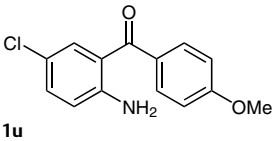
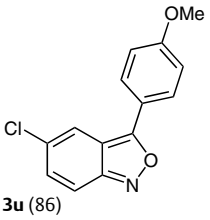
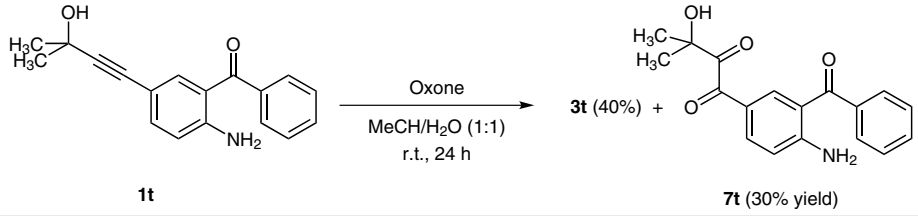
Entry	Substrate	Time (h)	Product/yield (%)[a]
10	 **1j**	20	 **3j** (86)
11	 **1k**	24	 **3k** (90)
12	 **1l**	23	 **3l** (91)
13	 **1m**	21	 **3m** (86)
14	 **1n**	23	 **3n** (–)
15	 **1o**	24	 **3o** (–)
16	 **1p**	24	 **3p** (–)[c]

Table 2 (continued)

Entry	Substrate	Time (h)	Product/yield (%)[a]
17	 **1q**	17	 **3q** (92)
18	 **1r**	24	 **3r** (54)[b]
19	**1r**	6	**3r** (80)[c]
20	 **1s**	15	 **3s** (95)[c]
21	 **1t**	24	 **3t** (40)[d]
22	 **1u**	8	 **3u** (86)

[a] Yield of isolated product.
[b] Starting material **1r** was recovered in 36% yield.
[c] Reaction temperature = 60 °C.
[d] Product **7t** was isolated in 30% yield.

The effect of the R^3 substituent on the reaction was surveyed. 2,1-Benzisoxazoles were obtained in good to high yields from substrates bearing aryl, vinyl or alkyl R^3 groups. Although, a variety of olefins, including chalcones, were cleaved oxidatively to give the corresponding acids with Oxone in acetonitrile/water mixture (1:1, v/v) at reflux temperature,[30] and Oxone/acetone-mediated syn-dioxygenation of benzo-fused olefins has been described,[31] our mild reaction conditions were compatible with the presence of the C=C double bond, accomplishing an alternative and very efficient synthesis of the corresponding 3-(β-styryl)-2,1-benzisoxazoles[9] **3d**–**k** from the readily available *o*-aminochalcones **1d**–**k** (Table 2, entries 4–11). Interestingly, the procedure was extended to the synthesis of (*E*)-3-[(2-furan-2-yl)vinyl]benzo[*c*]isoxazole (**3j**) (Table 2, entry 10). By contrast with the moderate yield (50%) of the 3-methyl-2,1-benzisoxazole reported in the oxidation of 2-aminoacetophenone (**1c**) promoted by hypervalent iodine, the Oxone-promoted oxidation of 2-aminoacylbenzenes bearing alkyl R^3 groups **1c**,**l**,**m** resulted in the formation of the corresponding anthranil derivatives **3c**,**l**,**m** in high yields (Table 2, entries 3, 12 and 13). A variety of R^2 groups were also tolerated. The present reaction conditions were compatible with the presence of Cl, phenyl, and alkynyl R^2 groups. In



1t **7t** (30% yield)

Scheme 6 Competitive side oxidation of the C≡C triple bond

the presence of the alkynyl group, better results were observed at 60 °C. Indeed, the yield of **3r** increased from 54% to 80% by carrying out the reaction at 60 °C instead of at room temperature (Table 2, entries 18 and 19). Only in the case of the reaction of **1t** did we observed the competitive side oxidation of the carbon–carbon triple bond[32] to give **7t** in 30% yield (Scheme 6).

The *ortho*-disubstituted derivative **1p** remained unaffected even at 60 °C (Table 2, entry 16).[33] Moreover, in contrast with the reported tolerability to Oxone of some iodo derivatives,[11c,d] we failed to obtain the desired iodo-2,1-benzisoxazole derivatives **3n**,**o** (Table 2, entries 14 and 15). Very likely, under our reaction conditions, the iodo-2-aminoacylbenzene derivatives **1n**,**o** can be oxidized by Oxone to give iodine(V) species, which trigger further unselective oxidative processes.[34]

In summary, we have developed a novel protocol for the synthesis of 2,1-benzisoxazoles via the oxidative cyclization reaction of 2-aminoacylbenzenes with Oxone. Such more environmentally friendly protocols, which utilize transition-metal-free, mild reaction conditions, and inexpensive and readily available reagents, provide an effective alternative strategy for the chemoselective construction of these target molecules, which occupy privileged positions in the fields of pharmaceuticals and materials science.

Unless otherwise stated, all starting materials, catalysts, and solvents were commercially available and were used as purchased. Reaction products were purified by flash chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures. Compounds **1a**–**c** are commercially available; compounds **1d**,[35] **1e**,[36] **1f**,**g**,[35] **1h**,[24a] **1i**,[37] **1j**,**k**,[24a] **1n**,[38] **1o**,[39] **1p**,[40] **1q**,[41] **3a**,[42] **3b**,[43] **3c**,[42] **3d**–**f**,[9] **3q**,[44] **3s**,[45] **3u**,[45] and **6a**[46] are known and were identified by comparison of their physical and spectral data with those reported in the cited references. Melting points were obtained using a Büki 500 apparatus and are uncorrected. IR spectra (KBr pellets or neat on NaCl plates) were recorded on a Perkin-Elmer Spectrum Two FT-IR spectrometer. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker Avance III spectrometer. Chemical shifts (in ppm) are referenced to tetramethylsilane (δ = 0) in $CDCl_3$ or in DMSO-d_6 as an internal standard (δ = 2.49). ^{13}C NMR spectra were obtained using the same instrument at 100.6 MHz and were calibrated with $CDCl_3$ (δ = 77.00) or DMSO-d_6 (δ = 30.50). HRMS spectra were recorded using a MALDI-TOF spectrometer: AB SCIEX TOF/TOF 5800 System.

2-Aminochalcones 1d–k; General Procedure

The aldehyde (5.0 mmol) was dissolved in EtOH (5 mL) and NaOH (1 pellet) and 2-aminoacetophenone (**1c**) (5.0 mmol) were successively added to the solution. The mixture was stirred at r.t. for 2–24 h. The reaction progress was monitored by TLC. When the reaction was complete, the mixture was diluted with a solution of NH_4Cl (0.5 M) and extracted with EtOAc (× 3). The combined organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue purified by silica gel flash column chromatography.

1-(2-Aminophenyl)-3-substituted Propan-1-ones 1l,m; Typical Procedure

Synthesis of 1-(2-Aminophenyl)-3-(4-methoxyphenyl)propan-1-one (1m)

$Pd(OAc)_2$ (0.008 g, 0.036 mmol) was added to a stirred solution of 1-(2-aminophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1e**) (0.192 g, 0.72 mmol) in DMF (3 mL). The mixture was purged with N_2 and HCOOK (0.160 g, 1.90 mmol) was added in one portion. The temperature was raised to 60 °C and the mixture was stirred at that temperature for 12 h under an N_2 atm. Next, CH_2Cl_2 and sat. Na_2CO_3 solution were added to the cooled mixture. The organic layer was separated, washed with H_2O, and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 98:2) to give 1-(2-aminophenyl)-3-(4-methoxyphenyl)propan-1-one (**1m**).

1-(2-Aminophenyl)-3-phenylpropan-1-one (1l)

White solid; yield: 0.101 g (99%); mp 69–71 °C.

IR (KBr): 3473, 3340, 1650, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (ddd, *J* = 8.1 Hz, *J* = 1.5 Hz, *J* = 0.4 Hz, 1 H), 7.32–7.18 (m, 6 H), 6.63 (ddd, *J* = 8.3 Hz, *J* = 1.2 Hz, *J* = 0.5 Hz, 1 H), 6.61 (ddd, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz, 1 H), 6.27 (br s, 2 H, NH_2), 3.28–3.24 (m, 2 H), 3.06–3.02 (m, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.5 (C=O), 150.4 (C), 141.5 (C), 134.3 (CH), 131.0 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 117.8 (C), 117.4 (CH), 115.8 (CH), 41.0 (CH_2), 30.6 (CH_2).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{15}H_{15}KNO$: 264.0791; found: 264.0784.

1-(2-Aminophenyl)-3-(4-methoxyphenyl)propan-1-one (1m)

Off-white semi-solid; yield: 0.168 g (91%).

IR (neat): 3473, 3340, 1639, 1039, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (ddd, *J* = 8.1 Hz, *J* = 1.5 Hz, *J* = 0.4 Hz, 1 H), 7.26–7.21 (m, 1 H), 7.18–7.14 (m, 2 H), 6.85–6.82 (m, 2 H), 6.65–6.59 (m, 2 H), 6.29 (br s, 2 H, NH_2), 3.78 (s, 3 H, OMe), 3.24–3.20 (m, 2 H), 3.00–2.96 (m, 2 H).

$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 201.7 (C=O), 158.0 (C), 150.4 (C), 134.2 (CH), 133.5 (C), 131.1 (CH), 129.3 (2 CH), 117.9 (C), 117.4 (CH), 115.8 (CH), 114.0 (2 CH), 55.3 (CH_3), 41.2 (CH_2), 29.8 (CH_2).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_2$: 256.1336; found: 256.1337.

Selective Iodination of 2-Aminoacylbenzenes 1a–c; Typical Procedure

Synthesis of (2-Amino-5-chloro-3-iodophenyl)(phenyl)methanone (1p)

(2-Amino-5-chlorophenyl)(phenyl)methanone (**1b**) (0.300 g, 1.29 mmol), I_2 (0.327 g, 1.29 mmol) and Ag_2SO_4 (0.402 g, 1.29 mmol) in EtOH (10 ml) were stirred for 12 h at r.t. After this time, the crude mixture was filtered to eliminate the precipitate of inorganic salt and then washed with sat. $Na_2S_2O_3$ solution. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (*n*-hexane) to give **1p**.

Yield: 0.444 g (94%).

1-(4-Amino-[1,1′-biphenyl]-3-yl)ethanone (1q)

$Pd(OAc)_2$ (0.009 g, 0.04 mmol) was added to a stirred solution of phenylboronic acid (0.146 g, 1.20 mmol) and *i*-Pr_2NH (0.162 g, 1.60 mmol) in EtOH/H_2O (3 mL/3 mL). The mixture was purged with N_2, the temperature raised to 70 °C, and the mixture stirred at the same temperature for 15 h under an N_2 atm. The cooled mixture was diluted with a solution of NH_4Cl (0.5 M) and extracted with EtOAc (× 3). The combined organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (*n*-hexane/EtOAc, 97:3) to give **1q**.

Yield: 0.106 g (63%).

Alkynylation of (2-Amino-5-iodophenyl)(phenyl)methanone (1n); Typical Procedure

Synthesis of [2-Amino-5-(phenylethynyl)phenyl](phenyl)methanone (1s)

$Pd[(PPh_3)]_4$ (0.005 g, 0.005 mmol) was added to a stirred solution of (2-amino-5-iodophenyl)(phenyl)methanone (**1n**) (0.147 g, 0.46 mmol), phenylacetylene (0.056 g, 0.55 mmol) and CuI (0.001 g, 0.005 mmol) in piperidine (5 mL). The mixture was purged with N_2 and stirred at r.t. for 5 h under an N_2 atm. The mixture was diluted with HCl (1.0 M and extracted with EtOAc (× 3). The combined organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (*n*-hexane/EtOAc, 90:10) to give **1s**.

[2-Amino-5-(oct-1-yn-1-yl)phenyl](phenyl)methanone (1r)

Brown oil; yield: 0.095 g (68%).

IR (neat): 3462, 3350, 2225, 1640, 825, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H), 7.55–7.44 (m, 4 H), 7.31 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 6.18 (br s, 2 H, NH_2), 2.32 (t, *J* = 7.1 Hz, 2 H), 1.57–1.50 (m, 2 H), 1.42–1.26 (m, 6 H), 0.87 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.6 (C=O), 150.2 (C), 139.7 (C), 137.6 (CH), 137.2 (CH), 131.2 (CH), 129.1 (2 CH), 128.2 (2 CH), 117.8 (C), 117.0 (CH), 111.0 (C), 88.0 (C), 80.0 (C), 31.3 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 22.5 (CH_2), 19.4 (CH_2), 14.0 (CH_3).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{23}KNO$: 344.1417; found: 344.1410.

[2-Amino-5-(phenylethynyl)phenyl](phenyl)methanone (1s)

Pale yellow solid; yield: 0.127 g (93%); mp 140–142 °C.

IR (KBr): 3437, 3325, 2210, 1630, 1243, 758 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 3 H), 7.57–7.53 (m, 1 H), 7.49–7.42 (m, 5 H), 7.31–7.24 (m, 3 H), 6.69 (d, *J* = 8.6 Hz, 1 H), 6.28 (br s, 2 H, NH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.5 (C=O), 150.7 (C), 139.6 (C), 137.8 (CH), 137.1 (CH), 131.4 (CH), 131.3 (2 CH), 129.2 (2 CH), 128.28 (2 CH), 128.27 (2 CH), 127.9 (CH), 123.5 (C), 117.8 (C), 117.2 (CH), 110.0 (C), 89.2 (C), 87.4 (C).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{15}KNO$: 336.0791; found: 336.0788.

[2-Amino-5-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl](phenyl)methanone (1t)

Pale yellow solid; 0.115 g (90%); mp 151–153 °C.

IR (KBr): 3432, 3315, 2224, 1625, 840, 662 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H), 7.57–7.52 (m, 2 H), 7.50–7.45 (m, 2 H), 7.32 (dd, *J* = 8.6 Hz, *J* = 2.0 Hz, 1 H), 6.66 (d, *J* = 8.6 Hz, 1 H), 6.25 (br s, 3 H, OH, NH_2), 1.55 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.5 (C=O), 150.7 (C), 139.6 (C), 137.8 (CH), 137.2 (CH), 131.4 (CH), 129.1 (2 CH), 128.3 (2 CH), 117.7 (C), 117.1 (CH), 109.5 (C), 91.6 (C), 81.8 (C), 65.6 (C), 31.6 (2 CH_3).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{18}H_{17}KNO_2$: 318.0896; found: 318.0890.

(2-Amino-5-chlorophenyl)(4-methoxyphenyl)methanone (1u)

To a mixture of 4-methoxyphenylboronic acid (0.252 g, 1.66 mmol), 2-amino-5-chlorobenzaldehyde (0.130 g, 0.83 mmol), K_2CO_3 (0.344 g, 2.49 mmol), and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.0012 g, 0.025 mmol) in dioxane/acetone (2 mL/0.5 mL) was added tri-*t*-butylphosphonium tetrafluoroborate (0.014 g, 0.050 mmol) under an N_2 atm. The temperature was raised to 80 °C and the reaction mixture was stirred at that temperature for 6 h under an N_2 atm. After concentration under reduced pressure, the crude residue was purified by silica gel chromatography (*n*-hexane/EtOAc, 92:8) to give product **1u**.

Brown oil; yield: 0.087 g (40%).

IR (neat): 3468, 3355, 1644, 782, 747 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 2 H), 7.43–7.40 (m, 1 H), 7.22 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1 H), 6.98–6.95 (m, 2 H), 6.68 (d, *J* = 8.8 Hz, 1 H), 5.82 (br s, 2 H, NH_2), 3.88 (s, 3 H, OCH_3).

$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 196.5 (C=O), 162.7 (C), 148.8 (C), 133.5 (CH), 132.7 (CH), 131.8 (2 CH), 131.5 (C), 130.9 (C), 128.8 (C), 118.4 (CH), 113.6 (2 CH), 55.5 (OCH_3).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{14}H_{12}ClKNO_2$: 300.0194; found: 300.0196.

Oxidative Cyclization of 2-Aminoacylbenzenes 1; Typical Procedure

Synthesis of 3-[(*E*)-2-(4-Fluorophenyl)vinyl]-2,1-benzisoxazole (3g)

Oxone (0.270 g, 0.44 mmol) was added to a solution of (*E*)-1-(2-aminophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**1g**) (0.106 g, 0.44 mmol) in MeCN/H_2O (2.5 mL/2.5 mL). The mixture was stirred at r.t. and the progress was monitored by TLC and GC–MS. After stirring for 24 h, H_2O (150 mL) and CH_2Cl_2 (150 mL) were added. The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The filtrate was evaporated and subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 98:2) to give 2,1-benzisoxazole **3g**.

Pale yellow solid; 0.075 g (72%); mp 124–126 °C.

IR (KBr): 1639, 1599, 1507, 1227, 967, 820, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (dt, *J* = 8.8 Hz, *J* = 1.0 Hz, 1 H), 7.59–7.53 (m, 4 H), 7.30 (ddd, *J* = 9.1 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, 1 H), 7.22 (dd, *J* = 16.5 Hz, *J* = 0.6 Hz, 1 H), 7.12–7.08 (m, 2 H), 7.01 (ddd, *J* = 8.8 Hz, *J* = 6.4 Hz, *J* = 0.8 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 163.31 (*J* = 250.4 Hz, C), 163.30 (C), 157.4 (C), 133.8 (*J* = 1.1 Hz, CH), 131.9 (*J* = 3.4 Hz, C), 130.9 (CH), 129.0 (*J* = 8.2 Hz, CH), 124.1 (CH), 119.7 (CH), 116.1 (*J* = 21.9 Hz, CH), 115.4 (C), 115.3 (CH), 111.8 (*J* = 2.6 Hz, CH).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}FNO$: 240.0825; found: 240.0820.

3-[(*E*)-2-(2-Fluorophenyl)vinyl]-2,1-benzisoxazole (3h)

Pale yellow solid; 0.072 g (70%); mp 108–110 °C.

IR (KBr): 1487, 1461, 1232, 962, 815, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 16.6 Hz, 1 H), 7.65 (dt, *J* = 8.8 Hz, *J* = 1.1 Hz, 1 H), 7.62 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1 H), 7.57 (ddd, *J* = 9.1 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, 1 H), 7.43 (d, *J* = 16.6 Hz, 1 H), 7.33–7.28 (m, 2 H), 7.19 (td, *J* = 7.6 Hz, *J* = 1.0 Hz, 1 H), 7.12 (ddd, *J* = 11.0 Hz, *J* = 8.2 Hz, *J* = 1.2 Hz, 1 H), 7.03 (ddd, *J* = 8.8 Hz, *J* = 6.4 Hz, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 163.3 (C), 161.0 (*J* = 252.6 Hz, C), 157.4 (C), 130.9 (CH), 130.6 (*J* = 8.6 Hz, CH), 128.2 (*J* = 3.1 Hz, CH), 127.7 (*J* = 2.7 Hz, CH), 124.5 (*J* = 3.6 Hz, CH), 124.3 (CH), 123.7 (*J* = 11.6 Hz, C), 119.8 (CH), 116.2 (*J* = 22.0 Hz, CH), 116.0 (C), 115.4 (CH), 114.5 (*J* = 7.4 Hz, CH).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}FNO$: 240.0825; found: 240.0828.

3-[(*E*)-2-(3-Bromophenyl)vinyl]-2,1-benzisoxazole (3i)

Pale yellow solid; 0.097 g (90%); mp 135–137 °C.

IR (KBr): 1620, 1563, 1517, 967, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 1.8 Hz, *J* = 1.4 Hz, 1 H), 7.64 (dt, *J* = 8.8 Hz, *J* = 1.1 Hz, 1 H), 7.58 (ddd, *J* = 9.1 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, 1 H), 7.54–7.46 (m, 3 H), 7.32 (ddd, *J* = 9.1 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, 1 H), 7.31–7.30 (m, 1 H), 7.28–7.26 (m, 1 H), 7.04 (ddd, *J* = 8.8 Hz, *J* = 6.4 Hz, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.8 (C), 157.4 (C), 137.8 (C), 133.2 (CH), 132.1 (CH), 130.9 (CH), 130.4 (CH), 129.8 (CH), 126.0 (CH), 124.5 (CH), 123.2 (C), 119.6 (CH), 116.2 (C), 115.4 (CH), 113.2 (CH).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}BrNO$: 300.0024; found: 300.0016.

3-[(*E*)-2-(2-Furyl)vinyl]-2,1-benzisoxazole (3j)

Orange solid; 0.087 g (86%); mp 96–98 °C.

IR (KBr): 1629, 1522, 1451, 957, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dt, *J* = 8.8 Hz, *J* = 1.1 Hz, 1 H), 7.54 (ddd, *J* = 9.1 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, 1 H), 7.50 (ddd, *J* = 1.8 Hz, *J* = 1.2 Hz, *J* = 0.5 Hz, 1 H), 7.35 (dt, *J* = 16.1 Hz, *J* = 0.5 Hz, 1 H), 7.29 (ddd, *J* = 9.1 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, 1 H), 7.21 (dt, *J* = 16.1 Hz, *J* = 0.5 Hz, 1 H), 6.99 (ddd, *J* = 8.8 Hz, *J* = 6.4 Hz, *J* = 0.8 Hz, 1 H), 6.58 (ddd, *J* = 3.4 Hz, *J* = 1.2 Hz, *J* = 0.6 Hz, 1 H), 6.49 (dd, *J* = 3.3 Hz, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 163.3 (C), 157.4 (C), 151.9 (C), 143.9 (CH), 130.9 (CH), 123.9 (CH), 121.6 (CH), 119.8 (CH), 116.0 (C), 115.2 (CH), 112.9 (CH), 112.4 (CH), 109.8 (CH).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}NO_2$: 212.0712; found: 212.0706.

3-[(*E*)-2-(3,4-Dichlorophenyl)vinyl]-2,1-benzisoxazole (3k)

Pale yellow solid; 0.124 g (90%); mp 180–182 °C.

IR (KBr): 1639, 1100, 881, 820, 743 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.12 (dd, *J* = 2.1 Hz, *J* = 0.3 Hz, 1 H), 8.01 (dt, *J* = 8.8 Hz, *J* = 1.1 Hz, 1 H), 7.90 (d, *J* = 16.6 Hz, 1 H), 7.79 (ddd, *J* = 8.4 Hz, *J* = 2.1 Hz, *J* = 0.5 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 16.6 Hz, 1 H), 7.60 (ddd, *J* = 9.1 Hz, *J* = 1.1 Hz, *J* = 0.8 Hz, 1 H), 7.42 (ddd, *J* = 9.1 Hz, *J* = 6.4 Hz, *J* = 1.0 Hz, 1 H), 7.14 (ddd, *J* = 8.8 Hz, *J* = 6.4 Hz, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 162.8 (C), 156.7 (C), 136.4 (C), 131.7 (CH), 131.6 (C), 131.4 (CH), 131.2 (C), 130.7 (CH), 128.8 (CH), 127.3 (CH), 124.4 (CH), 120.4 (CH), 115.8 (C), 114.40 (CH), 114.35 (CH).

HRMS MALDI-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}Cl_2NO$: 290.0139; found: 290.0147.

3-(2-Phenylethyl)-2,1-benzisoxazole (3l)

Off-yellow semi-solid; yield: 0.081 g (91%).

IR (neat): 1645, 1522, 1461, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 1 H), 7.29–7.15 (m, 7 H), 6.87–6.83 (m, 1 H), 3.44 (t, *J* = 7.8 Hz, 2 H), 3.16 (t, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.2 (C), 157.0 (C), 139.9 (C), 130.7 (CH), 128.6 (2 CH), 128.3 (2 CH), 126.6 (CH), 122.9 (CH), 119.7 (CH), 115.5 (C), 114.9 (CH), 34.0 (CH_2), 28.8 (CH_2).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{15}H_{13}KNO$: 262.0634; found: 262.0630

3-[2-(4-Methoxyphenyl)ethyl]-2,1-benzisoxazole (3m)

Off-yellow semi-solid; yield: 0.099 g (86%).

IR (neat): 1645, 1609, 1517, 1034, 825, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 9.1 Hz, 1 H), 7.27–7.21 (m, 2 H), 7.08–7.06 (m, 2 H), 6.85 (dd, *J* = 8.8 Hz, *J* = 6.4 Hz, 1 H), 6.81–6.79 (m, 2 H), 3.76 (s, 3 H, OMe), 3.40 (d, *J* = 7.7 Hz, 2 H), 3.10 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.4 (C) , 158.3 (C), 157.1 (C), 130.7 (CH), 132.1 (C), 129.3 (2 CH), 122.9 (CH), 119.8 (CH), 115.5 (C), 114.9 (CH), 114.1 (2 CH), 55.3 (CH_3), 33.1 (CH_2), 29.1 (CH_2).

HRMS MALDI-TOF: *m*/*z* [M + K]$^+$ calcd for $C_{16}H_{15}KNO_2$: 292.0740; found 292.0734.

5-Oct-1-yn-1-yl-3-phenyl-2,1-benzisoxazole (3r)

Brown oil; yield: 0.039 g (54%).

IR (neat): 2225, 1634, 1548, 815 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.99 (m, 2 H), 7.90 (t, *J* = 1.2 Hz, 1 H), 7.57–7.47 (m, 4 H), 7.28 (dd, *J* = 9.3 Hz, *J* = 1.3 Hz, 1 H), 2.43 (t, *J* = 7.1 Hz, 2 H), 1.67–1.59 (m, 2 H), 1.51–1.43 (m, 2 H), 1.36–1.31 (m, 4 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.3 (C), 156.7 (C), 134.0 (CH), 130.4 (CH), 129.3 (2 CH), 128.2 (C), 126.6 (2 CH), 123.4 (CH), 120.4 (C), 115.4 (CH), 114.3 (C), 92.0 (C), 80.4 (C), 31.4 (CH_2), 28.7 (2 CH_2), 22.6 (CH_2), 19.5 (CH_2), 14.1 (CH_3).

HRMS MALDI-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO$: 304.1701; found: 304.1698.

2-Methyl-4-(3-phenyl-2,1-benzisoxazol-5-yl)but-3-yn-2-ol (3t)

Pale yellow solid; 0.032 g (40%); mp 99–101 °C.

IR (KBr): 3412, 2322, 1614, 1548, 1176, 810, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.98 (m, 2 H), 7.93 (t, *J* = 1.3 Hz, 1 H), 7.58–7.46 (m, 4 H), 7.27 (dd, *J* = 9.3 Hz, *J* = 1.3 Hz, 1 H), 6.60 (br s, 1 H, OH), 1.65 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.8 (C), 156.6 (C), 133.6 (CH), 130.6 (CH), 129.3 (2 CH), 128.0 (C), 126.7 (2 CH), 124.4 (CH), 120.6 (C), 115.6 (CH), 114.2 (C), 95.0 (C), 81.8 (C), 65.7 (C), 31.5 (2 CH_3).

HRMS MALDI-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{16}NO_2$: 278.1181; found: 278.1186.

Silver-Catalyzed Oxidation of 2-Aminobenzophenone (1a) with 50% H_2O_2

$AgNO_3$ (0.020 g, 0.139 mmol) and 50% H_2O_2 (1 mL) were added to a solution of 2-aminobenzophenone (**1a**) (0.274 g, 1.39 mmol) in MeCN (4.0 mL). The mixture was stirred at 60 °C and the reaction progress was monitored by TLC. After stirring for 24 h, to the cooled mixture were added H_2O (150 mL) and CH_2Cl_2 (150 mL). The organic layer was separated and the aq layer extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The filtrate was evaporated and the residue subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 70:30) to give 3-phenyl-2,1-benzisoxazole (**3a**) (0.082 g, 30%) and 1,2-bis(2-benzoylphenyl)diazene-1-oxide (**5a**) (0.063 g, 22%).

Oxidation of 2-Aminobenzophenone (1a) with *m*-CPBA

m-CPBA (1.489 g, 8.63 mmol) was added to a solution of 2-aminobenzophenone (**1a**) (0.34 g, 1.72 mmol) in MeCN (5.0 mL). The mixture was stirred at 60 °C and the reaction progress was monitored by TLC. After stirring for 2 h, to the cooled mixture were added 2 M NaOH (150 mL) and CH_2Cl_2 (150 mL). The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The filtrate was evaporated and the residue subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 70:30) to give (2-nitrophenyl)(phenyl)methanone (**6a**) (0.183 g, 47%) and 1,2-bis(2-benzoylphenyl)diazene-1-oxide (**5a**).

1,2-Bis(2-benzoylphenyl)diazene-1-oxide (5a)

Orange solid; 0.119 g (28%); mp 102–104 °C.

IR (KBr): 1675, 1527, 1354, 764, 718, 636 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 4 H), 7.56–7.47 (m, 4 H), 7.44–7.32 (m, 10 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 195.5 (C=O), 193.7 (C=O), 146.7 (C), 141.8 (C), 137.8 (C), 136.7 (C), 134.8 (C), 134.7 (C), 133.1 (CH), 132.8 (CH), 131.4 (CH), 130.9 (CH), 130.2 (CH), 129.8 (2 CH), 129.07 (CH), 129.05 (2 CH), 128.8 (CH), 128.48 (2 CH), 128.45 (CH), 128.3 (2 CH), 123.2 (CH), 122.6 (CH).

HRMS MALDI-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_3$: 407.1396; found: 407.1393.

1-(4-Amino-3-benzoylphenyl)-3-hydroxy-3-methylbutane-1,2-dione (7t)

Oxone (0.176 g, 0.29 mmol) was added to a solution of [2-amino-5-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl](phenyl)methanone (**1t**) (0.081 g, 0.29 mmol) in MeCN/H_2O (2.5 mL/2.5 mL). The mixture was stirred at r.t. and the reaction progress was monitored by TLC. After stirring for 24 h, H_2O and CH_2Cl_2 (150 mL) were added to the mixture. The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The filtrate was evaporated and subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 85:15) to give 2-methyl-4-(3-phenyl-2,1-benzisoxazol-5-yl)but-3-yn-2-ol (**3t**) (0.032 g, 40%) and 1-(4-amino-3-benzoylphenyl)-3-hydroxy-3-methylbutane-1,2-dione (**7t**).

Brown solid; 0.027 g (30%), mp 96–98 °C.

IR (KBr): 1727, 1614, 1426, 1252, 906, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 2.1 Hz, 1 H), 7.84 (dd, *J* = 8.8 Hz, *J* = 2.1 Hz, 1 H), 7.64–7.62 (m, 2 H), 7.59–7.55 (m, 1 H), 7.51–7.47 (m, 2 H), 6.92 (br s, 3 H, OH, NH_2), 6.77 (d, *J* = 8.8 Hz, 1 H), 1.47 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.5 (C=O), 198.4 (C=O), 191.9 (C=O), 155.8 (C), 139.2 (CH), 138.8 (C), 134.6 (CH), 131.9 (CH), 129.2 (2 CH), 128.4 (2 CH), 120.5 (C), 117.3 (CH), 116.8 (C), 76.6 (C), 26.8 (2 CH_3).

HRMS MALDI-TOF: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}NO_4$: 312.1236; found: 312.1230.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561471.

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