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Development of a General Protocol to Prepare 2*H*-1, 3-Benzoxazine Derivatives

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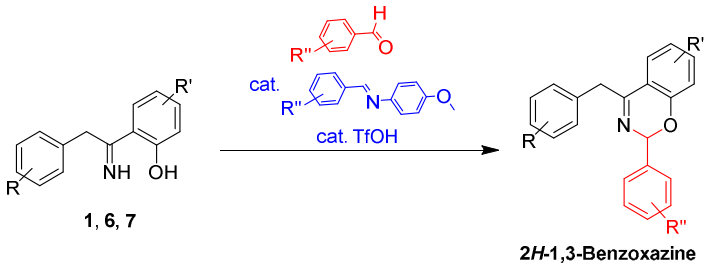


ABSTRACT: A practical synthesis and detailed development process of 2*H*-1, 3-benzoxazine derivatives catalyzed by aldimine and trifluoromethanesulfonic acid is described. A broad range of substrates with diverse steric and electronic properties were explored. Aliphatic/aromatic/heteroaromatic substrates all proceed well under conditions which have been optimized into a robust, scalable process.

Keywords: 2*H*-1,3-benzoxazine, Aldimine, Acid catalysis, Hemiaminal

■ INTRODUCTION

2*H*-1,3-benzoxazine and derivatives are interesting structural motifs present in natural products[1], agricultural bactericides[2] and pharmaceuticals[3]. As shown in Figure 1, a 2*H*-1,3-benzoxazine substructure is present in the key precursor for the enantioselective Pd-catalyzed C-N coupling[4] to the benzoxazino-indole chiral hemiaminal core of elbasvir [5], a potent inhibitor of the HCV NS5A protein which is currently undergoing late-stage clinical trials. With only a handful of syntheses of this structural motif reported in the literature,[6] an efficient and general synthesis of 2*H*-1,3-benzoxazines was desired. Herein, we present the development of a practical methodology with broad substrate scope and scalability.

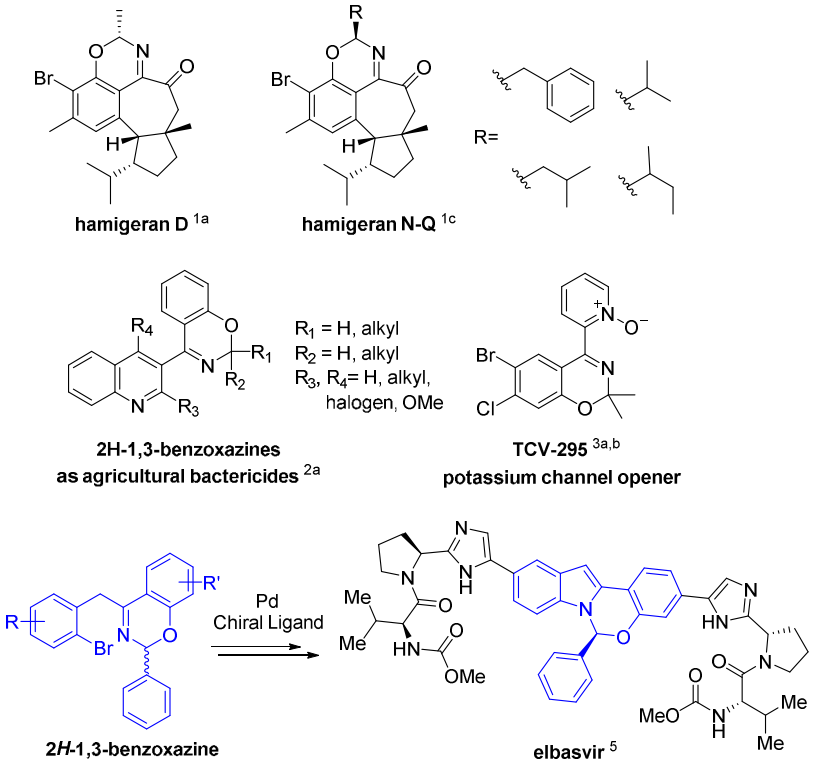


Figure 1. 2*H*-1,3-benzoxazine natural products and related bioactive molecules.

■ Results and discussion

Our preliminary attempts to use **1** and benzaldehyde to form 2*H*-1,3-benzoxazine **2** under standard acid-catalyzed conditions (Figure 2) gave an unsatisfactory reaction profile. The desired product **2** was generated in only 20% yield with formation of a significant amount over-reacted aldol product **3**. On a structurally-related project within Merck, we had successfully used p-OMe aldimine and TFA for hemiaminal formation and in that case, the reaction was driven to completion by the crystallization of the aniline TFA salt. While this same aldimine method did not translate directly to compound **2** (Figure 2), it did provide us with a lead for development.

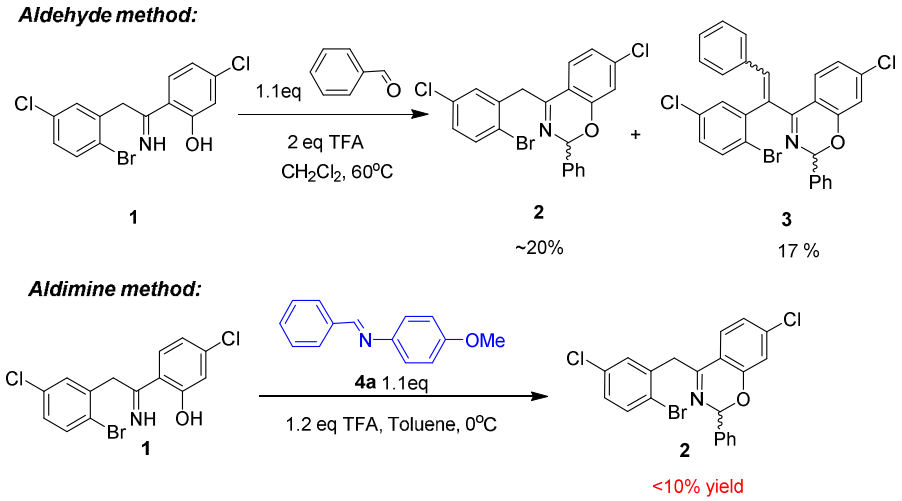
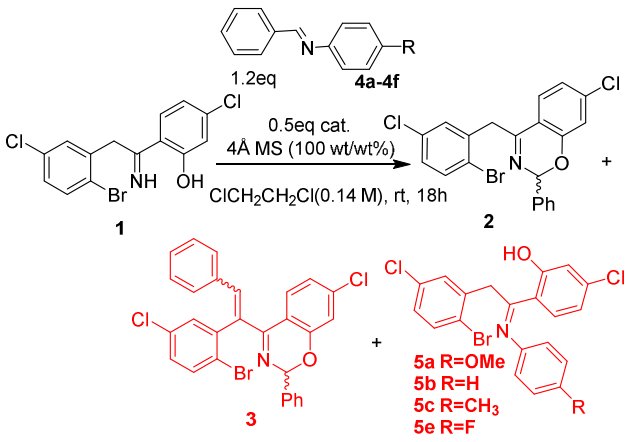


Figure 2. Early attempts of 2*H*-1,3-benzoxazines formation

Our investigations into aldimine-mediated 2*H*-1,3-benzoxazines formation started with the evaluation of several additives[7] from which triflic acid (TfOH) and triflic anhydride (Tf_2O) appeared the most promising. The reactions were driven to completion by removal of water with molecular sieves. Six aldimines, differing in their para-substituents were prepared (**4a-4f**, R = OMe, H, Me, Cl, F, CF_3) and screened (Table 1). The 4-F-aldimine **4e** gave high product ratios; 78% and 73% (LC area %) with Tf_2O and TfOH, respectively (entry 7 and entry 8). Interestingly however, the 4-OMe aldimine **4a** led to the highest conversions (Entry 11 and 12), albeit with significant formation of imine by-product **5a**. This observation led to the hypothesis that the presence of excess benzaldehyde could suppress the formation of imine by-product **5a.** Gratifyingly, the addition of 0.5 equiv. benzaldehyde to the 4-OMe aldimine reactions yielded >95 LC area% of desired product (Entry 13 and 14). In conclusion, both 4-F and 4-OMe aldimines (**4e** and **4a**) performed well as did both triflate sources.[8] However, for further development we decided to focus only on the less expensive triflic acid.

Table 1. Initial screening with different aldimines



entry	4a-4f R=	Catalyst	Result (LC area %)			
			1	**2**	**3**	**5a-5e**
1	H (**4b**)	Tf_2O	10	56	7	15**(5b)**
2	H (**4b**)	TfOH	11	45	9	26**(5b)**
3	CH_3 (**4c**)	Tf_2O	15	59	10	20 **(5c)**
4	CH_3 (**4c**)	TfOH	5	44	8	51 **(5c)**
5	Cl (**4d**)	Tf_2O	--	87	8	--
6	Cl (**4d**)	TfOH	16	50	--	--
7	F (**4e**)	Tf_2O	12	78	3	--
8	F (**4e**)	TfOH	23	73	--	--
9	CF_3 (**4f**)	Tf_2O	2	62	23	--
10	CF_3 (**4f**)	TfOH	30	40	14	--
11	OMe(**4a**)	Tf_2O	1	69	2	24**(5a)**
12	OMe(**4a**)	TfOH	3	49	---	48**(5a)**
13 [a]	OMe(**4a**)	Tf_2O	1	95	3	--
14 [a]	OMe(**4a**)	TfOH	--	96	2	2 **(5a)**

[a] Reactions were carried out with 0.5 equiv. of benzaldehyde

Since the 4-OMe and 4-F aldimines (**4a** and **4e**) appeared the most promising, we decided to study only these two more extensively. Solvent, equivalents of triflic acid and aldimine were evaluated. Table 2 shows that this screening provided a distinct pattern. While both **4a** and **4e** performed similarly in chlorinated solvents (CH_2Cl_2 and 1, 2-Dichloroethane) in the presence of

excess aldimine, **4a** was significantly better at sub-stoichiometric levels of aldimine (entries 4 *vs*. 9). Likewise, when the triflic acid charge was lowered from 0.3 to 0.05 equivalents, **4a** (4-OMe) again outperformed **4e** (4-F, entries 5 *vs.* 10). Higher level of over-reacted Aldol by product **3** was observed in reactions with **4e** (entry 9 and 10 *vs.* Entry 4 and 5). This could be due to the higher reactivity of electron deficient aldimine **4e** (4-F) towards Aldol addition.

Table 2. Comparison of 4-F aldimine vs 4-OMe aldimine [a]

Entry	Solvent	Aldimine **4a**, **4e**	Equiv. aldimine	Equiv. TfOH	Result（LC area%）			
					1	**2**	**3**	**5a, 5e**
1	$ClCH_2CH_2Cl$	**4a**	1.2	0.3	1	86	8	--
2	**CH_2Cl_2**	**4a**	1.2	0.3	1	91	4	0.5 (**5a**)
3	**Toluene**	**4a**	1.2	0.3	18	68	2	1.3 (**5a**)
4	$ClCH_2CH_2Cl$	**4a**	**0.6**	0.3	1	94	2	1.0 (**5a**)
5	$ClCH_2CH_2Cl$	**4a**	1.2	**0.05**	0.5	94	4	--
6	$ClCH_2CH_2Cl$	**4e**	1.2	0.3	0.8	91	7	--
7	**CH_2Cl_2**	**4e**	1.2	0.3	0.9	90	5	--
8	**Toluene**	**4e**	1.2	0.3	7	73	6	--
9	$ClCH_2CH_2Cl$	**4e**	**0.6**	0.3	3	77	13	--
10	$ClCH_2CH_2Cl$	**4e**	1.2	**0.05**	1	75	18	0.2 (**5e**)

[a] Reactions were carried out with **1** (1 equiv.), benzaldehyde (1.1 equiv.), aldimine, TfOH and 4Å MS (100 wt/wt %) in solvent (0.14 M of **1**) at room temperature for 18h.

All previous experiments had been run in the presence of 100 wt% of 4A molecular sieves relative to the substrate and at relatively low concentration (0.14 M of **1**). With conditions in hand to form the desired product cleanly and in high yield, we decided to make the process more practical by minimizing the quantities of molecular sieves and solvent. The results are shown in Table 3. We first looked at different loadings (100, 50 and 0 wt/wt%) of molecular sieves at 0.14 M of **1** (entry 1 to 3). It was discovered that there was no significant impact on reaction performance when the molecular sieves were reduced to as low as 50 wt/wt%. A similar trend

was also observed with reactions conducted at higher concentration (entry 4 to 7). In all cases the reaction mixture remained a mobile slurry.

Table 3. Optimization of molecular sieves loading and reaction concentration [a]

Entry	4A MS (wt %)	Conc. of **1** (M)	Result（LC area %）			
			1	**2**	**3**	**5a**
1	**100**	0.14	3	93	2	2
2	**50**	0.14	4	89	2	6
3	**0**	0.14	15	16	0.8	22
4	**100**	**0.28**	2	94	2	2
5	**50**	**0.28**	2	86	2	7
6	**0**	**0.28**	10	67	2	21
7	**50**	**0.4**	2	90	3	6

[a] Reactions were carried out with **1** (1 equiv.), benzaldehyde (1.1 equiv.), aldimine **4a** (1.2 equiv.), TfOH (0.3 equiv) and 4Å .MS in CH_2Cl_2 at room temperature for 18h.

As noted previously, the use of sub-stoichiometric quantities of aldimine was well tolerated and the reaction profile appeared to become cleaner at lower equivalents (Table 4), although the reaction was significantly slower when only 0.1 equivalent **4a** was used (entries 2 vs. 5 and 6). TfOH could also be used at lower concentrations (entry 2 vs. 3), but at less than 5 mol%, there was an adverse impact on the rate of reaction (entries 3 vs. 4). Our primary goal was to minimize the waste generated in the process, and we ultimately found that the optimal balance to achieve a high conversion, a clean profile and an acceptable reaction rate was the use of 0.1 equiv. aldimine **4a** and 0.2 equiv. TfOH.

Table 4. Optimization of equiv. of Acid and equiv. of Aldimine **4a**[a]

Entry	Equiv. **4a**	Equiv. TfOH	Result（LC area%） **1**	**2**	**3**	**5a**
1	1.2	0.3	2	90	3	6
2	**0.5**	0.3	2	95	2	0.9
3	**0.5**	**0.05**	1	95	3	0.6
4	**0.5**	0.01	15	83	2	0.5
5[b] (48h)	**0.1**	0.3	5	93	2	0.7
6[b] (48h)	**0.1**	0.2	9	88	2	0.7

[a] Reactions were carried out with **1** (1 equiv), benzaldehyde (1.1 equiv), aldimine, TfOH and 4Å MS (50 wt/wt %) in CH_2Cl_2 (0.4 M of **1**) at room temperature for 18h. [b] Slow reaction, incomplete conversion at 18h. The 48h data point is reported.

Considering one of the key principles of green chemistry, we sought to move away from chlorinated solvents to develop a more environmentally acceptable process.[9] Table 5 shows the impact of a range of common solvents at ambient temperature in comparison with the previously used CH_2Cl_2 (entry 1 to 5). Gratifyingly, both 2-MeTHF and IPAc showed a significantly improved reaction rate and profile.

Table 5. Development of an environmental friendly process with greener solvents [a]

Entry	Solvent	Temp	Result (LC area %) **1**	**2**	**3**	**5a**
1	CH_2Cl_2	rt	26	72	1	--
2	**Toluene**	rt	88	12	--	--
3	**2-MeTHF**	rt	2	91	5	0.5
4	**IPAc**	rt	3	92	3	0.2
5	**MeCN**	rt	26	70	3	1

[a] Reactions were carried out with imine **1** (1 equiv), benzaldehyde (1.1 equiv), aldimine **4a** (0.1 equiv), TfOH (0.2 equiv) and 4Å MS (50 wt/wt%) in solvent (0.4 M of **1**) for 18h.

With the knowledge that product **2** could be crystallized from MeOH with high purity and recovery, the 2-MeTHF system was further optimized due to its highly efficient binary azeotrope

with MeOH that could potentially be exploited to avoid an aqueous work-up. All reaction parameters with this solvent system (including alternative dehydrating agents) were evaluated again.[10] But the previous optimal conditions (0.1 equiv. aldimine, 0.2 equiv. TfOH) still gave the best overall profile. The concentration could be increased to 0.46 M and the loading of molecular sieves was increased to 60wt% to achieve a more robust process for scale-up. In the final optimized process (demonstrated at 500 g scale, Figure 3) the molecular sieves were filtered at the end of reaction. After an aqueous wash to remove TfOH, the solvent is then switched from 2-MeTHF to MeOH. This led to the crystallization of the product which can be isolated in 83% yield with 97% LC purity.

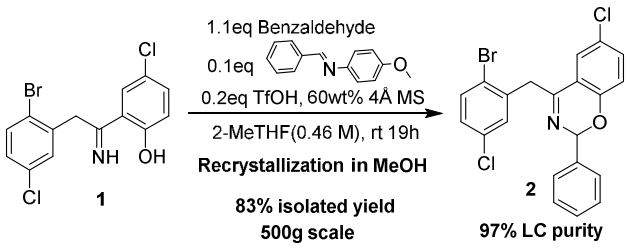
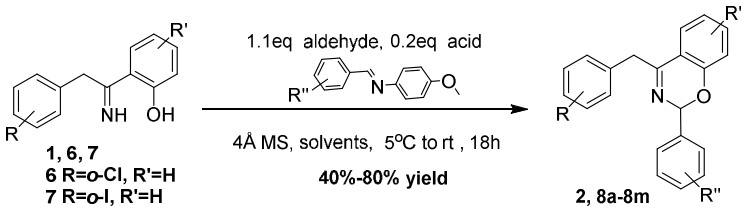


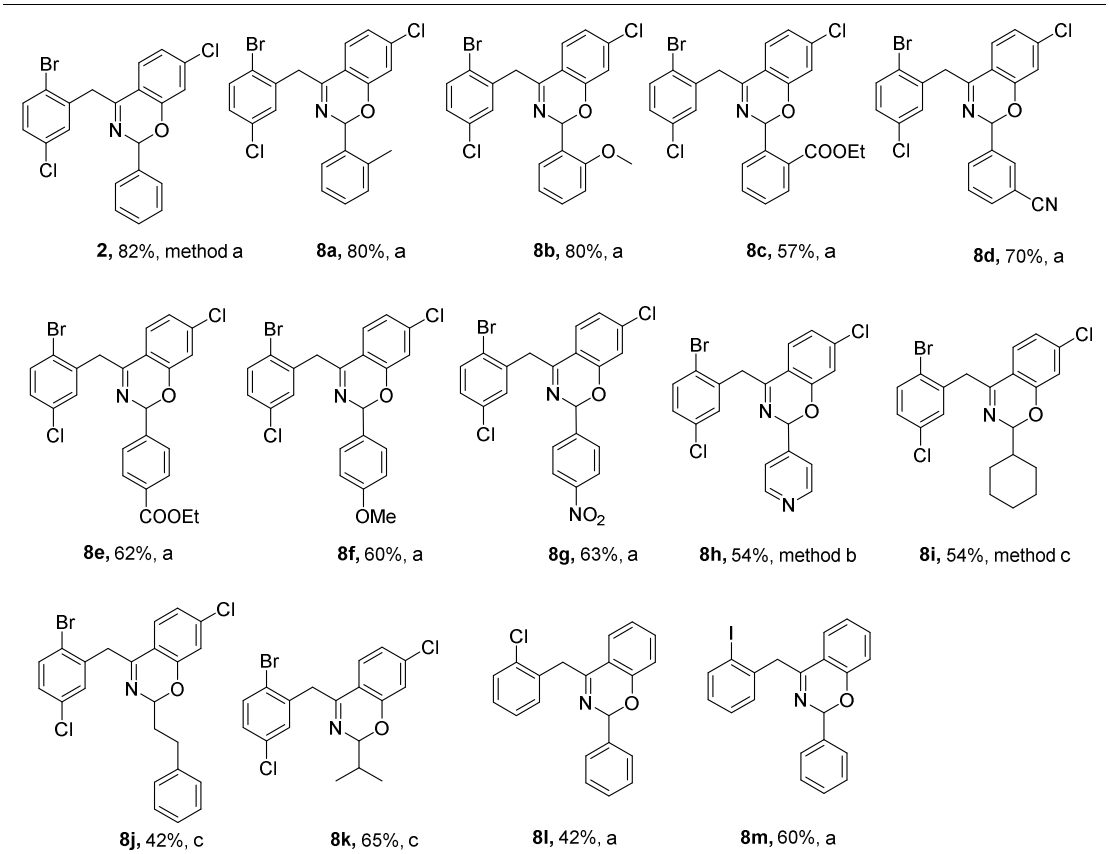
Figure 3. 500g Demonstration of 2*H*-1,3-benzoxazine **2** formation

With these optimized conditions in hand, we then looked at the scope of this new 2*H*-1,3-benzoxazine formation methodology. First, a number of aromatic aldehydes/aldimines with different electronic and steric effects were evaluated (Table 6, **2, 8a** to **8g**). Under the standard conditions (method a[11]), all reactions proceeded smoothly and generated the desired product in moderate to good yields (60-80%). We then studied a heteroaromatic system (**8h**) and three different aliphatic aldehydes/aldimines (**8i** to **8k**). The performance of the standard protocol was inferior in these cases. However, a change in reaction solvent and catalytic additives (method b: with TFA in CH_2Cl_2 and method c: with TfOH in CH_2Cl_2) gave the desired products in more

acceptable yields. Finally, several substitution patterns on the left aromatic ring were studied (**8l** and **8m**). In general, without any further attempts to optimize yield our general 2*H*-1,3-benzoxazine methodology worked well for these substrates.

Table 6. 2*H*-1, 3-Benzoxazine formation with different phenol imines and aldehydes



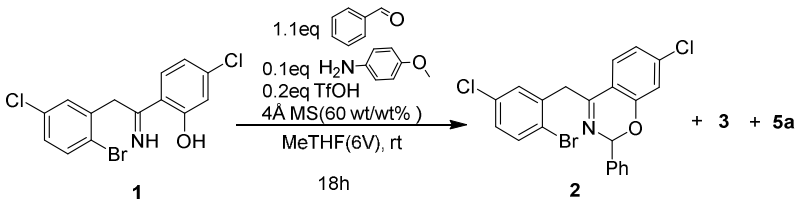


[a] **Method a**: reactions were carried out with **1** (1 equiv), aldehyde (1.1 equiv), aldimine (0.1 equiv), TfOH (0.2 equiv) and 4Å MS (50 wt/wt %) in MeTHF (0.4 M of **1**) at rt for 18h. [b]

Method b: reactions were carried out with **1** (1 equiv), aldehyde (1.1 equiv), aldimine (1 equiv), 2,2,2-trifluoroacetic acid (0.2 equiv) and 4Å MS (100 wt/wt %) in CH_2Cl_2 (0.28 M of **1**) at rt for 18h. [c] **Method c**: reactions were carried out with **1** (1 equiv), aldehyde (1.1 equiv), aldimine (1 equiv or 0.2 equiv), TfOH (0.2 equiv) and 4Å MS (100 wt/wt %) in CH_2Cl_2 (0.28 M of **1**) at rt for 18h.

While we developed our general protocol with isolated aldimine for convenience, we were eager to demonstrate that the 4-methoxyaniline could also be used in a catalytic process, thus hopefully also providing more insight to the reaction mechanism. Four experiments were carried out as shown in Table 7. Experiment 4 showed the exact same reaction profile as our standard conditions (experiment 1). Experiment 2 and 3 showed slightly lower conversion and more formation of by-product **5a**, which indicated that a certain amount of mixing time of aniline and aldehyde is required to achieve a good reaction profile.

Table 7. Studies of using of aniline instead of aldimine



Exp	Conditions	Result (LC area percent %)			
		1	**2**	**3**	**5a**
1	Aldimine pre-formed (standard condition)	2	84	2	2
2	All reagents added at same time	8	68	1	9
3	Benzaldehyde，aniline and 4Å MS stirred for **30min** before addition of other reagents	4	76	2	8
4	Benzaldehyde，aniline and 4Å MS stirred for **60min** before addition of other reagents	2	84	2	2

Based on these observations a plausible mechanism is proposed in Figure 4. The reaction of aniline and benzaldehyde appeared to be relatively slow under the reaction conditions and more than 30 min were required to achieve high conversion to aldimine, and minimization of formation of **5a**. Under acidic conditions, the activated aldimine could presumably be attacked by **1** to form a hemi-aminal **Int 1**. Instead of releasing free aniline which would lead to more formation of by-product **5a,** we propose that **Int 1** in the presence of the excess of benzaldehyde will form benzyl iminium **Int 2**. In the next step **Int 2** will regenerate the catalytic aldimine shuttle as well as oxonium **Int 3** which will collapse into the desired product **2**.

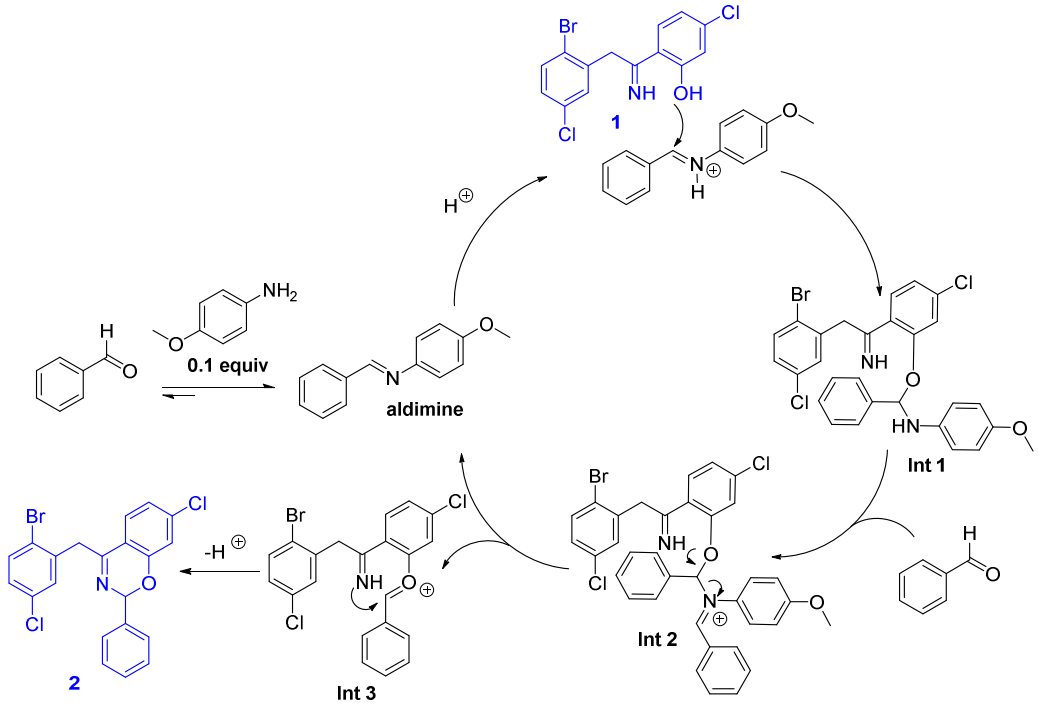


Figure 4. Proposed mechanism for 2*H*-1, 3-benzoxazine formation

■ Conclusion

In this study, we report the details behind the development of a general set of conditions for the formation of 2*H*-1, 3-benzoxazines, which are important intermediates for a class of

Merck HCV drug candidates and precursors for a novel enantioselective Pd-catalyzed C-N coupling.[4] A broad range of substrates with diverse steric and electronic properties, including aliphatic/aromatic/heteroaromatic ones, were evaluated under the developed conditions. Furthermore, we have optimized conditions for the key intermediate of elbasvir into a robust and scalable process which was demonstrated on 500 g scale.

■ Experimental section

General information. All experiments described were carried out under nitrogen atmosphere. All reagents were stored under nitrogen atmosphere prior to use in experiments. Powdered 4Å molecular sieves (MS) was purchased from Beijing Innochem Science & Technology Co. Ltd. and pre-activated in heating oven at 300°C for 20 h prior to experiments. IR spectra were measured on NEXUS 670 FT-IR. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker DPX-500 NMR Spectrometers. Chemical shifts are reported in ppm relative to the residual deuterated solvent. Reactions were monitored by reverse-phase HPLC on Agilent 1260 HPLC instrument and LCMS on Agilent 1260 HPLC with 6120 Mass Spec system. High resolution mass spectra were recorded on a Xevo G2 QTof (Waters MS Technologies) mass spectrometer by electrospray ionization.

*Synthesis of 2-(2-(2-bromo-5-chlorophenyl)-1-iminoethyl)-5-chlorophenol (**1**) (synthetic scheme in SI):* Into a 2000 mL flask was charged 2-(2-bromo-5-chlorophenyl) acetic acid **9** (60.4 g, 242 mmol) and trifluoromethanesulfonic acid (1.10 kg). A solution was formed after stirring the mixture for 10 min, and then 3-chlorophenol (27.1 g, 211 mmol) was added. The solution was heated to 55 °C overnight. LCMS showed complete conversion. The

mixture was cooled to rt and poured into 3 kg of ice-water. The suspension was stirred for 30 min and then filtered. The solid was washed with water (300 mL x 3) and then dissolved in ethyl acetate (1000 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. This resulted in 2-(2-bromo-5-chlorophenyl)-1-(4-chloro-2-hydroxyphenyl)ethanone **10** (82.0 g, crude) as a white solid. It was used directly in the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.10 (s, 1H), 7.81 (d, 1H, *J* = 8.5 Hz), 7.55 (d, 1H, *J* = 8.5 Hz), 7.26 (d, 1H, *J* = 3.5 Hz), 7.20 (dd, 1H, *J* = 8.5 Hz, 2.5 Hz), 7.05 (d, 1H, *J* = 2.5 Hz), 6.95 (dd, 1H, *J* = 8.5Hz, 2.0 Hz), 4.42 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.8, 163.3, 142.7, 135.6, 133.9, 133.6, 131.6, 130.8, 129.3, 122.9, 119.9, 118.8, 117.6, 45.2. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_9BrCl_2O_2$ H] 358.9241; found 358.9240. FTIR(neat): 3074 (br), 1627, 1605, 1567, 1461, 1410, 1352, 1260 cm^{-1}. Spectroscopic data for 2-(2-bromo-5-chlorophenyl)-1-(4-chloro-2-hydroxyphenyl)ethanone were identical to those reported in the literature.[4] Into a 1000ml round bottom flask was placed 2-(2-bromo-5-chlorophenyl)-1-(4-chloro-2-hydroxyphenyl)ethanone **10** (82.0 g, crude), ammonia in MeOH (400 ml, ca.9 N). The resulting mixture was stirred at room temperature overnight. The solid was filtered and washed with MeOH (60 ml x 2), and then dried under reduced pressure to give 2-(2-(2-bromo-5-chlorophenyl)-1-iminoethyl)-5-chlorophenol (**1**, 67.1 g, 187 mmol, 77 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 15.23 (br, 1H), 8.85 (br, 1H), 7.62 (d, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.5 Hz), 7.28-7.25 (m, 2H), 7.04 (d, 1H, *J* = 2.0 Hz), 6.85 (dd, 1H, *J* = 9.0, 2.5 Hz), 4.22 (s, 2H).^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 175.8, 164.3, 139.2, 135.0, 134.6, 134.3, 132.2, 130.1, 128.8, 123.6, 118.8, 118.3, 116.6, 42.7. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{10}BrCl(^{37}Cl)NO$ H] 359.9372; found 359.9377. FTIR (neat): 2597 (br), 1594, 1491, 1461, 1366 cm^{-1}. Spectroscopic data for **1** were identical to those reported in the literature.[4]

General Method A for 2H-1, 3-Benzoxazine derivative synthesis: A suspension of 2.5 g of pre-activated powdered 4Å MS (50 wt/wt%) in 2-Methyl-THF (30 ml) was cooled to 0°C, and stirred for 10min. Phenol (**1**, 5.00 g, 13.9 mmol), aldehyde (15.3 mmol) and the corresponding aldimine (1.39 or 13.9 mmol) were added, and the resulting mixture was stirred for 2min maintaining 0-5^{o}C. Trifluoromethanesulfonic acid (0.418 g, 2.79 mmol) was added. The ice bath was removed and reaction mixture was warmed to rt and stirred overnight. The reaction was monitored by LCMS. The molecular sieves were filtered and washed with 2-MeTHF(5 mL). The combined organic phases were washed with 5 wt% $NaHCO_3$ solution (25 mL), water (25 mL) , dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Target compounds were purified by different purification methods.

General Method B for 2H-1,3-Benzoxazine derivative **synthesis:** A suspension of 4 g of pre-activated powdered 4Å MS (100 wt/wt%) and aldehyde (12.3 mmol) in CH_2Cl_2 (40 ml) was stirred for 30min at rt . Phenol (**1**, 4.00 g, 11.1 mmol), corresponding aldimine (11.1 mmol) and 2,2,2-trifluoroacetic acid (0.254 g, 2.23 mmol) were added and the resulting mixture was stirred at rt for 18 h. LCMS analysis showed completion of reaction. The reaction mixture was quenched with 5 wt% $NaHCO_3$ solution (30 mL) and then extracted with ethyl acetate (100 mL×2). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to obtain the crude product, which was purified by reverse phase combi-flash chromatography.

General Method C for 2H-1, 3-Benzoxazine derivative synthesis: A suspension of 6 g of pre-activated powdered 4Å MS (100 wt/wt%) and aldehyde (18.4 mmol) in CH_2Cl_2 (60 ml) was stirred for 30 min at rt. Phenol (**1**, 6.00 g, 16.7 mmol), corresponding aldimine (16.7 or 3.34 mmol) and trifluoromethanesulfonic acid (0.501 g, 3.34 mmol) were added and the resulting

mixture was stirred at rt for 18 h. LCMS analysis showed completion of reaction. The reaction was quenched with 5 wt% $NaHCO_3$ solution (30 mL), and extracted with ethyl acetate (100 mL×2). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to obtain the crude product, which was purified by reverse phase combi-flash chromatography.

General procedure for the synthesis of aldimine 4a-4f: Into a round bottom flask were placed aldehyde (1 eq), aniline (0.95 eq) and toluene (10 vol). The mixture was stirred at rt overnight. The reaction was monitored by LCMS. Upon completion, the reaction mixture was concentrated to dryness. Then toluene (10 vol) was added and the resulting mixture was concentrated to dryness. This process was repeated twice. The crude aldimine was used directly in the next step without further purification. *Reaction to prepare 4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-phenyl-2H-benzo[e][1,3]oxazine* ***2*****:** The reaction was carried out using general method A with 60 wt/wt% of powdered 4Å MS and 0.1 equiv. of corresponding aldimine. The crude product was recrystallized from MeOH (5vol) to yield **2** as a light-yellow solid (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.55-7.52 (m, 3H), 7.42-7.34 (m, 3H), 7.30 (d, 1H, J = 3.5 Hz,) 7.29 (s, 1H), 7.12 (dd, 1H, J = 8.5Hz, 2.5 Hz), 6.95-6.91 (m, 2H), 6.57 (1H, s), 4.16 (ABq, 2H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 16.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 161.5, 155.8, 139.2, 138.9, 138.1, 133.8, 133.5, 130.6, 128.8, 128.7, 128.5, 127.0, 126.3, 122.6, 121.9, 117.3, 116.2, 88.9, 40.8. HRMS TOF MS (m / z): $[M + H]^+$ calcd for $[C_{21}H_{14}BrCl_2NO\ H]$ 445.9709; found 445.9713. FTIR(neat): 3060, 1633, 1596, 1454, 1364, 1344 cm^{-1}. Spectroscopic data for **2** were identical to those reported in the literature.[4]

4-(1-(2-bromo-5-chlorophenyl)-2-phenylvinyl)-7-chloro-2-phenyl-2H-benzo[e][1,3]oxazine ***3***: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.65 (d, 1H, J = 8.2 Hz), 7.62 – 7.53

(m, 2H), 7.53 – 7.43 (m, 2H), 7.41 – 7.27 (m, 5H), 7.24 – 7.10 (m, 4H), 7.08 – 7.01 (m, 2H), 7.00 – 6.89 (m, 1H), 6.67 – 6.53 (m, 1H, weak). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 164.0 (weak), 155.5 (weak) 141.5, 138.7, 138.0, 137.7, 136.4, 134.7, 133.9, 133.5, 132.5, 131.7, 129.6, 129.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.4, 127.1, 121.8, 117.3, 89.0. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{28}H_{18}BrCl_2NO\ H]$ 534.0022; found 534.0027. FTIR(neat): 3434(br), 3062, 3029, 1600, 1475, 1293, 1218, 1026 cm^{-1}.

2-(2-(2-bromo-5-chlorophenyl)-1-((4-methoxyphenyl)imino)ethyl)-5-chlorophenol ***5a***: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 15.15 (s, 1H), 7.53 (d, 1H, *J* = 8.5 Hz), 7.14 (d, 1H, *J* = 8.6 Hz), 7.13 - 7.09 (m, 1H), 7.06 (d, 1H, *J* = 2.0 Hz), 7.00 (d, 1H, *J* = 2.0 Hz), 6.88 (m, 4H), 6.73 (dd, 1H, *J* = 8.6, 2.1 Hz), 4.16 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 170.0, 163.5, 157.7, 138.7, 138.6, 138.0, 134.1, 134.0, 130.3, 129.2, 128.7, 122.1, 121.9, 118.9, 118.6, 116.9, 114.6, 55.5, 36.2. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{21}H_{16}BrCl_2NO_2\ H]$ 463.9814; found 463.9814. FTIR (neat): 3451(br), 2950, 2837, 1610, 1562, 1506, 1246, 1200 cm^{-1}.

500g scale up procedure for the synthesis of *4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-phenyl-2H-benzo[e][1,3]oxazine* *2*: A suspension of 320 g of pre-activated powdered 4Å MS (60 wt/wt%) in 2-Methyl-THF (3060 ml) was cooled to 0°C, and stirred for 10min. Phenol (**1**, 510 g, 1.42 mol), benzaldehyde (166g, 1.56 mol) and the aldimine **4a** (30.0g, 142 mmol) were added, and the resulting mixture was stirred for 2min maintaining 0-5^{o}C. Trifluoromethanesulfonic acid (42.6 g, 284 mmol) was added in 10 min. The ice bath was removed and reaction mixture was warmed to room temperature and stirred for 19h. The reaction was monitored by LCMS. Upon completion, the molecular sieves were filtered and washed with 2-MeTHF (500 mL). The combined organic phases were washed with 5 wt% $NaHCO_3$ solution

(2500 mL), water (2500 mL) and concentrated to 1.2kg under reduced pressure (batch temperature was controlled below 30°C). MeOH (5000 mL) was added and followed by addition of seed (100 mg). The slurry was stirred at rt for 5h. The product was collected by filtration, washed by MeOH (1000mL) and dried at 30°C under reduced pressure to yield 524g **2** as yield yellow solid (83% yield, 97% LC purity).

*2-(2-(2-Chlorophenyl)-1-iminoethyl) phenol **6** (synthetic scheme in SI):* 2-(2-Chloro-phenyl)acetic acid **11** (100 g, 586 mmol), acetonitrile (500 mL) and 1 mL of DMF were charged into a 1 L flask. Oxalyl dichloride (96.7 g, 762 mmol) was added drop wise at 25 °C over 20 min. The resulting solution was stirred for 2h. HPLC analysis showed complete conversion. The solution was concentrated under reduced pressure to give crude 2-(2-chlorophenyl)acetyl chloride. The crude product was dissolved in acetonitrile (500 mL) and phenol (57.9 g, 616 mmol) was added. The solution was cooled to 5°C. N, N-Diisopropylethylamine (90.9 g, 703 mmol) was added drop wise over 30min at 5-10°C. The reaction mixture was stirred at rt overnight. Upon completion, the reaction mixture was poured into a mixture of ethyl acetate/H_2O (1000 mL/1000 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (200 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. This resulted in phenyl 2-(2-chloro-phenyl) acetate **12** as a black oil which was used directly in the next step.

Crude phenyl 2-(2-chloro-phenyl) acetate **12** and aluminum trichloride (104 g, 780 mmol) were charged into a 500 mL flask. The resulting suspension was stirred for 2h at 100°C and turned into a brown syrup. LCMS analysis showed complete conversion. The mixture was cooled to rt which produced a solid. The solid was isolated, crushed and then added to a 1 L ice cold solution of 3N HCl (prepared from 500 mL 6N HCl and 500 mL ice water). The resulting

aqueous solution was extracted with ethyl acetate (500 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to obtain the crude product, which was purified via silica gel chromatography eluting with a gradient of ethyl acetate in petroleum ether ranging from 0 to 2% to yield 56.9 g of 2-(2-chlorophenyl)-1-(2-hydroxyphenyl)ethanone **13** as a white solid (39 % yield over three steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.08 (s, 1H), 7.91 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.51 (td, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.45-7.43 (m, 1H), 7.29-7.26 (m, 3H), 7.02 (dd, 1H, *J* = 8.5 Hz, 1.0 Hz), 6.95 (td, 1H, *J* = 7.0 Hz, 1.0 Hz), 4.48 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 202.5, 162.6, 136.6, 134.5, 132.3, 131.6, 129.9, 129.5, 128.8, 127.0, 119.1 (2 C), 118.6, 42.8. LRMS ESI MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{11}ClO_2\ H]$ 247; found 247. FTIR (neat): 1643, 1612, 1572, 1475, 1444, 1408, 1333 cm^{-1}. Spectroscopic data for 2-(2-chlorophenyl)-1-(2-hydroxyphenyl)ethanone **13** were identical to those reported in the literature.[4]

2-(2-Chloro-phenyl)-1-(2-hydroxyphenyl)ethanone **13** (17.0 g, 68.9 mmol) and ammonia in methanol (170 mL, ca. 9N) were charged into a 500 mL flask. The color of the solution changed to yellow and a precipitate was formed. The mixture was stirred overnight at rt. TLC analysis showed complete conversion. The yellow solid was collected by filtration, washed with methanol and dried to yield 8.47g of **6** (50 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)15.05 (s, 1H), 9.03 (s, br, 1H), 7.69 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.52-7.50 (m, 1H), 7.41-7.32 (m, 3H), 7.28-7.24 (m, 1H), 7.04 (dd, 1H, *J* = 8.5 Hz, 1.0 Hz), 6.89 (td, 1H, *J* = 8.0 Hz, 1.0 Hz), 4.28 (d, 1H, *J* = 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.1, 162.9, 135.3, 133.2, 132.4, 131.6, 130.1, 129.6, 127.9, 127.5, 118.5, 118.4, 117.8, 40.4. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{12}ClNO\ H]$ 246.0685; found 246.0688. FTIR (neat): 2605 (br), 1599, 1515, 1472, 1434, 1250 cm^{-1}. Spectroscopic data for **6** were identical to those reported in the literature.[4]

*2-(1-imino-2-(2-iodophenyl)ethyl)phenol **7** (synthetic scheme in SI):* 2-(2-Bromo-phenyl)acetic acid **14** (126 g, 586 mmol), acetonitrile (500 mL) and 1 mL of DMF were charged into a 1 L flask. Oxalyl dichloride (96.5 g, 762 mmol) was added drop wise at 25°C over 20min. The resulting solution was stirred for 2h. HPLC analysis showed complete conversion. The solution was concentrated under reduced pressure to give crude 2-(2-bromophenyl)acetyl chloride. The crude product was dissolved in acetonitrile (500 mL) and phenol (57.9 g, 616 mmol) was added. The solution was cooled to 5 °C. N, N-Diisopropylethylamine (90.9 g, 703 mmol) was added drop wise over 30 min at 5-10 °C. The reaction mixture was stirred at rt overnight. Upon completion, the reaction mixture was poured into a biphasic mixture of ethyl acetate/H_2O(1000 mL /1000 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (200 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. This resulted in phenyl 2-(2-bromo-phenyl) acetate **15** as a black oil which was used directly in the next step.

Crude phenyl 2-(2-Bromo-phenyl) acetate **15** and aluminum trichloride (104 g, 780 mmol) were charged into a 500 mL flask. The suspension was stirred for 2h at 100°C and a brown syrup was formed. LCMS analysis showed complete conversion. The mixture was cooled to rt and a solid was produced. The solid was isolated, crushed and added to a 1.26 L ice cold solution of 3N HCl (prepared from 630 mL 6N HCl and 630 mL ice water). The resulting aqueous layer was extracted with ethyl acetate (500 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to obtain the crude product, which was purified via silica gel chromatography eluting with gradient of ethyl acetate in petroleum ether ranging from 0 to 2% to yield 25.6 g of 2-(2-bromophenyl)-1-(2-hydroxyphenyl)ethanone **16** as a white solid (15 % yield over three steps).^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.09 (s, 1H), 7.92 (dd, 1H, J = 8.0 Hz,

1.5 Hz), 7.64 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.54-7.51 (m, 1H), 7.35-7.32 (m, 1H), 7.28-7.26 (m, 1H), 7.22-7.19 (m, 1H), 7.03 (dd, 1H, *J* = 8.5Hz, 1.0Hz), 6.98-6.95 (m, 1H), 4.51 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 202.4, 162.6, 136.6, 134.2, 132.8, 131.7, 129.9, 129.0, 127.6, 125.1, 119.12, 119.08, 118.6, 45.3. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{11}BrO_2\ H]$ 291.0020; found 291.0018. FTIR (neat): 2915, 1638, 1610, 1577, 1469, 1438, 1407, 1335, 1270 cm^{-1}. Spectroscopic data for 2-(2-bromophenyl)-1-(2-hydroxyphenyl)ethanone **16** were identical to those reported in the literature.[4]

2-(2-Bromophenyl)-1-(2-hydroxyphenyl)ethanone **16** (1.50 g, 5.2 mmol), NaI (2.32 g, 15.5 mmol), CuI (196 mg, 1 mmol), trans-dimethylcyclohexane-1,2-diamine (293 mg, 2 mmol) and dioxane (15 ml, degassed) were charged into a 20 mL sealed tube. The tube was sealed and heated under microwave conditions at 130 ^{o}C for 12h. Seven reactions were conducted in parallel and combined for the workup. Water (200 mL) was added to the combined reaction solutions and the resulting mixture was extracted with ethyl acetate (150 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to obtain the crude product, which was purified via silica gel chromatography eluting with ethyl acetate in petroleum ether (gradient from 0-2%) to yield 1-(2-hydroxyphenyl)-2-(2-iodophenyl)ethanone **17** (5.00 g, 14.8 mmol, 41%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.08 (s, 1H), 7.93-7.90 (m, 2H), 7.54-7.51 (m, 1H), 7.36 (td, 1H, *J* = 7.5 Hz, 1.0 Hz), 7.26 (dd, 1H, *J* = 8.0 Hz, 2.0 Hz), 7.05-7.01 (m, 2H), 6.99-6.95 (m, 1H), 4.52 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 202.5, 162.6, 139.5, 137.8, 136.6, 130.9, 129.9, 129.0, 128.5, 119.2, 119.1, 118.7, 101.4, 50.0. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{11}IO_2\ H]$ 338.9882; found 338.9888. FTIR (neat): 2906, 1633, 1609, 1577, 1405, 1333, 1265 cm^{-1}. Spectroscopic data for 1-(2-hydroxyphenyl)-2-(2-iodophenyl)ethanone **17** were identical to those reported in the literature.[4]

2-(2-Iodo-phenyl)-1-(2-hydroxyphenyl)ethanone **17** (5.00 g, 14.8 mmol) and ammonia in methanol (50 ml, ca 9N) were charged in a 100 mL flask. The color of the solution changed to yellow, and a precipitate was formed. The resulting mixture was stirred overnight. TLC analysis showed complete conversion. The solid was collected by filtration, washed with methanol and dried to yield 4.5 g 2-(2-(2-iodophenyl)-1-iminoethyl) phenol (**7**) as a yellow solid in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 15.03 (s, br, 1H), 8.99 (s, br, 1H), 7.96 (dd, 1H, *J* = 8.0 Hz, 1.0 Hz), 7.69 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.44-7.38 (m, 2H), 7.25 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz), 7.08 (td, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.04 (dd, 1H, *J* = 8.5 Hz, 1.0 Hz), 6.90 (td, 1H, *J* = 7.0 Hz, 1.0 Hz), 4.30 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.1, 162.9, 140.2, 137.0, 133.2, 131.6, 129.7, 129.0, 127.8, 118.49, 118.46, 117.8, 102.0, 47.6. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{14}H_{12}INO\ H]$ 338.0042; found 338.0050. FTIR (neat): 2596 (br), 1598, 1515, 1472, 1426, 1331, 1248 cm^{-1}. Spectroscopic data for **10** were identical to those reported in the literature.[4]

4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-(o-tolyl)-2H-benzo[e][1,3]oxazine **8a** *(Table 6)*: **8a** was synthesized using general method A with 100 wt/wt% of powdered 4Å MS and 1.0 equiv. of the corresponding aldimine. The crude product was purified by slurrying in MeOH to produce **8a** as an off white solid (80 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.52-7.49 (m, 2H), 7.34 (d, 1H, *J* = 8.0 Hz), 7.30-7.22 (m, 4H), 7.11 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.96-6.92 (m, 2H), 6.61(br, 1H), 4.18 (ABqd, 2H, $\Delta\delta_{AB}$ = 0.03, *J* = 16.0, 1.5 Hz), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 162.0, 156.2, 139.1, 138.1, 136.6, 136.5, 133.8, 133.5, 130.8, 130.7, 128.9, 128.6, 127.5, 126.3, 126.0, 122.7, 122.0, 117.1, 116.2, 87.5, 40.8, 19.2. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{22}H_{16}BrCl_2NO\ H]$ 459.9865; found 459.9886. FTIR (neat): 3065,

1638, 1597, 1457, 1360, 1343 cm^{-1}. Spectroscopic data for **8a** were identical to those reported in the literature.[4]

4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-(2-methoxyphenyl)-2H-benzo[e][1,3]oxazine ***8b (Table 6)*****: 8b** was synthesized using general method A with 100 wt/wt% of powdered 4Å MS and 1.0 equiv. of the corresponding aldimine. The crude product was purified by slurrying it in methanol (3 vol) to produce **8b** as an off-white solid (80 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.51 (d, 1H, J = 8.5 Hz), 7.48 (dd, 1H, J = 12.0, 1.5 Hz), 7.38-7.35 (m, 1H), 7.32 (d, 1H, J = 2.5 Hz), 7.29-7.27 (m, 1H), 7.09 (dd, 1H, J = 8.0, 3.0 Hz), 7.02-6.97 (m, 2H), 6.91-6.89 (m, 3H), 4.23 (d, 1H, J = 16.0 Hz), 4.12 (d, 1H, J = 16.0 Hz), 3.88 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 161.7, 157.2, 156.4, 139.0, 138.2, 133.8, 133.5, 130.42, 130.36, 128.6, 128.57, 127.0, 126.3, 122.6, 121.6, 120.6, 117.1, 115.8, 111.2, 85.1, 55.7, 40.9. HRMS TOF MS (m / z): $[M + H]^+$ calcd for $[C_{22}H_{16}BrCl_2NO_2\ H]$ 475.9814; found 475.9836. FTIR (neat): 3066, 1634, 1591, 1458, 1283, 1240 cm^{-1}. Spectroscopic data for **8b** were identical to those reported in the literature.[4]

Ethyl 2-(4-(2-bromo-5-chlorobenzyl)-7-chloro-2H-benzo[e][1,3]oxazin-2-yl)benzoate ***8c (Table 6)*****: 8c** was synthesized using general method A with 50 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1%NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16min) to yield **8c** as a white solid (57 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (dd, 1H, J = 8.0, 1.5 Hz), 7.76 (dd, 1H, J = 8.0, 1.0 Hz), 7.56-7.51 (m, 2H), 7.43 (td, 1H, J = 8.5, 1.0 Hz), 7.32-7.29 (m ,3H), 7.11 (dd, 1H, J =8.5, 2.5 Hz), 6.95-6.92 (m, 2H), 4.36 (qd, 2H, J = 8.0, 1.0 Hz), 4.15 (ABqd, 2H, $\Delta\delta_{AB}$ = 0.03, J = 16.5, 1.5 Hz), 1.38 (t, 3H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 167.5, 161.7, 156.2, 139.2, 139.1, 138.1,

133.8, 133.5, 131.8, 130.7, 130.3, 130.2, 128.6, 128.5, 128.1, 126.3, 122.6, 122.0, 117.1, 116.3, 85.9, 61.2, 40.8, 14.2. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{24}H_{18}BrCl_2NO_3\ H]$ 517.9920; found 517.9930. FTIR (neat): 2974, 1707, 1634, 1596, 1460 cm^{-1}. Spectroscopic data for **8c** were identical to those reported in the literature.[4]

3-(4-(2-bromo-5-chlorobenzyl)-7-chloro-2H-benzo[e][1,3]oxazin-2-yl)benzonitrile ***8d*** ***(Table 6)*****: 8d** was synthesized using general method A with 50 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16 min) to yield **8d** as an off-white solid in 70 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 1H, *J* = 1.0 Hz), 7.79 (d, 1H, *J* = 8.0 Hz), 7.66-7.64 (m, 1H), 7.54 (d, 1H, *J* = 9.0 Hz), 7.51 (t, 1H, *J* = 7.5 Hz), 7.37-7.35 (m, 1H), 7.26 (d, 1H, *J* = 7.5 Hz), 7.14 (dd, 1H, *J* = 8.5 Hz, 2.5 Hz), 7.00-6.97 (m, 2H), 6.52 (s, 1H), 4.17 (ABqd, 2H, $\Delta\delta_{AB}$ = 0.06, *J* = 16.5 Hz, 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 162.4, 155.2, 140.5, 139.6, 137.8, 133.8, 133.5, 132.2, 131.5, 130.9, 130.8, 129.3, 128.8, 126.3, 122.7, 122.5, 118.5, 117.3, 116.1, 112.6, 87.4, 40.7. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{22}H_{13}BrCl_2N_2O\ H]$ 470.9666; found 470.9666. FTIR (neat): 3061, 2225, 1637, 1597, 1461, 1361, 1343 cm^{-1}. Spectroscopic data for **8d** were identical to those reported in the literature.[4]

Ethyl 4-(4-(2-bromo-5-chlorobenzyl)-7-chloro-2H-benzo[e][1,3]oxazin-2-yl)benzoate ***8e*** *(Table 6)*: **8e** was synthesized using general method A with 50 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16min) to yield **8e** as a yellow solid in 62 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.06 (d, 2H, J = 6.5 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.52 (d, 1H, J = 8.5 Hz), 7.32

(d, 1H, J = 8.0 Hz), 7.27 (s, 1H), 7.12 (dd, 1H, J = 8.5, 2.0 Hz), 6.97 (d, 1H, J = 2.0 Hz), 6.95 (dd, 1H, J = 8.0, 2.0 Hz), 6.59 (s, 1H), 4.38 (q, 2H, J = 7.0 Hz), 4.16 (ABq, 2H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 16.5 Hz), 1.40 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl3): δ (ppm) 166.2, 161.8, 155.5, 143.5, 139.4, 137.9, 133.8, 133.5, 130.8, 130.7, 129.7, 128.7, 127.0, 126.3, 122.7, 122.2, 117.3, 116.2, 88.2, 61.0, 40.7, 14.3. HRMS TOF MS (m / z): $[M + H]^+$ calcd for $[C_{24}H_{18}BrCl_2NO_3$ H] 517.9920; found 517.9924. FTIR (neat): 3064, 1702, 1629, 1599, 1579, 1458 cm^{-1}. Spectroscopic data for **8e** were identical to those reported in the literature.[4]

4-(2-bromo-5-chlorobenzyl)-7-chloro-2-(4-methoxyphenyl)-2H-benzo[e][1,3]oxazine ***8f*** ***(Table 6)*****: 8f** was synthesized using general method A with 50 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16 min). This resulted in **8f** as a white solid in 60 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)7.52 (d, 1H, *J* = 8.5 Hz), 7.46 (dt, 2H, *J* = 10.0, 2.5 Hz), 7.30-7.27 (m, 2H), 7.11 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.94-6.90 (m, 4H), 6.52 (s, 1H), 4.18 (ABq, 2H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 15.0 Hz), 3.82 (s, 3H). ^{13}C NMR (125 MHz, CDCl3): δ (ppm) 161.5, 159.9, 155.8, 139.1, 138.1, 133.8, 133.5, 131.1, 130.6, 128.6, 128.4, 126.2, 122.7, 121.8, 117.3, 116.2, 113.8, 88.7, 55.3, 40.8. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{22}H_{16}BrCl_2NO_2$ H] 475.9814; found 475.9830. FTIR(neat): 2974, 1704, 1634, 1598, 1460, 1418, 1341 cm^{-1}. Spectroscopic data for **8f** were identical to those reported in the literature.[4]

4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-(4-nitrophenyl)-2H-benzo[e][1,3]oxazine ***8g*** ***(Table 6)*****: 8g** was synthesized using general method A with 50 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was slurried in acetonitrile (5vol) to yield **8g** as a yellow solid in 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.24 (dt, 2H, *J* =

9.0, 2.0 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 7.53 (d, 1H, *J* = 8.5 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 2.5 Hz), 7.14 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.00-6.98 (m, 2H), 6.58 (s, 1H), 4.17 (ABqd, 2H, $\Delta\delta_{AB}$ = 0.04, *J* = 16.5, 1.0 Hz).^{13}C NMR (125 MHz, CDCl3): δ (ppm) 162.3, 155.2, 148.0, 145.7, 139.6, 137.8, 133.8, 133.5, 130.9, 128.8, 128.0, 126.4, 123.6, 122.8, 122.5, 117.3, 116.2, 87.5, 40.7. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{21}H_{13}BrCl_2N_2O_3$ H] 490.9559; found 490.9552. FTIR (neat): 3077, 1635, 1599, 1512, 1464, 1345 cm^{-1}. Spectroscopic data for **8g** were identical to those reported in the literature.[4]

*4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-(pyridin-4-yl)-2H-benzo[e] [1,3]oxazine **8h** (Table 6)*: **8h** was synthesized using general method B. The crude was purified by reverse phase combi-flash (Mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16min) to yield **11h** as a yellow syrup in 54% yield. ^{1}H NMR (500 MHz, CD_3CN): δ (ppm) 8.56 (m, 2H), 7.57(d, 1H, *J* = 8.5 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.40-7.39 (m, 2H), 7.36 (d, 1H, *J* = 2.5 Hz), 7.20 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.08-7.04 (m, 2H), 6.47 (s, 1H), 4.21 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN): δ (ppm) 163.9, 156.8, 151.6, 149.0, 140.4, 135.5, 134.4, 133.1, 130.2, 128.5, 124.8, 123.9, 123.3, 118.5, 118.3, 88.7, 41.9. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{20}H_{13}BrCl(^{37}Cl)N_2O$ H] 448.9639; found 448.9657. FTIR (neat): 2918, 1713, 1630, 1597, 1451, 1347 cm^{-1}. Spectroscopic data for **8h** were identical to those reported in the literature.[4]

*4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-cyclohexyl-2H-benzo[e][1,3]oxazine **8i** (Table 6)*: **8i** was synthesized using general method C with 100 wt/wt% of powdered 4Å MS and 1.0 equiv. of the corresponding aldimine**.** The crude product was purified by reverse phase combi-flash chromatography (mobile phase: 100% acetonitrile, 16 min). This resulted in an oil, which solidified upon storing overnight. The solid was slurried in acetonitrile to yield **8i** as a white solid in 54 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)7.50 (d, 1H, *J* = 8.5 Hz), 7.23 (d, 1H, *J*

= 2.5 Hz), 7.21-7.19 (m, 1H), 7.09 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.87-6.85 (m, 2H), 5.30 (d, 1H, *J* = 5.0 Hz), 4.11 (d, 1H, *J* = 7.0 Hz), 3.99 (d, 1H, *J* = 7.0 Hz), 1.90-1.68 (m, 6H), 1.30-1.15 (m, 5H). ^{13}C NMR (125 MHz, CDCl3): δ (ppm) 160.3, 156.5, 138.7, 138.3, 133.7, 133.4, 130.5, 128.5, 126.1, 122.6, 121.3, 116.8, 116.0, 92.6, 43.4, 40.7, 27.8, 27.3, 26.4, 25.93, 25.89. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{21}H_{20}BrCl_2NO\ H]$ 452.0178; found 452.0196. FTIR(neat): 2905, 2848, 1637, 1595, 1559, 1414, 1340 cm^{-1}. Spectroscopic data for **8i** were identical to those reported in the literature.[4]

4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-phenethyl-2Hbenzo[e][1,3]oxazine ***8j*** *(Table 6)*: **8j** was synthesized using general method C with 100 wt/wt% of powdered 4Å MS and 1.0 equiv. of the corresponding aldimine**.** The crude product was purified by reverse phase combi-flash chromatography (mobile phase: 100% acetonitrile, 16min) to yield **8j** as a yellow oil in 42 % yield. ^{1}H NMR (500 MHz, CD_3CN): δ (ppm) 7.56 (d, 1H, 8.5 Hz), 7.45 (d, 1H, 8.5 Hz), 7.31 (d, 1H, *J* = 2.5 Hz), 7.26-7.23 (m, 2H), 7.19-7.15 (m, 4H), 6.99 (dd, 1H, *J* = 8.5, 2.0 Ha), 6.90 (d, 1H, *J* = 2.0 Hz), 5.44-5.41 (m, 1H), 4.10 (ABq, 2H, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 15.0 Hz), 2.78-2.68 (m, 2H), 2.09-2.05 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN): δ (ppm) 161.3, 156.8, 142.7, 140.2, 139.3, 134.9, 133.8, 132.5, 129.50, 129.47, 129.43, 127.6, 126.9, 124.3, 122.6, 117.6, 117.5, 89.5, 41.2, 37.7, 31.1. HRMS TOF MS (*m* / *z*): $[M + H]^+$ calcd for $[C_{23}H_{18}BrCl(^{37}Cl)NO\ H]$ 476.0000; found 476.0021. FTIR (neat): 3024, 2919, 1628, 1597, 1451, 1346 cm^{-1}. Spectroscopic data for **8j** were identical to those reported in the literature.[4]

4-(2-Bromo-5-chlorobenzyl)-7-chloro-2-isopropyl-2H-benzo[e][1,3]oxazine ***8k*** *(Table 6)*: **8k** was synthesized using general method C with 100 wt/wt% of powdered 4Å MS and 0.2 equiv. of the corresponding aldimine**.** The crude product was purified by reverse phase combi-flash chromatography (mobile phase: 100% acetonitrile, 16min) to yield **8k** as a yellow oil in 65

% yield. ^{1}H NMR (500 MHz, CD_3CN): δ (ppm) 7.55 (d, 1H, J = 8.5 Hz), 7.44 (d, 1H, J = 8.5 Hz). 7.31 (d, 1H, J = 2.5 Hz), 7.17 (dd, 1H, J = 8.5, 2.5 Hz), 6.98 (dd, 1H, J = 8.5, 2.5 Hz), 6.90 (d, 1H, J = 2.0 Hz), 5.19 (dt, 1H, J = 5.0, 2.0 Hz), 4.09 (ABq, 2H, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 15.0 Hz), 2.06-2.00 (m, 1H), 0.93 (d, 6H, J = 5.0 Hz)). ^{13}C NMR (125 MHz, CD_3CN): δ (ppm) 161.4, 157.4, 140.2, 139.2, 134.8, 133.8, 132.4, 129.4, 127.5, 124.2, 122.3, 117.5, 117.3, 94.1, 41.2, 34.6, 17.5. HRMS TOF MS (m / z): $[M + H]^+$ calcd for $[C_{18}H_{16}BrCl_2NO\ H]$ 411.9865; found 411.9877. FTIR (neat): 3024, 1628, 1596, 1451, 1440, 1347 cm^{-1}. Spectroscopic data for **8k** were identical to those reported in the literature.[4]

*4-(2-Chlorobenzyl)-2-phenyl-2H-benzo[e][1,3]oxazine **8l** (Table 6)*: **8l** was synthesized using general method A with 100 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-90%, 16min) to yield **8l** as a white solid in 42 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.62-7.59 (m, 2H), 7.43-7.31 (m, 7H), 7.21-7.17 (m, 2H), 6.94-6.91 (m, 2H), 6.50 (s, 1H), 4.29 (d, 1H, J = 15.0 Hz), 4.20 (d, 1H, J = 20.0 Hz).^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 163.3, 155.2, 139.6, 134.9, 134.0, 133.7, 130.4, 129.5, 128.5, 128.4, 128.1, 127.1, 126.9, 125.5, 121.5, 118.1, 116.8, 88.5, 38.4. HRMS TOF MS (m / z): $[M + H]^+$ calcd for $[C_{21}H_{16}ClNO\ H]$ 334.0993; found 334.0992. FTIR (neat): 3024, 1628, 1596, 1451, 1440, 1347 cm^{-1}. Spectroscopic data for **8l** were identical to those reported in the literature.[4]

*4-(2-Iodobenzyl)-2-phenyl-2H-benzo[e][1,3]oxazine **8m** (Table 6)*: **8m** was synthesized using general method A with 60 wt/wt% of powdered 4Å MS and 0.1 equiv. of the corresponding aldimine. The crude product was purified by reverse phase combi-flash chromatography (mobile phase A: water (0.1% NH_4HCO_3), mobile phase B: acetonitrile, 80%-

90%, 16min) to yield **8m** as a white solid in 60 % yield. ^{1}H NMR (500 MHz, CD_3CN): δ (ppm) 7.89 (d, J = 7.5 Ha, 1H), 7.63-7.60 (m, 2H), 7.43-7.40 (m, 2H), 7.38-7.33 (m, 3H), 7.28-7.25 (m, 2H), 6.96-6.92 (m, 3H), 6.51 (s, 1H), 4.23 (ABqd, 2H, $\Delta\delta_{AB}$ = 0.04, J = 16.0, 25.5 Hz). ^{13}C NMR (125 MHz, CD_3CN): δ (ppm) 163.4, 155.2, 140.1, 139.54, 139.46, 133.7, 129.7, 128.5, 128.40, 128.36, 128.34, 127.2, 125.7, 121.5, 118.1, 116.8, 101.4, 88.5, 46.3. HRMS TOF MS (*m* / *z*): [M + H]$^{+}$ calcd for [$C_{21}H_{16}$INO H] 426.0355; found 426.0356. FTIR (neat): 3030, 1630, 1604, 1451, 1336, 1224 cm^{-1}. Spectroscopic data for **8m** were identical to those reported in the literature.[4]

■ ASSOCIATED CONTENT

Supporting Information

Synthetic schemes for the preparation of compound **1**, **6** and **7**, copies of selective ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI:

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Notes

The authors declare no competing financial interest.

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7. Trimethylsilyl trifluoromethanesulfonate (TMSOTf), trifluoroacetic acid, methanesulfonic acid and acetic acid were evaluated in addition to triflic acid and trific anhydride.

8. While both SM**1** and aldimine **4a** can potentially react with Tf_2O. Under the employed reaction conditions the solubility of SM1 is very low. So it was assumed that the Tf_2O primarily formed an active intermediate with the aldimine. Subsequent 19F NMR studies supported the presence of this activated aldimine throughout the course of the reaction. More details and spectra are included in the supporting information.

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10. Detailed conditions and data are included in the supporting information.

11. Detailed conditions are reported in the experimental section.