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Preparation and Redox Properties of *N*,*N*,*N*-1,3,5-Trialkylated Flavin Derivatives and Their Activity as Redox Catalysts

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Abstract: Eight different flavin derivatives have been synthesized and the electronic effects of substituents in various positions on the flavin redox chemistry were investigated. The redox potentials of the flavins, determined by cyclic voltammetry, correlated with their efficiency as catalysts in the H_2O_2 oxidation of methyl *p*-tolyl sulfide. Introduction of electron-withdrawing groups increased the stability of the reduced catalyst precursor.

Keywords: cyclic voltammetry · flavins · redox catalysis · redox chemistry

Introduction

Flavins have proven to be efficient mediators in a range of oxidation reactions. The chemical processes that use flavin catalysts mimic enzymatic processes mainly performed by Baeyer–Villiger monooxygenases (BVMOs).[1] In particular the cyclohexanone monooxygenase,[2] cyclopentanone monooxygenase,[3] and 4-hydroxyacetophenone monooxygenase[4] catalyze the oxidation of organic sulfides to sulfoxides as well as Baeyer–Villiger oxidations.[1] Also monoamine oxygenases that catalyze oxidative deamination are dependent on a flavin co-factor.[5]

The first example of the participation of a flavin in stoichiometric amounts in the oxidation of organic substrates was provided by Mager and co-workers[6] in a reaction of phenylalanine with dihydroalloxazine in the presence of O_2 and H_2O_2 almost four decades ago. Bruice and co-workers later reported on the oxidations of aldehydes,[7] sulfides,[8] and tertiary amines[9] by stoichiometric 4a-hydroperoxy-5-alkyl-3-methyllumiflavins. The latter group also studied monooxygen donation to iodide, tertiary amines, and sulfides[10] from the 4a-hydroperoxy-5-ethyl-3-methyllumiflavin and its analogues. In the same article they reported on the monooxygen donation potentials of 4a-hydroperoxyflavins relative to those of percarboxylic acids and other hydroperoxides.[10]

The catalytic use of flavins is still quite limited, but examples of catalytic oxidations of secondary amines to nitrones,[11] tertiary amines to *N*-oxides,[12] and sulfides to sulfoxides[13] by hydrogen peroxide as stoichiometric oxidant have been reported. Flavins have also been employed as catalysts in Baeyer–Villiger oxidations of activated ketones[14] and in the dihydroxylation of alkenes as part of the biomimetic triple catalytic oxidation system.[15] Recently, Murahashi et al. reported on the flavin-catalyzed oxidation of sulfides and amines with molecular oxygen as terminal oxidant.[16]

To fully understand the mechanism of flavin-catalyzed oxidations and to be able to modify and design efficient flavins for oxidation reactions, an intimate knowledge of their chemical and electronic properties is highly desirable.[7,8a,9,10,17] The substituent effect on chemical properties and redox potentials of a range of flavins has been studied by a number of groups.[18] Our group has previously studied the reactivity of different flavins as catalysts in oxidation of sulfides and tertiary amines.[13a]

A very stable and efficient flavin catalyst **1**, alkylated at the 1-, 3-, and 5-positions, was discovered by our group.[12] Mager and co-workers had previously reported on the autoxidative behavior of a similarly substituted dihydroflavin.[17a] It was found that not only is **1** more robust than any of the previously reported flavins, it also has superior catalytic activity.

Since then, this catalyst has been successfully applied in oxidations of tertiary amines to *N*-oxides[12,13a,15] and sulfides to sulfoxides (Scheme 1).[13] It has also been successfully incorporated into the osmium-catalyzed dihydroxylation of olefins resulting in an efficient and environmentally friendly,

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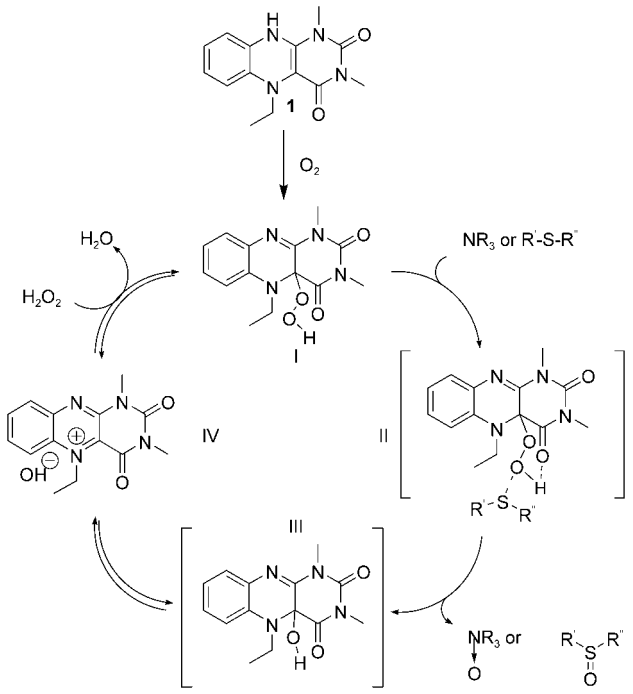


Scheme 1. The proposed catalytic cycle.

triple-catalytic system in which hydrogen peroxide is employed as the terminal oxidant.[15]

In previous work by our group,[13a] we have shown that electron-withdrawing fluorine substituents in the 7- and 8-positions of the flavin result in an even more stable catalyst precursor, with the drawback that a somewhat longer time is required for activation of the catalyst. The longer induction period is rationalized by the need of an initial oxidation of the catalyst precursor with molecular oxygen (Scheme 1), and this step is slower for the electron deficient 7,8-difluoro analogue **2**. Once the catalyst has entered the catalytic cycle as **I** it can transfer its electrophilic oxygen to the substrate via transition state **II** forming the hydroxyflavin intermediate **III**. The hydroxyl group is then eliminated from **III** restoring the aromatic 1,4-diazine form **IV**. To complete the cycle, **IV** reacts with hydrogen peroxide to regenerate the active catalyst species **I**.

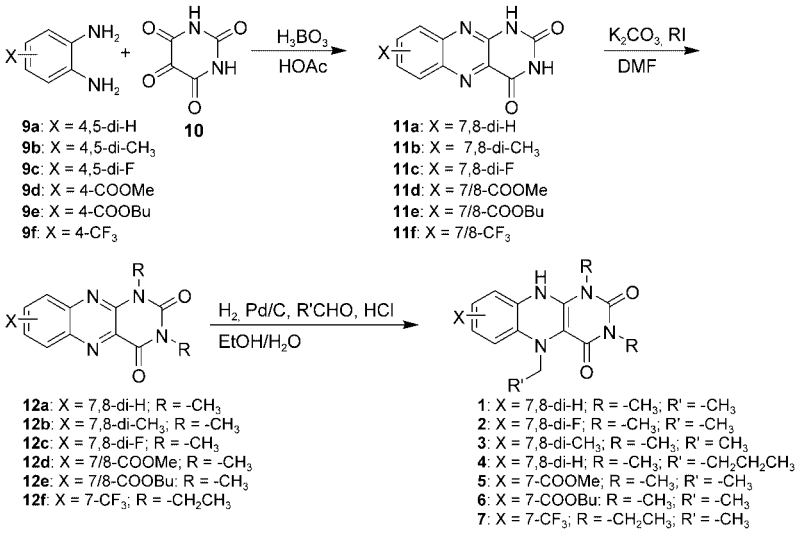
In this paper we report on the preparation and the catalytic and electronic properties of a range of 6,9- and 7- and/or 8-substituted *N*,*N*,*N*-1,3,5-trialkylated flavin derivatives. Cyclic voltammetry was used to determine the redox potentials of the novel flavins.

Results and Discussion

Eight different flavin derivatives **1**–**8** were synthesized and examined. Three of these (**1**–**3**) have previously been studied as catalysts for the oxidation of sulfides[13] and tertiary amines[12,13a] in our group.

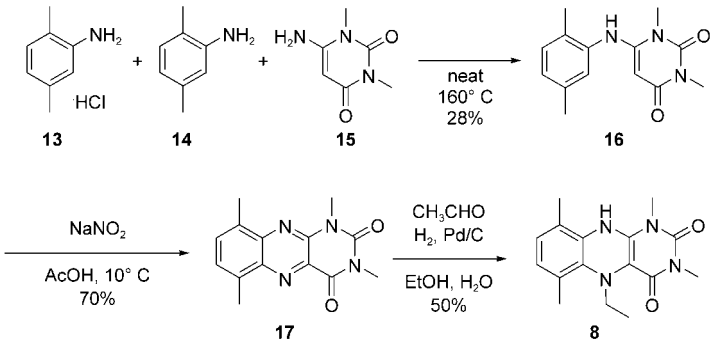
Dihydroflavins **1**–**7** were prepared in three steps as depicted in Scheme 2. The first step involves a condensation of the respective diamine **9a**–**f** with **10**, resulting in the tricyclic alloxazine ring system **11a**–**f** in good yields. Subsequent N-alkylation with methyl or ethyl iodide in the second step gives the *N*,*N*-1,3-dimethyl- or -diethylalloxazine in good yields. The final step is a reductive alkylation of the N5-position with acetaldehyde (butanal for **4**) and H_2 with Pd on activated charcoal.

When the 7/8-trifluoromethyl alloxazine **11f** was treated with ethyl iodide the 1,3-diethyl 7-trifluoromethyl alloxazine **12f** was obtained in 57% yield. Substrates **12d** and **12e** were obtained as mixtures of the 7- and 8-regioisomers. In the final step, in which an ethyl group is introduced at N5, the methoxy- and butoxy carbonyl dialkyl alloxazines **12d** and **12e** reacted somewhat differently. The dihydroflavin **5** was obtained mainly as the 7-isomer with only about 10% contamination of the 8-isomer in 64% combined yield, whereas dihydroflavin **6** (from **12e**) afforded the 7- and 8-isomers in a 1.7:1 ratio in 29% combined yield. The isomeric mixtures were used as such for the electrochemical measurements, since the products are too air sensitive for column chromatography or other means of purification after the final step.



Scheme 2. General pathway to the reduced catalyst precursors **1**–**7**.

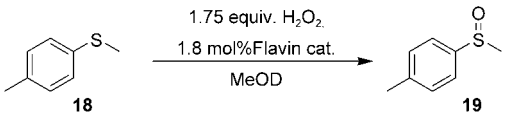
A different approach had to be used for the synthesis of 6,9-dimethylalloxazine **17**, since the 2,5-dimethyl-1,2-diaminobenzene is not commercially available (Scheme 3). Reaction of 2,5-dimethylaniline hydrochloride **13** with 1,3-dimethyl-6-aminouracil **15** in 2,5-dimethylaniline **14** at 160°C



Scheme 3. Synthesis of pre-catalyst **8**.

resulted in the formation of the product (**16**) in 28% yield. Cyclization with $NaNO_2$ to the tricyclic alloxazine ring structure yielded product **17** in 70% isolated yield. For the formation of the reduced catalyst precursor the standard reductive alkylation was applied as described above and the catalyst **8** was obtained in 50% yield.

Kinetics: We have previously observed an induction period in the oxidation of methyl *p*-tolyl sulfide with 7,8-difluoro dihydroflavin **2** as catalyst[13a] (Scheme 4, Figure 1a). This is thought to arise from the fact that the electron-deficient dihydroflavin catalysts are less susceptible towards oxidation by molecular oxygen.[19]



Scheme 4. The reaction for the kinetic study.

In order to verify this behavior we conducted the following study: after completed oxidation of methyl *p*-tolyl sulfide, we added another equivalent each of sulfide and hydrogen peroxide to the reaction mixture. The conversion was followed by ^{1}H NMR spectroscopy. A total of three runs were conducted and a remarkable enhancement of the reaction rate was observed in the second run (Figure 1b). This indeed supports our hypothesis that during the first run there is an induction period during which the active catalyst species is slowly generated from **2** by reaction with molecular oxygen. Once the active species is formed the reaction is fast and follows the typical first-order rate expression.

The activity of dihydroflavins **3**–**8** was also studied and the results are summarized in Table 1. The *N*5-butyl-substituted dihydroflavin **4** and **5** showed good catalytic activity. The results for dihydroflavin **3** have been published before by our group and are included for comparison. In the case of **3** the reaction does not proceed further than ~40% due to oxidative degradation of the catalyst. The dihydroflavin **6** showed very low activity due to that the catalyst fell out of the reaction mixture.

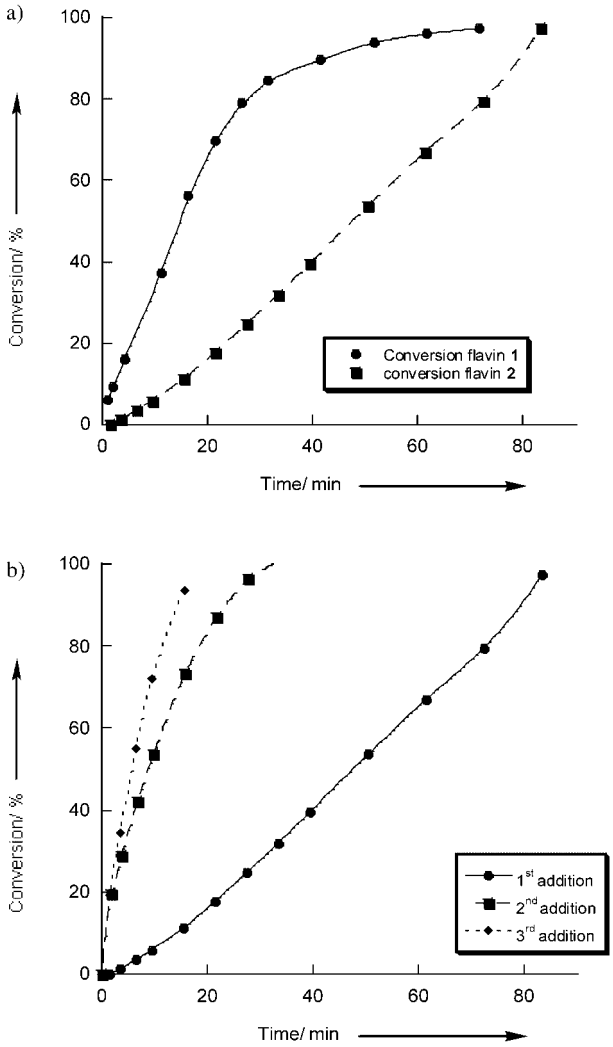


Figure 1. Oxidation of sulfide **18** to sulfoxide **19** by H_2O_2, a) with flavins **1** and **2** as catalysts, b) with flavin **2** in three consecutive runs.

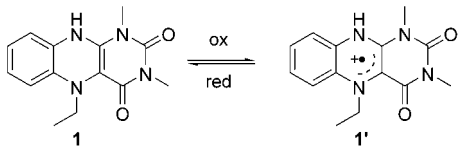
Redox potentials of flavin derivatives from cyclic voltammetry: To gain a better understanding of the electronic properties of the different flavin catalysts, we measured their half-wave potentials by cyclic voltammetry. As described above, the catalyst precursor is oxidized when it enters the catalytic cycle. Since direct investigation of the oxidation process of the dihydroflavins as it enters the catalytic cycle is difficult, we concentrated on the simple one-electron oxidation depicted in Scheme 5. The acquired data reflect the thermodynamics for the activation step of the flavin catalyst precursor. The results are summarized in Table 2.

The oxidations of all flavins presented herein were fully reversible on the electrochemistry timescale. They are one-electron processes, evident from a peak split larger than 60 mV and from the bulk electrolysis of dihydroflavin **1**, which gave a charge of approximately 1 F per mole of **1**.[20] The potentials reflect our observation on the catalytic activity of the flavins studied.

Table 1. The results for the dihydroflavin activity in oxidation of **18** to **19**.[a]

	Dihydroflavin	t [min]	Conversion [%]	k_{obs} [$\times 10^{-4}$ s^{-1}]	Rel. rate[b]
1	**1**	60	96	9.0	1
2	**2**[c]	60	67	–[d]	0.3
		80	97	–[d]	
	2[e]	34	100	–[d]	1.4
	2[f]	21	100	21.9	2.4
3[g]	**3**	60	40	–[d]	0.7
4	**4**	60	99	15.2	1.7
5	**5**	60	81	–[d]	0.4
		90	95		
6	**6**	60	15	–[d]	0.07
7	**7**	60	10	–[d]	0.04
8	**8**	–	n.r.[h]	–	–

[a] The reactions were run with substrate **18** (0.223 mmol), catalyst (1.8 mol%), and H_2O_2 (1.75 equiv) in CD_3OD (0.6 mL). [b] The relative rates were obtained from the pseudo-first-order rate constant k_{obs} or estimated from the rate in the early phase of the reaction. [c] First addition. [d] Cannot be determined due to change of the concentration of the active catalyst during the reaction. [e] Second addition. [f] Third addition. [g] Taken from reference [13a]. [h] n. r. = no reaction detected within 20 min.



1 **1'**

Scheme 5. Electrochemical oxidation/reduction of flavin **1** to **1'** (model catalyst).

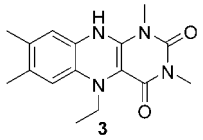
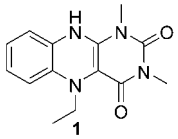
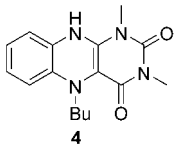
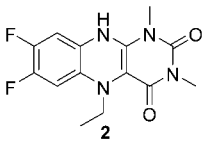
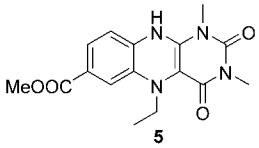
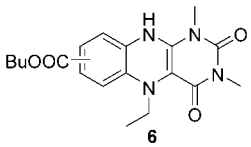
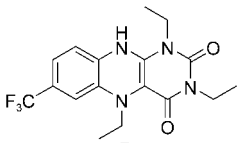
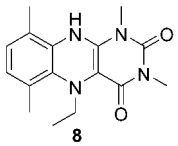
The catalyst precursor **3** (Table 2, Entry 1), with electron-donating methyl groups in the 7- and 8-positions is most susceptible towards oxidation, as evident from the most negative oxidation potential of the derivatives studied. As previously observed, this catalyst shows good initial activity in catalysis, but the reaction slows down remarkably at around 40% due to sensitivity towards autoxidative degradation.[13a]

Upon introduction of an electron-withdrawing group at the 7-position (flavins **5**–**7**) or at the 7- and 8-positions (flavin **2**), the oxidation potential becomes less negative, and, hence, the catalyst precursors are more difficult to oxidize. As described above, the 7,8-difluoro derivative is less susceptible towards oxidation by molecular oxygen and needs an activation period, which is in agreement with the higher oxidation potential relative to **1** and **3**.

It is important to note that though pre-catalysts **5** and **6** were used as the isomeric mixtures for the measurements, the observed oxidation potential is for the major isomer. The signal for the impurity is buried under that of the major isomer.

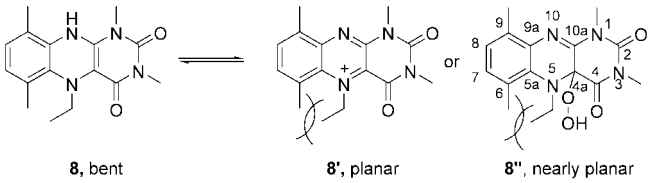
The catalyst precursor **7**, which has an oxidation potential between those for **5** and **8**, showed poor catalytic activity; this result is surprising since its oxidation potential is close to that of **5**, and the latter is active in catalysis. The trifluoromethyl group is strongly electron withdrawing and this may make the loss of OH^- from **III** to **IV** much less favorable for catalyst **7**, rendering the poor activity of the catalyst. This catalyst also showed poor solubility in the reaction media. The 6,9-dimethyl-substituted dihydroflavin **8** is oxidized at highest potential. This is consistent with the results obtained from the catalytic reactions, where **8** also showed poor catalytic activity (see above). If we compare this with flavin **3**, which also has two methyl substituents, the difference in oxidation potential is about 0.25 V. Although the effect of the 6,9-substituent pattern is ambiguous, the high oxidation potential of **8** cannot be explained solely by the electronic effect of the substituents, but other factors need

Table 2. Redox potentials of flavins **1**–**8**.[a]

Entry	Flavin	E_0 [V]
1	 **3**	−0.414
2	 **1**	−0.305
3	 **4**	−0.304
4	 **2**	−0.207
5[b]	 **5**	−0.182
6[c]	 **6**	−0.182
7	 **7**	−0.176
8	 **8**	−0.162

[a] For conditions see the Experimental Section. [b] Main isomer, 9:1 ratio of 7- and 8-isomers. [c] 1.7:1 ratio of 7- and 8-isomers.

to be considered. For this particular derivative the effect of the methyl substituents at the 6- and 9-positions is to a large extent steric rather than electronic as illustrated in Scheme 6.



Scheme 6. Illustration of the steric effect of the 6-methyl group.

There is theoretical evidence provided by Vázquez et al.[21] on the conformation of flavins in their reduced and oxidized forms. The reduced form has a significant antiaromatic character, which leads to distortion from the plane of the molecule. This makes the catalyst precursor **8** quite stable, since the *N*5-ethyl group is oriented away from the 6-methyl group. The oxidized form **8**′ on the other hand is aromatic and planar, bringing the C6 and N5 substituents closer to one another in space, introducing steric repulsion that results in an increased free-energy of **8**′. In **8**″, the active catalytic species in the oxidation, the 4a-carbon atom is an sp^3 hybridized carbon atom and not part of the aromatic system. However, the double bond between N10 and C10a together with the electron pair on N5 that is conjugated to the π-system makes the molecule relatively flat. Rizzo et al. have reported a similar effect in an analogous system with methyl groups on the N9 and N10 atoms.[18d]

Linear free-energy relationship: To find the correlation between the oxidation potentials of the dihydroflavins **1**–**7** and the electronic effects of their susbstituents, we plotted the $\log[E^{ox}/E_0^{ox}]$ against their respective Hammett σ values. E^{ox} is the oxidation potential of the catalyst precursors and E_0^{ox} is the oxidation potential of the unsubstituted dihydroflavin **1**, which is set as the standard reaction. Since the proton abstraction occurs at N10, we defined the substituent at C8 as *meta* and that at C7 as *para*. This assignment was used for the calculation of the σ values. Since the oxidation potentials reflect the free energy of the reaction for the different substrates, we can use them directly for the Hammett plot, presented in Figure 2.

As evident from Figure 2, there is an excellent linear correlation between $\log[E^{ox}/E_0^{ox}]$ and σ with a deviation $R=0.997$. The Hammett ρ value, which reflects the sensitivity of the substrate to the electronic effect of the substituent in the reaction, is the slope of the line obtained from the plot.[22] The negative slope of -0.418 indicates that electron-donating groups render the electrochemical oxidation of the dihydroflavin more facile; this result is consistent with the kinetic studies as well as the direct conclusions drawn from the oxidation potentials.

The trend for the substituent effect on the redox potentials found in this study fit well with what has been reported earlier by Rizzo[18c] and Rotello[18i,j] for analogous flavin systems. They have shown good linear free-energy relationship correlation between the electronic properties provided by the substituents on positions 7 and/or 8 and the reduction potentials for the flavins studied. Rotello et al. showed in there study that the substituent on C7 has a greater effect on the reduction of a flavin in a nonaqueous environment.[18j]

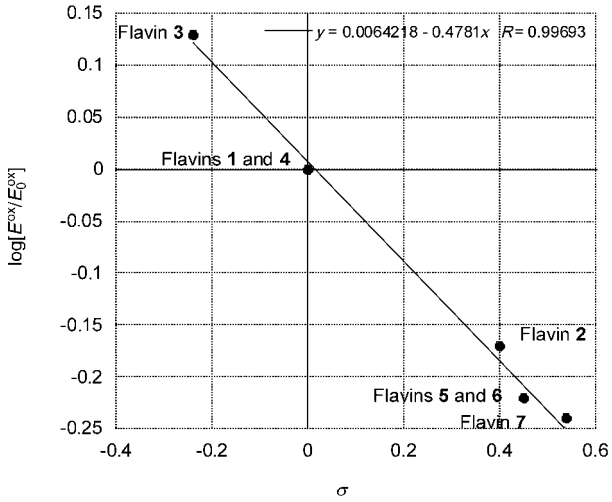


Figure 2. The Hammett plot of $\log[E^{ox}/E_0^{ox}]$ against Hammett σ values.

Conclusion

The results obtained from the cyclic voltammetry are in good agreement with our results on the relative catalytic activity of the reduced flavin analogues **1**–**8**. We conclude that electron-donating groups facilitate the oxidation of dihydroflavins and that there is a linear free-energy relationship between the oxidation potentials and the Hammet σ values. The different susceptibility toward oxidation may affect the catalytic activity in two respects. The electron-rich dihydroflavin **3**, which is most easily oxidized, enters the catalytic cycle without any detectable induction period. However, its performance as catalyst is hampered by autoxidative degradation. The electron-deficient catalyst precursor **2**, on the other hand, needs a long induction period, but once it is activated it is a fast and efficient catalyst that is stable toward autoxidative degradation. This is clearly demonstrated in the multiple addition experiment, with three consecutive catalytic runs without adding more catalyst. The reaction was in fact faster in the second and third run.

Experimental Section

General methods: ^1H (300 or 400 MHz) and ^{13}C (75 or 100 MHz) NMR spectra were recorded on a Varian Mercury spectrometer. Chemical shifts (δ) are reported in ppm, with residual solvent as internal standard and coupling constants (J) are given in Hz. Merck silica gel 60 (240–

400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck pre-coated silica gel 60-F_{254} plates. Cyclic voltammograms were recorded on an Autolab Potentiostat (Ecochimie Netherlands), controlled by GPES software (version 4.8). A glassy carbon disc electrode (diameter 3 mm) was used as the working electrode and was polished prior to each experiment by using an aqueous alumina powder slurry. A platinum wire served as a counter electrode and nonaqueous Ag/Ag^+ was used as the reference electrode. All potentials are half-wave potentials and are given versus the $Fc^{+/0}$ couple. Cyclic voltammograms were obtained for approximately 1 mM solutions of the analyte in dry acetonitrile, containing 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte. Unless otherwise noted, all chemicals were obtained from commercial suppliers and used without further purification.

Reductive alkylation of alloxazines 11 and 17—general procedure: All the steps are performed under strict argon atmosphere, unless otherwise noted! The 1,3-alkylated alloxazines (0.037 M) were mixed in the degassed solvent (1.25:1 volume ratio of EtOH/H_2O), together with the Pd/C catalyst (0.081 mg/22.5 mL solvent), acetaldehyde (32 equiv) and concentrated hydrochloric acid (55 equiv), while passing a gentle stream of argon through the solvent mixture. The mixture was subjected to 30 psi hydrogen pressure on an autoclave. After the reaction was complete the mixture was filtered through a 3–4 cm thick Celite layer (flushed with argon prior) placed in a Schlenk fritt. The liquids were collected in a proper sized Schlenk flask. The Celite was washed with degassed ethanol (20–40 mL) while maintaining the argon atmosphere. After the filtration the Schlenk fritt was removed and concentrated NH_4OH (~6 mL to 0.83 mmol starting material) and $Na_2S_2O_4$ (~2 g to 0.83 mmol starting material) were added. A splash head connected to a glass tube, which in turn was connected to a solvent trap with a gas outlet cooled by N_2(l) was connected to the Schlenk flask, and the solvents were removed under vacuum. The remaining solids were suspended in a small amount of degassed water and filtered through another Schlenk fritt equipped with a tap, under argon. The solids were washed carefully with small portions (to avoid loss of product due to a slight solubility in water) of degassed water. The product was dried under vacuum and used as such.

Dihydroflavins 1–3 were prepared using the previously published procedure .[12,13a]

Reductive butylation of 1,3-dimethylalloxazine (12a)—synthesis of 1,3-dimethyl-5-butyl-5,10-dihydroalloxazine (4): By following the general protocol, but by employing freshly distilled butanal, compound **4** was obtained as a bright yellow solid in 64% yield (156 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.83 (m, 1H; Ar-H), 6.54 (m, 1H; Ar-H), 5.74 (brs, 1H; NH), 3.47 (s, 3H; CH_3), 3.41 (t, ^3J(H,H) = 7.8 Hz, 2H; CH_2), 3.34 (s, 3H; CH_3), 1.59 (m, 2H; CH_2), 1.25 (m, 2H; CH_2), 0.842 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 157.98, 150.51, 146.20, 137.18, 134.81, 125.22, 123.28, 122.11, 114.80, 100.49, 55.76, 29.08, 28.79, 28.46, 20.27, 14.19 ppm.

1,3-Dimethyl-5-ethyl-7-methoxycarbonyl-5,10-dihydroalloxazine (5): This compound was prepared using the general procedure on a 1.35 mmol scale, with **12d** (0.406 g), acetaldehyde (2.3 mL), hydrochloric acid (2.3 mL), Pd/C (0.133 g) in ethanol/water (20/16 mL). Reaction time was 44 h. The reaction was worked up by using the general procedure after which the product, a 9:1 mixture of the 7- and 8-isomers, was isolated as an orange powder in 64% combined yield. Data for the major isomer (7-isomer): ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.46–7.49 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 7.44 (apps, 1H; Ar-H), 6.59–6.61 (d, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 6.33 (brs, 1H; NH), 3.85 (s, 3H; CH_3), 3.46–3.54 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2), 3.48 (s, 3H; CH_3), 3.34 (s, 3H; CH_3), 1.15–1.19 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 166.4, 158.1, 150.4, 145.6, 139,5, 136.7, 127.1, 125,7, 123.1, 114.5, 114.4, 52.2, 50.7, 29.0, 28.5, 11.8 ppm; HRMS (FAB): *m/z* calcd for $C_{16}H_{18}N_4O_4$: 330.1328; found: 330.1313.

1,3-Dimethyl-5-ethyl-7/8-butoxycarbonyl-5,10-dihydroalloxazine (6): This compound was prepared by following the general procedure on a 0.83 mmol scale with 1,3-dimethyl-7/8-butoxycarbonyl alloxazine (0.283 g), acetaldehyde (1.6 mL), hydrochloric acid (1.6 mL), Pd/C (0.081 g) in ethanol/water (12.5/10 mL). Reaction time was 24 h. After workup the product was isolated as a mixture of the 7- and 8- isomers, 1.7:1 ratio, in 29% combined yield.

Data for the 7-isomer: ^{1}H NMR (400 MHz, CD_2Cl_2, 25°C): δ = 7.46–7.48 (d, ^3J(H,H) = 8 Hz, 1H; Ar-H), 7.43 (s, 1H; Ar-H), 6.62–6.64 (d, ^3J(H,H) = 8 Hz, 1H; Ar-H), 6.2 (brs, 1H; NH), 4.20–4.27 (m, 2H; CH_2), 3.44–3.49 (q, ^3J(H,H) = 6.8 Hz, 2H; CH_2), 3.43 (s, 3H; CH_3), 3.28 (s, 3H; CH_3), 1.64–1.72 (m, 2H; CH_2), 1.42–1.48 (m, 2H; CH_2), 0.95–0.98 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3).

Data for the 8-isomer: ^{1}H NMR (400 MHz, CD_2Cl_2, 25°C): δ = 7.50–7.52 (d, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 7.14 (s, 1H; Ar-H), 6.70–6.72 (d, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 5.97 (brs, 1H; NH), 4.20–4.27 (m, 2H; CH_2), 3.54–3.59 (m, 2H; CH_2), 3.42 (s, 3H; CH_3), 3.26 (s, 3H; CH_3), 1.64–1.72 (m, 2H; CH_2), 1.42–1.48 (m, 2H; CH_2), 0.95–0 98 ppm (t, J = 7.2 Hz, 3H; CH_3); HRMS (FAB): *m/z* calcd for $C_{19}H_{24}N_4O_4$ [M^+]: 372.1798; found: 372.1705.

1,3,5-Triethyl-7-trifluoromethyl-5,10-dihydro alloxazine (7): This compound was prepared on a 0.68 mmol scale with 1,3-diethyl-7-trifluoromethyl alloxazine (0.229 g), acetaldehyde (1.4 mL), hydrochloric acid (1.4 mL), Pd/C (0.081 g) in ethanol/water (12.5/10 mL) as described in the general procedure. Reaction time was 47 h. The reaction was worked up by using the general procedure, after which the product, a mixture of the desired product together with some nonalkylated product, was isolated as yellow powder in 54% yield. Spectral data for the desired product **7**: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.08–7.10 (d, ^3J(H,H) = 8 Hz, 1H; Ar-H), 6.77–6.79 (d, ^3J(H,H) = 8 Hz, 1H; Ar-H), 6.74 (s, 1H; Ar-H), 6.12 (brs, 1H; NH), 3.96–4.02 (q, ^3J(H,H) = 7.2 Hz, 4H; 2CH_2), 3.52–3.57 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2), 1.32–1.35 (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.19–1.23 (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.18–1.21 ppm (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 157.53, 149.58, 145.46, 140.9, 135.31, 125.06, 124.72 (d, ^2J(C, F) = 33 Hz), 122.3 (q, ^3J = 4 Hz), 120.76, 112.6, 111.58 (q, ^3J = 3.8 Hz), 100.17, 49.77, 37.41, 37.04, 14.02, 13.26, 12.32 ppm; HRMS (FAB): *m/z* calcd for $C_{17}H_{19}F_3N_4O_2$ [M^+]: 368.1460; found: 368.1452.

Data for the nonalkylated product: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 6.85–6.87 (d, J = 8 Hz, 1H; Ar-H), 6.49 (s, 1H; Ar-H), 6.18–6.20 (d, J = 8 Hz, 1H; Ar-H), 5.58 (brs, 1H; NH), 4.9 (s, 1H; NH) 3.86–3.92 (q, J = 7.2 Hz, 2H; CH_2), 3.69–3.75 (q, J = 7.2 Hz, 2H; CH_2), 1.29–1.33 (t, J = 7.2 Hz, 3H; CH_3), 1.23–1.26 ppm (t, J = 7.2 Hz, 3H; CH_3).

1,3,6,9-Tetramethyl-5-ethyl-5,10-dihydroalloxazine (8): By following the standard procedure for reductive alkylation of alloxazine compound **17** (100 mg) was converted into compound **8** in 50% yield (55.5 mg). The product was obtained as a bright yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.78 (d, ^3J(H,H) = 7.5 Hz, 1H; Ar-H), 6.71 (d, ^3J(H,H) = 7.5 Hz, 1H; Ar-H), 5.67 (brs, 1H; NH), 3.50 (s, 3H; CH_3), 3.35 (s, 3H; CH_3), 3.1 (brs, 2H; CH_2), 2.26 (s, 3H; CH_3), 2.17 (s, 3H; CH_3), 1.04 ppm (t, ^3J(H,H) = 6.9 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 158.42, 150.83, 147.48, 135.62, 133.54, 130.98, 126.68, 126.02, 119.27, 100.70, 49.11, 29.82, 28.29, 17.41, 16.17, 11.16 ppm; HRMS (FAB): *m/z* calcd for $C_{16}H_{20}N_4O_2$ [M^++H]: 300.1665; found: 301.1661.

Methyl 3,4-diaminobenzoate (9d): 3,4-Diaminobenzoic acid (2.28 g, 15 mmol) was dissolved in methanol (50 mL). Sulfuric acid (2 mL) was added to the solution, which was stirred over night. The reaction was quenched by addition of 2 M NaOH solution (200 mL) and extracted with CH_2Cl_2 (3×150 mL). The organic phases were separated and dried over Na_2SO_4, evaporated, and dried under vacuum. The product was isolated without further purification as pale orange solid in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.44–7.469 (dd, ^4J(H,H) = 2 Hz, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 7.39–7.40 (d, ^4J(H,H) = 2 Hz, 1H; Ar-H), 6.65–6.67 (d, ^3J(H,H) = 8.4 Hz, 1H; Ar-H), 3.84 (s, 3H; CH_3), 3.6 ppm (brs, 4H; 2NH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 167.47, 140.53, 133.22, 123.36, 121.17, 118.44, 115.0, 51.77 ppm.

Butyl 3,4-diaminobenzoate (9e): The 3,4-diaminobenzoic acid (2.28 g, 15 mmol) was dissolved in butanol (10 mL) and concentrated sulfuric acid (2 mL) was added while stirring. The reaction was stirred over night and worked up as described above. After column chromatography (gradient CH_2Cl_2/EtOAc, 400:60, 400:80, 200:60 mL) the product was isolated as light brown powder in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.45–7.48 (dd, ^4J(H,H) = 2.1 Hz, ^3J(H,H) 8.1 Hz, 1H; Ar-H), 7.40–7.41

(d, ^4J = 2.1 Hz, 1H; Ar-H), 6.65–6.67 (d, ^3J(H,H) = 8.1 Hz, 1H; Ar-H), 4.23–4.27 (t, ^3J(H,H) = 6.6 Hz, 2H; CH_2), 3.6 (brs, 4H; $2NH_2$), 1.69–1.74 (m, 2H; CH_2), 1.41–1.51 (m, 2H; CH_2), 0.93–0.98 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.1, 140.4, 133.2, 123.3, 121.6, 118.4, 115.0, 64.4, 64.2, 31.0, 30.3, 19.4, 13.9 ppm.

General procedure for the formation of the alloxazine ring structure: A mixture of alloxane monohydride (**10**) (1.05 equiv) and boric acid, H_3BO_3, (1.12 equiv) in glacial acetic acid was added to a solution of the diamine in glacial acetic acid. The mixture was stirred for 1–24 h at 50 °C or room temperature. For the symmetric diamines, the condensation was conducted under heating in shorter reaction time, whereas for the unsymmetric diamines the reaction temperature was decreased to room temperature to avoid a 1:1 regioisomeric mixture of the product. The products were isolated by filtration, and the filtrate was washed with acetic acid followed by diethyl ether, water, and again diethyl ether.

7/8-Methoxycarbonyl alloxazine (11d): A mixture of **10** (0.1204 g, 0.752 mmol) and H_3BO_3 (0.0496 g, 0.8018 mmol) in glacial acetic acid (6 mL) was added to a stirred solution of **9d** (0.119 g, 0.716 mmol) in glacial acetic acid (4 mL). The resulting mixture was stirred over night. The precipitated product was filtered off and washed with acetic acid followed by diethyl ether. The washing was continued with water and finally diethyl ether. After drying under vacuum the product, a yellow powder, was obtained in 66% yield as a mixture of 7-and 8-regio isomers in 44:56 ratio.

Data for the 7-methoxycarbonyl isomer: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.9 (brs, 2H; 2NH), 8.61 (dd, ^5J(H,H) = 0.6 Hz, ^4J(H,H) = 2.0 Hz, 1H; Ar-H), 8.28–8.32 (dd, ^4J(H,H) = 2.0 Hz, ^3J(H,H) = 8.9 Hz, 1H; Ar-H), 7.94–7.97 (dd, ^5J(H,H) = 0.6 Hz, ^3J(H,H) = 8.9 Hz, 1H; Ar-H), 3.97 ppm (s, 3H; CH_3)

Data for the 8-methoxycarbonyl isomer: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.9 (brs, 2H; 2NH), 8.35 (dd, ^5J(H,H) = 0.6 Hz, ^4J(H,H) = 1.9 Hz, 1H; Ar-H), 8.22–8.25 (dd, ^5J(H,H) = 0.6 Hz, ^3J(H,H) = 8.8 Hz, 1H; Ar-H), 8.12–8.16 (dd, ^4J(H,H) = 1.9, ^3J(H,H) = 8.8 Hz, 1H; Ar-H), 3.97 ppm (s, 3H; CH_3).

7/8-Butoxycarbonyl alloxazine (11e): Compound **9e** (0.8316 g, 4 mmol) was dissolved in glacial acetic acid (70 mL). Compound **10** (0.8415 g, 5.25 mmol) and H_3BO_3 (0.344 g, 5.55 mmol) were added and the mixture was stirred for 7 h. The precipitated product was filtered off, washed as above and dried under vacuum. A mixture of the 7- and 8-regioisomers in 45:55 ratio was obtained in 75% combined yield as yellow powder.

Data for the 7-butoxycarbonyl isomer: ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.07 (brs, 1H; NH), 11.85 (brs, 1H; NH), 8.63 (d, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.29–8.33 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 7.96–7.99 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 4.34–4.38 (t, ^3J(H,H) = 6.5 Hz, 2H; CH_2), 1.71–1.80 (m, 2H; CH_2), 1.41–1.53 (m, 2H; CH_2), 0.94–0.96 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): δ = 164.9, 160.1, 150.0, 147.6, 144.9, 138.1, 133.7, 133.3, 129.0, 128.5, 126.9, 65.0, 30.2, 18.8, 13.6 ppm.

Data for the 8-butoxycarbonyl isomer: ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.07 (brs, 1H; NH), 11.85 (brs, 1H; NH), 8.36 (d, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.24–8.27 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 8.14–8.17 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 4.36–4.39 (t, ^3J(H,H) = 6.5 Hz, 2H; CH_2), 1.71–1.80 (m, 2H; CH_2), 1.41–1.53 (m, 2H; CH_2), 0.94–0.96 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): δ = 164.9, 160.1, 150.0, 148.1, 140.8, 133.3, 131.8, 131.7, 130.8, 127.6, 65.2, 30.1, 18.8, 13.6 ppm.

7/8-Trifluoromethyl alloxazine (11f): Compound **9f** (0.1321 g, 0.75 mmol) in hot acetic acid (1.5 mL) was added to a mixture of **10** (0.1265 g, 0.79 mmol) and H_3BO_3 (0.0513 g, 0.83 mmol) in hot acetic acid (4.4 mL). The reaction time was 3 h. After filtration and washing as above the product, a mixture of 7- and 8-isomers in a ratio of 84:16, was isolated in 53% yield as off white powder (one should be careful with the washing here because the product is more soluble in diethyl ether).

Data for the 7-trifluoromethyl isomer: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 12.1 (brs, 1H; NH), 11.9 (brs, 1H; NH), 8.34–8.39 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 8.22 (s, 1H; Ar-H), 7.97–8.01 ppm (dd, ^4J(H,H) = 1.7 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H).

Data for the 8-trifluoromethyl isomer: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 12.1 (brs, 1H; NH), 11.9 (brs, 1H; NH), 8.54 (s, 1H; Ar-H), 8.12–8.15 (dd, ^4J(H,H) = 1.5 Hz, ^3J(H,H) = 8.9 Hz, 1H; Ar-H), 8.06–8.09 ppm (d, ^3J(H,H) = 8.9 Hz, 1H; Ar-H).

1,3-Dimethyl-7/8-methoxycarbonyl alloxazine (12d): Compound **11d** (0.5 g, 1.8 mmol) was dissolved in dimethylformamide (DMF; 76 mL). Potassium carbonate (0.8125 g, 5.88 mmol) and methyl iodide (0.267 g, 2.02 mmol) were added, and the mixture was stirred for 4 h. The inorganic solids were filtered off and the solvent was evaporated. The remaining solids were suspended in CH_2Cl_2 (200 mL) and extracted with diluted brine (100 mL) and brine (100 mL). The organic phases were separated and dried over $MgSO_4$. The product, a yellow powder, was isolated as 54:46 mixture of the 7- and 8-isomers in 76% yield. IR (film): $\tilde{\nu}$ = 3004, 2956, 1725, 1681, 1620, 1566 cm^{-1}.

Data for the 1,3-dimethyl-7-methoxycarbonyl isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.98 (dd, ^5J(H,H) = 0.6 Hz, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.41–8.44 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.9 Hz, 1H; Ar-H), 8.01–8.04 (dd, ^5J(H,H) = 0.6 Hz, ^3J(H,H) = 8.9 Hz, 1H; Ar-H), 4.0 (s, 3H; CH_3), 3.81 (s, 3H; CH_3), 3.58 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.9 (2), 159.5, 150.8, 146.2, 142.9, 134.8, 133.6, 133.5, 130.8, 128.7, 53.0, 30.0, 29.5 ppm.

Data for the 1,3-dimethyl-8-methoxycarbonyl isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.67–8.68 (dd, ^5J(H,H) = 0.6 Hz, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.32–8.35 (dd, ^5J(H,H) = 0.6 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 8.25–8.29 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 4.01 (s, 3H; CH_3), 3.81 (s, 3H; CH_3), 3.58 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.9 (2), 159.6, 150.6, 145.5, 141.7, 139.2, 131.4, 131.2, 130.5, 128.3, 53.1, 29.9, 29.6 ppm.

1,3-Dimethyl-7/8-butoxycarbonyl alloxazine (12e): The starting alloxazine **11e** (0.4715 g, 1.5 mmol) was dissolved in DMF (70 mL). First K_2CO_3 (0.6634 g, 4.8 mmol) and then methyl iodide (0.449 g, 3.165 mmol) were added to the solution. The mixture was stirred over night and the product worked up as described above. Flash column purification (pentane/EtOAc 1:2) yielded the product, a yellow powder, as a 1:1 mixture of 7- and 8-regioisomers in 96% yield. IR (film): $\tilde{\nu}$ = 3051, 2960, 2936, 1732, 1683, 1621, 1567 cm^{-1}.

Data for the 1,3-dimethyl-7-butoxycarbonyl isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.0 (d, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.41–8.44 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 9 Hz, 1H; Ar-H), 8.00–8.02 (d, ^3J(H,H) = 9 Hz, 1H; Ar-H), 4.36–4.41 (t, ^3J(H,H) = 6.3 Hz, 2H; overlap with 8-isomer, CH_2), 3.81 (s, 3H; CH_3), 3.58 (s, 3H; overlap with 8-isomer, CH_3), 1.74–1.83 (m, 2H; overlap with 7-isomer, CH_2), 1.45–1.58 (m, 2H; overlap, CH_2), 0.97–1.02 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.4, 159.4, 150.7, 146.5, 145.4, 139.1, 133.4, 133.3, 131.0, 130.8, 128.1, 65.8, 30.8, 29.9, 29.4, 19.4, 13.9 ppm.

Data for the 1,3-dimethyl-8-butoxycarbonyl isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.66–8.67 (d, ^4J(H,H) = 1.8 Hz, 1H; Ar-H), 8.33–8.36 (d, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 8.26–8.30 (dd, ^4J(H,H) = 1.8 Hz, ^3J(H,H) = 8.7 Hz, 1H; Ar-H), 4.39–4.43 (t, ^3J(H,H) = 6.6 Hz, 2H; overlap with 7-isomer, CH_2), 3.82 (s, 3H; CH_3), 3.58 (s, 3H;overlap with 7-isomer, CH_3), 1.74–1.83 (m, 2H; overlap with 7-isomer, CH_2), 1.45–1.58 (m, 2H; overlap, CH_2), 0.98–1.03 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3).

1,3-Diethyl-7-trifluoromethyl alloxazine (12f): Compound **11f** (0.34 g, 1.20 mmol) was dissolved in DMF (60 mL). Ethyl iodide and K_2CO_3 were added as above and the mixture was stirred for 3 h. After the usual workup the product was isolated as a single isomer in 57% yield as yellow powder. IR (film): $\tilde{\nu}$ = 3042, 2973, 2939, 1726, 1674, 1633, 1566, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.44–8.46 (d, ^3J(H,H) = 8.8 Hz, 1H; Ar-H), 8.34 (s, 1H; Ar-H), 7.88–7.91 (dd, ^4J(H,H) = 1.9 Hz, ^3J(H,H) = 8.8 Hz, 1H; Ar-H), 4.49–4.54 (q, ^3J(H,H) = 7.0 Hz, 2H; CH_2), 4.23–4.28 (q, ^3J(H,H) = 7.1 Hz, 2H; CH_2), 1.39–1.43 (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 1.34–1.38 ppm (t, ^3J(H,H) = 7.1 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.0, 149.6, 145.8, 142.7, 140.8, 138.8, 134.8 + 135.2 (d, ^2J(C, F) = 33 Hz), 132.2, 131.9 + 129.3 (d, ^1J(C, F) = 260 Hz), 126.0 (q, ^3J(C, F) = 3 Hz), 124.7 (q, ^3J(C, F) = 3 Hz), 38.5, 38.2, 13.2, 13.0 ppm. ^{19}F NMR (400 MHz, $CDCl_3$, 25 °C): δ = −63.6 ppm.

6-(2,5-Dimethylphenylamino)-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (16): Compounds **13** (1.0 g, 6.37 mmol) and **15** (987 mg, 6.37 mmol) were suspended in **14** (1.5 mL). The mixture was heated to 160 °C for one hour, while gas evolution was observed. The mixture was allowed to cool to room temperature and water was added. The mixture was then filtered and the filtrate extracted with diethyl ether. After drying with $MgSO_4$ the solvent was removed under reduced pressure. Addition of diethyl ether to the residue resulted in precipitation of the product as a white solid (470 mg, 28 %). When the experiment was repeated, addition of water to the cool mixture and filtration directly yielded the product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.09$ (d, ^3J(H,H) = 7.5 Hz, 1H; Ar-H), 7.04 (d, ^3J(H,H) = 7.8 Hz, 1H; Ar-H), 6.93 (s, 1H; Ar-H), 5.82 (br s, 1H; NH), 4.61 (s, 1H; CH), 3.56 (s, 3H; CH_3), 3.29 (s, 3H; CH_3), 2.30 (s, 3H; CH_3), 2.17 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.26$, 153.10, 152.24, 137.47, 134.89, 131.90, 131.45, 129.05, 128.11, 78.33, 29.32, 28.02, 21.01, 17.33 ppm.

1,3,6,9-Tetramethylalloxazine (17): Compound **16** (151 mg, 0.6 mmol) was dissolved in hot glacial acetic acid (1.2 mL). The mixture was then cooled to −10 °C. $NaNO_2$ (60 mg, 0.87 mmol) in of water (0.3 mL) was added dropwise to the reaction mixture over a period of 1 min. The color changed to brown-red and a precipitate formed. The mixture was stirred for an additional 15 min at room temperature. After filtration the remaining solid was washed with small amounts of water and then dried in vacuo. Compound **17** was obtained as a yellow solid in 70 % yield. IR (film): $\tilde{\nu} = 3028$, 3005, 2954, 2923, 1724, 1679, 1562 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.54$ (d, ^3J(H,H) = 7.2 Hz, 1H; Ar-H), 7.40 (d, ^3J(H,H) = 6.8 Hz, 1H; Ar-H), 3.74 (s, 3H; CH_3), 3.55 (s, 3H; CH_3), 2.78 (s, 3H; CH_3), 2.63 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 160.11$, 151.05, 144.12, 142.69, 139.63, 137.26, 133.82, 133.61, 128.74, 127.80, 29.51, 29.23, 17.49, 17.14 ppm.

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