

# Accelerated Discovery in Photocatalysis by a Combined Screening Approach Involving MS Tags

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## **Supporting Information**



**ABSTRACT:** Herein we report on the development of an MS tag screening strategy that accelerates the discovery of photocatalytic reactions. By efficiently combining mechanism- and reaction-based screening dimensions, the respective advantages of each strategy were retained, whereas the drawbacks inherent to each screening approach could be eliminated. Applying this approach led to the discovery of a mild photosensitized decarboxylative hydrazide synthesis from mesoionic sydnones and carboxylic acids as starting materials.

he development of new transformations and the I improvement of existing methodologies toward "greener" alternatives are central tasks of many research programs throughout organic chemistry.<sup>1</sup> In this regard, catalysis has revolutionized the way valuable molecular scaffolds are constructed under mild conditions and even enabled the identification of numerous breakthroughs and unknown reactivity modes.<sup>2</sup> Many discoveries derive from an in-depth understanding of well-established reactions and their underlying mechanisms, consecutively enabling the transfer of this gained knowledge to new classes of suitable catalysts and substrates. Whereas this "rational-design" approach has led to many beautiful transformations,<sup>3</sup> the breakthrough discovery potential is limited. The exploration of new reactivity modes is often enabled by utilizing discovery-oriented screening approaches<sup>4</sup> because they allow a broader and systematic evaluation of chemical space.<sup>5</sup> These discovery-oriented screening methodologies contribute to a deep understanding of the underlying reactivity principles, which can ultimately be used in "comprehension-guided" rational-design approaches.<sup>6</sup> A prominent strategy for the discovery of new transformations are reaction-based screening approaches, where the formation of a new reaction product is usually identified by GC- or LC-MS analysis (Scheme 1a).<sup>7</sup> Hereby, preselected substrates, catalysts, or reaction conditions are screened in a systematic fashion. Whereas the setup required for such a screening approach is readily available and automatization is possible, this concept has one inherent drawback with respect to catalytic reactions: Detectable amounts of product have to be formed, requiring the matching of diverse reaction parameters. For this purpose, a large number of parameters must be varied, which leads to time-consuming and, in the end, costly protocols with an overall limited hit rate.

In mechanism-based discovery-oriented screening approaches, one single step out of the whole catalytic cycle is evaluated by means of a suitable analytical tool, for example, mass spectrometry,<sup>9</sup> cyclic voltammetry,<sup>10</sup> or luminescence spectroscopy.<sup>6,11</sup> Such approaches therefore identify classes of substrates that interact with a catalyst and provide useful mechanistic insights (Scheme 1b). However, because this approach covers only one step of what is often a complex catalytic cycle, the development of a transformation requires either significant postscreening or rational reaction design.

Recently, we reported on a screening strategy in the research field of visible-light photocatalysis that merges mechanism- and reaction-based screening approaches.<sup>12,13</sup> The appropriate combination of these two 1D screening approaches retains their respective advantages in terms of breakthrough discovery potential while eliminating the drawbacks inherent to each approach, which is well demonstrated by our discovery of two unexpected uphill energy-transfer reactions.

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<sup>a</sup>Cat, catalyst; Sub, substrate; Q, quencher; PC, photocatalyst.

Scheme 2. Workflow Diagram Illustrating the Conceptual Approach of the Combined Mechanism- and Reaction-Based Screening Strategy That Lead to the Discovery of a Photosensitized Decarboxylative Hydrazide Synthesis<sup>a</sup>



"Installation of a phosphorus-based MS tag into a previously discovered sydnone quencher renders the second screening step highly efficient with respect to the required catalyst, reagent, and solvent quantities. Values in yellow or green circles represent quenching fractions of the respective substrate with [Ir-F] as a photocatalyst. PC, photocatalyst; Q<sub>1</sub> quencher; R, reagent; MeCN, acetonitrile.

Although this concept bears enormous potential for the discovery of (new) reactions and reactivity modes, it still suffers from three major limitations:

- (1) The GC–MS analysis of each reaction mixture is timeconsuming.
- (2) The identification of polar reaction products by GC– MS is not possible.
- (3) Overall high quantities of reagents, catalysts, and solvents are required due to the analytical limit-of-detection.

We envisioned that the covalent installation of a suitable MS tag onto a lead substrate previously identified by luminescence

quenching might eliminate the previously mentioned disadvantages (Scheme 1c).<sup>14</sup> The installed MS tag would allow an intuitive and quick analysis of the reaction outcome using electrospray ionization mass spectrometry (ESI–MS). Furthermore, because of the extremely low detection limits that this analytical technique possesses, the required quantities of reagents, catalysts, and solvents would be significantly decreased. A significant drawback of such a technique, however, is the need for the covalent installation of a suitable MS tag and the need to investigate the properties of the tagged compound. In this context, also the full automatization of such a screening approach is hardly possible.

Letter

We started our conceptual study by investigating the interaction of 25 randomly selected potential quenchers, featuring diverse functional groups, using  $[Ir(dF(CF_3)$  $ppy)_2(dtbbpy)](PF_6)$  ([Ir-F],  $dF(CF_3)ppy = 2-(2,4-difluor$ ophenyl)-3-trifluoromethylpyridine, dtbbpy = 4.4'-di-tertbutyl-2,2'-bipyridine) as a photocatalyst in the first mechanism-based luminescence quenching screening dimension (Scheme 2). The photocatalyst [Ir-F] was selected due to its high excited-state redox potentials ( $E(M^{III*}/M^{II}) = +1.15 \text{ V}$ vs  $Fc/Fc^+$  and  $E(M^{III}/M^{IV^*}) = -1.16 \text{ V vs } Fc/Fc^+)^{15}$  and its high triplet excited-state energy ( $E_{\rm T} = 61.82 \pm 0.30$  kcal/ mol),<sup>13</sup> thus covering both the electron-transfer (ET) and energy-transfer (EnT) domains of chemical space. Among the 25 screened substrates, we identified 6 new quenchers (Q3, Q10, Q14, Q22, Q23, and 1(Q20)) characterized by a significant quenching fraction. Among them, phenylsydnone 1 was identified to strongly interact with photoexcited [Ir-F]. Sydnones are prominent compounds of the mesoionic family and have been mainly studied for their cycloaddition reactivity (noncatalyzed,<sup>16</sup> copper-catalyzed,<sup>17</sup> or light-induced<sup>18</sup>). To the best of our knowledge, visible-light photocatalyzed reactions involving mesoionic compounds have not been reported. Consequently, the high degree of quenching of phenylsydnone 1 prompted us to select it as lead compound for the second MS tag reaction-based screening. Because of its high chemical robustness, low reactivity, and excellent ionization properties, a phosphorus-based MS tag was covalently installed into the phenylsydnone scaffold in two straightforward steps, yielding MS-tagged phenylsydnone  $1_{tag}$ .<sup>19</sup> We then selected 96 diverse reactants covering chemical space to discover new reactions by applying the second MS tag reaction-based screening dimension. Using a 96-well plate with the [Ir-F] photocatalyst, tagged  $1_{tag}$  and the respective reactant R1-R96 in each vial dissolved in a total reaction volume of 200  $\mu$ L of acetonitrile, we irradiated the reaction mixtures using blue LEDs ( $\lambda_{max}$  = 455 nm). After 24 h of irradiation, the outcome of the reactions was investigated by ESI-MS.<sup>20</sup> By simply comparing the obtained spectra with two reference spectra ((I) only  $\mathbf{1}_{tag}$  and  $h\nu$  in MeCN; (II) [Ir-F],  $1_{tag}$ , and  $h\nu$  in MeCN), additional peaks may indicate the formation of a reaction product. In total, 17 out of 96 combinations gave rise to new ESI-MS peaks. Some of the masses could be directly transformed into possible product motifs using only the mass spectra.<sup>20</sup> During the analysis of the reaction-based screening results, we noticed a recurring pattern of the formation of a new MS peak when a carboxylic acid functionality was present within the reactant's structure. To verify and reproduce our screening results, we decided to run this reaction on a 0.3 mmol scale using untagged 4fluorophenyl sydnone 1 in the presence of cyclohexanecarboxvlic acid 2a and [Ir-F] under otherwise unchanged screening conditions. After the reaction and the subsequent purification process, we identified diacylhydrazide 3a as the formed reaction product, verified by nuclear magnetic resonance (NMR) spectroscopy and by X-ray crystallography (see Figure 1).

Next, we started optimizing the reaction parameters, such as the nature of the photocatalyst, the irradiation wavelength, or the solvent, using 4-fluorophenyl sydnone 1a and cyclohexanecarboxylic acid 2a as benchmark reagents. Gratifyingly, the yield of 3a could be increased from 13 to 67% by switching to  $[Ru(bpz)_3](PF_6)_2$  ([Ru], bpz = 2,2'-bipyrazine) as the



**Figure 1.** Crystal structure of *N*,*N*-diacylhydrazide **3a**. Thermal ellipsoids are shown with 30% probability.

photocatalyst, employing a catalyst loading of 2.5 mol %, and increasing the equivalents of the carboxylic acid 2a<sup>21</sup> while using acetonitrile (0.1 M) as solvent.<sup>22</sup> With the optimized reaction conditions in hand, we next investigated the scope and synthetic limitations of this decarboxylative hydrazide synthesis (Scheme 3a). Performing the reaction on a 10-fold higher scale worked well, delivering the product in 61% isolated yield. The utilization of cyclic secondary carboxylic acids with five- or three-membered ring systems was successful, delivering the products in 49 or 46% yield, respectively (3b, 3c).<sup>23</sup> When acetic acid was used as a coupling partner, the desired product 3d could be obtained in a moderate yield of 51%. Benzoic or phenylacetic acid could also be converted; however, the yield decreased to 36 and 43% (3e and 3f). The incorporation of fluorine substituents or alkyne moieties into the carboxylic acid functionality was tolerated and provided the corresponding products 3g and 3h in good yield (77-81%). Tertiary carboxylic acids could also be employed, as shown by the use of pivalic acid delivering hydrazide 3i in 45% yield. Gratifyingly, the use of unsaturated fatty acids was also possible, resulting in the formation of hydrazide 3j in 63% yield. The up-scaling of this reaction resulted in a slightly diminished yield of 55% (3.0 mmol scale). We next investigated the scope with respect to modifications of the sydnone's aryl moiety. Diverse functional groups, such as methoxy (31), iodo (3m), acetyl (3n), or hydroxyl (3o) substituents, were tolerated, delivering the hydrazide products in good to excellent yields (67-78%, 3k-o). The replacement of the phenyl group by a methyl group had no influence on the reaction: Methyl hydrazide 3p could be isolated in 85% yield. The reaction further tolerates the presence of alkyl or aryl substituents at the C-4-position of the phenyl sydnone. The hydrazide products 3q-s could be obtained in good yield (78-82%). Besides, an inversion of regioselectivity is observed for those latest examples. To further investigate the functional group tolerance and the preservation of this photocatalytic hydrazide synthesis, an additive-based robustness screen was performed.<sup>24</sup> The results are summarized in histograms (Scheme 3b). We were delighted to see that in most cases the yield of the product was not affected by the presence of an additional additive, indicating an overall high robustness of the transformation. With an average recovered additive yield of 76%, the reaction is furthermore characterized by an extremely high functional group preservation.

The obtained *N*,*N*-diacylhydrazide product scaffold **3** is of huge importance for many diverse applications in pesticide,<sup>25</sup> materials,<sup>26</sup> and pharmaceutical chemistry.<sup>27</sup> Furthermore, the products are important key intermediates for the synthesis of numerous heterocycles.<sup>28</sup> As shown in Scheme 4a, the products can be easily transformed to chiral 1,2,4-triazolium

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Scheme 3. (a) Substrate Scope and (b) Additive-Based Robustness Screen Results for the Photosensitized Decarboxylative Hydrazide Synthesis<sup>a</sup>



<sup>*a*</sup>[a] General conditions: **1**a–s (0.3 mmol), **2** (6.0 mmol, 20.0 equiv), [Ru] (2.5 mol %), MeCN (0.1 M),  $\lambda_{max}$  = 455 nm, rt, 24 h. All stated yields are isolated. [b] HPLC purification required. [c] Product structure confirmed by X-ray analysis; see ref 20. [d] 40.0 equiv of acetic acid used. [e] Robustness screen performed using 0.1 mmol of **1**a; see the Supporting Information for the experimental details and procedure.

salt N-heterocyclic carbene (NHC) precursors 4, which can be used for enantioselective catalysis.<sup>29</sup>

The proposed mechanism of this transformation, which is in accordance with diverse performed mechanistic experiments (see the SI for further information) and literature reports on the direct sensitization of mesoionic sydnones ( $\lambda < 300 \text{ nm}$ )<sup>18</sup>, is depicted in Scheme 4b. The [Ru<sup>II</sup>] photocatalyst is excited by visible light to its triplet excited state ( $E_T = 48.4 \text{ kcal}/$ 

Scheme 4. (a) Product Diversification of the Reaction Products To Access Chiral 1,2,4-Triazolium Salts as NHC Precatalysts and (b) Proposed Energy-Transfer Mechanism (Supported by Diverse Mechanistic Experiments) for the Photosensitized Decarboxylative Hydrazide Synthesis<sup>a</sup>



<sup>*a*</sup>NHC, N-heterocyclic carbene. For the experimental procedure and details of mechanistic experiments, see the Supporting Information.

mol).<sup>11a</sup> Triplet-triplet energy transfer from  ${}^{3*}[Ru^{II}]$  to sydnone 1 ( $E_T$  = 48.5 kcal/mol)<sup>18b</sup> recycles the [Ru<sup>II</sup>] ground-state photocatalyst. The sensitization of 1 promotes the formation of Earl's bicyclic lactone intermediate 5, which yields diazirene 6 after decarboxylation. For unsubstituted sydnones (R = H), IM1 is formed after the addition of the carboxylic acid. The corresponding products 3a-p are obtained after consecutive rearrangement. In the case of sydnone substitution (R = aryl or alkyl), nitrilimine IM2 is formed, which yields the corresponding products 3q-s after carboxylic acid addition and rearrangement. A reaction quantum yield of  $\Phi$  = 0.59, UV-vis and Stern-Volmer analysis, TEMPO-trapping experiments, as well as diverse deuterium and <sup>13</sup>C-labeling experiments support this mechanistic hypothesis.<sup>30</sup> Transient absorption studies to prove the energy-transfer activation nature of 1 are currently being investigated in our laboratories.

In conclusion, we have successfully developed a screening methodology involving MS tags that allowed the accelerated discovery of a photocatalytic reaction. By combining mechanism- and reaction-based screening, the limitations of each individual screening approach are eliminated while establishing a highly efficient strategy potentially allowing the discovery of ground-breaking photocatalytic reactions. Indeed, the covalent installation of a suitable MS tag both facilitates the identification of newly formed bond (dis)connections and allows a significant reduction of the required amount of reagents, catalysts, and solvents. Applying this approach resulted in the discovery of a highly functional-group-tolerant photosensitized decarboxylative hydrazide synthesis from mesoionic sydnones and carboxylic acids as starting materials. We are convinced that the application of combined screening approaches will accelerate diverse ground-breaking discoveries,

ultimately expanding the toolbox of organic chemistry for highly efficient and straightforward catalytic protocols.

## ASSOCIATED CONTENT

### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b03936.

Experimental details, characterization data, mechanistic experiments, and copies of NMR spectra of new compounds (PDF)

# **Accession Codes**

CCDC 1867622–1867625 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

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(19) Luminescence quenching analysis revealed a quenching fraction of the phosphorus-based MS tag of F = 24%, most likely due to reductive quenching of the excited-state [**Ir-F**] photocatalyst by the iodide. Because this quenching fraction is low compared with the one of the mesoionic sydnone **1**, the influence of the background quenching on the screening should be rather low. Details can be found in the Supporting Information.

(20) See the Supporting Information for the experimental details and procedure.

(21) After the reaction, 18.9 equiv of the carboxylic acid could be recovered. Effectively 1.1 equiv of the carboxylic acid was therefore consumed; see the Supporting Information for details.

(22) Details concerning the optimization of this transformation can be found in the Supporting Information.

(23) Preparative HPLC separation was required for the purification of the reaction products 3a, 3b, 3e, 3f, and 3i.

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(30) Experimental procedures and results of diverse mechanistic experiments can be found in the Supporting Information.

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