New Approach to Biomimetic Transamination Using Bifunctional [1,3]-Proton Transfer Catalysis in Thioxanthenyl Dioxide Imines

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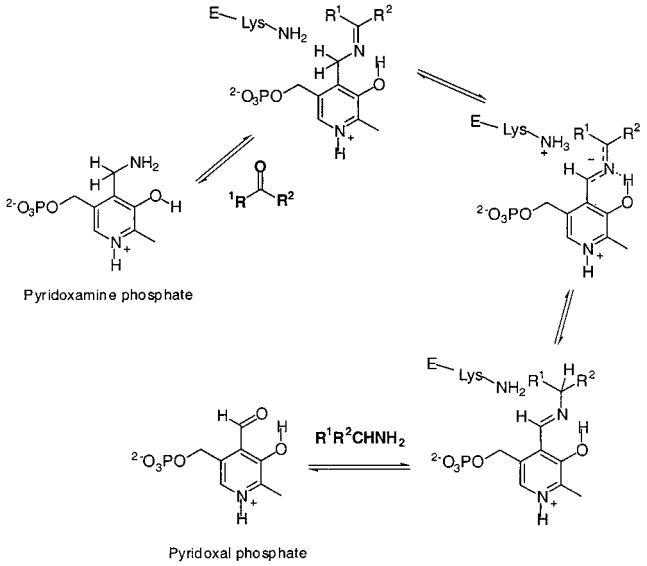
A pyridoxamine equivalent, 9-aminothioxanthene 10,10-dioxide, has been designed that is capable of affording transamination in good to excellent yields of natural as well as artificial amino acids. Amidines and guanidines in catalytic amounts were capable of performing [1,3]-proton transfer in the imines under mild conditions, whereas various simple amines failed. The use of chiral catalysts resulted in modest asymmetric induction (ee ≤ 45%). The electronic dependence in para-substituted phenyl glyoxylate imines, isotope effects, and computational studies support a stepwise, bifunctional mechanism for amidine and guanidine catalysts. Attempts toward an autocatalytic model system are described.

Introduction

Transamination constitutes an important process in most biological systems as a pathway of metabolism of amino acids/α-keto acids.[1] The production of amino acids is one of the most important reactions in native as well as artificial systems as it is the foundation for enzymes/proteins (native systems) and chiral building blocks (artificial systems). It would thus be highly desirable to construct a simple artificial analogue of the amino transferase enzyme, making the transamination both effective and stereocontrolled. Many efforts have been made to seek efficient and simple systems capable of achieving transamination. Efforts to mimic transamination used the cofactor, pyridoxal (vitamin B_6, Scheme 1), which is involved in all the different reaction pathways performed by the amino transferase enzymes.

Other approaches involve the use of simple pyridine derivatives to mimic the action of pyridoxal (commonly referred to as an"electron sink"). The principal idea is to create an electron-poor center, thereby stabilizing the intermediate aza-allylic anion. A general problem with pyridoxamine-based transamination is that ΔG is close to 0, which may lead to undesirably low yields,[2] but has advantage when a catalytic cycle with high turnover is sought. Other approaches make use of conjugation in the product,- and in this way shift the equilibrium toward the thermodynamically more stable product, in our case the amino acid imine. The transamination reaction itself consists of a [1,3]-proton-transfer reaction across an aza−allyl anionic intermediate (Scheme 1).[3] In a native system, this is performed by the amino group of the lysine residue in the enzyme active site.[4] In artificial systems,

Scheme 1



bases such as alkoxides and simple amines have been used. The first rational investigation of the transamination reaction was performed by Cram et al.,[5] who investigated the suprafacial/antarafacial character of the proton-transfer step, as well as the stereoselectivity of the reaction, using *N*-(α-methylneopentylidene)-α-phenylethylamine and KO^{t}Bu as base. Martell[6] has also made several studies concerning the mechanistic viewpoint of transamination, elucidating the different mechanistic details of pyridoxal-catalyzed reactions. Soloshonok et al.[7] have presented a number of papers on the

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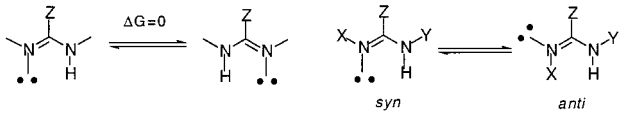
Scheme 2



transamination of fluoro substituted ketimines, using mild bases such as triethylamine (TEA) and diazabicyclo-[3.3.0]undec-7-ene (DBU) and also attempts toward asymmetric induction using alkoxides of ephedrines to achieve asymmetric catalysis, resulting in an ee of 36%. Cainelli et al.[8] reported on the transamination of benzhydryl imines of simple aldehydes using 0.1 equiv of KO^{t}Bu as base in THF at room temperature, resulting in good yields with aldimines. The use of ketimines resulted in enolization and concomitant condensation of the substrate. Other efforts to achieve asymmetric induction have been made by Zwanenburg et al.[9] with the aid of a chiral amino alcoholate catalyst resulting in a maximum asymmetric induction of 44% ee. Some model systems have been presented in the field of supramolecular chemistry in efforts to mimic the native system as far as reaction rates and stereoselectivity are concerned. Breslow et al.[10] have presented cyclodextrin-containing models, where the cavity of the cyclodextrin acted as the active site of the "enzyme". This resulted in an enhanced reaction rate as well as a fair asymmetric induction. The basic sidearm was placed on the upper rim of the cyclodextrin cavity, in the form of either an imidazole unit or an ethylenediamine arm. This model system also presented a bifunctionally acting base.

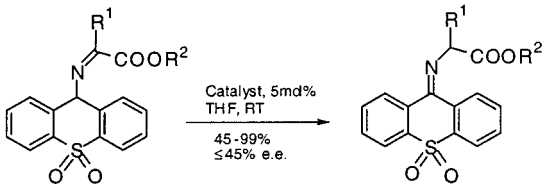
Other approaches to mimic the action of the enzyme lysine residue unit have been made by Ahlberg et al.,[11] incorporating an aminoalkyl or azapropellane sidearm in a pyridoxal-based model system, though a later investigation showed that the preferred conformation of the aza propellane was not optimal for a bifunctional action.[12]

Our research has focused on accomplishing mild and efficient [1,3]-proton-transfer reactions in the model systems. We have also explored the possibility of bifunctional catalysis. The desired bifunctionality should preferably consist of a species (the catalyst) that is degenerate between its two tautomers (Scheme 2). Two such classes of species proved to be symmetric amidines and guanidines.

Results and Discussion

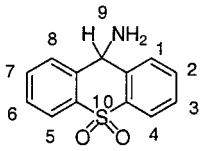
Exploratory Work. In the design of the transamination system, it was important to find an amine that upon formation of imines could be easily deprotonated and the equilibrium shifted toward the desired product (rearranged imine). When scanning the literature, we found that Carpino et al.[13] had reported a thioxanthene system in a new protecting group for amines/amino acids by

Scheme 3



	R^1=	R^2=
1	-Ph	-Me
2	-*i*-Pr	-Et
3	-Me	-Et
4	-CH_2CH_2COOMe	-Me

formation of the corresponding carbamate. This protecting group appeared very attractive, since removal of the 9-proton was very easily accomplished by such mild bases as pyridine and by even heating in aprotic polar solvents alone (DMF, DMSO). A small modification of the thioxanthene moiety was made, and it emerged as 9-aminothioxanthene 10,10-dioxide, previously prepared by Catscoulakos.[14] DBU and triethylamine were initially



9-aminothioxanthene-10,10-dioxide (**17**)

employed for comparison of yields and reaction rate constants. The substrates tested were all α-keto esters converted to the corresponding amino acid esters (Scheme 3). It has been reported previously that an equilibrium mixture of the two possible imines can be afforded by just synthesizing the model substances, though in our examples no products were observed other than the desired product imines together with the starting materials.[15] The designed system was thus not prone to thermal equilibration between the two isomeric imines possible.

Boiling the imines (**1**−**4**) in triethylamine resulted only in recovered nonrearranged starting material. Increasing the pK_a of the corresponding acids to DBU afforded complete rearrangement in all cases but for **1**. This is probably due to the conjugative effect of the nearby phenyl group, resulting in an equilibrium mixture between imines **1a** and **1b**. Other tested catalysts are given in Chart 1 together with their pK_a values in water. For the purpose of kinetic studies, the use of DBU proved futile since the reaction rate (even at −10 °C) was much too fast to be observed by any non-stopped-flow method. The reaction with DBU as catalyst was completed within seconds after addition. The use of benzamidine (**9**), on the other hand, resulted in a reaction rate suitable for observation by NMR. The reactions were generally complete within 4 h (Table 1).

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Chart 1

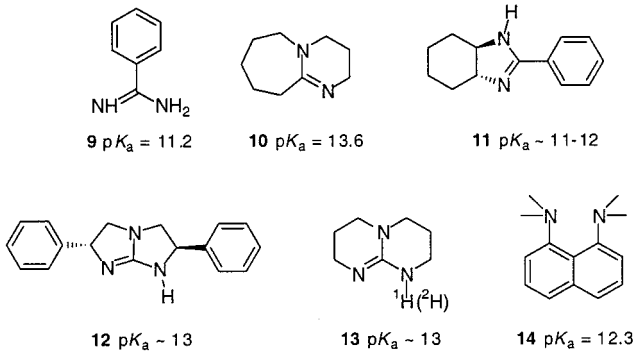


Table 1. Yield of Rearranged Imines, with 5 Mol % of Benzamidine and DBU, Respectively, in THF at 20 °C[a]

			yield (in %) of imine **b**	
compd	R1	R2	benzamidine	DBU
3a	−Me	−Et	98	>99
2a	−*i*-Pr	−Et	98	>99
4a	$-CH_2CH_2CO_2Me$	−Me	98	>99
5a	$-p$-$NO_2C_6H_4$	−Et	42	45
6a	$-p$-FC_6H_4	−Me	51	56
1a	−Ph	−Me	60	68
7a	$-p$-MeC_6H_4	−Me	68	74
8a	$-p$-$OMeC_6H_4$	−Me	72	81

[a] All yields are recorded after 4 h.

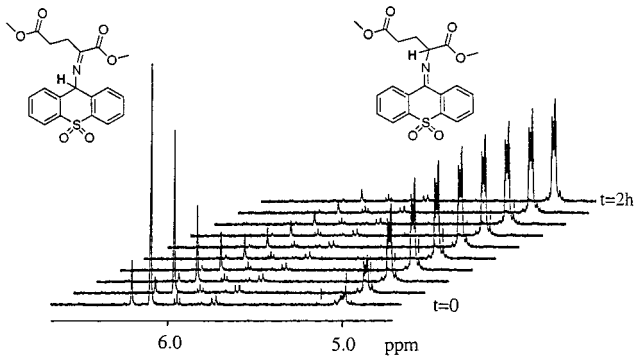


Figure 1. NMR spectrum of the 9-methine proton and the 2-methine proton of compounds **4a** and **4b**, respectively. Added amount of benzamidine (**9**) was 10 mol %, and the time interval between the first measurement (bottom line) to the last measurement (top line) was 2 h.

Kinetics. Kinetics were studied by means of NMR in THF-d_8, and the reaction rate was determined by measuring the integral of the disappearing 9-methine proton of the starting material (Figure 1). The reaction rate did indeed vary with the R group, but there seemed to be no obvious explanation as to the observed differences (Figure 2), other than possibly a steric contribution. For example, the kinetics of compound **2** turned out to obey a linear first-order reaction rate, whereas the other compounds studied were all nonlinear, probably because of approach to an equilibrium. In all cases, it turned out that a prolonged reaction time (<18 h) resulted in cleavage of the product imine (**b**), as one of the resulting products after cleavage could clearly be identified as 9-thioxanthone 10,10-dioxide. The use of DBU as catalyst resulted in slightly higher yields in all cases, and as mentioned earlier, the reactions were very fast. The only reaction that did not result in a quantitative yield was with compound **1**. Compound **1** was thus studied more extensively as to effect of solvent. We observed the lowest

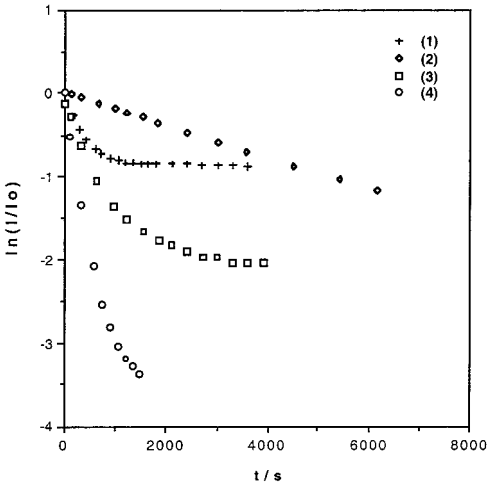


Figure 2. Reaction−rate profiles of compounds **1**−**4** measured as the disappearance of the starting material. Benzamidine (**9**) was used as catalyst (10 mol %), and reactions were performed in THF-d_8 at 35 °C. The *y*-axis gives the logaritms of the ratios of the integrals of the moving proton in substrate and product, and the *x*-axis gives the time in seconds.

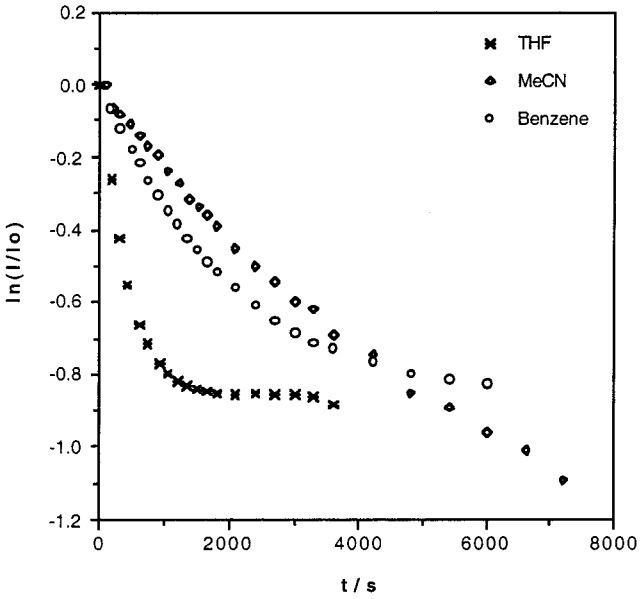


Figure 3. Solvent dependence on the rate of the proton-transfer step of **1**. 10 mol % of benzamidine (**9**) was used at a temperature 35 °C. Same plot variables as in Figure 2.

initial reaction rate with the most polar solvent (acetonitrile, Figure 3). A possible explanation could be that the rate-determining step in the proton-transfer reaction is protonation of the aza allylic anion. The use of acetonitrile, however, increased the yield (79%) and gave an observed linear first-order behavior in kinetics. The use of an apolar solvent (benzene) resulted in a lower yield (55%) as well as nonlinear reaction profile, due to the equilibration.

Substrate and Catalyst Conformation and Bifunctional Catalysis. In exploring the concept of bifunctional catalysis of the base (such as benzamidine), knowledge of the conformation of the substrate as well as the base is important. The substrate imines may assume an *E*- or *Z*-configuration. The NMR spectra of the substrate imines contain signals from two isomers, most clearly shown for the methine singlet at ca. δ6, with

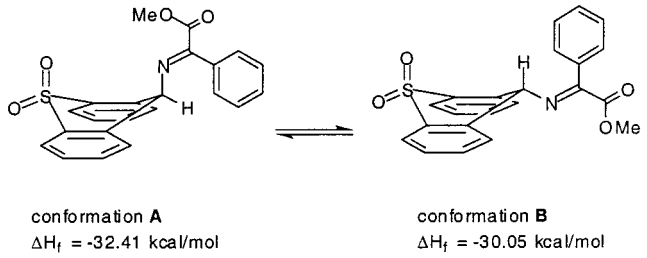


Figure 4. Two different boat-shaped conformations of compound **1**. Heats of formation were calculated by the semiempirical PM3 method. The *E* isomer was lower in energy for both conformations.

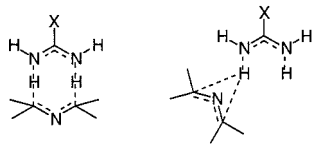
the high-field signal dominating (85−98%). Compound **3a**, however, had reversed preference (80:20). An alternative interpretation of the NMR spectra would be a conformation equilibrium of the thioxanthenyl ring system as shown in Figure 4. Earlier investigations indicate a boat-shaped conformation of the central ring.[16] The solid-state structure of 9-cyclohexylthioxanthene 10,10-dioxide was reported to have the cyclohexyl substituent in the axial position.[17]

A way to distinguish between the two alternative interpretations would be to freeze out the thioxanthenyl ring flip. To investigate if the two conformers could be observed by NMR, a sample of **1a** in THF-d_8 was cooled to −90 °C, but did not give any evidence for a dynamic behavior slow enough to be observed on the NMR time scale. The barrier to inversion between the two conformers could hence be assumed to be small. Another possibility would be a strongly biased equilibrium or that we are dealing with a planar three-ring system, though this seemed highly unlikely, since both our theoretical studies as well as earlier investigations point at a boat-shaped conformation of the central ring. A NOESY spectrum of imine **1a** (in THF-d_8), showed no cross coupling peaks between the 9-methine and any other proton. This behavior would be expected if the proton were situated in the axial position in agreement with the chemical shift considerations. Heating a sample of **7a** in $^2H_2$-1,1,2,2-tetrachloroethane to 95 °C did not lead to significant broadening of the signals. Such a high barrier is expected for *E*/*Z* isomerization but not for thioxanthenyl ring inversion.

Conformer **B** is favorable to approach by a base to abstract the 9-methine proton for both steric and electronic reasons. The resulting intermediate would be a more planar resonance stabilized anion before reprotonation to the rearranged imine. Conformer **A**, on the other hand, has to undergo a larger conformational change to achieve such stabilization. We consider it reasonable to assume that **B** is the preferred conformation for all compounds except maybe for **3a**, as suggested by the NOESY spectrum.

The second stereochemical issue is the conformation of the catalyst. To achieve concerted bifunctional catalysis, the catalyst must be able to both donate and abstract a proton. Two such classes of basic compounds are amidines and guanidines. DBU, however, cannot meet up to the requirements. Benzamidine **9** and the commercially available 1,3,4,6,7,8-hexahydro-2*H*-pyrimido-

Chart 2



[1,2-*a*]pyrimidine (**13-^{1}H**) can act as bifunctional catalysts. One other candidate, amidine **11**, reported by Buddrus et al.,[18] is, however, prevented from having its free electron pair in a cis conformation to the proton (Scheme 2). This restriction proved to be crucial since attempted transamination with **11** yielded only unreacted starting material. A possible explanation for the incapability of this amidine to catalyze proton transfer could be its inability to both abstract and donate a proton simultaneously and, hence, partially sustain our idea about bifunctional action via a double-hydrogen-bonded intermediate (Chart 2). Such an interpretation is contradicted by the action of DBU being an efficient catalyst, with no possibility for bifunctional catalysis.

Computational Approach to Substrate and Transition Structures. We have performed a computational study of the conformations of the substrates, transition states, and products by simple semiempirical calculations (PM3) and by use molecular mechanics for the ground states. All the substrate imines except **3a** are predicted to prefer an *E* configuration according to both PM3 and MMFF calculations. Both imines **a** and **b** are saddle-shaped, **b** even a little more than **a**.

Judging from the calculated structure of conformer **A**, it appears that approach by a base to abstract the 9-proton is more hindered. We reasoned that optimal conditions for efficient bifunctional proton-transfer catalysis would be governed by a conformation of starting imine in which the C(9)−H bond is perpendicular to the imine plane also for electronic reasons. To gain information about the mechanism, we decided to localize transition structures for proton-transfer reaction by computations using formamidine as base. It turned out that we were unable to find any transition state for concerted bifunctional proton transfer. Instead, formamidine gave a transition structure for **1** corresponding to the first step in a stepwise mechanism in which the imine nitrogen atom acts as a base (Figure 5, TS1). The proton of that nitrogen is hydrogen-bonded to the syn oxygen of the sulfone. Furthermore, a proton of the other nitrogen atom is hydrogen bonded to the carbonyl oxygen of the ester group. These hydrogen bonds are most likely important for both reactivity and stereoselectivity of the proton-transfer reaction. The second hydrogen bond points at an alternative mechanism for the protonation step in which the proton is tranfered to the oxygen atom giving an enol intermediate, which rearranges to the product imino ester. In such a mechanism, the configuration of the product would be determined in the last ketonization step. We were unable to localize a transition state for proton transfer to the oxygen. Instead, a transition structure was localized for the protonation at the carbon atom (TS2) having a hydrogen bond to the carbonyl oxygen. TS1 is 0.32 kcal/mol higher than TS2. The calculations refer to gas-phase reaction, and the two reaction steps have opposite charge developments, which

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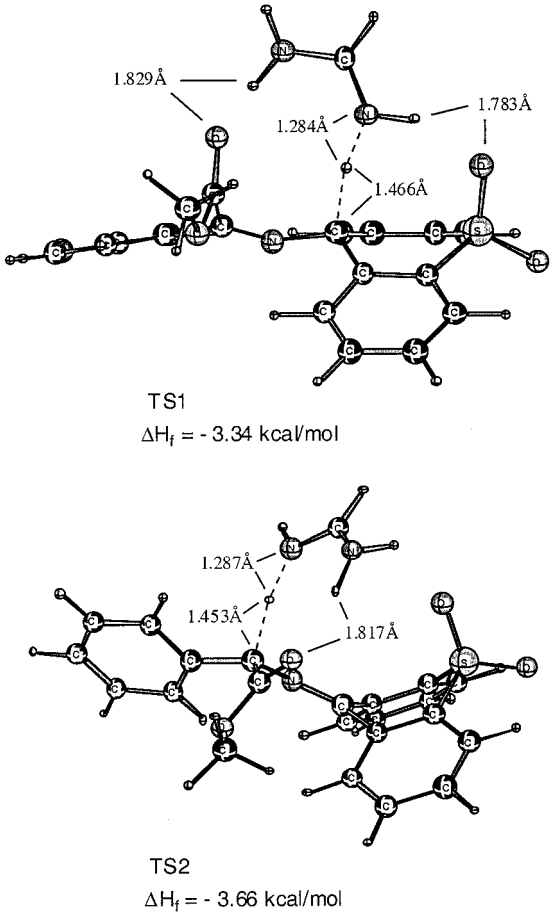

Figure 5. Two transition structures for the stepwise proton transfer of **1** by formamidine calculated by the semiempirical PM3 method.

certainly affects the quantitative properties of the transition structures and energies. We are currently working on higher level computations in order to gain information of the mechanism and to guide us in the search for better enantioselectivity.

Isotope Effect. To further elucidate the nature of the reaction, a deuterated base was synthesized (**13**-^{2}**H**) with a degree of deuteration of >98% according to NMR.[19] The base was used in excess (1.1 equiv). This resulted in 66 ± 2% deuteration of the rearranged imine (**2b**). Using an iterative method, simulation of the course of bifunctional reaction, gave 66% deuteration assuming a kinetic isotope effect of 1.0, and it was possible to determine a maximum value for the isotope effect of 1.2 (giving 64% deuterated product). This is identical to the value found by Ahlberg et al. for amidine-catalyzed 1,3-proton-transfer reactions in indene derivatives.[20] Such a small isotope effect is hardly compatible with a rate-determining protonation.

Asymmetric Catalysis. These results were further evaluated in our attempts toward asymmetric catalysis, by the synthesis and use of a phenyl glycine based guanidine **12** first synthesized by Corey et al.[21] The pseudo-C_2 symmetry of this base is a prerequisite for efficient asymmetric induction due to the tautomeric properties

Table 2. Yield of Rearraranged Imines According to Scheme 3, with 5 Mol % of Guanidine (12) as Catalyst in THF at 23 °C[a]

compd	R1	R2	yield of imine **b** (%)	ee (%)
1	−Ph	−Me	63	43
2	−*i*-Pr	−Et	95	45
3	−Me	−Et	98	24
4	$-CH_2CH_2COOMe$	−Me	98	0

[a] All yields are recorded after 4 h.

of the guanidine. The enantiomeric excess of this base varied between 0 and 45% (Table 2). Imine **4** resulted in a racemic mixture of **4b**. Somewhat higher asymmetric induction was achieved for **1**−**3**. The lack of asymmetric induction of **4** may be a result of the high reaction rate observed in THF (Figure 2). Imine **2** resulted in the highest enantiomeric excess (45%), followed by imine **1** (43%). Both these imines contain rather sterically demanding substituents, which may be a reason for the increased asymmetric induction. Chiral amines, such as dihydroquinidine, did not give rise to any proton transfer.

Stepwise versus Concerted Catalysis. Even though several studies indicate that amidines do act bifunctionally,[22] Ahlberg et al. claim that in bifunctional catalysis the *concerted* mechanism is higher in energy than a *stepwise* mechanism.[20] One observation substantiating this idea appears on addition of base to all imines−a colored solution immediately emerges. A possible explanation would be that we have a charge-transfer complex (between base and substrate) leading to coloration or an intermediate ion formation. To eliminate the possibility of charge-transfer complexation, a simple test was done with KO^{t}Bu as base. This base is incapable of forming a charge-transfer complex, but a colored solution still resulted upon addition of the base, hence eliminating the possibility of a charge-transfer complex as a cause for the observed coloration. In final essence, we are left with the option of an intermediate anion. We envisage, however, that a two-point interaction as in bifunctional catalysis increases the possibility of enantioselective protonation (Chart 1).

The Electronic Influence. The effect on the proton-transfer reaction was examined by substitution of the phenyl ring in compound **1**. Substituents were *p*-OMe, *p*-Me, *p*-F, and *p*-NO_2 (Chart 2). A moderate influence on the reaction rate was observed, with the rate constant varying within 1 order of magnitude depending on the substituent (Figure 6).

With the use of LFER para-substituent parameters (σ_p),[23] a Hammett plot (Figure 7) displayed a poorly linear relationship, with a $\rho = -0.58$, which is a low value for a rate-determining protonation step but could be explained by a hydrogen bond to the carbonyl oxygen as in TS1 or to the acceptor carbon in the deprotonation transition state. It would have been further enlightening to study the reaction rate behavior of compounds **1** and **5**−**8**, but since these reactions proceeded at a very high reaction rate under identical conditions, any comparison was impossible. Little has been studied on the electronic effect of para substitution of phenyl derivatives of substrates in transamination reactions. The only report (to our

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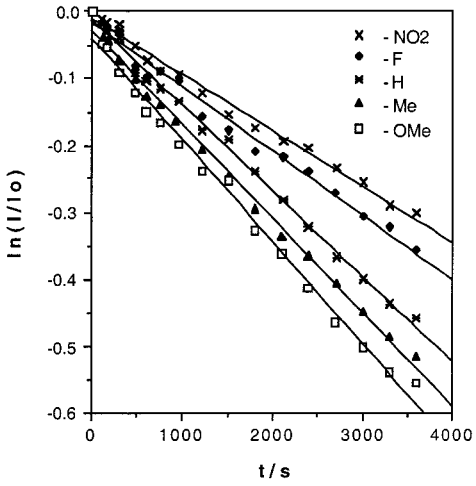


Figure 6. Varying reaction rates of compounds **1** and **5**−**8**. All performed in CD_3CN/THF-d_8 (5:2), with 10 mol % benzamidine (**9**) at 303 K, and measured as the disappearance of the imine (**a**).

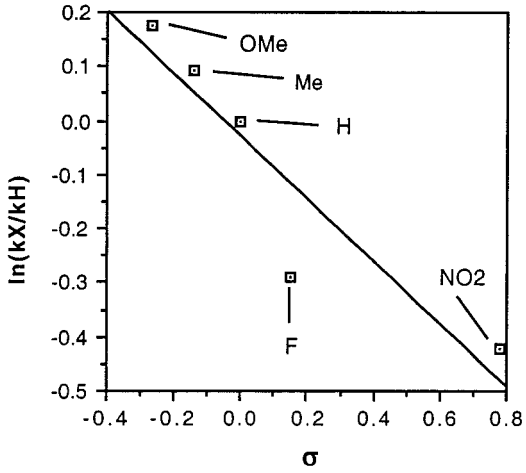
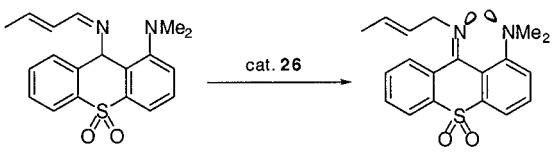


Figure 7. Hammett plot for the observed reaction rates as depicted in Figure 6, yielding a $\rho = -0.58$.

knowledge) investigated the rearrangement of a series of para-substituted phenylalanine derivatives in the context of transamination.[24] That investigation pointed at an accelerated reaction rate when electron-donating substituents in the para position were present, such as *p*-aminophenylalanine, whereas *p*-nitrophenylalanine was found to be inactive.

Autocatalytic Model. Since DBU could catalyze transamination in our model systems, we decided to incorporate a basic moiety in the thioxanthene ring system. The base was incorporated into the model system as a dimethyl amino group in the 1-position (**24**). The



25 **26**

idea was to use the rearranged imine to act as its own base in an autocatalytic manner.[25] The product imine has a proton sponge like structure[26] (compare, e.g., 1,8-(bis-dimethylamino)naphthalene, **14**). Since the nitrogen−carbon bond in the imine moiety is planar, a similar crowding of the free electron pairs in the product imine is obtained resulting in a stronger base than the starting imine (**25**) and, hence, should be able to act as a base to accomplish [1,3]-proton transfer. In addition, some calculations (molecular mechanics and semiempirical PM3) were made that pointed toward a negative ΔH for the desired reaction. However, the only imines that could be formed with amine **24** were with highly reactive aldehydes such a crotonaldehyde. Other (enolizable) aldehydes were simply enolized by the diamine, resulting in condensation. Efforts to rearrange this crotyl imine failed. Only unrearranged starting material was recovered when subjected to several bases such as KO^{t}Bu, DBU, or benzamidine. This could very well be the result of a sterically demanding environment of the 9-proton caused by the dimethyl amino group in the 1-position or an energetically unfavorable product.

Synthesis. The key amine in the study was synthesized according to the route outlined in Scheme 4, starting from commercially available thioxanthone, which was oxidized by $NaIO_4/RuCl_3$.[27] 9-Thioxanthone 10,10-dioxide was converted to its oxime (**15**) by reaction with $HONH_2 \cdot HCl$ in pyridine and ethanol and thereafter acetylated by acetic anhydride/pyridine. The acetylated oxime **16** was reduced to the key amine **17** by reduction of $BH_3 \cdot THF$ complex. The earlier reported yield of this amine was not reproducible, but instead turned out be lower. The workup of this product proved to be an ordeal, since the use of the borane reagent produced a thick white precipitate, complicating isolation of the product. Attempts to produce the simple imine by reacting 9-thioxanthone 10,10-dioxide with ammonia (in the presence of $TiCl_4$ as catalyst) failed, since the product of this reaction was much too unstable to allow isolation and concomitant reduction. Nonaromatic imines were synthesized by reacting the key amine **17** with the desired α-keto ester in CH_2Cl_2, in the presence of dry $MgSO_4$, for 16 h at room temperature. In the case of aromatic imines, the reaction was performed in dry benzene in the presence of molecular sieves (4 Å), with $BF_3 \cdot OEt_2$ as the activating catalyst, and heated to reflux for 12 h. Glyoxylates with different para-substitution patterns were synthesized according to the method by Babudri et al. using the LiCl/CuBr-catalyzed Grignard reaction with methyl chlorooxoacetate.[28] Synthesis of amidine **11** and guanidine **12** were performed according to known literature procedures. Deuteration of compound **13-^{1}H** to produce **13-^{2}H** was accomplished by repeated solvation and evaporation of the guanidine three times from CD_3OD.

Synthesis of the 1-dimethylaminothioxanthone dioxide structure (**24**, Scheme 5) was performed by an earlier reported procedure by Snieckus et al.[29] with the starting 2-*N*,*N*-(dimethylamino)-*N*,*N*-diethylbenzamide (**20**) prepared according to the method reported by Murphy et al.[30] The resulting key ketone **22** was converted to the

(24) Taylor, D. C.; Wightman, F. *Phytochemistry* **1987**, *26*, 2167−2179.

(25) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382.

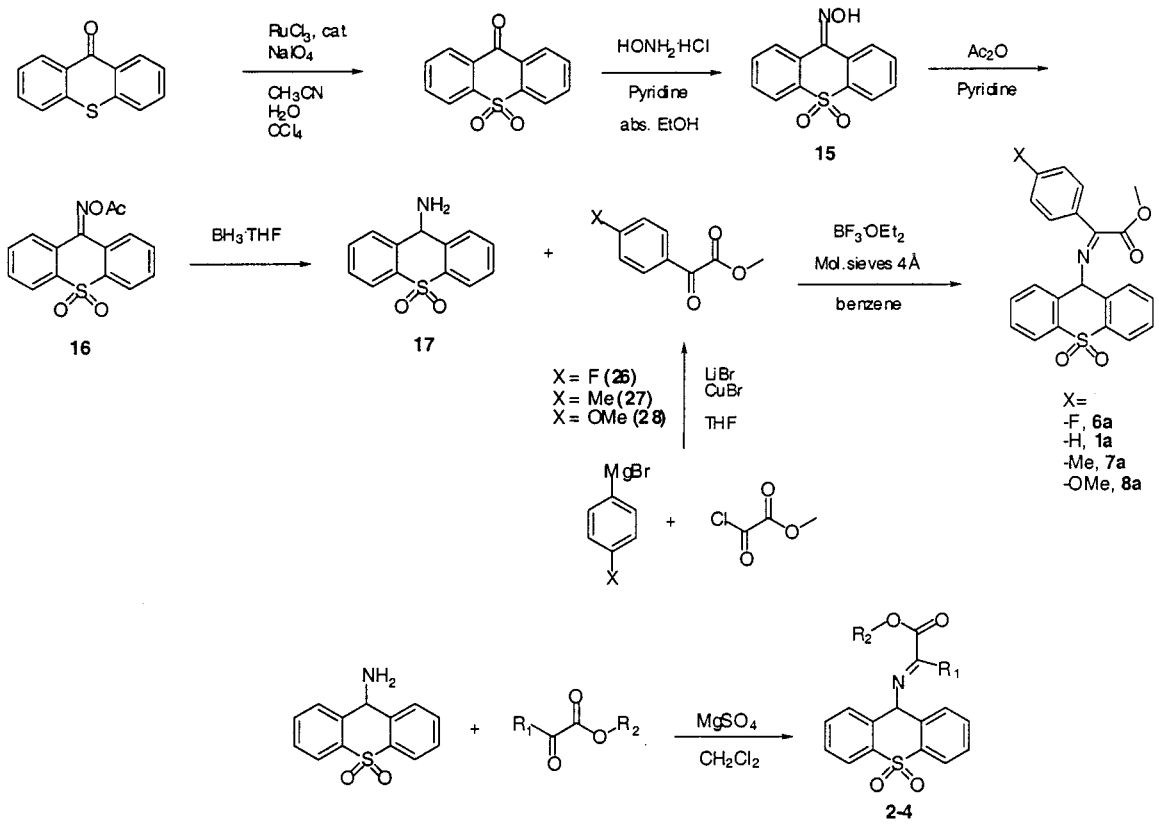
(26) Hibbert, F.; Hunte, P. P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1895−1899.

(27) Su, W. *Tetrahedron Lett.* **1994**, *35*, 4955−4958.

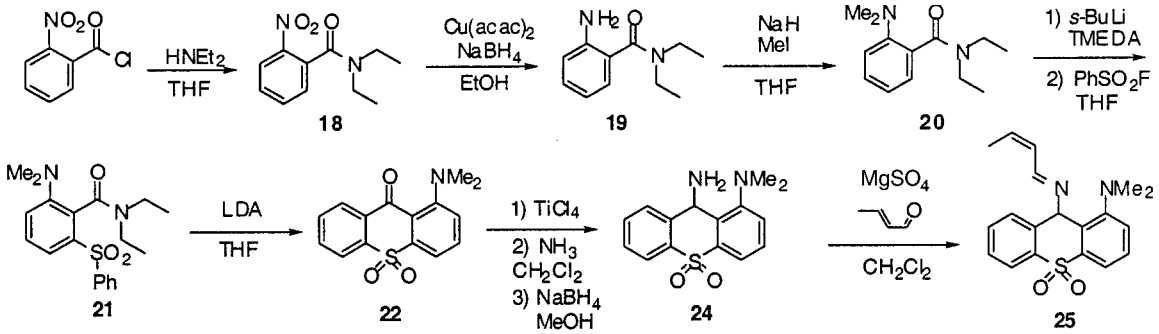
(28) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513−13520.

(29) Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508−6509.

Scheme 4



Scheme 5



amine by formation of imine **23** in NH_3 with $TiCl_4$ as catalyst. The imine was converted into its amine **24** by reduction in MeOH/$NaBH_4$. The final product (**25**) was produced by reaction of **24** in CH_2Cl_2 with croton aldehyde in the presence of $MgSO_4$ at room temperature.

Conclusions

We have described a new mild and efficient biomimetic transamination method for α-amino acid esters. Amines, such as triethylamine and dihydroquinidine, failed to catalyze the proton transfer, whereas the more basic benzamidine and DBU proved to give high yields, DBU, in addition, gave high reaction rates. The use of chiral catalysts resulted in an asymmetric induction with ee's up to 45%. Introduction of substituents in the para position of the phenylglycine precursor (**1**) resulted in a small variation in the observed first-order reaction constants (varying only within 1 order of magnitude). The low negative value of ρ indicates that we might be dealing with a hydrogen bond to the exocyclic carbon or carbonyl oxygen in the transition state rather than a rate-determining protonation step. The electronic dependence in para-substituted phenyl glyoxylate imines, isotope effects, and conformational studies support a stepwise, bifunctional mechanism for amidine and guanidine catalysts. This is further substantiated by our observation of coloration of the reaction solution upon addition of the base. The computations support a stepwise mechanism with two essentially equi-energetic transition states, and the amidine transition state gives valuable information of how to improve the stereoselectivity of the reaction. An attempt to construct an autocatalytic system failed because of difficulties to synthesize the required imines. Experiments aiming at improved enantioselective reactions are in progress.

Experimental Section

NMR (^1H, ^{13}C) was performed at 400 and 100 MHz, respectively. Melting points are reported herein as uncorrected melting points. All commercially available starting materials were used as received unless otherwise noted. Thin-layer

(30) Murphy, J. A.; Roome, S. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1349−1358.

chromatography was performed on silica gel plates with aluminum supports. Purification of all imines was performed on a chromatotron using premade plates with neutral aluminum oxide. Investigations of enantioselectivity was performed by quenching the sample with gaseous HCl and a small amount of water. The sample was dried and thereafter treated with trifluoroacetic anhydride or CBz-Cl together with excess pyridine and allowed to stand at room temperature for 30 min to produce the corresponding *N*-trifluoroacetyl- or Cbz-protected amino acid esters. The sample was thereafter passed through a short silica column to remove any basic remains. A small part of the sample was taken out, diluted with acetonitrile, and injected onto a column (column dimensions 30 × 0.5 cm) with 2−10% 2-propanol in hexane as the mobile phase at a flow rate of 0.5 mL/min.

The isotope effect experiments were analyzed in Excel using a iterative method based upon the rate equation

$$\frac{d[P_{H(D)}]}{dt} = k_{H(D)}[N_{H(D)}][S]$$

where P, N, and S refer to product, catalyst, and substrate and H(D) refers protonated and deuterated species, respectively. The reverse reaction was neglected in the calculations. The responses to an increment in time were added to previous values of P, N, and S until 100% reaction.

The molecular modeling calculations were performed on a Silicon Graphics O2 workstation using the SPARTAN 5.0.3 program.[31] The geometries were evaluated with full optimization employing the semiempirical PM3 Hamiltonian or molecular mechanics MMFF force field. The conformational search was performed employing the systematic Monte Carlo method. Transition states were localized, and vibrational frequencies were calculated for transition states verifying the existence of a single imaginary frequency for the proper reaction coordinate. Default convergence criteria for SCF convergence were used, whereas transition structure optimization required several thousand cycles and small steps in each cycle (0.1 au).

General Experimental Procedures. Transaminations were performed at ca. 0.02 mmol (∼10 mg) scale of imine dissolved in THF or THF/CH_3CN (5:2) with a concentration of 0.035 M substrate. A stock solution of benzamidine (0.05 M, in THF) was added, and the solution was stirred at room temperature for 4 h. The solvent was evaporated, and the crude material was purified by chromatography on a chromatotron. Imines **2a**,**b**−**4a**,**b** were simply passed through a short column of neutral Al_2O_3 (attempts to purify on silica gel resulted in hydrolysis). Compounds **1a**,**b** and **6a**,**b**−**8a**,**b** were separated on Al_2O_3 (neutral) with 10% ether/CH_2Cl_2. Due to problems in separation of **5a** and **5b**, no further attempts were made to purify the individual compounds.

Kinetics were run in THF-d_8 for imines **2a**−**4a** and CD_3CN/THF-d_8 (5:2) for imines **1a** and **5a**−**8a**, in a total volume of 0.7 mL, at a concentration of 0.035 M. Solvents were used as received, and runs were made at 303 K. Benzamidine was added as a stock solution in THF-d_8 (0.05 M).

General Procedure for Synthesis of Compounds 1a and 5a−8a. *N*-(9-Thioxanthenyl 10,10-dioxide)methyl Benzoylformyl Imine (1a). Methyl benzoylformate (2.04 mmol, 0.29 mL) was dissolved in dry benzene (15 mL) in a dry round-bottomed flask. Dry benzene was added (20 mL). $BF_3{\cdot}OEt_2$ (2.04 mmol, 0.26 mL) was added, and the solution was stirred at room temperature for 5 min. 9-Aminothioxanthene 10,10-dioxide (2.04 mmol, 500 mg) was added, and the heterogeneous mixture was heated to reflux for 15 min and thereafter allowed to cool to room temperature. Activated molecular sieves (4 Å) were added, and the resulting reaction mixture was heated to reflux for 12 h. The solvent was removed by evaporation in vacuo. The resulting crude solid was dissolved in methylene chloride and filtered to afford a clear solution. The crude material was purified by chromatography (R_f = 0.35, 10% ether/CH_2Cl_2) and recrystallized from heptane/toluene to afford white crystals: yield 75%; mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.16−8.13 (m, 2H), 8.02−7.99 (m, 2H), 7.61−7.52 (m, 7H), 7.47−7.43 (m, 2H), 5.93 (s, 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.33, 165.20, 140.20, 136.67, 133.39, 132.67, 132.62, 129.24, 128.22, 128.20, 126.70, 124.14, 60.98, 52.78; HRMS (FAB+) calcd for $C_{22}H_{18}NO_4S$ (M + 1) 392.0957, found 392.0962; FT-IR (KBr pellet cm^{-1}) 1740, 1637, 1298, 1164.

***N*-(2-Methylbenzoylformyl)-9-thioxanthenyl 10,10-dioxide imine (1b):** mp 155−156 °C; R_f = 0.27 (10% ether/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.25 (ddd, J = 6.98,1.69, 0.67 Hz, 1H), 8.16 (ddd, J = 7.62, 1.69, 0.48 Hz, 1H), 8.06 (ddd, J = 7.41, 1.90, 0.42 Hz, 1H), 7.72−7.62 (m, 6H), 7.51−7.37 (m, 4H), 7.87 (s, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.12, 157.22, 139.94, 139.26, 138.51, 137.78, 133.26, 132.26, 131.00, 130.25, 129.20, 128.62, 128.52, 128.18 (br), 127.56, 125.33 (br), 123.18 (br), 70.10, 53.01; HRMS (FAB+) calcd for $C_{22}H_{18}NO_4S$ (M + 1) 392.0957, found 392.0963; FT-IR (KBr pellet cm^{-1}) 1735, 1603, 1299, 1171.

General Procedure for Synthesis of Imines 2a−4a. *N*-(9-Thioxanthenyl 10,10-dioxide)ethyl Isopropylformylimine (2a). 9-Aminothioxanthene 10,10-dioxide (0.408 mmol, 100 mg) and ethyl 3-methyl-2-oxobutyrate (0.408 mmol, 0.60 μL) were mixed together in a dry round-bottomed flask. Dry toluene was added (3.0 mL). The resulting mixture was lightly heated to dissolve all components in the reaction. The reaction solution was allowed to cool to ambient temperature, whereupon molecular sieves (4 Å, activated) were added. The reaction flask was heated to reflux for 17 h. The molecular sieves were separated and rinsed well with several portions of CH_2Cl_2. The combined organic layers were evaporated in vacuo to afford a yellow oil. The crude material was purified by chromatography (5% ether in CH_2Cl_2, R_f = 0.68) to afford a pale yellow oil, which crystallized upon standing: yield 75%; mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (dd, J = 7.5, 1.5 Hz, 2H), 7.51 (dd, J = 7.50, 1.67 Hz, 2H) 7.50−7.44 (m, 2H), 7.41−7.38 (m, 2H), 5.94 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.12 (sept, J = 6.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ_ 174.06, 164.81, 140.56, 136.57, 132.44, 127.85, 126.02, 123.93, 61.90, 59.61, 35.80, 19.81, 14.19; HRMS (EI+) calcd for $C_{20}H_{21}NO_4S$ (M) 371.1192, found 371.1200; FT-IR (KBr pellet cm^{-1}) 1730, 1662, 1257, 1166.

***N*-(2-Isopropylethylformyl)-9-thioxanthenyl 10,10-dioxide imine (2b):** R_f = 0.64 (10% ether in CH_2Cl_2); mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 8.21−8.19 (m, 1H), 8.02 (ddd, J = 7.5, 1.3, 0.7 Hz, 1H), 7.94 (ddd, J = 8.6, 1.6, 0.4 Hz, 1H), 7.72−7.69 (m, 1H), 7.66−7.63 (m, 2H), 7.61 (dd, J = 7.6, 1.5 Hz, 1H), 7.58 (dd, J = 7.5, 1.5 Hz, 1H), 4.44 (d, J = 7.0 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.43 (octet, J = 6.8 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.58, 157.82, 139.88, 137.86, 133.44, 133.19, 132.21, 131.52, 130.62, 129.94, 129.19, 127.91, 125.11, 122.91, 73.14, 61.51, 33.28, 19.43, 18.56, 14.52; HRMS (FAB+) calcd for $C_{20}H_{22}NO_4S$ (M + 1) 372.1270 found 372.1269; FT-IR (KBr pellet cm^{-1}) 1732, 1635, 1319, 1167.

***N*-(9-Thioxanthenyl 10,10-dioxide)ethyl methylformyl imine (3a):** yield 73%; R_f = 0.60 (10% ether/CH_2Cl_2); mp 45−50 °C; ^{1}H NMR ($CDCl_3$) δ 8.14−8.11 (m, 2H), 7.55−7.50 (m, 6H), 6.19 (s, 1H), 4.48 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.71, 164.96, 139.57, 136.62, 132.74, 128.15, 125.60, 124.27, 62.77, 58.01, 16.22, 14.38; HRMS (FAB+) calcd for $C_{18}H_{18}NO_4S$ (M + 1) 344.0957, found 344.0952; FT-IR (KBr pellet cm^{-1}) 1741, 1632, 1311, 1151.

***N*-(2-Ethylmethylformyl)-9-thioxanthenyl 10,10-dioxide imine (3b):** R_f = 0.57 (10% ether/CH_2Cl_2); mp 52−54 °C; ^{1}H NMR ($CDCl_3$) δ 8.23−8.20 (m, 1H), 8.03 (ddd, J = 7.53, 1.88, 0.43 Hz, 1H), 7.95 (ddd, J = 7.53, 1.88, 0.45 Hz, 1H), 7.75−7.72 (m, 1H), 7.65 (dd, J = 6.58, 0.9 Hz, 1H), 7.59 (dd, J = 6.48, 0.84 Hz, 1H), 7.58−7.56 (m, 2H), 4.91 (q, J = 6.51 Hz, 1H), 4.30 (q, J = 7.11 Hz, 2H), 1.56 (d, J = 6.51 Hz, 3H), 1.34 (t, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.04, 157.02, 133.31,

(31) Hehre, W. J.; Burke, L. D.; Shusterman A. J.; Pietro, W. J. SPARTAN, version 5.0.3; Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA, 92715.

132.35, 130.77, 130.02, 128.71, 127.76, 125.21, 123.07, 61.79, 61.46, 20.00, 14.42; HRMS (FAB+) calcd for $C_{18}H_{18}NO_4S$ (M + 1) 344.0957, found 344.0943; FT-IR (KBr pellet cm^{-1}) 1745, 1641, 1315, 1160.

***N*-(9-Thioxanthenyl 10,10-dioxide)dimethylglutarate-2-imine (4a):** yield 86%; mp 58−60 °C; R_f = 0.21 (10% eter/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, J = 7.5, 1.7 Hz, 2H), 7.58−7.46 (m, 4H), 7.32 (d, J = 7.7 Hz, 2H), 6.15 (s, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.20 (t, J = 6.6 Hz, 2H), 2.90 (t, J = 6.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.31, 166.22, 163.91, 140.37, 136.52, 132.52, 127.98, 126.19, 124.07, 59.97, 52.80, 52.04, 31.86, 29.25; HRMS (FAB+) calcd for $C_{20}H_{20}NO_6S$ (M + 1) 402.1012 found 402.1021; FT-IR (KBr pellet cm^{-1}) 1748, 1736, 1650, 1299, 1162.

***N*-(2-Dimethylglutarate)-9-thioxanthenyl 10,10-dioxide imine (4b):** mp 61−63 °C; R_f = 0.10 (10% ether/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.18−8.15 (m, 1H), 7.98 (dd, J = 7.3, 2.2 Hz, 1H), 7.90 (dd, J = 7.5, 1.8 Hz, 1H), 7.85−7.83 (m, 1H), 7.73−7.69 (m, 2H), 7.66−7.60 (m, 2H), 4.99−4.96 (m, 1H), 3.79 (s, 3H), 3.44 (s, 3H), 2.31−2.07 (m, 4H); ^{13}C NMR (THF-d_8) δ 173.42, 171.65, 159.46, 141.40, 140.65, 139.73, 133.64, 133.08, 132.49, 131.64, 130.84, 129.73, 128.45, 125.50, 123.39, 65.54, 52.623, 51.34, 30.28, 29.95; HRMS (FAB+) calcd for $C_{20}H_{20}NO_6S$ (M + 1) 402.1012, found 402.1018; FT-IR (KBr pellet cm^{-1}) 1752, 1739, 1661, 1305, 1181.

***N*-(9-Thioxanthenyl 10,10-dioxide)ethyl(*p*-nitrobenzoyl)formylimine (5a):** yield 79%; R_f = 0.26 (30% eter/CH_2Cl_2); yield 69%; ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 8.09 (dd, J = 7.50, 1.0 Hz, 1H), 8.03 (dd, J = 7.50, 1.1 Hz, 1H), 7.77 (d, J = 8.9 Hz, 2H), 7.72−7.64 (m, 4H), 7.56−7.54 (m, 2H), 5.92 (s, 1H), 4.27 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.41, 158.58, 147.92, 145.21, 139.94, 139.04, 137.76, 133.35, 132.47, 131.31, 130.89, 130.52, 128.77, 128.30, 127.98, 125.46, 124.08, 123.10, 69.39, 62.61, 32.01, 22.82, 14.17; HRMS (FAB+) calcd for $C_{23}H_{19}N_2O_6S$ (M + 1) 451.0965, found 451.0959; FT-IR (KBr pellet cm^{-1}) 1732, 1620, 1521, 1348, 1313, 1165.

***N*-(Methyl(*p*-fluorobenzoyl)formyl)-9-thioxanthenyl 10,-10-dioxide imine (5b)** could not be separated from **5a** and was characterized in the mixture.

***N*-(9-Thioxanthenyl 10,10-dioxide)methyl(*p*-fluorobenzoyl)formylimine (6a):** yield 76%; R_f = 0.22 (10% ether/CH_2Cl_2); yield 65%; mp 156−158 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, J = 7.38, 1.9 Hz, 1H), 8.10 (dd, J = 7.61, 1.7 Hz, 1H), 8.05 (dd, J = 7.60, 1.8 Hz, 1H), 7.68 (tdd, J = 6.73, 2.59, 1.4 Hz, 2H), 7.62−7.52 (m, 4H), 7.48 (dd, J = 7.25, 1.8 Hz, 1H), 7.24 (m, 2H), 5.92 (s, 1H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.12, 163,72, 140.03, 136.66, 132.67, 130.52, 130.42, 128.26, 126.65, 124.17, 116.55, 116.33, 61.05, 52.89; HRMS (FAB+) calcd for $C_{22}H_{17}FNO_4S$ (M + 1) 410.0863, found 410.0869; FT-IR (KBr pellet cm^{-1}) 1781, 1655, 1328, 1148.

***N*-(Methyl-(*p*-fluorobenzoyl)formyl)-9-thioxanthenyl-10,10-dioxide imine (6b):** R_f = 0.12 (10% ether/CH_2Cl_2); mp 154−155 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, J = 7.77, 1.4 Hz 1H), 8.11 (dd, J = 7.52, 1.0 Hz, 1H), 8.05 (dd, J = 7.52, 1.0 Hz, 1H), 7.68 (tdd, J = 7.58, 2.81, 1.4 Hz, 2H), 7.69−7.61 (m, 2H), 7.59−7.55 (m, 2H), 7.48 (dd, J = 7.58, 0.9 Hz, 1H), 7.12−7.06 (m, 2H), 5.82 (s, 1H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.00, 164.06, 161.60, 157.52, 139.98, 139.22, 137.80, 134.20, 134.17, 133.31, 132.33, 131.12, 131.02, 130.36, 129.39, 129.31, 128.44, 128.05, 125.38, 123.10, 116.21, 116.00, 69.31, 53.15; HRMS (FAB+) calcd for $C_{22}H_{17}FNO_4S$ (M + 1) 410.0863, found 410.0886; FT-IR (KBr pellet cm^{-1}) 1763, 1650, 1310, 1123.

***N*-(9-Thioxanthenyl 10,10-dioxide)methyl(*p*-methylbenzoyl)formylimine (7a):** yield 64%; R_f = 0.28 (10% ether/CH_2Cl_2); yield 60%; mp 165−167 °C; R_f = 0.2 (10% ether in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, J = 7.0, 2.57 Hz, 2H), 7.88 (dd, J = 7.0, 0.2 Hz, 2H), 7.54−7.51 (m, 4H), 7.47−7.44 (m, 2H), 7.35 (d, J = 7.9 Hz, 2H), 5.91 (s, 1H), 3.88 (s, 3H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.48, 165.15, 143.36, 140.37, 136.61, 132.65, 130.74, 129.94, 128.21, 128.14, 126.72, 124.08, 60.82, 52.72, 21.84; HRMS (FAB+) calcd for $C_{23}H_{20}NO_4S$ (M + 1) 406.1114, found 406.1111; FT-IR (KBr pellet cm^{-1}) 1726, 1541, 1309, 1161.

***N*-(Methyl(*p*-methylbenzoyl)formyl)-9-thioxanthenyl 10,10-dioxide imine (7b):** R_f = 0.15 (10% ether/CH_2Cl_2); mp 162−164 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, J = 7.32, 1.52 Hz, 1H), 8.13 (dd, J = 7.40, 1.54 Hz, 1H), 8.04 (dd, J = 7.40, 1.52 Hz, 1H), 7.67 (tdd, J = 7.28, 2.14, 1.56 Hz, 2H), 7.60 (tdd, J = 7.60, 2.14, 1.44 Hz, 2H), 7.49 (d, J = 8.36 Hz, 2H), 7.46 (dd, J = 6.85, 0.58 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 5.79 (s, 1H), 3.73 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.35, 156.99, 139.97, 139.33, 138.50, 137.79, 135.66, 133.29, 132.24, 131.07, 130.99, 130.24, 129.96, 128.61, 128.16, 127.45, 125.30, 123.07, 69.94, 53.03, 21.42; HRMS (FAB+) calcd for $C_{23}H_{20}NO_4S$ (M + 1) 406.1114, found 406.1107; FT-IR (KBr pellet cm^{-1}) 1731, 1539, 1321, 1154.

***N*-(9-Thioxanthenyl 10,10-dioxide)methyl(*p*-methoxybenzoyl)formyl imine (8a):** Yield 59%; R_f = 0.29 (20% ether/CH_2Cl_2); yield 58%; mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 7.25, 2.1 Hz, 2H), 7.95 (d, J = 8.90 Hz, 2H), 7.54−7.51 (m, 4H), 7.47−7.46 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 5.88 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.61, 164.49, 163.23, 140.54, 136.59, 132.65, 130.04, 128.11, 126.75, 126.04, 124.06, 114.61, 60.73, 55.78, 52.70; HRMS (FAB+) calcd for $C_{23}H_{20}NO_5S$ (M + 1) 422.1063, found 422.1058; FT-IR (KBr pellet cm^{-1}) 1755, 1683, 1312, 1166.

***N*-(Methyl(*p*-methoxybenzoyl)formyl)-9-thioxanthenyl 10,10-dioxide imine (8b):** R_f = 0.18 (20% ether/CH_2Cl_2); mp 166−167 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, J = 7.87, 1.43 Hz, 1H), 8.12 (dd, J = 7.63, 1.43 Hz, 1H), 8.04 (dd, J = 7.64, 1.40 Hz, 1H), 7.67 (tdd, J = 8.20, 1.64, 0.90 Hz, 2H), 7.61 (tdd, J = 7.50, 1.65, 1.20 Hz, 2H), 7.52 (d, J = 8.40 Hz, 2H), 7.47 (dd, J = 8.21, 0.90 Hz, 1H), 6.95 (d, J = 8.40 Hz, 2H), 5.78 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.46, 159.83, 156.92, 139.98, 139.35, 137.80, 133.30, 132.26, 131.11, 131.00, 130.71, 130.25, 128.74, 128.61, 128.15, 125.32, 123.09, 114.66, 69.56, 55.55, 53.03; HRMS (FAB+) calcd for $C_{23}H_{20}NO_5S$ (M + 1) 422.1063, found 422.1066; FT-IR (KBr pellet cm^{-1}) 1723, 1627, 1302, 1138.

(+)-2-Phenyl-(3a*r*,7a*f*)-3a,4,5,6,7a-hexahydro-1*H*-benzimidazole (11): yield 86%; mp 152−153 °C; $[\alpha]^{21}_D$ = 191 (c = 3.98, pyridine); ^{1}H NMR ($CDCl_3$) δ 7.76−7.73 (m, 2H), 7.35−7.25 (m, 3H), 5.32 (s, 1H), 3.09 (m, 2H), 2.31 (m, 2H), 1.82 (m, 2H), 1.54 (m, 2H), 1.38 (m, 2H).

(3*R*,7*R*)-3,7-Diphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (12): yield 33%; mp 155−157 °C; $[\alpha]^{21}_D$ = 20.1 (c = 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 4H), 7.30 (m, 4H), 7.21 (m, 2H), 5.15 (t, J = 6.3 Hz, 2H), 3.48 (t, J = 7.5 Hz, 2H), 3.00 (dd, J = 6.1 Hz, J = 7.6 Hz, 2H).

9-Thioxanthonoxime 10,10-dioxide (15): R_f = 0.36 (10% ether in CH_2Cl_2); yield 85%; ^{1}H NMR (DMSO-d_6) δ 8.47 (dd, J = 7.8, 1.01 Hz, 1H), 8.11 (dd, J = 6.5, 1.3 Hz, 1H), 8.05 (dd, J = 7.03, 1.29 Hz, 1H), 7.91 (dd, J = 7.17, 1.12 Hz, 1H), 7.75 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 142.91, 137.48, 136.63, 135.02, 134.34, 133.63, 131.81, 131.56, 130.72, 129.01, 127.68, 123.98, 123.57.

9-Thioxanthon oxime *O*-acetate 10,10-dioxide (16): yield quantitative. R_f = 0.58 (10% ether in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.22 (m, 2H), 8.12 (m, 1H), 8.05 (m, 1H), 7.70 (m, 4H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.94, 150.16, 138.56, 137.60, 133.40, 133.12, 132.51, 131.63, 131.16, 131.07, 128.54, 128.10, 124.52, 123.89, 19.90.

9-Aminothioxanthene 10,10-dioxide (17): yield 62%; mp 165−168 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, J = 7.69, 1.34 Hz, 2H), 7.75 (d, J = 7.71 Hz, 2H), 7.59 (m, 2H), 7.50 (td, 2H), 5.29 (s, 1H), 2.13 (s, 2H, $-NH_2$); ^{13}C NMR ($CDCl_3$) δ 143.44, 137.73, 133.28, 128.28, 127.14, 124.48, 52.70; FT-IR (KBr pellet cm^{-1}) 3409, 3327, 1278, 1139.

2-Nitro-*N*,*N*-diethylbenzamide (18): yield 83%; ^{1}H NMR ($CDCl_3$) δ 8.19 (dd, J = 8.3, 1.2 Hz, 1H), 7.71 (m, 1H), 7.57 (m, 1H), 7.40 (dd, J = 7.6, 1.1 Hz, 1H), 3.60 (br s, 2H), 3.13 (q, J = 7.14 Hz, 2H), 1.30 (t, J = 7.13 Hz, 3H), 1.07 (t, J = 7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.07, 144.85, 134.30, 133.51, 129.45, 127.88, 124.64, 42.64, 38.82, 13.47, 11.88.

2-Amino-*N*,*N*-diethylbenzamide (19): yield quantitative; ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 1H), 7.06 (dd, J = 8.0, 1.5 Hz, 1H), 6.71 (m, 2H), 4.13 (s, 2H, $-NH_2$), 3.42 (br. s, 4H), 1.23

(m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.56, 144.68, 129.99, 126.79, 121.57, 117.46, 116.48, 68.86, 46.31, 24.13, 23.30.

2-(*N*,*N*-Dimethylamino)-*N*,*N*-diethylbenzamide (20). To a solution of 2-amino-*N*,*N*-diethylbenzamide (0.032 mol, 6.09 g) in dry THF (50 mL) was added NaH (0.080 mol, 3.2 g, 60% dispersion in mineral oil). MeI (0.080 mol, 4.98 mL) was added, and the reaction mixture was refluxed for 17 h. The reaction mixture was then allowed to cool to room temperature and thereafter carefully poured into a saturated NH_4Cl solution (ca. 150 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to afford a brown oil. The raw material was purified by vacuum distillation and retrieved as a pale yellow oil: yield quantitative; $n^{21}_D = 1.5394$; bp 110 °C (0.05 mbar); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 1H), 7.18 (m, 1H), 6.93 (m, 2H), 3.80 (m, 1H), 3.33 (m, 1H), 3.20 (m, 1H), 3.09 (m, 1H), 2.80 (s, 6H), 1.24 (t, J = 7.13 Hz, 3H), 1.10 (t, J = 7.13 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.75, 149.70, 130.17, 129.88, 128.81, 121.08, 117.37, 43.92, 43.09, 39.16, 14.12, 12.98. HRMS (FAB+) calcd for $C_{13}H_{21}N_2O$ (M + 1) 221.1655, found 221.1652; FT-IR (NaCl tablet cm^{-1}) 1621, 1456, 1287.

2-(*N*,*N*-Dimethylamino)-6-(phenylsulfonyl)-*N*,*N*-diethylbenzamide (21). Dry and distilled TMEDA (21.78 mmol, 3.13 mL) was dissolved in dry THF (140 mL), and the mixture was cooled to −78 °C. *s*-BuLi (21.78 mmol, 1.2 M, 18.15 mL) was added, and the solution was stirred for 10 min. 2-(*N*,*N*-Dimethylamino)-*N*,*N*-diethylbenzamide (18.15 mmol, 4.0 g, 4.16 mL) dissolved in dry THF (40 mL) was added droppwise. After completion of addition, the reaction mixture was stirred for 30 min at −78 °C. Benzenesulfonyl fluoride (24.94 mmol, 3.0 mL) dissolved in dry THF (40 mL) was added droppwise to the lithiated diethyl amide. After completion of addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h, after which time it was quenched with saturated NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude product was purified via flash chromatography R_f = 0.36 (10% ether in CH_2Cl_2) and retrieved as a viscous greenish liquid: yield 92%; $n^{21}_D = 1.5760$; ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.74 (dd, J = 8.0, 1.07 Hz, 1H), 7.47 (m, 3H), 7.39 (t, J = 8.02 Hz, 1H), 7.21 (dd, J = 8.0, 1.0 Hz, 1H), 3.69 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.73 (s, 6H), 1.32 (t, J = 7.15 Hz, 3H), 1.10 (t, J = 7.18 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.41, 151.83, 142.28, 139.61, 133.43, 132.03, 129.83, 129.17, 128.85, 124.59, 123.93, 44.88, 43.61, 39.37, 13.41, 12.73; HRMS (FAB+) calcd for $C_{19}H_{25}N_2O_3S$ (M + 1) 361.1588 found 361.1597; FT-IR (NaCl tablet cm^{-1}) 1625, 1323, 1163, 1451, 1278.

1-(*N*,*N*-Dimethylamino)thioxanthen-9-one 10,10-Dioxide (22). To a cooled solution (0 °C) of LDA, prepared in situ from diisopropylamine (46 mmol, 6.46 mL, dry and distilled) and BuLi (33.29 mmol) in 140 mL of dry THF, was added dropwise a solution of 2-(*N*,*N*-dimethylamino)-6-(phenylsulfonyl)-*N*,*N*-diethylbenzamide (16.64 mmol, 6.0 g) in 100 mL of dry THF. After completion of the addition, the reaction mixture was stirred at 0 °C for 30 min. The reaction was thereafter quenched with saturated NH_4Cl (150 mL), and the organic phase was separated. The aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were washed with saturated NaCl (100 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification was made by passing the raw material through a silica column using $CHCl_3$ as eluent: R_f = 0.48 (10% ether in CH_2Cl_2); yield 84%; mp 170−172 °C; ^{1}H NMR (CD_2Cl_2) δ 8.14 (m, 1H), 8.06 (m, 1H), 7.77 (m, 2H), 7.58 (m, 1H), 7.51 (dd, J = 7.5, 1.2 Hz, 1H), 7.20 (dd, J = 9.00, 1.16 Hz, 1H), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.82, 153.90, 143.32, 139.10, 134.37, 133.65, 133.58, 133.28, 129.03, 123.26, 121.65, 116.92, 113.55, 44.67; HRMS (EI+) calcd for $C_{15}H_{13}NO_3S$ (M) 287.0613, found 287.0614; FT-IR (KBr pellet cm^{-1}) 1643, 1296, 1268, 1154.

1-(*N*,*N*-Dimethylamino)thioxanthen-9-imine 10,10-Dioxide (23). To a solution of 1-(*N*,*N*-dimethylamino)thioxanthen-9-one 10,10-dioxide (1.19 g, 4.14 mmol) in dry CH_2Cl_2 (140 mL), cooled on an ice bath, was added $TiCl_4$ (0.897 mL, 8.28 mmol, 2.0 equiv). The mixture was stirred at room temperature for 10 min, before the dark purple heterogeneous mixture was bubbled through with gaseous NH_3 for 45 min, after which time CH_2Cl_2 (25 mL) was added. The mixture was filtered and evaporated to dryness. The raw material was purified on a chromatotron (R_f = 0.27, 10% ether/CH_2Cl_2). Approximately 30% of the raw material was isolated as the starting ketone: yield 71%; mp 150−152 °C deg; ^{1}H NMR ($CDCl_3$) δ 11.78 (br s, 1H, =NH), 8.15 (br. d, J = 6.7 Hz, 1H), 8.10 (m, 1H), 7.77 (dd, J = 7.7, 1.0 Hz, 1H), 7.70 (m, 2H), 7.53 (t, J = 7.76 Hz, 1H), 7.32 (dd, J = 7.0, 1.0 Hz, 1H), 2.78 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 162.84, 152.20, 139.54, 137.40, 136.66, 133.17, 131.46, 130.84, 127.49, 123.04, 122.91, 122.84, 116.37, 43.70; HRMS (FAB+) calcd for $C_{15}H_{15}N_2O_2S$ (M + 1) 287.0855, found 287.0852; FT-IR (KBr pellet cm^{-1}) 3224, 1602, 1296, 1163.

1-(*N*,*N*-Dimethylamino)thioxanthen-9-amine 10,10-Dioxide (24). $NaBH_4$ (7.17 mmol, 277 mg, 4 equiv) was dissolved in MeOH (7 mL). 1-(*N*,*N*-Dimethylamino)thioxanthen-9-imine 10,10-dioxide (1.79 mmol, 513 mg, 1 equiv) dissolved in CH_2Cl_2 (7 mL) was added to the $NaBH_4$/MeOH solution. The reaction mixture was stirred at room temperature for 17 h. The solvent was evaporated in vacuo, the residue was dissolved in CH_2Cl_2, and the inorganic remains were filtered off. The solvent was removed, and the crude product was purified on a chromatotron: R_f = 0.12 (10% ether in CH_2Cl_2); yield 50%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 7.82 Hz, 1H), 7.80 (dd, J = 7.96, 1.1 Hz, 1H), 7.55 (m, 2H), 7.46 (m, 2H), 7.35 (dd, J = 8.0, 1.2 Hz, 1H), 5.52 (s, 1H, 9-H), 2.89 (s, 6H), 2.27 (br. s, 2H, $-NH_2$); ^{13}C NMR ($CDCl_3$) δ 153.13, 143.84, 139.27, 137.61, 136.10, 133.06, 128.71, 128.62, 127.88, 124.50, 124.17, 118.88, 48.55, 45.67; HRMS (FAB+) calcd for $C_{15}H_{17}N_2O_2S$ (M + 1) 289.1012, found 289.1024; FT-IR (KBr pellet cm^{-1}) 3388, 3352, 1287, 1154.

***N*-(9-(1-*N*,*N*-Dimethylamino)thioxanthene 10,10-dioxide)crotylimine (25).** To a solution of 1-(*N*,*N*-dimethylamino)thioxanthen-9-amine 10,10-dioxide (0.163 mmol, 47 mg) in dry CH_2Cl_2 (2 mL) was added crotonaldehyde (0.163 mmol, 13.4 μL). Dried $MgSO_4$ (500 mg) was added, and the mixture was stirred at room temperature for 14 h. The drying agent was filtered off and the solvent evaporated in vacuo. The semisolid residue was purified by chromatography (R_f = 0.54, 20% ether in CH_2Cl_2). The pure product was retrieved as pale yellow crystals: yield 81%; mp 181−183 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, J = 7.4, 0.8 Hz, 1H), 7.89 (dd, J = 7.3, 1.4 Hz, 1H), 7.75 (dd, J = 8.0, 1.4 Hz, 1H), 7.58−7.47 (m, 4H), 7.42 (dd, J = 8.1, 1.3 Hz, 1H), 6.30 (s, 1H), 6.27−6.09 (m, 2H), 2.76 (s, 6H), 1.80 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.63, 153.97, 142.23, 139.70, 139.09, 138.28, 133.61, 132.94, 132.35, 130.43, 129.50, 128.74, 125.42, 124.59, 120.09, 62.94, 46.09, 18.62. HRMS (FAB+) calcd for $C_{19}H_{21}N_2O_2S$ (M + 1) 341.1325, found 341.1320; FT-IR (KBr pellet cm^{-1}) 1684, 1310, 1158.

Methyl *p*-fluorophenylpyruvate (26): yield 67%; ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, J = 9.1, 5.3 Hz, 2H), 7.19 (dd, J = 8.0, 6.1 Hz, 2H), 3.97 (s, 3H).

Methyl *p*-toluylpyruvate (27): yield 72%; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 9.2 Hz, 2H), 3.97 (s, 3H), 2.44 (s, 3H).

Methyl *p*-methoxyphenylpyruvate (28): yield 75%; ^{1}H NMR ($CDCl_3$) δ 8.04−7.99 (m, 2H), 7.00−6.95 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for new compounds and Figure S1 showing component evolution in the isotope effect experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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