Chemical Science

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Blue light-promoted photolysis of aryldiazoacetates†

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Aryldiazoacetates can undergo photolysis under blue light irradiation (460–490 nm) at room temperature and under air in the presence of numerous trapping agents, such as styrene, carboxylic acids, amines, alkanes and arenes, thus providing a straighforward and general platform for their mild functionalization.

Introduction

The chemistry of diazocompounds has been intensively studied over the past decades.[1] Today, a number of catalytic, racemic thermal processes,[2] as well as highly stereoselective methods describing cyclopropanations,[3] O–H,[4] N–H[5] and C–H[6] insertions, (formal) cycloadditions[7] and rearrangements[8] have been established, thus allowing the straightforward preparation of a variety of molecules.

In contrast to the numerous protocols reported on thermal processes, photochemical studies with diazocompounds have been performed mostly several decades ago,[9] and modern applications are relatively scarce.[10,11] Among these, Suero and co-workers have recently demonstrated that a hypervalent iodine reagent carrying a diazoacetate moiety could be employed in a photoredox-catalyzed protocol for the C–H functionalization of a variety of arenes.[11b] In the sequence, the diazocompounds produced could be further engaged in classical reactions, thus representing an overall formal process to access carbyne equivalents. The authors of this communication also noticed the effect of blue light on aryldiazoacetates **1**, but did not synthetically exploit this to any significant extent.

In recent years, the chemistry of donor/acceptor metal carbenes has been broadly developed for synthesis.[1] These intermediates, typically prepared from aryldiazoacetates or vinyldiazoacetates, have attenuated reactivity compared to metal carbenes lacking a donor group. Donor/acceptor carbenes derived from the thermal decomposition of aryldiazoacetates have been shown to undergo relatively selective cyclopropanations,[12] N–H[13] and C–H[14] insertions.

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As opposed to these methods, one might argue that milder, metal-free strategies can be accessible by the use of photochemical conditions, thus being of special importance in scenarios where stereocontrol (typically governed by a metal catalyst) is not a prime concern, such as in chemical-biology applications.[15] Based on this background, and motivated by the realization that the use of light could avoid the need for high temperatures and the use of metal catalysts, we have conducted a systematic study on the photochemically-induced reactions of aryldiazoacetates. This approach opens up a new window of chemical reactivity that leads to the mild functionalization of organic molecules, while also being more economical and sustainable.

Results and discussion

Spectroscopic studies

With this mindset, our investigation started by analyzing the UV-Vis absorbance spectra of two aryldiazoacetates **1a** and **1b**, and comparing them to ethyl 2-diazoacetate **2a** and dimethyl 2-diazomalonate **2b**. The donor/acceptor diazo compounds **1a** and **1b** present an almost identical absorbance spectra in the visible region. In contrast to the acceptor-only diazo compounds **2a** and **2b**, both **1a** and **1b** display bathochromic shifts in the region of 400–500 nm (violet/blue), which can be presumably attributed to a n–π* transition of the diazo group[16] (Fig. 1).

Solvent evaluation studies

In agreement to these observations, preliminary tests promoting the blue-light irradiation of diazocompound **1a** in the presence of different solvents, at room temperature and under air led to a variety of compounds in moderate to excellent yields (Scheme 1). These products were derived from [2 + 1] cycloadditions (**3a** and **3b**); O–H insertion events (**4a**, **4b** and **4c**. The generation of **4c** can be attributed to an ylide formation derived from the O-attack of the THF ring to the free carbene, followed by an elimination event, leading to the formation of
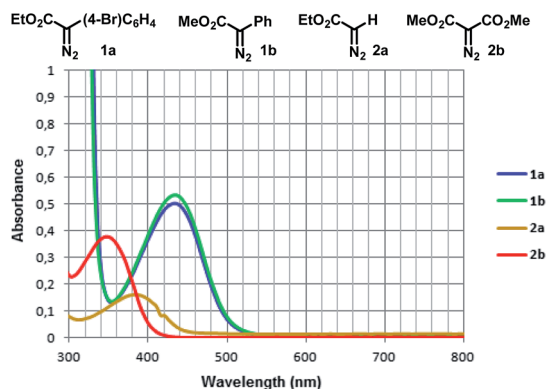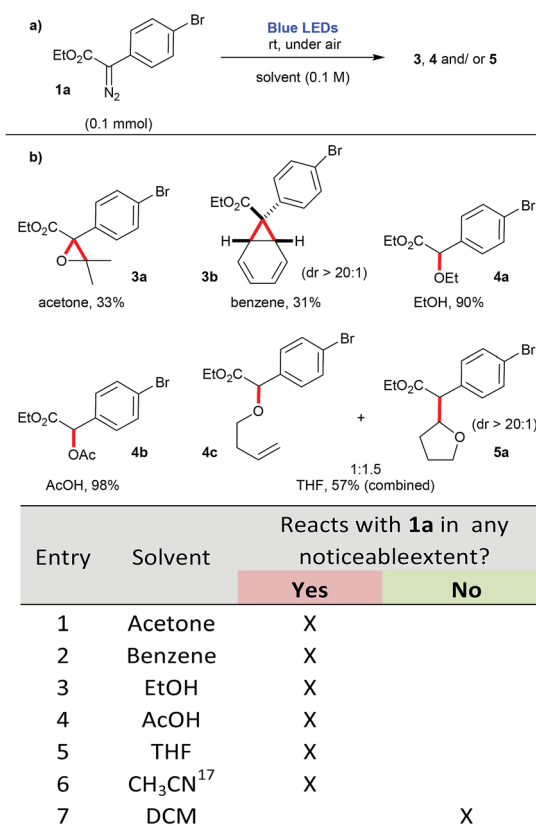
Fig. 1   UV-Vis absorbance spectra of diazocompounds **1a**, **1b**, **2a** and **2b** in DCM (all in 0.05 mM).

Scheme 1   Evaluation of different solvents in the photolysis of **1a** using blue light irradiation.

the C=C bond); and a C–H insertion event (**5a**). In contrast, when DCM was employed, no appreciable reaction with the solvent was detected. Instead, a complex mixture is observed, presumably derived from dimerization pathways and other self-reactions involving **1a**. The compounds formed are the expected products of a carbene, that is being produced as a reactive intermediate derived from the blue light irradiation of aryldiazoacetate **1a** [17] (Scheme 1).

Although this photolysis phenomenon is well known for other diazocompounds using UV-light, [9,16,18] one can note here

that the presence of a donor group at the aryldiazoacetates **1a** and **1b** (or the removal of an acceptor group, as one can observe the same trend comparing the UV-Vis absorption spectra of **2a** and **2b**) is responsible for a significant bathochromic shift in their UV-Vis absorbance spectra, thus allowing the photolysis process to occur in the visible region. [10,16]

Synthetic applications

Next, the synthetic potential of this new photochemical process involving aryldiazoacetates **1** was evaluated (Scheme 2). As a consequence of the previous investigation, DCM was chosen as the optimal solvent. A range of trapping agents, such as styrene **6** (5 equiv.), carboxylic acids **7** (2 equiv.), amines **8** (3 equiv.), cyclic alkanes **9** (100 equiv.) and arenes **10** (5 equiv.) were examined. In most cases, good yields of the corresponding products were obtained using a moderate excess of the trapping agents, except in the case of cyclic alkanes **9**, in which the trapping agent was used as the solvent.

In the case of styrene **6** as a carbene trap, a number of aryldiazoacetates **1a–1j** were employed to produce the corresponding cyclopropanes **3c–3l** in good yields, 37–94% and high diastereoselectivities, varying from 10 : 1 to >20 : 1 (Scheme 2). Only cyclopropane **3g** was produced in a somewhat low efficiency (37% yield), due to the competing formation of a diastereoisomeric mixture of β-propiolactones, [19] as the result of an intramolecular C–H insertion event (Scheme 2).

Carboxylic acids **7** were found to be excellent carbene traps as they undergo efficient O–H insertions to afford the corresponding esters **4d–4p** in generally good yields, 61–99% (Scheme 3a). In this context, control experiments demonstrate that when stronger acids are employed, such as but-2-ynoic acid
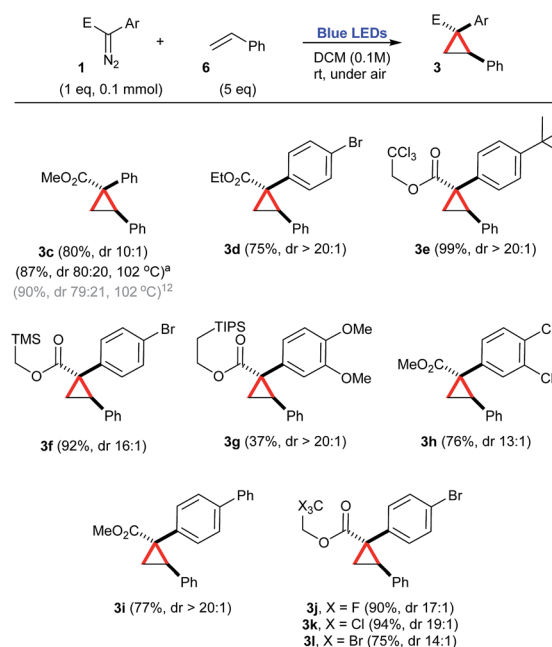
Scheme 2   Cyclopropanation of styrene in the presence of a number of aryldiazoacetates, under blue light irradiation. [a]Prepared under thermal conditions. [12]
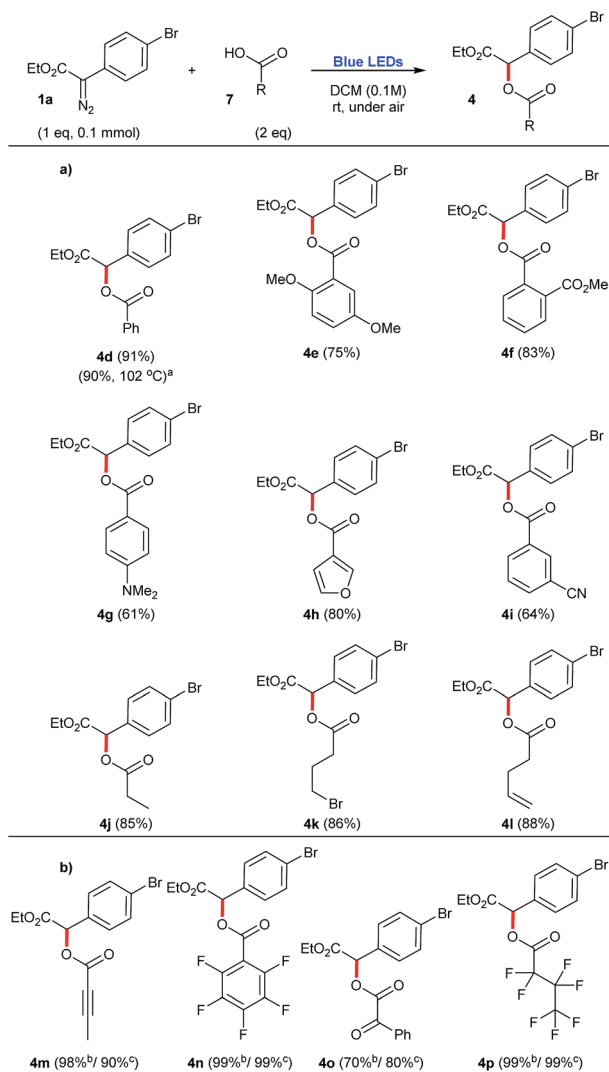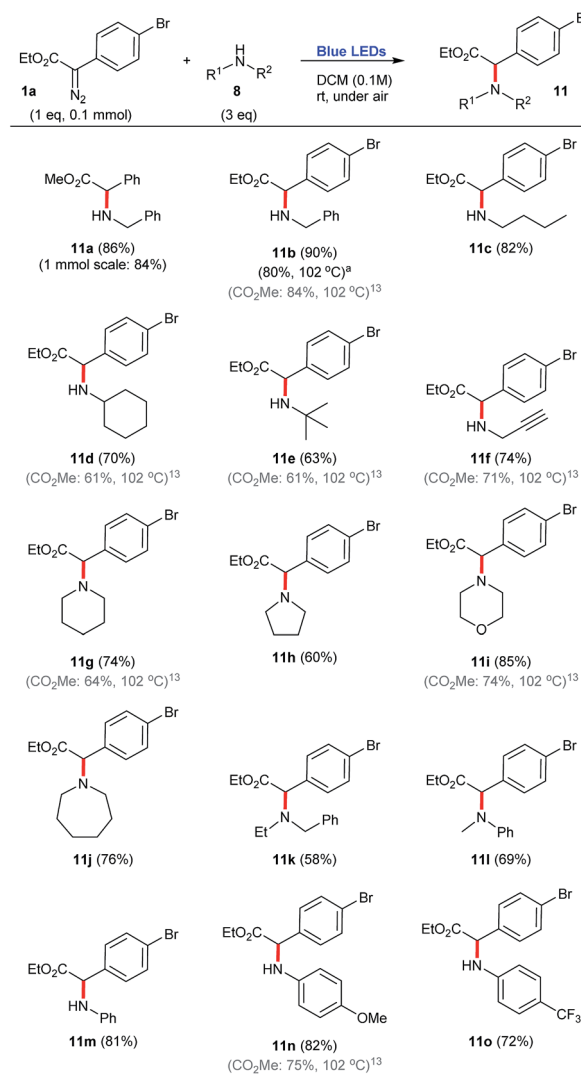
Scheme 3 O−H insertion reactions employing aryldiazoacetate **1a** and a number of carboxylic acids, under blue light irradiation. (a) Scope of O−H insertions that work exclusively under photochemical conditions. (b) Examples of O−H insertions that work also under thermal conditions (in the absence of blue light). [a]Prepared under thermal conditions. [b]Yield for the process irradiated with blue light; [c]yield for the process in the dark.

7m, 2,3,4,5,6-pentafluorobenzoic acid **7n**, 2-oxo-2-phenylacetic acid **7o**, and 2,2,3,3,4,4,4-heptafluorobutanoic acid **7p**, the corresponding O−H insertions also proceed in the dark (Scheme 3b). Therefore, the preparation of substrates **4m–4p** does not proceed *via* a photochemical process, but it rather follows most likely a classical mechanism of protonation of the starting diazocompound **1a**, followed by a S_N2 displacement of N_2, that is typically found in the esterification mechanism of carboxylic acids using diazomethane.[20] For instance, upon addition of **7p** to the other components of the reaction mixture, the O−H insertion occurs almost instantly (which is accompanied by the colour change of solution from yellow to transparent and vigorous release of N_2).

Concerning the use of primary, secondary and aromatic amines **8** as carbene traps, a variety of N−H insertions can be

accomplished in good yields, 58–90%, to produce the corresponding coupled products **11**. In this context, it is possible to note that bulky amines produced slightly lower yields, 58–69% (*e.g.* **11e**, **11k**, **11l**), while linear and other unhindered secondary congeners lead to the corresponding coupled products **11** in higher efficiencies, 81–90% (*e.g.* **11a**, **11b**, **11c**, **11i**, **11m**). Of note, pyrrolidine produced the coupled product **11h** in a somewhat lower yield, 60% (Scheme 4).

When cyclic alkanes **9**, such as cyclohexane **9a**, cyclopentane **9b**, and cycloheptane **9c** are employed as carbene traps, they need to be used in large excess (100 eq.), in order to afford the corresponding C−H insertion products **5** in a range of moderate to good yields, 55–79% (Scheme 5). In addition, the use of cyclohexadiene **9d** as substrate produces an equimolar mixture of allylic C−H insertion (**5f**) and cyclopropanation (**5g**).[21,22] Furthermore, intramolecular C−H insertions can also be performed. For instance, under these reaction conditions, *tert*-butyl 2-phenyl-2-diazoacetate **1k** and isopropyl 2-phenyl-2-

Scheme 4 N−H insertion reactions employing aryldiazoacetate **1a** and a number of amines, under blue light irradiation. [a]Prepared under thermal conditions.[13]
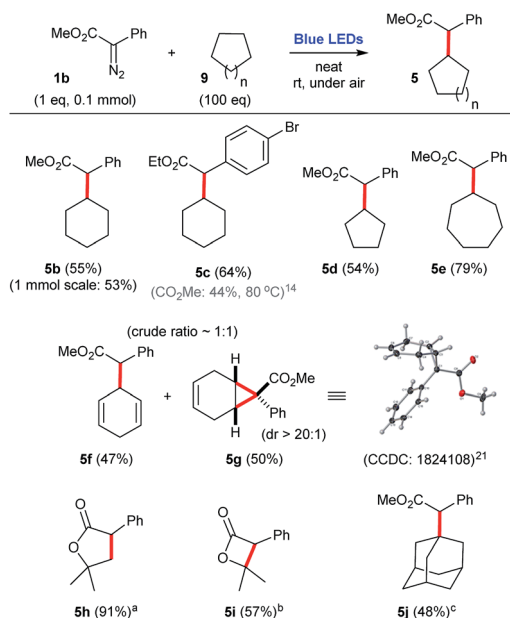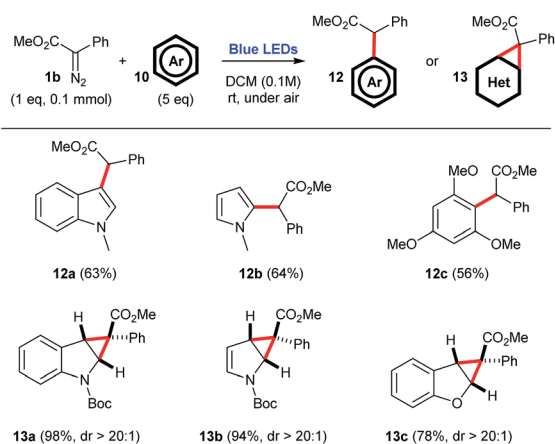
Scheme 5 C–H insertion reactions employing aryldiazoacetate **1b** and a number of cyclic alkanes and other substrates, under blue light irradiation. [a]Intramolecular process using *tert*-butyl 2-phenyl-2-diazoacetate (0.2 mmol). [b]Intramolecular process using isopropyl 2-phenyl-2-diazoacetate (0.2 mmol). [c]Intermolecular process employing adamantane (5 equiv.).

diazoacetate **1l** are both converted to the 5-membered lactone **5h**, in 91% yield, and the 4-membered lactone **5i**, in 57% yield, respectively. In the case of more reactive cyclic alkanes, such as adamantane **9e**, it is possible to use lower amounts of trapping alkane (5 eq.) to produce the corresponding C–H inserted product **5j** in a respectful 48% yield (Scheme 5).

The use of arenes **10** as carbene traps can either produce cyclopropanation products or C–H insertion products (Scheme 6).

For instance, when electron-rich *N*-methyl indole **10a**, *N*-methyl pyrrole **10b**, or 1,3,5-trimethoxybenzene **10c** are employed, the corresponding C–H inserted products **12a–12c**

Scheme 6 C–H insertion or cyclopropanation reactions employing aryldiazoacetate **1b** and a number of arenes, under blue light irradiation.

are selectively produced, in 56–64% yield. However, when Boc-protected indole **10d**, Boc-protected pyrrole **10e**, or benzo-furan **10f** are employed, one observes the selective formation of the corresponding cyclopropanation products **13a–13c**, in high yields 74–98%, and perfect diastereocontrol, dr > 20 : 1. Of note, both Boc-protected compounds **13a** and **13b** produce a mixture of rotamers, as evidenced by the coalescence of ^{1}H NMR signals upon heating (see the ESI†).

In order to demonstrate the possibility of scaling up the previously described reactions, substrates **5b** and **11a** have been also prepared in a 1 mmol-scale, without any significant change in efficiency (Schemes 4 and 5). Importantly, every reaction reported in previous Schemes 2–6 has been also attempted in the dark, and except for the molecules described in Scheme 3b, all failed to provide the corresponding insertion or cyclopropanation products, but rather afforded only recovered starting materials. These control experiments confirm that these processes are indeed promoted photochemically.

Another important consideration is the comparison of the photochemical reactions with the purely thermal reactions. A number of compounds presented in the previous schemes have been also prepared by Davies and co-workers *via* metal-free thermal processes.[12–14] In order to compare the efficiencies of these previously reported protocols with the one reported herein, their yields have been also mentioned, with the corresponding references. In this context, a metal-free thermal cyclopropanation method has been reported for the preparation of **3c**, heating the starting aryldiazoacetate **1a** and styrene **6** at the reflux of PhCF$_3$, at 102 °C.[12] While in the previous report, **3c** is obtained in a slightly higher yield (90%), the 4 : 1 dr reported for this process is considerably inferior to the photochemical transformation reported here, that affords **3c** in 80% isolated yield, dr 10 : 1 [crude dr 9 : 1] (Scheme 2). Also taking advantage of this thermal protocol for the generation of free carbenes, the O–H insertion of benzoic acid **7a** was performed in the presence of diazocompound **1a** and produced **4d** with the same efficiency as our photochemical process, 90% yield (Scheme 3).

In addition, the preparation of amine **11a** *via* the photochemical process reported herein describes a 90% yield, while the thermal reaction following Davies' conditions (reflux of PhCF$_3$, 102 °C) has been accomplished in our hands in 80% yield; and the corresponding methyl ester derivative has been reported in 84% yield.[13] In agreement to this observation, other photochemical processes described here for N–H insertions using ethyl aryldiazoacetate **1a** also consistently produced higher yields when compared to methyl analogues employed in thermal processes (Scheme 4).[13]

Furthermore, an analogous thermal process for the C–H insertion of cyclohexane **9a** into methyl 2-phenyl-2-diazoacetate **1b** has been described in 44% yield, at 80 °C,[14] while the photochemical process reported herein, at room temperature, produces the corresponding ethyl derivative **5c** in 64% yield (Scheme 5).

In addition, for comparison purposes, both donor/acceptor diazocompounds **1a** and **1b** have been compared to acceptor-only diazo compound **2a** and acceptor/acceptor diazocompound **2b** for the C–H functionalization of cyclohexane. In agreement to the absorbance spectra shown in Fig. 1, both **1a**
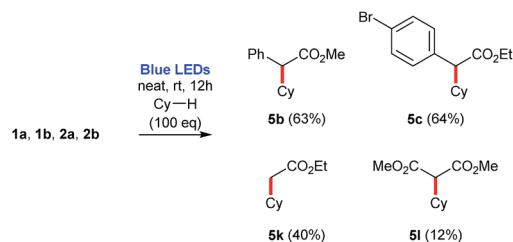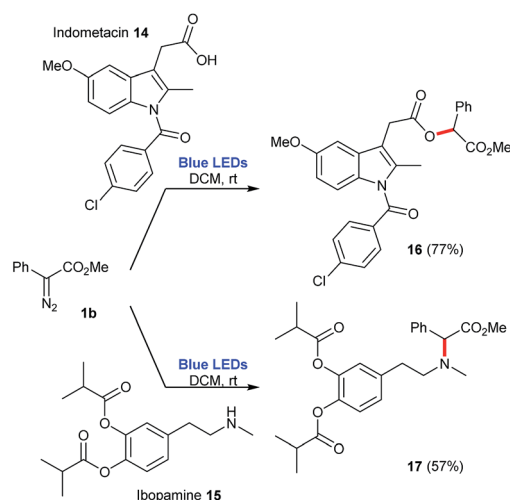
Scheme 7 Comparison of C–H insertion reactions involving diazo-compounds **1a**, **1b**, **2a** and **2b** and cyclohexane. Yields are estimated based on the ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.
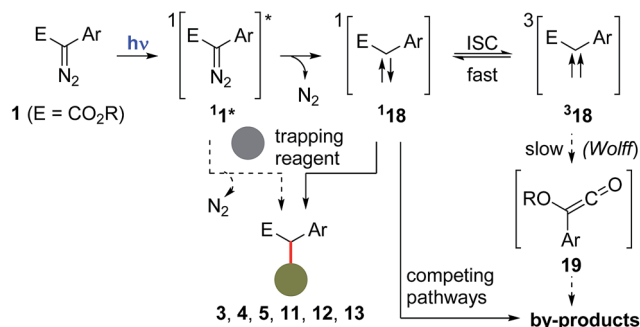
and **1b** undergo blue light-promoted photolysis more effectively than **2a** and **2b** to afford the corresponding C–H insertion products (Scheme 7).

Finally, this photochemical protocol was also evaluated for the functionalization of more complex molecules, indometacin **14** and ibopamine **15**. In the case of indometacin **14**, it is possible to employ a 1 : 1 mixture of **14:1b** to afford the corresponding ester **16** in 77% yield. In the case of ibopamine **15**, the optimization of this reaction allowed the reversion of stoichiometry, this time using a 1 : 3 mixture of **15:1b** to produce the corresponding tertiary amine **17** in 57% yield (Scheme 8).

Concerning the mechanism of these photochemical reactions and the nature of the carbenes involved, they are likely to proceed *via* the photoexcitation of the starting diazocompound **1** to a higher energy singlet state [1]**1***, followed by the extrusion of N_2, to afford a singlet carbene [1]**18**, which can then be trapped by a reacting partner (*e.g.* **6**, **7**, **8**, **9** or **10**) to afford the observed final compounds (*e.g.* **3**, **4**, **5**, **11**, **12** or **13**).[13,23] Alternatively, at this point, it is not possible to rule out that the excited diazocompound [1]**1*** could react directly with a trapping partner to afford the corresponding final product.[24] Although inter system crossing (ISC) converting [1]**18** to [3]**18** is generally a fast process, in this case, experimental evidences suggest that this is a reversible event.[25] Subsequent conversion of [3]**18** to the corresponding

Scheme 9 Proposed mechanistic scenario involved in the formation of the products **3**, **4**, **5**, **11**, **12** and **13**, and plausible explanations for the formation of by-products.

ketene **19** (*via* a Wolff-rearrangement) would serve as an additional source for the formation of by-products (Scheme 9).

Conclusions

In summary, this study demonstrates that aryldiazoacetates **1** can absorb in the wavelength region of approximately 400–500 nm (visible region), thus being able to undergo photolysis by blue light irradiation in the presence of a variety of partners to afford products of cyclopropanation, O–H, N–H and C–H insertions. Furthermore, this new technology is mild, selective and has been demonstrated to be scalable up to 1 mmol, therefore opening new venues for potential applications in organic synthesis and chemical-biology.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

Scheme 8 Functionalization of pharmaceuticals employing the blue-light promoted photolysis of methyl phenyldiazoacetate **1b**.

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