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Advanced Synthesis & Catalysis

Catalyst- and Substrate-Dependent Chemodivergent Reactivity of Stabilised Sulfur Ylides with Salicylaldehydes

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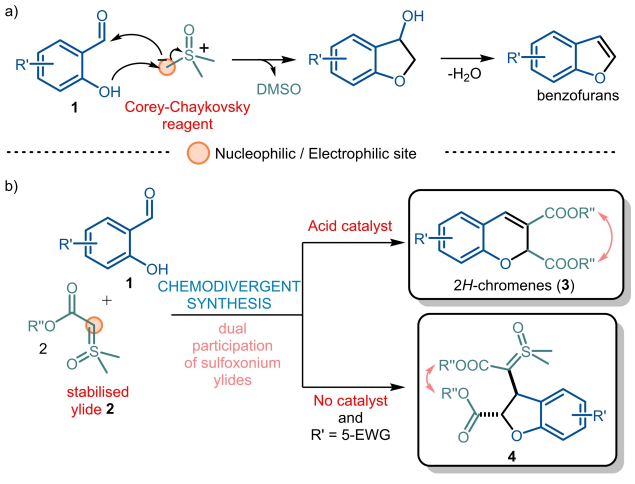
Abstract: Stabilised sulfur ylides are synthetically appealing compounds, which reactivity under Brønsted acid catalysis has been poorly explored. Herein, we report a new catalyst- and substrate- dependent chemodivergent reaction between stabilised sulfur ylides and salicylaldehydes, leading to the (suprising) formation of 2*H*-chromenes or dihydrobenzofurans products. Particular attention was set on the unusual mechanisms involved. Two unique reaction routes including two ylide units in the reactions are proposed. These pathways were validated by performing a selectivity switch in some cases, enabled by the modulation of the nucleophilicity of the sulfur ylide, and by the loading of the Brønsted acid catalyst in the reaction.

Keywords: Sulfur Ylides; Chemodivergency; Chromenes; Dihydrobenzofurans; Organocatalysis

Introduction

In recent times, sulfoxonium ylides have received great attention in organic synthesis, thanks to a combination of versatile reactivity and convenience (ease of preparation, safety, etc.).[1] The traditional prominence of these ylides, and especially of their unstabilized methylidene congener (the Corey-Chaykovsky reagent, dimethylsulfoxonium methylidene ylide), is due to their proficiency in formal (2 + 1) cycloadditions with carbonyl compounds, delivering epoxides,[2] aziridines,[3] and cyclopropanes.[4] In these reactions, the ylide acts as synthetic equivalent of a CH_2 carbene synthon. Such equivalency can be in fact extended to different cyclizations.[5] For example, attack of the Corey-Chaykovsky reagent to a salicylaldehyde **1**, followed by DMSO displacement by the phenolic oxygen, affords, upon dehydration, the corresponding benzofurans (Scheme 1a).[5a]

In the context of our interest in the development of new catalytic methodologies,[6] we explored the reac-



Scheme 1. a) Reaction between dimethylsulfoxonium methylide and salicylaldehydes **1**. b) This work: chemodivergent reaction between stabilised sulfoxonium ylides **2** and salicylaldehydes **1**.

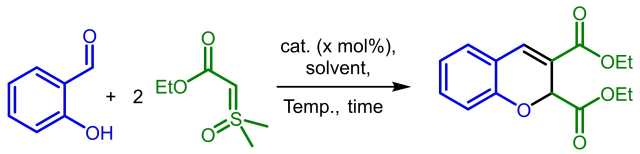
tivity of stabilized sulfoxonium ylides **2** with salicylaldehydes **1**. We quickly realized that these ylides **2** lead to distinct outcomes, compared to their unstabilised methylidene counterpart, leading to products **3** and/or **4** arising from the participation of two ylides in the reactions (compare Scheme 1a and 1b).[7] Intrigued by the peculiarity of these transformations, and by the substrate and catalyst dependent chemodivergency,[8] we set up to optimize the reaction protocol, while devising a mechanistic rationalization of such non-obvious reactivity. It is also worth to recall the importance of the 2*H*-chromene scaffold, which recurs in a variety of natural and biologically active compounds.[9] Besides, disubstituted sulfoxonium ylides (*i.e.* **4**) are generally considered as difficult to obtain.[10]

Results and Discussion

We began our investigation by reacting salicylaldehyde **1a** and sulfoxonium ylide **2a** in the absence of any catalyst. However, only starting materials were recovered from the reaction mixture (Table 1, entry 1). On the contrary, product **3aa** embedding two ester groups and featuring a 2*H*-chromene skeleton was observed in the presence of Lewis or Brønsted acid catalysts. Performing the reaction with $Sc(OTf)_3$ (entry 2) a lower yield was obtained than with diphenyl phosphoric acid (entry 3). Different solvents were tested and similar results were achieved in THF and CH_2Cl_2 (entries 3 and 4, see SI for further solvent screening). We moved then to evaluate the catalyst loading (entries 4–6) and, since very similar results were obtained with 5 and 10 mol%, we decided to continue the optimisation studies using the lower loading. By running the reaction in THF as solvent, either at room temperature or at 40 °C (entries 7 and 8), similar results were obtained. Inasmuch as temperature had no relevant influence, we moved back to use CH_2Cl_2 as solvent, and considered the possible influence of adventitious water, which was not found to be detrimental to the reaction. Using $MgSO_4$ as additive (entry 9), a decrease of the yield was in fact observed. Considering a possible partial degradation of the relatively unstable ylide **2a** under the acidic reaction conditions, as well as an observed slow catalyst deactivation during the reaction, we tested the addition of the sulfoxonium ylide **2a** and/or the catalyst in portions. Portionwise addition of ylide **2a** improved the yield only slightly (entry 10), while the addition in portions of the catalyst led to a more pronounced improvement (entry 11). Portionwise addition of both catalyst and ylide **2a** was instead unproductive (entry 12).

Keeping the conditions displayed in Table 1, entry 11 as optimal, we moved to evaluate the generality of the reaction (Tables 2 and 3). Regarding sulfoxonium ylides **2** (Table 2), variation of the ester moiety

Table 1. Optimization of reaction conditions: selected results.[a]

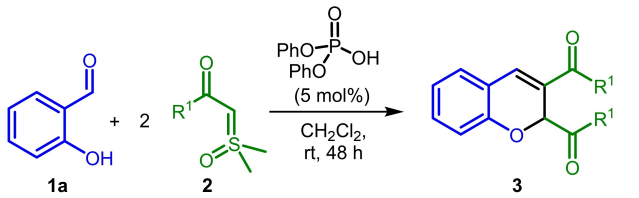


1a **2a** **3aa**

Entry	Cat. (x mol%)	Solvent	Temp. (time)	Yield[b] (%)
1	/	CH_2Cl_2	rt (18 h)	< 5
2	$Sc(OTf)_3$ (10)	THF	rt (18 h)	32
3	$(PhO)_2POOH$ (10)	THF	rt (18 h)	49
4	$(PhO)_2POOH$ (10)	CH_2Cl_2	rt (18 h)	52
5	$(PhO)_2POOH$ (5)	CH_2Cl_2	rt (18 h)	50
6	$(PhO)_2POOH$ (2.5)	CH_2Cl_2	rt (18 h)	20
7	$(PhO)_2POOH$ (5)	THF	rt (18 h)	48
8	$(PhO)_2POOH$ (5)	THF	40 °C (18 h)	50
9[c]	$(PhO)_2POOH$ (5)	CH_2Cl_2	rt (18 h)	35
10[d]	$(PhO)_2POOH$ (5)	CH_2Cl_2	rt (48 h)	65
11[e]	**$(PhO)_2POOH$ (5)**	**CH_2Cl_2**	**rt (48 h)**	**72**
12[d,e]	$(PhO)_2POOH$ (5)	CH_2Cl_2	rt (48 h)	63

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.63 mmol), cat. (x mol%), solvent (0.5 mL), temp., time.
[b] Determined after column chromatography on silica gel.
[c] 30 mg of $MgSO_4$ were added to the reaction mixture.
[d] 1.5 equiv. of **2a** (0.37 mmol) were added at the reaction set up, and additional 1.5 equiv. (0.37 mmol) were added after 8 h.
[e] 2.5 mol% of catalyst were added at the reaction set up, and additional 2.5 mol% were added after 8 h.

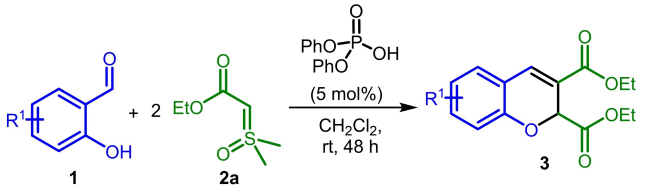
Table 2. Scope and limitations of the reaction between salicylaldehyde **1a** and sulfoxonium ylides **2**.[a]



Entry	2	R^1	3	Yield[b] (%)
1	**2a**	EtO	**3aa**	72
2	**2b**	MeO	**3ab**	70
3	**2c**	*n*-BuO	**3ac**	64
4	**2d**	*i*-BuO	**3ad**	75
5	**2e**	*t*-BuO	**3ae**	62
6	**2f**	AllylO	**3af**	60
7	**2g**	BnO	**3ag**	30
8	**2h**	PhO	**3ah**	< 5
9	**2i**	Ph	**3ai**	< 5

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.63 mmol), catalyst (5 mol%, 2.5 mol% added at reaction set up, 2.5 mol% after 8 h), CH_2Cl_2 (0.5 mL), rt, 48 h.
[b] Determined after column chromatography on silica gel.

Table 3. Scope and limitations of the reaction between salicylaldehydes **1** and sulfoxonium ylide **2a**.[a]

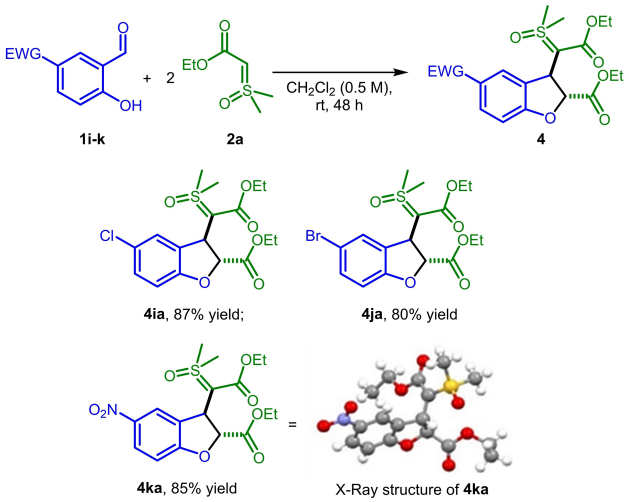


Entry	1	1: R^1	3	Yield[b] (%)
1	**1b**	4-Me	**3ba**	60
2	**1c**	5-Me	**3ca**	63
3	**1d**	3-MeO	**3da**	81
4	**1e**	4-MeO	**3ea**	41
5	**1f**	5-MeO	**3fa**	74
6	**1g**	4,5-(OCH_2O)	**3ga**	65
7	**1h**	6-Cl	**3ha**	45
8	**1i**	5-Cl	**3ia**	40
9	**1j**	5-Br	**3ja**	30
10	**1k**	5-NO_2	**3ka**	< 5

[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.63 mmol), catalyst (5 mol%, 2.5 mol% was added at reaction set up, 2.5 mol% after 8 h), CH_2Cl_2 (0.5 mL), rt, 48 h.
[b] Determined after column chromatography on silica gel.

could be smoothly achieved with short-chain substituents like a methyl group (**2b**) (entry 2), as well as with longer-chain ones (**2c**) (entry 3). Moreover, good results were obtained employing bulkier substituents such as the isobutyl and the *tert*-butyl groups (ylides **2d** and **2e**, entries 4 and 5). The use of an allylic ester did not significantly affect the yield of product **3af** (entry 6), while benzylic sulfoxonium ylide **2g** gave the corresponding 2*H*-chromene **3ag** in a low 30% yield (entry 7). Less nucleophilic ylides bearing a phenol ester (**2h**) or a ketone (**2i**) as electron withdrawing groups, were found to be unreactive under these conditions (entries 8 and 9).

We then explored the reactivity of the archetypal sulfoxonium ylide **2a** with differently substituted salicylaldehydes **1b–k** (Table 3). Methyl-substituted salicylaldehydes **1b** and **1c** delivered products **3ba** and **3ca** (entries 1 and 2) in comparable, yet somewhat lower, yields compared to parent 2*H*-chromene **3aa**. An electron donating group at the *ortho* (3-MeO) or *para* (5-MeO) position to the hydroxylic group led to slightly increased yields for products **3da** and **3fa** (entries 3 and 5). On the contrary, the same methoxy substituent, at position 4, caused a drop in the yield for product **3ea** (entry 4). When sesamol-derived aldehyde **1g** was employed, product **3ga** was obtained with good results (entry 6). Conversely, lower yields were generally achieved employing salicylaldehydes having electron-withdrawing substituents on the aromatic ring. A chloro substituent, at the *ortho* (6-Cl) or *meta* (5-Cl) position to the formyl group, led to products **3ha** and **3ia** in moderate yields (entries 7 and 8). When 5-bromosalicylaldehyde **1j** was subjected to the optimized reaction conditions, the yield for chromene **3ja** dropped even further (entry 9). Finally, 5-nitrosalicylaldehyde **1k** did not afford the desired product **3ka** (entry 10). Indeed, the only product present in the crude mixture of the reaction between **1k** and **2a** was not the expected chromene **3ka**, but a different compound **4ka** still embedding two ester units but featuring a 2,3-dihydrobenzofuran core and a peculiar exocyclic disubstituted sulfoxonium ylide (Scheme 2).

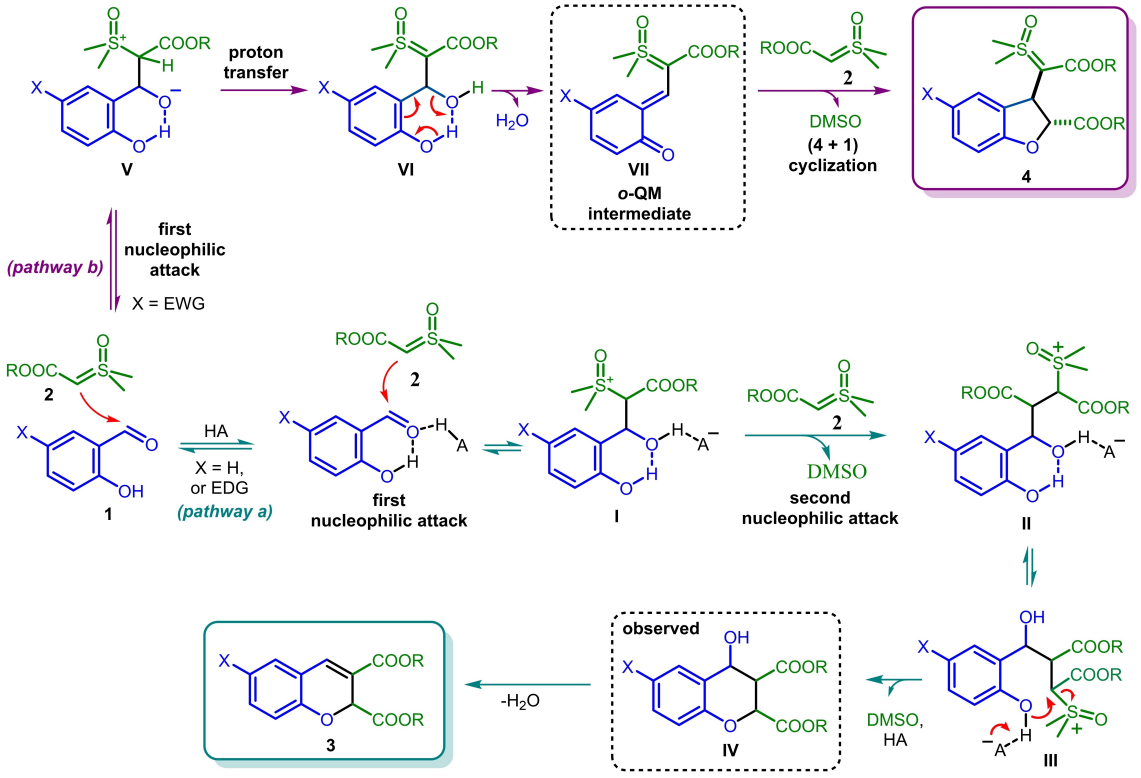


Scheme 2. Uncatalyzed reaction between ylide **2a** and electron-poor salicylaldehydes **1i–k**, and X-ray structure of product **4ka**.

The structure and stereochemistry of **4ka** were established by single-crystal X-ray analysis.[11] Additional investigation indicated that formation of this product does not require the presence of the catalyst. Furthermore, salicylaldehydes **1i** and **1j** could also undergo the same type of uncatalyzed reaction, leading to products **4ia** and **4ja** in 80–87% yields. The presence of **4ia** and **4ja** in the crude mixtures of the catalyzed reactions towards **3ia** and **3ja** (Table 3, entries 8 and 9) justifies, at least in part, the low yields obtained for these chromenes.

We then moved to elucidate the mechanism of these transformations. Taking advantage of different control experiments (see SI), various pathways and intermediates could be excluded. Ultimately, two routes accounting for the formation of products **3** and **4** could be hypothesized (Scheme 3). First of all, it is important to underline that the acidity of the different species is crucial for the chemoselectivity of the reaction. Regarding products **3** *(pathway a)* catalyst coordination to salicylaldehyde **1** is proposed. This promotes a first, likely reversible, nucleophilic attack by ylide **2**, and generates sulfoxonium intermediate **I**. Then, a rather unusual[12] nucleophilic displacement of DMSO by a second ylide may occur, forming a second sulfoxonium intermediate (**II**). Regeneration of the catalyst and intramolecular S_N2 substitution (**III**) can lead to chromane **IV** (observed in the crude mixture and isolated at short reaction times), which dehydrates to give a 2*H*-chromene of type **3**. Regarding the formation of products **4** (*pathway b*), the presence of an electron-withdrawing substituent at *para* position to the hydroxylic group, which is coordinated to the aldehyde, makes the formyl moiety sufficiently reactive to suffer a nucleophilic attack by ylide **2** without catalyst intervention, leading to sulfoxonium intermediate **V**. At this point, the pronounced basicity of the negatively charged oxygen (due to the absence of catalyst coordination, see **V** *vs* **I**) induces a proton transfer process, with the subsequent formation of ylide **VI**. Dehydration affords an *ortho*-quinone methide (*o*-QM)[13] species **VII**, wherein conjugation with the ylide stabilizes the dearomatised electron-poor *o*-QM portion. Next, a formal (4 + 1) cyclization reaction with DMSO displacement can occur between **VII** and **2**, forming 2,3-dihydrobenzofurans **4**.

On the basis of the pathways depicted in Scheme 3, we conjectured that the chemoselectivity of the process could be, at least in part, controlled by the amount of catalyst employed. Performing the reaction between aldehyde **1j** and sulfoxonium ylide **2a**, without catalyst or with a large amount of it (50 mol%), an inversion of the selectivity in favor of **4ja** or **3ja**, respectively, was in fact observed (Figure 1, left). Besides, the yield of **3ja** increased slightly by moving from the standard 5 mol% to the high 50 mol% catalyst



Scheme 3. Possible reaction pathways accounting for the formation of products **3** and **4**.

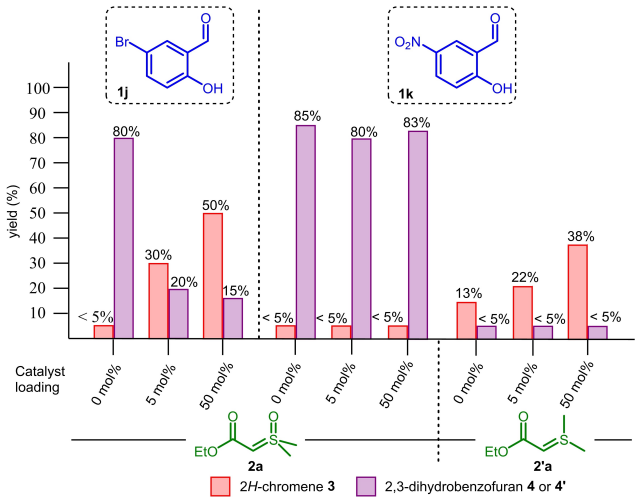


Figure 1. Catalyst- and ylide- controlled chemoselectivity switch.

loading. On the contrary, the more acidic/reactive salicylaldehyde **1k** led to the exclusive formation of product **4ka**, irrespective of the amount of catalyst employed (Figure 1, middle). Thus, to reverse the selectivity of the reaction with **1k**, we considered the use of an ylide species more nucleophilic than sulfoxonium ylide **2a**, such as the corresponding sulfonium derivative **2'a**. In fact, according to Scheme 3, a more nucleophilic sulfonium ylide may favor a second nucleophilic attack to a catalyst-bound intermediate **I'**. Furthermore, the less acidic nature of sulfonium *vs* sulfoxonium salts could hinder the proton-transfer step in intermediate **V'**. Both factors should combine towards channeling the reaction through the pathway leading to 2*H*-chromene **3ka**. Indeed, performing the reaction between aldehyde **1k** and sulfonium ylide **2'a**, we were delighted to observe that only product **3ka** was present in the reaction mixture, with no traces of the corresponding 2,3-dihydrobenzofuran derivative **4'ka** (Figure 1, right). The yield of **3ka** could be even increased to a moderate level, by using a larger amount of catalyst. In contrast with sulfoxonium ylides, which do not form products **3** in the absence of catalyst, sulfonium ylide **2'a** could deliver small amounts of **3ka** even without catalyst being present.[14,15] On the other hand, the reaction of ylide **2'a** with the electron neutral neutral salicylaldehyde **1a** was found to give the product **3aa** in low yield (see SI), possibly due to the poor stability of this ylide under the reaction conditions.

Conclusions

In conclusion, we discovered a chemodivergent reaction between salicylaldehydes **1** and stabilized sulfoxonium ylides **2**, leading to 2*H*-chromenes **3** or *trans*-2,3 dihydrobenzofurans **4** embedding a disubstituted sulfoxonium ylide moiety. The chemoselectivity of the reaction depends on a combination of catalyst activation and substitution pattern on the salicylaldehyde aromatic ring. In more detail, the use of a Brønsted acid catalyst steers the reaction towards the formation of 2*H*-chromene structures **3**, while electron-withdrawing groups on the aldehyde allow the reactions to proceed without catalyst, leading to the 2,3-dihydrobenzofuran counterparts **4**. Two competing reaction pathways accounting for the formation of these structures were proposed. In these pathways, the chemoselectivity derives from a competition between a proton-transfer step, favoured in the absence of catalyst and leading to 2,3-dihydrobenzofurans **4**, *vs* a nucleophilic addition of a second ylide to a reaction intermediate, which ultimately delivers 2*H*-chromenes **3**. These hypotheses were validated by reversing the chemoselectivity of the reaction, at least in some cases, through the modulation of the catalyst loading and the nucleophilicity of the sulfur ylide. In general terms, the results herein reported introduce a new entry in the multifarious, and sometimes surprising, reactivity of sulfoxonium ylides with polyfunctional substrates.[1g,5] Besides, the capability of a catalyst to steer the reaction towards the formation of 2*H*-chromenes **3**, *vs* benzofurans **4** obtained without catalyst, highlights the competency of catalytic species in outcompeting innate reaction pathways and reactivities.[16]

Experimental Section

General Procedure for the Synthesis of Products 3

In a small vial equipped with a magnetic stirring bar, salicylaldehyde **1** (1.0 equiv., 0.25 mmol) sulfoxonium ylide **2** (2.5 equiv., 0.62 mmol), CH_2Cl_2 (500 μL) and catalyst $(PhO)_2POOH$ (3.1 mg, 0.013 mmol, 5 mol% in two equal portions, the first one immediately and the second one after 8 h) were added. The resulting solution was stirred for 48 h at room temperature and then directly purified by column chromatography on silica gel, to afford the desired compound **3** as a solid.

Diethyl 2*H*-chromene-2,3-dicarboxylate (3aa)

Following the general procedure using salicylaldehyde **1a** and sulfoxonium ylide **2a**, product **3aa** was obtained as white solid in 72% yield (49.7 mg) after column chromatography on silica gel (*n*-hexane/Et_2O = 5:1). ^{1}H NMR and ^{13}C NMR analysis reported below are in accordance with the literature.[17] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.51 (d, J = 0.7 Hz, 1H), 7.30–7.24 (m, 1H), 7.17 (dd, J = 7.5, 1.7 Hz, 1H), 6.99 (ddd, J = 8.2, 1.3, 0.6 Hz, 1H), 6.94 (m, 1H), 5.78 (s, 1H), 4.36–4.24 (m, 2H), 4.20–4.05 (m, 2H), 1.34 (t, J = 7.4, 3H), 1.18 (t, J = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.1, 164.4, 153.8, 133.4, 132.4, 129.1, 122.2, 121.4, 119.8, 116.5, 71.8, 61.6, 61.1, 14.2, 14.0. **EI-MS** (m/z, relative intensity): 276 (M+, 2%), 203 (M+ –CO_2Et, 100%).

General Procedure for the Synthesis of Products 4

In a small vial equipped with a magnetic stirring bar, salicylaldehyde **1** (1.0 equiv, 0.25 mmol) and sulfoxonium ylide **2a** (2.5 equiv., 0.62 mmol) were dissolved in 500 µL of CH_2Cl_2. The resulting solution was stirred for 18 h at room temperature and then directly purified by column chromatography on silica gel to afford compounds **4**.

Ethyl-3-(1-(dimethyl(oxo)-λ6-sulfaneylidene)-2-ethoxy-2-oxoethyl)-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (4ka)[11]

Following the general procedure using salicylaldehyde **1k** and sulfoxonium ylide **2a**, product **4ka** was obtained as white solid in 85% yield (84.8 mg) after column chromatography on silica gel (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.11 (dd, J = 8.8, 2.5 Hz, 1H), 7.89 (dd, J = 2.5, 1.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 5.19 (d, J = 8.7 Hz, 1H), 4.64 (d, J = 8.6 Hz, 1H), 4.37–4.25 (m, 2H), 4.02–3.77 (m, 2H), 3.58 (s, 3H), 3.44 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H), 0.85 (bt, J = 6.81, 3H). **^{13}C NMR** (400 MHz, $CDCl_3$) δ = 170.4, 164.2, 142.5, 132.0, 125.4, 119.6, 109.3, 86.8, 61.9, 59.3, 58.7, 44.9, 43.5, 41.7, 14.2, 14.0. **ESI-MS** = 367 [M + Na +].

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[14] Qualitatively, a similar reactivity pattern was observed in reactions with *N*-phenyl salicylaldimines, see SI.

[15] In the reaction between salicylaldehyde **1a** and sulfoxonium ylide **2a** in the absence of catalyst, we observed formation of a small amount of a product with ^{1}H NMR signals compatible with the corresponding 2,3-dihydrobenzofuran **4aa**, when the reactions were performed in more polar solvents (*e.g.* THF). This result suggests the possibility of chemoselectivity switch towards formation of benzofurans **4** for electron-rich/neutral salicyaldehydes **1**, and confirms the unique role played by the catalyst in steering the reactions with sulfoxonium ylides **2** towards the formation of 2*H*-chromenes **3**.

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