

NMR Spectroscopic Investigations in Diverse Light-Driven Systems

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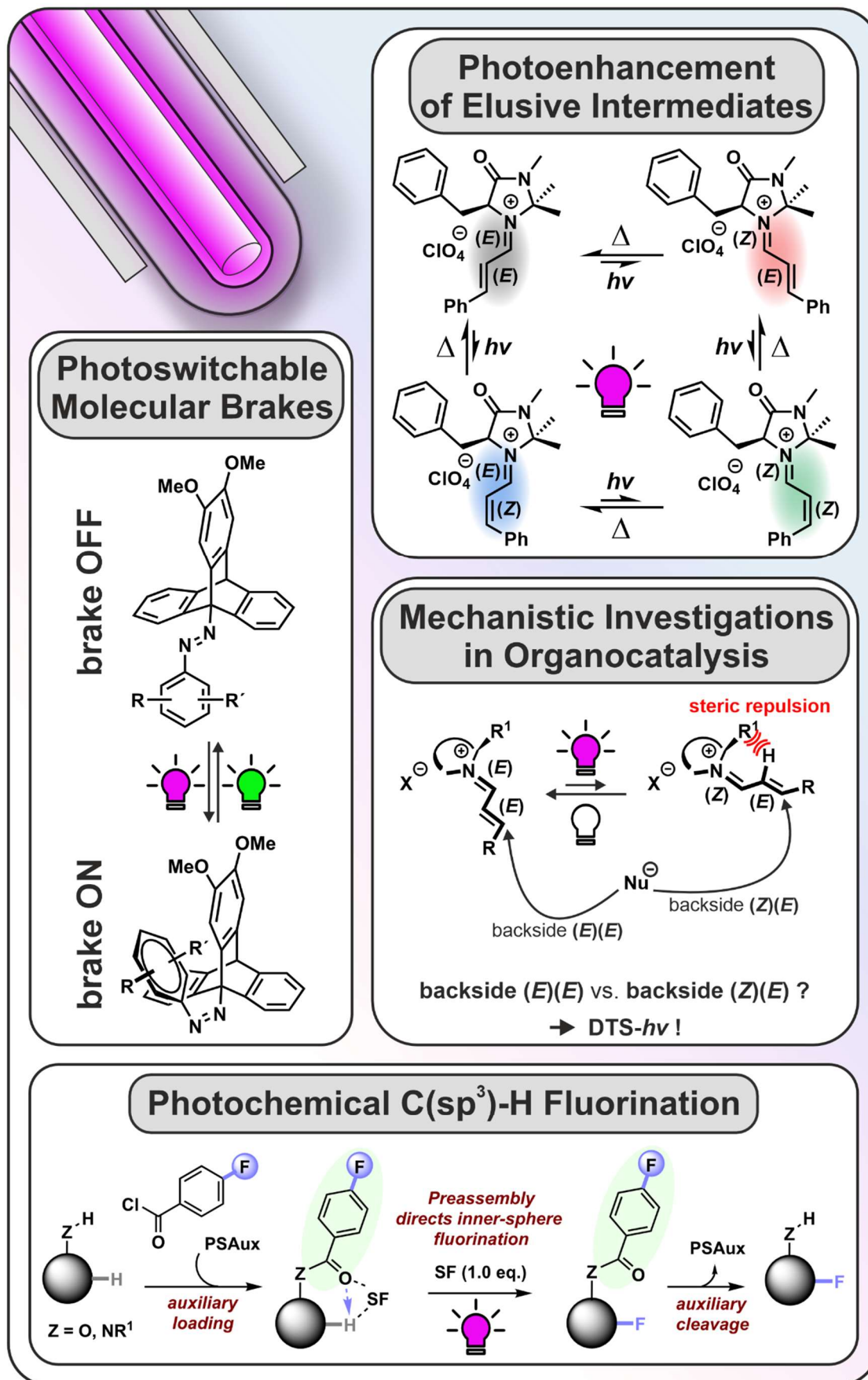
It ain't much, but it's honest work.

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1. Introduction and Outline



1.1 *In Situ* Illumination NMR Spectroscopy as Powerful Tool in Photochemistry

Sustainability is becoming increasingly important worldwide. Albeit often unconscious, chemistry is an indispensable part of everyday life and is accordingly constantly changing towards more sustainability. Therefore, photochemistry with light as inexpensive, non-contaminating, non-hazardous, renewable and so overall environmentally friendly energy source developed as one major research field and has experienced a nearly exponential growth within the last decades.¹ Uncountable photochemical and photocatalytic applications have been reported, however structural and mechanistic investigations are in comparison relatively sparse. This is unfortunate, since every research chemist depends on such investigations for an understanding of the processes taking place. Only in this way an evidence-driven e.g. optimization of existing synthetic strategies towards increasing yields and substrate scopes or development of completely new light-driven systems is possible. Several analytical methods can be used for the mechanistic investigation of photochemical processes. UV/Vis spectroscopy² and EPR spectroscopy³ are frequently applied spectroscopic tools due to their high time resolution and sensitivity. Using UV/Vis spectroscopy, information about a single chromophore and its excited state,^{2c,4} but also energy transfers to other species⁵ or the formation of intermediates or reactive complexes as electron donor acceptor (EDA) complexes⁶ can be received. EPR spectroscopy provides information about the structures of radicals and radical pathways.⁷ These methods enable the detection of very short-lived species directly after the photoexcitation event and for a long time it was thought that decrypting the photoexcitation event is the key to understand the complete photochemical reaction. That has changed when our research group underlined in a first example the importance of the subsequent downstream pathways in photocatalysis.⁸ Here, NMR spectroscopic investigations revealed several significantly deviating mechanistic pathways after photoexcitation, which were inaccessible *via* time resolved UV/Vis spectroscopy. Since then, NMR spectroscopy rose to an integral part of the elucidation of photochemical processes.^{8,9} There are several reasons why NMR spectroscopy is so well suited for the analysis of such downstream pathways, despite its inevitable lower time resolution and sensitivity. It is the only spectroscopic method that provides direct information about the atomic connectivity of molecules within ongoing reactions.¹⁰ The only comparable method is the X-ray crystallography. Here, the real molecular structure can also be assessed, however since crystals are required for the analysis an online reaction monitoring is not possible. Furthermore, NMR spectra can easily be recorded in a quantitative manner, which allows a simultaneous acquisition of the concentrations of all detectable intermediates, products and side-products.¹¹

However, traditional NMR spectroscopy is only suitable for photochemical applications, when illumination of the sample outside the spectrometer (*ex situ*) is sufficient. In the case, that illumination of the sample inside the NMR spectrometer (*in situ*) is mandatory, special illumination setups have to be used. Therefore, numerous *in situ* illumination setups have been developed within the past decades.¹² Although all setups have in common to consist of a light source and a light guiding system, most diverse designs have been developed and the advantages and disadvantages of the different concepts are recapitulated in the following. In particular, two illumination sources have prevailed for *in situ* illumination NMR spectroscopy, namely light amplification by stimulated emission of radiation (LASERs) and light emitting diodes (LEDs), which symbolize the two extreme cases in terms of light intensity, costs and applicability. For a long time LASERs were the most applied illumination source for NMR spectroscopy¹³ since they emit a monochromatic light beam with high intensity.¹⁴ This monochromatic emission is of great usefulness in the case of selective excitation is required within a mixture of photoactive species with very close absorption bands. The high light intensity is often beneficial for kinetics of photochemical reactions, because their reaction rate responses in general proportional to the light intensity.¹⁵ The same relates for NMR spectroscopic experiments like chemical induced dynamic nuclear polarization transfer (photo-CIDNP), a method for the indirect detection of radical species.¹⁶ Here, more pronounced photo-CIDNP effects are obtained after irradiation with high intense light. Disadvantages of LASERs as illumination sources are the high acquisition costs, which can accumulate to a major issue if several excitation wavelengths are necessary. In addition, in case structural or quantitative investigations under prolonged illumination are required this high light intensity can result in drastic photodegradation of the sample.¹⁷ For these purposes, LEDs are the preferred illumination source. In accordance with Haitz' law, more and more powerful LEDs have been developed within the last few decades at ever decreasing costs and meanwhile LEDs for all sorts of wavelengths between UV-C and near IR are purchasable.¹⁸ Especially due to the low costs and the easy applicability LEDs meanwhile evolved into the most applied light source in synthetic photochemistry laboratories and therefore also for related mechanistic investigations to mimic synthetic conditions as good as possible.^{8,9,19} LEDs do not generate a monochromatic light beam, but a light cone with an average emission bandwidth of 25 nm. These optical characteristics can however be improved if necessary. Lenses can achieve focusing of the light cone and if a narrower bandwidth is required, low- and/or high-pass filters can be applied; both however at the cost of a reduced light intensity. If synthetic or mechanistic results have to exactly be reproduced, one must consider to use always the

same LED, because LEDs, even from the same manufacturer-batch, can deviate in terms of peak wavelength and light output power (± 5 nm, $\pm 20\%$).¹²

To guide the light from the light source to the NMR sample, three different principles are distinguished: from the bottom/side, from the top or from the inside. Illumination from the bottom/side was used for one of the first photo-CIDNP experiments.²⁰ Here the light source is positioned inside the NMR probe or underneath. It has the big advantage that all sorts of NMR tubes can be applied. Therefore, e.g. air and/or moisture sensitive samples can be prepared as for traditional NMR measurements. Spinning can be used to increase field homogeneity and in case illumination occurs only from one side also illumination homogeneity can be improved. However, the major drawback is that modified NMR probes have to be applied for this illumination principle. Either holes have to be drilled or even important individual components as radio frequency (rf) or gradient coils have to be removed.²¹ Therefore, often only simple or old NMR probes are employed here, which impedes the user to take advantage of the full power of NMR spectroscopy. In the case that only simple NMR experiments are required but reproducible illumination is imperative, for example quantitative 1D-kinetics, this principle can however be advantageous. Illumination from the top is executed similar as from the bottom, but without the need to modify the NMR probe. Instead more complicated light guiding systems consisting of mirrors, prisms and lenses²² or customized NMR tubes²³ have to be applied, which can complicate to set up the illumination experiments. In case illumination solely occurs from the bottom or the top a uniform illumination is not possible, which can be problematic if optical dense samples have to be investigated. In such a case, illumination from the inside is the most suitable illumination principle. This is in general achieved using optical fibers as light guide. In the first reported setups the raw end of the fiber was placed directly above²⁴ or in the middle region of the rf coils²⁵ yielding non-uniform illumination as from the top or the bottom. State-of-the-art is however to use a coaxial glass insert to shield the optical fiber from the solution and to position and additionally roughen the fiber along the whole range of the rf coils.²⁶ Therefore, this illumination principle really yields uniform illumination. Due to the insert the active volume within the rf coil region is reduced. This can be advantageous in case of optical dense solutions have to be investigated^{13g} but disadvantageous for low concentrated samples. Sample spinning is not possible. Nevertheless, illumination from the inside using optical fibers is the most flexible light guiding principle. LASER and LED light can be similarly coupled into the fiber without further optical components and if a different excitation wavelength is required, the light source can be changed within seconds. Standard NMR samples can be prepared as for routine NMR spectroscopy, air and/or moisture sensitive samples are more challenging but are also possible.

1.2 Outline

In this thesis, the omnipresence of light-driven systems in organochemistry and likewise the importance of comprehensive mechanistic investigations for an understanding of the underlying processes is shown. Detailed insights into most diverse topics ranging from the identification of so far elusive intermediates and the search for the origin of enantioselectivity in asymmetric iminium ion catalysis to the development and investigations of photoswitchable molecular brakes and new photochemical C(sp³)-H fluorination strategies are presented; achieved especially by applying *in situ* illumination NMR spectroscopy. For all systems, the same *in situ* illumination setup with an LED as light source and an optical fiber as light guide was employed, which underpins the extraordinary versatility of this illumination principle. In very special cases also *ex situ* illumination was used. In a temperature range from room temperature down to -143 °C several 1D and 2D homo- and multinuclear NMR experiments were performed to identify the corresponding photo-induced intermediates and reaction pathways. These investigations were corroborated by quantitative kinetic studies of the underlying transformations. For selected examples, additionally the influence of intermolecular aggregation on these processes was evaluated using diffusion ordered spectroscopy (DOSY). In summary, this work highlights by the example of photochemistry the importance of profound mechanistic investigations and shows how especially applying *in situ* illumination NMR spectroscopy sheds light on the reactions proceeding in diverse photochemical applications.

In chapter two, the structural space of the key intermediates in asymmetric iminium ion catalysis was explored. So far, the stereoselectivity of this organocatalytic transformation strategy is accounted to an interplay of populations and kinetics of two α,β -unsaturated iminium ion isomers which differ in the configuration of the iminium double bond, called (*E,E*) and (*Z,E*). However, these iminium ions possess also a second double bond. Thus, also iminium ion intermediates differing in the configuration of this C=C double bonds are feasible, called (*E,Z*) and (*Z,Z*). As reflected in the Curtin-Hammett principle, major intermediates not necessarily yield the major product stereoisomer, *i.e.* a reaction pathway proceeding over lower populated iminium ion isomers can be dominant. Therefore, the question arose whether the so far undetected (*Z*)-C=C double bond iminium ion isomers (*E,Z*) and (*Z,Z*) are also present under synthetic conditions and thus may affect the reaction mechanism in iminium ion catalysis. To mimic synthetic conditions during the NMR spectroscopic investigations as good as possible a model iminium ion containing MacMillan's 1st generation catalyst was applied, which is a frequently applied iminium ion catalyst motif. Using this model substrate, the influence of UV-illumination on the configurational space of this iminium ion was investigated *via* a

low temperature *in situ* illumination NMR spectroscopy approach, since photoillumination is a well-established method to trigger isomerization of double bonds. In doing so the so far elusive (*E,Z*) and (*Z,Z*) isomers for this iminium ion intermediate could be observed and explicitly assigned. Measuring high sensitivity NMR spectra and exploiting the selective response of these low populated iminium ion intermediates to UV-illumination, even traces of the high energetic (*E,Z*) under general synthetic conditions were identified, *i.e.* without illumination and at room temperature. Furthermore, analyzing thermal back isomerization processes *via* quantitative NMR spectroscopy enabled monitoring the stabilities of the (*Z*)-configured isomers. As a consequence, conditions were found to stabilize the high energetic (*Z*)-C=C double bond iminium ion isomers (*E,Z*) and (*Z,Z*) for several hours *via* ion pair aggregation, which was disclosed by DOSY.

Chapter three furthermore deals with investigations on asymmetric iminium ion catalysis. Based on the findings from chapter two, it was aimed at clarifying the influence of the iminium ion C=N double bond configuration on the stereoselectivity of iminium ion catalyzed β -functionalization reactions. So far, especially computational chemistry proposes that a parallel influence of (*E,E*)/(*Z,E*) ratio and a faster reaction rate of the (*E,E*) isomer accounts for the received stereoselective reaction outcome. To corroborate these theoretical results experimentally a mechanistic tool called DTS-*h* ν (decrypting transition states by light) was applied, which was developed in this research group. This experimental approach utilizes the capacity of double bonds to isomerize upon photoillumination. Therefore, the same addition reaction can be performed with different (*E,E*)/(*Z,E*) ratios. Analyzing the associated enantiomeric ratios and/or reaction rates provides then an insight whether the configuration of the suspected double bonds plays a significant role for stereoselectivity and/or reactivity or not. With intent to develop an optimum DTS-*h* ν model system for asymmetric iminium ion catalysis, these investigations were started with searching for the ideal model iminium ion. Herein, different stabilized iminium ions obtained from MacMillan's for asymmetric catalysis frequently applied 1st and 2nd generation catalyst were investigated *via* low temperature *in situ* illumination NMR spectroscopy revealing differing stabilities of the (*Z*)-configured isomers which reflect the steric influences of the differently substituted imidazolidinone moieties. As basic additives are crucial to promote the reactivity of such stabilized iminium ions similarly their effect on the stabilities of the different configuration isomers was scrutinized, revealing a correlation between the relative nucleophilicity of the basic additive and the stability of the (*Z*)-configured isomers. With this knowledge and further found in literature it was expected to successfully decrypt the role of the C=N double bond. However, it must be noted that all the stability measures mandatory for these mechanistic studies add up to a so far unsolved insufficient reactivity of this DTS-*h* ν

model system. Nevertheless, possibilities how to potentially master this major challenge are suggested.

In chapter four, which was created in cooperation with the group of Prof. Dr. Henry Dube, azotriptycenes as one class of photoswitchable molecular brakes were comprehensively scrutinized by a combined low temperature NMR spectroscopy and quantum chemical approach. The applied light-controlled molecular brakes base on an azo compound with an aryl substituent on the one and an alkyl-like triptycene at the other side. These brakes can exist in two different states: brake ON in *cis*- and brake OFF in *trans*-configuration of the central azo double bond. Similar to other molecular brakes, braking happens upon mechanical blocking. Mechanical blocking in this system was intended to follow intermeshing of the aryl rotor and the triptycene backbone due to the closer spatial proximity of both molecular fragments in the *cis*-configured state. The aim was not only to confirm the proposed intermeshing and to assign the structures of the different brake ON states, but furthermore to analyze the dynamics of the decelerated rotations and to determine the associated kinetics. In general, such rotations are too fast at ambient temperature to be accessible by NMR spectroscopy. Therefore, very low temperatures were necessary to decelerate the rotational processes until they were slow enough to yield separate NMR signals for the different *cis*-configured brake ON structures. Temperatures down to -143 °C were necessary to obtain the required separated NMR signals, which was disclosed *via* variable temperature NMR. As a result, the structures of the different *cis*-states could be assigned. The intermeshing in the *cis*-states could be confirmed by exclusive through space magnetization transfers between the aryl and triptycene fragment, which are missing in the related *trans*-state. Photoswitching between the different azo double bond configurations was revealed by *in situ* illumination NMR spectroscopy, meaning reversible braking and accelerating of the two C-N single bond rotations is possible upon illumination with light of different wavelengths. The particular motions between the different *cis*-states were qualitatively determined by applying chemical exchange saturation transfer (CEST) and rotating frame Overhauser enhancement spectroscopy (ROESY). 1D selective exchange spectroscopy (EXSY) buildup experiments provided a quantitative analysis of the corresponding kinetics yielding values in good agreement to those predicted theoretically.

Chapter five was done in collaboration with the group of Dr. Joshua-Philip Barham. The focus was on the design of new highly efficient light-powered fluorination strategies of unactivated C(sp³)-H bonds using SelectFluor as easy to handle and low toxic fluorine source. Several strategies employing this principle have already been reported. However, as they only partially tolerate alcohol- or amine- containing groups, fluorination of complex molecules is hampered. In addition, regioselectivity is often a problem

because this follows factors endogenous to the substrate and as consequence cannot be controlled by the chemist itself. It was found that benzoates serve as a versatile photosensitizer, which cannot only fluorinate simple substrates when applied as catalyst. Furthermore, this class of photosensitizer can also be applied as auxiliary that is easily attached to otherwise interfering alcohol- or amine-groups and removed downstream to the fluorination reaction without affecting the yield. This gives on the one hand access to fluorinate complex molecules as successfully demonstrated on some pharmaceutical active compounds; but especially it enables to control regioselectivity based on the auxiliary placement. This regioselectivity bases on a charge transfer assembly between the auxiliary bound to the substrate and SelectFluor, which could be confirmed by luminescence measurements. Detailed NMR spectroscopic investigations provided further insights in the reaction mechanism, especially on the role of the substrate. By measuring quantitative *in situ* illumination NMR kinetics an induction period upstream to the fluorination reaction itself was discovered. That this induction period and as consequence the overall reaction time can be shortened was found by increasing substrate loading. DOSY revealed a substrate dependent de-aggregation of SelectFluor, which seems to affect the success of the fluorination reaction. Determining the volume of the SelectFluor-aggregate in presence of very reactive and rather unreactive substrates, a smaller SelectFluor volume was obtained in presence of the more reactive substrate.

In an appendix, results of *in situ* illumination NMR spectroscopic investigations are summarized, which were acquired as part of a collaborative project with the working groups of Dr. Andrea Kneuttinger, Prof. Dr. Reinhard Sterner, Prof. Dr. Burkhard König und Prof. Dr. Remco Sprangers. Within this project a changing activity of an enzyme containing a photoresponsive, unnatural amino acid, called AzoF, was discovered upon alternatively illuminating with two different wavelengths. Photoswitching between the *cis*- and *trans*- configuration of the AzoF and in turn inducing local oscillations is suggested as explanation for this enhanced enzyme activity. To corroborate this theory, the photoswitching capacity of the isolated amino acid AzoF was investigated using amongst others a specially designed light source for *in situ* illumination of a NMR sample with two alternating wavelengths.

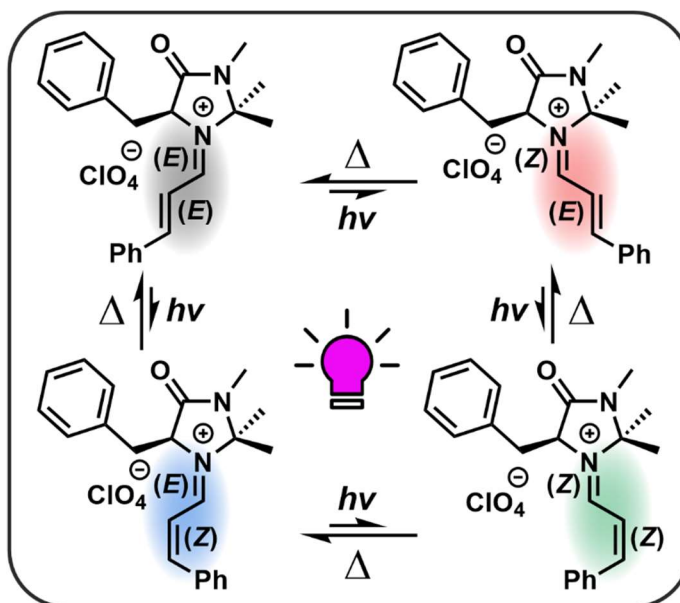
1.3 References

- 1 a) K. Zeitler, *Angew. Chemie - Int. Ed.*, 2009, **48**, 9785–9789; b) W. R. Browne and B. L. Feringa, *Annu. Rev. Phys. Chem.*, 2009, **60**, 407–428; c) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113; d) M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2012, **134**, 8289–8292; e) M. Majek and A. Jacobi Von Wangelin, *Acc. Chem. Res.*, 2016, **49**, 2316–2327; f) I. Ghosh, L. Marzo, A. Das, R. Shaikh and B. König, *Acc. Chem. Res.*, 2016, **49**, 1566–1577; g) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, **116**, 10276–10341; h) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; i) B. König, *European J. Org. Chem.*, 2017, **2017**, 1979–1981; j) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chemie - Int. Ed.*, 2018, **57**, 10034–10072; k) L. Buzzetti, G. E. M. Crisenza and P. Melchiorre, *Angew. Chemie - Int. Ed.*, 2019, **58**, 3730–3747.
- 2 a) J. Wang, G. Burdzinski, J. Kubicki and M. S. Platz, *J. Am. Chem. Soc.*, 2008, **130**, 11195–11209; b) Y. Zhang, J. Kubicki and M. S. Platz, *J. Am. Chem. Soc.*, 2009, **131**, 13602–13603; c) U. Megerle, M. Wenninger, R. J. Kutta, R. Lechner, B. König, B. Dick and E. Riedle, *Phys. Chem. Chem. Phys.*, 2011, **13**, 8869–8880; d) J. Xue, H. L. Luk, S. V. Eswaran, C. M. Hadad and M. S. Platz, *J. Phys. Chem. A*, 2012, **116**, 5325–5336; e) P. K. Verma, F. Koch, A. Steinbacher, P. Nuernberger and T. Brixner, *J. Am. Chem. Soc.*, 2014, **136**, 14981–14989; f) E. Riedle, M. K. Roos, S. Thallmair, C. F. Sailer, N. Krebs, B. P. Fingerhut and R. de Vivie-Riedle, *Chem. Phys. Lett.*, 2017, **683**, 128–134.
- 3 a) K. C. Christoforidis, M. Louloudi, E. R. Milaeva, Y. Sanakis and Y. Deligiannakis, *Mol. Phys.*, 2007, **105**, 2185–2194; b) M. Goswami, A. Chirila, C. Rebreyend and B. de Bruin, *EPR Spectroscopy as a Tool in Homogeneous Catalysis Research*, Springer US, 2015, vol. 58.
- 4 B. König, *Chemical Photocatalysis*, De Gruyter, 2013.
- 5 I. Ghosh, R. S. Shaikh and B. König, *Angew. Chemie - Int. Ed.*, 2017, **56**, 8544–8549.
- 6 a) C. G. S. Lima, T. D. M. Lima, M. Duarte, I. D. Jurberg and M. W. Paixão, *ACS Catal.*, 2016, **6**, 1389–1407; b) B. Liu, C. H. Lim and G. M. Miyake, *J. Am. Chem. Soc.*, 2017, **139**, 13616–13619; c) J. Sun, Y. He, X. De An, X. Zhang, L. Yu and S. Yu, *Org. Chem. Front.*, 2018, **5**, 977–981.
- 7 a) J. C. Walton, *Analysis of Radicals*, John Wiley & Sons, Ltd, 2012; b) K. U. Ingold and D. A. Pratt, *Chem. Rev.*, 2014, **114**, 9022–9046.
- 8 C. Feldmeier, H. Bartling, K. Magerl and R. M. Gschwind, *Angew. Chemie - Int. Ed.*, 2015, **54**, 1347–1351.
- 9 a) J. Niu, Z. A. Page, N. D. Dolinski, A. Anastasaki, A. T. Hsueh, H. T. Soh and C. J.

- Hawker, *ACS Macro Lett.*, 2017, **6**, 1109–1113; b) K. Chen, N. Berg, R. M. Gschwind and B. König, *J. Am. Chem. Soc.*, 2017, **139**, 18444–18447; c) N. D. Dolinski, Z. A. Page, F. Eisenreich, J. Niu, S. Hecht, J. Read de Alaniz and C. J. Hawker, *ChemPhotoChem*, 2017, **1**, 125–131; d) Y. Ji, D. A. DiRocco, C. M. Hong, M. K. Wismer and M. Reibarkh, *Org. Lett.*, 2018, **20**, 2156–2159; e) L. Čechová, J. Kind, M. Dračinský, J. Filo, Z. Janeba, C. M. Thiele, M. Cigáň and E. Procházková, *J. Org. Chem.*, 2018, **83**, 5986–5998; f) D. Lehnher, Y. Ji, A. J. Neel, R. D. Cohen, A. P. J. Brunskill, J. Yang and M. Reibarkh, *J. Am. Chem. Soc.*, 2018, **140**, 13843–13853; g) N. D. Dolinski, Z. A. Page, E. H. Discekici, D. Meis, I. H. Lee, G. R. Jones, R. Whitfield, X. Pan, B. G. McCarthy, S. Shanmugam, V. Kottisch, B. P. Fors, C. Boyer, G. M. Miyake, K. Matyjaszewski, D. M. Haddleton, J. R. de Alaniz, A. Anastasaki and C. J. Hawker, *J. Polym. Sci. Part A Polym. Chem.*, 2019, **57**, 268–273; h) D. Petzold, P. Nitschke, F. Brandl, V. Scheidler, B. Dick, R. M. Gschwind and B. König, *Chem. - A Eur. J.*, 2019, **25**, 361–366; i) S. Wang, N. Lokesh, J. Hioe, R. M. Gschwind and B. König, *Chem. Sci.*, 2019, **10**, 4580–4587; j) N. Berg, S. Bergwinkl, P. Nuernberger, D. Horinek and R. M. Gschwind, *J. Am. Chem. Soc.*, 2021, **143**, 724–735; k) R. Rothfelder, V. Streitferdt, U. Lennert, J. Cammarata, D. J. Scott, K. Zeitler, R. M. Gschwind and R. Wolf, *Angew. Chemie - Int. Ed.*, 2021, **60**, 24650–24658; l) S. Yakubov, W. J. Stockerl, X. Tian, A. Shahin, M. J. P. Mandigma, R. M. Gschwind and J. P. Barham, *Chem. Sci.*, 2022, **13**, 14041–14051.
- 10 R. T. Williamson and B. L. Marquez, *Magn. Reson. Chem.*, 2017, **55**, 252–252.
- 11 J. Bargon and L. T. Kuhn, *In situ NMR Methods in Catalysis*, Springer Berlin Heidelberg, 2007.
- 12 P. Nitschke, N. Lokesh and R. M. Gschwind, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2019, **114–115**, 86–134.
- 13 a) A. De Marco, A. M. Petros, M. Llinás, R. Kaptein and R. Boelens, *Biochim. Biophys. Acta (BBA)/Protein Struct. Mol.*, 1989, **994**, 121–137; b) M. Goetz and I. Sartorius, *J. Am. Chem. Soc.*, 1993, **115**, 11123–11133; c) H. C. Siebert, R. Kaptein, J. J. Beintema, U. M. Soedjanaatmadja, C. S. Wright, A. Rice, R. G. Kleinedam, S. Kruse, R. Schauer, P. J. W. Pouwels, J. P. Kamerling, H. J. Gabius and J. F. G. Vliegthart, *Glycoconj. J.*, 1997, **14**, 531–534; d) M. Goetz and I. Sartorius, *J. Phys. Chem. A*, 2003, **107**, 8539–8546; e) O. B. Morozova, R. Kaptein and A. V. Yurkovskaya, *J. Phys. Chem. B*, 2012, **116**, 8058–8063; f) O. B. Morozova, R. Kaptein, R. Z. Sagdeev and A. V. Yurkovskaya, *Appl. Magn. Reson.*, 2013, **44**, 233–245; g) E. Stadler, A. Eibel, D. Neshchadin and G. Gescheidt, *Zeitschrift fur Phys. Chemie*, 2017, **231**, 625–636.
- 14 M. Bertolotti, *The History of the Laser*, 2004.

- 15 J. Mattay and A. Griesbeck, *Photochemical key steps in organic synthesis: an experimental course book*, 2008.
- 16 a) R. Kaptein, *Biol. Magn. Reson.*, 1982, 145–191; b) M. Goez, *Chapter 3 Photo-CIDNP Spectroscopy*, Elsevier Ltd., 1st edn., 2009, vol. 66.
- 17 a) P. Hartmann, M. J. P. Leiner and P. Kohlbacher, *Sensors Actuators, B Chem.*, 1998, **51**, 196–202; b) M. Vacha, Y. Koide, M. Kotani and H. Sato, *Chem. Phys. Lett.*, 2004, **388**, 263–268; c) M. Rochkind, S. Pasternak and Y. Paz, *Molecules*, 2015, **20**, 88–110.
- 18 a) D. A. Steigerwald, J. C. Bhat, D. Collins, R. M. Fletcher, M. O. Holcomb, M. J. Ludowise, P. S. Martin and S. L. Rudaz, *IEEE J. Sel. Top. Quantum Electron.*, 2002, **8**, 310–320; b) *Nat. Photonics*, 2007, **1**, 23; c) S. C. Singh, Nova Scientific Publisher, UK, 2009, pp. 1–36.
- 19 a) J. Kind, L. Kaltschnee, M. Leyendecker and C. M. Thiele, *Chem. Commun.*, 2016, **52**, 12506–12509; b) N. Mallo, P. T. Brown, H. Iranmanesh, T. S. C. MacDonald, M. J. Teusner, J. B. Harper, G. E. Ball and J. E. Beves, *Chem. Commun.*, 2016, **52**, 13576–13579; c) D. M. Schultz, F. Lévesque, D. A. DiRocco, M. Reibarkh, Y. Ji, L. A. Joyce, J. F. Dropinski, H. Sheng, B. D. Sherry and I. W. Davies, *Angew. Chemie - Int. Ed.*, 2017, **56**, 15274–15278; d) J. Bernarding, F. Euchner, C. Bruns, R. Ringleb, D. Müller, T. Trantzschel, J. Bargon, U. Bommerich and M. Plaumann, *ChemPhysChem*, 2018, **19**, 2453–2456; e) M. Žabka and R. M. Gschwind, *European J. Org. Chem.*, , DOI:10.1002/ejoc.202200048; f) W. J. Stockerl and R. M. Gschwind, *Chem. Commun.*, 2023, **59**, 1325–1328.
- 20 a) W. B. Moniz and C. F. Poranski, *J. Am. Chem. Soc.*, 1975, **97**, 3258; b) R. Kaptein, K. Dijkstra, F. Müller, C. G. Van Schagen and A. J. W. G. Visser, *J. Magn. Reson.*, 1978, **31**, 171–176; c) R. Kaptein, K. Dijkstra and K. Nicolay, *Nature*, 1978, **274**, 293–294.
- 21 T. Paululat, M. Rabe and D. V. Berdnikova, *J. Magn. Reson.*, 2021, **327**, 106990.
- 22 I. Kuprov, M. Goez, P. A. Abbott and P. J. Hore, *Rev. Sci. Instrum.*, 2005, **76**, 1–7.
- 23 J. E. Bramham and A. P. Golovanov, *Commun. Chem.*, 2022, **5**, 1–10.
- 24 C. L. Lerman and M. Cohn, *Biochem. Biophys. Res. Commun.*, 1980, **97**, 121–125.
- 25 J. E. Scheffler, C. E. Cottrell and L. J. Berliner, *J. Magn. Reson.*, 1985, **63**, 199–201.
- 26 a) I. Kuprov and P. J. Hore, *J. Magn. Reson.*, 2004, **171**, 171–175; b) C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39–44.

2. Photo Enhancement Reveals (*E,Z*) and (*Z,Z*) Configurations as Additional Intermediates in Iminium Ion Catalysis



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Willibald J. Stockerl performed all the experimental work. He synthesized the model iminium ion and conducted all NMR spectroscopic investigations. R. M. Gschwind supervised and directed the project. **Willibald J. Stockerl** wrote the supporting information and together with R. M. Gschwind the manuscript.

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2.1 Abstract

Imidazolidinone based α,β -unsaturated iminium ions are the reactive species within countless synthetic protocols in asymmetric organocatalysis. However, (*E,Z*) and (*Z,Z*) imidazolidinone iminium ions, *i.e.* (*Z*)-C=C configurations, have been elusive so far. Herein we describe how *in situ* photoisomerization enables the observation and assignment of high energetic (*Z*)-configured intermediates below the detection limit of NMR spectroscopy for (*E,Z*) and (*Z,Z*) iminium perchlorate complexes derived from MacMillan's 1st generation catalyst and cinnamaldehyde. Traces of the (*E,Z*) isomer could be even detected under synthetic conditions at 25°C in acetonitrile. Using back isomerization studies and diffusion ordered spectroscopy, conditions were found to stabilize the (*E,Z*) and (*Z,Z*) isomers for several hours *via* ion pair aggregation. Thus, at least (*E,Z*) isomers should be considered for future investigations in asymmetric iminium ion catalysis.

2.2 Introduction

Iminium ions generated upon condensation of α,β -unsaturated carbonyl compounds and chiral imidazolidinones play a key role for numerous β -functionalizations.¹ Especially the MacMillan group established a new field of highly stereoselective transformations in organocatalysis employing these chiral imidazolidinones as catalysts.² Recently, the impact of this pioneering work on pharmaceutical research was acknowledged by awarding the Nobel Prize in Chemistry 2021 to David MacMillan and Benjamin List “for the development of asymmetric organocatalysis”.³ However, compared to the huge amount of synthetic applications, information about the structural space of the involved iminium ion intermediates and especially about the appearance of (*Z*)-configured C=C double bonds are sparse. Until now, only (*E,E*) and (*Z,E*) iminium ions are experimentally disclosed in solution⁴ (see Figure 1 top; (*E,E*)/(*Z,E*) ratios between 98:2 and 88:12)^{4b} and as crystal structures.^{4b,c} So far, mechanistic investigations mainly focused on the major (*E,E*) isomer.⁵ Some publications additionally discuss the influence of the C=N bond configuration on the enantioselectivity and agree that it is controlled by an interplay of (*E,E*)/(*Z,E*) populations and kinetics.^{4b,6} However, these imidazolidinone based α,β -unsaturated iminium ions possess also a second C=C double bond, which can isomerize. Thus, (*E,Z*) and (*Z,Z*) intermediates (see Figure 1 bottom) have the potential to influence the catalysis but have been mainly neglected so far. One exception is a mechanism proposed by List and co-workers, in which a (*E,Z*)-configured substrate was used in a transfer hydrogenation and consistently an (*E,Z*) intermediate was discussed.⁷

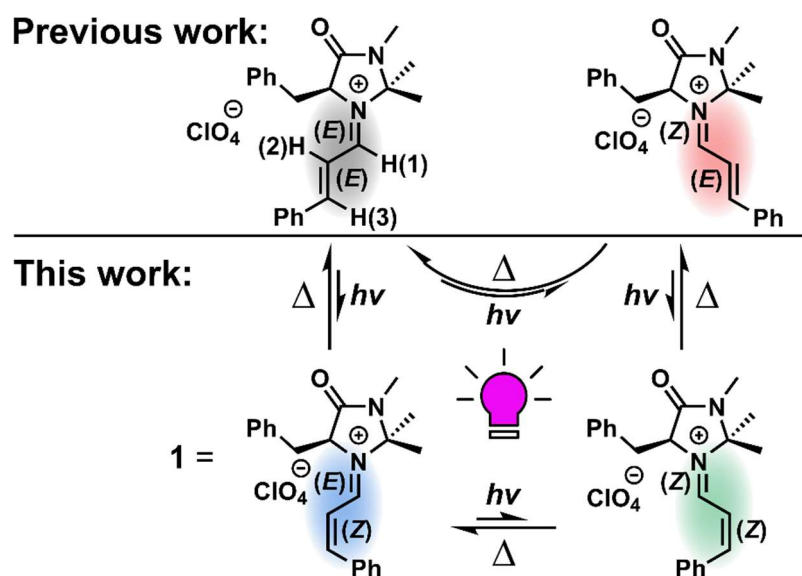


Figure 1. (*E,E*) and (*Z,E*) imidazolidinone based iminium ions of **1** have been experimentally disclosed so far.⁴ In this work, the elusive (*E,Z*) isomer is observed in the dark; in addition photoisomerization reveals both (*E,Z*) and (*Z,Z*) plus photostationary states and backisomerization kinetics under various experimental conditions.

As reflected in the Curtin-Hammett principle, major substrate isomers not necessarily lead to the major product stereoisomer and a reaction pathway proceeding over lower populated isomers can be dominant. In addition, the high isomerization barriers of double bonds can allow for individual ground state/transition state pathways. Accordingly, in chiral phosphoric acid catalysis we showed that the energetically high lying ground state energies of low populated (Z)-iminium ions has to be considered to explain the active transition state combinations.⁸ Therefore we were wondering, whether so far undetected (E,Z) and (Z,Z) imidazolidinone iminium ions may affect also the stereoinduction in iminium ion catalysis. In principle, chemical exchange saturation transfer (CEST) exists to observe intermediates below the detection limit of NMR spectroscopy.^{8b,9} Quantitative CEST provides information about chemical shifts, populations and exchange kinetics but cannot shift populations. For our system, CEST cannot be applied, because the chemical shift dispersion of the configurational isomers is too small for selective irradiations (<0.2 ppm). Therefore, we sought for a different method to elucidate the hidden (E,Z) and (Z,Z) intermediates in model systems for asymmetric iminium catalysis. Photochemical, thermal or other kinds of isomerization can change the population of configurational isomers.¹⁰ Especially photoinduced isomerization is a well-established concept to switch between (E) and (Z) isomers and is successfully applied for a broad variety of small organic molecules¹¹ and supramolecular systems.¹² Furthermore, for achiral less restricted α,β -unsaturated iminium ions, (E,Z) and (Z,Z) structures were reported more than 30 years ago *via* photoisomerization.¹³

Therefore, in this study we investigated whether the so far elusive (E,Z) and (Z,Z) isomers are also observable for the chiral, steric hindered imidazolidinone type iminium ions successfully applied in asymmetric catalysis. Photoinduced (E) $\rightarrow$ (Z) isomerization allowed us to access and characterize (E,Z) and (Z,Z) iminium ions with MacMillans 1st generation catalyst (see Figure 1). Variations of temperature, solvents and concentration were used to affect photostationary state (PSS) and back isomerization *via* ion pair aggregation to modulate the lifetime of all four isomers. In addition, high sensitivity spectra were recorded in the dark to elucidate thermodynamic populations.

2.3 Results and Discussion

To investigate whether photo isomerization enables the exploration of the configurational space of imidazolidinone based α,β -unsaturated iminium ions including (Z)-configured C=C double bonds, iminium ion **1** with perchlorate as stabilizing counterion^{5b} (see Figure 1) was chosen as model substrate. As reported repeatedly,⁴ two configurational isomers of this iminium ion can clearly be detected in solution, in a ratio of 97:3 for (E,E) and (Z,E), respectively (for further details see supporting information, chapter 2.5.2). To simultaneously trigger and detect photochemical isomerization of the C=N and C=C double bond we applied *in situ* illumination NMR spectroscopy.¹⁴ For a start, a sample of **1** in CD₃CN (10 mM) was investigated at -40 °C (see Figure 2), because our previous studies on iminium ions in binary complexes with chiral phosphoric acid showed a fast and effective thermal (Z) $\rightarrow$ (E) isomerization as competitive reaction at elevated temperatures.¹⁵

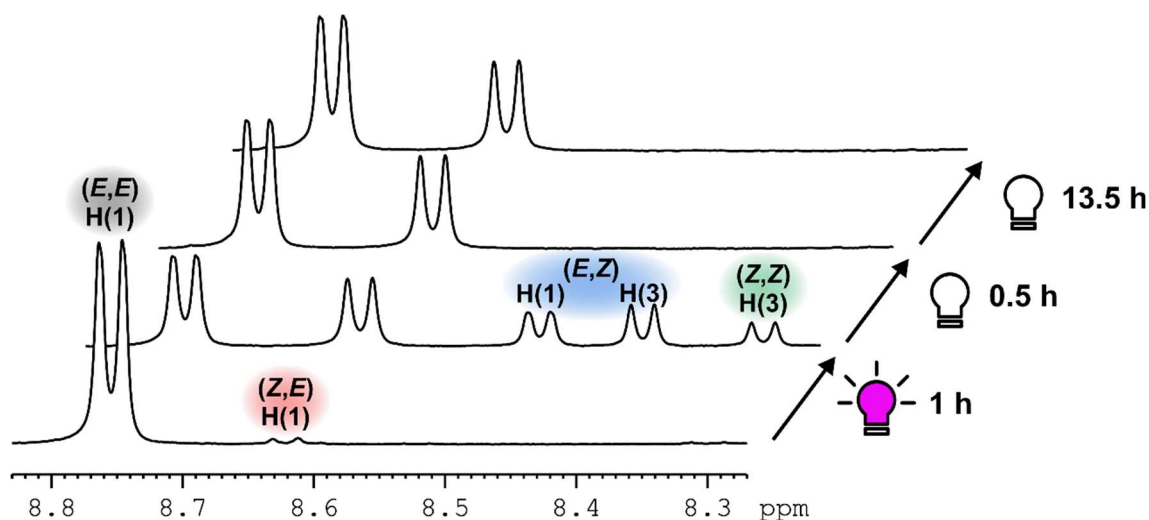


Figure 2. Stacked ¹H NMR spectra show how photoinduced (E) $\rightarrow$ (Z) and thermal (Z) $\rightarrow$ (E) back isomerization affect the populations of all four configuration isomers for a 10 mM sample of **1** in CD₃CN at -40 °C. For labels see Figure 1.

Illumination with UV-light (365 nm) for 1 h yields an increase of population of the (Z,E) isomer from 3% to 31% (100% = sum of all observed isomers). At the same time, two additional iminium ion signal sets are generated with a moderate population of 16% and 9% (Figure 2). The moderate light intensity in our LED setup¹⁴ requires 1 h until the isomer populations stay reasonably constant. That means, during photo isomerization, thermal back isomerization already may occur. Therefore, in case of fast back isomerization rates low PSS populations and short lifetimes in the dark are expected. In fact, the signals of (E,Z) and (Z,Z) vanish within ca. 30 min after switching of the illumination, while the high population of (Z,E) remains for at least 14 h. Next, the photostability of all isomers was tested. Upon continuous UV-illumination, the PSS can

be preserved without significant photodegradation for at least 16 h. This allowed us to elucidate the structure of all present signal sets by a series of 1D- (^1H ; $^{13}\text{C}\{^1\text{H}\}$) and 2D-NMR experiments (^1H , ^1H COSY; ^1H , ^{13}C HMBC; ^1H , ^{13}C HSQC) under continuous illumination (see supporting information, chapter 2.5.4). Additionally we analysed in detail the through space interactions based on nuclear Overhauser effects (NOE). As a result, the two UV-generated iminium ion signal sets can explicitly be assigned as the elusive (*E,Z*) and (*Z,Z*) isomers. Having the complete assignment of all isomers and their potential photo enhancement factors at hand, we searched for traces of (*E,Z*) and (*Z,Z*) in the dark without previous illumination. At room temperature the populations in the dark should resemble the thermodynamics in most of the reported iminium ion catalysis. Therefore, the detection of (*E,Z*) and (*Z,Z*) intermediates without illumination would highlight the importance of (*Z*)-configured C=C bonds for mechanistic considerations in catalysis.

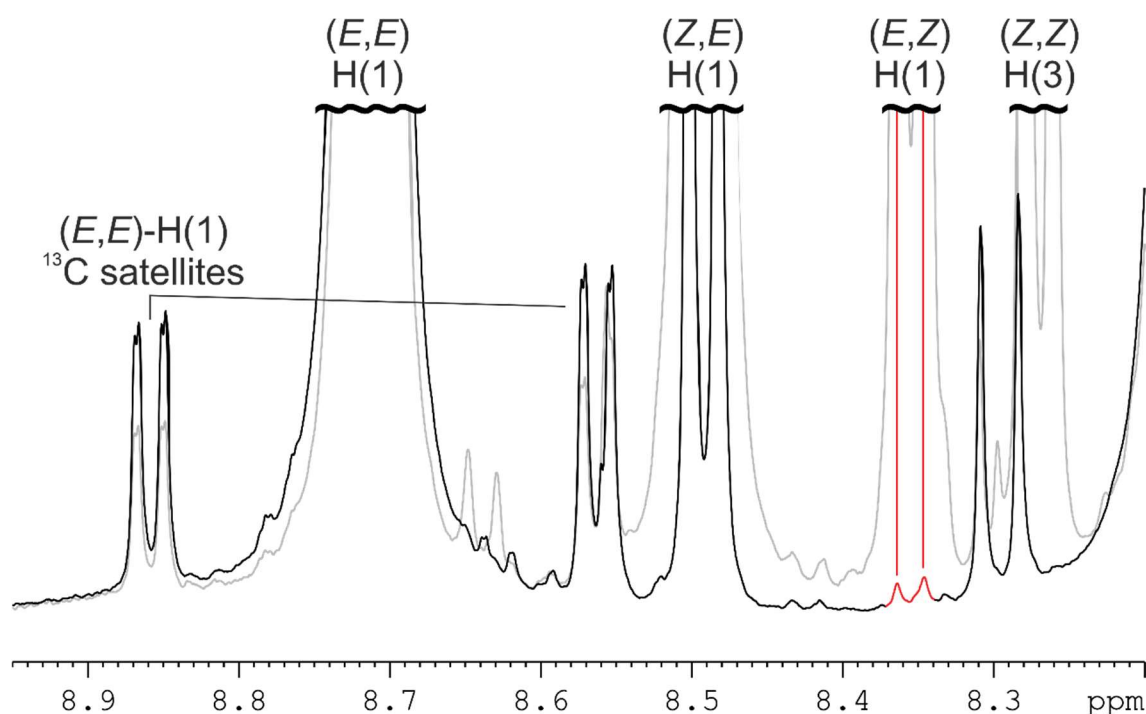


Figure 3. ^1H NMR spectra of **1** in CD_3CN (10 mM) recorded at 25 °C with a proton optimized cryogenically cooled NMR probe. In thermal equilibrium (black spectrum) three signals were detected in the dark (one is shown here highlighted in red; see supporting information, chapter 2.5.5 for the others) matching to (*E,Z*). Due to the low intensity, an explicit assignment of the signals to (*E,Z*) is only possible *via* its selective photo enhancement upon UV-light (grey spectrum).

To gain highest possible sensitivity, we selected a proton optimized cryogenically cooled NMR probe and recorded a quantitative ^1H NMR experiment. Already after 2048 scans an impressive signal to noise ratio was obtained (Figure 3 and supporting information, chapter 2.5.5) and thus even signals around 5000-times smaller than the (*E,E*)-H(1) signal could be observed. Several signals, with intensities down to 2.3% of the ^{13}C

satellites of (*E,E*)-H(1) were detected as potential candidates for (*E,Z*) and (*Z,Z*) providing similar chemical shifts and multiplicities. However, their intensities are by far too low for a classical assignment or structure elucidation. Here, the unambiguous assignment to (*E,Z*) or (*Z,Z*) out of the various candidates is only possible *via* selective photo enhancement. Indeed, the signal at 8.36 ppm (see red highlighted signal in Figure 3) and others not shown (see supporting information, chapter 2.5.5) respond to UV-illumination with a ca. 38-fold gain in intensity and can thus explicitly be assigned to an iminium ion isomer. Spectra accumulation under continuous illumination allows to retain the tremendous population gains even at low temperatures and less sensitive room temperature or heteronuclei optimized NMR probes (for details see supporting information, chapter 2.5.4). A comparison of all sets of spectra allows to assign the signal at 8.36 ppm clearly to (*E,Z*). As expected from the lower intensities of (*Z,Z*) vs. (*E,Z*) in the PSS and the minimal intensities of (*E,Z*) in the dark, the (*Z,Z*) isomer was not detected. Nevertheless, to the best of our knowledge this is the first experimental evidence of (*E,Z*) without illumination and a ratio of (*E,E*)/(*Z,E*)/(*E,Z*) = ca. 97.4:2.5:0.1 was obtained. The small population of 0.1% of (*E,Z*) reflects an energetically high but still accessible ground state at room temperature. Given the high isomerization barriers of double bonds, (*Z*)-ground states should be connected to (*Z*)-transition states and (*E*)-ground states to (*E*)-transition states. Therefore, an energetically high, but accessible ground state can lower the $\Delta\Delta G$ to the transition state. As a consequence the (*E,Z*) iminium configuration should be included into mechanistic considerations in iminium ion catalysis in the future and may have an impact on the *ee*-distributions.

Next, we investigated the thermal stabilities of all four configuration isomers. A reduced thermal back isomerization is the key to a successful and effective photo enhancement of high energetic (*Z*)-configured isomers since photoinduced (*E*) $\rightarrow$ (*Z*) isomerization and thermal (*Z*) $\rightarrow$ (*E*) back isomerization are direct antagonists. Therefore, we investigated the effect of temperature, solvents and concentration on the PSS and the back isomerization by quantitative NMR spectroscopy (for details see supporting information, chapter 2.5.6). First, we tested how temperatures between 20 °C to -40 °C affect the stabilities of the different isomers (Figure 4 top left and for further details see supporting information, chapter 2.5.6.2). At a temperature of 20 °C and UV-illumination mainly an (*E*) $\rightarrow$ (*Z*) isomerization of the C=N double bond is observed at the NMR time scale. For (*E,Z*) and (*Z,Z*) also small signals can be obtained, but their populations are not sufficient for a quantitative evaluation (< 0.2%). A ratio of (*E,E*)/(*Z,E*) = ca. 74:26 is received in the PSS and thermal equilibrium is reestablished with a rate constant of $k_{(Z) \rightarrow (E)} 1.01 \pm 0.03 \cdot 10^{-3} \text{ s}^{-1}$, *i.e.* within ca. 1 h. The (*E*) $\rightarrow$ (*Z*) photo isomerization performance improves at lower temperatures. The competing (*Z*) $\rightarrow$ (*E*) isomerization is

significantly reduced, thus more (*Z*)-configured isomers are detected upon UV-illumination and their stability in the dark increases. At -40 °C a (*E,E*)/(*Z,E*)/(*E,Z*)/(*Z,Z*) ratio of ca. 44:31:16:9 is present in the PSS.

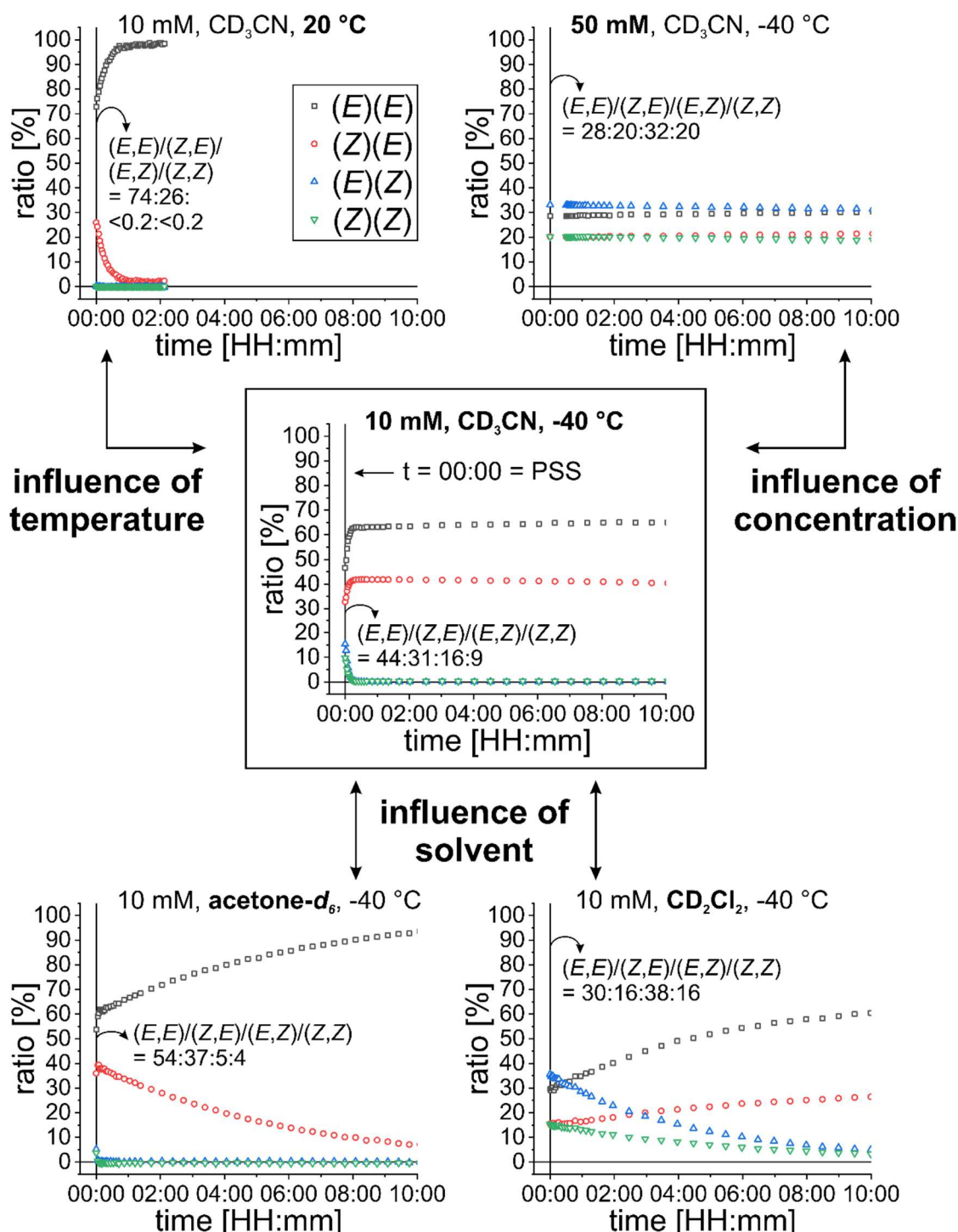


Figure 4. Plots of the thermal (*Z*) → (*E*) back isomerization of the different configuration isomers of **1** starting from PSS. Herein, the influence of temperature (top left), concentration (top right) and solvents (bottom) are compared to the reference plot (10 mM, acetonitrile-*d*₃, -40 °C) in the center. For details see supporting information, chapter 2.5.6.

Switching off the illumination results in a fast decline of (*E,Z*) and (*Z,Z*) configured isomers. This proceeds ca. 290-times faster compared to the isomerization of (*Z,E*) to (*E,E*). Next, the impact of several solvents on the stability of the (*Z*)-configured isomers was addressed (Figure 4 bottom and for further details supporting information, chapter 2.5.6.3). We chose CD₃CN, acetone-*d*₆ and CD₂Cl₂ which possess different polar ($\epsilon(\text{CH}_3\text{CN}) = 35.9$, $\epsilon(\text{acetone}) = 20.6$, $\epsilon(\text{CH}_2\text{Cl}_2) = 8.9$)¹⁶ and basic properties ($\text{CH}_2\text{Cl}_2 < \text{CH}_3\text{CN} < \text{acetone}$)¹⁷ which should reflect their trend in nucleophilicity in aprotic solvents. In acetone-*d*₆ only tiny amounts of (*E,Z*) and (*Z,Z*) could be observed upon UV-illumination with a PSS of (*E,E*)/(*Z,E*)/(*E,Z*)/(*Z,Z*) = 54:37:5:4. The rate constant for the thermal back isomerization of (*Z,E*) → (*E,E*) increased by a factor of 3.7 compared to CD₃CN. In contrast, in CD₂Cl₂ 70% of (*Z*)-configured isomers are detected in the PSS together with a significantly decelerated thermal (*Z*) → (*E*) isomerization. The (*E,Z*) → (*E,E*) back isomerization was ca. 70-times slower than in CD₃CN. The huge differences of the PSS populations and thermal back isomerization rates and their correlation with the relative nucleophilicities of the solvents indicate a nucleophile-catalyzed isomerization mechanism as reported in literature.¹⁸ Finally, we investigated the effect of the concentration at -40 °C. Increasing the concentration from 10 mM to 25 mM caused only slight changes (see supporting information, chapter 2.5.6.4). To our surprise at 50 mM the relative amount of (*E,Z*) and (*Z,Z*) doubled in the PSS (16% → 32% for (*E,Z*) and 9% → 20% for (*Z,Z*)) and the associated back isomerization nearly stopped, e.g. decelerated for (*E,Z*) → (*E,E*) by a factor of ca. 2070 (see Figure 4 top right). A similar stabilization effect was observed in acetone. At 50 mM and -40 °C also in acetone-*d*₆ an average value of (*E,E*)/(*Z,E*)/(*E,Z*)/(*Z,Z*) = 29:21:30:20 was obtained under continuous UV-illumination (see supporting information, chapter 2.5.4.2). Since ion pairs¹⁹ including steric hindered iminium systems²⁰ are known to aggregate in polar aprotic solvents, the results at 50 mM suggest that aggregation over a certain threshold may effectively impede the solvent based isomerization pathway.

To reveal the aggregation in the thermodynamic equilibrium, we performed DOSY spectra in the dark with different concentrations, solvents and temperatures (for solvent effects see supporting information, chapter 2.5.7). In CD₃CN at -40 °C, very similar volumes of (*E,E*) are received at *c* = 10 (1063 ± 21 Å³) and 25 mM (1036 ± 36 Å³). At 50 mM an increased volume was found (1152 ± 12 Å³). The smallest values (e.g. 810 ± 16 Å³ for) were obtained at 20 °C independent of the concentration. Given a volume of 412 Å³ for a monomeric contact ion pair (see supporting information, chapter 2.5.7.2), the DOSY data suggest that our model iminium ion forms the following aggregates: dimers at 20 °C and all concentrations; mixed dimer/trimer-aggregates at -40 °C and 10 mM or 25 mM; mainly trimers at -40 °C and *c* = 50 mM. Thermal back

isomerization occurs fastest at conditions where the smallest (*E,E*) volumes were obtained. Thus, ion pair aggregation seems to shield the iminium ions from nucleophilic attacks of the solvent molecules. At a threshold value of trimers the solvent based isomerization is apparently stopped. This strong effect of aggregation on solvent induced back isomerization opens up a new stabilization possibility for energetic high laying ion pair isomers. In case very low temperatures cannot be applied to effectively stop back isomerization of ion pairs also moderate low temperatures in combination with elevated concentrations can be used.

2.4 Conclusion

In conclusion, the elusive (*E,Z*) and (*Z,Z*)-isomers of a chiral imidazolidinone-type α,β -unsaturated iminium ion were disclosed *via in situ* illumination NMR spectroscopy as example that intermediates otherwise not accessible can be revealed *via* photoisomerization. The presence of (*E,Z*) was even confirmed in the dark by exploiting its explicit response to UV-triggered isomerization. The competitive thermal (*Z*) $\rightarrow$ (*E*) back isomerization was quantitatively analysed to illustrate the stability of the different (*Z*)-configured isomers, which is key to detect such energetically high laying species *via* NMR spectroscopy. A correlation between nucleophilicity of the solvent and thermal back isomerization suggests a solvent based mechanism. Ion pair trimers effectively impede back isomerization. Thus, ion pair aggregation seems to be an effective method to shield against nucleophilic attacks from the solvent. Since we could confirm the existence of (*E,Z*) under general synthetic conditions we think that this isomer should be considered for future mechanistic investigations or synthetic applications in asymmetric iminium ion catalysis.

2.5 Supporting Information

2.5.1 General

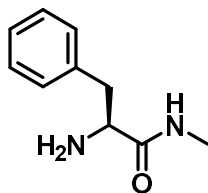
Commercially available chemicals were, unless otherwise stated, used without further purification. *Trans*-cinnamaldehyde was distilled under reduced pressure ($2 \cdot 10^{-1}$ mbar) at 100 °C, degassed using the freeze-pump-thaw method and stored inside the glove box. Acetone was dried dynamically using 3Å molecular sieve, degassed by the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask. EtOH and Et₂O were distilled over sodium and benzophenone and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve. CD₃CN and CD₂Cl₂ were distilled over CaH₂, degassed using the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve.

UV/Vis-spectra were recorded using an AvaLight-DH-S-BAL as light source and an AvaSpec-2048 for detection.

NMR experiments for routine measurements were recorded on a Bruker Avance 400 MHz at 25 °C. Detailed NMR spectroscopic investigations were performed on a Bruker Avance III HD 600 (600.03 MHz) with a 5 mm fluorine selective TBIF probe, on a Bruker Avance NEO 600 (600.03 MHz) with a 5 mm CryoProbe Prodigy BBO or on a Bruker Avance III HD 600 (600.25 MHz) with a 5 mm TCI CryoProbe using the reported *in situ* illumination setup with 5 mm amberized thin wall NMR tubes and for illumination at 365 nm a LG Innotek LEUVA66X00RV00 LED or an OSRAM LZ4-04UV0R-00000 was used.¹⁴ For combined *in situ* illumination-NMR-UV/Vis spectroscopy the reported setup was used analogously.²¹ NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software and reported as follows: ppm, multiplicity, coupling constant, integral. All spectra are referenced to the solvent residual signal: Acetone-*d*₆: $\delta(^1\text{H}) = 2.05$ ppm, $\delta(^{13}\text{C}) = 29.84$ ppm; CD₂Cl₂: $\delta(^1\text{H}) = 5.32$ ppm, $\delta(^{13}\text{C}) = 53.84$ ppm; CD₃Cl: $\delta(^1\text{H}) = 7.26$ ppm, $\delta(^{13}\text{C}) = 77.16$ ppm; CD₃CN: $\delta(^1\text{H}) = 1.94$ ppm, $\delta(^{13}\text{C}) = 118.26$ ppm. Further plotting of the spectra was performed with Origin 2019 and Corel Draw 2020 software.

2.5.2 Synthesis of model iminium ion 1

2.5.2.1 (S)-2-Amino-N-methyl-3-phenylpropanamide (2)



2

2 was synthesized following a literature procedure.^{5d}

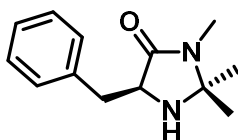
(S)-Phenylalanine (6.99 g, 42.30 mmol, 1.0 eq.) was suspended in MeOH (17.1 mL). The suspension was cooled down to 0 °C followed by a slow addition of thionyl chloride (6.04 g, 3.68 mL, 50.76 mmol, 1.2 eq.) under vigorous stirring. The newly formed white suspension was first heated to r.t. and then stirred under reflux for 23 h, which resulted in a light brown solution. Volatile components were removed under reduced pressure and subsequent a MeNH₂-EtOH-solution (8.0 M, 21.15 mL, 169.20 mmol, 4.0 eq.) was slowly added. The solution was stirred for 23 h at r.t. under generation of a white precipitate. After another remove of volatile components *in vacuo* the precipitate was dissolved in an aq. sat. NaHCO₃-solution (60 mL) followed by an extraction with CH₂Cl₂ (3 · 55 mL) and drying over MgSO₄. Purification by recrystallization (*n*-hexane/ EA 2:1) and drying under reduced pressure yielded **2** as a white solid (4.01 g, 22.5 mmol, 53 %).

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.20 – 7.35 (m, 6H, H-Ar & NH), 3.68 (dd, *J* = 9.1, 4.1 Hz, 1H, COCH), 3.29 (dd, *J* = 13.8, 4.3 Hz, 1H, CH₂), 2.80 (d, *J* = 5.0 Hz, 3H, CH₃), 2.73 (dd, *J* = 13.7, 9.1 Hz, 1H, CH₂), 2.06 (s, 2H, NH₂).

¹³C-NMR (CDCl₃, 101 MHz, 25 °C): 174.9, 138.2, 129.4, 128.8, 126.9, 56.6, 41.2, 26.0.

Analytical data are in agreement with the literature.^{5d}

2.5.2.2 (S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one (3)



3

3 was synthesized following a literature procedure.^{4c}

The synthesis was carried out in oven-dried glassware under argon atmosphere. Amid **2** (2.20 g, 12.35 mmol, 1.0 eq.) was dissolved in anhydrous (anh.) and degassed (deg.)

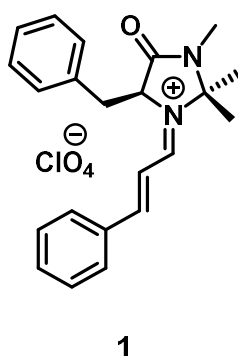
EtOH (30 mL). Anh. and deg. acetone (2.38 g, 3.01 mL, 40.0 mmol, 3.3 eq.) and 3 Å molecular sieve (5 g) were added followed by stirring for 18 h under reflux. Afterwards the reaction mixture was allowed to cool down to r.t. and the solution was purified by filtration. Removing volatile components using reduced pressure yielded **3** as a beige oil (2.58 g, 11.8 mmol, 96 %).

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.19 – 7.32 (m, 5H, *H*-Ar), 3.79 (dd, *J* = 6.6, 4.6 Hz, 1H, *CH*), 3.14 (dd, *J* = 14.2, 4.5 Hz, 1H, *CH*₂), 3.00 (dd, *J* = 14.2, 6.8 Hz, 1H, *CH*₂), 2.75 (s, 3H, *NCH*₃), 1.66 (bs, 1H, *NH*), 1.26 (s, 3H, *CH*₃), 1.15 (s, 3H, *CH*₃).

¹³C-NMR (CDCl₃, 101 MHz, 25 °C): 173.5, 137.3, 129.6, 128.7, 126.9, 75.7, 59.4, 37.4, 27.4, 25.5, 25.3.

Analytical data are in agreement with the literature.^{4c}

2.5.2.3 (*S,E*)-5-Benzyl-2,2,3-trimethyl-4-oxo-1-((*E*)-3-phenylallylidene)imidazolidin-1-ium perchlorate (**1**)



1 was synthesized following a literature procedure.^{5c}

Imidazolidinone **3** (559 mg, 2.56 mmol, 1.0 eq.) was dissolved in Et₂O (3.2 mL) and an aqueous HClO₄-solution (70 %, 136 μL, 1.69 mmol, 1.32 eq.) in EtOH/Et₂O 1:1 (6.4 mL) was added. After stirring for 15 min at r.t. the solvent was removed *in vacuo* giving the imidazolidinone salt as a yellow precipitant. The precipitant was redissolved in MeOH (6.4 mL), heated to 35 °C and *trans*-cinnamaldehyde (338 mg, 332 μL, 2.56 mmol, 2.0 eq.) was added. The reaction mixture was stirred for 1 h at 35 °C generating a red solution with a beige solid. Removing the supernatant solution, washing with anh. and deg. Et₂O (10 · 2.0 mL) and drying the residue under reduced pressure yielded **1** as a light beige solid (906 mg, 2.09 mmol, 82 %), which was stored inside glove box freezer.

¹H-NMR (CD₃CN, 400 MHz, 25 °C): 8.74 (dd, *J* = 10.7, 1.9 Hz, 1H, C(1) - *H*), 8.20 (d, *J* = 15.1 Hz, 1H, C(3) - *H*), 7.90 – 7.95 (m, 2H, arom. *H*), 7.69 – 7.75 (m, 1H, arom. *H*), 7.58 – 7.65 (m, 2H, arom. *H*), 7.24 – 7.35 (m, 4H, arom. *H* + C(2) - *H*), 7.06 – 7.12 (m,

^1H , arom. H), 5.18 – 5.23 (m, 1H, CH), 3.58 (dd, J = 14.7, 5.7 Hz, 1H, CH_2), 3.47 (dd, J = 14.7, 3.7 Hz, 1H, CH_2), 2.79 (s, 3H, NCH_3), 1.70 (s, 3H, CH_3), 0.80 (s, 3H, CH_3).

^{13}C -NMR (CD_3CN , 101 MHz, 25 °C): 168.2, 166.7, 165.2, 136.0, 134.7, 134.4, 132.4, 131.1, 130.6, 130.0, 129.1, 118.4, 86.5, 65.1, 37.2, 27.5, 26.0, 24.7.

Analytical data are in agreement with the literature.^{5c}

2.5.2.4 NMR-data

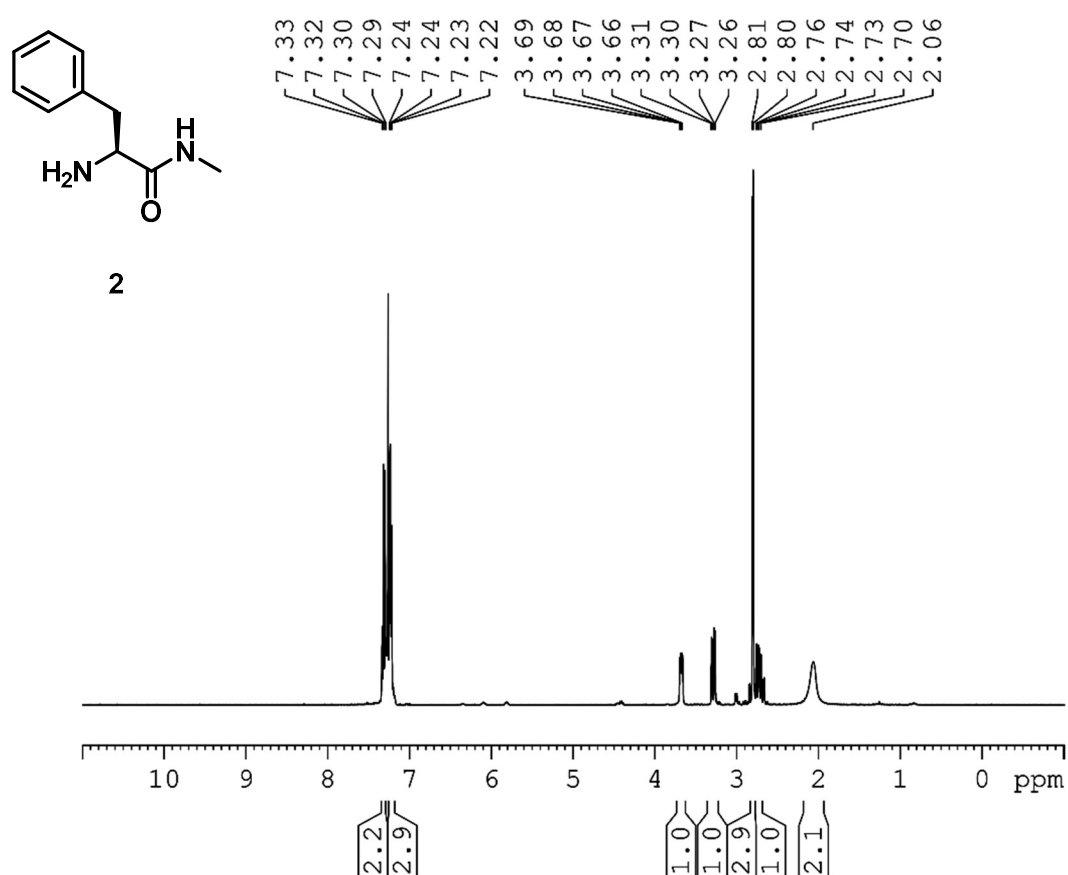


Figure S1. 1D-¹H spectrum (ns = 16) of **2** measured in CDCl₃ at 25 °C.

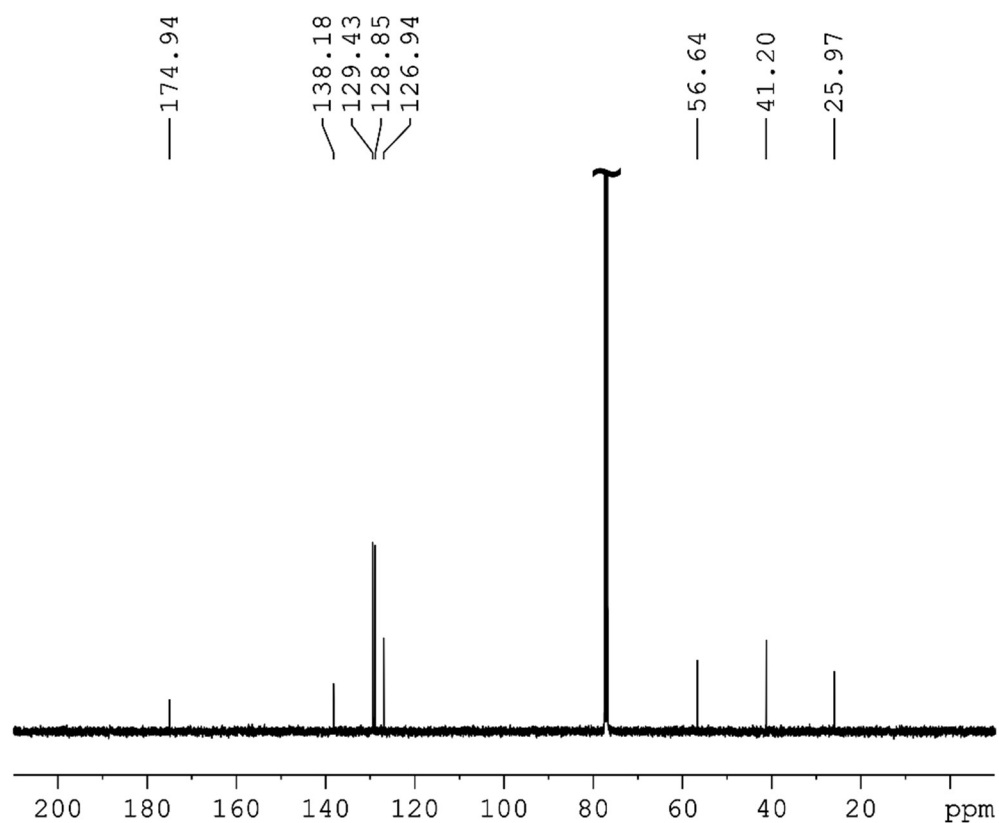


Figure S2. 1D-¹³C{¹H} spectrum (ns = 1024) of **2** measured in CDCl₃ at 25 °C.

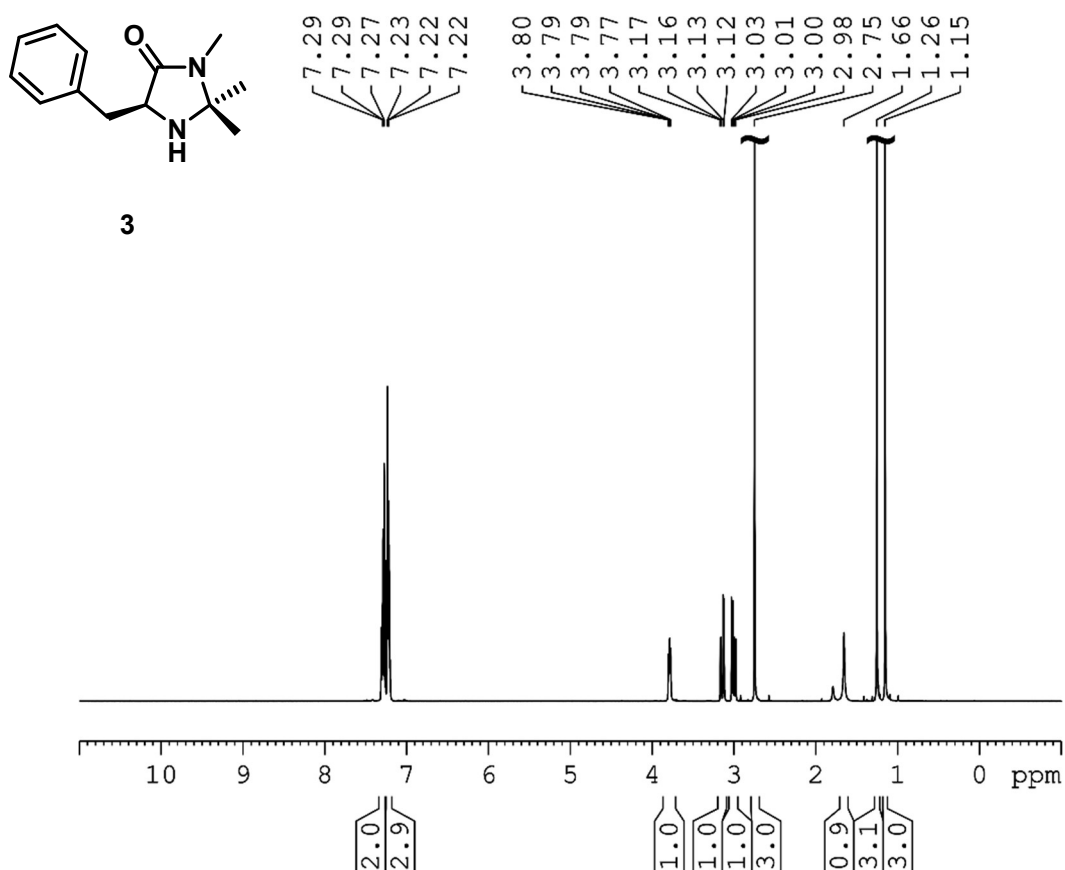


Figure S3. 1D-¹H spectrum (ns = 16) of **3** measured in CDCl₃ at 25 °C.

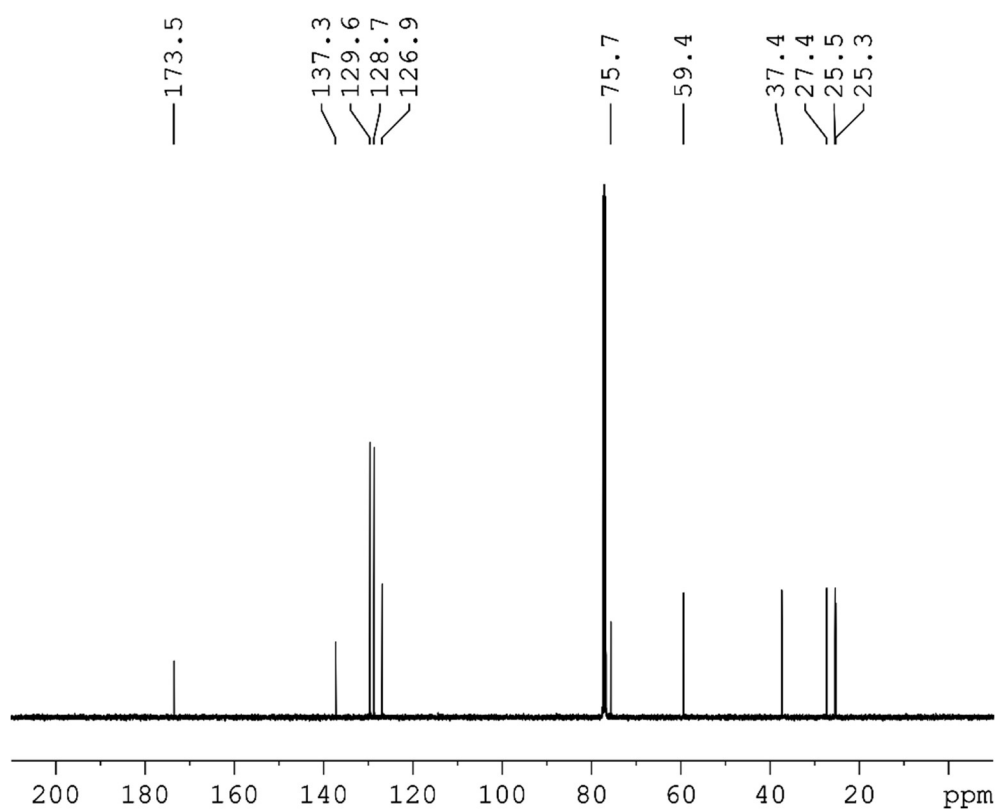


Figure S4. ¹D-¹³C{¹H} spectrum (ns = 1024) of **3** measured in CDCl₃ at 25 °C.

168.2
166.7
165.2
136.0
134.7
134.4
132.4
131.1
130.6
130.0
129.1
118.4
— 86.5
— 65.1
37.2
27.5
26.0
24.7

30

2.5.2.5 UV/Vis-data

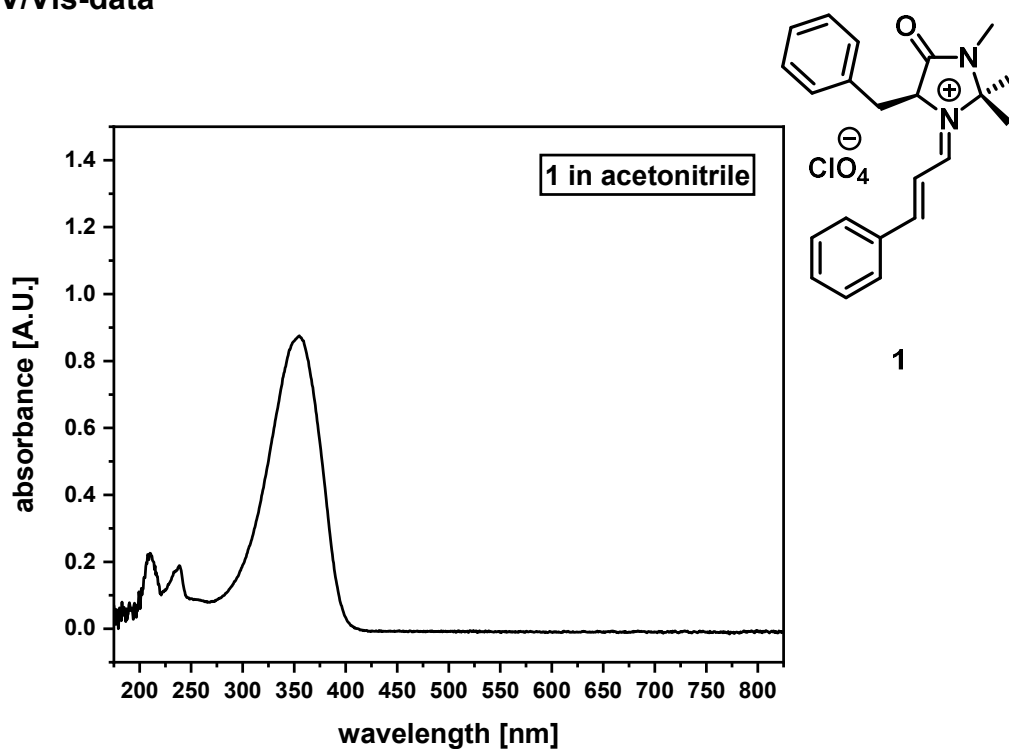


Figure S7. UV/Vis spectrum of **1** measured in CH₃CN at r.t.

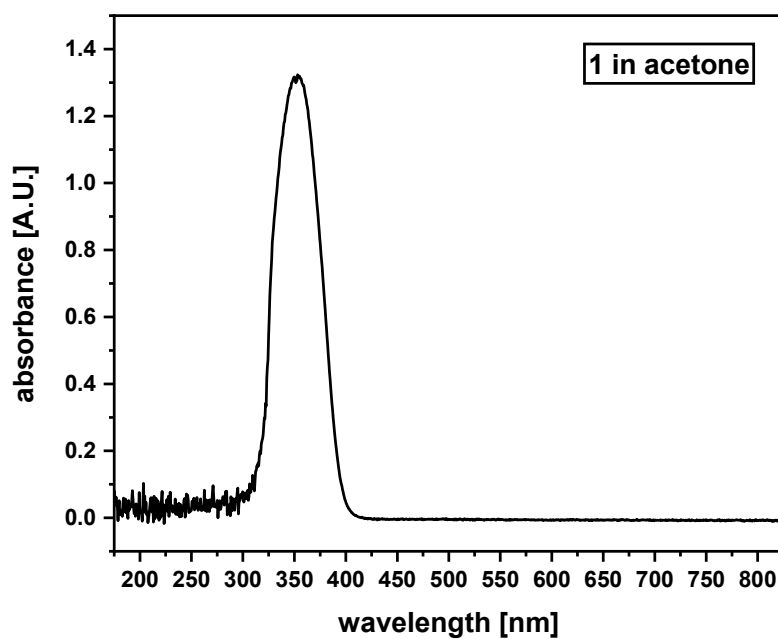


Figure S8. UV/Vis spectrum of **1** measured in acetone at r.t.

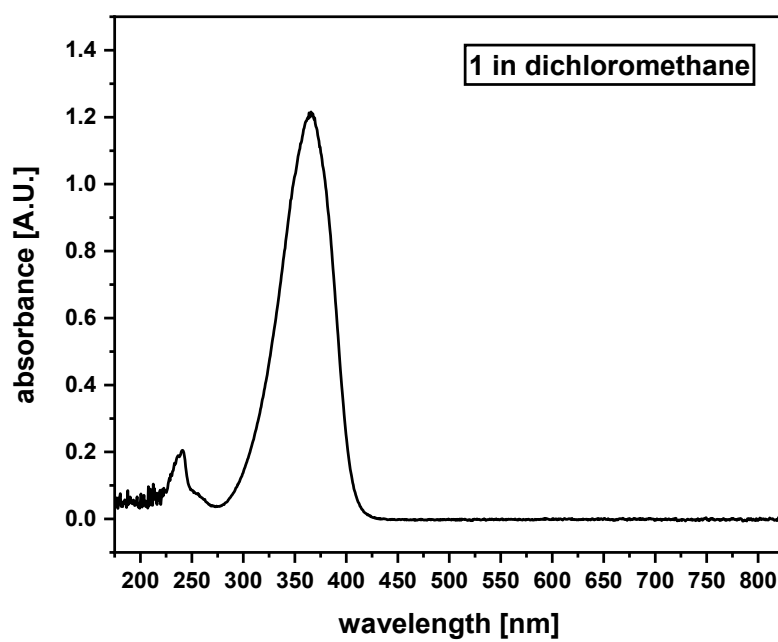


Figure S9. UV/Vis spectrum of **1** measured in CH₂Cl₂ at r.t.

2.5.3 NMR sample preparation

2.5.3.1 Preparation of the NMR samples for *in situ* illumination NMR spectroscopy

An oven dried 5 mm amberized thin wall NMR tube was charged inside the glove box with iminium ion **1** and connected to a Schlenk line. The respective solvent (0.3 mL) was added under argon atmosphere *via* a syringe. Afterwards an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μ m core) was inserted into the NMR tube using the Schlenk line technique and fastened with parafilm.¹⁴

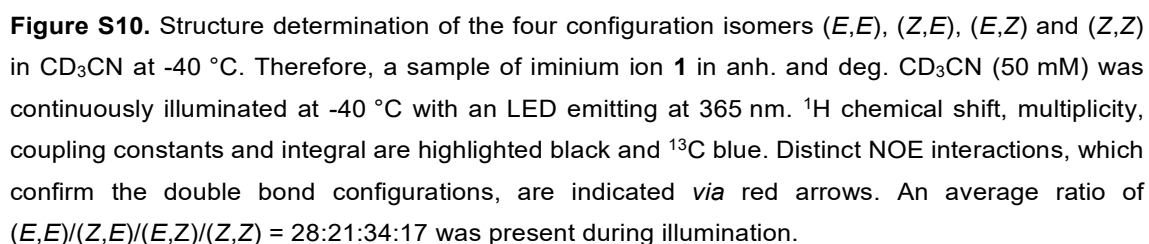
2.5.3.2 Preparation of the NMR samples for diffusion ordered spectroscopy (DOSY)

An oven dried 5 mm NMR tube was charged inside the glove box with iminium ion **1** and connected to a Schlenk line. The respective solvent (0.5 mL) and anh. TMS were added under argon atmosphere *via* syringes and the NMR tube was sealed with additional parafilm.

2.5.3.3 Preparation of the NMR sample for combined *in situ* illumination-NMR-UV/Vis spectroscopy

An oven dried 5 mm amberized thin wall NMR tube was charged inside the glove box with iminium ion **1**. The NMR tube was connected to a Schlenk line and anh. and deg. CD₃CN (0.3 mL) was added under argon atmosphere using a syringe. Following the literature,²¹ the PTFE reflector was added under argon and the coaxial insert was positioned at a distance of ca. 1 mm from the reflector. Lastly, the insert was fastened with parafilm at the NMR tube.

To assign the signals for (*E,E*), (*Z,E*), (*E,Z*) and (*Z,Z*) of iminium ion **1** in CD₃CN at -40 °C (Figure S10) a standard set of NMR experiments (1D-¹H; 1D-¹³C{¹H}; 2D-¹H, ¹H correlated spectroscopy (COSY); 2D-¹H, ¹H nuclear Overhauser enhancement spectroscopy (NOESY), 2D-¹H, ¹³C heteronuclear multiple bond correlation (HMBC); 2D-¹H, ¹³C heteronuclear single quantum coherence (HSQC)) was measured under continuous UV-illumination using the *in situ* illumination setup to populate simultaneously all four configuration isomers. The configuration of the C=N and C=C double bond can be clearly assigned *via* the associated coupling constants and explicit NOE patterns.



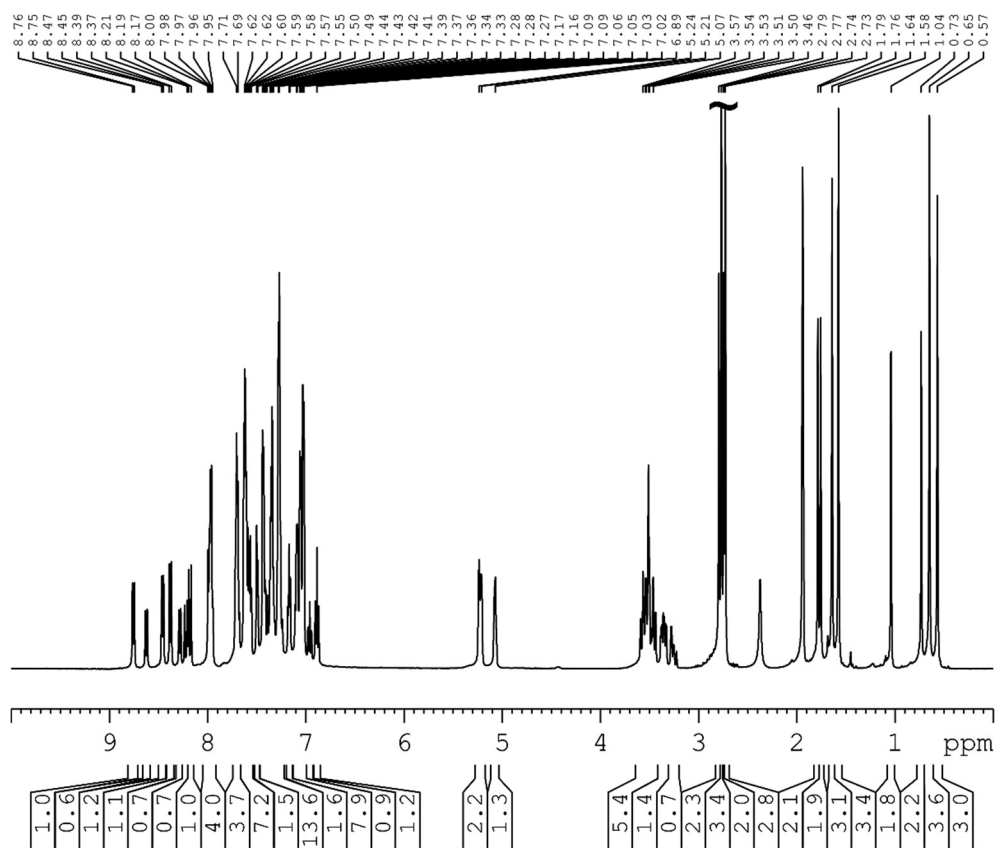


Figure S11. 1D- ^1H spectrum (ns = 16) of **1** in anh. and deg. CD_3CN (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination. The integrals are calibrated on the (*E,E*) isomer.

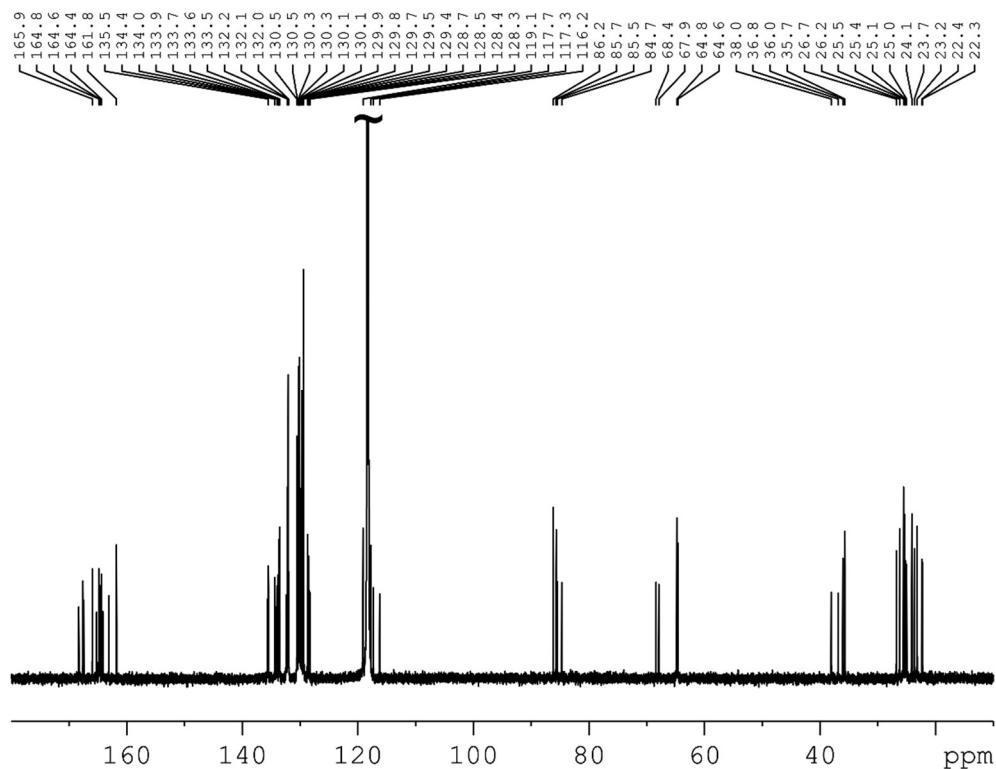


Figure S12. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 2048) of **1** in anh. and deg. CD_3CN (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

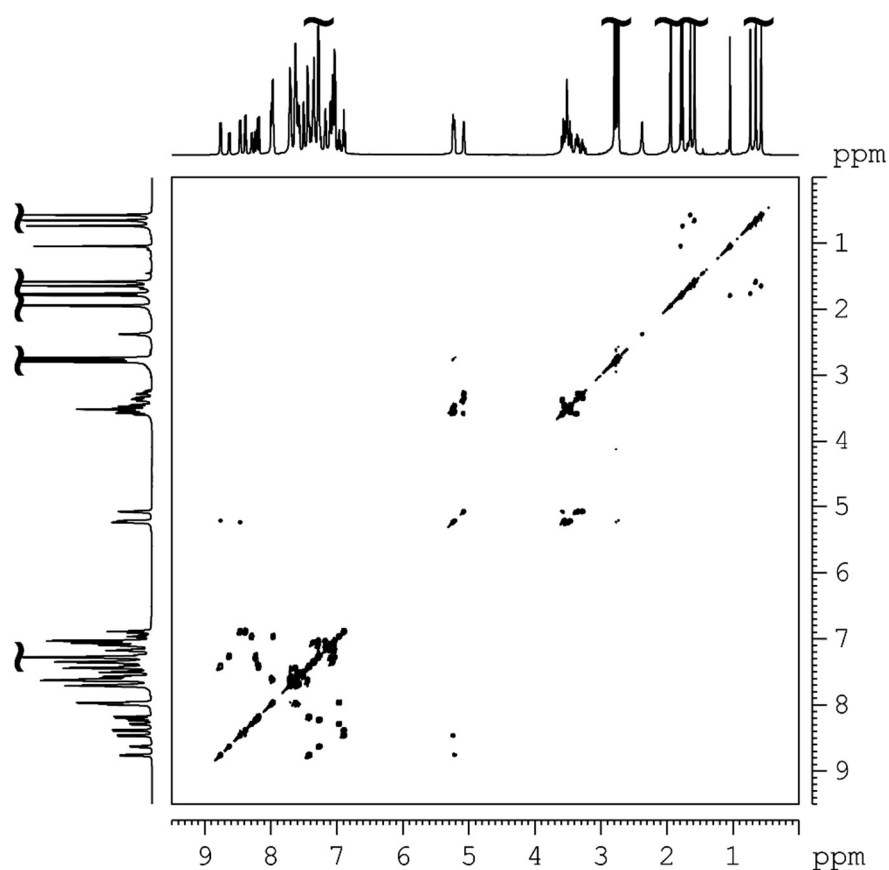


Figure S13. 2D- ^1H , ^1H COSY spectrum of **1** in anh. and deg. CD_3CN (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

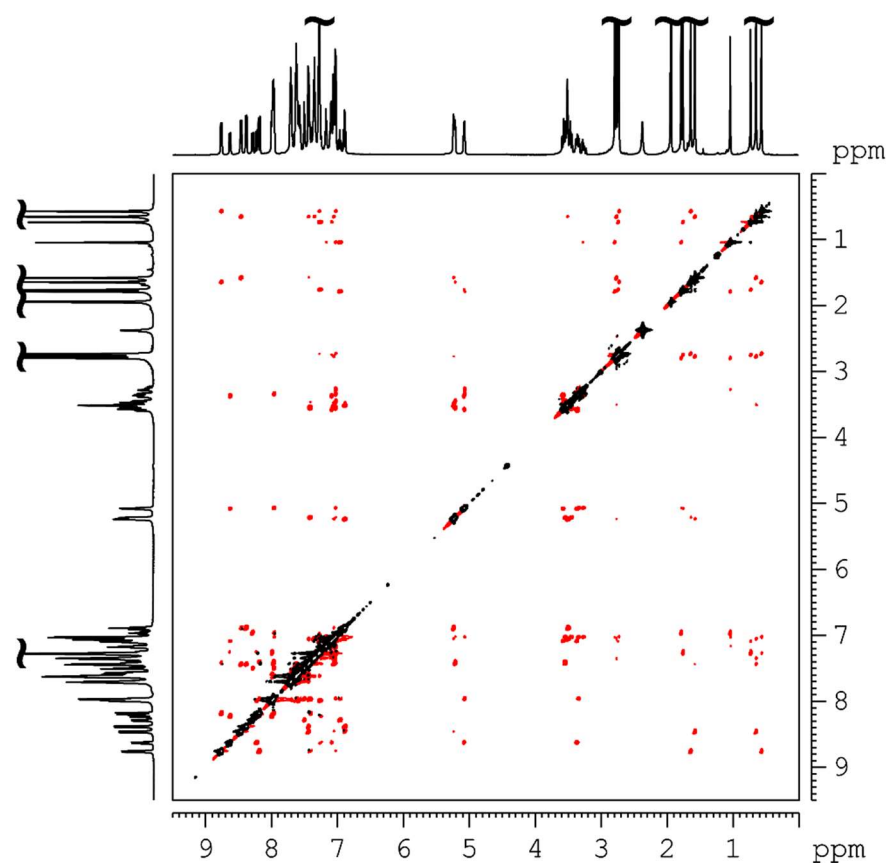


Figure S14. 2D- ^1H , ^1H NOESY spectrum (mixing time = 0.5 s) of **1** in anh. and deg. CD_3CN (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

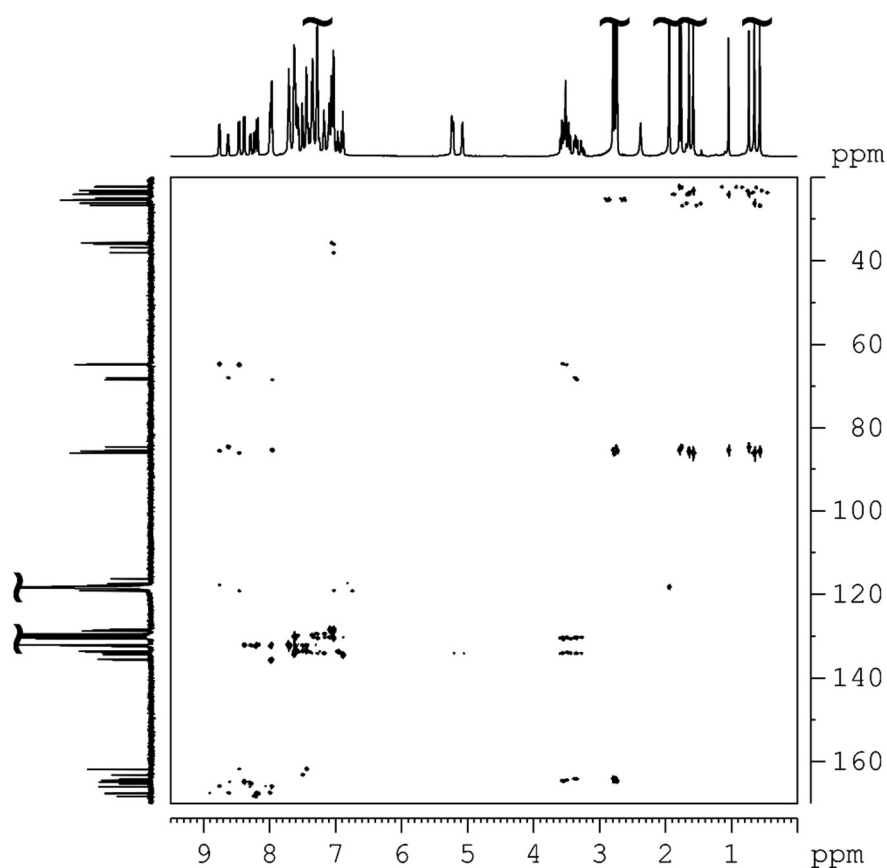


Figure S15. 2D-¹H, ¹³C HMBC spectrum of **1** in anh. and deg. CD₃CN (50 mM) measured at -40 °C under continuous UV-illumination.

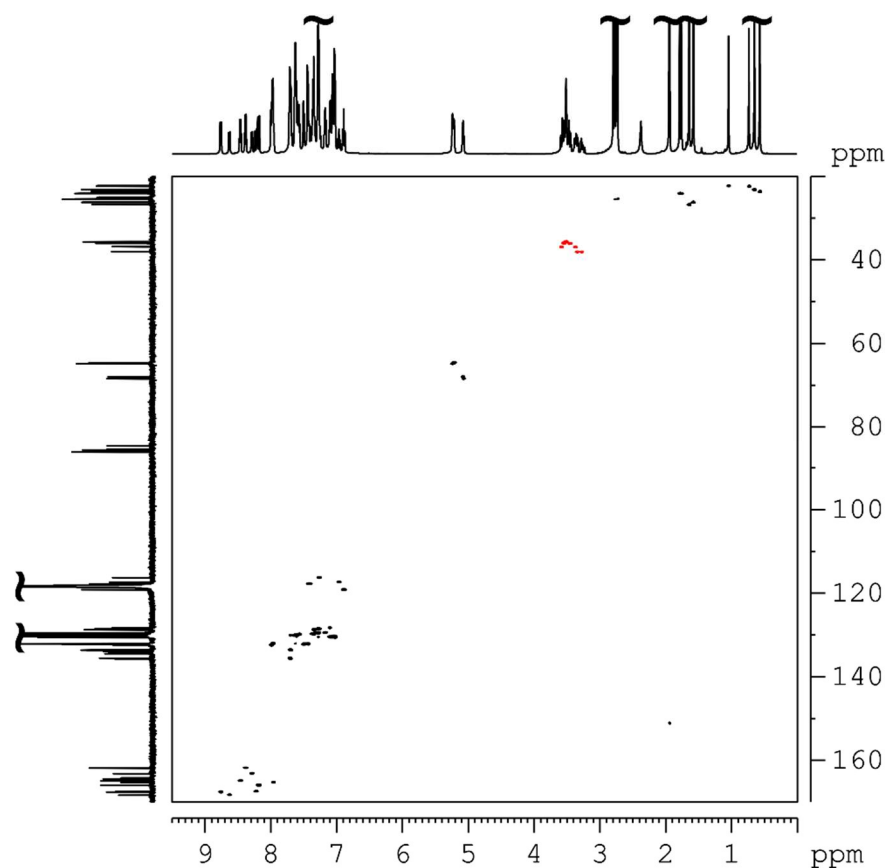


Figure S16. 2D-¹H, ¹³C HSQC spectrum of **1** in anh. and deg. CD₃CN (50 mM) measured at -40 °C under continuous UV-illumination.

2.5.4.2 Structure elucidation of iminium ion **1** at -40 °C in acetone-*d*₆

To assign the signals for (*E,E*), (*Z,E*), (*E,Z*) and (*Z,Z*) of iminium ion **1** in acetone-*d*₆ at -40 °C (Figure S17) a standard set of NMR experiments (1D-¹H; 1D-¹³C{¹H}; 2D-¹H, ¹H COSY; 2D-¹H, ¹H NOESY, 2D-¹H, ¹³C HMBC; 2D-¹H, ¹³C HSQC) was measured under continuous UV-illumination using the *in situ* illumination setup to populate simultaneously all four configuration isomers. The configuration of the C=N and C=C double bond can be clearly assigned *via* the associated coupling constants and explicit NOE patterns.

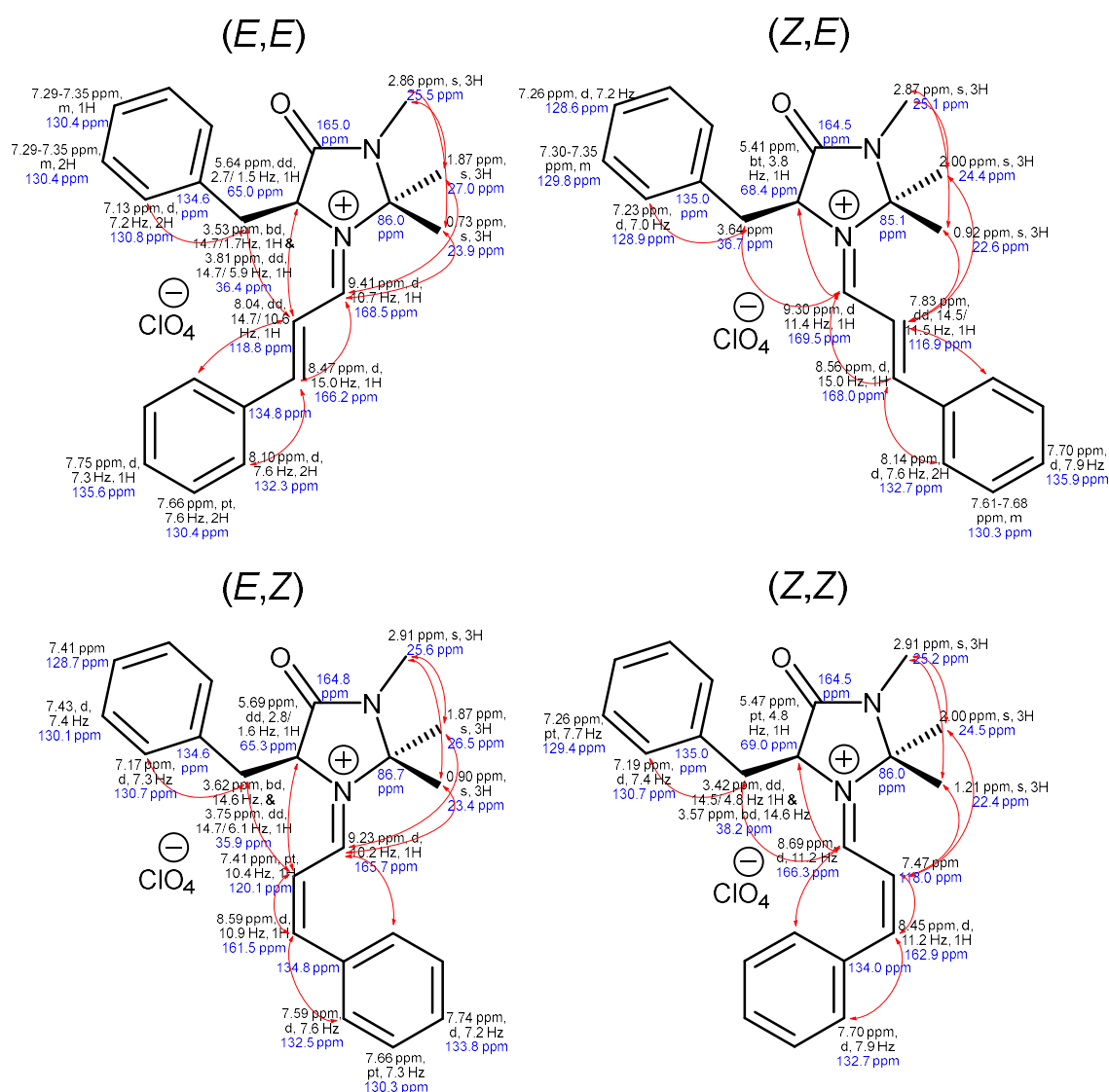


Figure S17. Structure determination of the four configuration isomers (*E,E*), (*Z,E*), (*E,Z*) and (*Z,Z*) in acetone-*d*₆ at -40 °C. Therefore, a sample of iminium ion **1** in acetone-*d*₆ (50 mM) was continuously illuminated at -40 °C with an LED emitting at 365 nm. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black and ¹³C blue. Distinct NOE interactions, which confirm the double bond configurations, are indicated *via* red arrows. An average ratio of (*E,E*)/(*Z,E*)/(*E,Z*)/(*Z,Z*) = 29:21:30:20 was present during illumination.

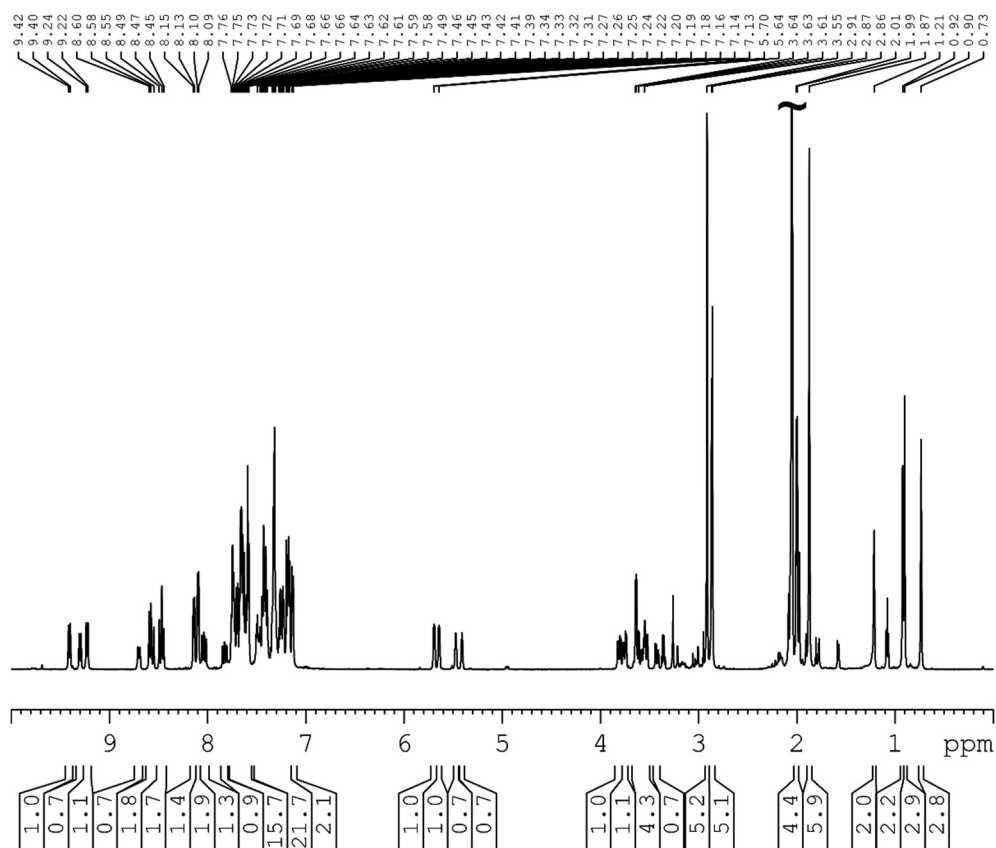


Figure S18. 1D- ^1H spectrum (ns = 16) of **1** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination. The integrals are calibrated on the (*E,E*) isomer.

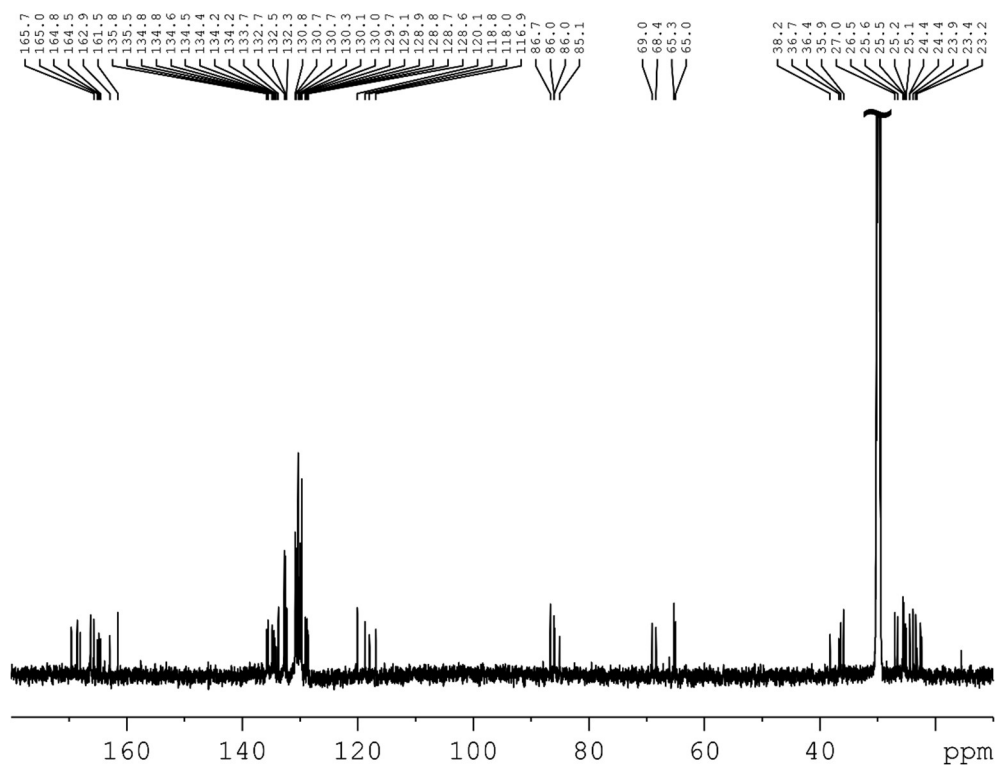


Figure S19. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 6144) of **1** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

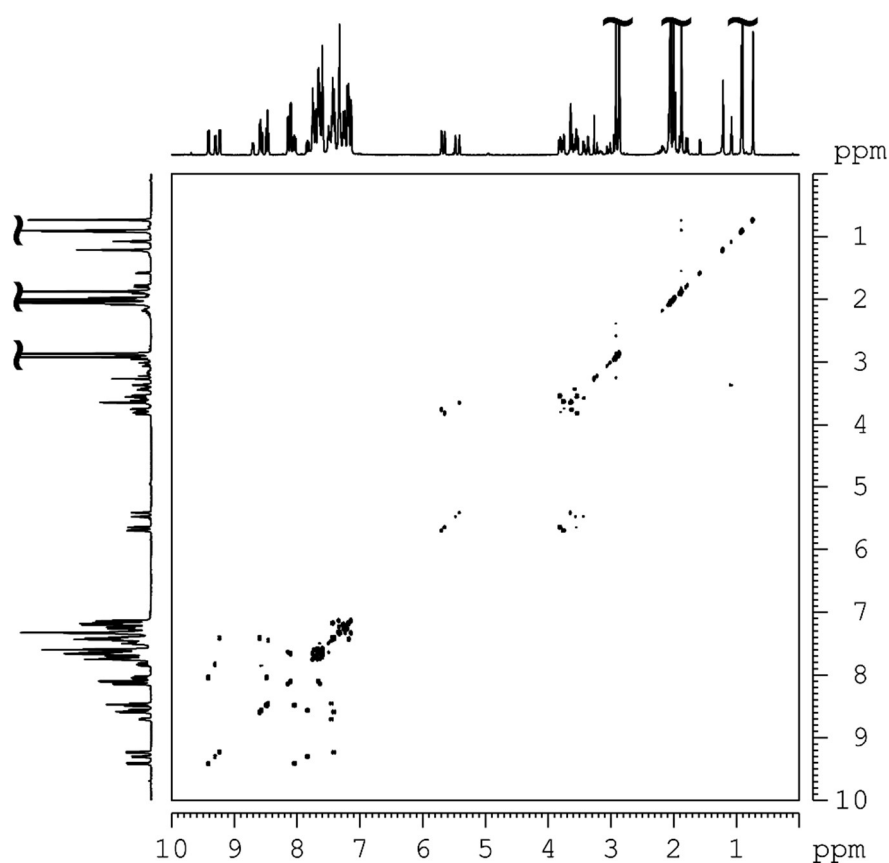


Figure S20. 2D-¹H, ¹H COSY spectrum of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

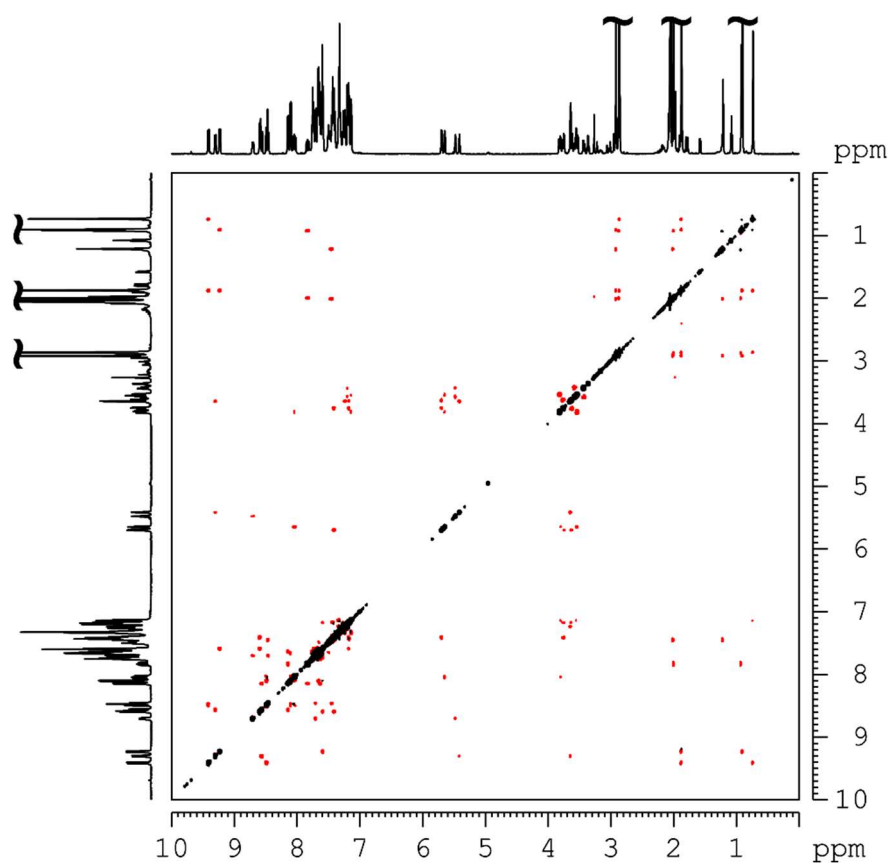


Figure S21. 2D-¹H, ¹H NOESY spectrum (mixing time = 0.5 s) of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

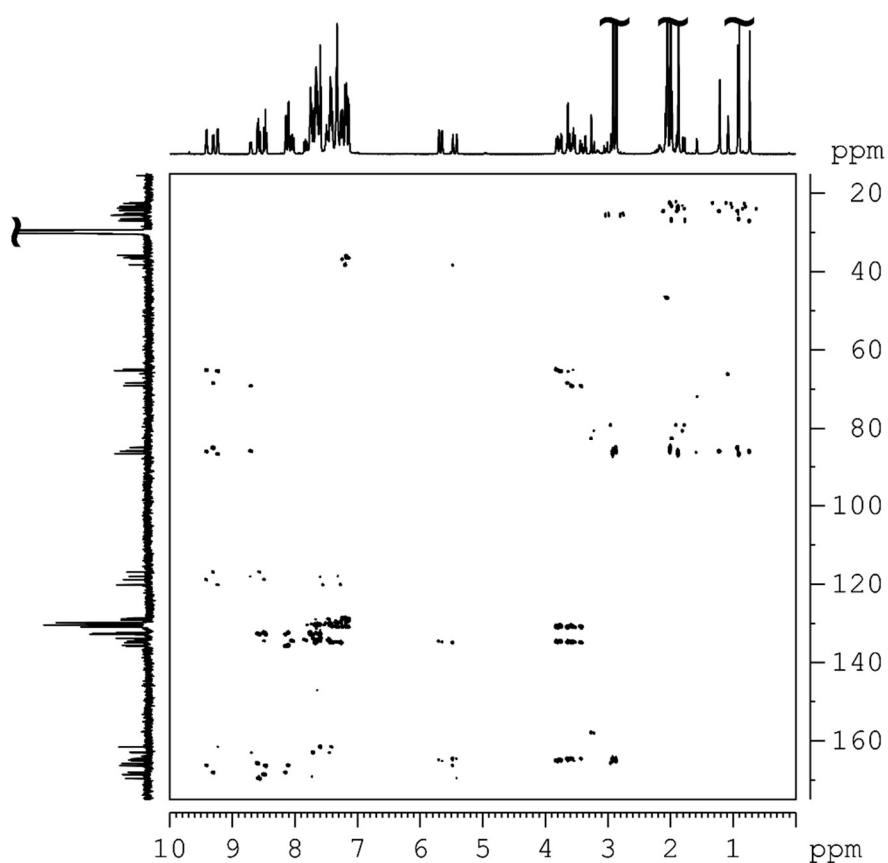


Figure S22. 2D-¹H, ¹³C HMBC spectrum of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

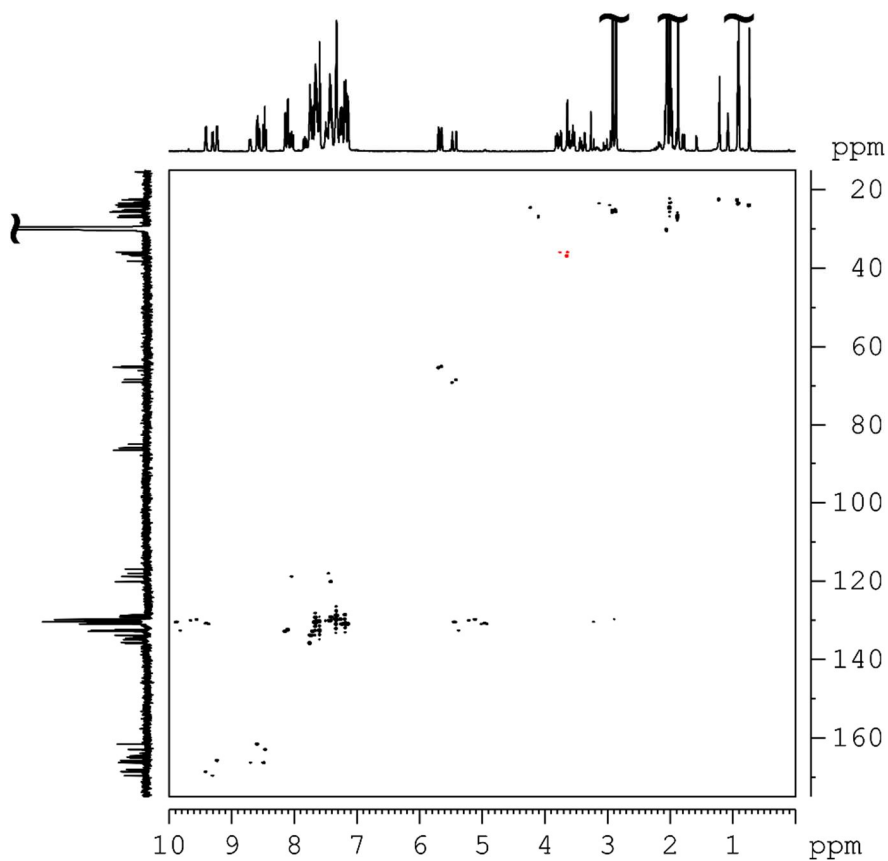


Figure S23. 2D-¹H, ¹³C HSQC spectrum of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

2.5.4.3 Structure elucidation of iminium ion **1** at -40 °C in CD₂Cl₂

To assign the signals for (*E,E*), (*Z,E*), (*E,Z*) and (*Z,Z*) of iminium ion **1** in CD₂Cl₂ at -40 °C (Figure S24) a standard set of NMR experiments (1D-¹H; 2D-¹H, ¹H COSY; 2D-¹H, ¹H NOESY, 2D-¹H, ¹³C HMBC; 2D-¹H, ¹³C HSQC) was measured under continuous UV-illumination using the *in situ* illumination setup to populate simultaneously all four configuration isomers. The configuration of the C=N and C=C double bond can be clearly assigned *via* the associated coupling constants and explicit NOE patterns. **1** is only moderately soluble in CD₂Cl₂ (< 50 mM). Thus, it was not possible to record a 1D-¹³C{¹H} with sufficient signal to noise ratio. ¹³C chemical shifts are assigned based on the 2D-¹H, ¹³C HMBC/HSQC spectra.

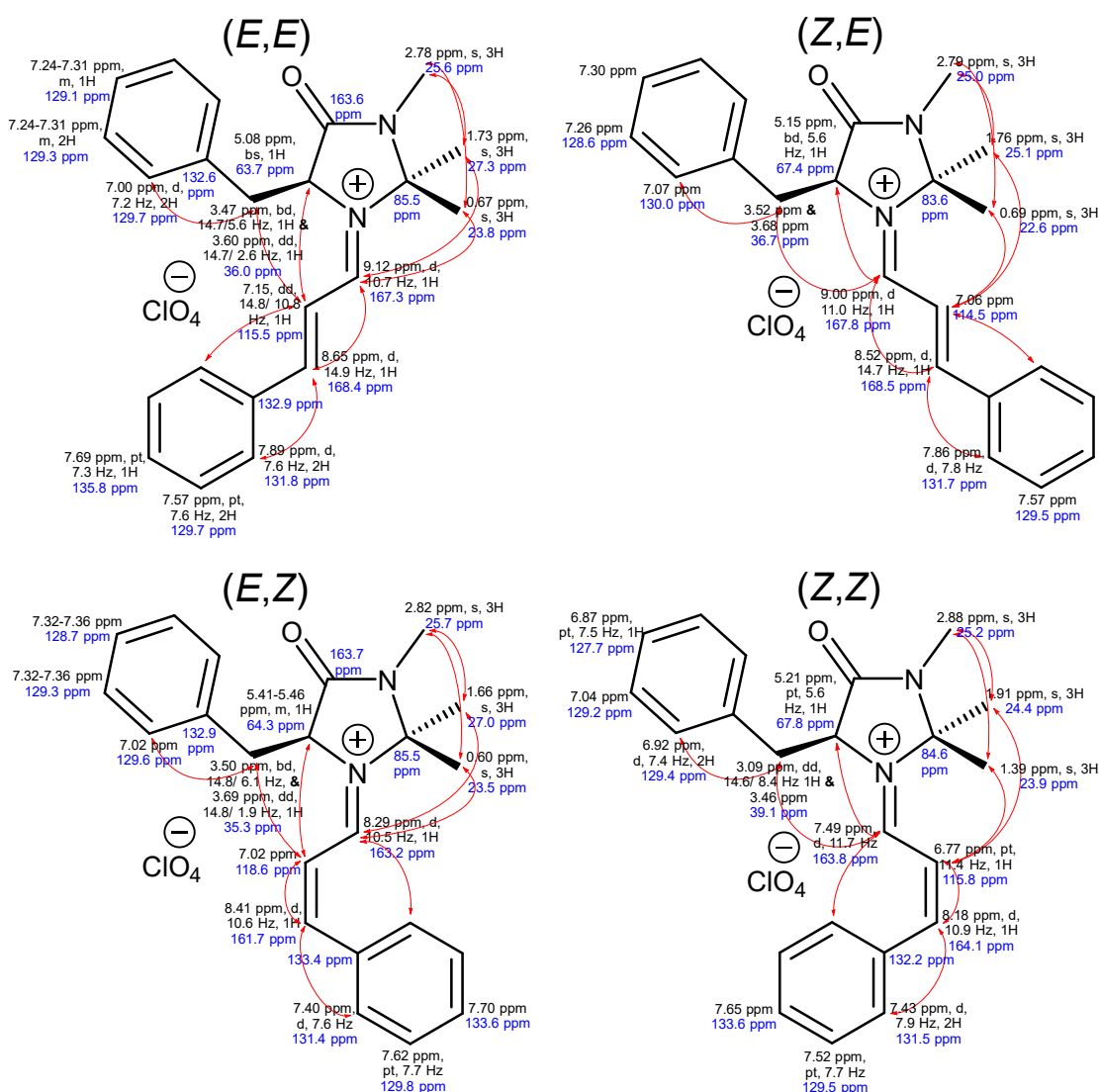


Figure S24. Structure determination of the four configuration isomers (*E,E*), (*Z,E*), (*E,Z*) and (*Z,Z*) in CD₂Cl₂ at -40 °C. Therefore, a sample of iminium ion **1** in anh. and deg. CD₂Cl₂ (10 mM) was continuously illuminated at -40 °C with an LED emitting at 365 nm. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black and ¹³C blue. Distinct NOE interactions, which confirm the double bond configurations, are indicated *via* red arrows. An average ratio of (*E,E*)/(*Z,E*)/(*E,Z*)/(*Z,Z*) = 45:8:41:6 was present during illumination.

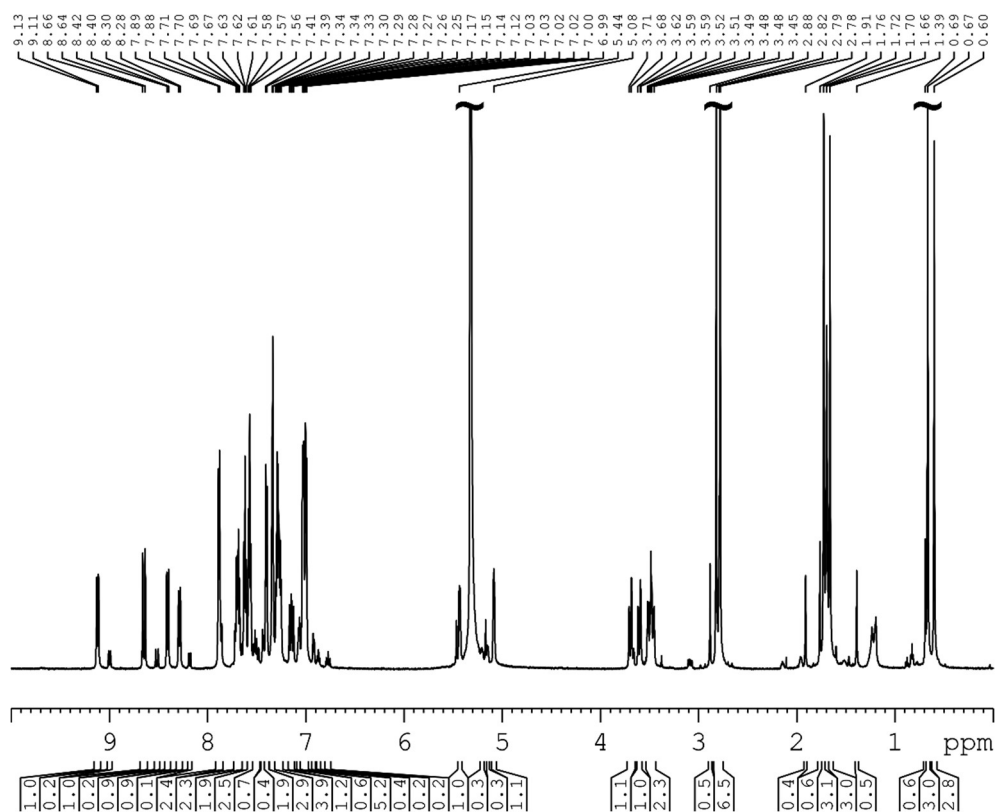


Figure S25. 1D- ^1H spectrum (ns = 16) of **1** in CD_2Cl_2 (10 mM) measured at -40°C under continuous UV-illumination. The integrals are calibrated on the (*E,E*) isomer.

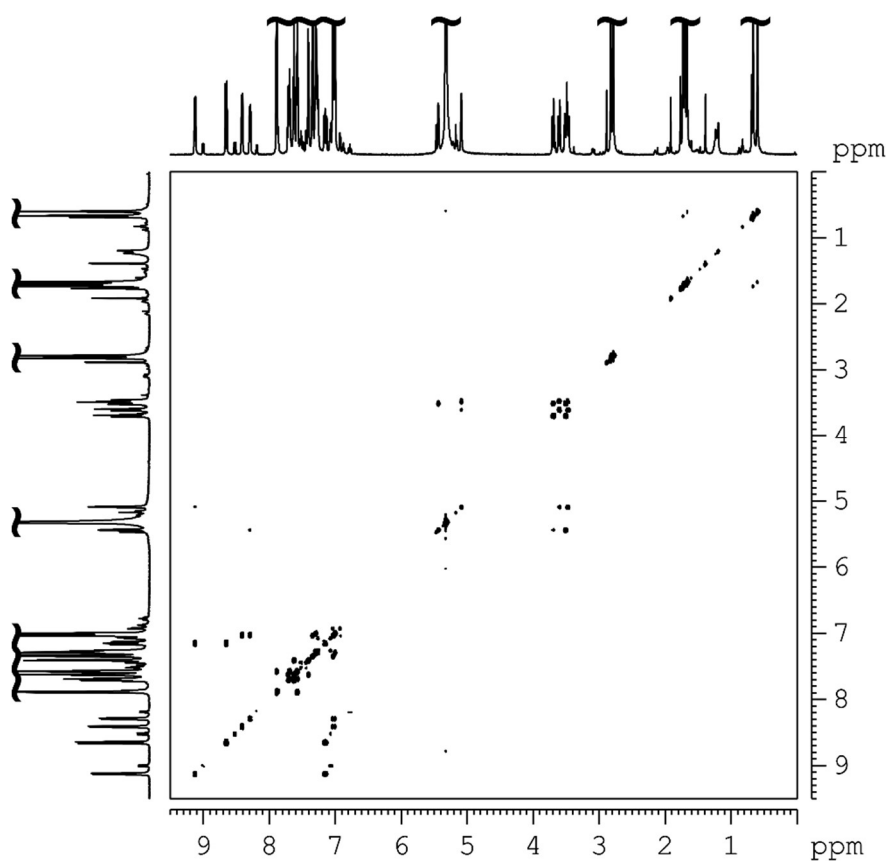


Figure S26. 2D- ^1H , ^1H COSY spectrum of **1** in CD_2Cl_2 (10 mM) measured at -40°C under continuous UV-illumination.

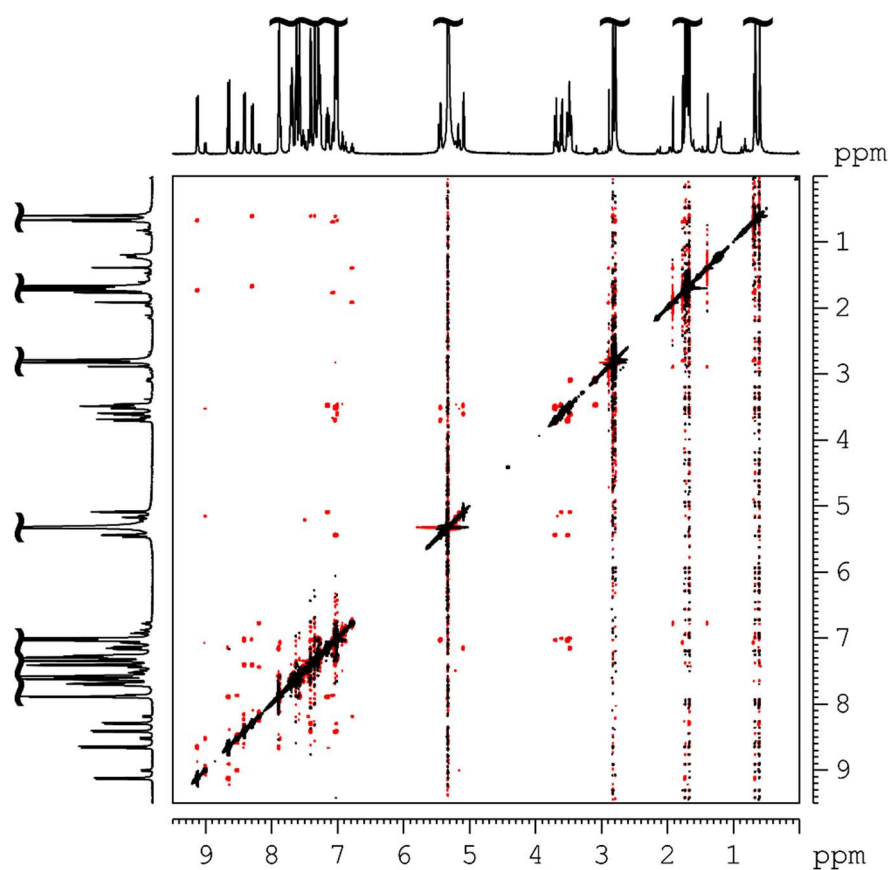


Figure S27. 2D-¹H, ¹H NOESY spectrum (mixing time = 0.5 s) of **1** in CD₂Cl₂ (10 mM) measured at -40 °C under continuous UV-illumination.

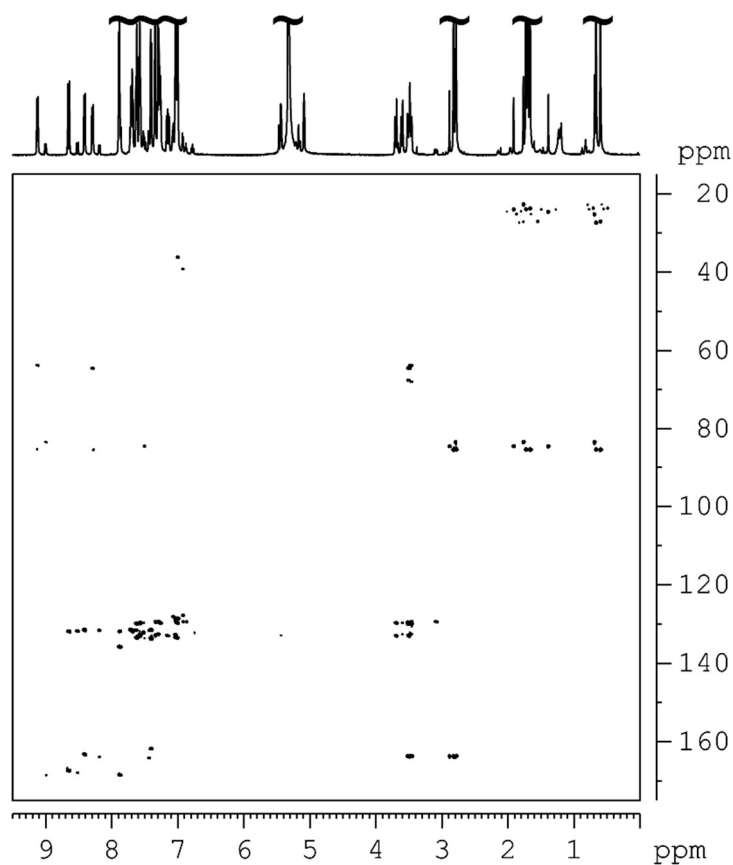


Figure S28. 2D-¹H, ¹³C HMBC spectrum of **1** in CD₂Cl₂ (10 mM) measured at -40 °C under continuous UV-illumination.

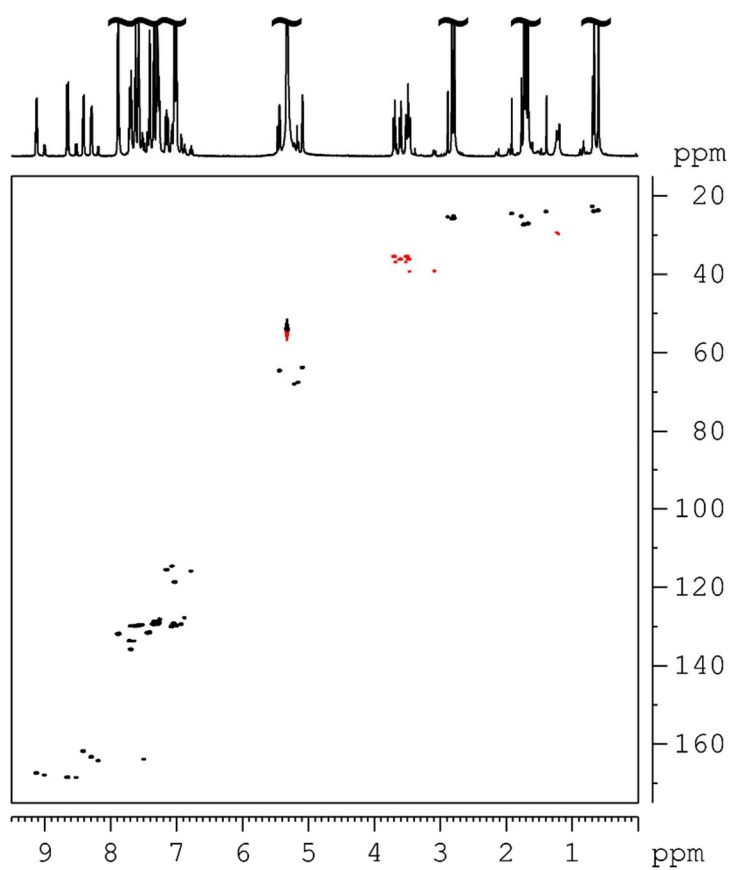


Figure S29. 2D- ^1H , ^{13}C HSQC spectrum of **1** in CD_2Cl_2 (10 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

2.5.5 Detection of (*E,Z*) in thermal equilibrium at 25 °C, *i.e.* under general synthetic conditions

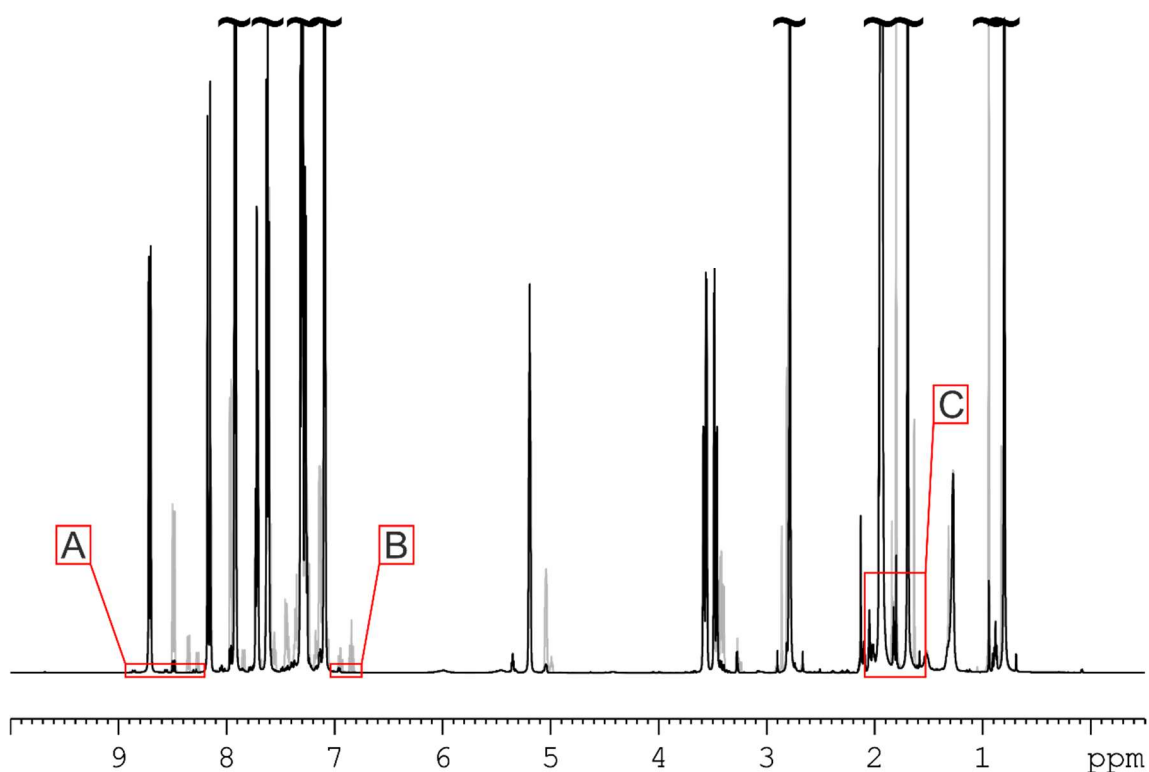


Figure S30. 1D- ^1H spectrum (ns = 1024 (grey spectrum), 2048 (black spectrum)) of **1** in anh. and deg. CD_3CN (10 mM) measured at 25 °C in the dark (black spectrum) and under continuous UV-illumination (grey spectrum). The three sections A, B and C, which contain the ^1H -signals to confirm the presence of (*E,Z*) in thermal equilibrium (*i.e.* without illumination) are depicted in detail in Figure S32-S34. Because only half of the scans were measured under continuous illumination, the intensities of the two spectra were adjusted via the solvent residual signal.

Routine NMR spectroscopy often suffers from its low sensitivity. To check whether next to the already reported (*E,E*) and (*Z,E*) isomers also traces of (*E,Z*) and (*Z,Z*) are present without additional illumination at room temperature (25 °C), we measured a quantitative 1D- ^1H NMR spectrum of **1** with highest possible signal to noise ratio (Figure S30, black spectrum). Therefore a proton optimized TCI CryoProbe was selected. Such a probe gives a signal to noise enhancement of up to a factor of 5 compared to an equivalent room temperature probe. Thus, accumulating 2048 scans gave already an impressive signal to noise ratio. Signals around 5000-times smaller than (*E,E*)H(1) or ca. 43-times less intense as the associated (*E,E*)H(1) ^{13}C satellites could be obtained (see Figure S32). Based on their chemical shift and multiplicity several signals were selected as potential candidates for (*E,Z*) and (*Z,Z*). However, their intensity is too low for a classic structure elucidation. This is only possible *via* selective photo enhancement (Figure S30, grey spectrum). Therefore, we illuminated the NMR sample *in situ* using a UV-LED

(OSRAM LZ4-04UV0R-00000, 365 nm peak wavelength, operated at 0.1 A). Three signals could be identified, which are already present in the dark and can be assigned to the (*E,Z*) isomer due to their explicit response to UV-illumination (Figure S32-S34). For (*Z,Z*) no such signals could be identified in the dark spectrum.

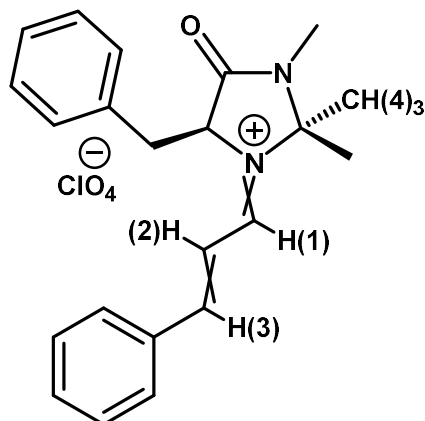


Figure S31. General depiction of iminium ion **1**. The four highlighted protons H(1), H(2), H(3) and H(4) were used to determine whether next to (*E,E*) and (*Z,E*) also traces of (*E,Z*) and (*Z,Z*) can be detected under general synthetic conditions, *i.e.* in thermal equilibrium without additional UV-illumination.

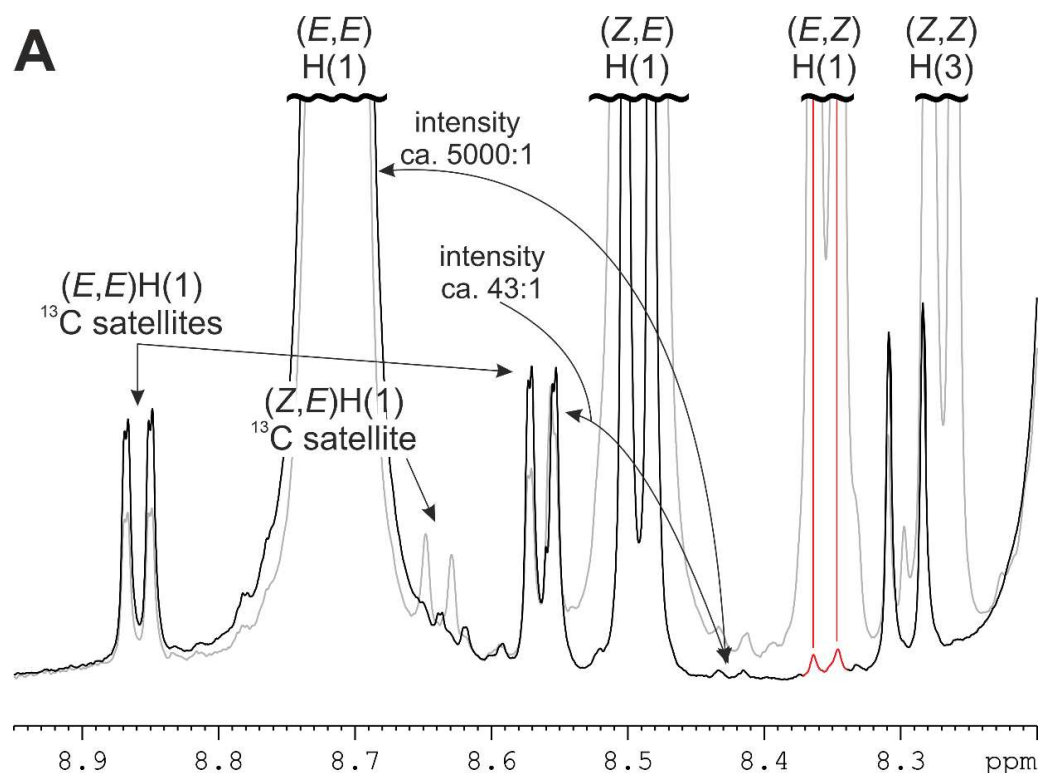


Figure S32. Detailed depiction of Figure S30, section A (128-fold expansion). Without illumination (black spectrum) a signal (highlighted red) could be identified, which may be assigned to (*E,Z*) due to similar chemical shift and multiplicity. As this signal responds to UV-illumination with a significant increase in intensity, this signal can be unambiguously assigned to (*E,Z*)H(1) (see Figure S31).

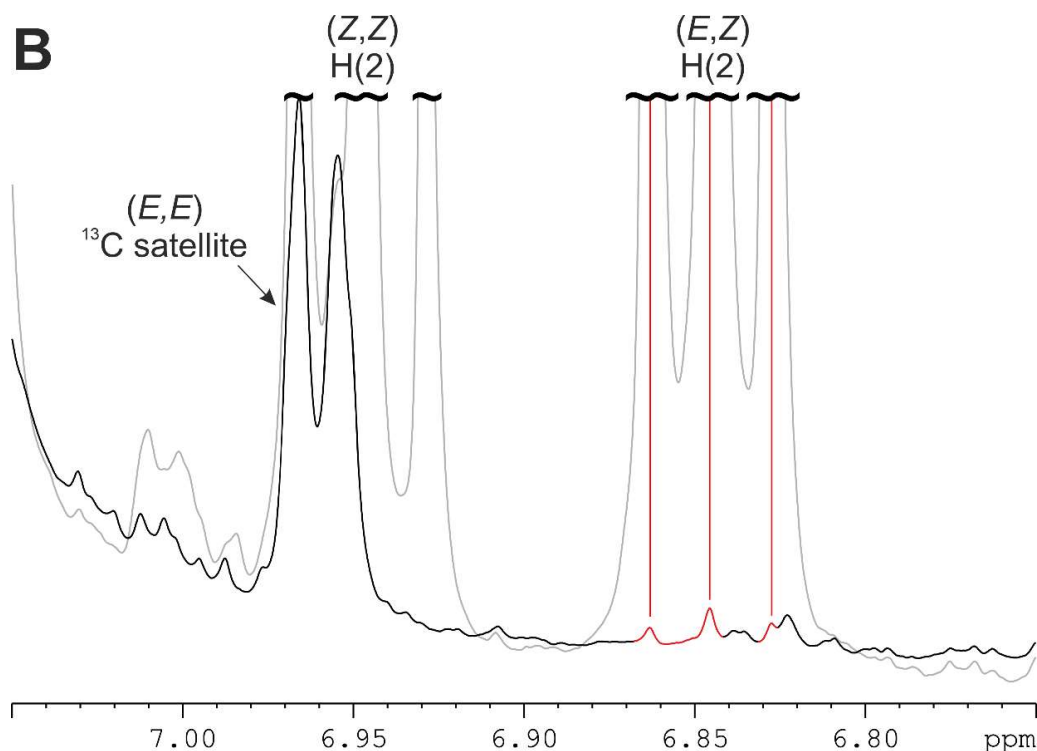


Figure S33. Detailed depiction of Figure S30, section B (128-fold expansion). Without illumination (black spectrum) a signal (highlighted red) could be identified, which may be assigned to (*E,Z*) due to similar chemical shift and multiplicity. As this signal responds to UV-illumination with a significant increase in intensity, this signal can be unambiguously assigned to (*E,Z*)H(2) (see Figure S31).

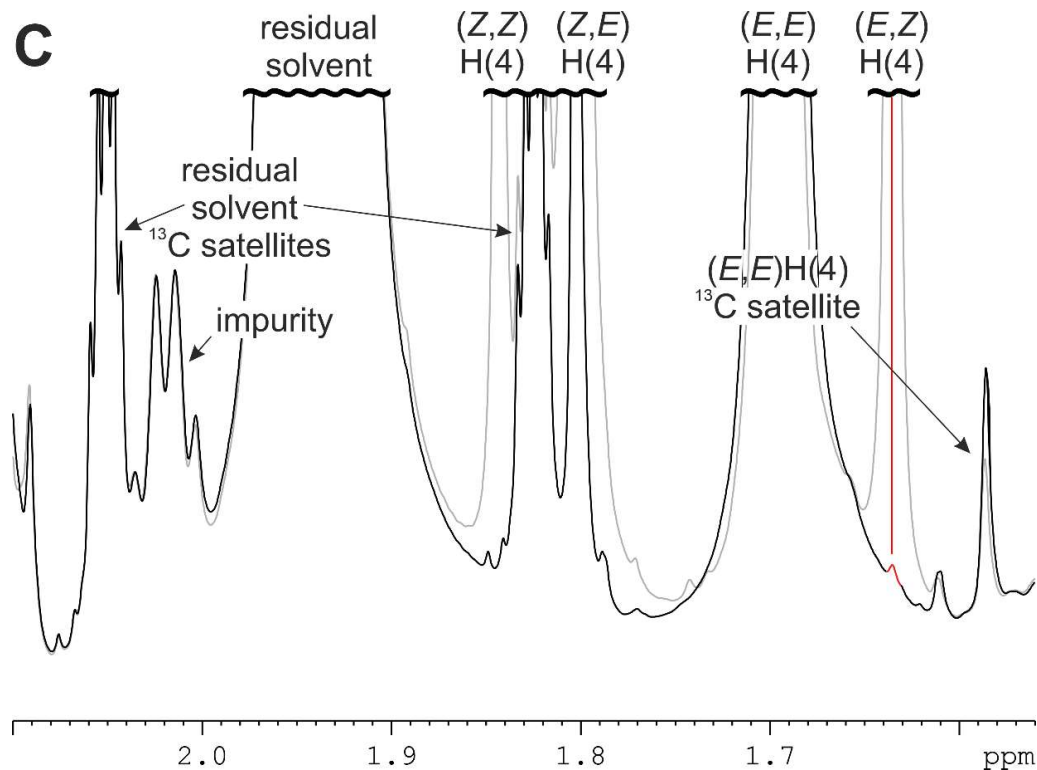


Figure S34. Detailed depiction of Figure S30, section C (16-fold expansion). Without illumination (black spectrum) a signal (highlighted red) could be identified, which may be assigned to (*E,Z*) due to similar chemical shift and multiplicity. As this signal responds to UV-illumination with a significant increase in intensity, this signal can be unambiguously assigned to (*E,Z*)H(4) (see Figure S31).

2.5.6 Determination of thermal (Z) → (E) isomerization rate constants for iminium ion 1 at various conditions

2.5.6.1 Method

The NMR samples were illuminated continuously with an UV-LED (LG Innotek LEUVA66X00RV00) operated with 0.5 A and emitting at a peak wavelength of 365 nm until at least the photostationary state of (Z,E) was achieved. Afterwards the illumination was stopped ($t = 0$ s) followed by recording the thermal (Z) → (E) isomerization processes *via* a quantitative 1D- ^1H NMR kinetic. For a quantitative evaluation we measured the 1D- ^1H NMR spectra as following: For a sufficient signal to noise ratio 16 scans were accumulated per spectrum. A relaxation delay of $d1 = 4$ s in combination with a 30° pulse ensured full relaxation before each scan and pulse lengths for ^1H -experiments were calibrated. Based on these curves, we obtained the different isomerization rates $k_{(Z) \rightarrow (E)}$ by mathematical fitting as first order reaction process (Equation 1).

$$y = A_1 * e^{-k_{(Z) \rightarrow (E)}x} + y_0$$

Equation 1. Mathematical fitting for thermal (Z) → (E) isomerization process as first order reaction process.

We investigated different temperatures, solvents and concentrations to analyze the stabilities of the different (Z)-configured double bond isomers.

2.5.6.2 Influence of Temperature

10 mM, CD₃CN, 20 °C

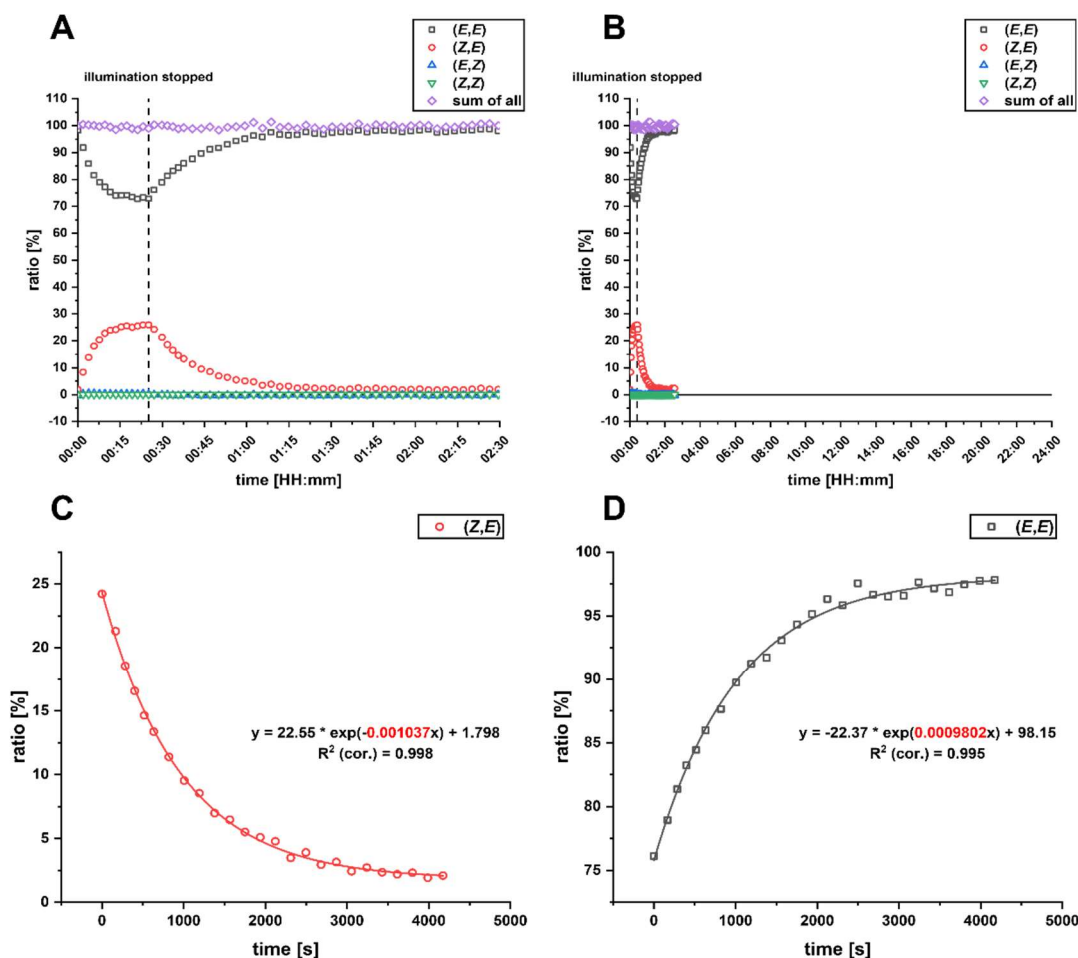


Figure S35. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at 20 °C in acetonitrile-*d*₃ (10 mM). **A:** First 2.5 h of the recorded 1D-¹H-kinetic show in detail how UV-illumination (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. The dashed vertical line indicates the end of illumination. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C** and **D:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S1.

10 mM, CD₃CN, 0 °C

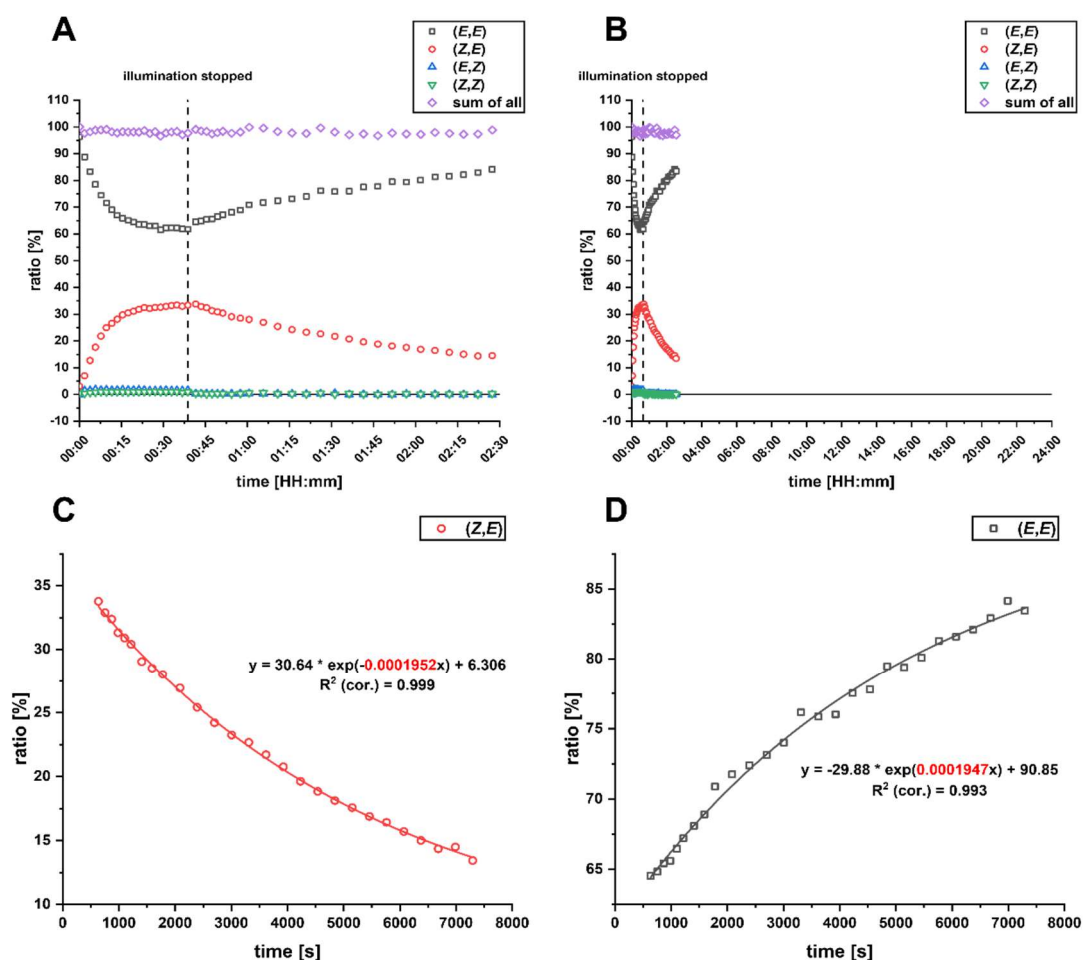


Figure S36. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at 0 °C in acetonitrile-*d*₃ (10 mM). **A:** First 2.5 h of the recorded 1D-¹H kinetic show in detail how UV-illumination (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. The dashed vertical line indicates the end of illumination. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C** and **D:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S1.

10 mM, CD₃CN, -20 °C

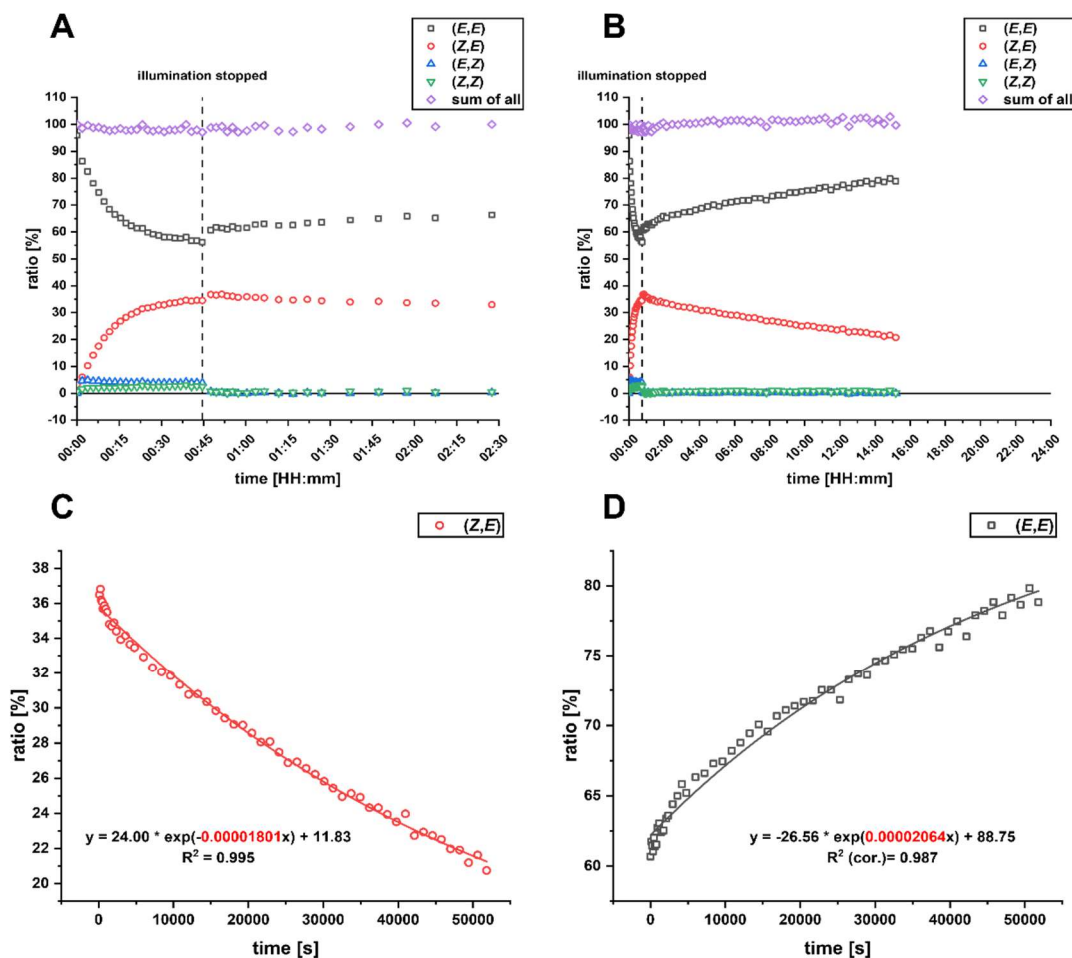
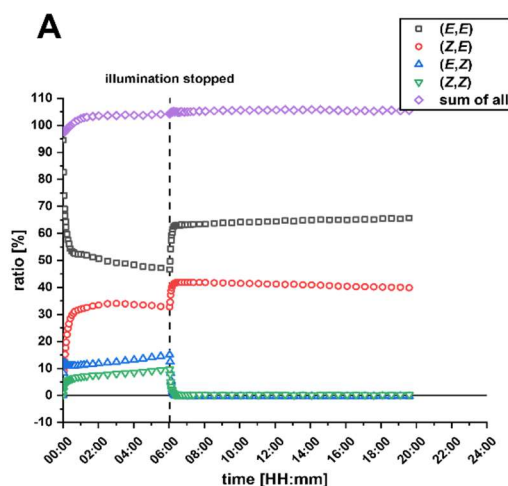


Figure S37. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -20 °C in acetonitrile-*d*₃ (10 mM). **A:** First 2.5 h of the recorded 1D-¹H kinetic show in detail how UV-illumination (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. The dashed vertical line indicates the end of illumination. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C** and **D:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S1.

10 mM, CD₃CN, -40 °C



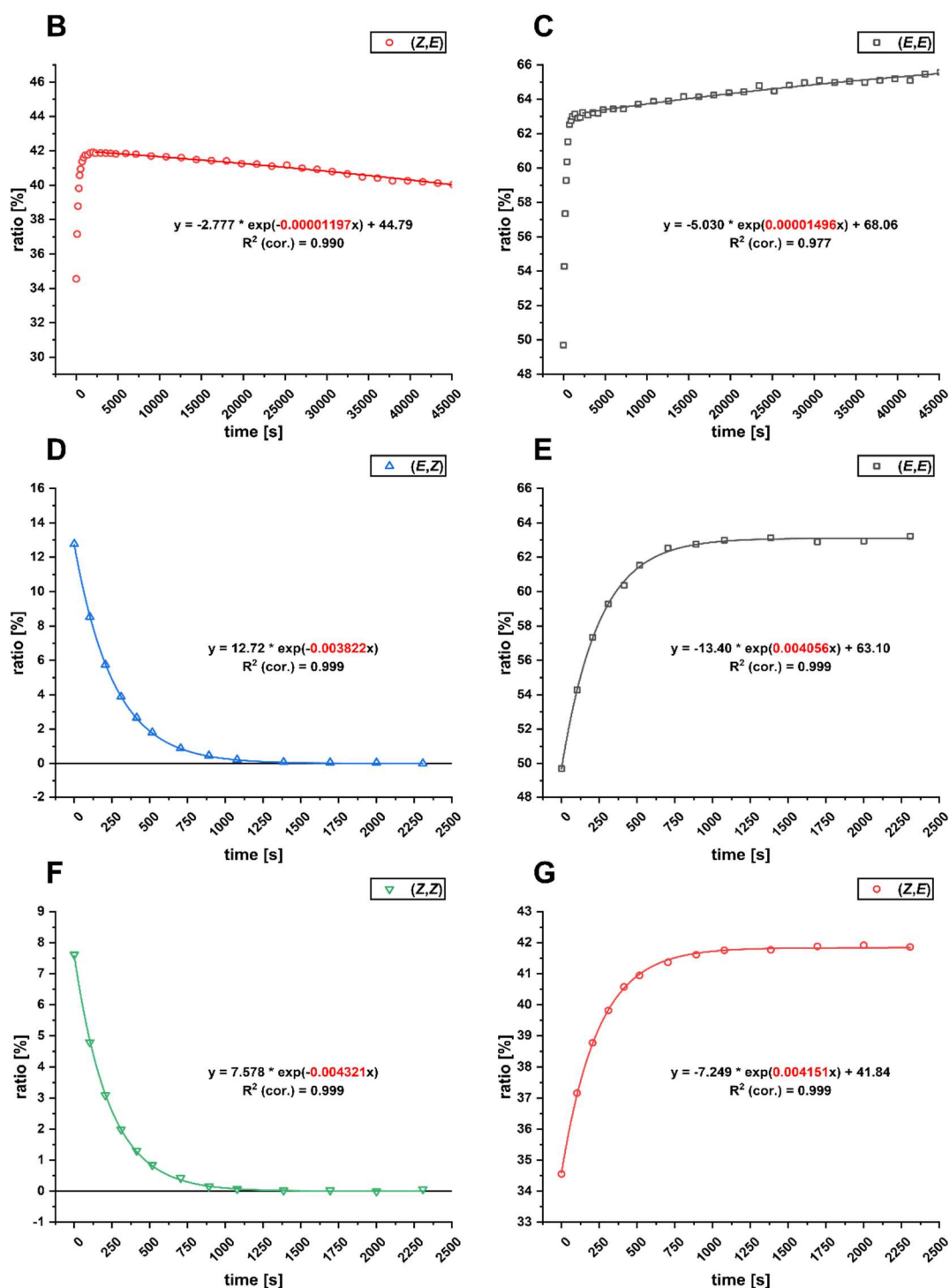


Figure S38. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in acetonitrile-*d*₃ (10 mM). **A:** Complete 1D-¹H kinetic show how UV-illumination (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. The dashed vertical line indicates the end of illumination. **B - G:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S1, S2 and S3.

Table S1. Temperature dependence (20, 0, -20, -40 °C) of thermal (*Z*) → (*E*) isomerization processes of iminium ion **1** in acetonitrile-*d*₃ (10 mM) after UV-triggered (*E*) → (*Z*) isomerization ($\lambda = 365$ nm). To obtain $k_{(Z) \rightarrow (E)}$ the associated isomerization curves (see Figure S35-S38) were mathematically fitted and Equation 1 was applied.

Entry	T [°C]		Process	$k_{(Z) \rightarrow (E)}$ [10^{-3} s^{-1}]
1	20	$(Z,E) \rightarrow (E,E)$	(<i>Z,E</i>)-decay	1.037
2			(<i>E,E</i>)-grow	0.9802
3		$(E,Z) \rightarrow (E,E)$	(<i>E,Z</i>)-decay	-
4			(<i>E,E</i>)-grow	-
5		$(Z,Z) \rightarrow (Z,E)$	(<i>Z,Z</i>)-decay	-
6			(<i>Z,E</i>)-grow	-
7	0	$(Z,E) \rightarrow (E,E)$	(<i>Z,E</i>)-decay	0.1952
8			(<i>E,E</i>)-grow	0.1947
9		$(E,Z) \rightarrow (E,E)$	(<i>E,Z</i>)-decay	-
10			(<i>E,E</i>)-grow	-
11		$(Z,Z) \rightarrow (Z,E)$	(<i>Z,Z</i>)-decay	-
12			(<i>Z,E</i>)-grow	-
13	-20	$(Z,E) \rightarrow (E,E)$	(<i>Z,E</i>)-decay	0.01801
14			(<i>E,E</i>)-grow	0.02064
15		$(E,Z) \rightarrow (E,E)$	(<i>E,Z</i>)-decay	-
16			(<i>E,E</i>)-grow	-
17		$(Z,Z) \rightarrow (Z,E)$	(<i>Z,Z</i>)-decay	-
18			(<i>Z,E</i>)-grow	-
19	-40	$(Z,E) \rightarrow (E,E)$	(<i>Z,E</i>)-decay	0.01197
20			(<i>E,E</i>)-grow	0.01496
21		$(E,Z) \rightarrow (E,E)$	(<i>E,Z</i>)-decay	3.822
22			(<i>E,E</i>)-grow	4.056
23		$(Z,Z) \rightarrow (Z,E)$	(<i>Z,Z</i>)-decay	4.321
24			(<i>Z,E</i>)-grow	4.151

2.5.6.3 Influence of Solvent

10 mM, acetone-*d*₆, -40 °C

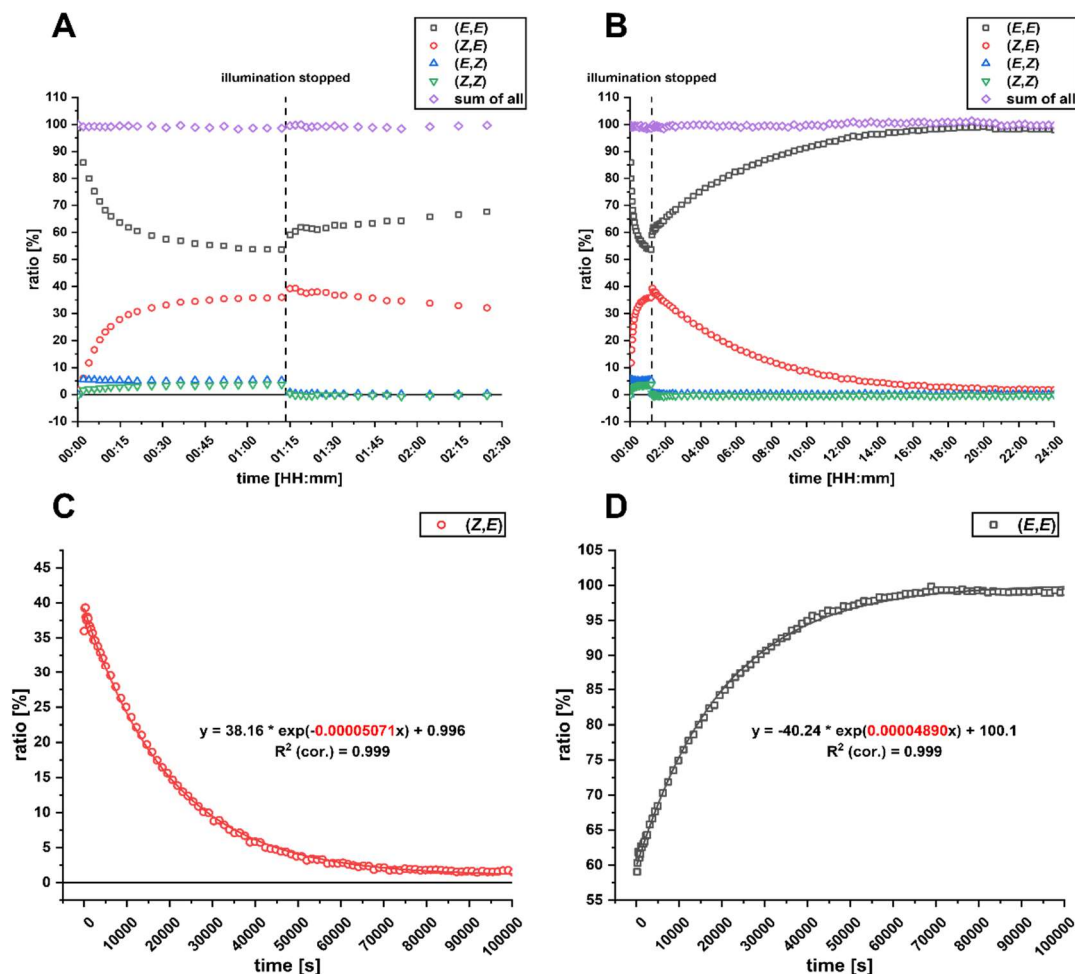


Figure S39. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in acetone-*d*₆ (10 mM). **A**: First 2.5 h of the recorded 1D-¹H kinetic show in detail how UV-illumination (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. The dashed vertical line indicates the end of illumination. **B**: To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C** - **H**: Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S2.

10 mM, CD₂Cl₂, -40 °C

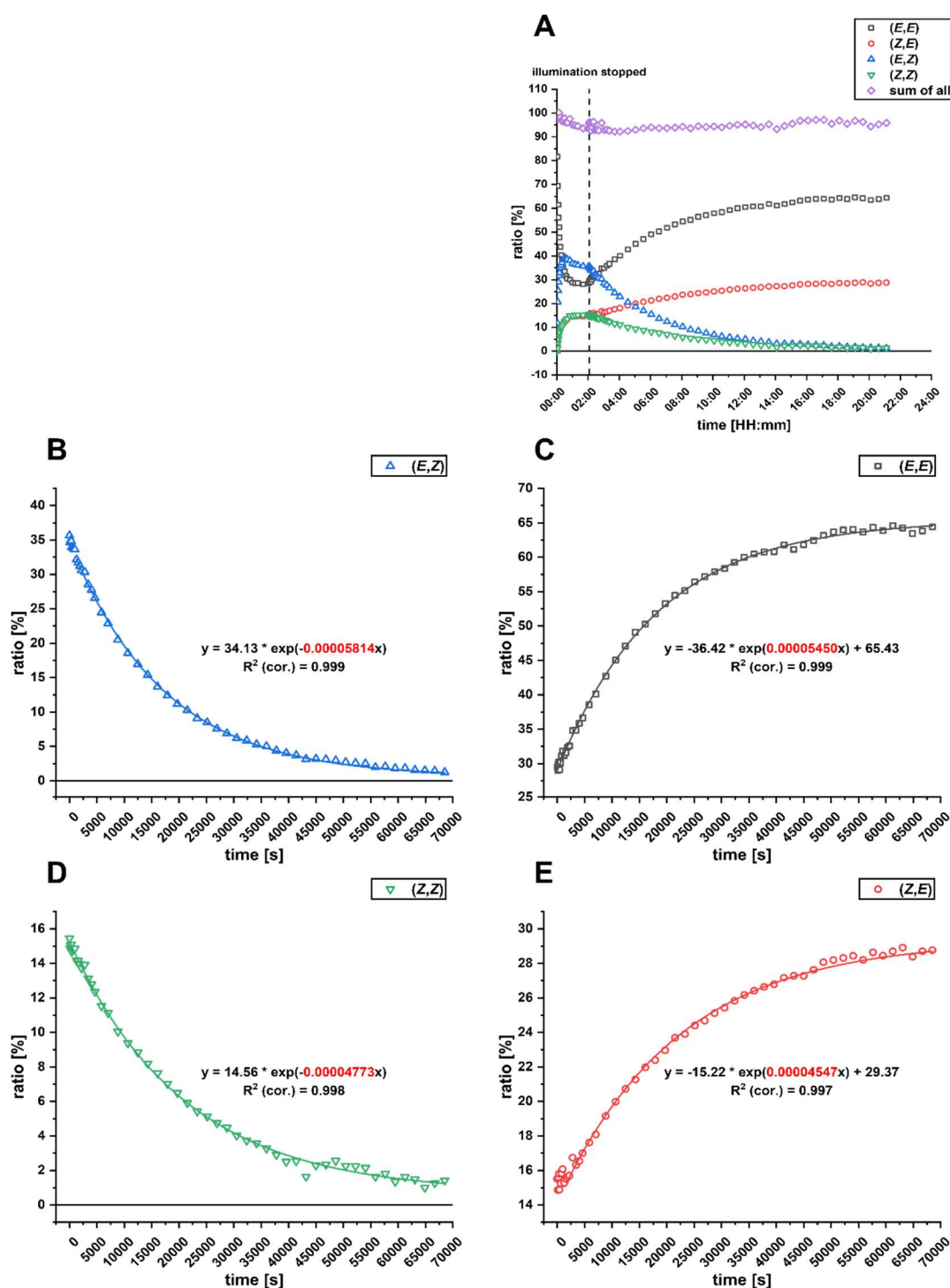


Figure S40. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in dichloromethane-*d*₂ (10 mM). **A**: Complete 1D-¹H kinetic shows how UV-illumination (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. The dashed vertical line indicates the end of illumination. **B** - **E**: Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond isomerization including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S2.

Table S2. Solvent dependence (acetone- d_6 , acetonitrile- d_3 , dichloromethane- d_2) (10 mM) of thermal (Z) $\rightarrow$ (E) isomerization processes of iminium ion **1** at -40 °C after UV-triggered (E) $\rightarrow$ (Z) isomerization (λ = 365 nm). To obtain $k_{(Z) \rightarrow (E)}$ the associated isomerization curves (see Figure S38-S40) were mathematically fitted and Equation 1 was applied.

Entry	Solvent	Process	$k_{(Z) \rightarrow (E)}$ [10^{-3} s^{-1}]
1	Acetone- d_6	(Z,E)-decay	0.05071
2		(Z,E) $\rightarrow$ (E,E)	
3		(E,E)-grow	0.0489
4		(E,Z)-decay	-
5		(E,Z) $\rightarrow$ (E,E)	
6		(E,E)-grow	-
7	CD ₃ CN	(Z,Z)-decay	-
8		(Z,Z) $\rightarrow$ (Z,E)	
9		(Z,E)-grow	-
10		(Z,E)-decay	0.01197
11		(Z,E) $\rightarrow$ (E,E)	
12		(E,E)-grow	0.01496
13	CD ₂ Cl ₂	(E,Z)-decay	3.822
14		(E,Z) $\rightarrow$ (E,E)	
15		(E,E)-grow	4.056
16		(Z,Z)-decay	4.321
17		(Z,Z) $\rightarrow$ (Z,E)	
18		(Z,E)-grow	4.151

2.5.6.4 Influence of Concentration

50 mM, CD₃CN, -40 °C

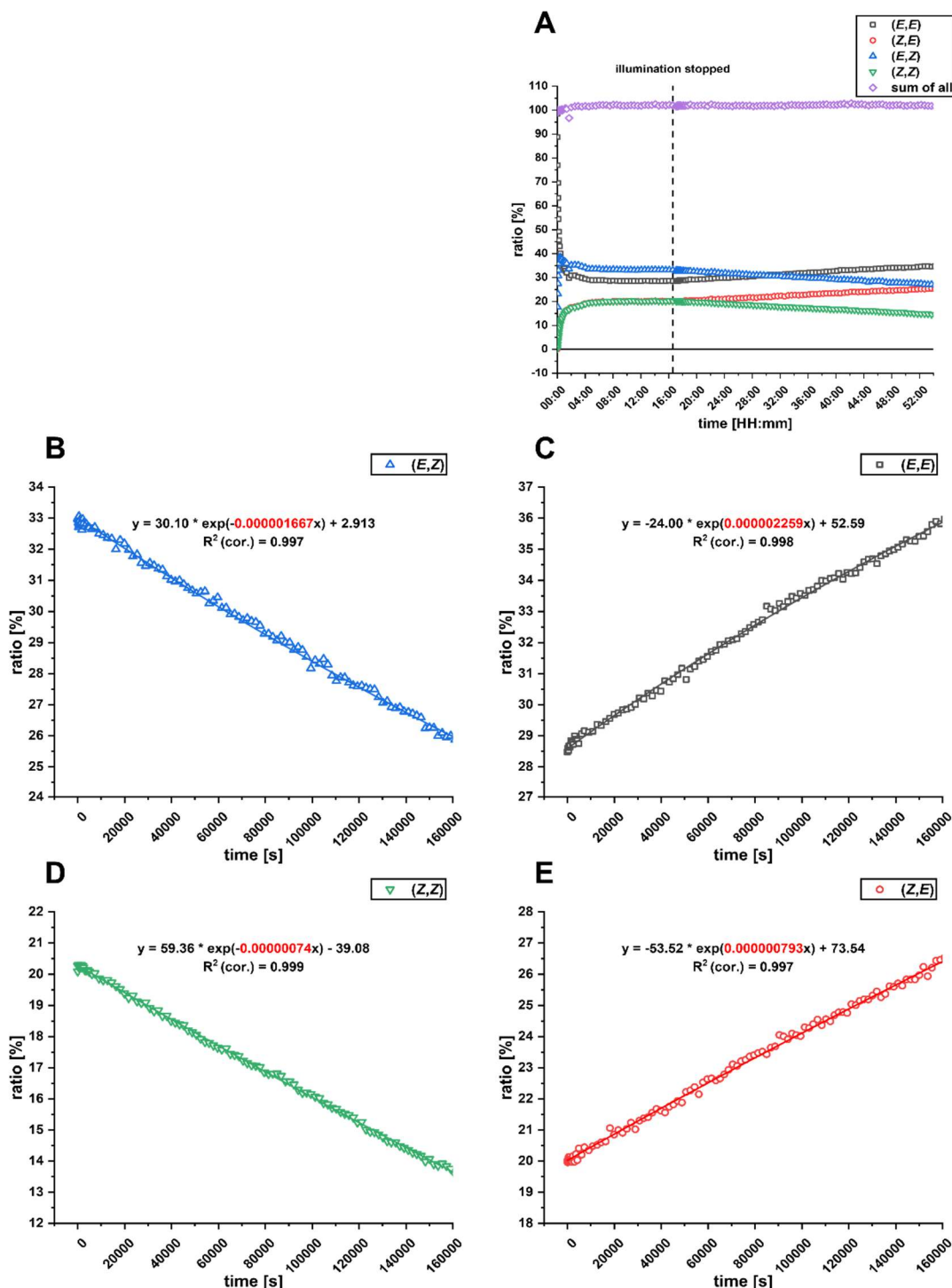
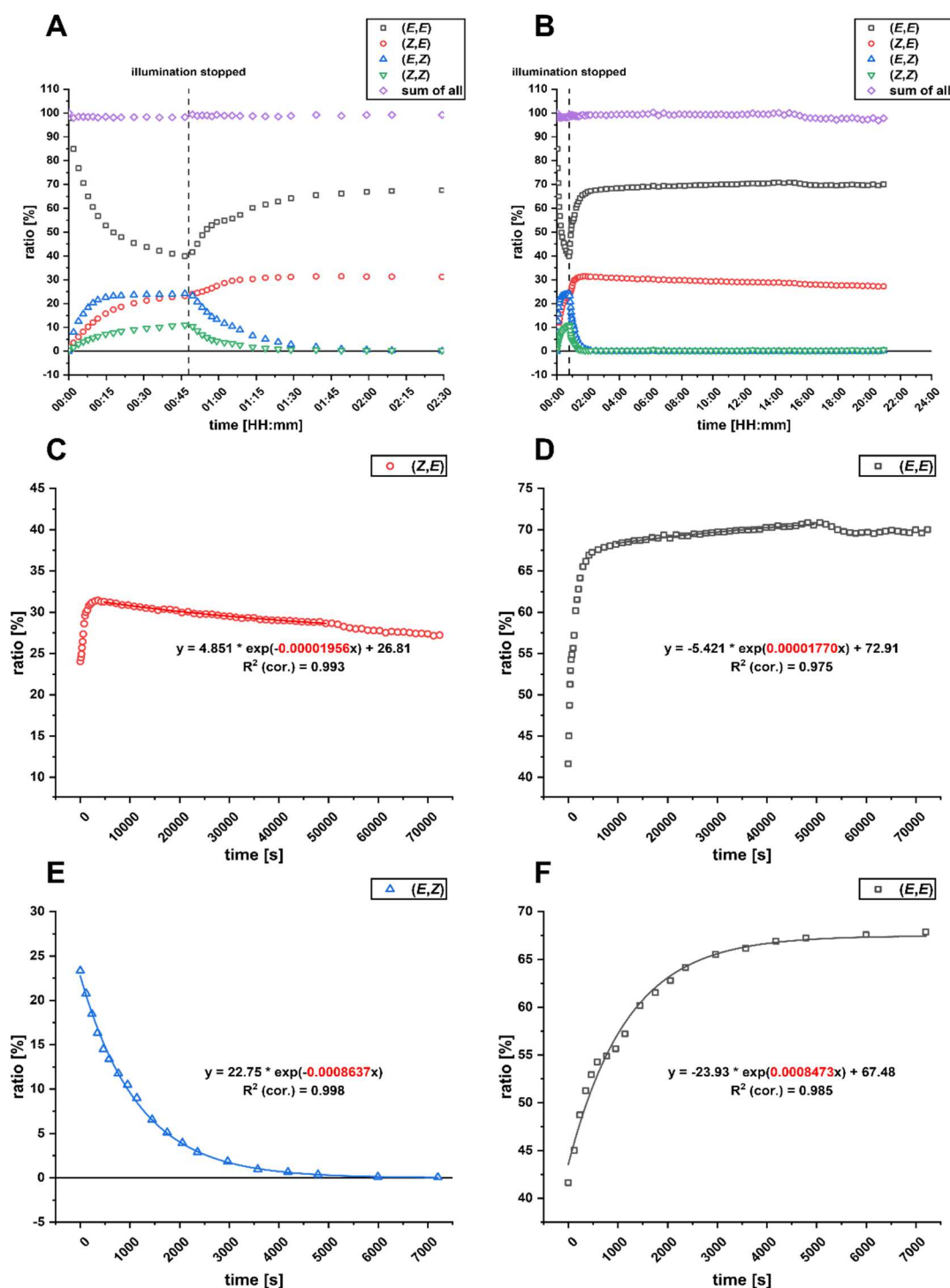


Figure S41. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in acetonitrile-*d*₃ (50 mM). **A:** Complete 1D-¹H kinetic shows how UV-illumination (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. The dashed vertical line indicates the end of illumination. **B - E:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S3.

25 mM, CD₃CN, -40 °C



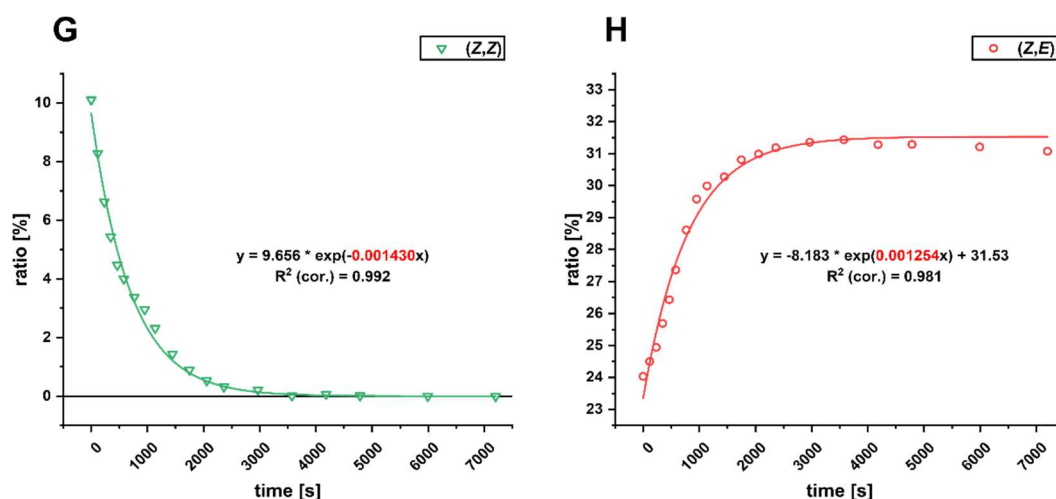


Figure S42. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in acetonitrile-*d*₃ (25 mM). **A:** First 2.5 h of the recorded 1D-¹H kinetic show in detail how UV-illumination (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. The dashed vertical line indicates the end of illumination. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C - H:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S3.

Table S3. Concentration dependence (50, 25, 10 mM) of thermal (Z) → (E) isomerization processes of iminium ion **1** in acetonitrile-d₃ at -40 °C after UV-triggered (E) → (Z) isomerization (λ = 365 nm). To obtain $k_{(Z) \rightarrow (E)}$ the associated isomerization curves (see Figure S38, S41, S42) were mathematically fitted and Equation 1 was applied.

Entry	c [mM]		Process	$k_{(Z) \rightarrow (E)}$ [10^{-3} s^{-1}]
1	50	$(Z,E) \rightarrow (E,E)$	(Z,E) -decay	-
2			(E,E) -grow	-
3		$(E,Z) \rightarrow (E,E)$	(E,Z) -decay	0.001667
4			(E,E) -grow	0.002259
5		$(Z,Z) \rightarrow (Z,E)$	(Z,Z) -decay	0.00074
6			(Z,E) -grow	0.000793
7	25	$(Z,E) \rightarrow (E,E)$	(Z,E) -decay	0.01956
8			(E,E) -grow	0.0177
9		$(E,Z) \rightarrow (E,E)$	(E,Z) -decay	0.8637
10			(E,E) -grow	0.8473
11		$(Z,Z) \rightarrow (Z,E)$	(Z,Z) -decay	1.43
12			(Z,E) -grow	1.254
13	10	$(Z,E) \rightarrow (E,E)$	(Z,E) -decay	0.01197
14			(E,E) -grow	0.01496
15		$(E,Z) \rightarrow (E,E)$	(E,Z) -decay	3.822
16			(E,E) -grow	4.056
17		$(Z,Z) \rightarrow (Z,E)$	(Z,Z) -decay	4.321
18			(Z,E) -grow	4.151

2.5.7 Aggregate-investigations of (*E,E*) by diffusion ordered spectroscopy (DOSY) using different concentrations, temperatures and solvents

2.5.7.1 Method

For DOSY measurements the dstebpgp3s pulse program, a convection suppressing DSTE (double stimulated echo) pulse sequence developed by Jerschow and Müller was applied in a pseudo 2D mode.²² The diffusion time delay was set to 100 ms and a gradient pulse of 1350 -2300 μ s was applied. Sine.100 as gradient program and a linear gradient ramp with 20 increments between 10% and 95% of the maximum gradient strength were used. For z-only gradients 100 %, -13.17%, -17.13% and -15.17% were used. NMR data were processed and evaluated with TopSpin 3.2 (Topspin T1/T2 Module). Diffusion coefficients and average volumes were obtained according to Jerschow and Müller.²²

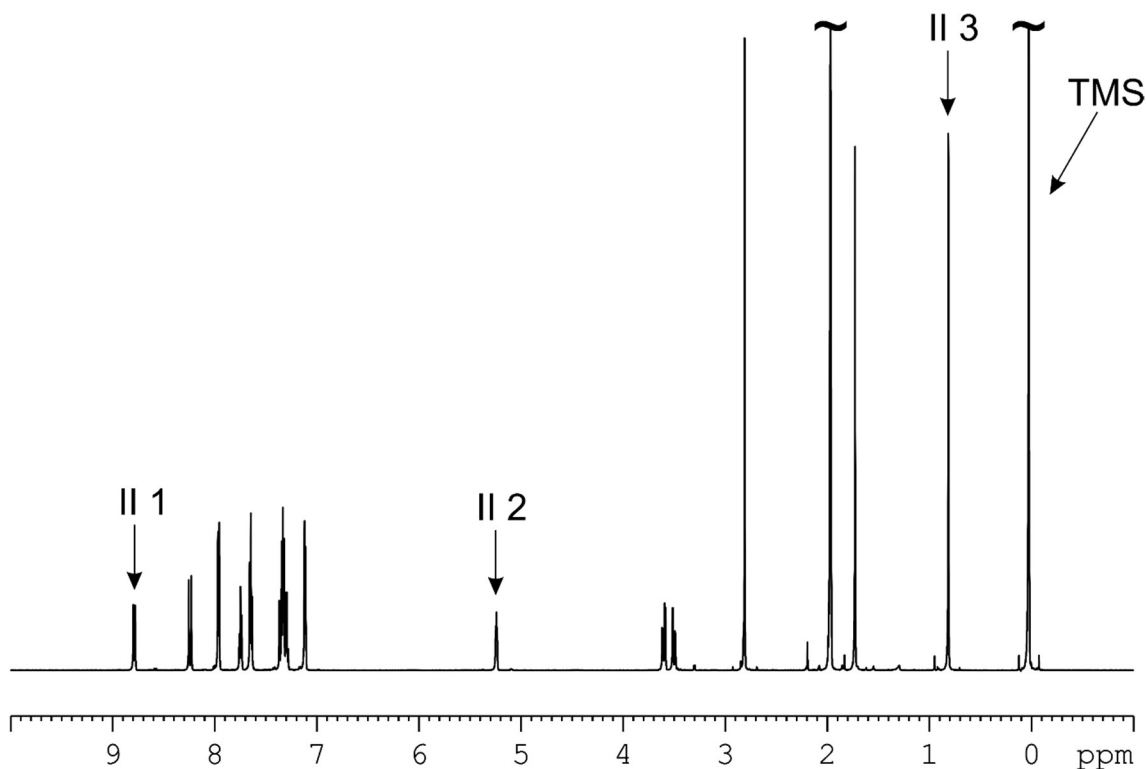


Figure S43. Representative 1D-¹H NMR spectrum of iminium ion **1** measured in anh. and deg. CD₃CN at 20 °C. The volumes given in Tables S4 and S5 correspond to mean values with standard deviation (SD). These DOSY-values were obtained by evaluation of the intense and non-overlapping signals II 1, II 2 and II 3 of (*E,E*).

2.5.7.2 Influence of concentration, temperature and solvent

We aimed to experimentally determine the volumes of (*E,E*) at different conditions, *i.e.* the influence of temperature, concentration and solvents on the aggregate size was investigated. Assuming that model iminium ion **1** forms a contact ion pair in aprotic solvents, a monomer volume of 412 Å³ was calculated for (*E,E*) based on the known intermolecular van der Waals radii of the corresponding functional groups and atoms.²³ Given this monomer volume, we are able to assign the DOSY volumes to a certain aggregate size.

The influence of the concentration on the aggregation of iminium ion **1** was determined by investigating differentially concentrated samples at 20 and -40 °C (Table S4).

Table S4. Mean diffusion coefficients and average volumes of (*E,E*) at different temperatures (20 and -40 °C) and concentrations (50, 25, 10 mM) in anh. and deg. CD₃CN.

Entry	T [°C]	c [mM]	mean diffusion coefficient [E-9 m ² /s] with SD	average volume [Å ³] with SD
1	20	50	5.58 ± 0.0731	844.5 ± 28.92
2		25	5.72 ± 0.0693	851.7 ± 27.0
3		10	5.87 ± 0.045	809.7 ± 16.16
4	-40	50	1.89 ± 0.00684	1152 ± 11.15
5		25	2.0 ± 0.0258	1036 ± 35.51
6		10	2.06 ± 0.0153	1063 ± 21.06

We similarly investigated the influence of different solvents, also at 20 and -40 °C (Table S5).

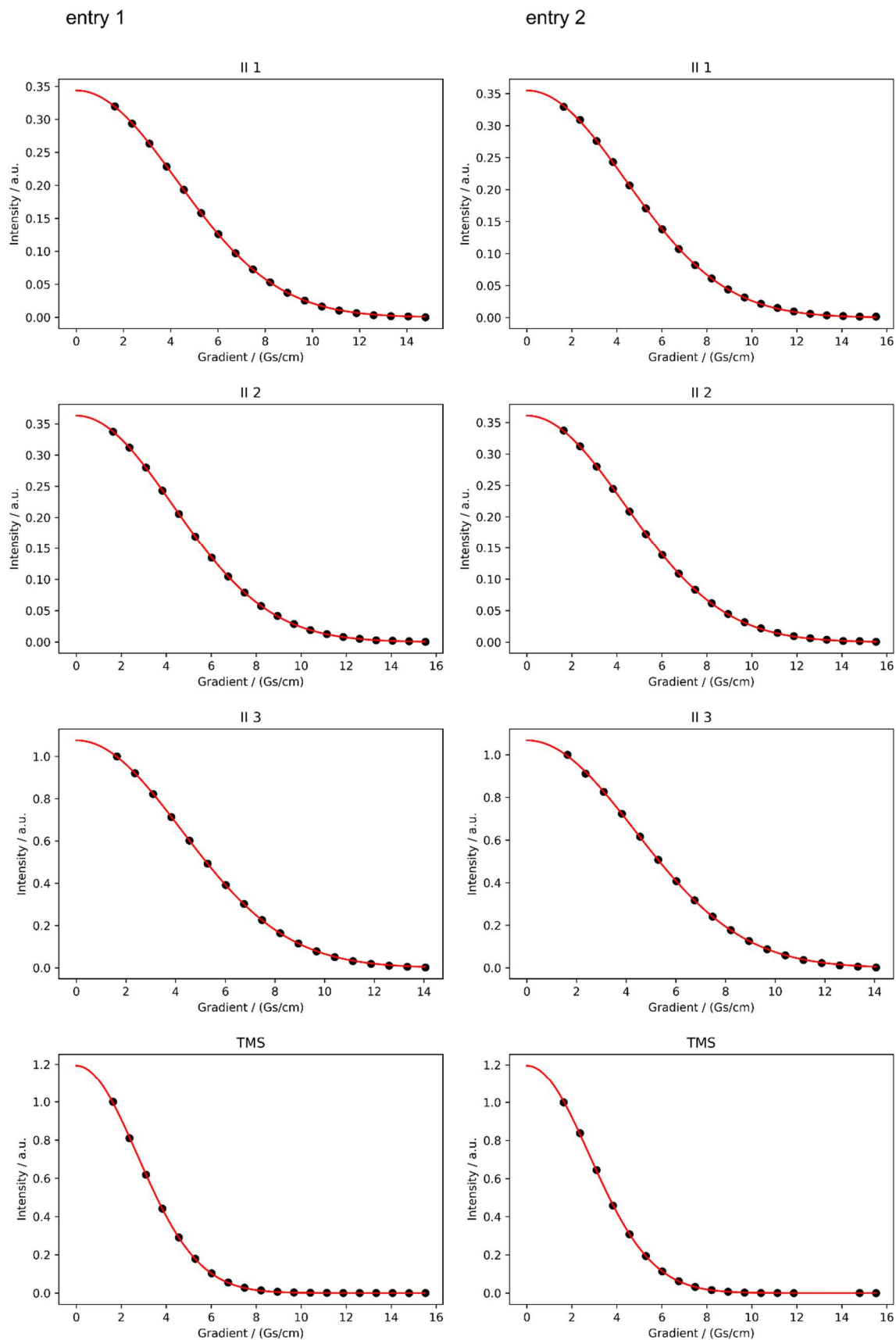
Table S5. Mean diffusion coefficients and average volumes of (*E,E*) at different temperatures (20 and -40 °C) and in different solvents (acetone-*d*₆, CD₃CN, CD₂Cl₂) (10 mM).

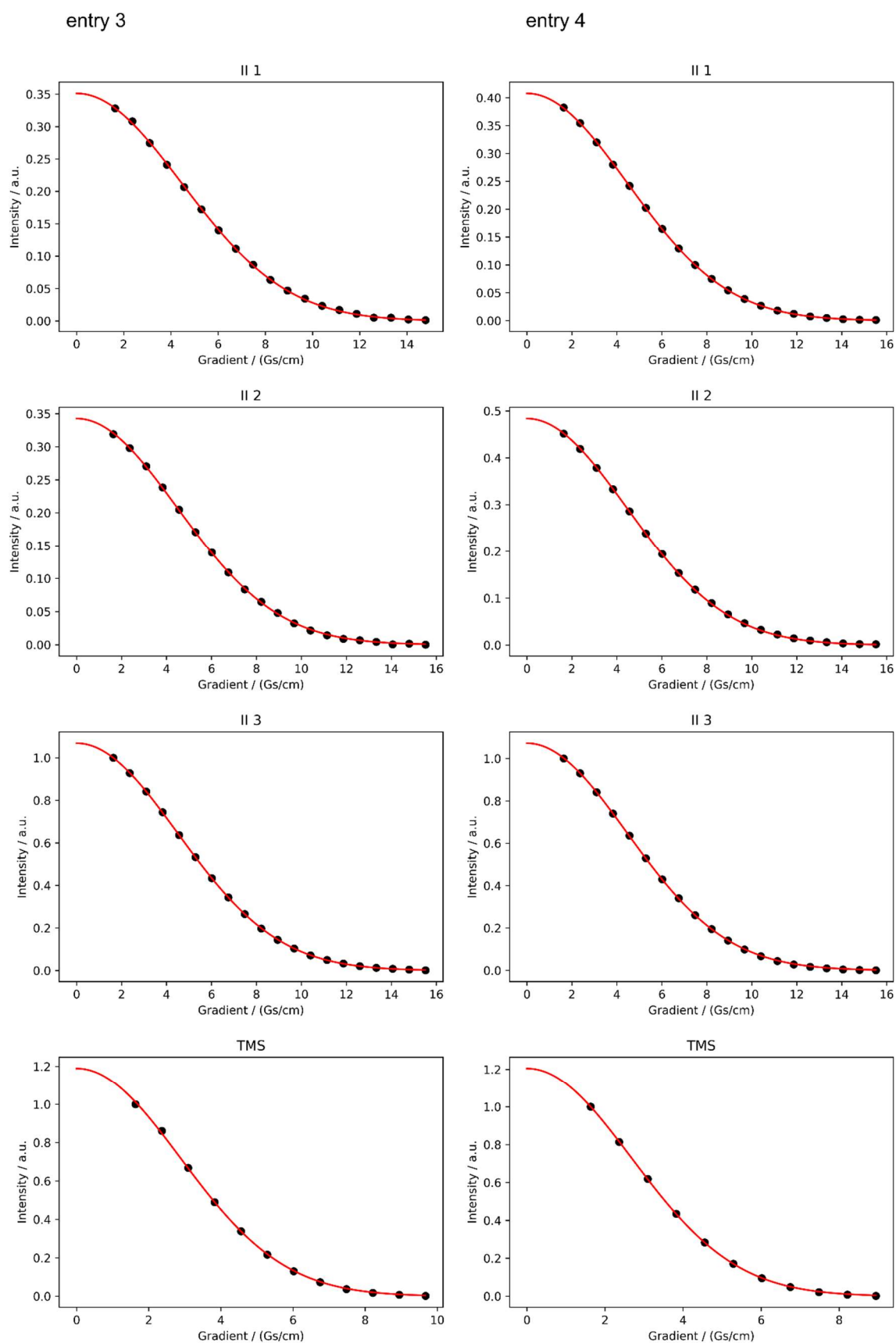
Entry	T [°C]	Solvent	mean diffusion coefficient [E-9 m ² /s] with SD	average volume [Å ³] with SD
1	20	acetone- <i>d</i> ₆	6.41 ± 0.107	1053 ± 44.7
2		CD ₃ CN	5.87 ± 0.045	809.7 ± 16.16
3		CD ₂ Cl ₂	4.54 ± 0.0167	753.9 ± 7.423
4	-40	acetone- <i>d</i> ₆	2.39 ± 0.0348	1276.8 ± 47.95
5		CD ₃ CN	2.06 ± 0.0153	1063 ± 21.06
6		CD ₂ Cl ₂	1.65 ± 0.00985	981.1 ± 15.03

Herein we found, that the biggest (*E,E*) volume was obtained in the most nucleophilic solvent. We believe this volume increase indicates an improving interaction of the iminium ion and the solvent molecule, similar to previous studies on enamine intermediates.²⁴

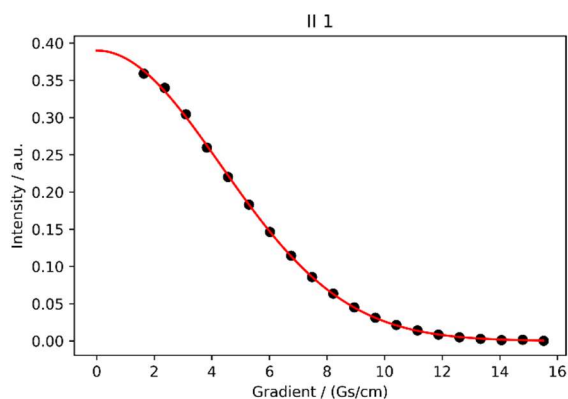
2.5.7.3 DOSY plots

Concentration dependence (see Table S4)

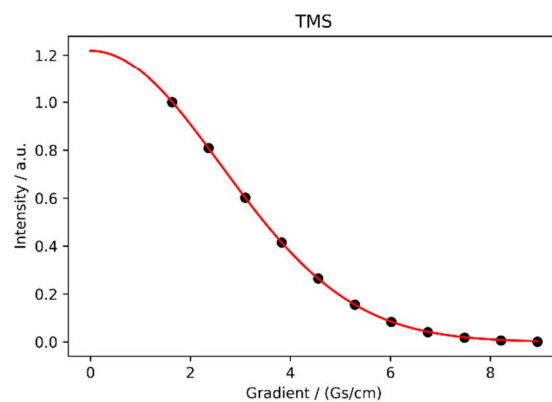
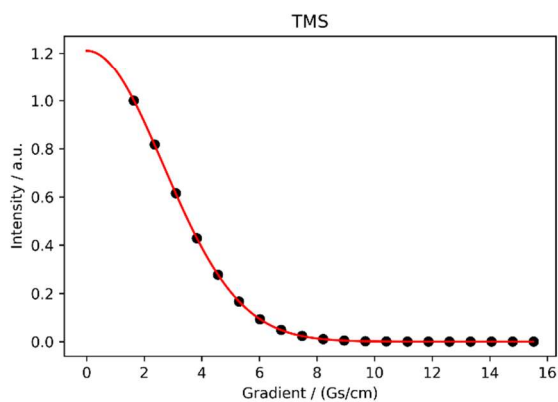
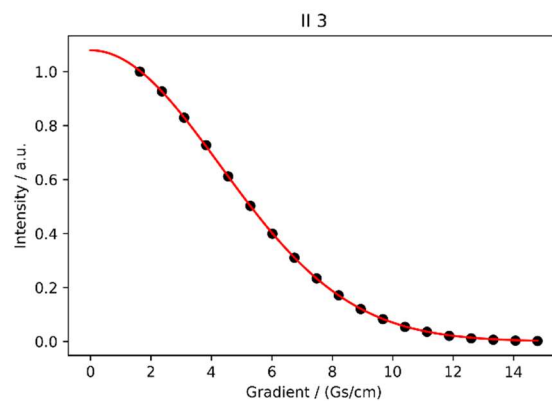
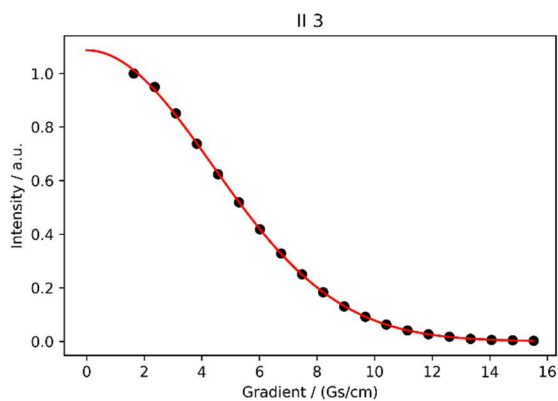
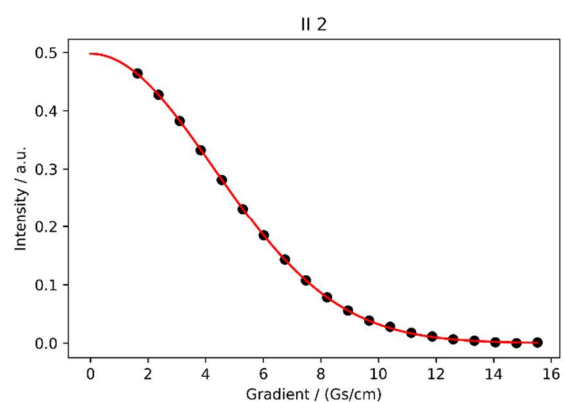
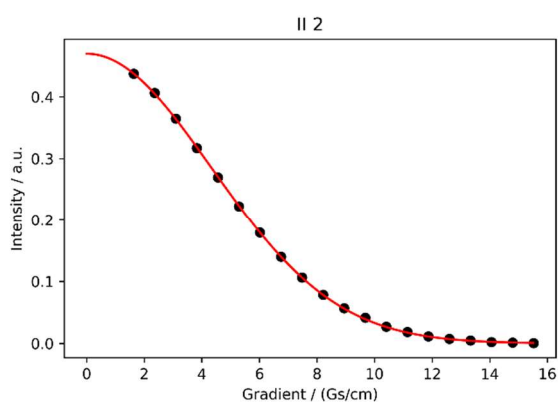
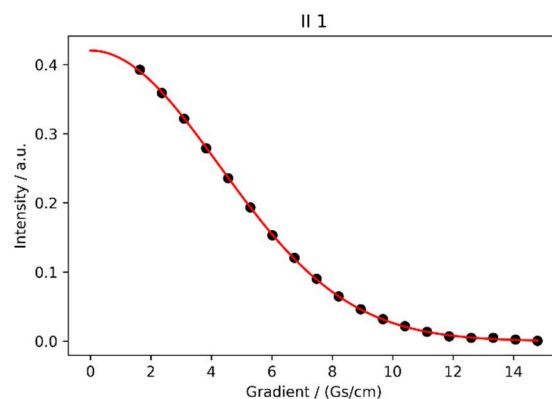




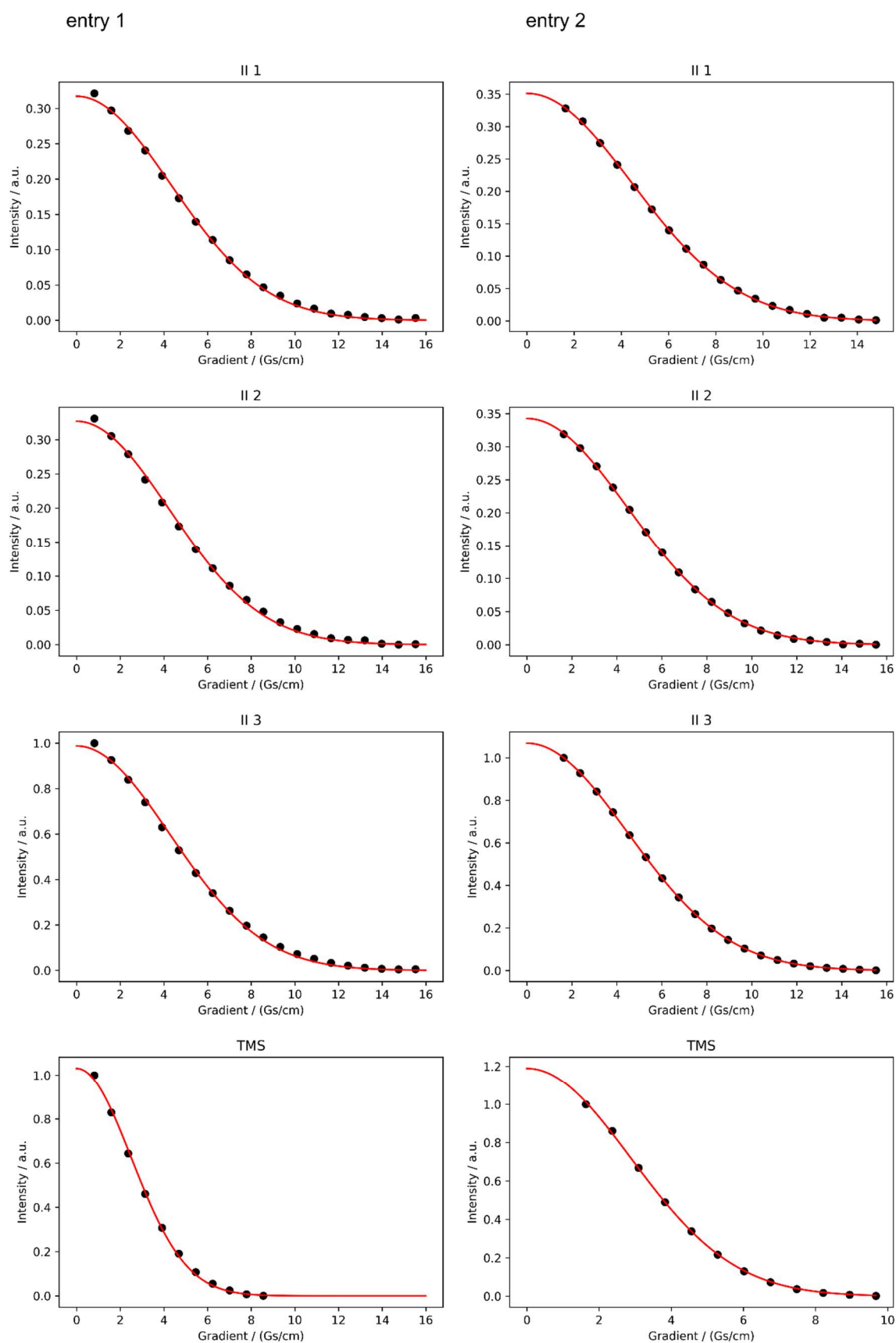
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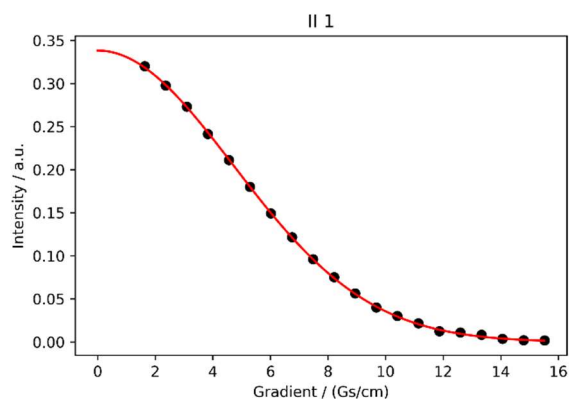
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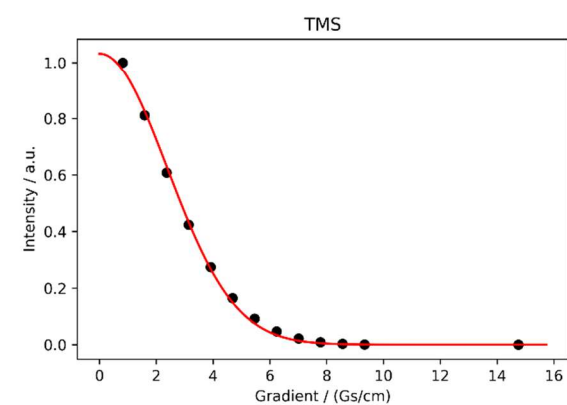
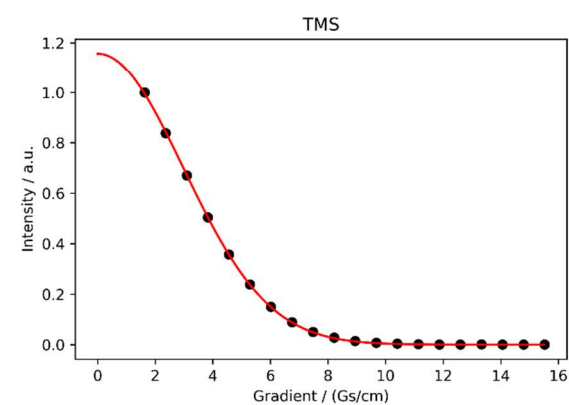
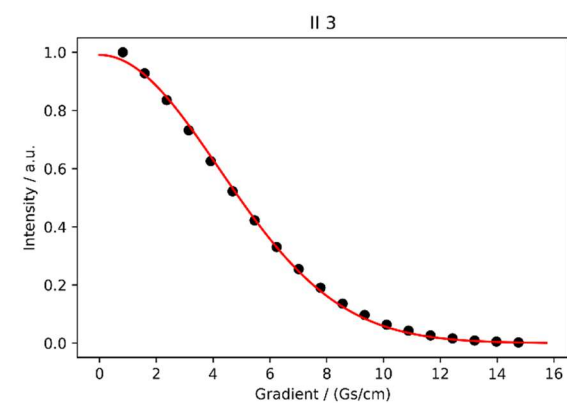
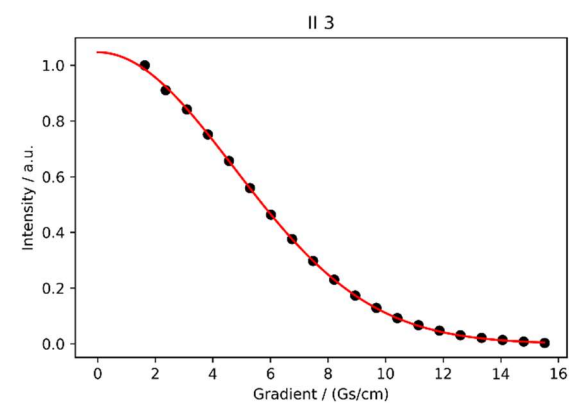
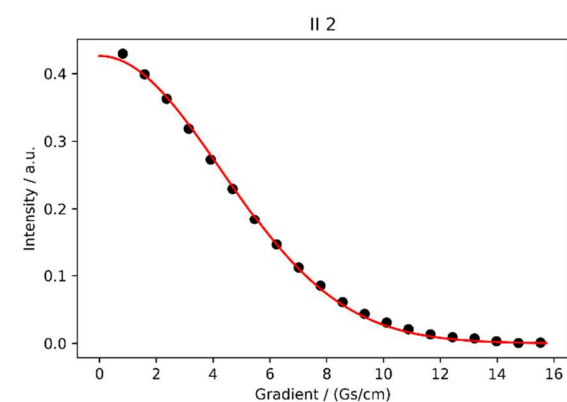
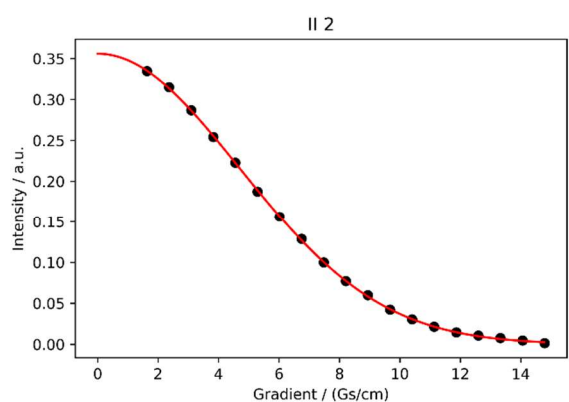
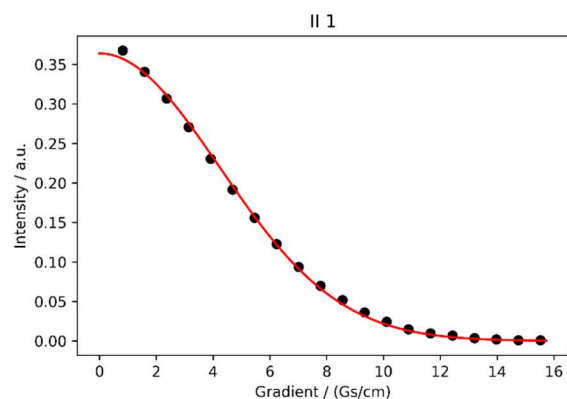
Solvent-dependence (see Table S5)



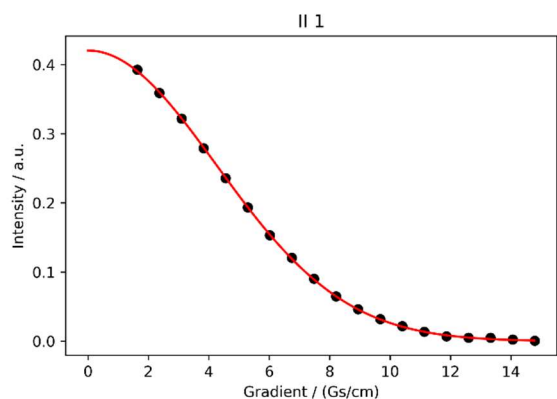
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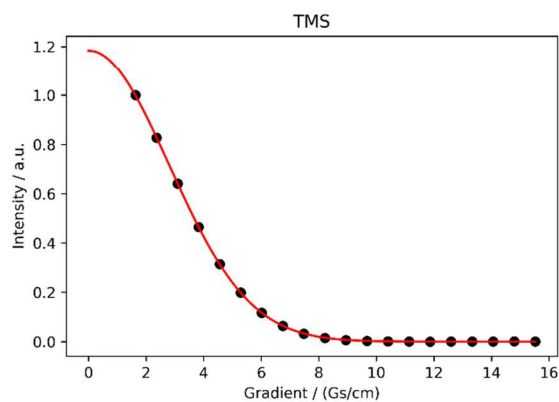
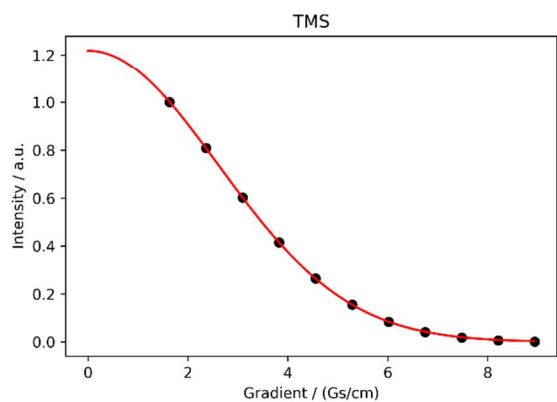
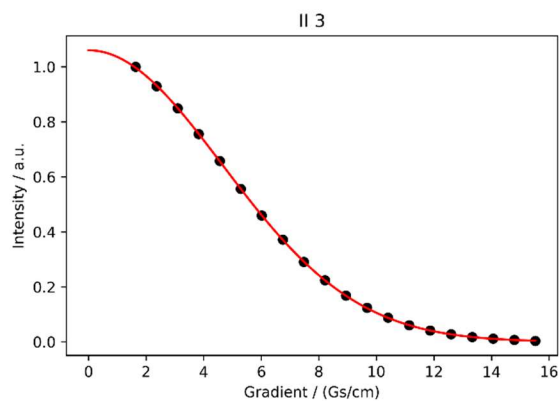
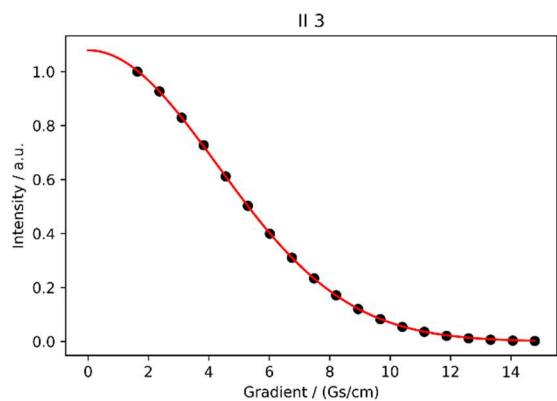
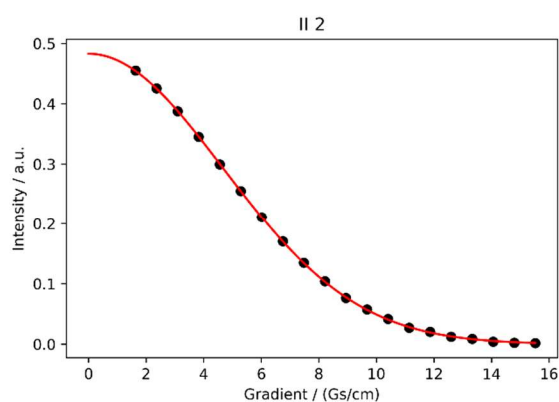
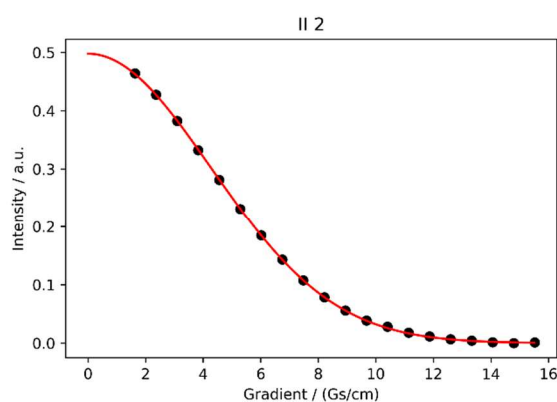
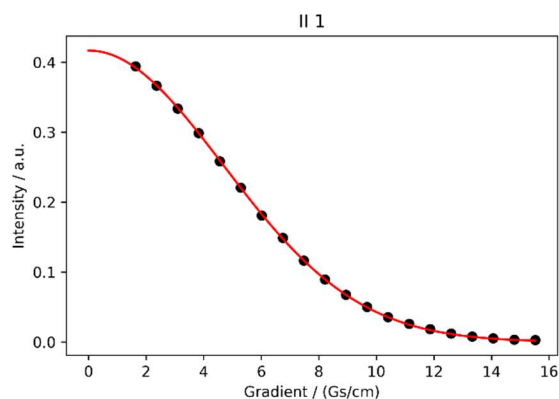
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entry 5



entry 6



2.5.8 Combined *in situ* illumination-NMR-UV/Vis spectroscopy of **1** in CD₃CN at -40 °C

We were wondering whether the amount of (*Z*)-configured isomers can be increased by a more selective photo illumination. However, for this adequately separated UV/Vis spectra of the different configuration isomers are essential, which we investigated using combined *in situ* illumination-NMR-UV/Vis spectroscopy. This method allows to simultaneously record UV/Vis and NMR spectra of photochemically generated species.²¹ Thus, potential new UV/Vis bands can more easily be interpreted due to e.g. additional structural information obtained *via* NMR spectroscopy.

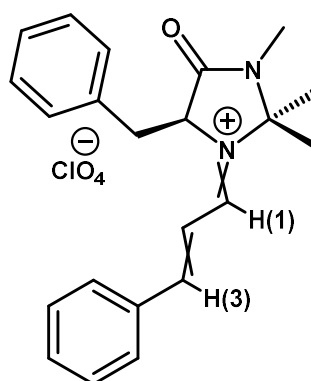


Figure S44. General depiction of iminium ion **1** with the two highlighted protons H(1), and H(3).

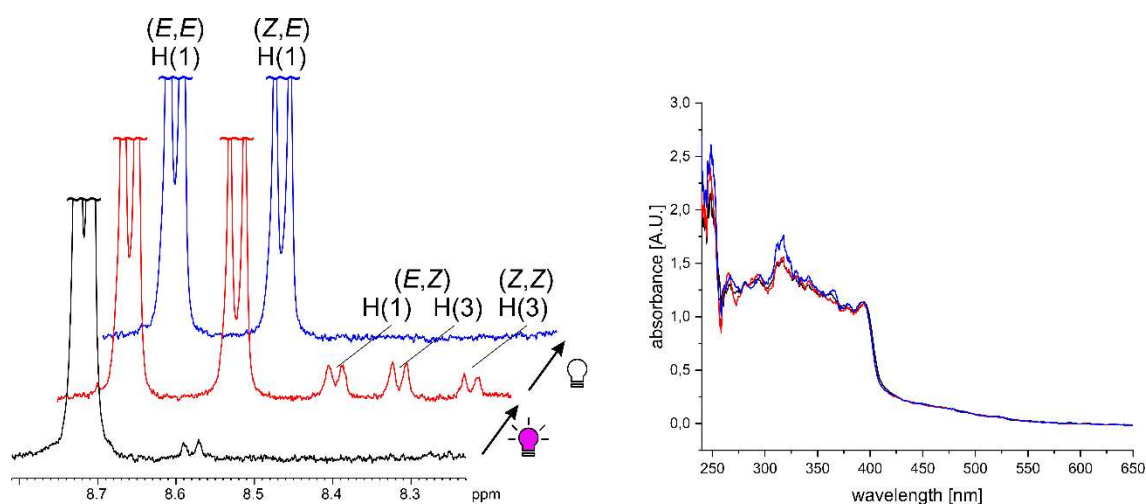


Figure S45. Photoinduced (*E*) → (*Z*) and thermal (*Z*) → (*E*) isomerization of iminium **1** in anh. and deg. CD₃CN (7.5 mM) at -40 °C. Left: Stacked 1D-¹H NMR spectra (section of the protons bound to the iminium ion carbon) in thermal equilibrium (black spectrum), during UV-illumination (red spectrum) and shortly after illumination is stopped (blue spectrum). Right: Associated UV/Vis-spectra.

In order to detect potential adequately separated UV/Vis signals of the low populated (*Z*)-configured isomers, a sample concentration was chosen which gives a saturated

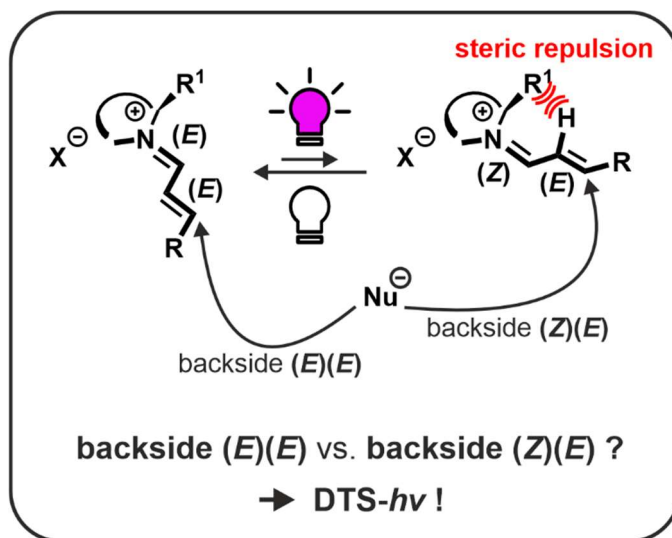
(E,E) absorption signal between ca. 275 and 425 nm. While a distinct population gain of (Z,E) and also adequate signals for (E,Z) and (Z,Z) can be observed in the NMR spectrum upon UV-illumination (Figure S45 left, red spectrum), no new absorption bands are detectable in the associated UV/Vis spectrum (Figure S45 right, red spectrum). This shows that all configuration isomers absorb within the same wavelength range. Therefore, a selective gain of one isomer by photo illumination seems not possible.

2.6 References

- 1 a) D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308; b) L. Raimondi, C. Faverio and M. F. Boselli, *Physical Sciences Reviews*, 2020, **5**, 20180087.
- 2 a) K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243–4244; b) W. S. Jen, J. J. M. Wiener and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 9874–9875; c) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370–4371; d) M. T. H. Fonseca and B. List, *Angew. Chem. Int. Ed.*, 2004, **43**, 3958–3960; e) T. D. Beeson and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 8826–8828; f) Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328–9329.
- 3 <https://www.nobelprize.org/prizes/chemistry/2021/summary/> (accessed October 2022).
- 4 a) S. Lakhdar, T. Tokuyasu and H. Mayr, *Angew. Chem. Int. Ed.*, 2008, **47**, 8723–8726; b) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak and T. Uchimaru, *Helv. Chim. Acta*, 2010, **93**, 603–634; c) U. Grošelj, A. K. Beck, W. B. Schweizer and D. Seebach, *Helv. Chim. Acta*, 2014, **97**, 751–796.
- 5 a) S. Lakhdar and H. Mayr, *Chem. Commun.*, 2011, **47**, 1866–1868; b) M. C. Holland, S. Paul, W. B. Schweizer, K. Bergander, C. Mück-Lichtenfeld, S. Lakhdar, H. Mayr and R. Gilmour, *Angew. Chem. Int. Ed.*, 2013, **52**, 7967–7971; c) M. C. Holland, J. B. Metternich, C. Mück-Lichtenfeld and R. Gilmour, *Chem. Commun.*, 2015, **51**, 5322–5325; d) M. C. Holland, J. B. Metternich, C. Daniliuc, W. B. Schweizer and R. Gilmour, *Chem. Eur. J.*, 2015, **21**, 10031–10038.
- 6 a) R. Gordillo, J. Carter and K. N. Houk, *Adv. Synth. Catal.*, 2004, **346**, 1175–1185; b) R. Gordillo and K. N. Houk, *J. Am. Chem. Soc.*, 2006, **128**, 3543–3553; c) E. H. Krenske, K. N. Houk and M. Harmata, *J. Org. Chem.*, 2015, **80**, 744–750.
- 7 J. Woon Yang, M. T. Hechavarria Fonseca, N. Vignola and B. List, *Angew. Chem. Int. Ed.*, 2005, **44**, 108–110.
- 8 a) P. Renzi, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.*, 2017, **139**, 6752–6760; b) J. Gramüller, M. Franta and R. M. Gschwind, *J. Am. Chem. Soc.*, 2022, **144**, 19861–19871.
- 9 a) V. Guivel-Scharen, T. Sinnwell, S. D. Wolff and R. S. Balaban, *J. Magn. Reson.*, 1998, **133**, 36–45; b) K. M. Ward, A. H. Aletras and R. S. Balaban, *J. Magn. Reson.*, 2000, **143**, 79–87; c) N. Lokesh, A. Seegerer, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.*, 2018, **140**, 1855–1862; d) V. Ramanujam, C. Charlier and A. Bax, *Angew. Chem. Int. Ed.*, 2019, **58**, 15309–15312.
- 10 C. Dugave and L. Demange, *Chem. Rev.*, 2003, **103**, 2475–2532.

- 11 D. Cameron and S. Eisler, *J Phys Org Chem.*, 2018, **31**, e3858.
- 12 A. Goulet-Hanssens, F. Eisenreich and S. Hecht, *Adv. Mater.*, 2020, **32**, 1905966.
- 13 M. Pankratz and R. F. Childs, *J. Org. Chem.*, 1988, **53**, 3278–3283.
- 14 C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39–44.
- 15 K. Rothermel, PhD thesis, University of Regensburg, 2019.
- 16 C. Reichard, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, 2010.
- 17 a) J. F. Coetzee and D. K. McGuire, *J. Phys. Chem.*, 1963, **67**, 1810–1814; b) M. S. Nozari, C. D. Jensen and R. S. Drago, *J. Am. Chem. Soc.*, 1973, **95**, 3162–3165.
- 18 a) M. Pankratz and R. F. Childs, *J. Org. Chem.*, 1985, **50**, 4553–4558; b) M. B. Schmid, K. Zeitler and R. M. Gschwind, *Chem. Eur. J.*, 2012, **18**, 3362–3370.
- 19 T. Brand, E. J. Cabrita and S. Berger, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2005, **46**, 159–196.
- 20 M. Melikian, J. Gramüller, J. Hioe, J. Greindl and R. M. Gschwind, *Chem. Sci.*, 2019, **10**, 5226–5234.
- 21 A. Seegerer, P. Nitschke and R. M. Gschwind, *Angew. Chemie - Int. Ed.*, 2018, **57**, 7493–7497.
- 22 A. Jerschow and N. Müller, *J. Magn. Reson.*, 1997, **125**, 372–375.
- 23 a) A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451; b) M. Mantina, A. C. Chamberlin, R. Valero, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. A*, 2009, **113**, 5806–5812.
- 24 M. B. Schmid, K. Zeitler and R. M. Gschwind, *Angew. Chemie - Int. Ed.*, 2010, **49**, 4997–5003.

3. Is there an (E,E)/(Z,E)-Dilemma? Experimental Investigations in Asymmetric Iminium Ion Catalysis using DTS-hv



Willibald J. Stockerl, Maximilian Philipp and Ruth M. Gschwind

Willibald J. Stockerl conceptualized together with R. M. Gschwind the project, did most of the synthetic work and conducted all NMR spectroscopic investigations. M. Philipp performed a part of the asymmetric iminium ion catalyzed reactions and the corresponding chiral HPLC measurements. R. M. Gschwind supervised and directed the project. **Willibald J. Stockerl** wrote the manuscript and the supporting information with input from R. M. Gschwind.

3.1 Abstract

Numerous asymmetric iminium ion catalyzed β -functionalizations of α,β -unsaturated carbonyl components have been developed in the last two decades. However, up to now the origin of enantioselectivity is especially experimentally rather unexplored. Herein we show on the example of the asymmetric iminium ion catalyzed Friedel-Crafts alkylation how to utilize photoisomerization of the iminium ion double bonds to apply a tool called DTS- $h\nu$. This experimental approach enables a mechanistic insight whether in our example the iminium ion C=N double bond configuration affects the stereoselective outcome. Applying α,β -unsaturated iminium ions based on MacMillan's 1st and 2nd generation catalyst and cinnamaldehyde we describe step-by-step what has to be factored to successfully apply this analytical tool. Unfortunately, meeting for this reaction all requirements mandatory for DTS- $h\nu$ is challenging. Thus, so far no final conclusion could be drawn within this work. Nevertheless, we suggest possibilities how to bypass the arisen challenges.

3.2 Introduction

The enormous importance of asymmetric organocatalysis is shown at the latest with the awarding of the Nobel Prize in Chemistry 2021 to Benjamin List and David MacMillan “for the development of asymmetric organocatalysis”.¹ Especially chiral secondary amines are here applied to stereoselectively functionalize aldehydes, ketones and the analogous α,β -unsaturated carbonyl components.² The β -functionalization of such α,β -unsaturated carbonyl components proceeds *via* iminium ion catalysis. Here, the carbonyl is activated by lowering the energy of the LUMO (lowest unoccupied molecular orbital). This activated intermediate, the iminium ion, is formed upon condensation of the carbonyl and the chiral secondary amine. Utilizing this principle, uncountable asymmetric functionalization strategies of carbonyl compounds have been published in the last two decades.³

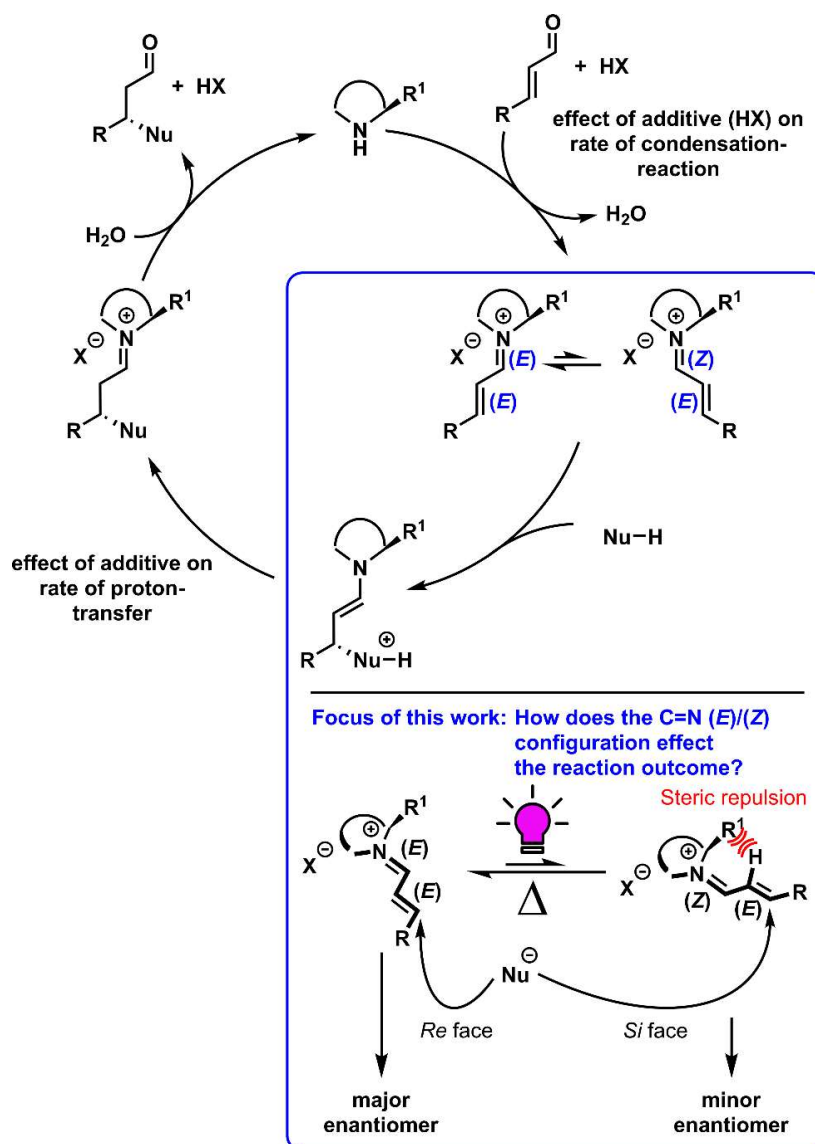


Figure 1. Catalytic cycle for the iminium ion catalyzed β -functionalization of α,β -unsaturated carbonyl compounds. The focus of this work was to gain insight into the influence of the $C=N$ double bond configuration on the stereoselectivity of this asymmetric addition reaction.

In parallel with the development of many new synthetic protocols, the associated mechanism was also investigated to a certain extent (Figure 1).⁴ So far, experimental studies and computational chemistry have been shown that the rate of iminium ion formation is positively influenced by a catalyst structure that facilitates an assisted proton transfer⁵ or by additives (HX) that serve as proton shuttles.⁶ Furthermore, the additive affects the rate of the intermediate σ -adduct formation. Herein, it was found that a weak acid such as $\text{CF}_3\text{CO}_2\text{H}$ (TFA) outperforms strong acids as HCl in terms of yield and enantioselectivity.⁷ Next to the additive a second factor is assumed to influence stereoselectivity in iminium ion catalysis, namely the iminium ion configuration. The condensation of the secondary amine and the α,β -unsaturated carbonyl component yields iminium ions with different double bond configurations. Until we could detect traces of imidazolidinone based (E,Z) iminium ions under general synthetic conditions, *i.e.* at ambient temperature without additional illumination, (ca. 0.1% of the sum of all isomers),⁸ only the two isomers (E,E) and (Z,E) were experimentally disclosed under these conditions in solution⁹ and as crystal structures.^{9b,9c} The (E,E) isomer is the thermodynamically preferred isomer due to an unfavorable steric repulsion in the (Z,E) isomer. Therefore, so far mainly the (E,E) isomer is considered for mechanistic investigations (see Figure 1).^{7b,10} Especially Seebach and co-workers prepared several α,β -unsaturated iminium ions based on imidazolidinone^{9c,11} or diarylprolinol moieties^{11,12} (these iminium ions probably correspond to the two most applied iminium ion catalyst motifs) and found (E,E)/(Z,E) ratios ranging from 98:2-88:12 in thermal equilibrium.^{9b} Since often enantiomeric product ratios of >99:1 are observed for the corresponding asymmetric iminium ion catalyzed reactions, a parallel influence of (E,E)/(Z,E) ratio and a faster reaction rate for the (E,E) isomer compared to (Z,E) is proposed to account for this stereoselective outcome.^{9b} This very speculative proposal is however only supported by computational chemistry.¹³

Therefore, we aimed for an experimental analysis of the influence of the (E,E)/(Z,E) ratio on the stereoselectivity of iminium ion catalyzed addition reactions. One mechanistic tool for an experimental insight into active transition states of such organocatalyzed addition reactions is the DTS-*h* ν method (decrypting transition states by light), which was developed in our research group.¹⁴ This method exploits the fact that the double bond configuration of the addition-reagents can be changed upon photoinduced isomerization. Thus, the same reaction can be performed with different (E)/(Z) ratios. One starting from thermal equilibrium and one with an increased (Z)-population due to photoinduced (E) $\rightarrow$ (Z) isomerization. Afterwards the reaction rate and/or enantiomeric excess (ee) of both reactions can be compared: If different results are obtained for both reactions, an influence of the double bond configuration to the underlying mechanism is explicitly

evidenced. In the case that more than two competing pathways are possible, additionally the two active pathways can be identified. In a previous study we already demonstrated and modulated the photoinduced isomerization of a imidazolidinone based α,β -unsaturated iminium ion and the stability of the obtained (Z)-configured isomers.⁸ Therefore we thought that DTS-*h* ν can also be applied to get an experimental insight in the role of the double bond configuration on the stereoselectivity of iminium ion catalysis. So far only (E,E) and (Z,E) were assumed to define stereoselectivity in iminium ion catalysis.^{9b} Additionally, during our studies only (Z,E) could be sufficiently and selectively populated and stabilized. Therefore we focused in this work to gain information on the role of the (E,E)/(Z,E) ratio on stereoselectivity in asymmetric iminium ion catalysis.

3.3 Results and Discussion

Iminium ions are the reactive species within the β -functionalization of α,β -unsaturated carbonyl compounds. Therefore, these iminium ions are only present as transient and low populated intermediates, which impedes mechanistic studies during the ongoing reaction. To enable experimental mechanistic studies, e.g. DTS-*h* ν , these iminium ions have to be present in an enriched and stable form. Especially Seebach and co-workers published several protocols how to synthesize various chiral and for catalysis relevant iminium ions using weakly coordinating anions for stabilization.^{9c,11,12} We chose to investigate iminium ions based on the chiral MacMillan's 1st and 2nd generation catalyst as these belong due to their excellent electrophilicity^{9a,15} to the probably most frequently applied catalyst motifs for asymmetric iminium ion catalysis. Herein, we selected the iminium ions **1** and **2** with hexafluorophosphate as stabilizing counter ion (see Figure 2 and for details on the synthesis see supporting information, chapter 3.5.2.1) as **1** was already applied for different experimental mechanistic investigations in iminium ion catalysis.^{7b} Also, we already investigated in detail the photoisomerization behavior of an iminium ion based on MacMillan's 1st generation catalyst.⁸

For DTS-*h* ν , the same reaction must be performed twice: In the dark, *i.e.* with an (E,E)/(Z,E) ratio according to the thermal equilibrium ("dark reaction") and with an increased amount of (Z,E) ("light reaction"), achieved *via* photoinduced (E) $\rightarrow$ (Z) isomerization. In principle, if illumination does not result in a significant photodegradation of the reagents or in a changing reaction mechanism, the "light reaction" can be performed under continuous illumination as we have shown in an earlier study in chiral phosphoric acid catalysis.¹⁴ However, Melchiorre and co-workers already reported visible light excitation of such iminium ions, enabling new organocatalyzed transformations upon a radical coupling mechanism.¹⁶ Therefore, the iminium ion catalyzed "light reaction" must occur as the "dark reaction" in its ground state, *i.e.* the "light reaction" cannot be performed under continuous illumination. As a consequence, photoinduced (E) $\rightarrow$ (Z) isomerization must occur upstream to the actual addition reaction and thus at conditions where (Z,E) can be sufficiently stabilized after the photoisomerization event. Therefore, similar to previous studies we employed low temperatures and high concentrations of the iminium ion.⁸ This should allow both, an effective photoinduced (E,E) $\rightarrow$ (Z,E) isomerization and a high stability of (Z,E) towards the competitive thermal (Z,E) $\rightarrow$ (E,E) back isomerization. To identify the response of iminium ion **1** and **2** to photo illumination, we applied *in situ* illumination NMR spectroscopy¹⁷ (Figure 2A and B and supporting information, chapter 3.5.5).

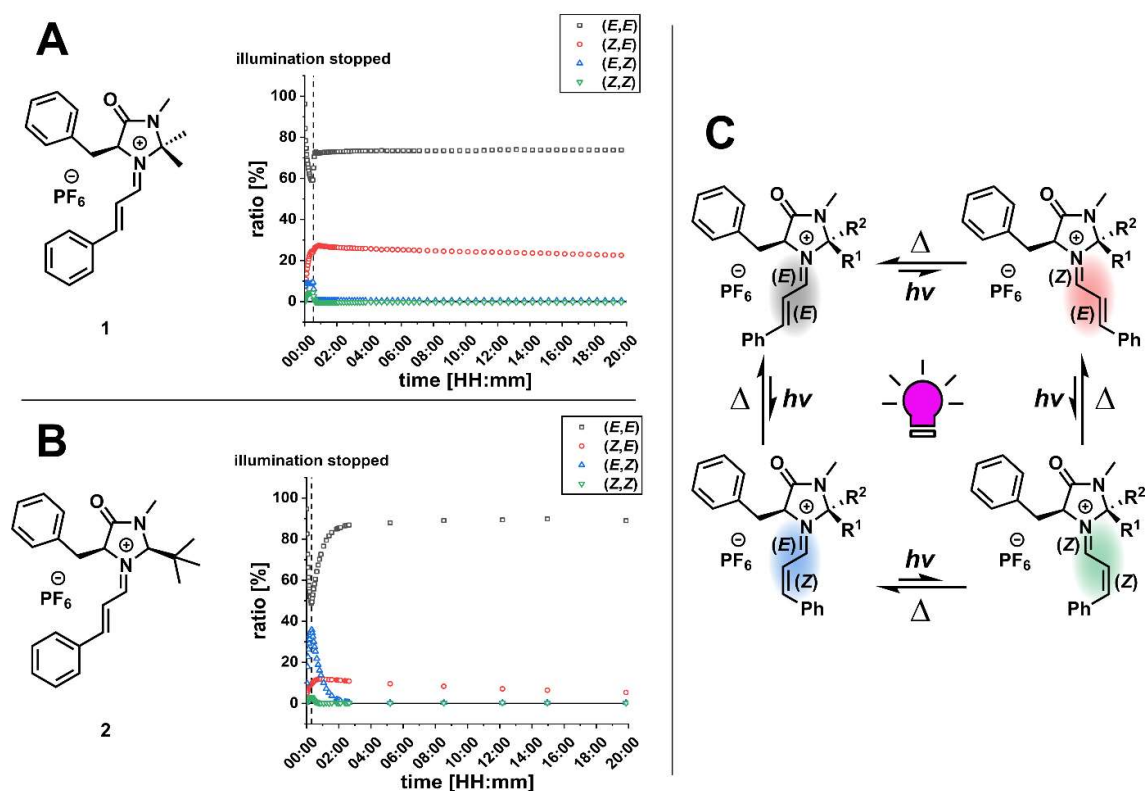


Figure 2. Overview of the photoinduced (E) → (Z) and thermal (Z) → (E) isomerization of imidazolidinone based iminium ions **1** and **2** at the low temperature of -40 °C in acetone-*d*₆ (50 mM). Photoisomerization was triggered via UV-illumination (365 nm). **A**: Ratio of all four double bond configuration isomers of **1** during photoinduced and thermal isomerization. **B**: Ratio of all four double bond configuration isomers of **2** during photoinduced and thermal isomerization. **C**: Representation of all four double bond configuration isomers (for **1** R¹ = R² = Me; for **2** R¹ = *tert*-Bu, R² = H). For further details see supporting information, chapter 3.5.5.

In both cases, a 50 mM sample in acetone-*d*₆ was subjected at -40 °C to UV-illumination (365 nm) according to their major absorption band between ca. 275 and 425 nm (see supporting information, chapter 3.5.2.5). As expected, upon UV-illumination we could observe a decrease of the (E,E) signals while the (Z,E) signals increased and additionally two new iminium signal sets arose. These new signal sets could unambiguously be assigned to (E,Z) and (Z,Z) by recording a series of 1D- and 2D-NMR experiments under continuous UV-illumination (1D-¹H; 1D-¹³C{¹H}; 2D-¹H, ¹H COSY; 2D-¹H, ¹H NOESY; 2D-¹H, ¹³C HMBC; 2D-¹H, ¹³C HSQC) (see supporting information, chapter 3.5.4). For iminium ion **1** UV-illumination at -40 °C yielded a photostationary state (PSS) of (E,E)/(Z,E)/(E,Z)/(Z,Z) = 61:25:10:4. For **2** we obtained at the same experimental conditions a preferred photoinduced isomerization of the C=C double bond ((E,E)/(Z,E)/(E,Z)/(Z,Z) = 50:10:37:3). The 2.5-fold decreased (Z,E) population in the PSS and increased thermal back isomerization rate constant for (Z,E) → (E,E) of **2** compared to **1** (see Figure 2A and B and supporting information, chapter 3.5.5) is highly probable due to the increased steric demand of the *tert*-butyl substituent. In contrast, the

(E,Z) population is increased by factor of 3.7 and simultaneously its stability towards thermal back isomerization. The thermal back isomerization is assumed to occur *via* a solvent-assisted pathway.^{8,18} As consequence, this solvent-interaction and hence isomerization may be also hindered due the steric demand of the *tert*-butyl substituent of **2**.

For **1** *in situ* illumination NMR kinetics were also recorded at even lower temperatures. By this, we were able to further decelerate especially the thermal (Z) → (E) isomerization processes. Thus, also higher populations of (Z)-configured isomers in the PSS were obtained since photoinduced (E) → (Z) and thermal (Z) → (E) isomerization are direct antagonists. At -70 °C, a PSS of (E,E)/(Z,E)/(E,Z)/(Z,Z) = 37:25:25:13 could be received. 10 h in the dark were necessary until all (Z)-C=C configured isomers signals decreased below the detection limit of routine NMR spectroscopy. For example the (E,Z) → (E,E) isomerization occurred with a rate constant of $k_{(Z) \rightarrow (E)} = 0.1473 \pm 0.006 \cdot 10^{-3} \text{ s}^{-1}$, *i.e.* ca. 66-times slower compared to -40 °C. The corresponding (Z,E) → (E,E) isomerization occurred with a rate constant ca. 4.2-times slower than at -40 °C. Therefore, after 48 h in the dark still a ratio of (E,E)/(Z,E) = 66:34 could be obtained. The thermal back isomerization processes were further decelerated at -93 °C, which is very close to the melting point of pure acetone-*d*₆ (-94 °C).¹⁹ Here, UV-illumination for ca. 16 h resulted in a similar population of (Z)-configured isomers as at -70 °C. However, after 20 h in the dark still distinct signals of the (E,Z) and (Z,Z) isomer could be observed (for details on the -70 °C and -93 °C measurements see supporting information, chapter 3.5.5.2). In this study, we aim to investigate whether enantioselectivity in asymmetric iminium ion catalyzed β-functionalization is governed by the (E,E)/(Z,E) ratio. Therefore, the ratio of these two isomers must be analyzed *via* DTS-hv. By exploiting the significantly differing thermal stabilities of the C=N and C=C double bond of **1**, a longlasting population of (Z,E) can selectively be generated by stopping UV-illumination as soon as the PSS is reached. However, due to the lower C=N and at the same time increased C=C double bond stability, this principle can hardly be applied to iminium ion **2**. Therefore, we focused on iminium ion **1** for the further investigations.

As synthetic platform to test the DTS-hv method we chose the enantioselective iminium ion catalyzed Friedel-Crafts alkylation of *N*-methyl pyrrole **3**, developed by MacMillan and Paras^{7a} because very good yields and enantioselectivities down to -30 °C were reported for this reaction. However, *N*-Methyl pyrrole **3** is known to self-polymerize upon illumination, which further prohibits continuous illumination for the “light reaction”.²⁰ For this reaction an intramolecular CH-π interaction within the imidazolidinone moiety of **1** was found resulting in a steric shielding of one face of the planar iminium ion. Therefore, it is proposed that the nucleophilic attack of **3** occurs selectively from the opposed

backside of the iminium ion (see Figure 3A).^{10a,10d} Based on this directing model, we assume that for this reaction only two transition states are competing, which differ in the configuration of the C=N double bond and thus are experimentally accessible using the DTS-hv approach. We call these two transition states backside (E,E) and backside (Z,E) (Figure 3B and 3C). In the case that the backside (E,E) transition state really yields the major enantiomer with a faster reaction rate, the “light reaction” with an decreased (E,E) or increased (Z,E) population should result in a drop in enantioselectivity and reaction rate (Figure 3B). If “dark reaction” and “light reaction” yield both the same ee and reaction rate, a major effect of the (E,E)/(Z,E) ratio on the enantioselectivity seems disproved.

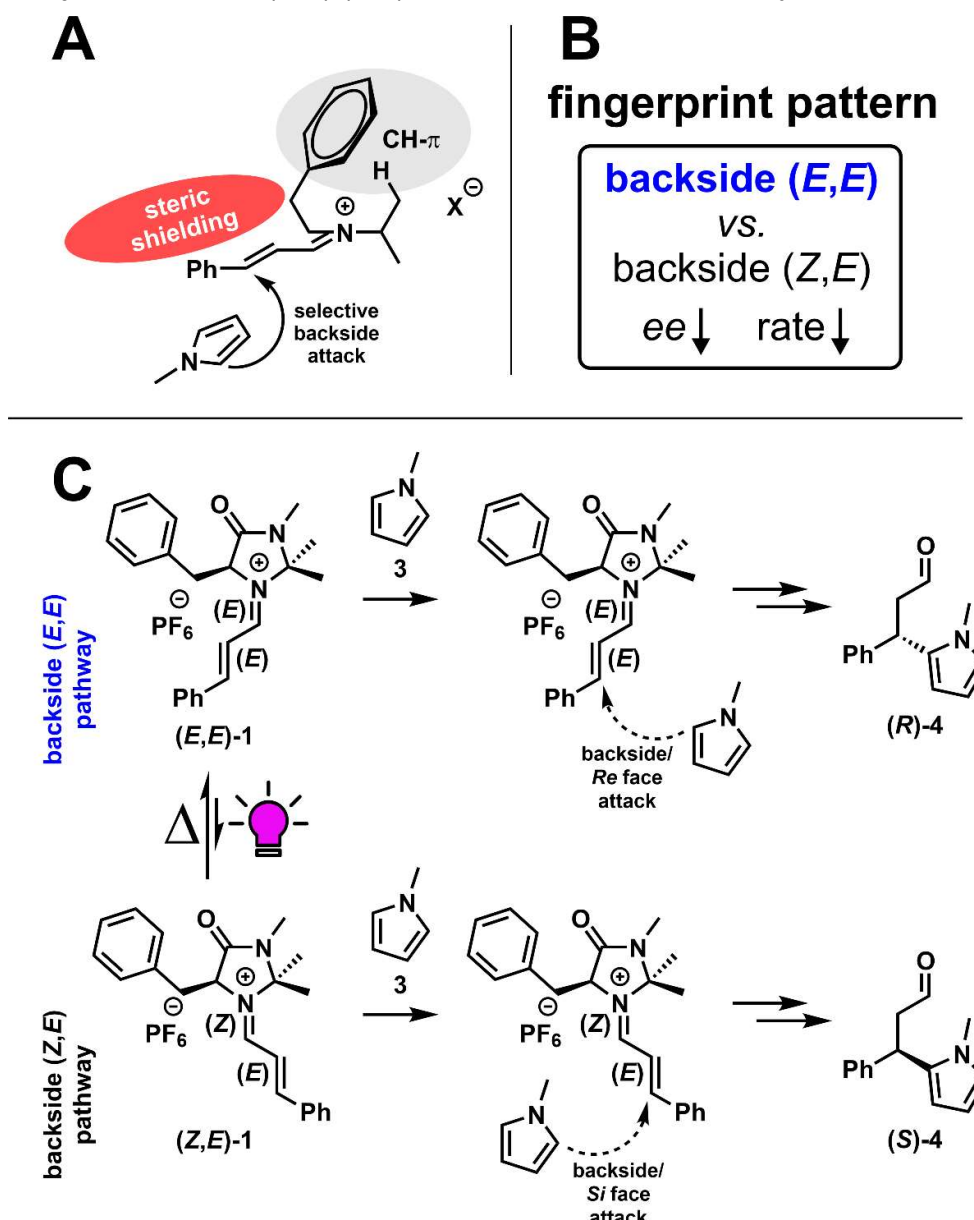


Figure 3. A: Reported directing model, which describes a steric shielding of the upper iminium ion face and as a consequence a selective nucleophilic backside attack in case 3 is applied as nucleophile.^{10a,10d} B: Expected fingerprint pattern upon photoinduced isomerization for the asymmetric iminium ion catalyzed β -functionalization of α,β -unsaturated carbonyl compounds. The transition state highlighted in blue gives the major enantiomer. C: More detailed representation of the two competing pathways, which are assumed to yield the two different product enantiomers.

Most (Z,E) was obtained at -70 °C or an even lower temperature. However, we assume that these temperatures are too low for a successful Friedel-Crafts alkylation of *N*-methyl pyrrole **3** within a reasonable time (e.g., at -30 °C 42 h were necessary for 87% yield).^{7a} Therefore, we chose to stay at a temperature of -40 °C. Furthermore, we substituted acetone-*d*₆ by CD₃CN, because we obtained a slightly improved stability of (Z,E) in this solvent ((E,E)/(Z,E) = 80:20 and 77:23 in acetone-*d*₆ and CD₃CN, respectively, 48 h in the dark after the PSS). Furthermore, in comparison to acetone, MeCN was already successfully applied as solvent for iminium ion catalyzed reactions.^{7b}

In this work, we aim to elucidate the influence of the (E,E)/(Z,E) ratio on the stereoselectivity in asymmetric iminium ion catalysis using DTS-*hν*. However, a second asymmetric (kinetic) control is already described.²¹ For the generation of the reactive iminium ion intermediate upon condensation an acidic additive (HX) is required (see Figure 1). But this acidic additive also influences the product formation rate and enantioselectivity: the more acidic the additive, the worse the yield and *ee*. This is because the stereodefining nucleophilic addition step must be accompanied by an irreversible deprotonation, which is caused by the deprotonated/basic form of the additive, *i.e.* the counter ion of the iminium ion. Otherwise an equilibrium controlled reversible addition step and therefore a racemic product distribution occurs. As a consequence, for example MacMillan and Paras achieved the highest yields and enantioselectivities when they employed the comparatively weak acid TFA.^{7a} Unfortunately, using TFA we were not able to synthesize the desired stable iminium ions as **1** and **2**. Such stable imidazolidinone based iminium ions could so far only be isolated using very strong acids as e.g. HPF₆^{9b,9c} or HClO₄.^{10b} Thus, to preserve this type of counter ion controlled asymmetric control with stable iminium ions, the reactions have to be carried out in the presence of fast and effective deprotonating additives. First, the potassium salt of trifluoroacetic acid (K⁺TFA⁻) was examined as this was already successfully applied to study counter ion effects for this asymmetric iminium ion catalysis using **1**.^{7b} Unfortunately, as soon as slightest traces of water are present we observed a fast and effective K⁺TFA⁻ promoted acid catalyzed hydrolysis of the otherwise very stable iminium ion **1** into the corresponding imidazolidinone and carbonyl compound (see supporting information, chapter 3.5.5.2). The hydrolysis can be suppressed when working with perfectly dried iminium ions, additives and solvents. In doing so, we could investigate the photoinduced (E) → (Z) isomerization of iminium ion **1** in presence of this additive (see supporting information, chapter 3.5.5.2). However, we could only observe a very poor photoinduced (E) → (Z) isomerization, from 1% (Z,E) in thermal equilibrium to maximum 2% upon UV-illumination. This is highly probable due to the relative nucleophilicity of the TFA anion, which similarly favors the nucleophilic catalyzed thermal

(Z) $\rightarrow$ (E) isomerization pathway as reported in literature.^{18a} As K⁺TFA⁻ seems no suitable additive for our investigations, we searched for other basic but less nucleophilic additives. We tested different sterically hindered organic bases, called non-nucleophilic bases. While 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) resulted in a complete decomposition of iminium ion **1** (see supporting information, chapter 3.5.5.2), 2,6-di-*tert*-butylpyridine (DBP) seemed a suitable additive. On the one hand, **1** is sufficiently stable towards traces of water in the presence of this additive and also adequate photoinduced (E) $\rightarrow$ (Z) isomerization could be observed. As expected, despite the lower relative nucleophilicity of DBP, its presence still results in a destabilization of (Z,E). Thus a lower (Z,E) population in the PSS and an increased thermal back isomerization towards (E,E) was obtained compared to additive-free conditions. Interestingly, in presence of DBP a significantly improved stability of the (Z)-configured isomers could be observed when we employed a lower concentration of **1** (see supporting information, chapter 3.5.5.2).

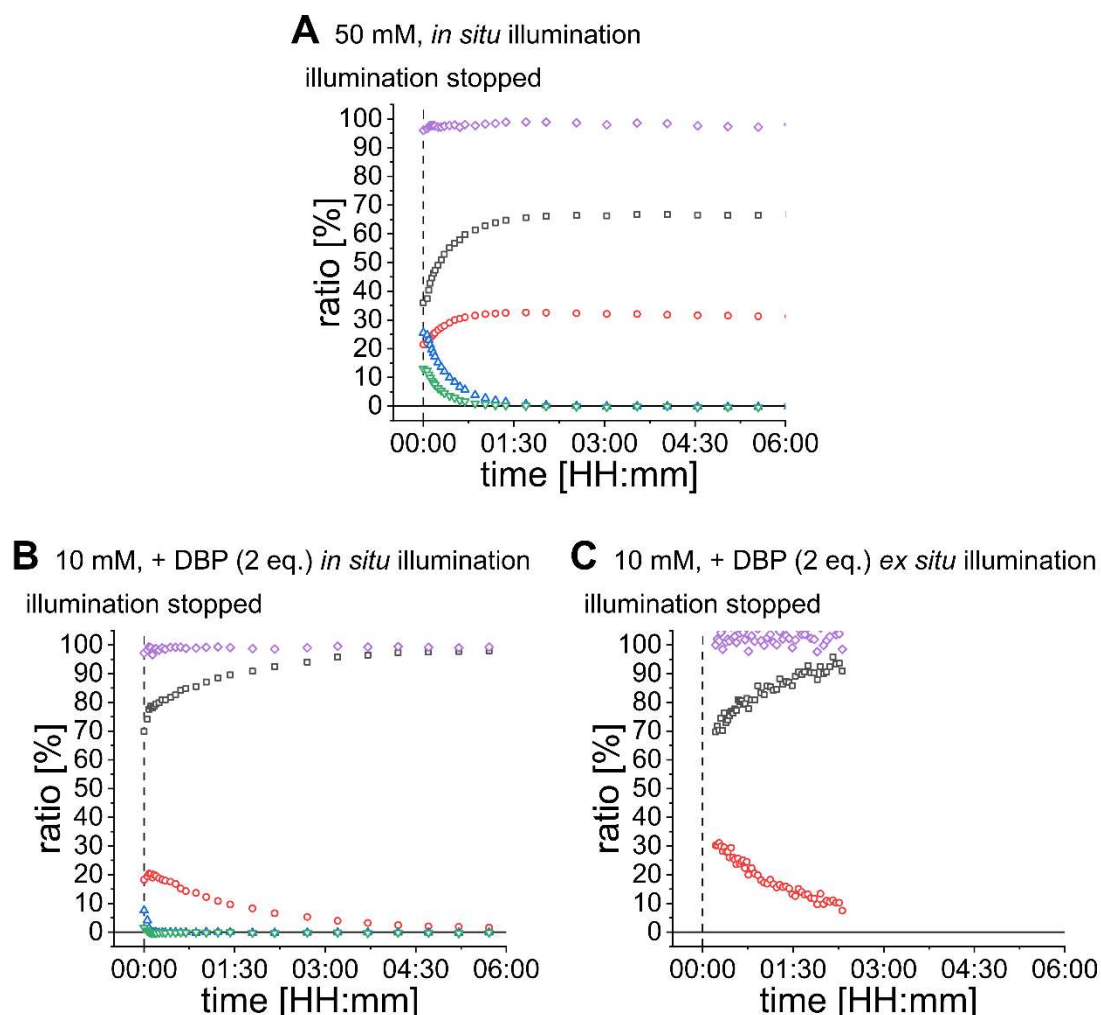


Figure 4. Plots of the thermal (Z) $\rightarrow$ (E) back isomerization of the different configuration isomers of **1** starting from PSS. **A:** **1** in CD₃CN (50 mM) at -40 °C after *in situ* UV-illumination (365 nm). **B:** **1** in CD₃CN (10 mM) + DBP (2 eq.) at -40 °C after *in situ* UV-illumination (365 nm). **C:** **1** in CD₃CN (10 mM) + DBP (2 eq.) at -40 °C after *ex situ* UV-illumination (365 nm).

Without any additive, maximum 32% of (Z,E) could be obtained upon UV-illumination for a sample of **1** (50 mM) in CD₃CN at -40 °C. This population stays reasonably constant for at least 48 h. In contrast, UV-illumination of **1** (10 mM) in CD₃CN at -40 °C with 2 eq. DBP gave maximum 21% of (Z,E) and the thermal equilibrium of (E,E)/(Z,E) is reestablished after ca. 5 h (see Figure 4A vs. B and supporting information, chapter 3.5.5.2). Nevertheless we thought that the (Z,E)-stability in presence of DBP is adequate to determine the influence of this configuration isomer on stereoselectivity *via* DTS-*hν*. As it is practically impossible to add reagents at low temperature to an already prepared *in situ* illumination NMR sample without heating the sample and thus losing (Z,E) due to thermal (Z) → (E) isomerization, we have to perform the “dark reaction” and “light reaction” outside the NMR spectrometer. Therefore, we used a Schlenk flask customized to connect a glass rod illumination setup (see supporting information, chapter 3.5.3.2). To check whether this *ex situ* illumination setup yields (Z,E) populations as observed with the *in situ* illumination NMR setup, we repeated the photoinduced isomerization of **1** in CD₃CN (10 mM) at -40 °C with 2 eq. DBP. We illuminated the sample for 1 h and recorded the subsequent thermal back isomerization at -40 °C *via* NMR spectroscopy (see Figure 4C and supporting information; chapter 3.5.5.2). Herein, an even higher amount of (Z,E) could be obtained using the *ex situ* illumination setup. This is highly probable due to a lower light intensity of the applied *in situ* illumination setups compared to *ex situ* illumination.²² Comparing both illumination principles, a ca. 1.6-times increased (Z,E) population was obtained upon *ex situ* illumination.

Having conditions where (Z,E) of **1** can be adequately populated and stabilized at -40 °C in presence of DBP as deprotonating additive we were finally able to perform the “dark reaction” and “light reaction”. A significantly differing (E,E)/(Z,E) ratio for both reactions is compulsory. Therefore, we set the reaction time for “dark reaction” and “light reaction” to 2 h. 2 h after UV-illumination is stopped, still ca. 5-times more (Z,E) is present as in thermal equilibrium (see Figure 4C). We aimed for isolating the aldehyde product **4** to determine the enantioselective outcome of this asymmetric iminium ion catalyzed β-functionalization *via* chiral HPLC (see Figure 5 left and supporting information, chapter 3.5.2.2, 3.5.2.3 and 3.5.2.6). To our surprise, only a racemic product distribution was obtained. Thus, we first assumed that the temperature and/or concentration, which is mandatory for our DTS-*hν* reaction favors another reaction pathway and as consequence results in a stereoselective outcome differing from those found in literature.^{7a,7b} This assumption seemed plausible as our group was able to identify in chiral phosphoric acid catalysis reaction pathways, which favor the formation of different enantiomers depending on the aggregate size of the catalyst.²³ Similar to the catalyst applied in this class of chiral phosphoric acid catalysis, the aggregation of our imidazolidinone iminium

ions can also be controlled by changing temperature and/or concentration.⁸ To underpin this assumption, we repeated this β -functionalization with conditions that were reported as enantioselective (see supporting information, chapter 3.5.2.2 and 3.5.2.3). However, repeating these reactions also resulted in a racemic product distribution. Unfortunately, this clearly points to stereoselectivity issues within our β -functionalization strategy. We found that MacMillan^{7a} and Mayr^{7b} did not use the aldehyde product **4** for their enantioselectivity determinations but the corresponding alcohol **6**, generated by subsequent *in situ* reduction with NaBH₄.

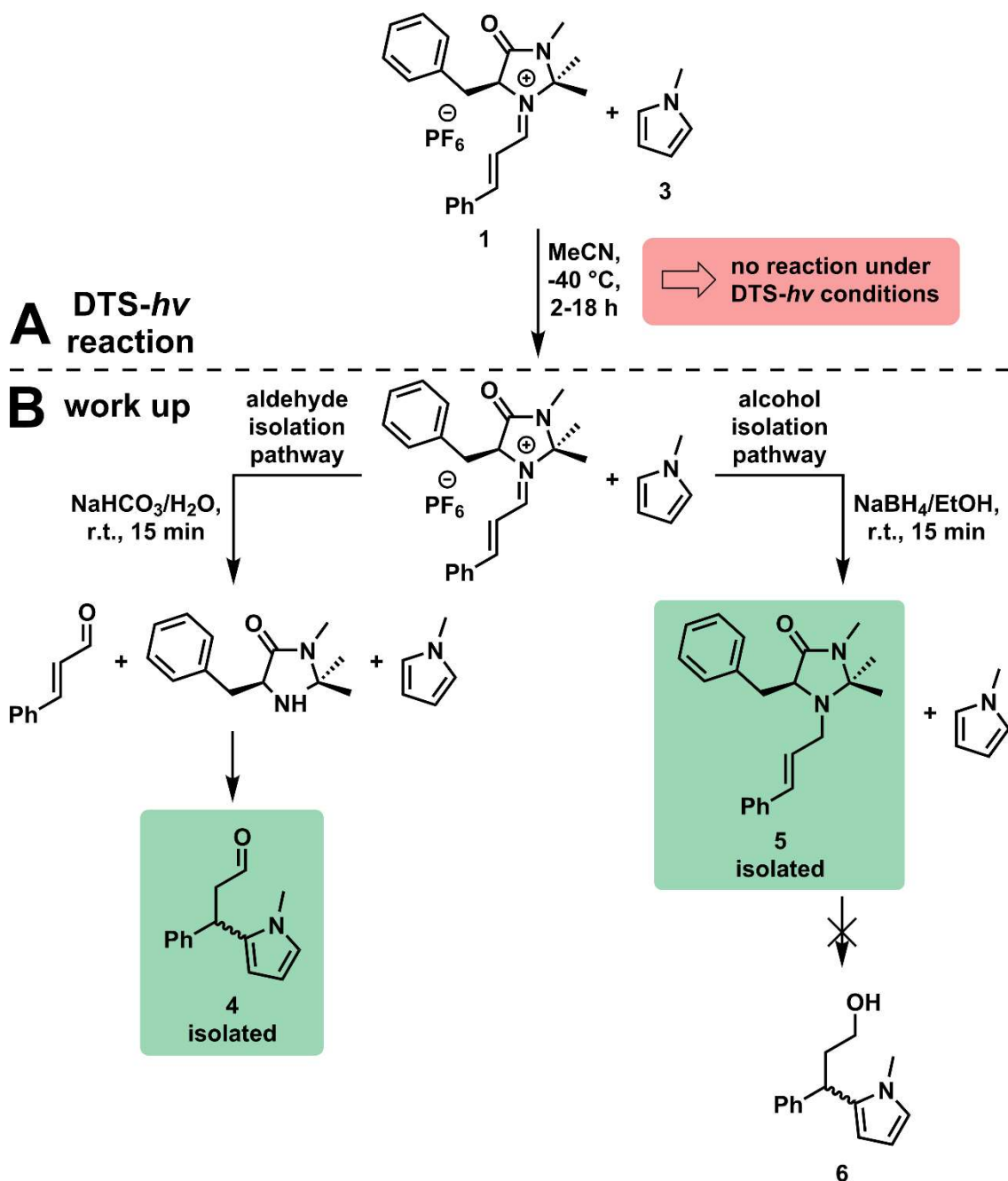


Figure 5. Detailed representation of the overall DTS-hv reaction including the different work ups to the aldehyde product **4** or the alcohol product **6**. Because DTS-hv reaction + alcohol isolation pathway yields no product but amine **5**, no reaction under DTS-hv conditions is assumed.

And indeed, by exactly repeating the enantioselective β -functionalization and *in situ* reduction to the alcohol product **6** developed by MacMillan and Paras^{7a} we could reproduce the reported ee of 90% (see supporting information, chapter 3.5.2.2. and 3.5.2.6). Unfortunately, performing our carefully optimized DTS-*h* ν reaction (see Figure 5A) and subsequent the literature-known alcohol isolation pathway as work up^{7a} (see Figure 5B right) no product could be obtained. Instead, amine **5** was isolated, which corresponds to the reduced form of iminium ion **1**. However, as we could generate the aldehyde product **4** *via* the DTS-*h* ν reaction and followed by the aldehyde isolation pathway (see Figure 5B left), we assume the following: No β -functionalization of iminium ion **1** occurs during the actual DTS-*h* ν reaction at -40 °C (see Figure 5A), highly probably due to an insufficient reaction rate at this low temperature. Instead, the aldehyde product **4** is generated during the aqueous work up at room temperature. In principal, the same could occur for the alcohol isolation pathway. However, the NaBH₄ promoted *in situ* reduction of iminium ion **1** to amine **5** seems to outperform the corresponding β -functionalization of **1** to **6**. Thus, only the reduced amine **5** is received after this work up.

Therefore, investigating the influence of the iminium ion double bond configuration on the stereoselectivity of the corresponding asymmetric β -functionalization seems not possible applying this DTS-*h* ν model system. For achieving this, clearly a higher reactivity is demanded. However, **1** seems the ideal model iminium ion because it provides an adequate and longlasting population of (Z,E) after photoinduced isomerization. Since low temperature is also mandatory for stabilizing (Z,E), this cannot be modified as well. Therefore, only changing the nucleophile may open up a possibility to achieve a reactivity sufficiently high for applying successfully DTS-*h* ν .

3.4 Conclusion

In conclusion, we presented a step-by-step guide for developing a DTS-*hν* model system to investigate the influence of the iminium ion C=N double bond configuration on the enantioselectivity of a frequently applied iminium ion catalyzed β-functionalization strategy. Because photoinduced enriching of in this case the (Z,E) iminium ion intermediate is the key requirement for DTS-*hν*, we first investigated the response of differently substituted imidazolidinone based iminium ions towards photoisomerization. Herein we detected varying stabilities of the four possible double bond configuration intermediates correlating with the different steric impacts of the installed substituents. Earlier reports highlight the need for basic additives for mechanistic investigations using such stabilized iminium ions. Therefore, we additionally scrutinized the effect of different basic additives on the stability of the high energetic (Z)-configured iminium ion intermediates. As these basic additives destabilize the (Z)-configured iminium ions according to their relative nucleophilicity this further supports an already described nucleophile catalyzed thermal back isomerization mechanism. Based on all this knowledge we believed to hold all requirements for successfully applying DTS-*hν*. However, we found that the low reactivity of the stabilized iminium ion and furthermore the compulsory low temperature to be a major challenge, which we were so far not able to meet.

3.5 Supporting Information

3.5.1 General

Commercially available chemicals were, unless otherwise stated, used without further purification. *Trans*-cinnamaldehyde was distilled under reduced pressure ($2 \cdot 10^{-1}$ mbar) at 100 °C, degassed using the freeze-pump-thaw method and stored inside the glove box. Acetone was dried dynamically using 3Å molecular sieve, degassed by the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask. EtOH, Et₂O and toluene were distilled over sodium and benzophenone and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve. CH₃CN and CD₃CN were distilled over CaH₂, degassed using the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve. *N*-Me-pyrrole was distilled over KOH resulting in a colorless liquid and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve. Ethyl acetate (EA), *n*-hexane and *n*-pentane for column chromatography were distilled under reduced pressure at 60 °C before usage.

Column chromatography was performed using Merck silica gel 60 (35-70 µm). Thin layer chromatography was done on TLC pre-coated aluminum sheets (Merck, silica gel 60 F254, 0.2 mm). Visualization was accomplished with UV light (254 nm) and/or staining with KMnO₄.

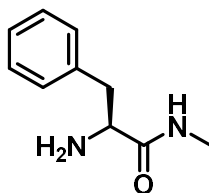
UV-spectra were recorded using an AvaLight-DH-S-BAL as light source and an AvaSpec-2048 for detection.

NMR experiments for routine measurements were recorded on a Bruker Avance 400 MHz at 25 °C. Photoinduced isomerization studies were performed on a Bruker Avance III HD 600 (600.03 MHz) with a 5 mm fluorine selective TBIF probe using the reported *in situ* illumination setup with 5 mm amberized thin wall NMR tubes.¹⁷ For illumination at 365 nm a LG Innotek LEUVA66X00RV00 LED was used and operated at 0.5 A. NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software and reported as follows: ppm, multiplicity, coupling constant, integral. All spectra are referenced to the solvent residual signal: Acetone-*d*₆: δ(¹H) = 2.05 ppm, δ(¹³C) = 29.84 ppm; CD₂Cl₂: δ(¹H) = 5.32 ppm, δ(¹³C) = 53.84 ppm; CD₃Cl: δ(¹H) = 7.26 ppm, δ(¹³C) = 77.16 ppm; CD₃CN: δ(¹H) = 1.94 ppm, δ(¹³C) = 118.26 ppm; Dimethyl sulfoxide-*d*₆ (DMSO-*d*₆): δ(¹H) = 2.50 ppm, δ(¹³C) = 39.52 ppm. Further plotting of the spectra was performed with Origin 2019 and Corel Draw 2020 software.

3.5.2 Synthetic part

3.5.2.1 Syntheses of iminium ions 1, 2 and 15 and their precursors

(S)-2-Amino-N-methyl-3-phenylpropanamide (7)



7

7 was synthesized following a literature procedure.^{10d}

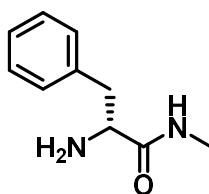
(S)-Phenylalanine (6.99 g, 42.30 mmol, 1.0 eq.) was suspended in MeOH (17.1 mL). The suspension was cooled down to 0 °C followed by a slow addition of thionyl chloride (6.04 g, 3.68 mL, 50.76 mmol, 1.2 eq.) under vigorous stirring. The newly formed white suspension was first heated to r.t. and then stirred under reflux for 23 h, which resulted in a light brown solution. Volatile components were removed under reduced pressure and subsequent a MeNH₂-EtOH-solution (8.0 M, 21.15 mL, 169.20 mmol, 4.0 eq.) was slowly added. The solution was stirred for further 23 h at r.t. under generation of a white precipitate. After another remove of volatile components *in vacuo*, the precipitate was dissolved in an aq. sat. NaHCO₃-solution (60 mL) followed by an extraction with CH₂Cl₂ (3 · 55 mL) and drying over MgSO₄. Purification by recrystallization (*n*-hexane/ EA 2:1) and drying under reduced pressure yielded **7** as a white solid (4.01 g, 22.5 mmol, 53 %).

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.20 – 7.35 (m, 6H, H-Ar & NH), 3.68 (dd, *J* = 9.1, 4.1 Hz, 1H, COCH), 3.29 (dd, *J* = 13.8, 4.3 Hz, 1H, CH₂), 2.80 (d, *J* = 5.0 Hz, 3H, CH₃), 2.73 (dd, *J* = 13.7, 9.1 Hz, 1H, CH₂), 2.06 (s, 2H, NH₂).

¹³C-NMR (CDCl₃, 101 MHz, 25 °C): 174.9, 138.2, 129.4, 128.8, 126.9, 56.6, 41.2, 26.0.

Analytical data are in agreement with the literature.^{10d}

(R)-2-Amino-N-methyl-3-phenylpropanamide (8)

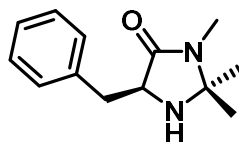


8

8 was synthesized analogously to **7**, however starting from (R)-Phenylalanine. **8** was yielded as white solid (5.43 g, 30.5 mmol, 72 %).

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.18 – 7.34 (m, 6H, H-Ar & NH), 3.61 (dd, *J* = 9.4, 4.1 Hz, 1H, COCH), 3.29 (dd, *J* = 13.8, 4.0 Hz, 1H, CH₂), 2.81 (d, *J* = 5.0 Hz, 3H, CH₃), 2.68 (dd, *J* = 13.8, 9.5 Hz, 1H, CH₂), 1.43 (s, 2H, NH₂).

(S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one (9)



9

9 was synthesized following a literature procedure.^{9c}

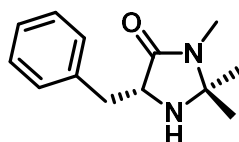
The synthesis was carried out in oven-dried glassware under argon atmosphere. Amid **7** (2.20 g, 12.35 mmol, 1.0 eq.) was dissolved in anhydrous (anh.) and degassed (deg.) EtOH (30 mL). Anh. and deg. acetone (2.38 g, 3.01 mL, 40.0 mmol, 3.3 eq.) and 3 Å molecular sieve (5 g) were added followed by stirring for 18 h under reflux. Afterwards the light brown reaction mixture was allowed to cool down to r.t. and the turbid solution was purified by filtration. Removing volatile components applying reduced pressure yielded **9** as a beige oil (2.58 g, 11.8 mmol, 96 %).

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.19 – 7.32 (m, 5H, *H*-Ar), 3.79 (dd, *J* = 6.6, 4.6 Hz, 1H, CH), 3.14 (dd, *J* = 14.2, 4.5 Hz, 1H, CH₂), 3.00 (dd, *J* = 14.2, 6.8 Hz, 1H, CH₂), 2.75 (s, 3H, NCH₃), 1.66 (bs, 1H, NH), 1.26 (s, 3H, CH₃), 1.15 (s, 3H, CH₃).

¹³C-NMR (CDCl₃, 101 MHz, 25 °C): 173.5, 137.3, 129.6, 128.7, 126.9, 75.7, 59.4, 37.4, 27.4, 25.5, 25.3.

Analytical data are in agreement with the literature.^{9c}

(R)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one (10)

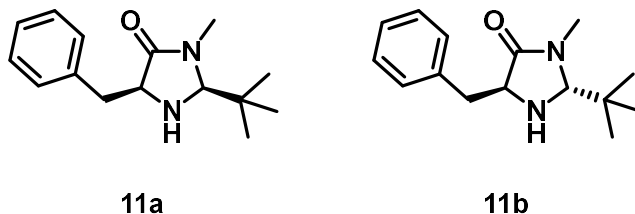


10

10 was synthesized analogously to **9**, however starting from **8**. **10** was yielded as slightly orange colored oil; the yield was not determined.

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.19 – 7.32 (m, 5H, *H*-Ar), 3.79 (dd, *J* = 6.7, 4.6 Hz, 1H, *CH*), 3.14 (dd, *J* = 14.1, 4.4 Hz, 1H, *CH*₂), 3.01 (dd, *J* = 14.1, 6.8 Hz, 1H, *CH*₂), 2.75 (s, 3H, *NCH*₃), 1.74 (bs, 1H, *NH*), 1.26 (s, 3H, *CH*₃), 1.16 (s, 3H, *CH*₃).

(2S,5S)-5-Benzyl-2-(tert-butyl)-3-methylimidazolidin-4-one (11a) & (2R,5S)-5-benzyl-2-(tert-butyl)-3-methylimidazolidin-4-one (11b)



11a and **11b** were synthesized following a literature procedure.^{9c}

The synthesis was carried out in oven-dried glassware under argon atmosphere. Amid **7** (2.32 g, 13.02 mmol, 1.0 eq.) and FeCl₃ (421 mg, 2.60 mmol, 0.2 eq.) were added to 4 Å molecular sieve (5 g) in anh. and deg. toluene (50 mL). Subsequent pivaldehyde (1.12 g, 1.42 mL, 13.02 mmol, 1.0 eq.) was added and the light brown reaction mixture was stirred under reflux for 18 h. The newly formed black solution was diluted with EA (200 mL), washed with an aq. and sat. NaHCO₃-solution (50 mL) and brine (2 · 30 mL) and dried over MgSO₄. Removing volatile components *in vacuo*, followed by column chromatography (EA/ *n*-hexane 3:1 → 6:1) resulted in the purified imidazolidinones **11a** (488 mg, 1.98 mmol, 15 %) and **11b** (1.25 g, 5.08 mmol, 38 %) as light brown solids.

11a:

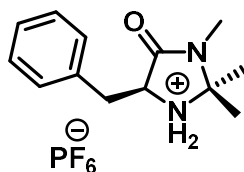
¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.19 – 7.33 (m, 5H, *H*-Ar), 4.06 (bs, 1H, *CH*), 3.71 (dd, *J* = 7.3, 3.8 Hz, 1H, *CH*), 3.16 (dd, *J* = 13.8, 4.0 Hz, 1H, *CH*₂), 2.94 (dd, *J* = 13.8, 7.6 Hz, 1H, *CH*₂), 2.92 (s, 3H, *NCH*₃), 1.69 (bs, 1H, *NH*), 0.84 (s, 9H, (*CH*₃)₃).

11b:

¹H-NMR (CDCl₃, 400 MHz, 25 °C): 7.20– 7.32 (m, 5H, *H*-Ar), 3.82 – 3.87 (m, 1H, *CH*), 3.80 (d, *J* = 1.8 Hz, 1H, *CH*), 3.11 (dd, *J* = 14.0, 4.2 Hz, 1H, *CH*₂), 2.89 (s, 3H, *NCH*₃), 2.88 (dd, *J* = 14.0, 7.2 Hz, 1H, *CH*₂), 1.85 (bs, 1H, *NH*), 0.90 (s, 9H, (*CH*₃)₃).

Analytical data are in agreement with the literature.^{9c}

(S)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium hexafluorophosphate (12)



12

12 was synthesized following a literature procedure.^{9c}

An aqueous HPF₆-solution (60 %, 3.75 mL, 25.56 mmol, 1.05 eq.) was diluted with Et₂O (300 mL) and cooled to 0 °C. Imidazolidinone **9** (5.32 g, 24.35 mmol, 1.0 eq.) in Et₂O (150 mL) was slowly added under stirring over a period of 40 min. The resulting white precipitate was stirred for further 20 min at 0 °C and allowed to warm up to r.t. Purification by washing with Et₂O (3 · 60 mL) and drying *in vacuo* yielded **12** as a white solid (7.75 g, 21.3 mmol, 87 %).

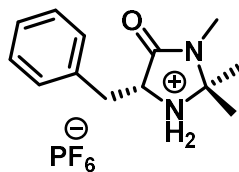
¹H-NMR (acetone-*d*₆, 400 MHz, 25 °C): 10.08 (bs, 1H, NH₂⁺), 9.65 (bs, 1H, NH₂⁺), 7.26 – 7.44 (m, 5H, *H*-Ar), 4.72 (dd, *J* = 9.9, 3.9 Hz, 1H, *CH*), 3.50 (dd, *J* = 15.1, 3.9 Hz, 1H, *CH*₂), 3.22 (dd, *J* = 15.1, 9.9 Hz, 1H, *CH*₂), 2.94 (s, 3H, NCH₃), 1.85 (s, 3H, CH₃), 1.75 (s, 3H, CH₃).

¹³C-NMR (acetone-*d*₆, 101 MHz, 25 °C): 166.5, 136.5, 130.1, 129.7, 128.3, 78.9, 59.4, 34.8, 25.5, 24.4, 22.6.

¹⁹F-NMR (acetone-*d*₆, 376 MHz, 25 °C): -71.5 (d, *J* = 708 Hz, PF₆⁻).

³¹P-NMR (acetone-*d*₆, 162 MHz, 25 °C): -142.6 (septett, *J* = 707 Hz, PF₆⁻).

(R)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium hexafluorophosphate (13)



13

13 was synthesized analogously to **12**, however starting from **10**. **13** was yielded as white solid (346 mg, 0.95 mmol, 17 %).

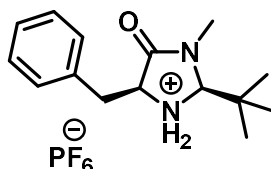
¹H-NMR (acetone-*d*₆, 400 MHz, 25 °C): 9.85 (bs, 1H, NH₂⁺), 9.20 (bs, 1H, NH₂⁺), 7.26 – 7.44 (m, 5H, *H*-Ar), 4.83 (dd, *J* = 10.2, 3.8 Hz, 1H, *CH*), 3.55 (dd, *J* = 15.2, 3.9 Hz, 1H,

CH_2), 3.20 (dd, $J = 15.2, 10.2$ Hz, 1H, CH_2), 2.95 (s, 3H, NCH_3), 1.88 (s, 3H, CH_3), 1.78 (s, 3H, CH_3).

^{19}F -NMR (acetone- d_6 , 376 MHz, 25 °C): -71.4 (d, $J = 708$ Hz, PF_6^-).

^{31}P -NMR (acetone- d_6 , 162 MHz, 25 °C): -142.6 (septett, $J = 708$ Hz, PF_6^-).

(2S,5S)-5-Benzyl-2-(tert-butyl)-3-methyl-4-oxoimidazolidin-1-ium hexafluorophosphate (**14**)



14

14 was synthesized following a literature procedure.^{9c}

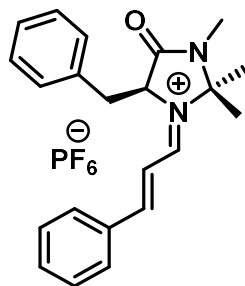
An aqueous HPF_6 -solution (60 %, 283 μL , 1.83 mmol, 1.0 eq.) in Et_2O (50 mL) was cooled to 0 °C. Imidazolidinone **11a** (451 g, 1.83 mmol, 1.0 eq.) in Et_2O (30 mL) was slowly added under stirring over a period of 40 min. The newly formed white precipitate was stirred for further 10 min at 0 °C and allowed to warm up to r.t. Purification by washing with Et_2O (50 mL) and drying *in vacuo* yielded **14** as a white solid (475 g, 1.21 mmol, 66 %).

^1H -NMR (CD_2Cl_2 , 400 MHz, 25 °C): 8.71 (bs, 1H, NH_2^+), 7.38 – 7.50 (m, 3H, $H\text{-Ar}$), 7.26 – 7.32 (m, 2H, $H\text{-Ar}$), 4.63 (d, $J = 7.6$ Hz, 1H, CH), 4.50 (bt, $J = 6.6$ Hz, 1H, CH), 3.77 (dd, $J = 14.8, 1.7$ Hz, 1H, CH_2), 3.28 (dd, $J = 14.8, 6.4$ Hz, 1H, CH_2), 2.97 (s, 3H, NCH_3), 0.71 (s, 9H, $(\text{CH}_3)_3$).

^{19}F -NMR (CD_2Cl_2 , 376 MHz, 25 °C): -71.2 (d, $J = 714$ Hz, PF_6^-).

^{31}P -NMR (CD_2Cl_2 , 162 MHz, 25 °C): -143.3 (septett, $J = 713$ Hz, PF_6^-).

(S,E)-5-Benzyl-2,2,3-trimethyl-4-oxo-1-((E)-3-phenylallylidene)imidazolidin-1-ium hexafluorophosphate (1)



1

1 was synthesized following a literature procedure.^{9c}

The synthesis was carried out in oven-dried glassware under argon atmosphere. Ammonium salt **12** (699 mg, 1.92 mmol, 1.0 eq.) and *trans*-cinnamaldehyde (266 mg, 253 μ L, 2.02 mmol, 1.05 eq.) were dissolved in anh. and deg. EtOH (1.0 mL). Catalytic amounts of triethylamine (10 μ L) were added and the reaction mixture was stirred for 24 h at r.t. In the meantime a yellow precipitate was formed. The solvent was removed under inert gas conditions using a teflon cannula followed by washing the precipitate with anh. and deg. Et₂O (2 · 20 mL) and a 1:7 mixture of anh. and deg. EtOH/ Et₂O (2 · 20 mL). Removing volatile components under reduced pressure yielded **1** as a light yellow solid (445 mg, 0.93 mmol, 48 %).

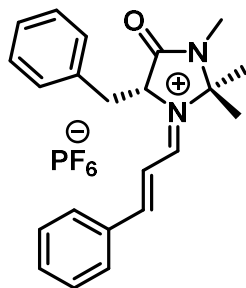
¹H-NMR (acetone-*d*₆, 400 MHz, 25 °C): 9.38 (dd, *J* = 10.6, 1.9 Hz, 1H, C(1) - *H*), 8.43 (d, *J* = 15.0 Hz, 1H, C(3) - *H*), 8.02 – 8.07 (m, 2H, arom. *H*), 7.89 (dd, *J* = 15.0, 10.6 Hz, 1H, C(2) - *H*), 7.72 – 7.77 (m, 1H, arom. *H*), 7.61 – 7.67 (m, 2H, arom. *H*), 7.28 – 7.36 (m, 3H, arom. *H*), 7.16 – 7.20 (m, 2H, arom. *H*), 5.58 – 5.63 (m, 1H, CH), 3.81 (dd, *J* = 14.7, 5.8 Hz, 1H, CH₂), 3.57 (dd, *J* = 14.7, 3.2 Hz, 1H, CH₂), 2.89 (s, 3H, NCH₃), 1.91 (s, 3H, CH₃), 0.94 (s, 3H, CH₃).

¹³C-NMR (acetone-*d*₆, 101 MHz, 25 °C): 168.7, 166.6, 165.2, 135.8, 134.9, 134.6, 132.4, 131.1, 130.6, 129.9, 129.1, 119.0, 86.5, 65.2, 37.1, 27.4, 25.8, 24.5.

¹⁹F-NMR (acetone-*d*₆, 376 MHz, 25 °C): -71.2 (d, *J* = 708 Hz, PF₆⁻).

³¹P-NMR (acetone-*d*₆, 162 MHz, 25 °C): -142.5 (septett, *J* = 709 Hz, PF₆⁻).

(R,E)-5-Benzyl-2,2,3-trimethyl-4-oxo-1-((E)-3-phenylallylidene)imidazolidin-1-ium hexafluorophosphate (15)



15

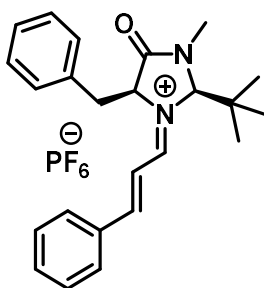
15 was synthesized analogously to **1**, however starting from **13**. **15** was yielded as white solid; the yield was not determined.

¹H-NMR (CD₃CN, 400 MHz, 25 °C): 8.72 (dd, *J* = 10.7, 1.9 Hz, 1H, C(1) - *H*), 8.15 (d, *J* = 15.0 Hz, 1H, C(3) - *H*), 7.89 – 7.94 (m, 2H, arom. *H*), 7.72 (tt, *J* = 7.4, 1.9 Hz, 1H, arom. *H*), 7.59 – 7.65 (m, 2H, arom. *H*), 7.24 – 7.34 (m, 4H, arom. *H* & C(2) - *H*), 7.07 – 7.11 (m, 2H, arom. *H*), 5.17 – 5.22 (m, 1H, CH), 3.57 (dd, *J* = 14.8, 5.7 Hz, 1H, CH₂), 3.47 (dd, *J* = 14.7, 3.7 Hz, 1H, CH₂), 2.79 (s, 3H, NCH₃), 1.69 (s, 3H, CH₃), 0.80 (s, 3H, CH₃).

¹⁹F-NMR (CD₃CN, 376 MHz, 25 °C): -71.6 (d, *J* = 707 Hz, PF₆⁻).

³¹P-NMR (CD₃CN, 162 MHz, 25 °C): -143.1 (septett, *J* = 707 Hz, PF₆⁻).

(2R,5S,E)-5-Benzyl-2-(tert-butyl)-3-methyl-4-oxo-1-((E)-3-phenylallylidene)imidazolidin-1-ium (2)



2

2 was synthesized following a literature procedure.^{9c}

The synthesis was carried out in oven-dried glassware under argon atmosphere. Ammonium salt **14** (226 mg, 576 μmol, 1.0 eq.) and *trans*-cinnamaldehyde (80 mg, 76 μL, 605 μmol, 1.05 eq.) were dissolved in anh. and deg. EtOH (0.5 mL). After addition of catalytic amounts of triethylamine (3.5 μL) a yellow suspension has formed. The reaction mixture was stirred for 24 h at r.t followed by removing the solvent under inert

gas conditions using a teflon cannula. The yellow residue was purified by washing with anh. and deg. Et₂O (3 · 20 mL). Last, volatile components were removed *in vacuo* giving **2** as a yellow solid (250 mg, 0.49 mmol, 85 %).

¹H-NMR (acetone-*d*₆, 400 MHz, 25 °C): 9.04 (d, *J* = 10.8 Hz, 1H, C(1) - *H*), 8.28 (d, *J* = 15.0 Hz, 1H, C(3) - *H*), 7.65 – 7.73 (m, 1H, arom. *H*), 7.58 – 7.63 (m, 2H, arom. *H*), 7.53 – 7.58 (m, 4H, arom. *H*), 7.44 – 7.50 (m, 2H, arom. *H*), 7.28 – 7.33 (m, 1H, arom. *H*), 6.61 (dd, *J* = 15.0, 10.8 Hz, 1H, C(2) - *H*), 5.64 (s, 1H, CH), 5.27 (dd, *J* = 8.7, 4.8 Hz, 1H, CH), 3.67 (dd, *J* = 15.0, 4.8 Hz, 1H, CH₂), 3.43 (dd, *J* = 14.9, 8.6 Hz, 1H, CH₂), 3.19 (s, 3H, NCH₃), 1.36 (s, 9H, (CH₃)₃).

¹³C-NMR (acetone-*d*₆, 101 MHz, 25 °C): 173.5, 168.0, 166.9, 137.4, 136.0, 134.3, 132.3, 130.8, 130.4, 130.3, 129.0, 118.4, 91.3, 65.5, 38.6, 38.3, 32.4, 26.9.

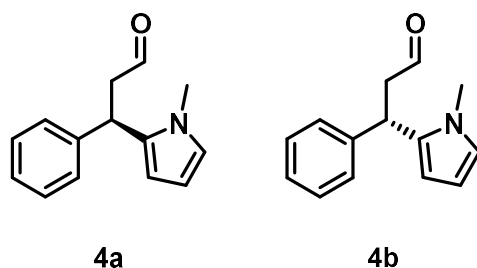
¹⁹F-NMR (acetone-*d*₆, 376 MHz, 25 °C): -71.3 (d, *J* = 708 Hz, PF₆⁻).

³¹P-NMR (acetone-*d*₆, 162 MHz, 25 °C): -142.6 (septett, *J* = 708 Hz, PF₆⁻).

Analytical data are in agreement with the literature.^{9c}

3.5.2.2 Syntheses of **4** and **6** for HPLC calibration

(R)-3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanal (4a) & (S)-3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanal (4b)



4a and **4b** were synthesized following a literature procedure.^{7b}

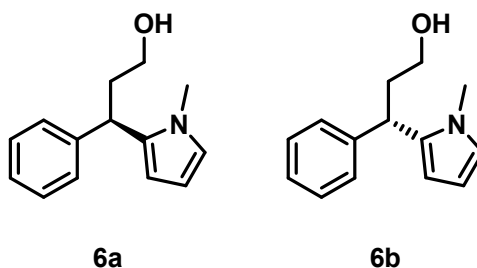
Iminium ions **1** (110 mg, 230 μmol, 0.5 eq.) and **15** (110 mg, 230 μmol, 0.5 eq.) were dissolved in MeCN (8 mL) and cooled to -20 °C. *N*-Methyl pyrrole (187 mg, 204 μL, 2.3 mmol, 5.0 eq.) and potassium trifluoroacetate (320 mg, 2.1 μmol, 4.57 eq.) were added and the yellowish reaction mixture was stirred for 3 h at -20 °C. Afterwards, the reaction was stopped by adding an aq. sat. NaHCO₃-solution (15 mL) and brine (7.5 mL) under vigorous stirring, followed by an extraction with CH₂Cl₂ (3 · 15 mL). The combined organic phases were dried over MgSO₄ and subsequent volatile components were removed *in vacuo*. After column chromatography (EA/ *n*-pentane 1:6) traces of the products **4a** and **4b** were obtained as light-brown solid. The yield was not determined.

¹H-NMR (DMSO-*d*₆, 400 MHz, 25 °C): 9.62 (t, *J* = 1.9 Hz, 1H, CHO), 7.24 – 7.31 (m, 2H, *H*-Ar), 7.14 – 7.21 (m, 3H, *H*-Ar), 6.60 (t, *J* = 2.2 Hz, 1H, *H*-Ar_N), 5.97 – 6.00 (m, 1H, *H*-Ar_N), 5.91 – 5.93 (m, 1H, *H*-Ar_N), 4.63 (dd, *J* = 8.5, 6.9 Hz, 1H, CH), 3.31 (s, 3H, NCH₃), 3.09 (ddd, *J* = 16.9, 8.7, 2.2 Hz, 1H, CH₂CO), 2.91 (ddd, *J* = 16.9, 6.7, 1.6 Hz, 1H, CH₂CO).

Chiral HPLC (CHIRALCEL OD-H, n-hexane/isopropyl alcohol (IPA) 97:3, flowrate 0.6 mL/min, 20 °C): *t_R* (1) = 16.5 min, 49 area%; *t_R* (2) = 17.8, 51 area%.

Analytical data are in agreement with the literature.^{7a}

(R)-3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanol (6a) & (S)-3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanol (6b)



6a and **6b** were synthesized following a literature procedure.^{7a}

Procedure 1 (for racemic product distribution):

A racemic mixture of **4** (12.8 mg, 60 μmol, 1.0 eq.) was dissolved in THF (2 mL) and H₂O (0.3 mL). EtOH (2.3 mL) and NaBH₄ (23.0 mg, 600 μmol, 10.0 eq.) were added to the colorless liquid and the resulting suspension was stirred for 15 min at r.t. The reaction was stopped by a careful addition of an aq. sat. NaHCO₃-solution (20 mL) and stirring for further 15 min, followed by an extraction with CH₂Cl₂ (3 · 25 mL). The combined organic phases were dried over MgSO₄ and subsequent volatile components were removed *in vacuo*. Without further purification, traces of **6a** and **6b** were obtained as light-brown oil. The yield was not determined.

Chiral HPLC (CHIRALCEL OD-H, n-hexane/isopropyl alcohol (IPA) 60:40, flowrate 0.6 mL/min, 20 °C): *t_R* (1) = 8.5 min, 48 area%; *t_R* (2) = 17.2 min, 52 area%.

Procedure 2 (for enantioselective product distribution):

Trans-cinnamaldehyde (330 mg, 315 μL, 2.5 mmol, 1.0 eq.) and (S)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidinone dichloroacetic acid (174 mg, 0.5 mmol, 0.2 eq.) were dissolved at r.t. in THF (5 mL) and H₂O (0.75 mL). *N*-Methyl pyrrole (1.0 g, 1.1 mL, 12.5 mmol, 5.0 eq.) was added and the resulting brownish solution was stirred for 38 h at r.t. Then EtOH (5.75 mL) and NaBH₄ (946 mg, 25.0 mmol, 10.0 eq.) were added and

the reaction mixture was stirred for further 15 min resulting in a yellow colored suspension. The reaction was stopped by carefully adding an aq. sat. NaHCO₃-solution (50 mL) over a period of 90 min. Afterwards, the reaction mixture was extracted with CH₂Cl₂ (3 · 25 mL). The combined organic phases were dried over MgSO₄ and subsequent volatile components were removed under reduced pressure. Column chromatography (EA/ *n*-pentane 1:2) gave the purified enantiomers **6a** and **6b** (395 mg, 1.83 mmol, 73 %) as light brown oil.

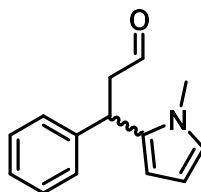
¹H-NMR (CD₂Cl₂, 400 MHz, 25 °C): 7.24 – 7.30 (m, 2H, *H*-Ar), 7.13 – 7.20 (m, 3H, *H*-Ar), 6.50 (pt, *J* = 2.2 Hz, 1H, *H*-Ar_N), 6.09 – 6.11 (m, 1H, *H*-Ar_N), 6.04 – 6.06 (m, 1H, *H*-Ar_N), 4.10 (pt, *J* = 7.5 Hz, 1H, CH), 3.52 – 3.67 (m, 2H, CH₂), 3.30 (s, 3H, NCH₃), 2.24 – 2.34 (m, 1H, CH₂), 2.02 – 2.12 (m, 1H, CH₂), 1.35 (bs, 1H, COH).

Chiral HPLC (CHIRALCEL OD-H, *n*-hexane/isopropyl alcohol (IPA) 60:40, flowrate 0.6 mL/min, 20 °C): *t_R* (1) = 8.5 min, 90 area%; *t_R* (2) = 17.4 min, 10 area%.

Analytical data are in agreement with the literature.^{7a}

3.5.2.3 Syntheses of **4** and **6** for DTS-*hv*

3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanal (**4**)



4

4 was synthesized based on literature procedures.

Procedure 1 (DTS-*hv*- or very similar conditions):^{7b}

The synthesis was carried out in oven-dried glassware under argon atmosphere. Iminium ion **1** (see table S1 for amount, 1.0 eq.) was dissolved in solvent S (8 mL) and cooled to temperature T. The basic additive and, after stirring for 5 min, *N*-Me-pyrrole (5.0 eq.) were added to the light-yellow solution, which resulted in an instant yellowish brown color intensification. After stirring for reaction time *t* at temperature T, the reaction was stopped by the addition of aq. sat. NaHCO₃-solution (15 mL) and brine (7.5 mL) under vigorous stirring, followed by an extraction with CH₂Cl₂ (3 · 15 mL) and drying over MgSO₄. Removing volatile components under reduced pressure and finally column chromatography (EA/ *n*-pentane 1:6) yielded traces of **4**. The yield was not determined. The obtained enantiomeric ratio was determined *via* chiral HPLC (CHIRALCEL OD-H, *n*-hexane/isopropyl alcohol (IPA) 97:3, flowrate 0.6 mL/min, 20 °C).

Basic additive: 1) DBP: 2,6-Di-*tert*-butylpyridine (2.0 eq.)

2) K⁺TFA⁻: Potassium trifluoroacetate (4.57 eq.)

Table S1. Overview of the enantiomeric ratios of **4** obtained using procedure 1.

Entry	1 [mM]	Solvent S	Temp. T [°C]	Time t [h]	additive	Enantiomeric ratio [area%] ^a
1	10	anh. & deg. MeCN	-40	2.0	1	50:50
2	10	anh. & deg. MeCN	-40	2.0	2	54:46
3	10	anh. & deg. MeCN	-20	2.0	1	49:51
4	10	anh. & deg. MeCN	-20	2.0	2	50:50
5	57.5	anh. & deg. MeCN	-20	0.5	2	50:50
6 ^b	57.5	MeCN/H ₂ O 40:1	-20	0.5	2	51:49

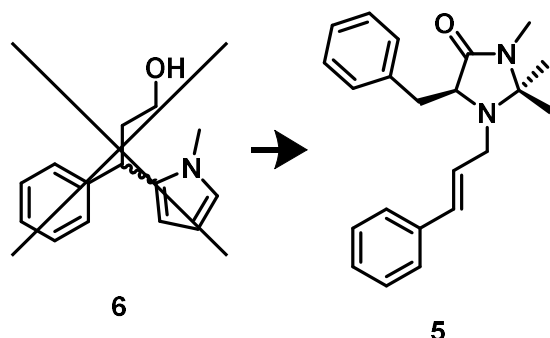
^a Enantiomeric ratio was determined *via* chiral HPLC (CHIRALCEL OD-H, n-hexane/isopropyl alcohol (IPA) 97:3, flowrate 0.6 mL/min, 20 °C).^b The same experimental conditions as reported in literature^{7b} have been used, however not the alcohol product **6** but the aldehyde product **4** was isolated.

Procedure 2 (control reaction):^{7a}

Trans-cinnamaldehyde (66.1 mg, 62.9 µL, 0.5 mmol, 1.0 eq.) and (S)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidinone dichloroacetic acid (34.7 mg, 0.1 mmol, 0.2 eq.) were dissolved at r.t. in a mixture of THF (1 mL) and H₂O (0.15 mL). *N*-Methyl pyrrole (203 mg, 222 µL, 2.5 mmol, 5.0 eq.) was added and the resulting yellowish solution was stirred for 30 h at r.t. Afterwards, an aq. sat. NaHCO₃-solution (15 mL) and brine (7.5 mL) were added to stop the reaction, followed by extracting with CH₂Cl₂ (3 · 25 mL). The combined organic phases were dried over MgSO₄ and subsequent volatile components were removed under reduced pressure. Column chromatography (EA/ *n*-pentane 1:6) resulted in traces of the purified aldehyde products **4a** and **4b** as light brown oil.

Chiral HPLC (CHIRALCEL OD-H, n-hexane/isopropyl alcohol (IPA) 97:3, flowrate 0.6 mL/min, 20 °C): *t*_R (1) = 17.9 min, 53 area%; *t*_R (2) = 19.5 min, 47 area%.

3-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropanol (6) → (S)-5-benzyl-1-cinnamyl-2,2,3-trimethylimidazolidin-4-one (5)



The synthesis was carried out in oven-dried glassware under argon atmosphere. Iminium ion **1** (120 mg, 0.25 mmol, 1.0 eq.) was dissolved in anh. and deg. MeCN (25 mL) and cooled to -40 °C. 2,6-Di-*tert*-butylpyridine (95.7 mg, 113 μ L, 0.5 mmol, 2.0 eq.) and, after stirring for 5 min, *N*-Me-pyrrole (101 mg, 111 μ L, 1.25 mmol, 5.0 eq.) were added to the light-yellow solution, which resulted in an instant yellowish brown color intensification. After stirring for further 2 h or 18 h at -40 °C, EtOH (25 mL) and NaBH₄ (94.6 mg, 2.5 mmol, 10.0 eq.) were added to the reaction mixture. After heating up to r.t. and stirring for 15 min, the reaction was stopped by the careful addition of an aq. sat. NaHCO₃-solution (10 mL) under vigorous stirring, followed by an extraction with CH₂Cl₂ (3 · 15 mL) and drying over MgSO₄. Removing volatile components under reduced pressure and finally column chromatography (EA/ *n*-pentane 2:1) gave traces of product **5**; not **6** as expected.

¹H-NMR (CD₂Cl₂, 400 MHz, 25 °C): 7.35 – 7.39 (m, 2H, *H*-Ar), 7.29 – 7.35 (m, 2H, *H*-Ar), 7.20 – 7.27 (m, 5H, *H*-Ar), 7.14 – 7.20 (m, 1H, *H*-Ar), 6.47 (bd, *J* = 15.9 Hz, 1H, C(3) - *H*), 6.22 (ddd, *J* = 15.9, 7.7, 5.9 Hz, 1H, C(2) - *H*), 3.55 – 3.59 (m, 1H, CH), 3.52 – 3.56 (m, 1H, C(1) - *H*), 3.41 (ddd, *J* = 14.9, 5.9, 1.6 Hz, 1H, C(1) - *H*), 3.01 (pt, *J* = 4.3 Hz, 2H, CH₂), 2.68 (s, 3H, NCH₃), 1.23 (s, 3H, CH₃), 1.10 (s, 3H, CH₃).

3.5.2.4 NMR-data

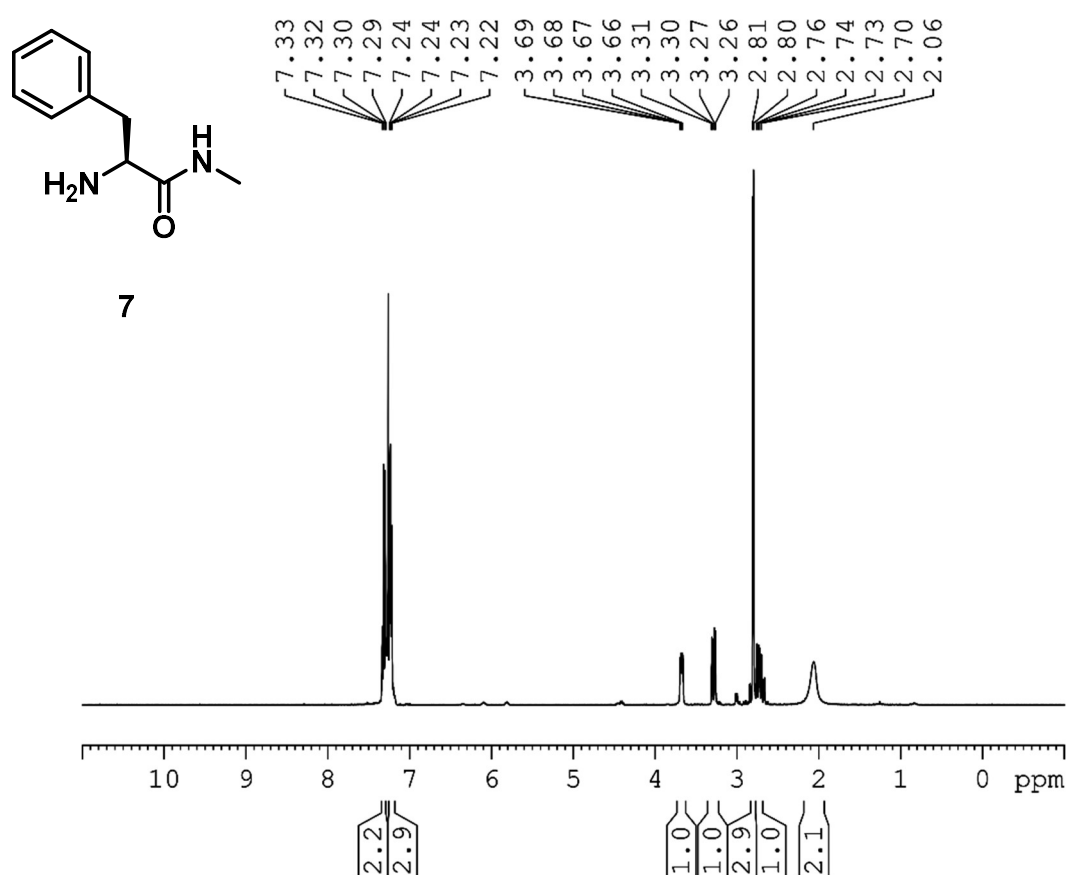


Figure S1. 1D-¹H spectrum (ns = 16) of **7** measured in CDCl₃ at 25 °C.

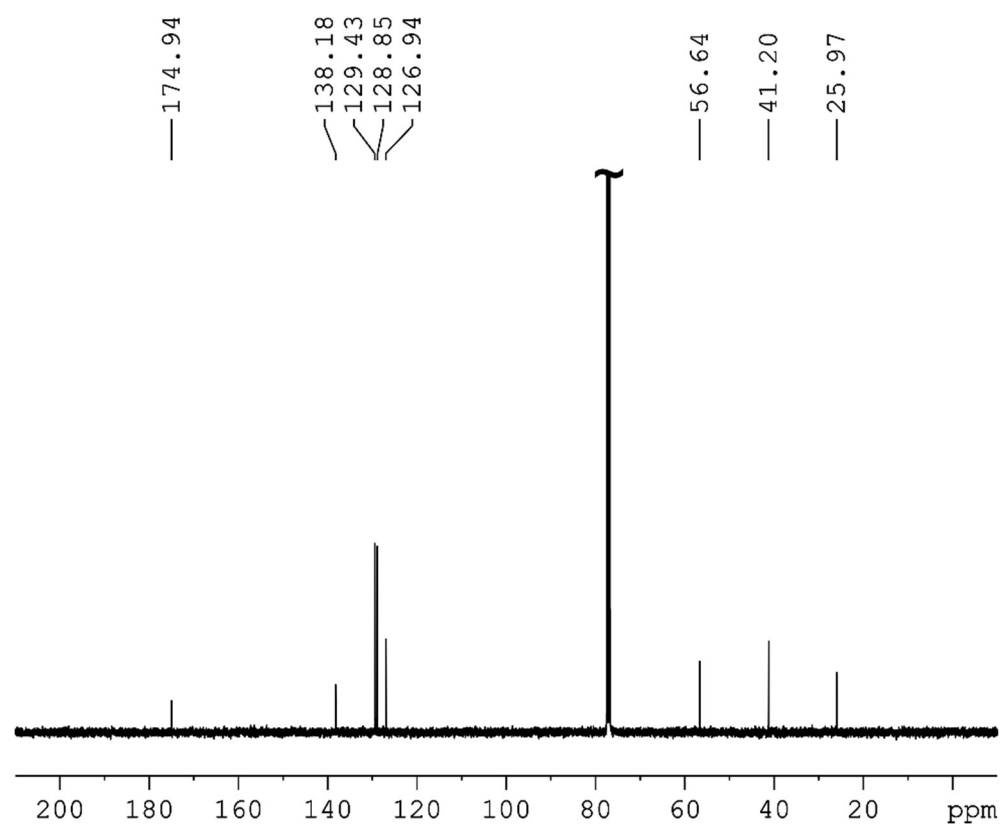


Figure S2. 1D-¹³C{¹H} spectrum (ns = 1024) of **7** measured in CDCl₃ at 25 °C.

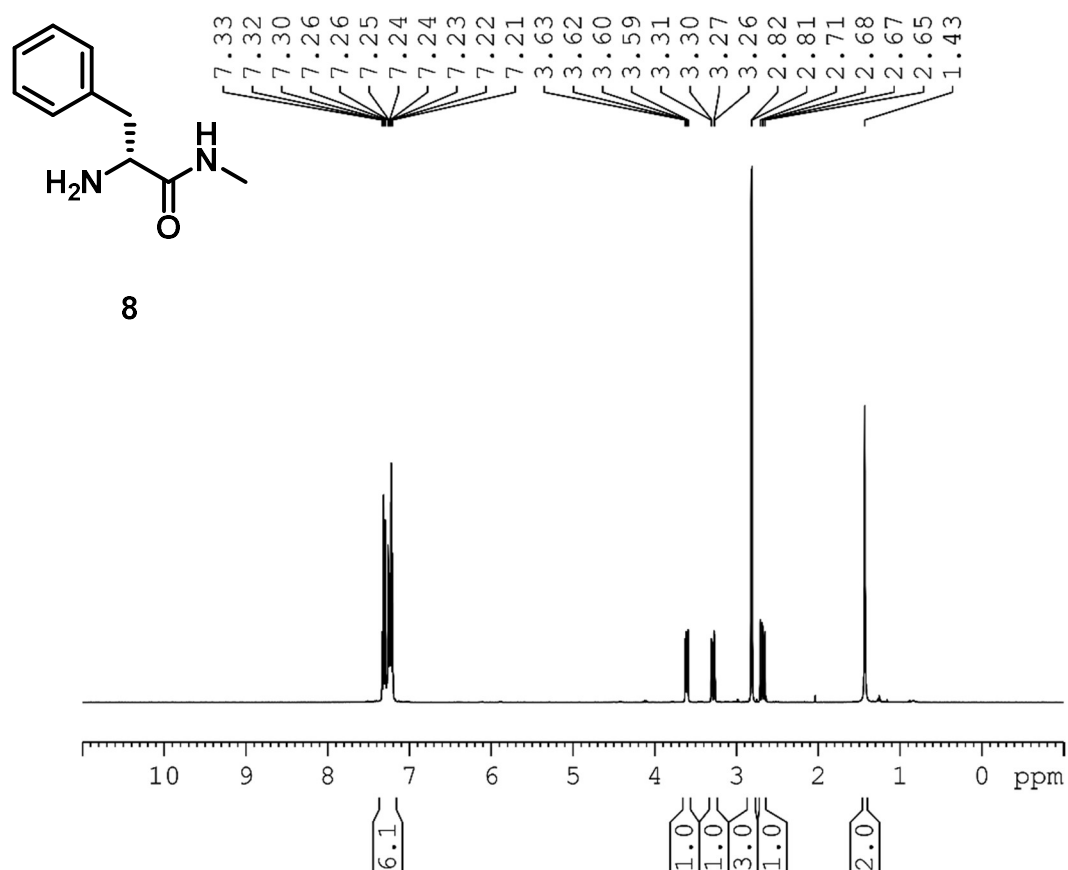


Figure S3. 1D-¹H spectrum (ns = 16) of **8** measured in CDCl₃ at 25 °C.

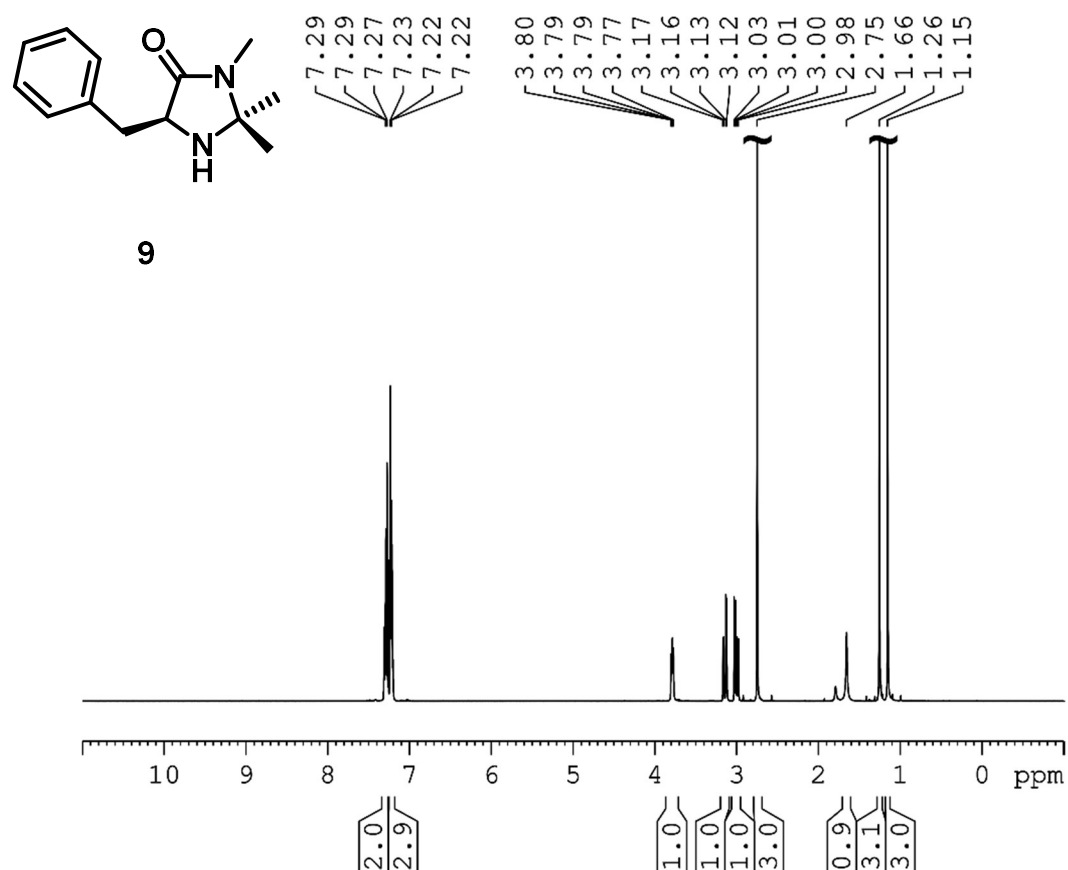


Figure S4. 1D-¹H spectrum (ns = 16) of **9** measured in CDCl₃ at 25 °C.

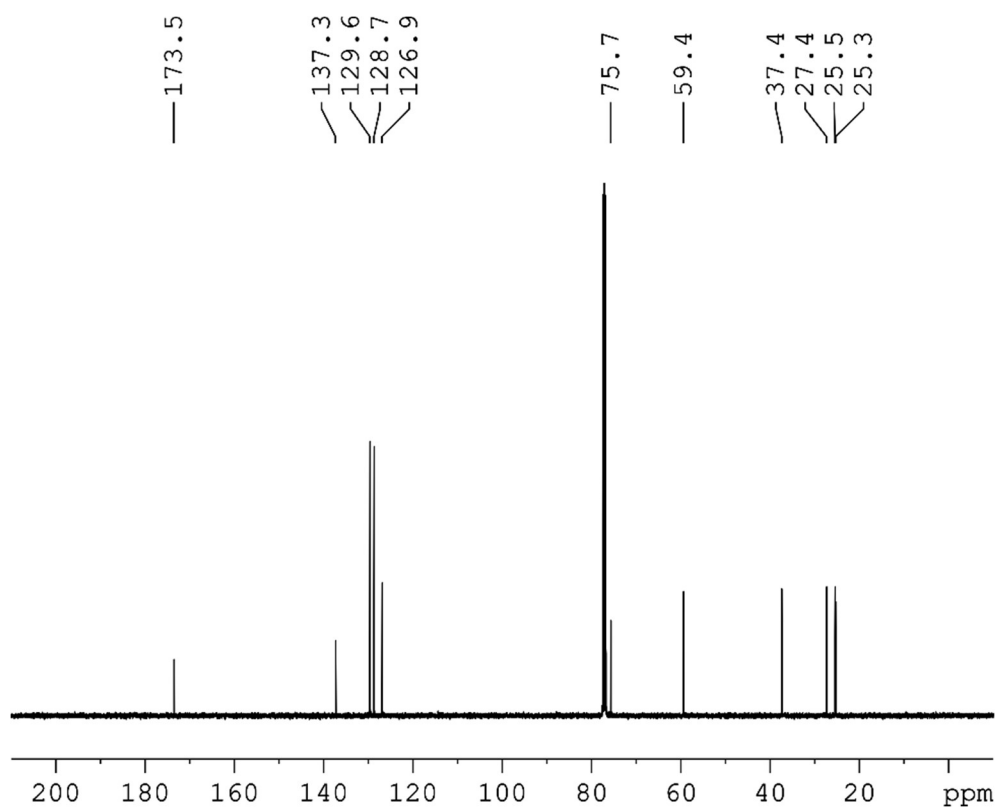


Figure S5. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 1024) of **9** measured in CDCl_3 at 25 °C.

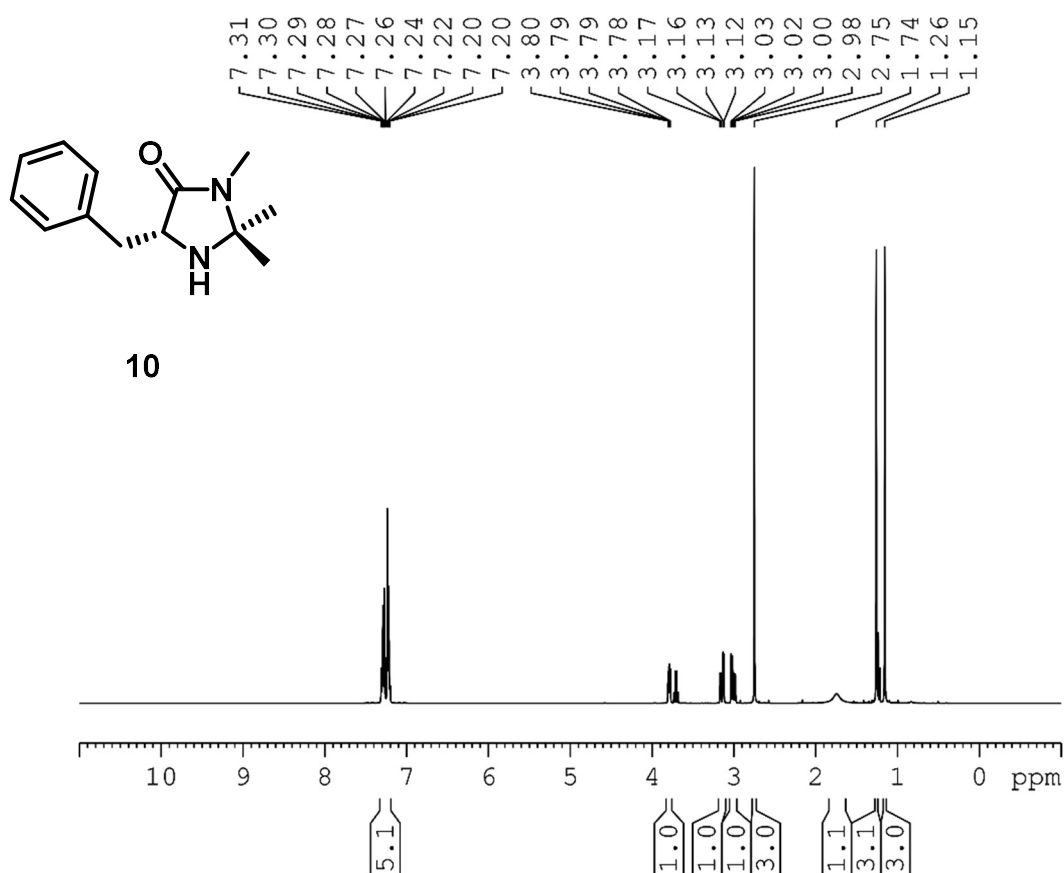


Figure S6. 1D- ^1H spectrum (ns = 16) of **10** measured in CDCl_3 at 25 °C.

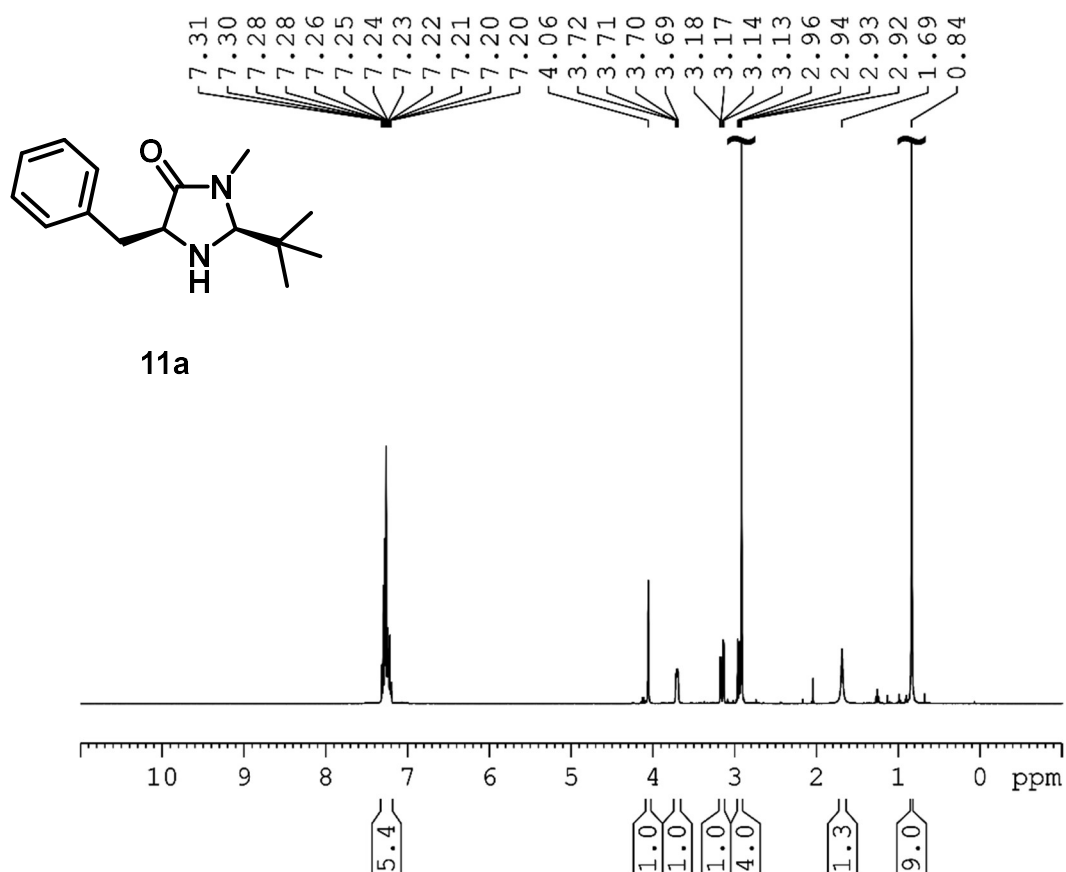


Figure S7. 1D-¹H spectrum (ns = 16) of **11a** measured in CDCl₃ at 25 °C.

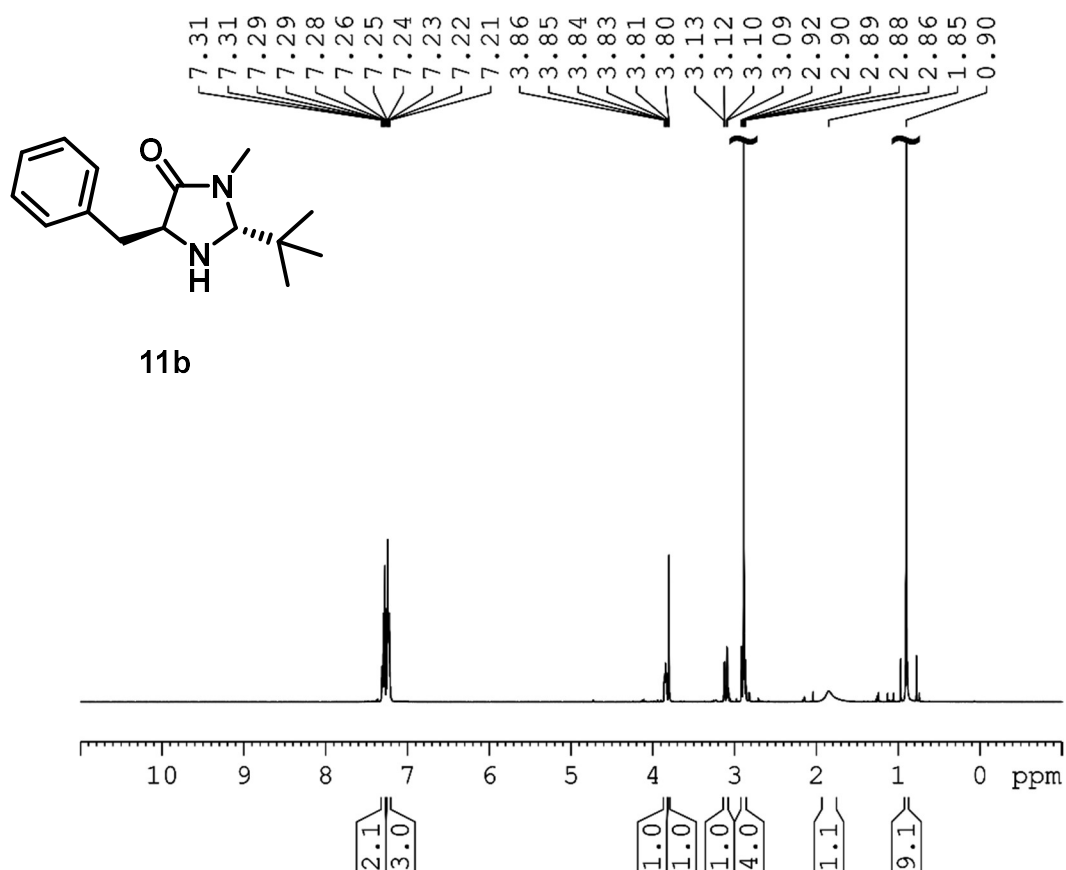


Figure S8. 1D-¹H spectrum (ns = 16) of **11b** measured in CDCl₃ at 25 °C.

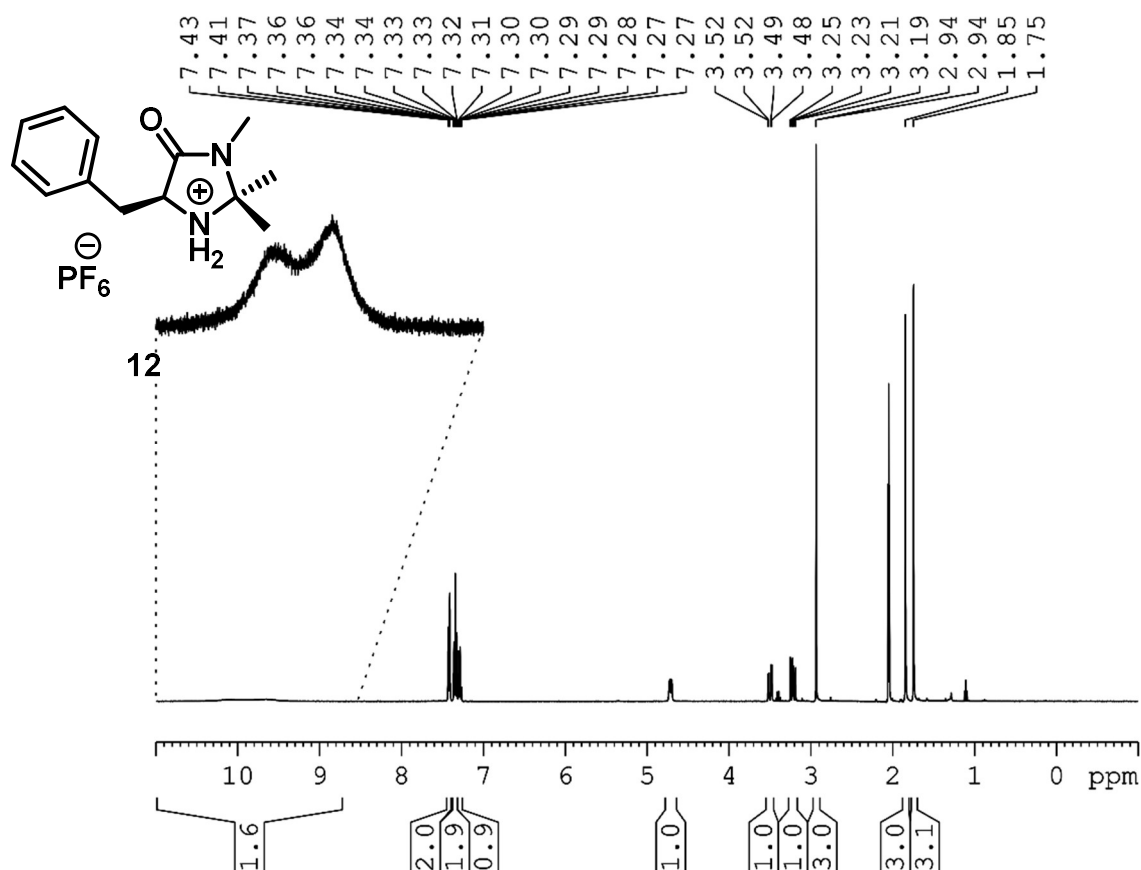


Figure S9. 1D-¹H spectrum (ns = 16) of **12** measured in acetone-*d*₆ at 25 °C.

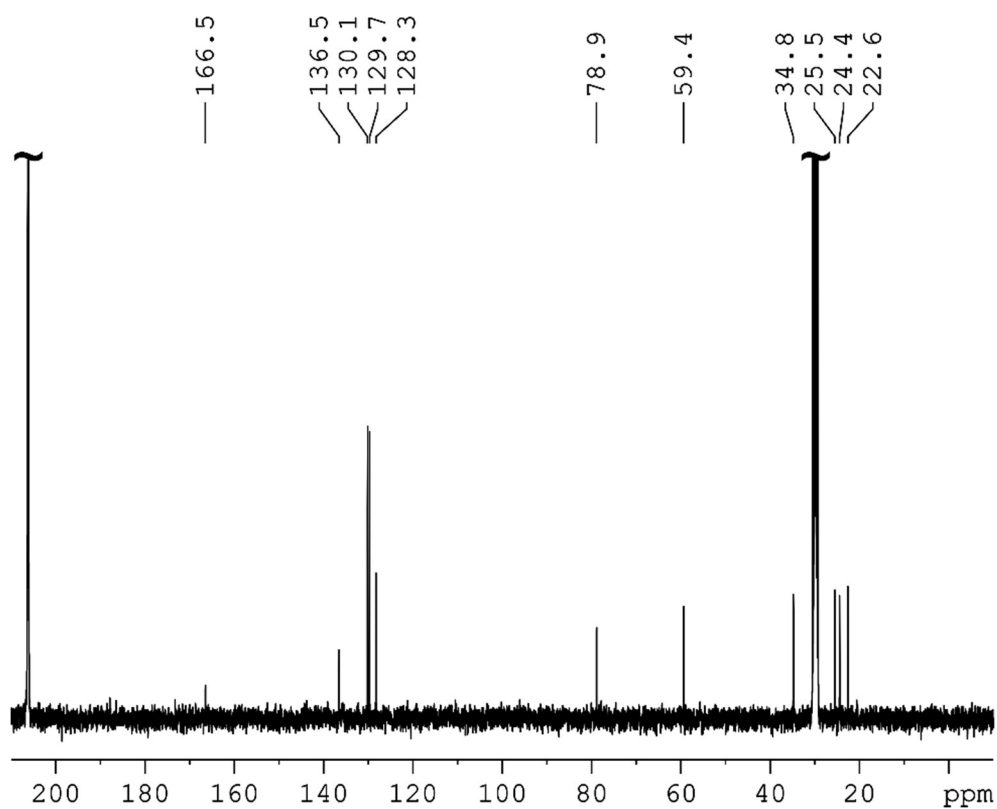


Figure S10. 1D-¹³C{¹H} spectrum (ns = 1024) of **12** measured in acetone-*d*₆ at 25 °C.

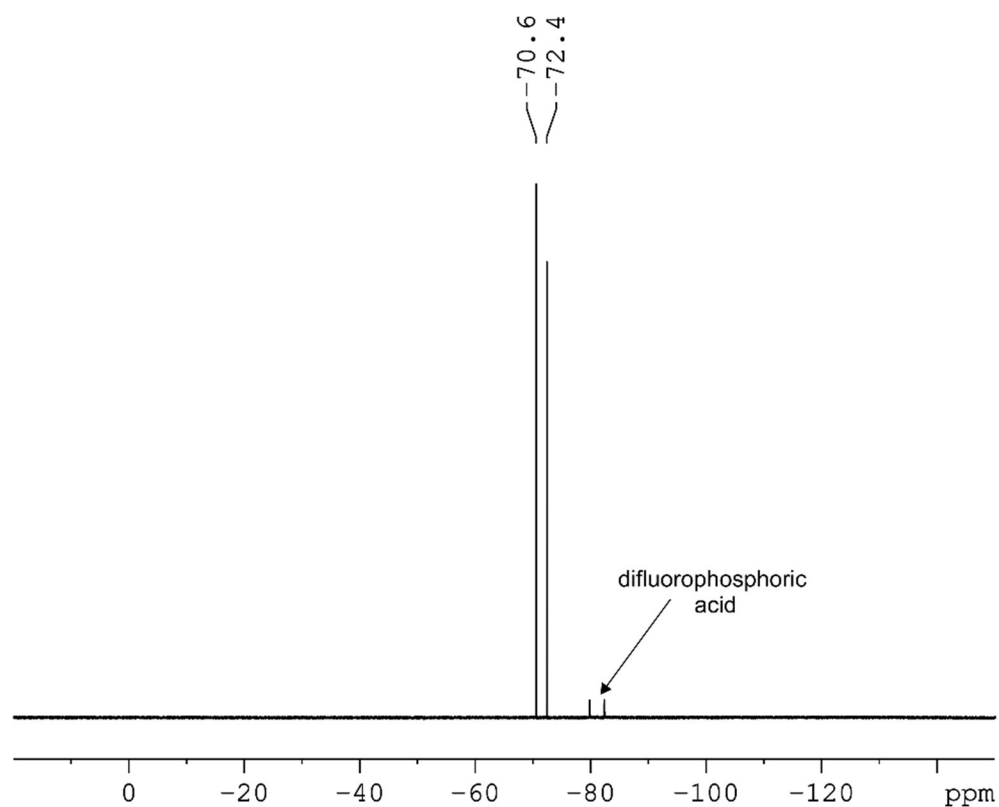


Figure S11. 1D- ^{19}F spectrum (ns = 16) of **12** measured in acetone- d_6 at 25 °C.

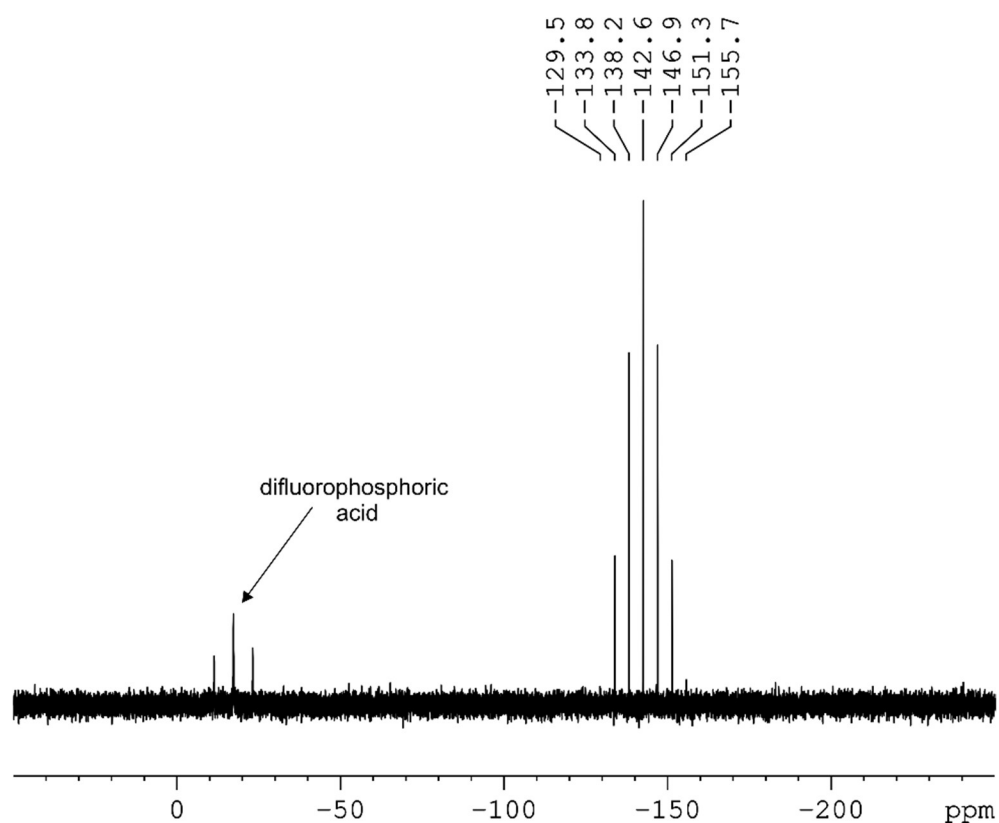


Figure S12. 1D- ^{31}P spectrum (ns = 64) of **12** measured in acetone- d_6 at 25 °C.

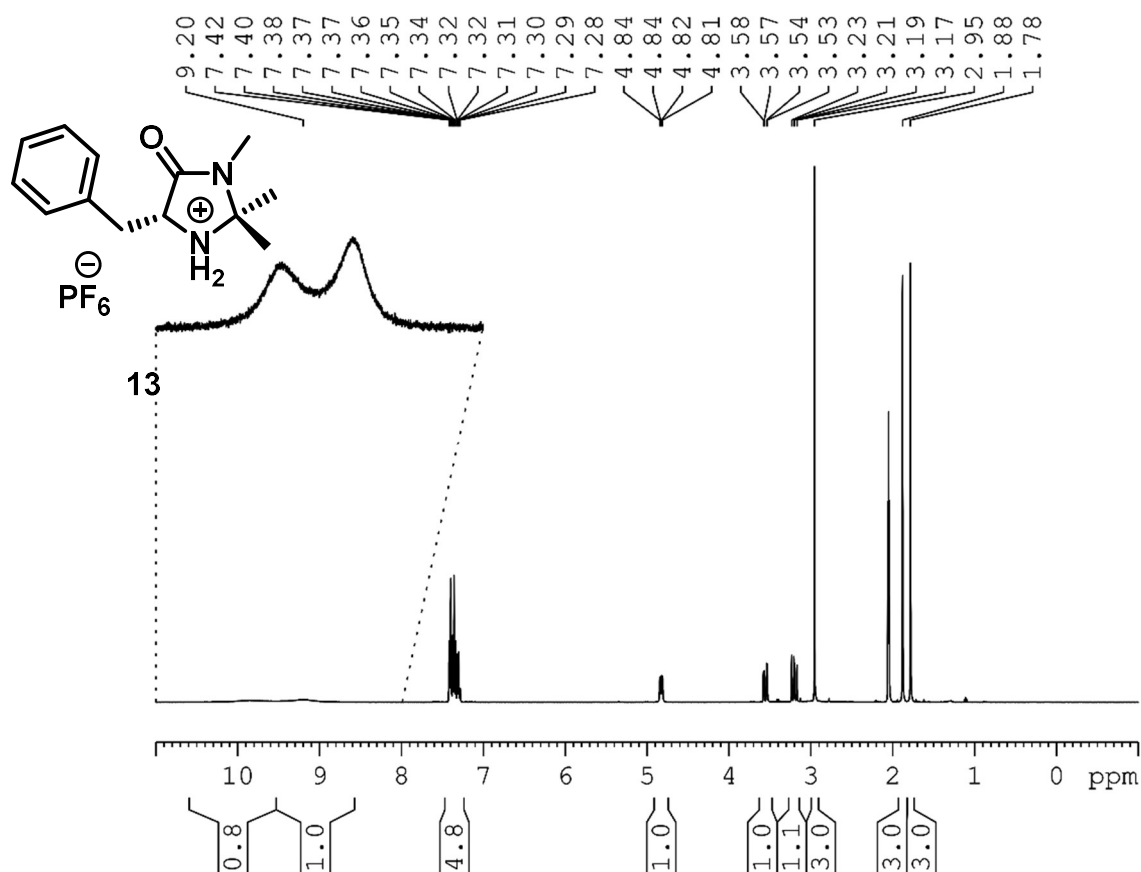


Figure S13. 1D- ^1H spectrum (ns = 16) of **13** measured in acetone- d_6 at 25 °C.

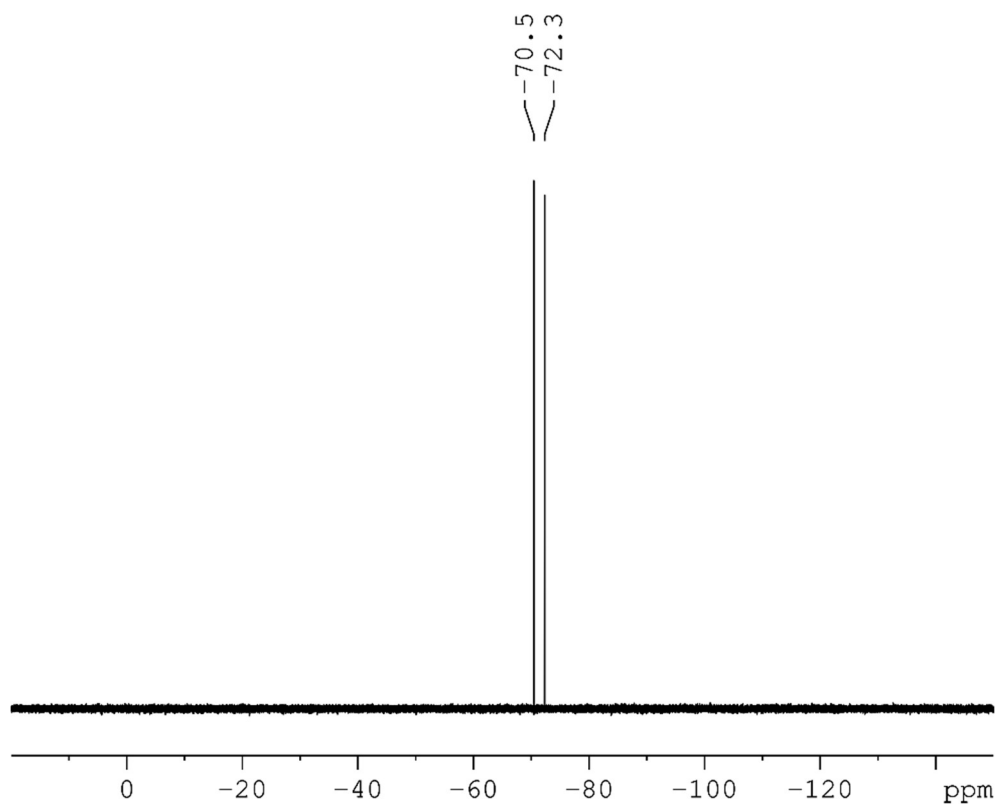


Figure S14. 1D- ^{19}F spectrum (ns = 16) of **13** measured in acetone- d_6 at 25 °C.

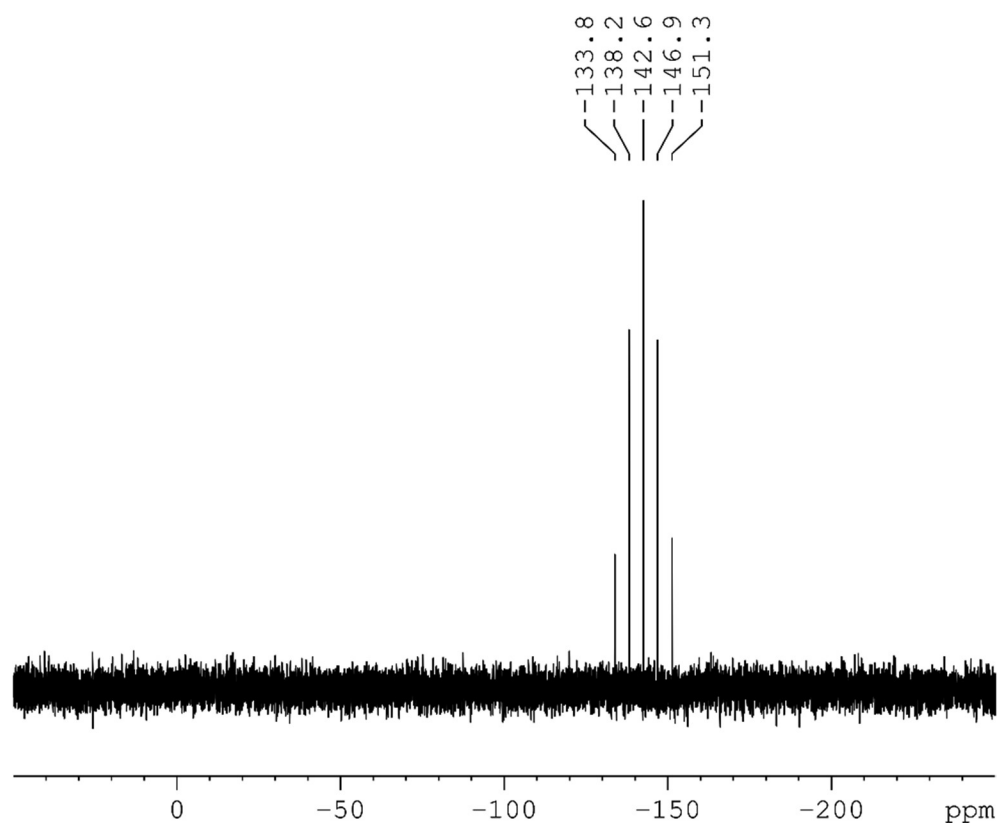


Figure S15. 1D- ^{31}P spectrum (ns = 64) of **13** measured in acetone- d_6 at 25 °C.

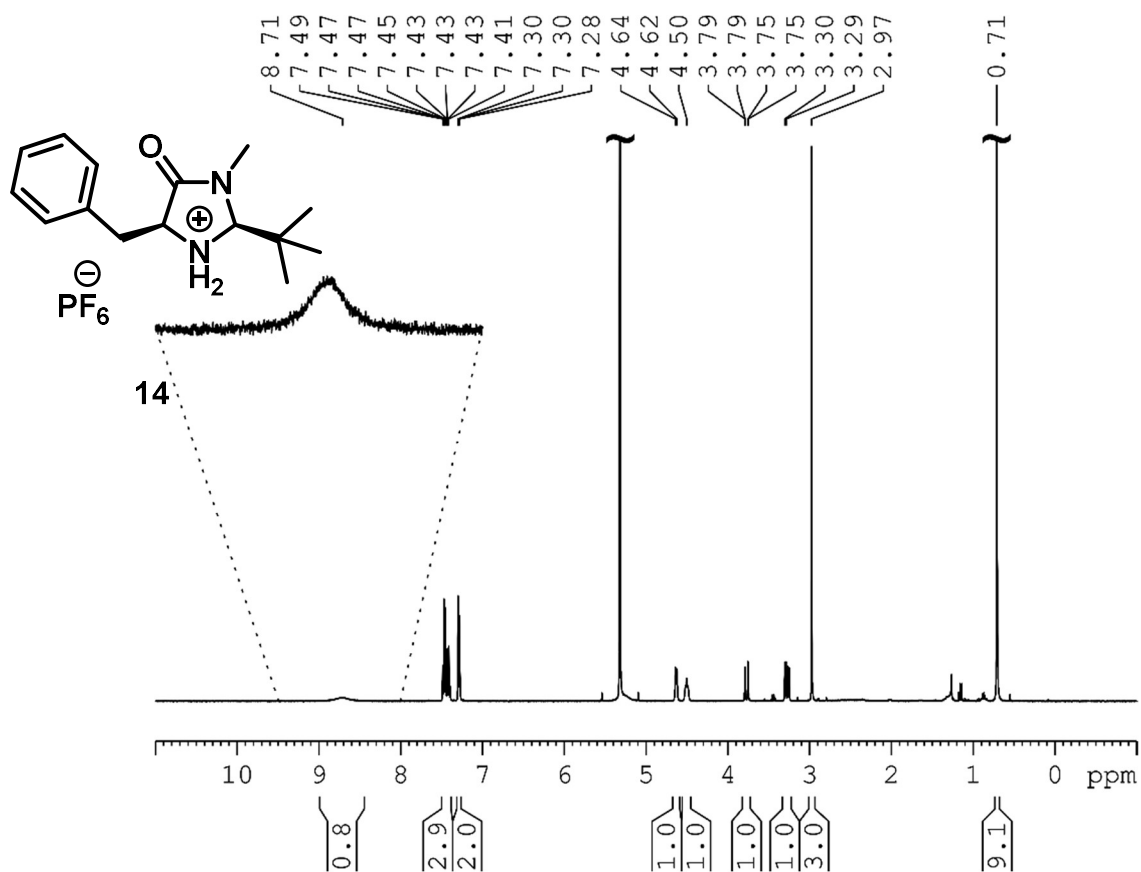


Figure S16. 1D- ^1H spectrum (ns = 16) of **14** measured in CD_2Cl_2 at 25 °C.

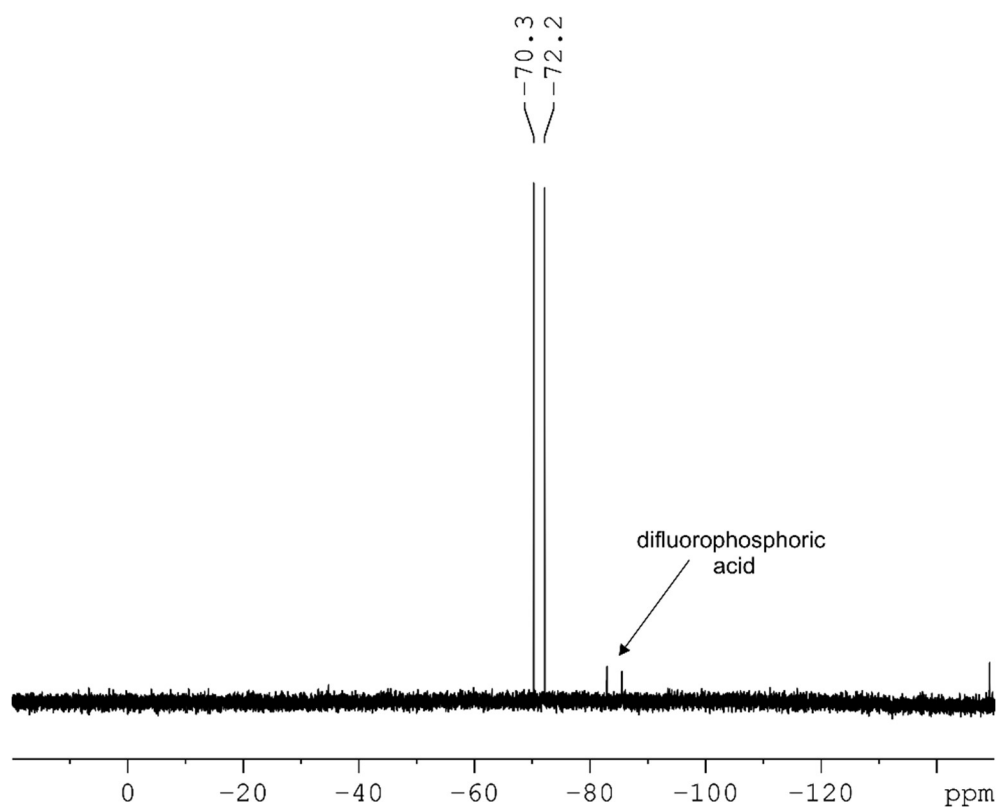


Figure S17. 1D- ^{19}F spectrum (ns = 16) of **14** measured in CD_2Cl_2 at 25 °C.

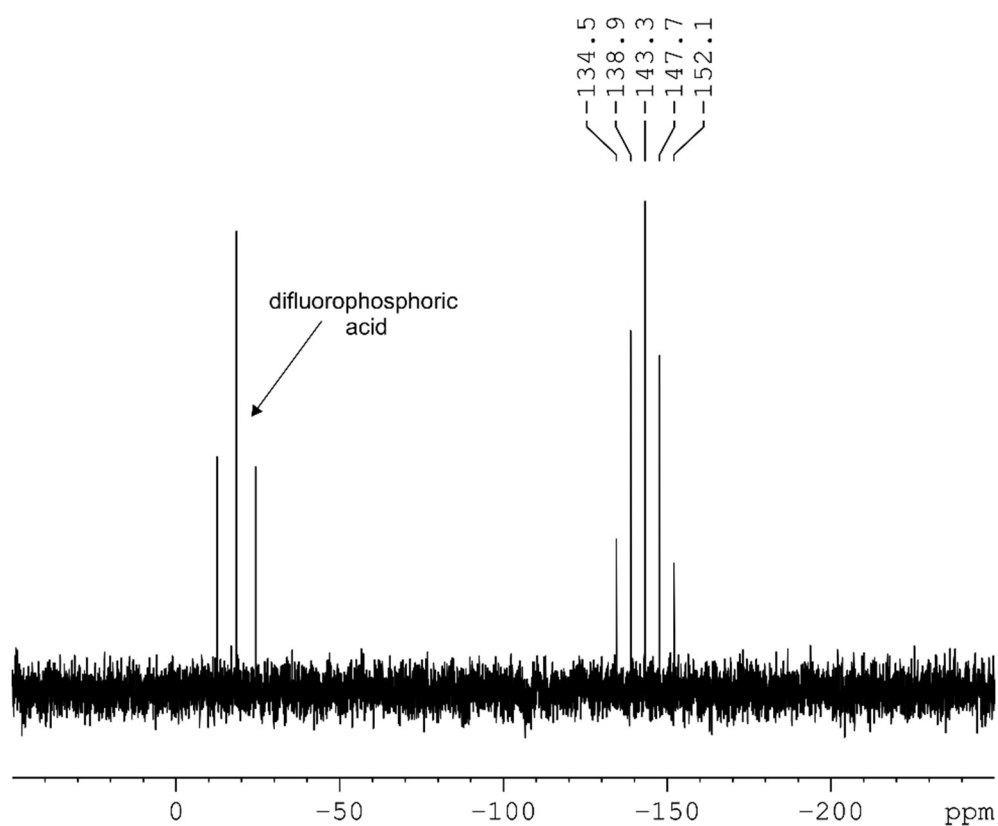


Figure S18. 1D- ^{31}P spectrum (ns = 64) of **14** measured in CD_2Cl_2 at 25 °C.

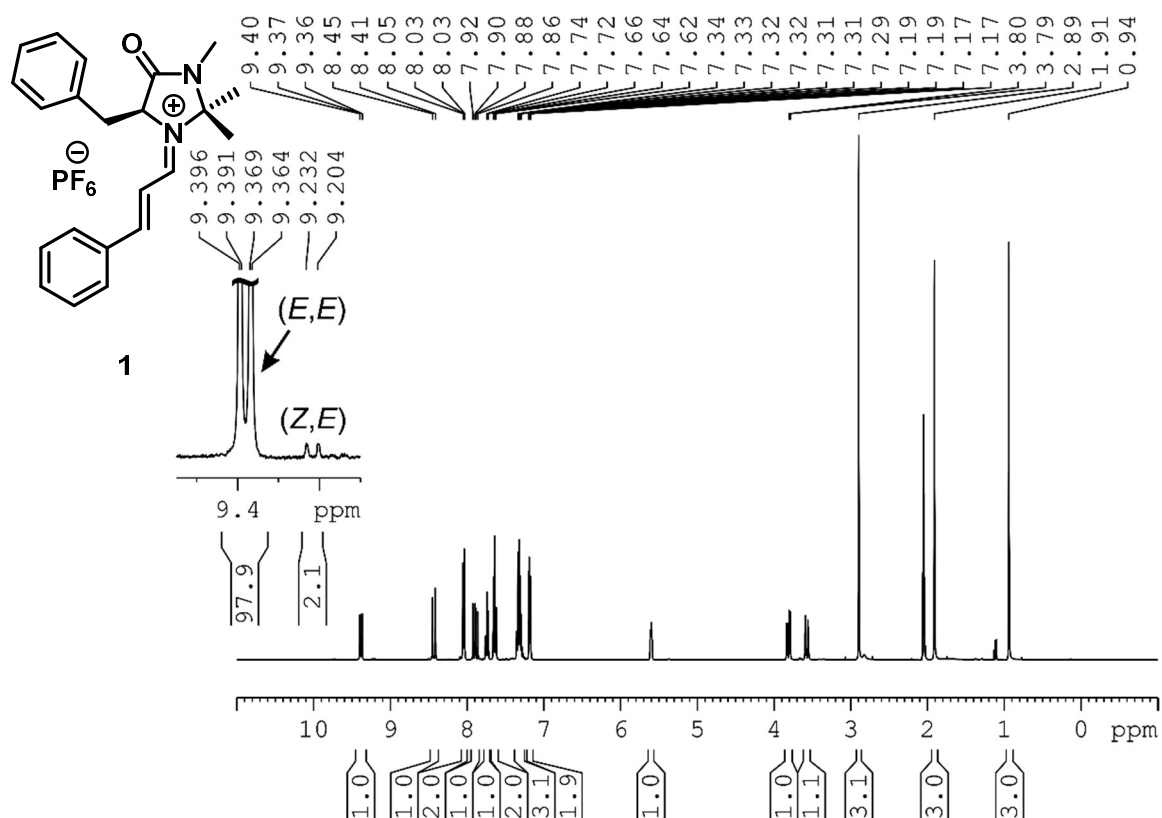


Figure S19. 1D-¹H spectrum (ns = 16) of **1** measured in acetone-*d*₆ at 25 °C. The upper left section shows a (E,E)/(Z,E) ratio of ca. 98:2.

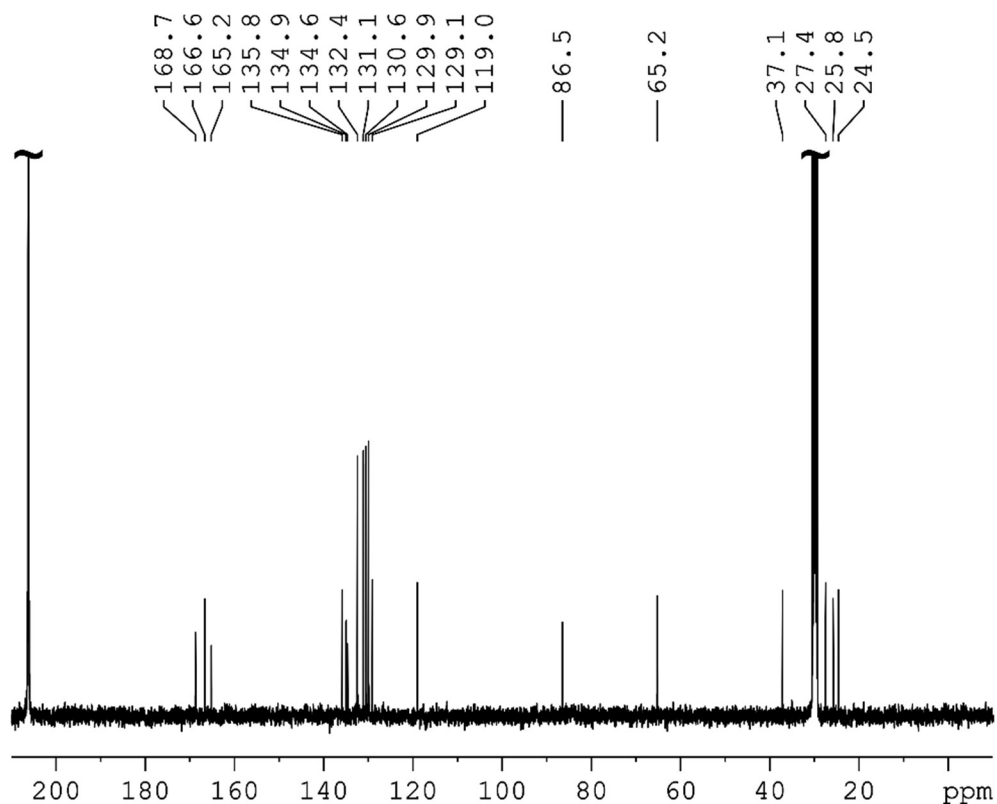


Figure S20. 1D-¹³C{¹H} spectrum (ns = 1024) of **1** measured in acetone-*d*₆ at 25 °C.

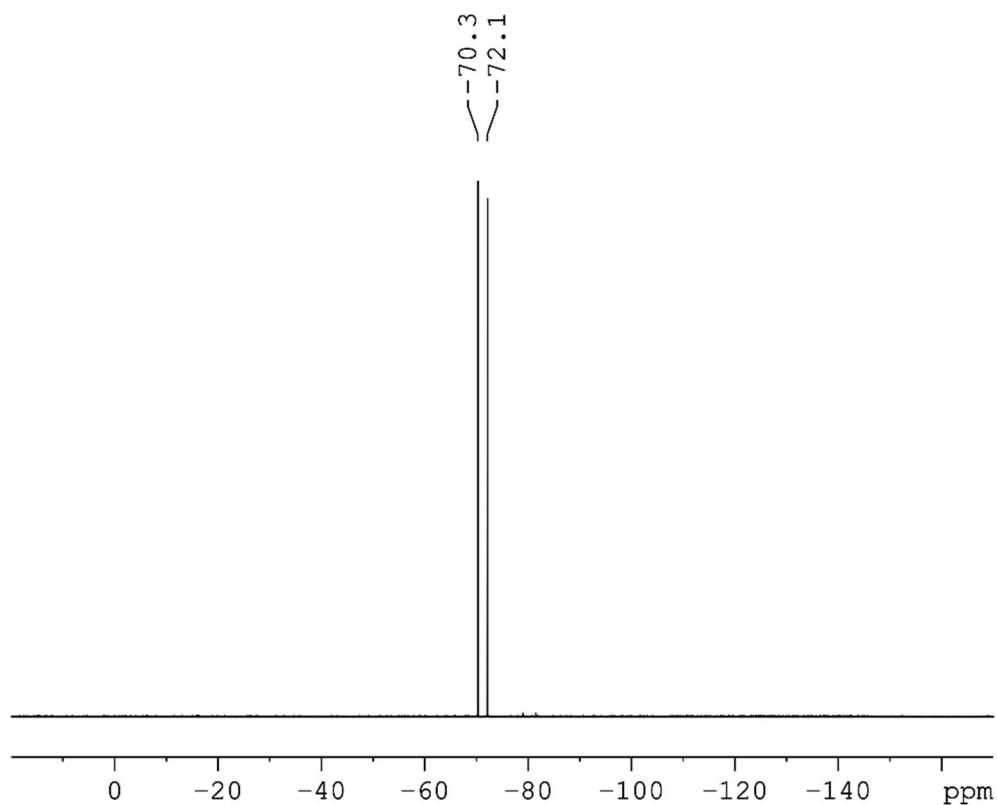


Figure S21. 1D- ^{19}F spectrum (ns = 16) of **1** measured in acetone- d_6 at 25 °C.

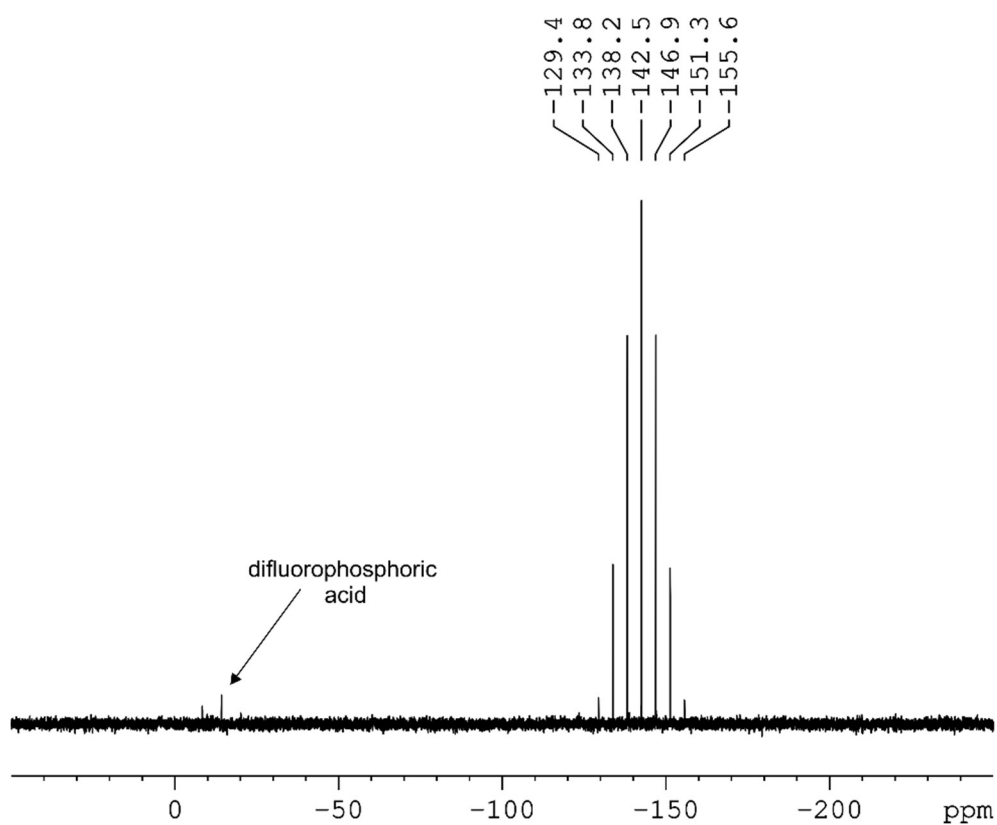


Figure S22. 1D- ^{31}P spectrum (ns = 64) of **1** measured in acetone- d_6 at 25 °C.

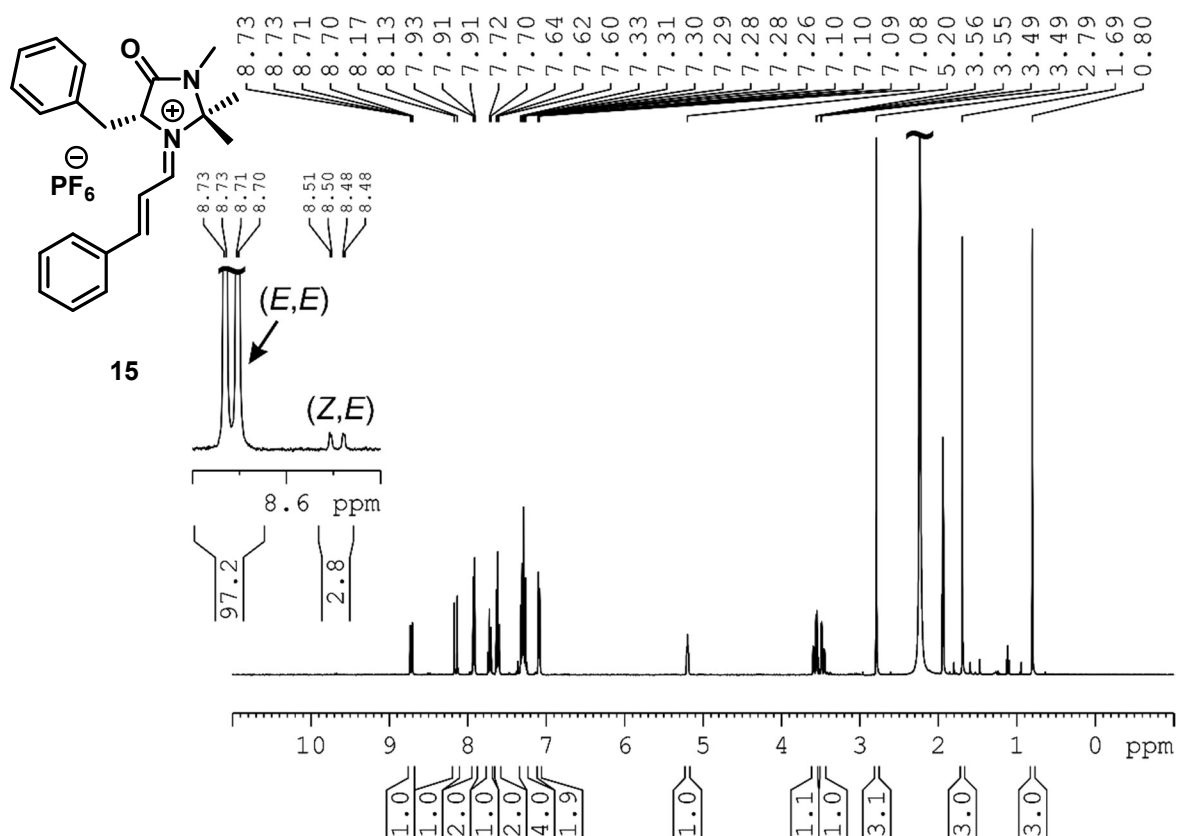


Figure S23. 1D- ^1H spectrum (ns = 16) of **15** measured in CD_3CN at 25 °C. The upper left section shows a (E,E)/(Z,E) ratio of ca. 97:3.

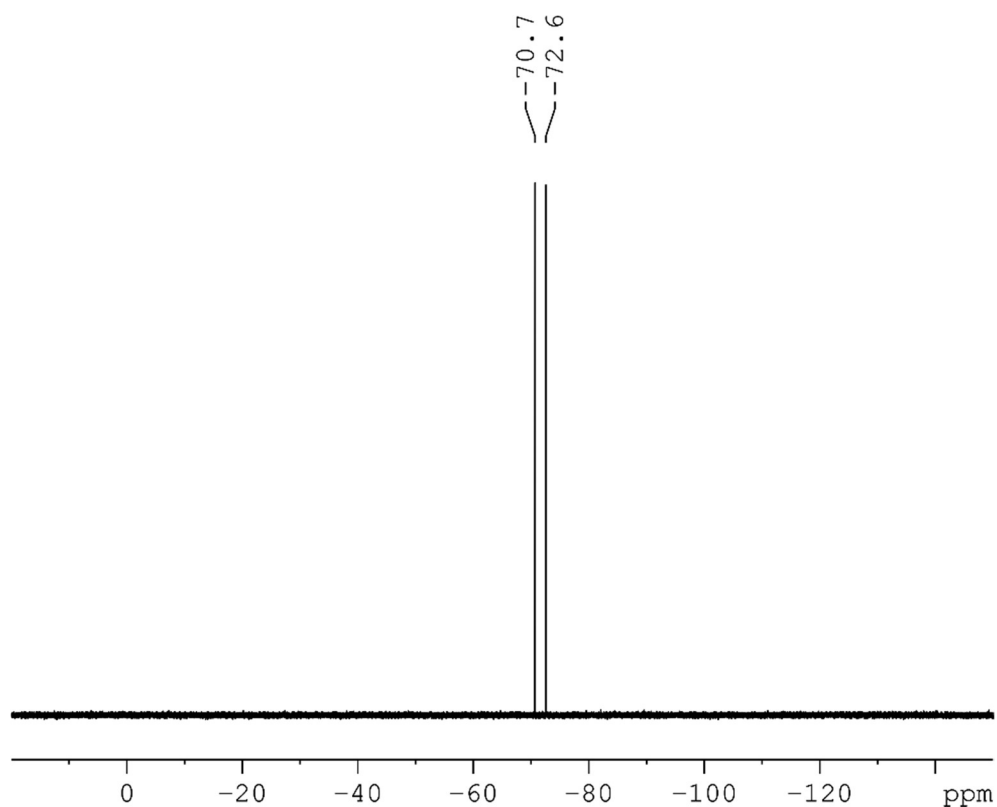


Figure S24. 1D- ^{19}F spectrum (ns = 16) of **15** measured in CD_3CN at 25 °C.

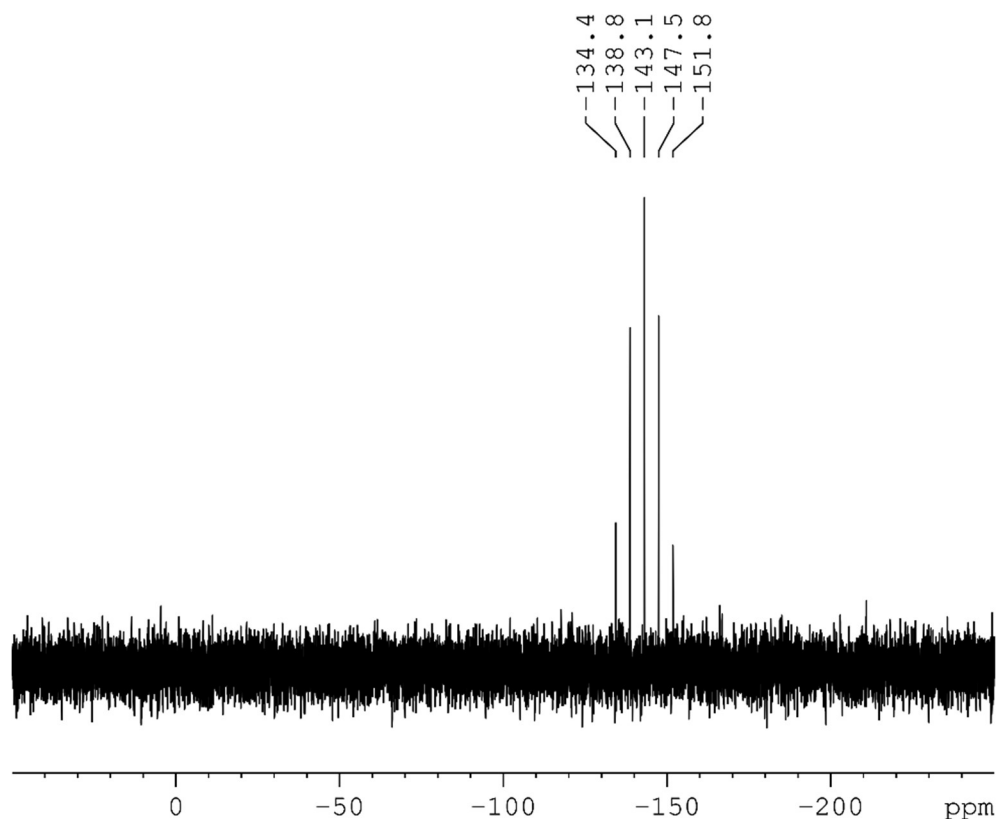


Figure S25. 1D- ^{31}P spectrum (ns = 64) of **15** measured in CD_3CN at 25 °C.

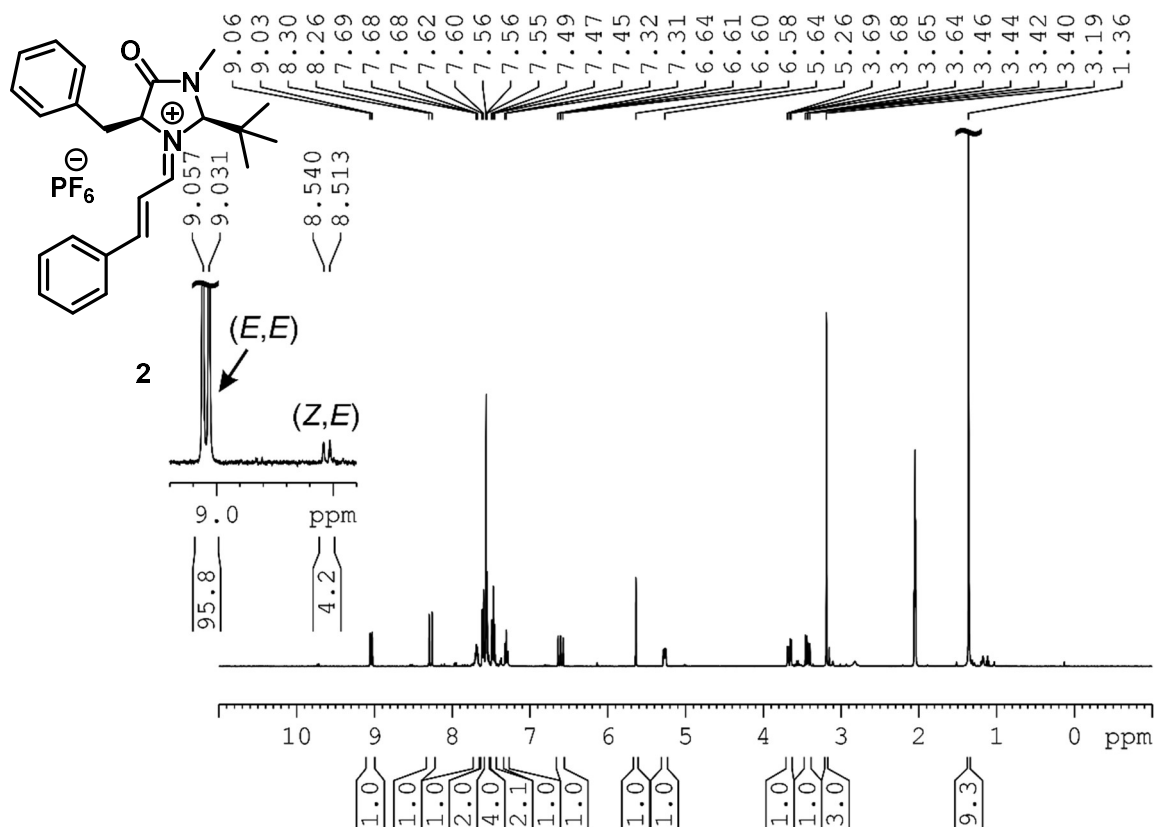


Figure S26. 1D- ^1H spectrum (ns = 16) of **2** measured in acetone- d_6 at 25 °C. The upper left section shows a (E,E)/(Z,E) ratio of ca. 96:4.

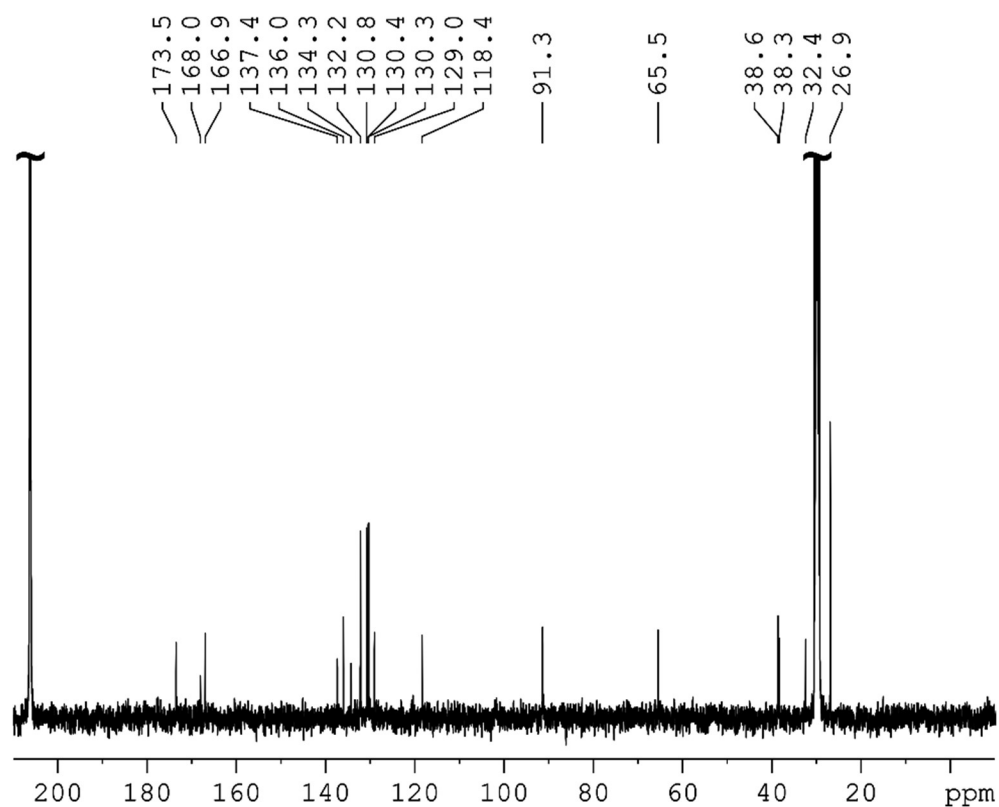


Figure S27. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 1024) of **2** measured in acetone- d_6 at 25 °C.

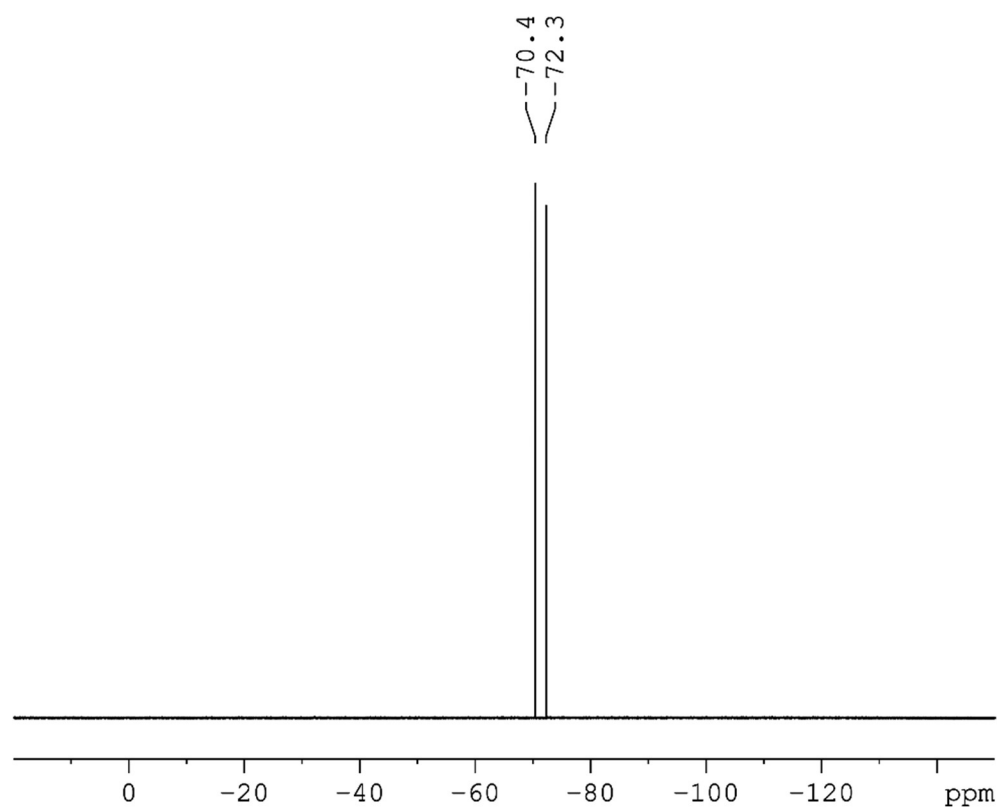


Figure S28. 1D- ^{19}F spectrum (ns = 16) of **2** measured in acetone- d_6 at 25 °C.

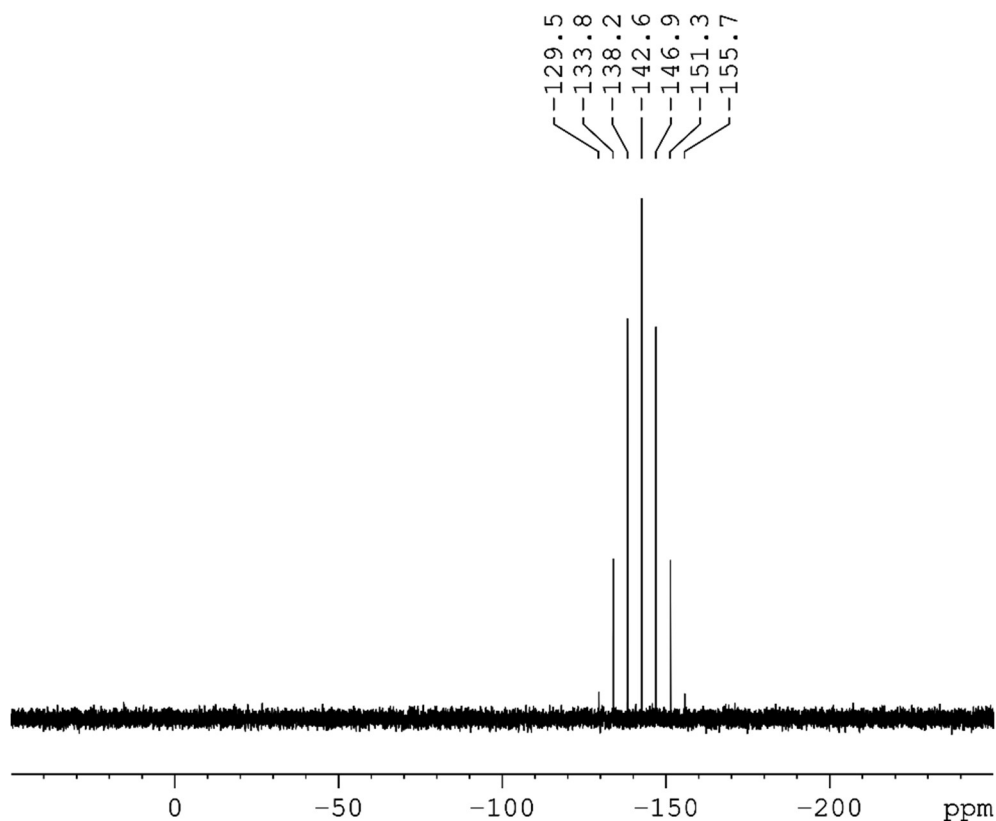


Figure S29. 1D- ^{31}P spectrum (ns = 64) of **2** measured in acetone- d_6 at 25 °C.

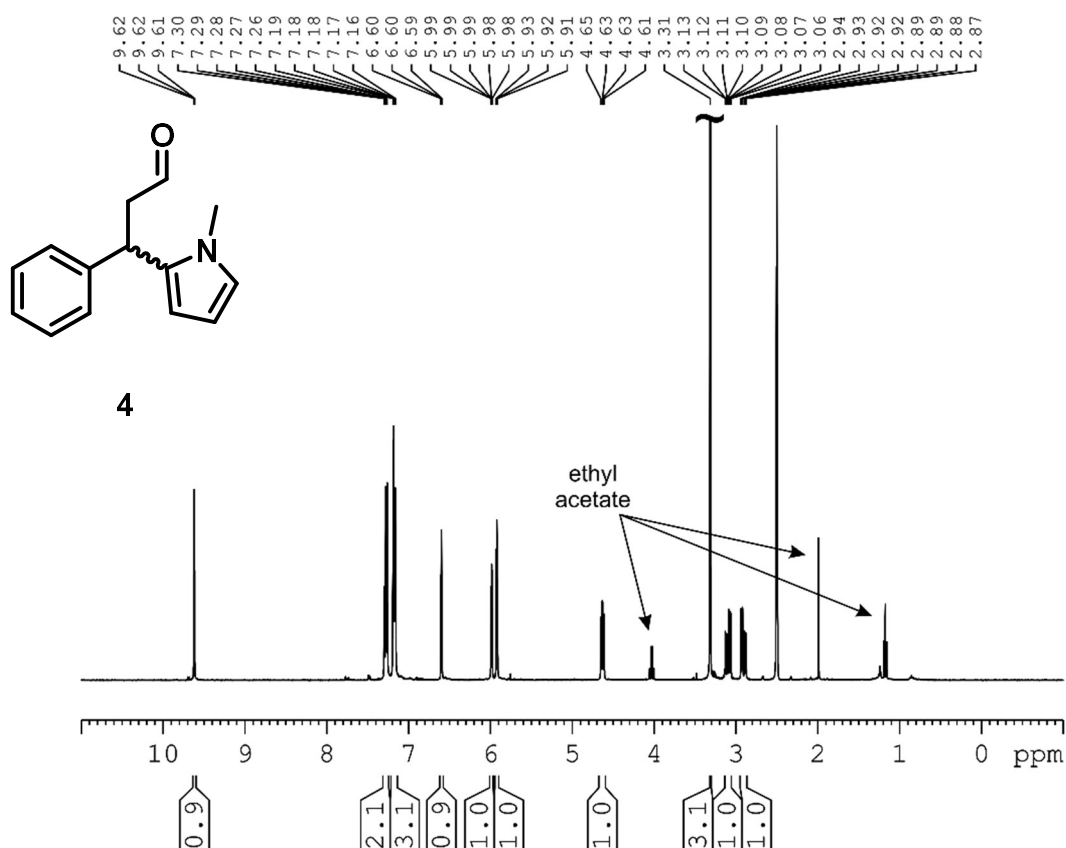


Figure S30. 1D- ^1H spectrum (ns = 16) of **4** measured in DMSO- d_6 at 25 °C.

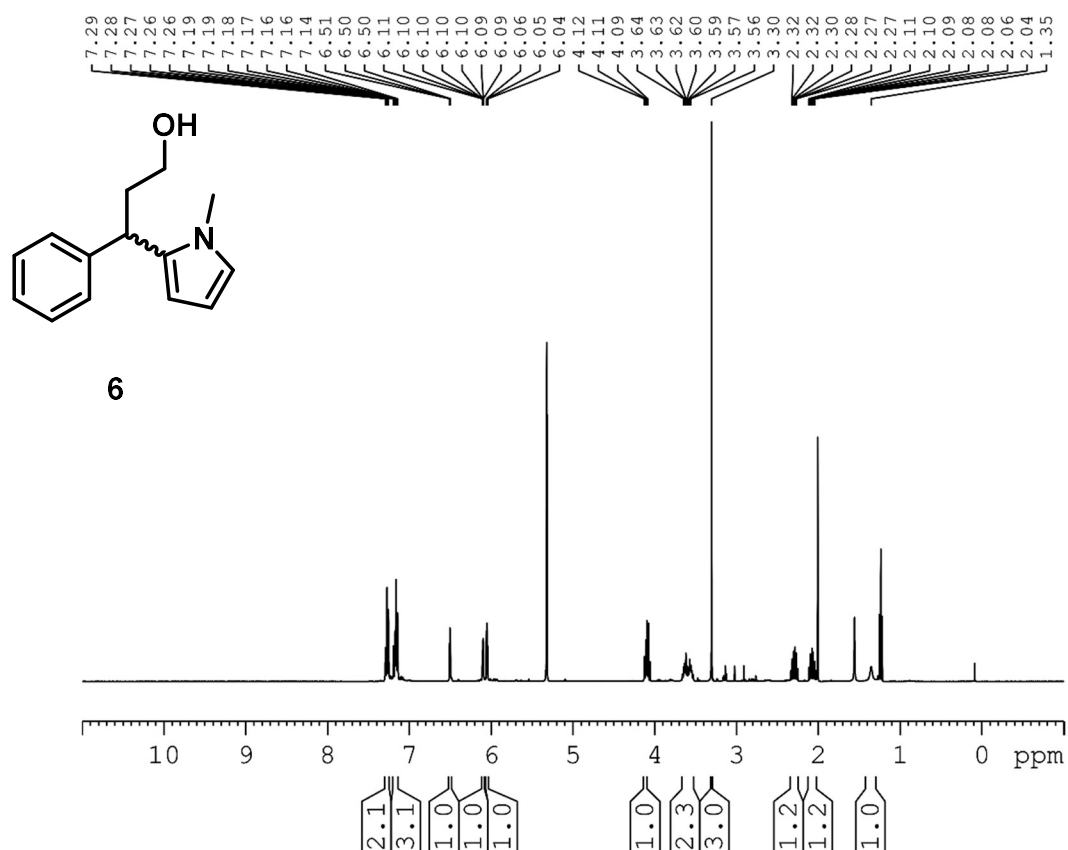


Figure S31. 1D-¹H spectrum (ns = 16) of **6** measured in CD₂Cl₂ at 25 °C.

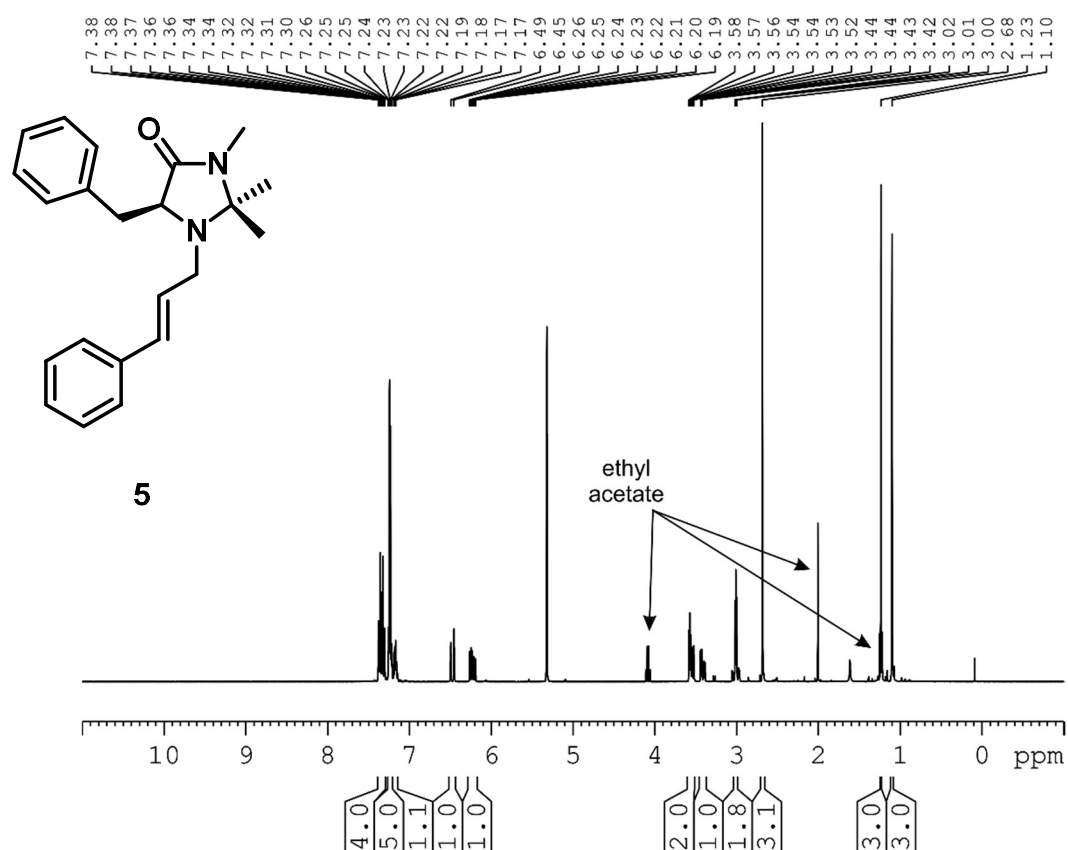


Figure S32. 1D-¹H spectrum (ns = 16) of **5** measured in CD₂Cl₂ at 25 °C.

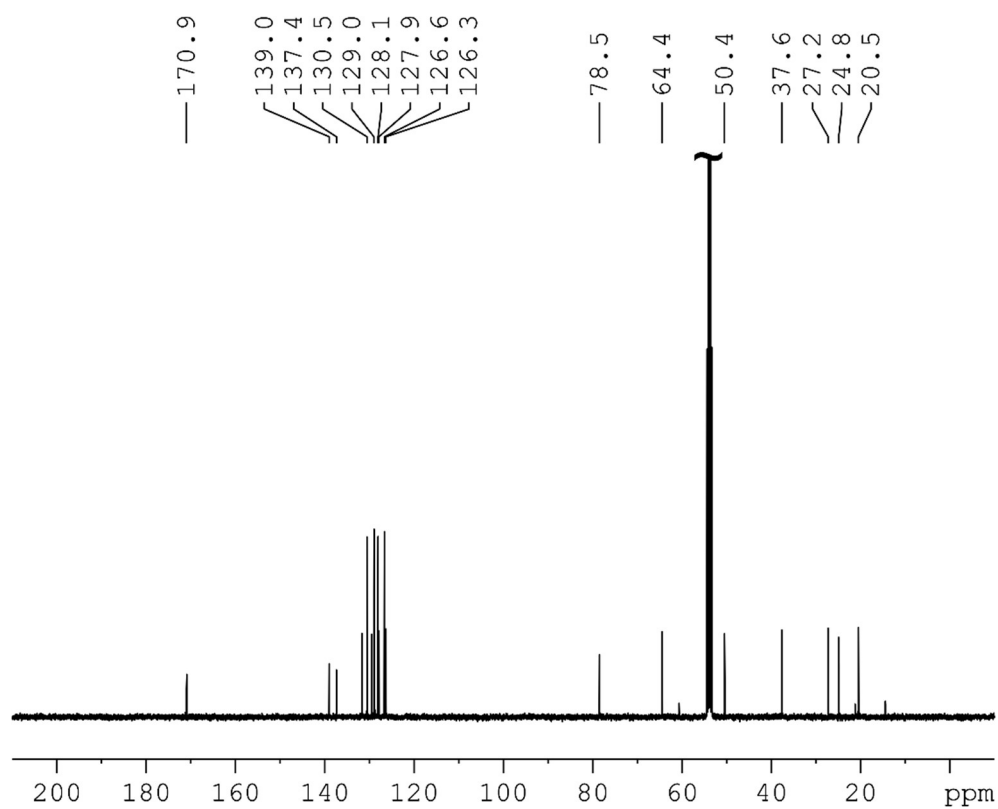


Figure S33. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 1024) of **5** measured in CD_2Cl_2 at 25 °C.

3.5.2.5 UV/Vis-data

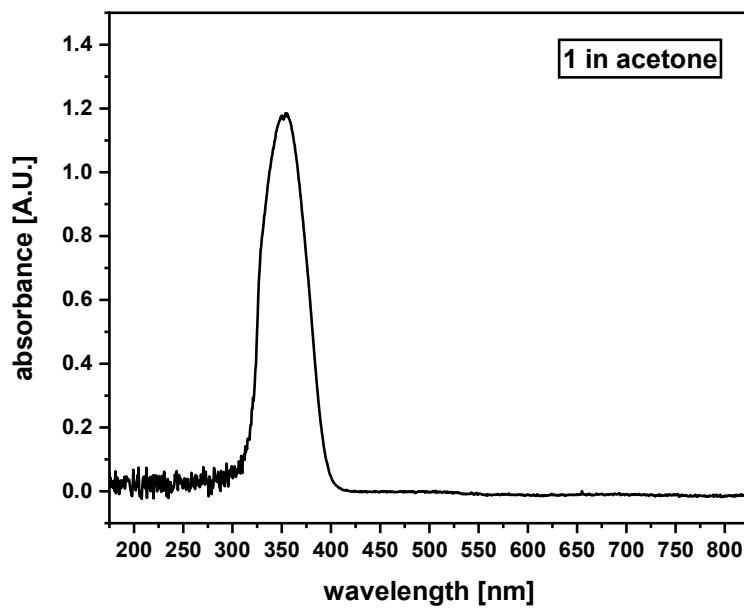


Figure S34. UV/Vis spectrum of **1** measured in acetone at r.t.

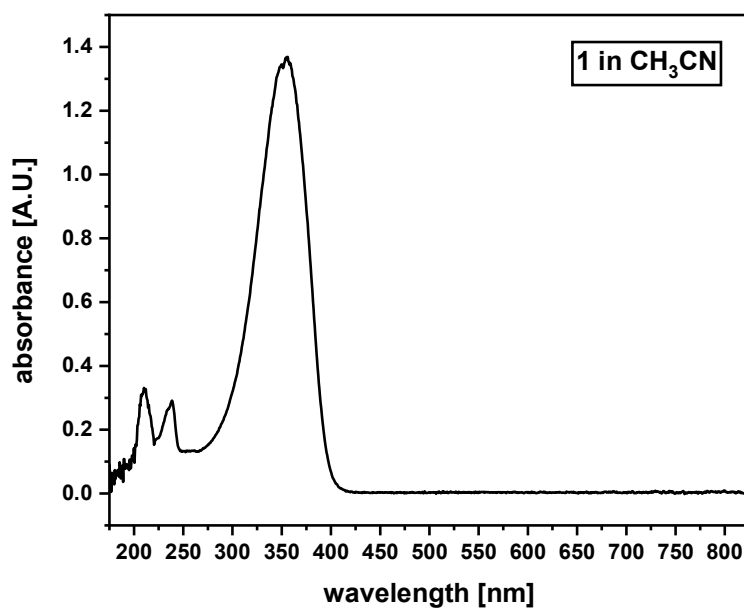


Figure S35. UV/Vis spectrum of **1** measured in CH₃CN at r.t.

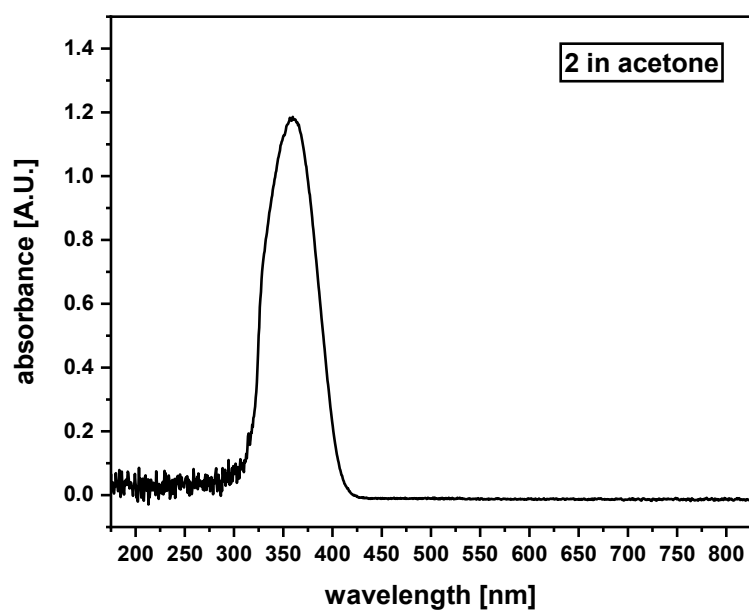
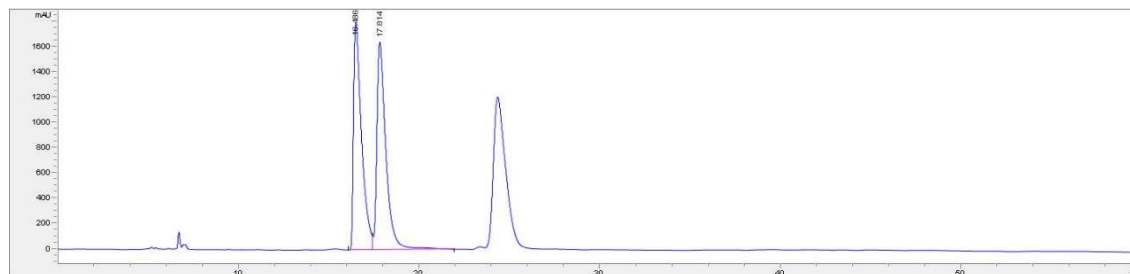


Figure S36. UV/Vis spectrum of **2** measured in acetone at r.t.

3.5.2.6 HPLC-data

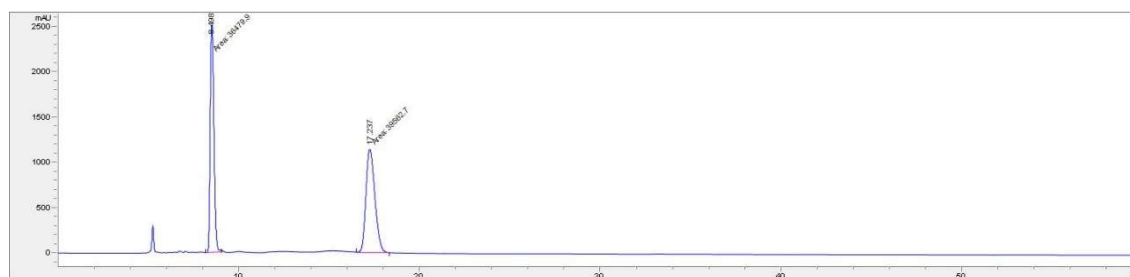
Syntheses of **4** and **6** for HPLC calibration

Racemic Synthesis of **4**



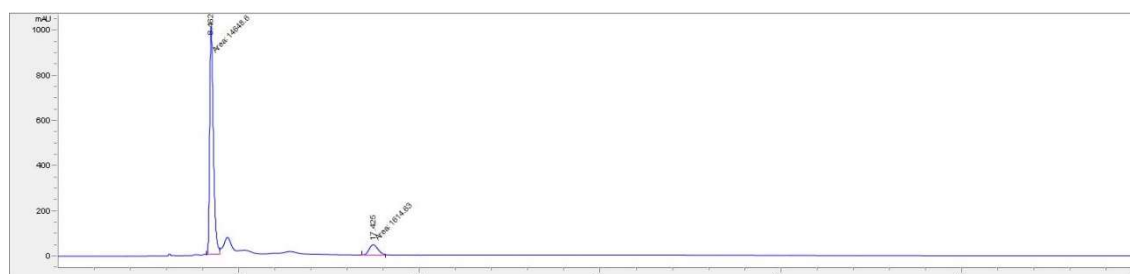
#	Time	Area	Height	Width	Area%	Symmetry
1	16.486	56015.8	1799.9	0.4551	49.336	0.366
2	17.814	57523.9	1648	0.5232	50.664	0.429

Racemic Synthesis of **6**



#	Time	Area	Height	Width	Area%	Symmetry
1	8.498	36479.9	2509.7	0.2423	47.973	0.725
2	17.237	39562.7	1142.9	0.5769	52.027	0.74

Enantioselective Synthesis of **6**

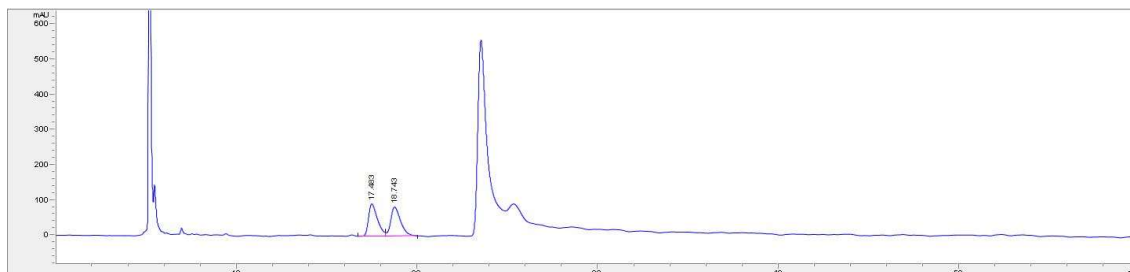


#	Time	Area	Height	Width	Area%	Symmetry
1	8.462	14648.6	1011.4	0.2414	90.072	0
2	17.425	1614.6	46.3	0.5808	9.928	0.805

Syntheses of 4 and 6 for DTS-hv

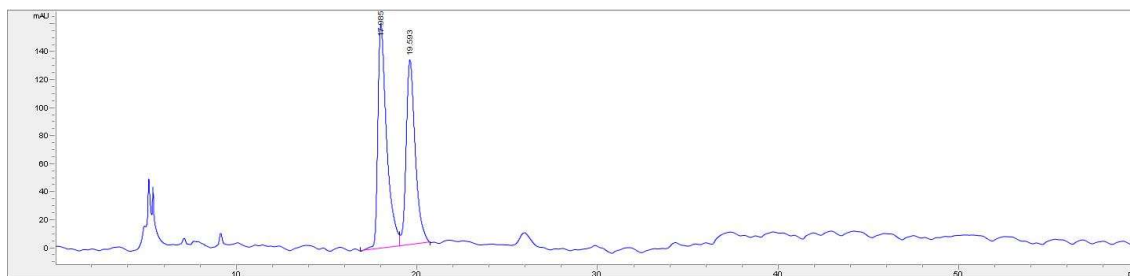
Procedure 1 (DTS-hv- or very similar conditions)

Table S1, Entry 1



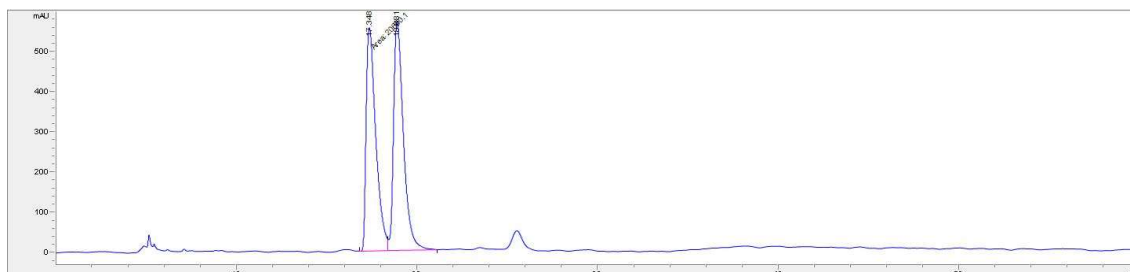
#	Time	Area	Height	Width	Area%	Symmetry
1	17.483	3165.7	91.6	0.5193	50.480	0.547
2	18.743	3105.6	82.3	0.5684	49.520	0.61

Table S1, Entry 2



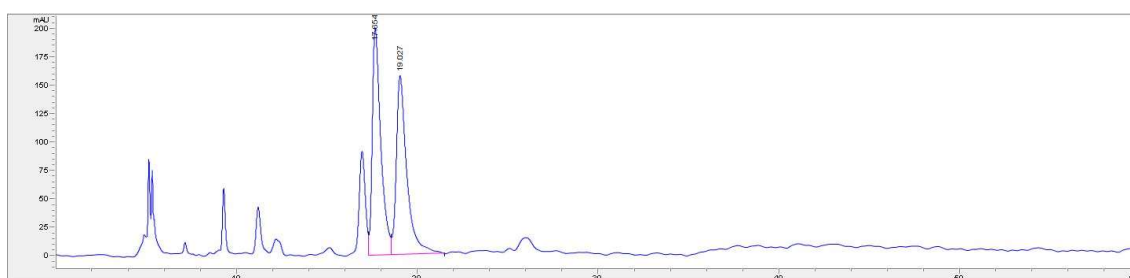
#	Time	Area	Height	Width	Area%	Symmetry
1	17.985	5538.2	160.8	0.5078	54.394	0.489
2	19.593	4643.5	132.5	0.5228	45.606	0.664

Table S1, Entry 3



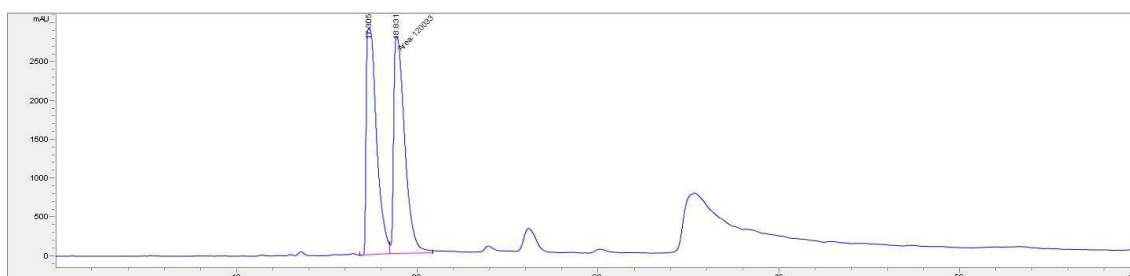
#	Time	Area	Height	Width	Area%	Symmetry
1	17.348	20650.1	554.3	0.6209	48.945	0.481
2	18.881	21540.5	565.6	0.5823	51.055	0.512

Table S1, Entry 4



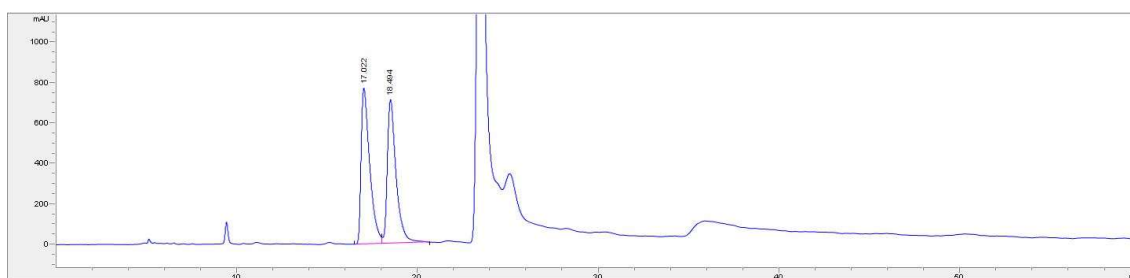
#	Time	Area	Height	Width	Area%	Symmetry
1	17.654	6577.9	200.5	0.4827	50.488	0.492
2	19.027	6450.7	157.9	0.5907	49.512	0.499

Table S1, Entry 5



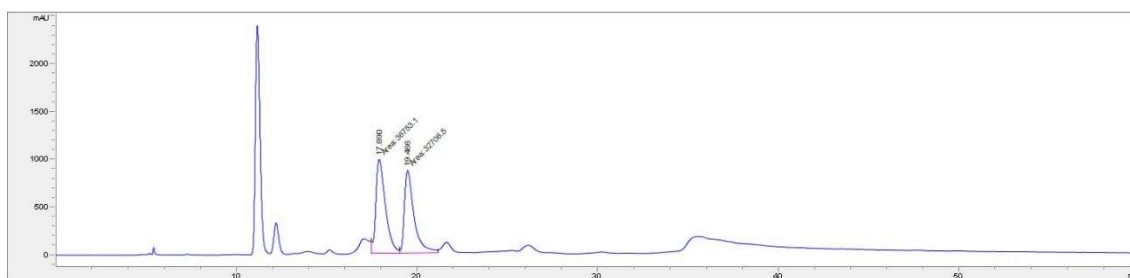
#	Time	Area	Height	Width	Area%	Symmetry
1	17.305	117664.2	2946.4	0.4819	49.502	0.336
2	18.831	120033.1	2823.7	0.7085	50.498	0.332

Table S1, Entry 6



#	Time	Area	Height	Width	Area%	Symmetry
1	17.022	25553.4	772.4	0.49	51.501	0.438
2	18.494	24063.8	712.2	0.5022	48.499	0.519

Procedure 2 (control reaction)



#	Time	Area	Height	Width	Area%	Symmetry
1	17.89	36753.1	989.6	0.619	52.913	0.533
2	19.466	32706.5	866.9	0.6288	47.087	0.485

3.5.3 NMR sample preparation

3.5.3.1 Preparation of the NMR samples for *in situ* illumination NMR spectroscopy

An oven dried 5 mm amberized thin wall NMR tube was charged inside the glove box with iminium ion **1** or **2** and potential solid additives (anh. potassium trifluoroacetate). After connecting the NMR tube to a Schlenk line, potential liquid additives (1,8-Diazabicyclo(5.4.0)undec-7-ene or 2,6-Di-tert-butylpyridine) were added under argon atmosphere using a Gilson® pipette and last the respective solvent (0.3 mL) *via* a syringe. Afterwards an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μ m core) was inserted into the NMR tube using the Schlenk line technique and fastened with parafilm.¹⁷

3.5.3.2 Preparation of the NMR sample for *ex situ* illumination NMR spectroscopy

An oven dried Schlenk flask that is customized to connect a glass rod illumination setup (Figure S37 left) was charged inside the glove box with iminium ion **1**. Anh. and deg. CH₃CN/CD₃CN 2:1 (1.5 mL) and 2,6-Di-tert-butylpyridine were added under argon atmosphere followed by inserting the glass rod illumination setup. The flask was cooled down to -40 °C using a cooling bath and illuminated with 365 nm for 1 h (Figure S37 right). Afterwards a 0.6 mL aliquot was transferred under argon atmosphere into an oven dried 5 mm NMR tube, which was already cooled to -40 °C in an antimagnetic Dewar (t = 0 s in the *ex situ* illumination NMR kinetic). Subsequent, the cooled NMR sample was inserted into the precooled NMR spectrometer and the quantitative 1D-¹H kinetic is started after a quick automatic tuning & matching and shimming program.

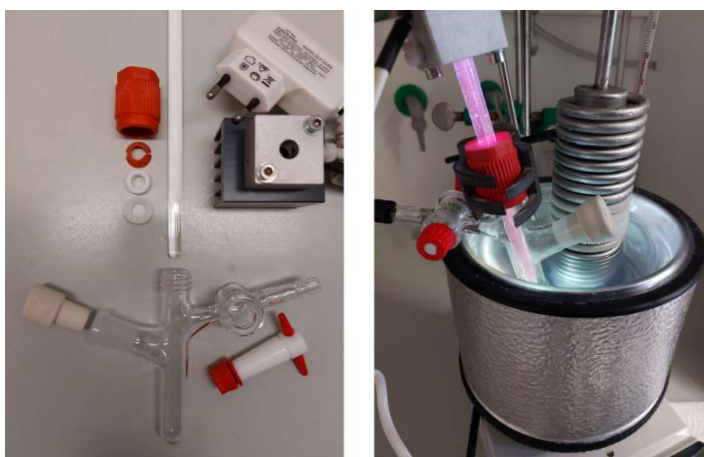


Figure S37. Glass rod illumination setup for *ex situ* illumination. Left: Overview of all components. Right: Illumination with an LED emitting at a peak wavelength of 365 nm of a sample under inert gas conditions and at -40 °C using the glass rod illumination setup.

3.5.4 Structure elucidation of iminium ion 1 and 2 at -40 °C

3.5.4.1 Structure elucidation of iminium ion 1 at -40 °C in acetone-*d*₆

To assign the signals for (E,E), (Z,E), (E,Z) and (Z,Z) of iminium ion **1** in acetone-*d*₆ at -40 °C (Figure S38) a standard set of NMR experiments (1D-¹H; 1D-¹³C{¹H}; 2D-¹H, ¹H correlated spectroscopy (COSY); 2D-¹H, ¹H nuclear Overhauser enhancement spectroscopy (NOESY), 2D-¹H, ¹³C heteronuclear multiple bond correlation (HMBC); 2D-¹H, ¹³C heteronuclear single quantum coherence (HSQC)) was measured under continuous UV-illumination using the *in situ* illumination setup to populate simultaneously all four configuration isomers. The configuration of the C=N and C=C double bond can be clearly assigned *via* the associated coupling constants and explicit NOE patterns.

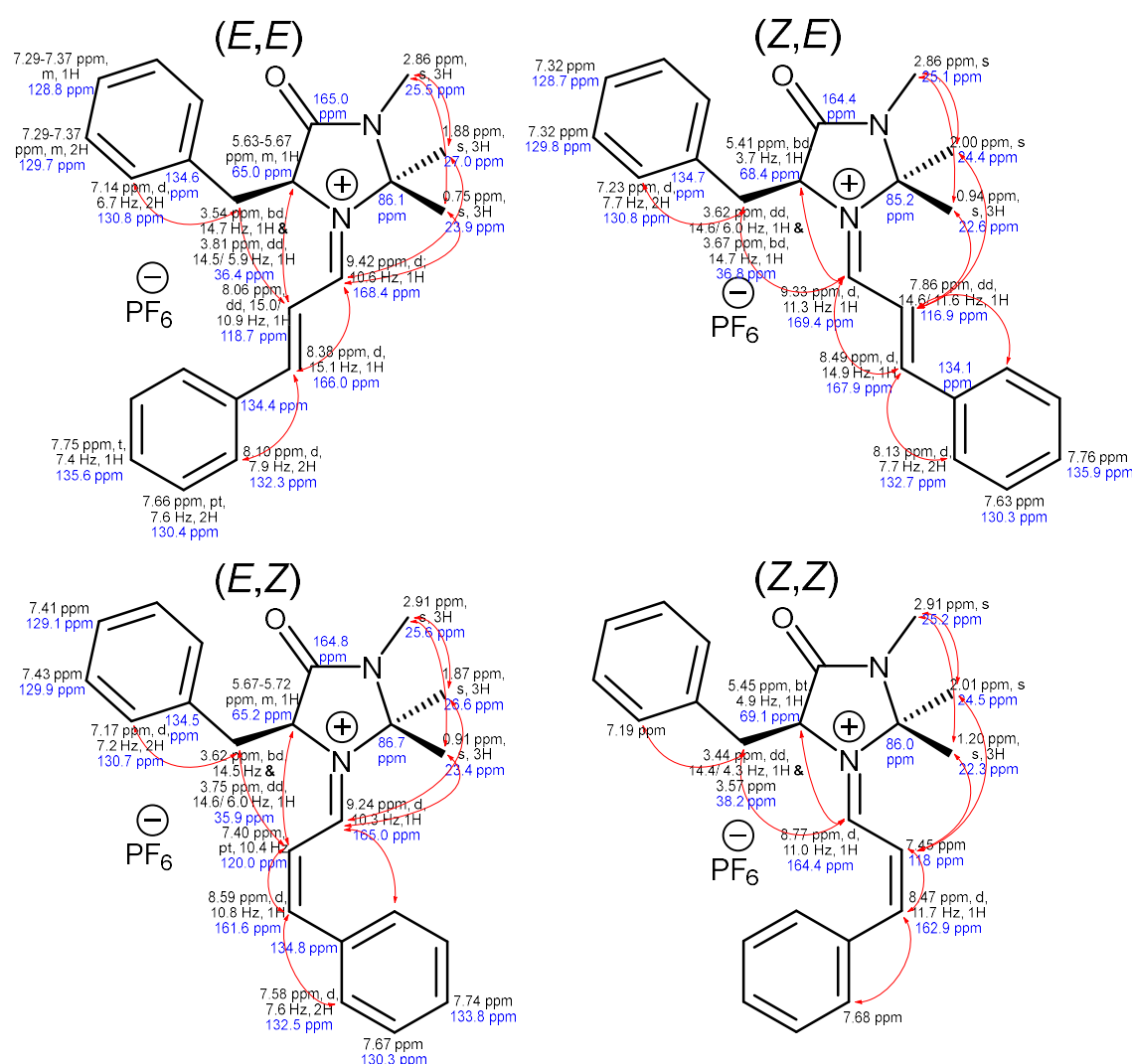
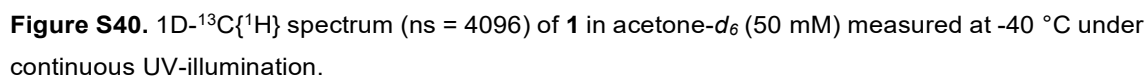
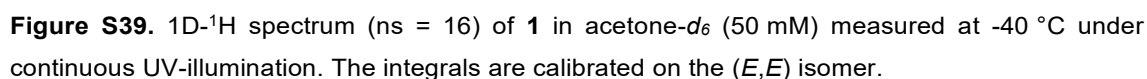


Figure S38. Structure determination of the four possible configuration-isomers (E,E), (Z,E), (E,Z) and (Z,Z) in acetone-*d*₆ at -40 °C. Therefore, a sample of iminium ion **1** in acetone-*d*₆ (50 mM) was continuously illuminated at -40 °C with an LED emitting at 365 nm. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black and ¹³C blue. Distinct NOE interactions, which confirm the double bond configurations, are indicated *via* red arrows. An average ratio of (E,E)/(Z,E)/(E,Z)/(Z,Z) = 45:9:42:4 was present during illumination.



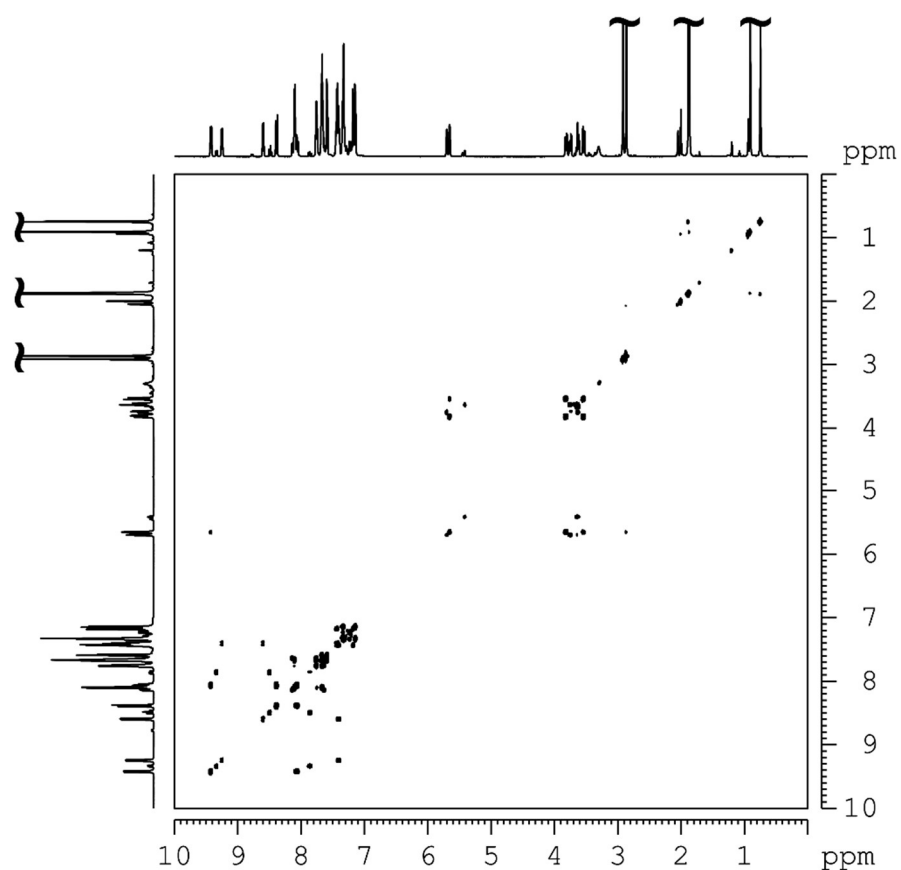


Figure S41. 2D- ^1H , ^1H COSY spectrum of **1** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

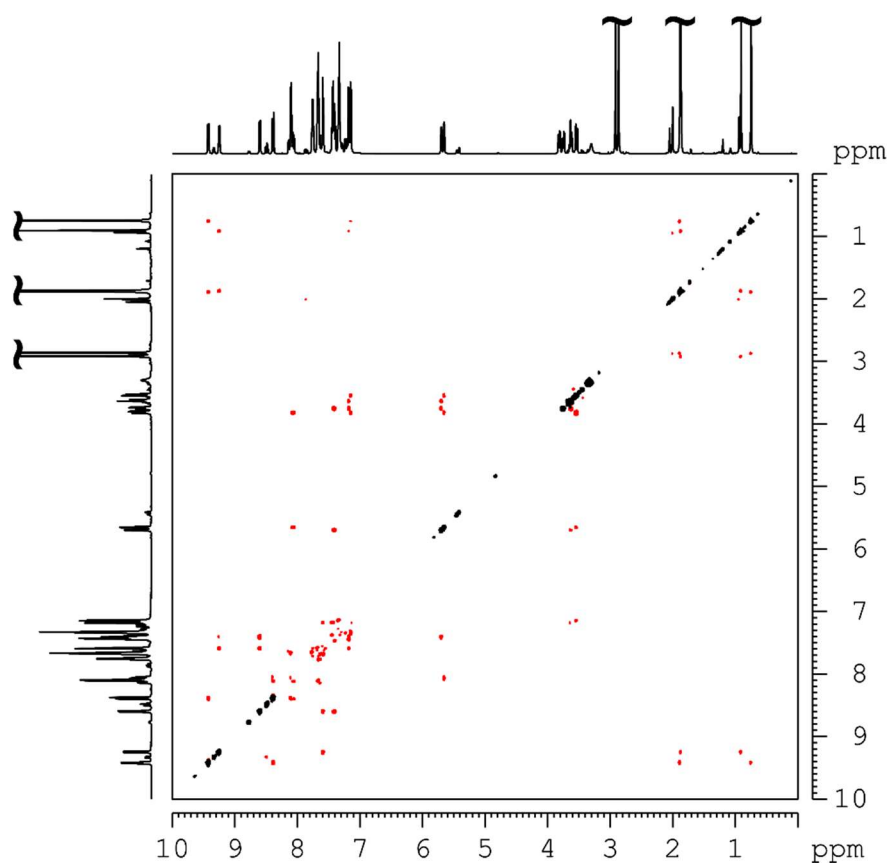


Figure S42. 2D- ^1H , ^1H NOESY spectrum (mixing time = 0.5 s) of **1** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

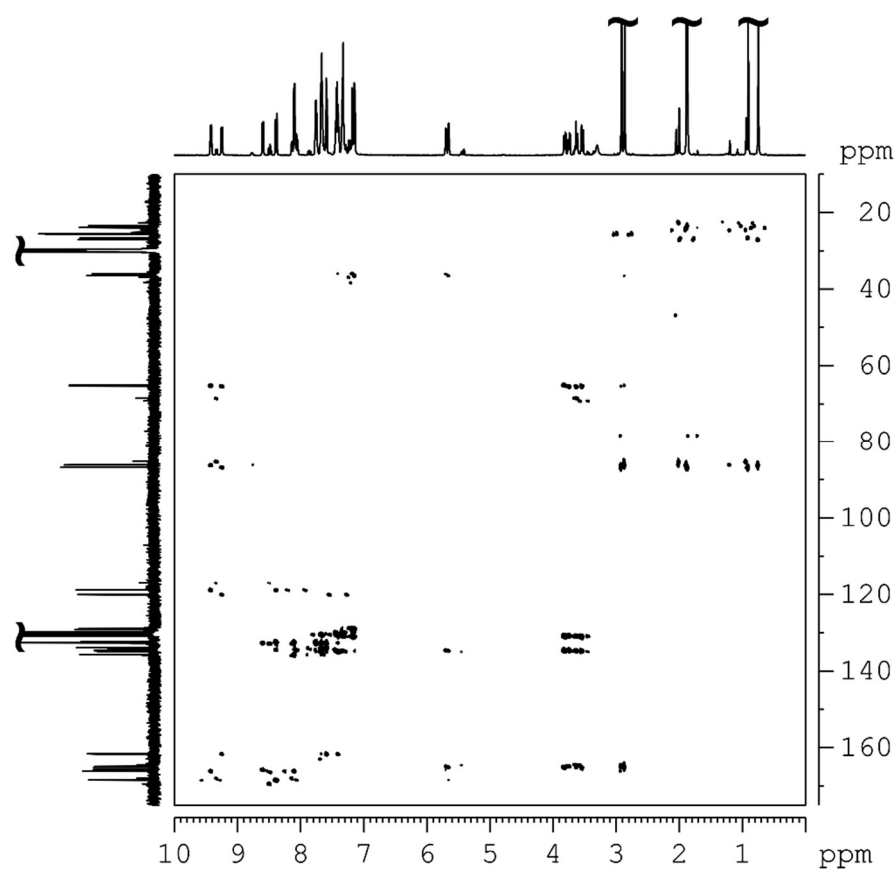


Figure S43. 2D-¹H, ¹³C HMBC spectrum of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

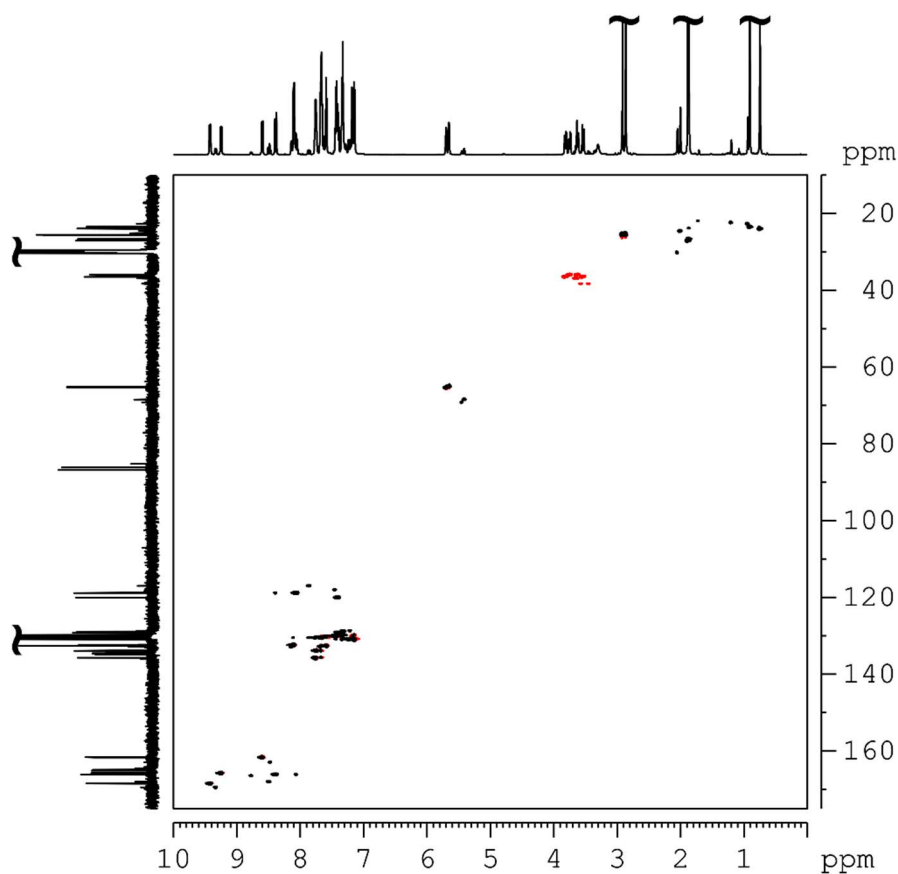


Figure S44. 2D-¹H, ¹³C HSQC spectrum of **1** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

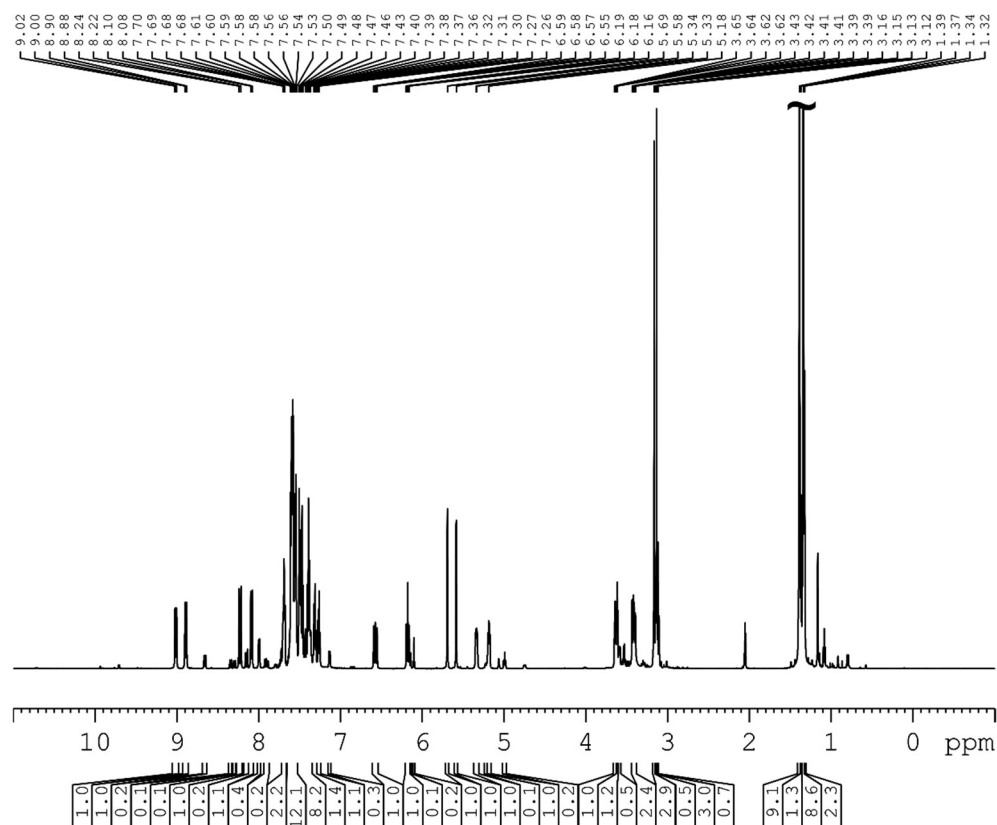


Figure S46. 1D-¹H spectrum (ns = 16) of **2** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination. The integrals are calibrated on the (E,E) isomer.

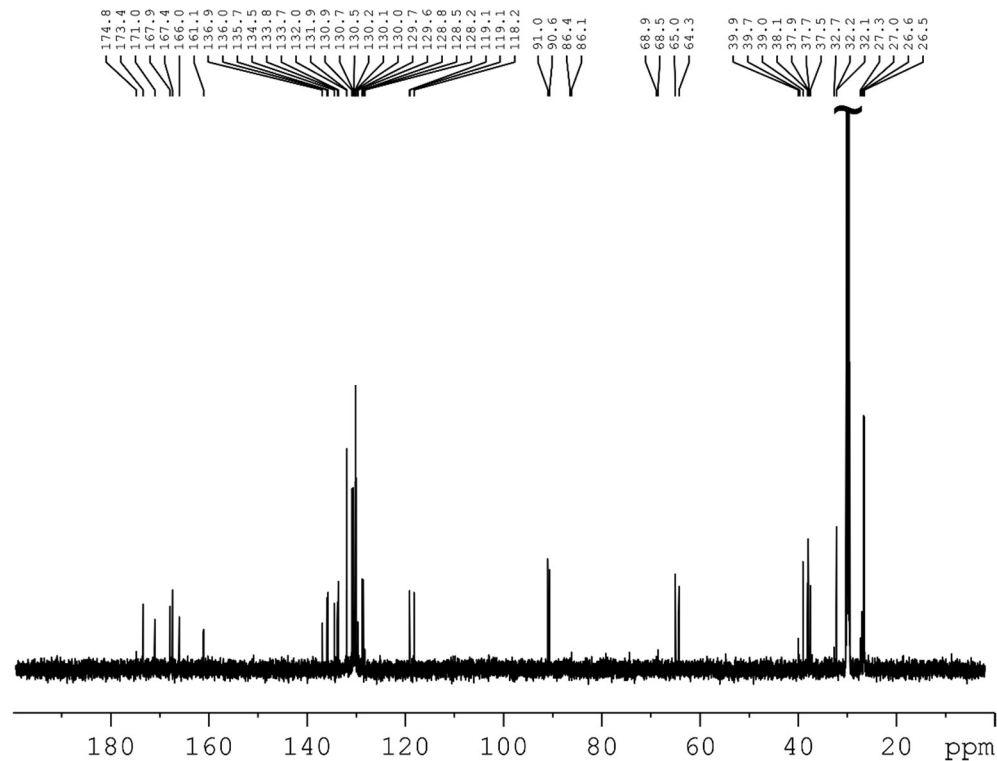


Figure S47. 1D-¹³C{¹H} spectrum (ns = 1024) of **2** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

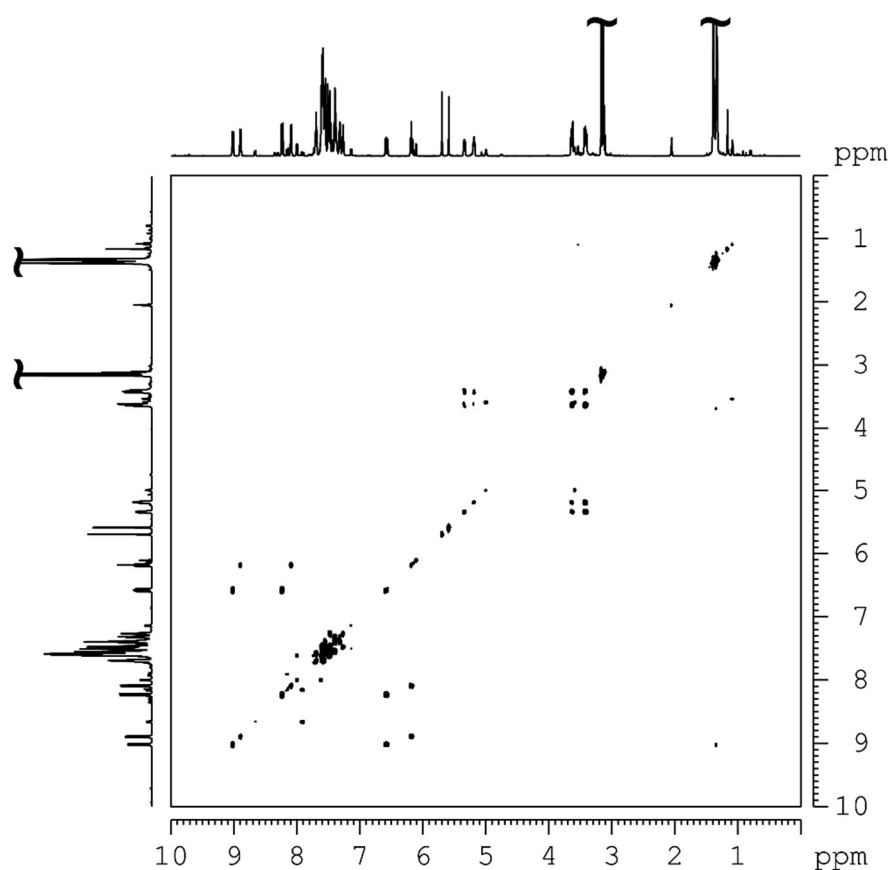


Figure S48. 2D- ^1H , ^1H COSY spectrum of **2** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

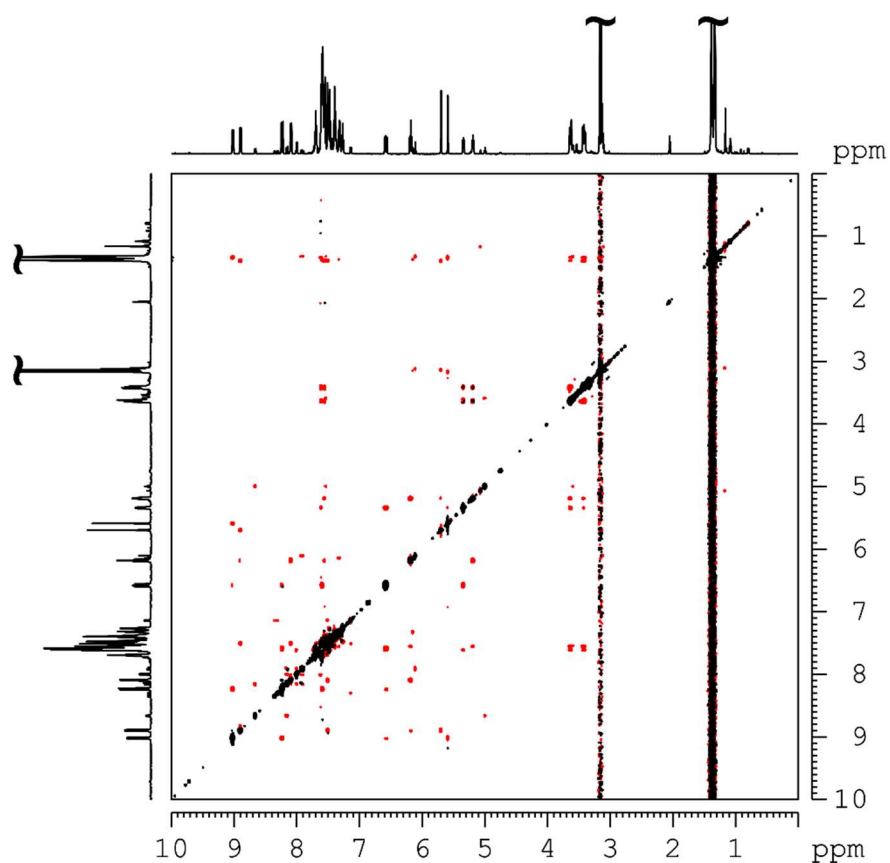


Figure S49. 2D- ^1H , ^1H NOESY spectrum (mixing time = 0.5 s) of **2** in acetone- d_6 (50 mM) measured at $-40\text{ }^\circ\text{C}$ under continuous UV-illumination.

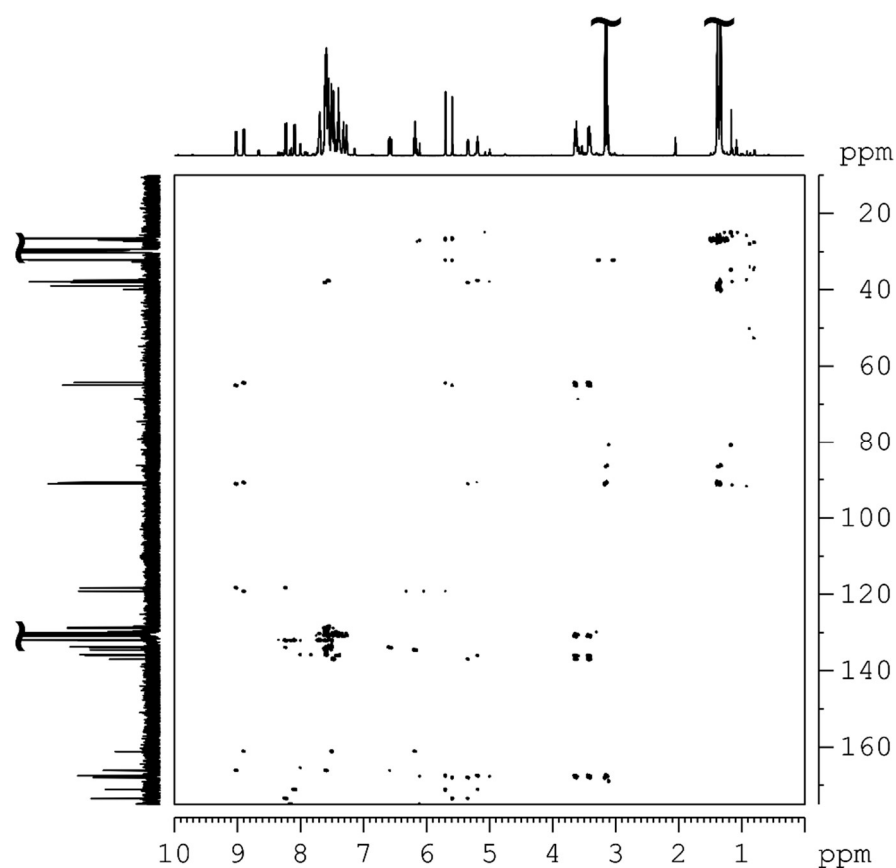


Figure S50. 2D-¹H, ¹³C HMBC spectrum of **2** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

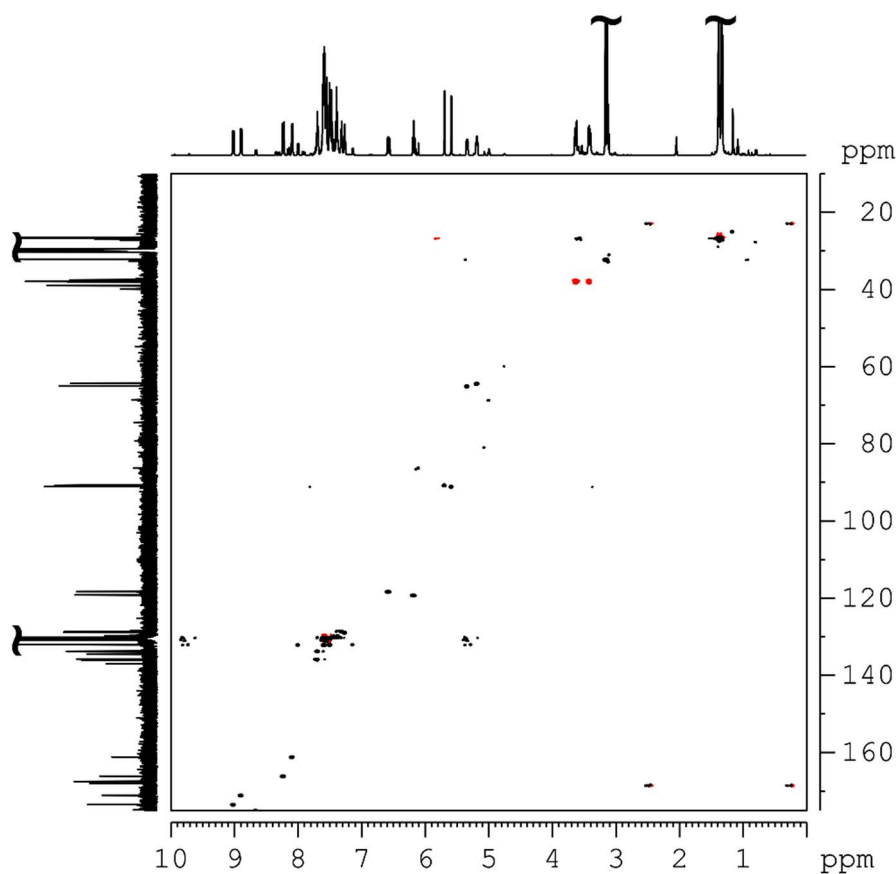


Figure S51. 2D-¹H, ¹³C HSQC spectrum of **2** in acetone-*d*₆ (50 mM) measured at -40 °C under continuous UV-illumination.

3.5.5 Photoinduced and thermal isomerization of iminium ion 1 and 2 at various conditions

3.5.5.1 Method

The NMR samples were illuminated continuously with an UV-LED (LG Innotek LEUVA66X00RV00) operated with 0.5 A and emitting at a peak wavelength of 365 nm until at least the photostationary state of (Z,E) was achieved. Afterwards the illumination was stopped ($t = 0$ s) followed by recording the thermal $(Z) \rightarrow (E)$ isomerization processes *via* a quantitative $1D\text{-}^1H$ NMR kinetic. For a quantitative evaluation the $1D\text{-}^1H$ NMR spectra were measured as following: For a sufficient signal to noise ratio 16 scans were accumulated per spectrum. A relaxation delay of $d1 = 4$ s in combination with a 30° pulse ensured full relaxation before each scan and pulse lengths for 1H -experiments were calibrated. Based on these curves, the isomerization rate $k_{(Z) \rightarrow (E)}$ can be obtained for these processes by mathematical fitting as first order reaction process (Equation 1).

$$y = A_1 * e^{-k_{(Z) \rightarrow (E)}x} + y_0$$

Equation 1. Mathematical fitting for thermal $(Z) \rightarrow (E)$ isomerization process as first order reaction process.

Different temperatures, solvents and additives have been screened to determine external influences on the stabilities of the different (Z)-configured double bond isomers.

3.5.5.2 Investigations of iminium ion 1 at different conditions

1 in acetone- d_6 (50 mM) at $-40^\circ C$, continuous UV-illumination

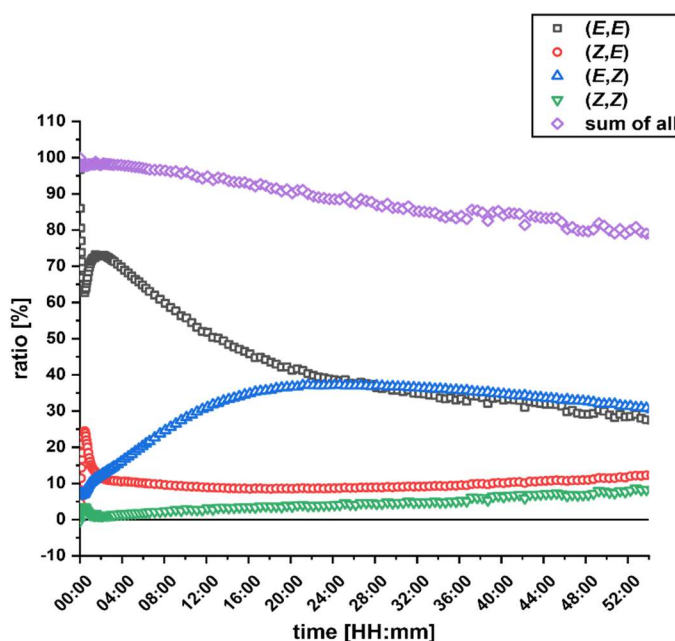
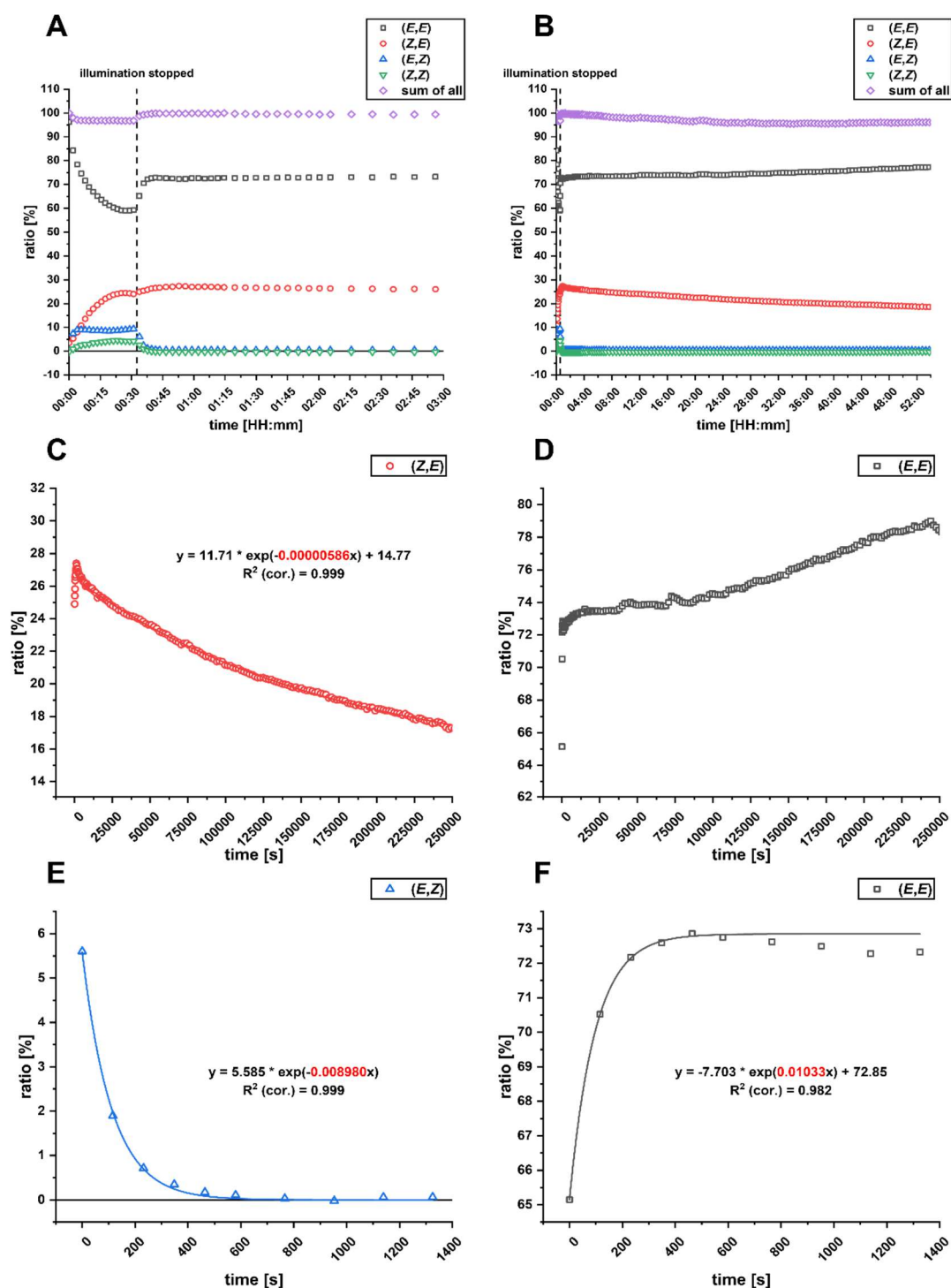


Figure S52. $1D\text{-}^1H$ kinetic of photoinduced isomerization of iminium ion **1** measured at $-40^\circ C$ in acetone- d_6 (50 mM) upon UV-illumination. More than 8 h of continuous illumination results in steady photodegradation (see purple curve).

1 in acetone- d_6 (50 mM) at -40 °C



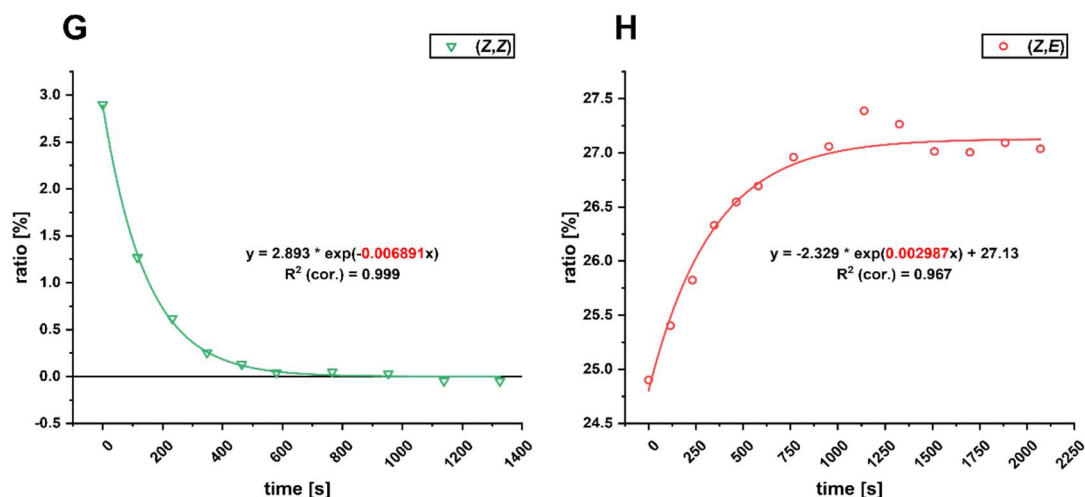
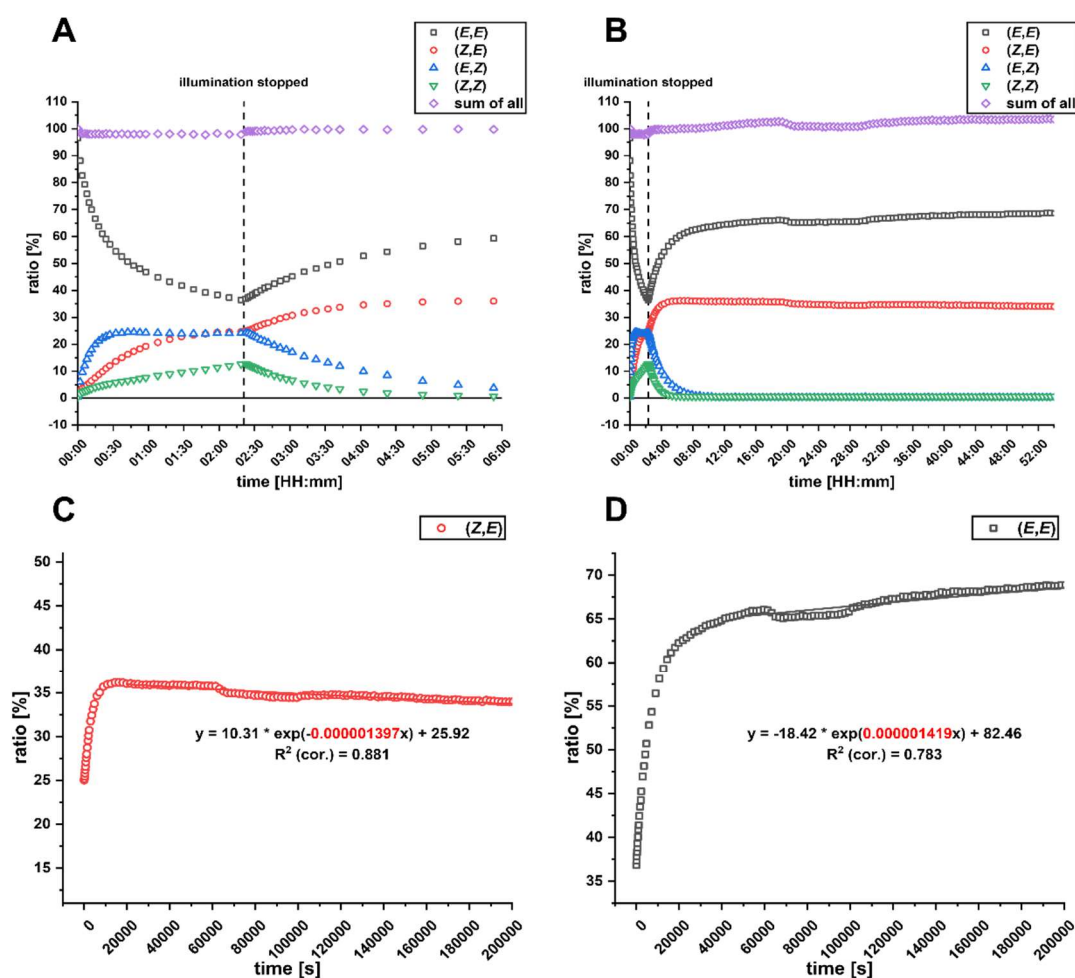


Figure S53. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in acetone-*d*₆ (50 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 54 h. **C - H:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for *k*_{(*Z*) → (*E*)} are given in Table S2.

1 in acetone-*d*₆ (50 mM) at -70 °C



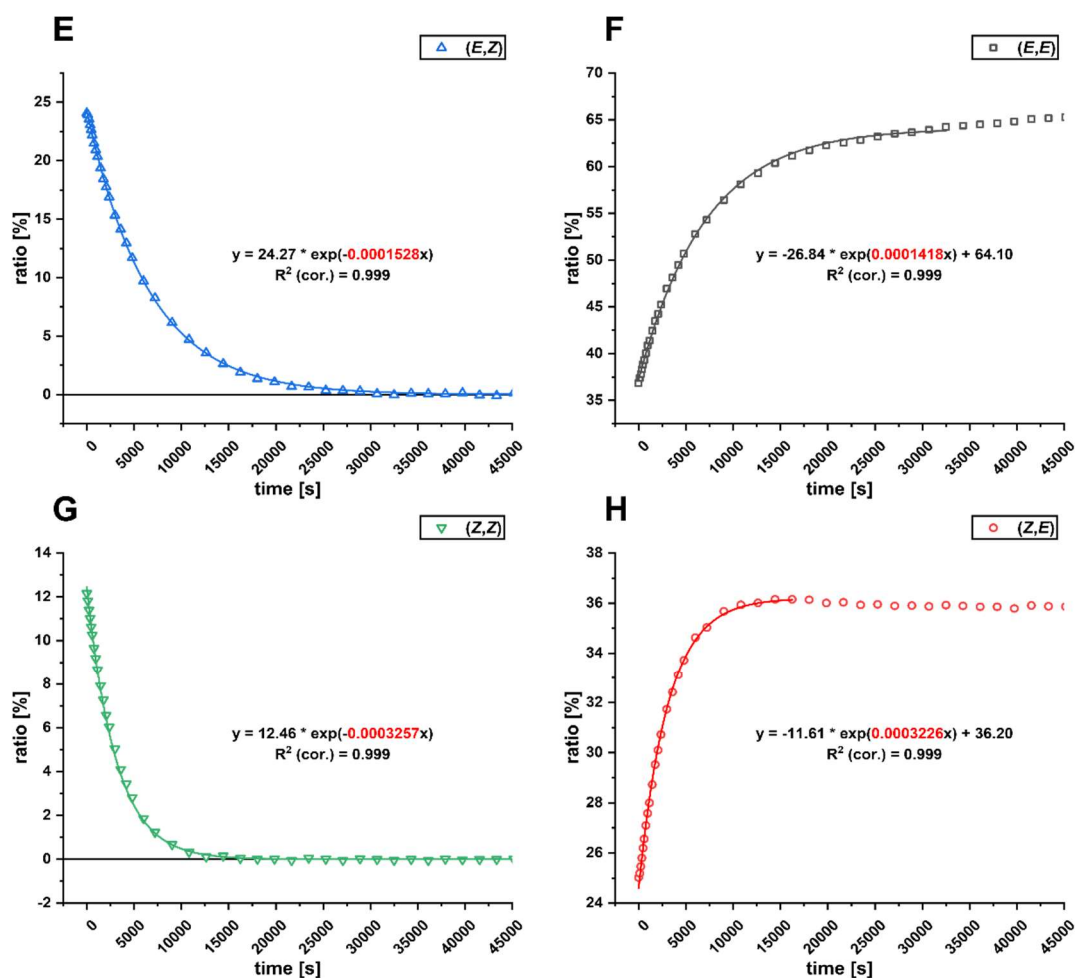


Figure S54. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -70 °C in acetone-*d*₆ (50 mM). **A:** First 6.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 54 h. **C - H:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for *k*_{(*Z*) → (*E*)} are given in Table S2.

1 in acetone- d_6 (50 mM) at -93 °C

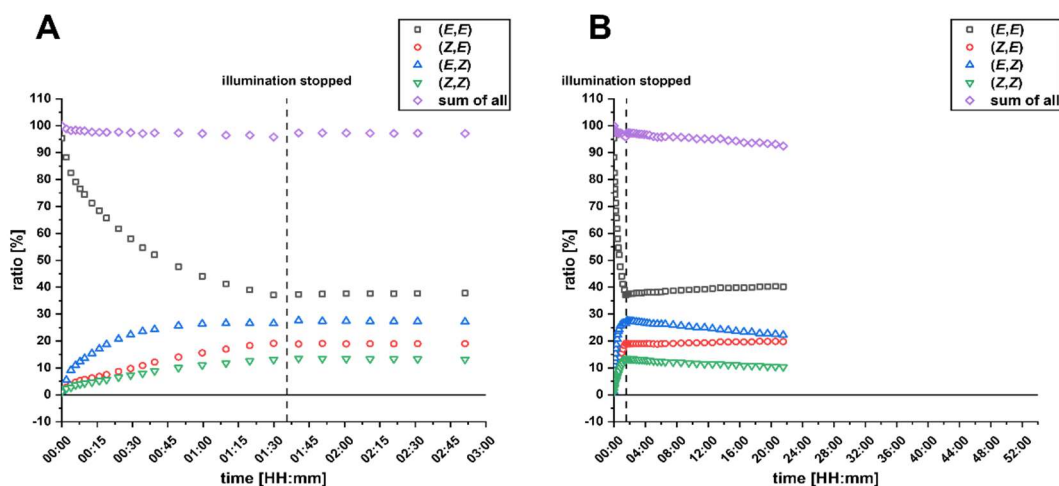
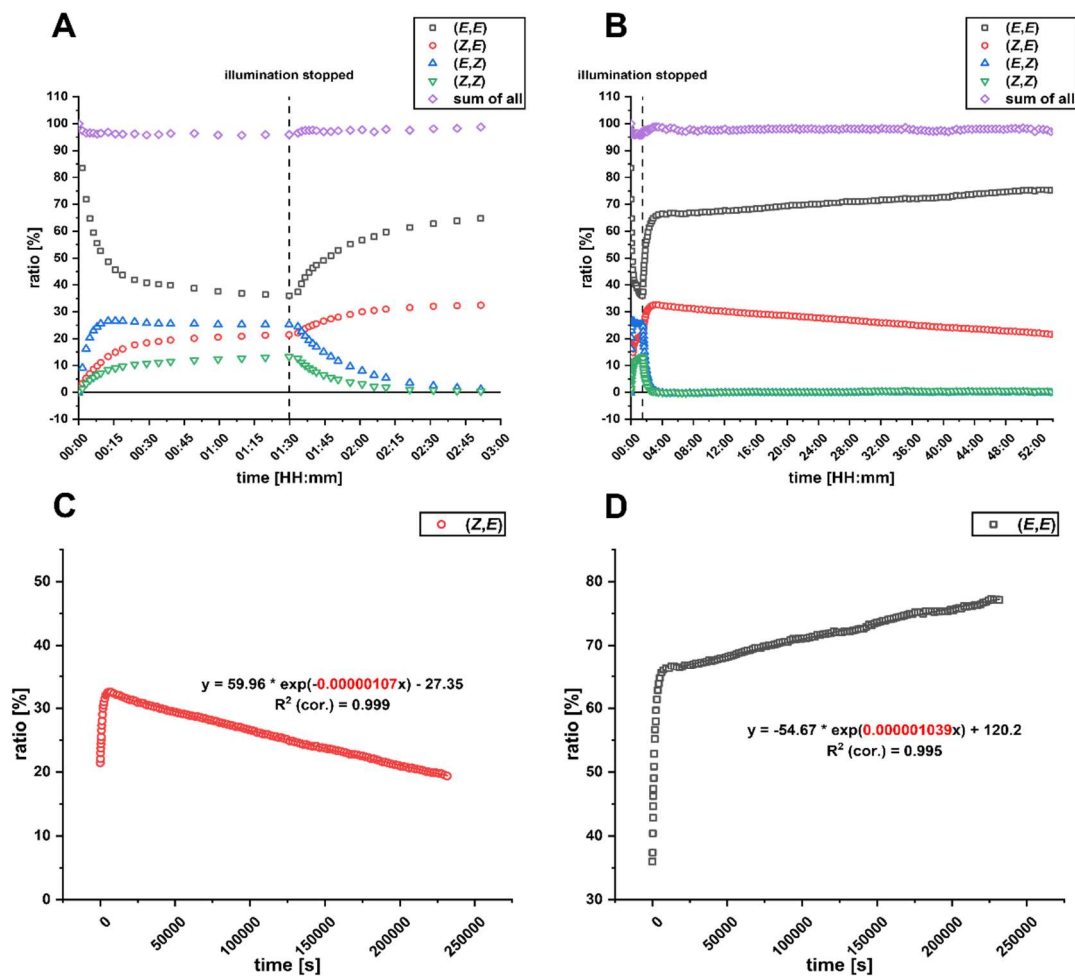


Figure S55. 1D- ^1H kinetic of photoinduced and thermal isomerization of iminium ion 1 measured at -93 °C in acetone- d_6 (50 mM). **A:** First 3.0 h of the recorded 1D- ^1H kinetic show in detail how UV-irradiation (365 nm) triggers (E) $\rightarrow$ (Z) isomerization and after stopping illumination the associated thermal (Z) $\rightarrow$ (E) isomerization processes. **B:** To facilitate comparison with other 1D- ^1H kinetics, the x-axes is set to 54 h.

1 in CD_3CN (50 mM) at -40 °C



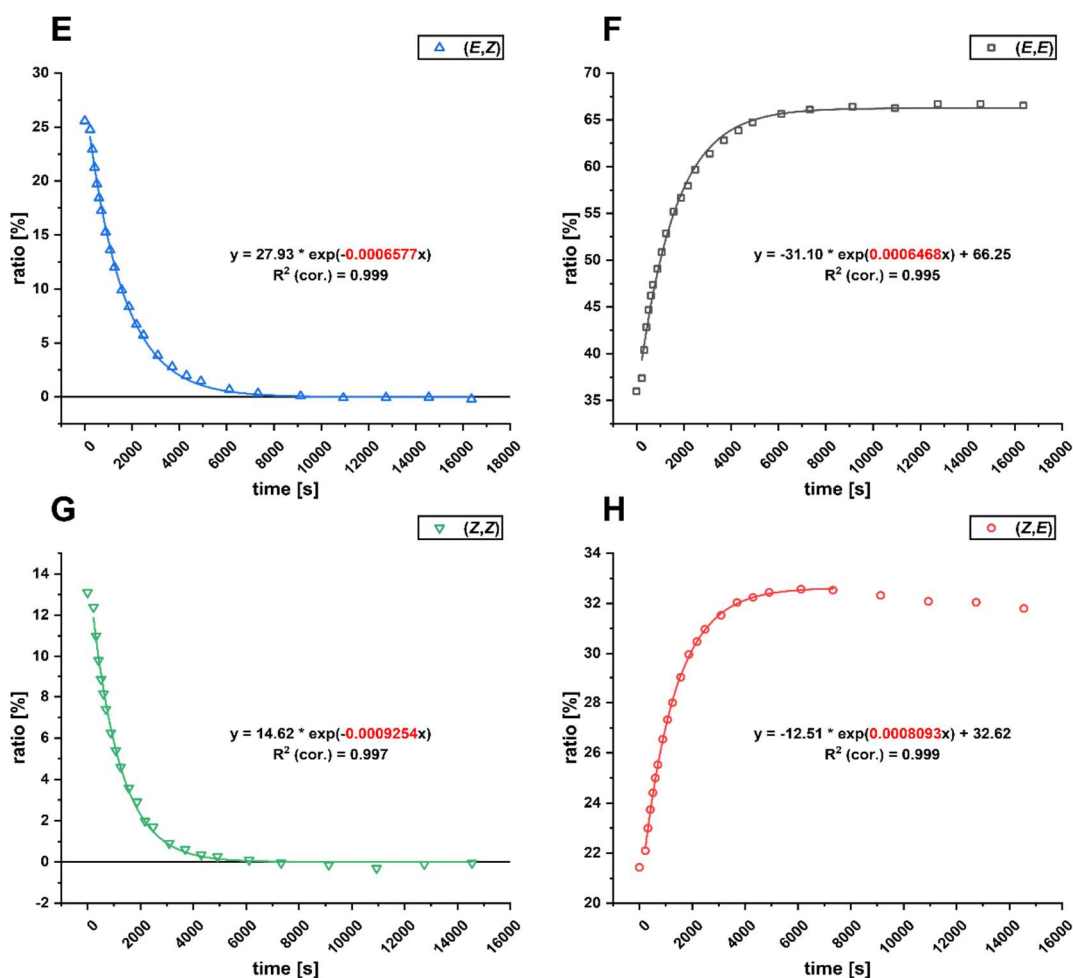


Figure S56. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** measured at -40 °C in CD₃CN (50 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 54 h. **C - H:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S2.

Table S2. Temperature dependence (-40, -70, -93 °C) or solvent dependence (acetone-*d*₆, CD₃CN) of thermal (Z) → (E) isomerization processes of iminium ion **1** after UV-triggered (E) → (Z) isomerization (λ = 365 nm). To obtain *k*_{(Z) → (E)} the associated isomerization curves (see Figure S53, S54 and S56) were mathematically fitted and Equation 1 was applied.

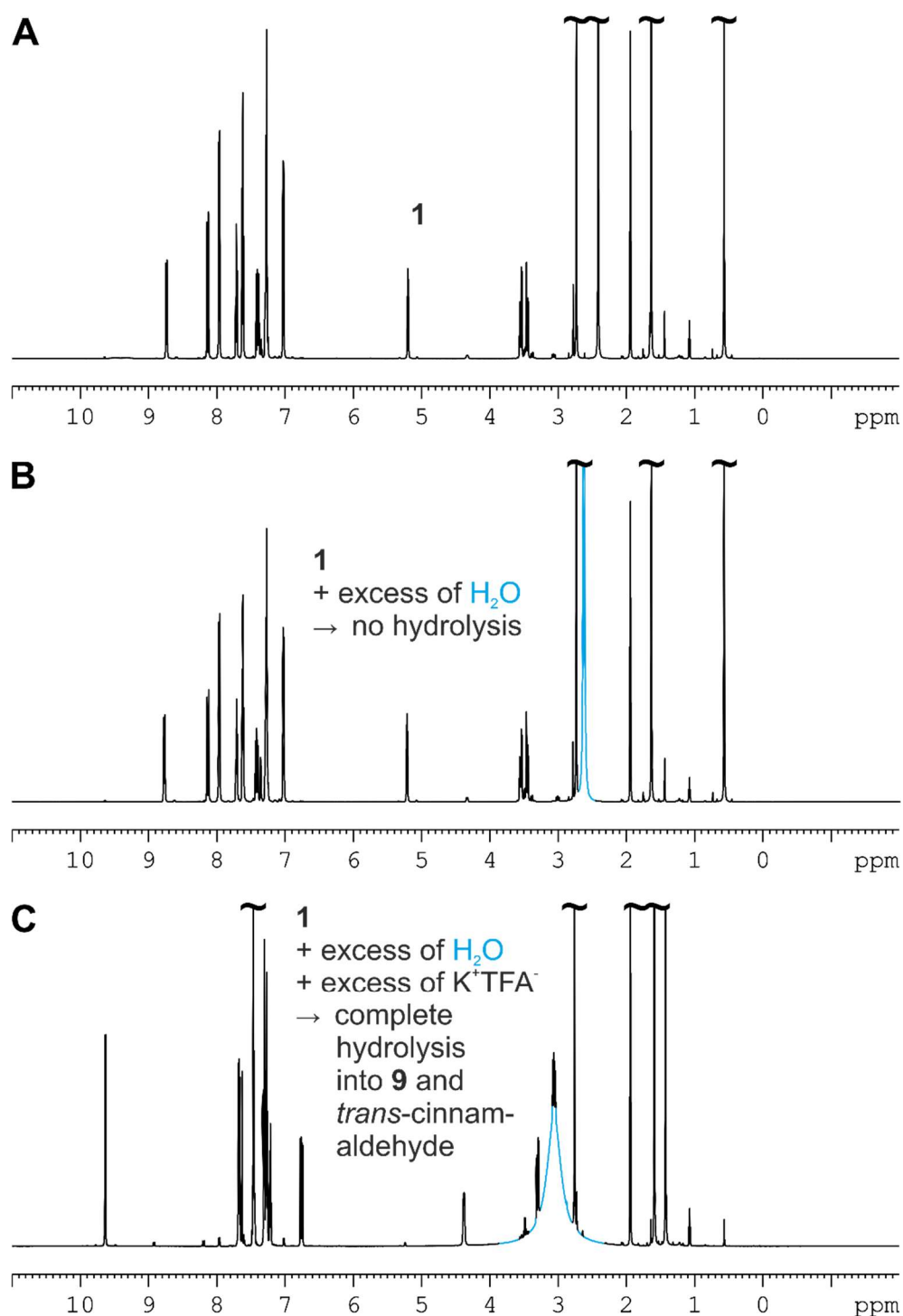
Entry	T [°C]	Solvent	Process		$k_{(Z) \rightarrow (E)}$ [10^{-3} s^{-1}]
1	-40	acetone- d_6	$(Z,E) \rightarrow (E,E)$	(Z,E)-decay	0.00586
2				(E,E)-grow	-
3			$(E,Z) \rightarrow (E,E)$	(E,Z)-decay	8.98
4				(E,E)-grow	10.33
5			$(Z,Z) \rightarrow (Z,E)$	(Z,Z)-decay	6.891
6				(Z,E)-grow	2.987

7	-70	acetone- d_6	$(Z,E) \rightarrow (E,E)$	(Z,E)-decay	0.001397
8				(E,E)-grow	0.001419
9			$(E,Z) \rightarrow (E,E)$	(E,Z)-decay	0.1528
10				(E,E)-grow	0.1418
11			$(Z,Z) \rightarrow (Z,E)$	(Z,Z)-decay	0.3257
12				(Z,E)-grow	0.3226

13	-40	CD ₃ CN	$(Z,E) \rightarrow (E,E)$	(Z,E)-decay	0.00107
14				(E,E)-grow	0.001039
15			$(E,Z) \rightarrow (E,E)$	(E,Z)-decay	0.6577
16				(E,E)-grow	0.6468
17			$(Z,Z) \rightarrow (Z,E)$	(Z,Z)-decay	0.9254
18				(Z,E)-grow	0.8093

1 + potassium trifluoroacetate (K^+TFA^-) (5 eq) in CD_3CN (50 mM) at -40°C

During the initial investigation of **1** in presence of K^+TFA^- we found distinct signals of the corresponding starting materials (**9** and *trans*-cinnamaldehyde). This amount of hydrolysis products was neither detectable for a pure sample of **1** (Figure S57 A), nor in presence of an excess of H_2O (Figure S57 B). As soon as we additionally added an excess of K^+TFA^- , a quantitative hydrolysis could be observed (Figure S57 C). Therefore, working with perfectly dried reagents is mandatory to investigate photoinduced and thermal isomerization processes of **1** in presence of K^+TFA^- (Figure S57 D).



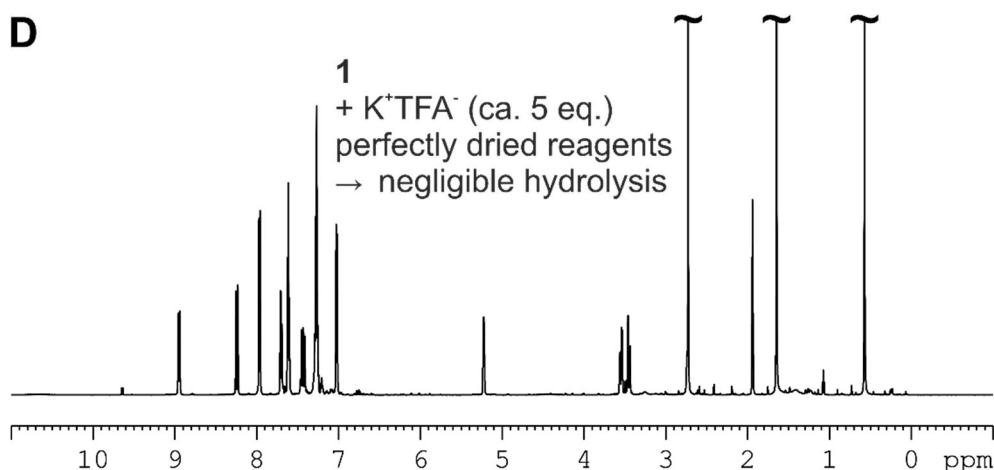


Figure S57. Stacked 1D-¹H spectra (ns = 16) of **1** showing the K⁺TFA⁻ promoted hydrolysis of **1** in presence of water. Therefore a sample of **1** in CD₃CN (ca. 35 mM) was investigated at -40 °C first pure (**A**), than with an excess of dest. H₂O (blue signal) (**B**) and finally with an excess of dest. H₂O and K⁺TFA⁻ (**C**). Using perfectly dried reagents only yields traces of hydrolysis products (**D**).

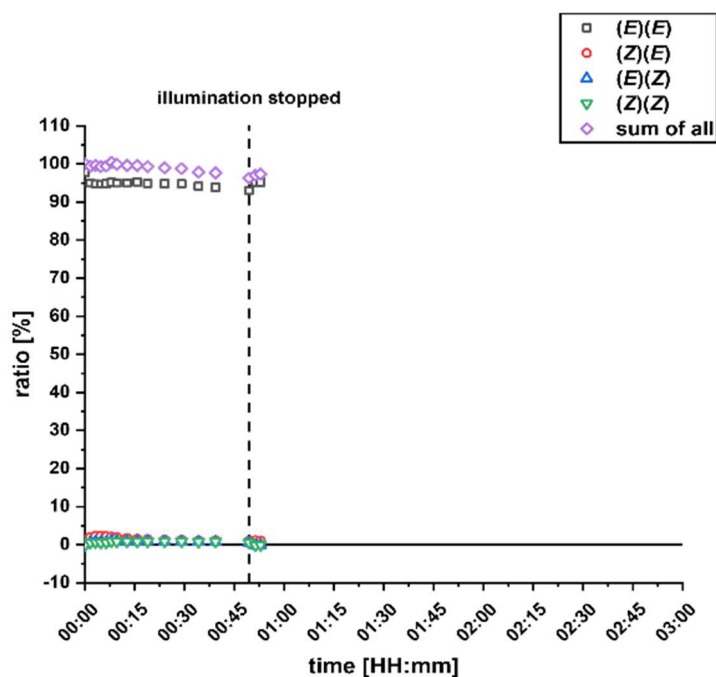


Figure S58. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** in presence of K⁺TFA⁻ (5 eq.) measured at -40 °C in CD₃CN (50 mM).

Earlier studies showed an nucleophile-catalyzed thermal isomerization mechanism for such iminium ions.^{8,18a} Therefore we assume that the relative nucleophilicity of the TFA anion significantly favors the thermal isomerization pathway and thus prevents an adequate photoinduced (E) → (Z) isomerization.

1 + 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) (5 eq) in CD₃CN (25 mM) at -40 °C

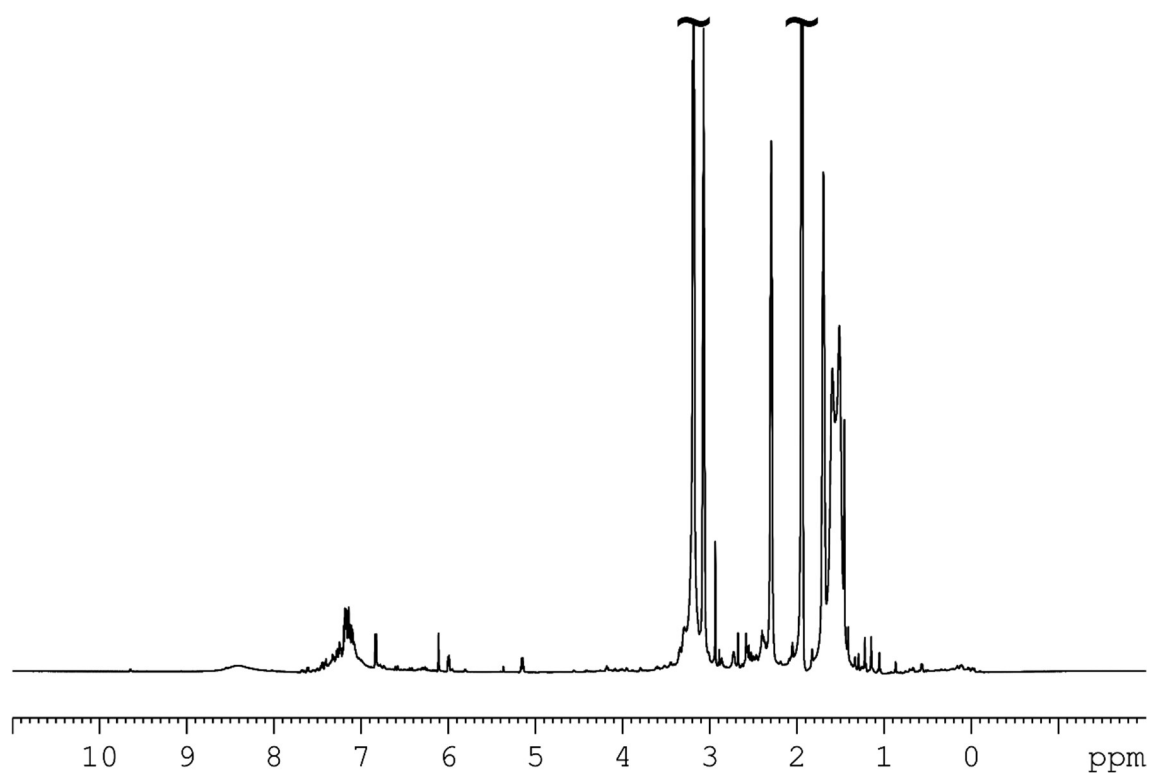


Figure S59. 1D-¹H spectrum (ns = 16) showing complete decomposition of **1** in presence of DBU (5 eq.) measured at -40 °C in CD₃CN (25 mM).

1 + 2,6-Di-*tert*-butylpyridine (DBP) (2 eq) in CD₃CN (57.5 mM) at -40 °C

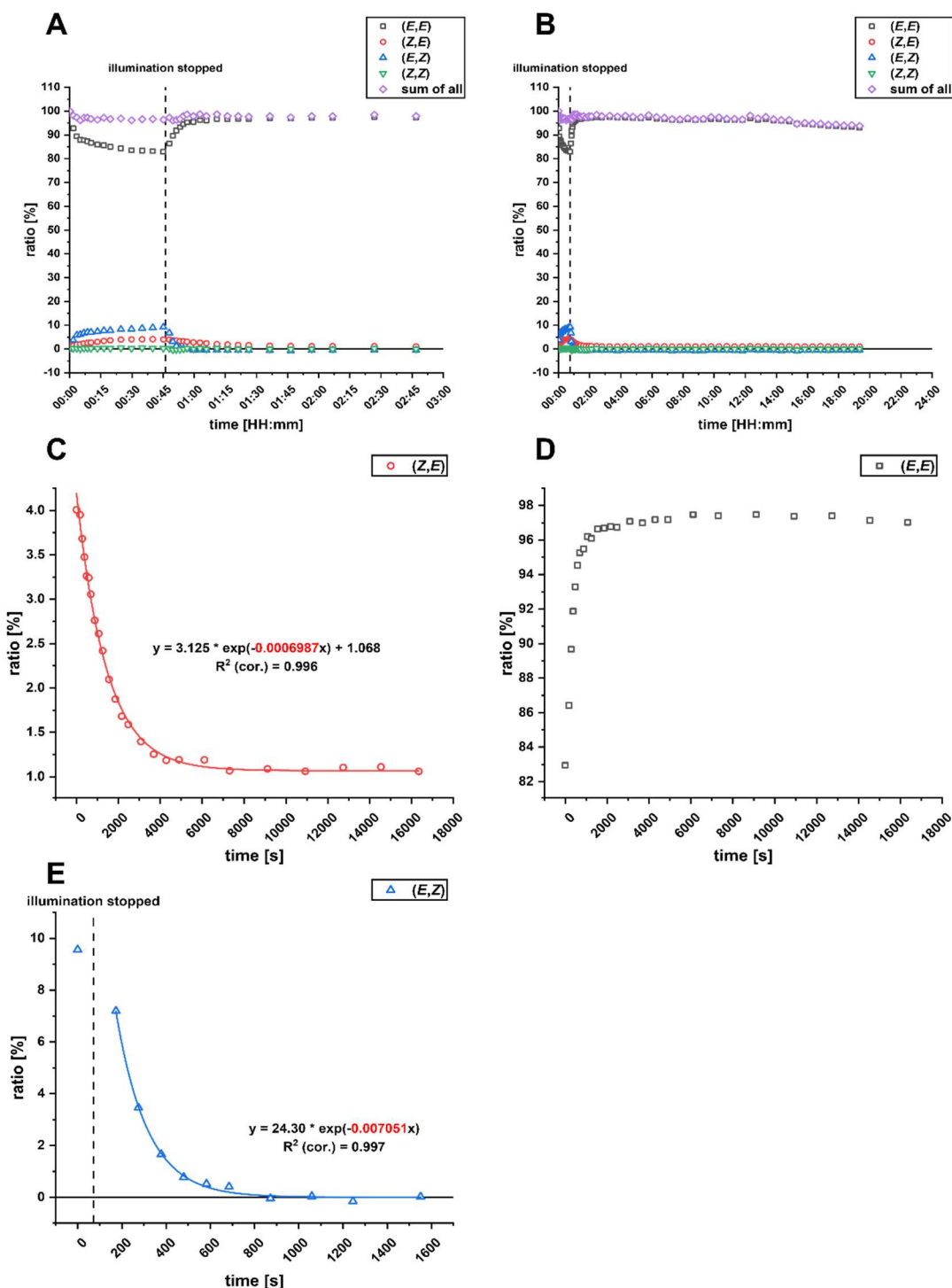


Figure S60. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** in presence of DBP (2 eq.) measured at -40 °C in CD₃CN (57.5 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C - E:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S3.

1 + 2,6-Di-*tert*-butylpyridine (DBP) (2 eq) in CD₃CN (25 mM) at -40 °C

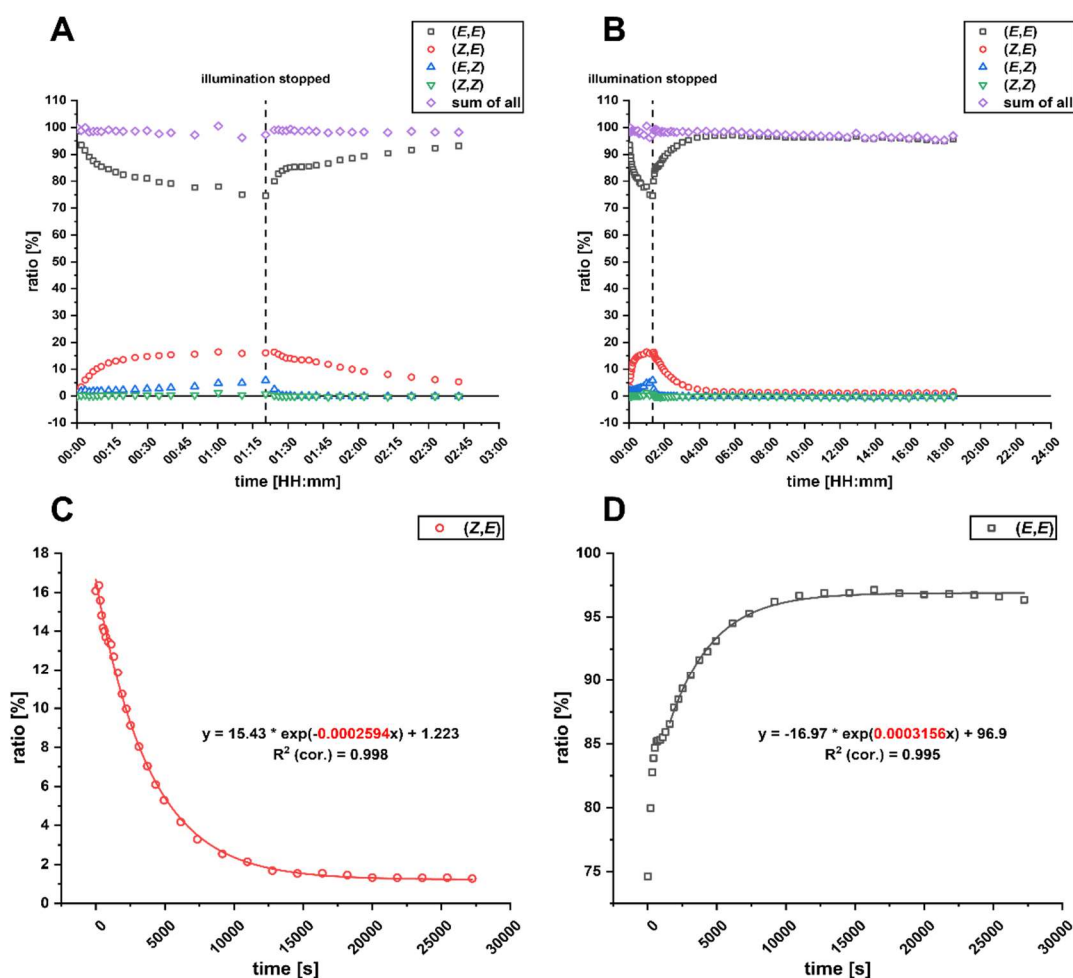


Figure S61. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** in presence of DBP (2 eq.) measured at -40 °C in CD₃CN (25 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C - D:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S3.

1 + 2,6-Di-*tert*-butylpyridine (DBP) (2 eq) in CD₃CN (10 mM) at -40 °C

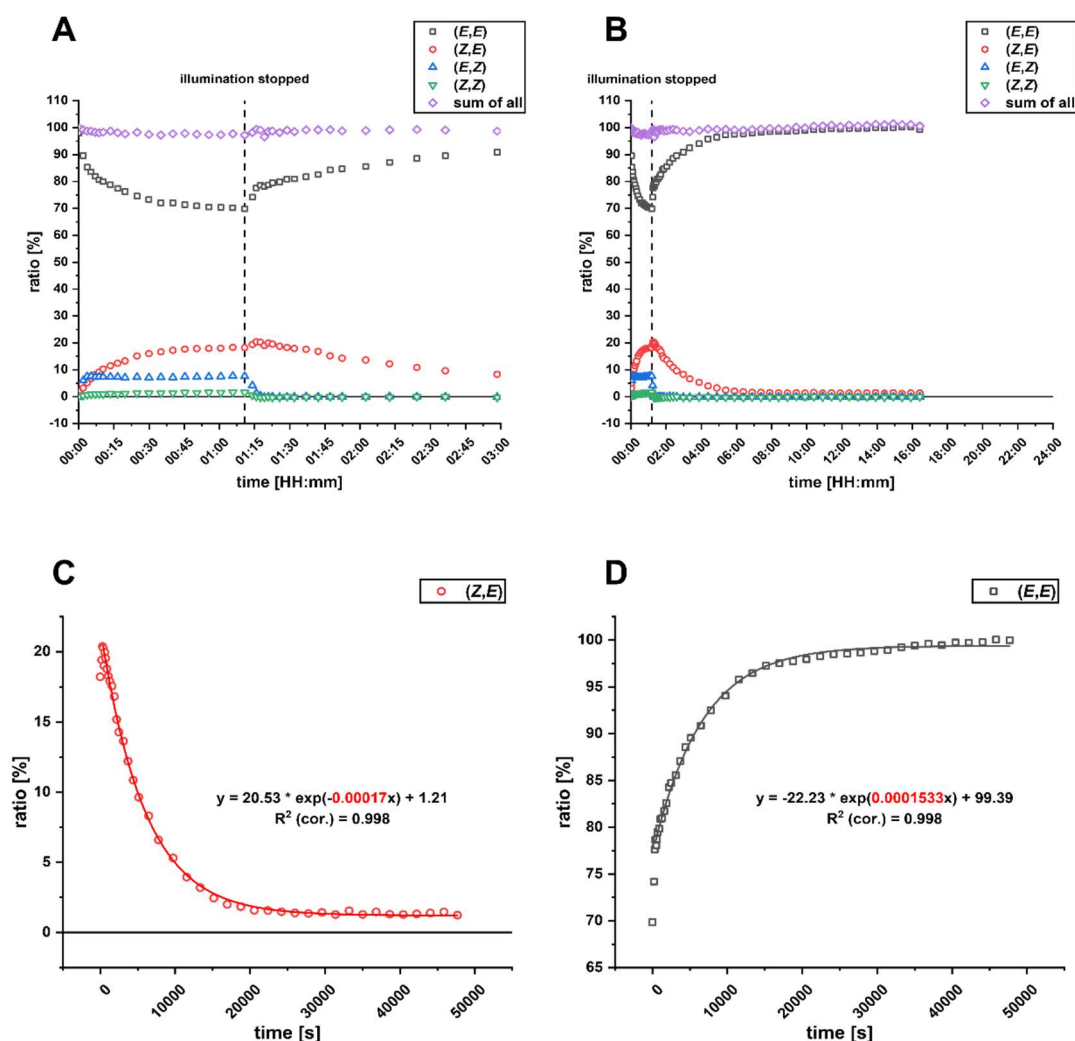


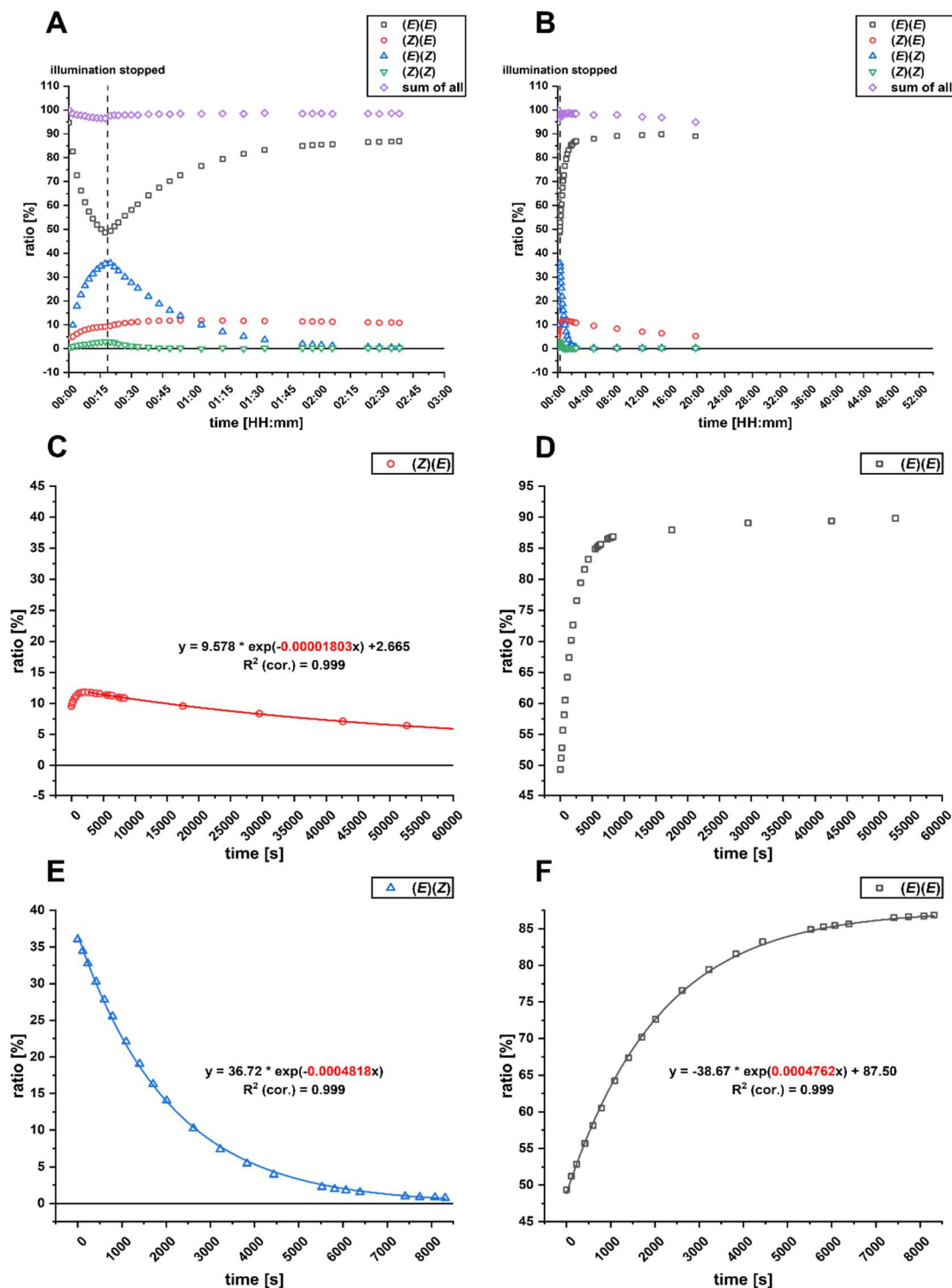
Figure S62. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **1** in presence of DBP (2 eq.) measured at -40 °C in CD₃CN (10 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (E) → (Z) isomerization and after stopping illumination the associated thermal (Z) → (E) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 24 h. **C - D:** Decay and grow curves for thermal (Z) → (E) isomerization of the C=N double bond including mathematical fitting. The obtained values for $k_{(Z) \rightarrow (E)}$ are given in Table S3.

Table S3. Concentration dependence (57.5, 25, 10 mM) of thermal (Z) → (E) isomerization processes of iminium ion **1** in presence of DBP (2 eq.) after UV-triggered (E) → (Z) isomerization ($\lambda = 365$ nm). To obtain $k_{(Z) \rightarrow (E)}$ the associated isomerization curves (see Figure S60-S62) were mathematically fitted and Equation 1 was applied.

Entry	c (1) [mM]	Process	$k_{(Z) \rightarrow (E)}$ [10^{-3} s^{-1}]
1	57.5	(Z,E) → (E,E)	0.6987
2		(E,E)-grow	-
3		(E,Z) → (E,E)	7.051
4		(E,E)-grow	-
5		(Z,Z) → (Z,E)	-
6		(Z,E)-grow	-
7	25	(Z,E) → (E,E)	0.2594
8		(E,E)-grow	0.3156
9		(E,Z) → (E,E)	-
10		(E,E)-grow	-
11		(Z,Z) → (Z,E)	-
12		(Z,E)-grow	-
13	10	(Z,E) → (E,E)	0.17
14		(E,E)-grow	0.1533
15		(E,Z) → (E,E)	-
16		(E,E)-grow	-
17		(Z,Z) → (Z,E)	-
18		(Z,E)-grow	-

3.5.5.3 Investigations of iminium ion 2

2 in acetone- d_6 (50 mM) at $-40\text{ }^{\circ}\text{C}$



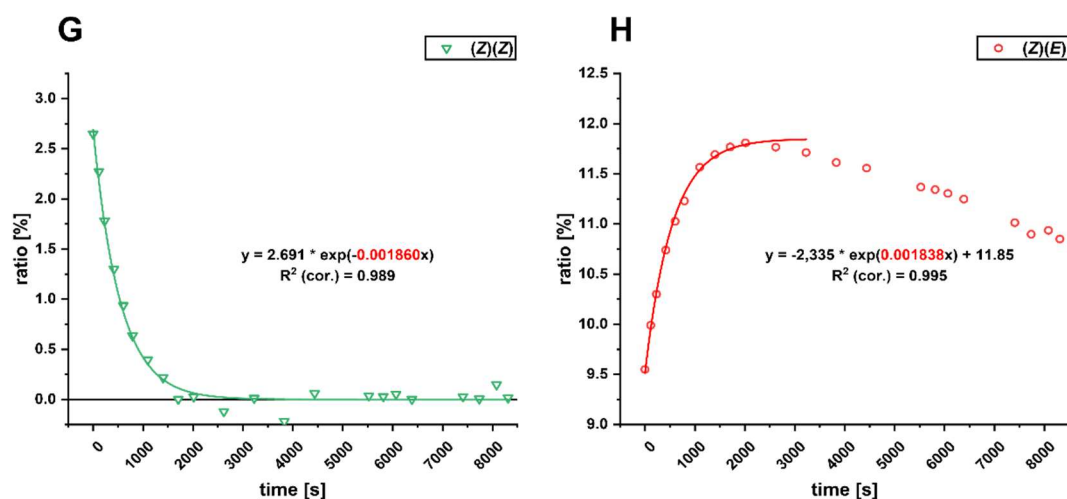


Figure S63. 1D-¹H kinetic of photoinduced and thermal isomerization of iminium ion **2** measured at -40 °C in acetone-*d*₆ (50 mM). **A:** First 3.0 h of the recorded 1D-¹H kinetic show in detail how UV-irradiation (365 nm) triggers (*E*) → (*Z*) isomerization and after stopping illumination the associated thermal (*Z*) → (*E*) isomerization processes. **B:** To facilitate comparison with other 1D-¹H kinetics, the x-axes is set to 54 h. **C - H:** Decay and grow curves for thermal (*Z*) → (*E*) isomerization of the C=N and C=C double bond including mathematical fitting. The obtained values for *k*_{(*Z*) → (*E*)} are given in Table S4.

Table S4. Thermal (*Z*) → (*E*) isomerization processes of iminium ion **2** in acetone-*d*₆ (50 mM) at -40 °C after UV-triggered (*E*) → (*Z*) isomerization (λ = 365 nm). To obtain *k*_{(*Z*) → (*E*)} the associated isomerization curves (see Figure S63) were mathematically fitted and Equation 1 was applied.

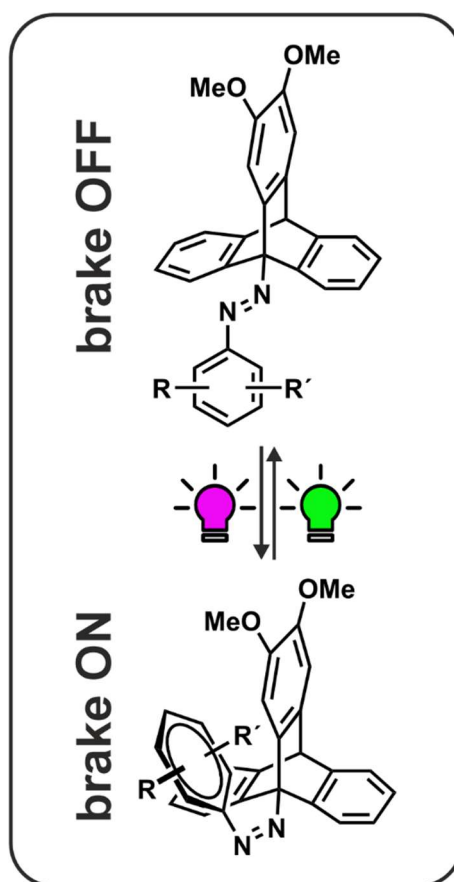
Entry	T [°C]	Solvent	Process	<i>k</i> _{(<i>Z</i>) → (<i>E</i>)} [10 ⁻³ s ⁻¹]
1	-40	acetone- <i>d</i> ₆	(<i>Z,E</i>)-decay	0.01803
2			(<i>E,E</i>)-grow	-
3			(<i>E,Z</i>)-decay	0.4818
4			(<i>E,E</i>)-grow	0.4762
5			(<i>Z,Z</i>)-decay	1.86
6			(<i>Z,E</i>)-grow	1.838

3.6 References

- 1 <https://www.nobelprize.org/prizes/chemistry/2021/summary/> (accessed October 2022).
- 2 a) B. List, *Chem. Commun.*, 2006, 819–824; b) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chemie - Int. Ed.*, 2008, **47**, 6138–6171; c) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178–2189.
- 3 a) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470; b) D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308; c) L. Raimondi, C. Faverio and M. F. Boselli, *Phys. Sci. Rev.*, 2020, **5**, 1–14.
- 4 M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen and K. A. Jørgensen, *Chem. Commun.*, 2011, **47**, 632–649.
- 5 a) G. J. S. Evans, K. White, J. A. Platts and N. C. O. Tomkinson, *Org. Biomol. Chem.*, 2006, **4**, 2616–2627; b) J. L. Cavill, R. L. Elliott, G. Evans, I. L. Jones, J. A. Platts, A. M. Ruda and N. C. O. Tomkinson, *Tetrahedron*, 2006, **62**, 410–421; c) J. L. Cavill, J. U. Peters and N. C. O. Tomkinson, *Chem. Commun.*, 2003, **3**, 728–729.
- 6 M. P. Patil and R. B. Sunoj, *J. Org. Chem.*, 2007, **72**, 8202–8215.
- 7 a) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370–4371; b) S. Lakhdar and H. Mayr, *Chem. Commun.*, 2011, **47**, 1866–1868.
- 8 W. J. Stockerl and R. M. Gschwind, *Chem. Commun.*, 2023, **59**, 1325–1328.
- 9 a) S. Lakhdar, T. Tokuyasu and H. Mayr, *Angew. Chemie - Int. Ed.*, 2008, **47**, 8723–8726; b) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak and T. Uchimar, *Helv. Chim. Acta*, 2010, **93**, 603–634; c) U. Grošelj, A. K. Beck, W. B. Schweizer and D. Seebach, *Helv. Chim. Acta*, 2014, **97**, 751–796.
- 10 a) R. Gordillo, J. Carter and K. N. Houk, *Adv. Synth. Catal.*, 2004, **346**, 1175–1185; b) M. C. Holland, S. Paul, W. B. Schweizer, K. Bergander, C. Mück-Lichtenfeld, S. Lakhdar, H. Mayr and R. Gilmour, *Angew. Chemie - Int. Ed.*, 2013, **52**, 7967–7971; c) M. C. Holland, J. B. Metternich, C. Mück-Lichtenfeld and R. Gilmour, *Chem. Commun.*, 2015, **51**, 5322–5325; d) M. C. Holland, J. B. Metternich, C. Daniliuc, W. B. Schweizer and R. Gilmour, *Chem. - A Eur. J.*, 2015, **21**, 10031–10038.
- 11 D. Seebach, U. Grošelj, M. D. Badine, W. B. Schweizer and A. K. Beck, *Helv. Chim. Acta*, 2008, **91**, 1999–2034.
- 12 U. Grošelj, D. Seebach, M. D. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi and T. Uchimar, *Helv. Chim. Acta*, 2009, **92**, 1225–1259.

- 13 a) R. Gordillo and K. N. Houk, *J. Am. Chem. Soc.*, 2006, **128**, 3543–3553; b) E. H. Krenske, K. N. Houk and M. Harmata, *J. Org. Chem.*, 2015, **80**, 744–750.
- 14 P. Renzi, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.*, 2017, **139**, 6752–6760.
- 15 J. B. Brazier, G. P. Hopkins, M. Jirari, S. Mutter, R. Pommereuil, L. Samulis, J. A. Platts and N. C. O. Tomkinson, *Tetrahedron Lett.*, 2011, **52**, 2783–2785.
- 16 a) M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti and P. Melchiorre, *Nat. Chem.*, 2017, **9**, 868–873; b) Ł. Woźniak, G. Magagnano and P. Melchiorre, *Angew. Chemie - Int. Ed.*, 2018, **57**, 1068–1072; c) C. Verrier, N. Alandini, C. Pezzetta, M. Moliterno, L. Buzzetti, H. B. Hepburn, A. Vega-Peñaloza, M. Silvi and P. Melchiorre, *ACS Catal.*, 2018, **8**, 1062–1066.
- 17 C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39–44.
- 18 a) M. Pankratz and R. F. Childs, *J. Org. Chem.*, 1985, **50**, 4553–4558; b) M. B. Schmid, K. Zeitler and R. M. Gschwind, *Chem. - A Eur. J.*, 2012, **18**, 3362–3370.
- 19 <https://www.eurisotop.com/acetone-d6-29> (accessed October 2022).
- 20 I. Rodríguez and J. González-Velasco, *J. Chem. Soc. Chem. Commun.*, 1990, **104**, 387–388.
- 21 Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328–9329.
- 22 P. Nitschke, N. Lokesh and R. M. Gschwind, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2019, **114–115**, 86–134.
- 23 M. Franta, J. Gramüller, P. Dullinger, S. Kaltenberger, D. Horinek and R. M. Gschwind, *Angew. Chemie - Int. Ed.*, 2023, **62**, 1–9.

4. Azotriptycenes: Photoswitchable Molecular Brakes



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A. Gerwien conceptualized this project together with H. Dube and synthesized all azotriptycenes, measured UV/Vis spectra and grew crystals for X-ray analysis. **Willibald J. Stockerl** performed and evaluated all advanced NMR spectroscopic investigations. L. Reißenweber re-synthesized the compounds and investigated interconversions between the differently configured azotriptycene-isomers via thermal and crystallization pathways. L. Reißenweber, A. Gerwien, N. N. Bach, S. Thumser and P. Mayer performed quantum chemical calculations. H. Dube supervised L. Reißenweber, A. Gerwien N. N. Bach, S. Thumser and P. Mayer in their contributions. R. M. Gschwind guided and supervised **Willibald J. Stockerl**. **Willibald J. Stockerl** wrote the NMR spectroscopic parts of the manuscript and ESI with input from R. M. Gschwind. H. Dube wrote all other sections of the manuscript and ESI.

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4.1 Abstract

The control of molecular motions is a central topic of molecular machine research. Molecular brakes are fundamental building blocks towards such goal as they allow deliberately decelerating specific motions after an outside stimulus is applied. Here we present azotriptycenes as structural framework for light-controlled molecular brakes. The intrinsic kinetics and their changes upon azotriptycene isomerization are scrutinized comprehensively by a mixed theoretical and variable temperature NMR approach. With azotriptycenes C-N bond rotation rates can be decelerated or accelerated reversibly by up to five orders of magnitude. Rate change effects are highly localized and are strongest for the C-N bond connecting a triptycene rotor fragment to the central diazo group. The detailed mechanistic insights provide a solid basis for further conscious design and applications in the future.

4.2 Introduction

Building molecular machines requires controlling molecular motions with greatest precision.¹ At present a number of fundamental molecular building blocks have been devised establishing highly controlled motions at a localized spot within a single entity e.g. molecular switches,² rotors,³ motors,⁴ pumps,⁵ or walkers.⁶ The necessary next steps now are transmission of such local motions away from where they are generated and the independent control of these motions in response to additional outside stimuli. In the first regard various concepts have been explored, for example covalent connection of different movable parts,⁷ active molecular entanglements,⁸ the recently reported mechanical molecular threading,⁹ or tight intermeshing in molecular gears.¹⁰ On the other hand, supramolecular or polymeric embedding of switches or motors results in upscaling of their molecular changes even to the macroscopic scale.¹¹ Similarly, surface functionalizations of movable molecular entities¹² or implementation into 3-dimensional porous structures¹³ allow to elicit macroscopic changes in response to the molecular alterations. In the second regard, another level of motion control is presented by adding stimuli-responsiveness to directly alter molecular motions upon an independent signal e.g. in molecular brakes,¹⁴ molecular gear boxes,¹⁵ switchable gears¹⁶ and motors,¹⁷ or in the lately reported actively energy powered molecular photogear.¹⁸ Light responsive molecular brakes¹⁹ are very interesting as they use a fast, efficient, and waste-free stimulus to control the speed of small-scale motions. In a typical example as pioneered by Yang and coworkers^{14b} the thermally activated rotation of one molecular fragment against another is altered by mechanical blocking: After the light stimulus is applied a bulky group is brought into close proximity to the moving fragment, thus sterically hindering and slowing down its motion. This can also be reversed and an initially blocked slow motion can be accelerated by a light stimulus by disengaging interlocked molecular fragments via a photoisomerization reaction. The azobenzene motive has successfully been employed by Yang in its diaryl-form within photoswitchable molecular brake architectures and extremely strong brake-effects have been achieved for the rotation of pentiptycenes.²⁰ Very strong light-induced braking effects were also reported by Tamaoki and coworkers within macrocyclic structures.²¹

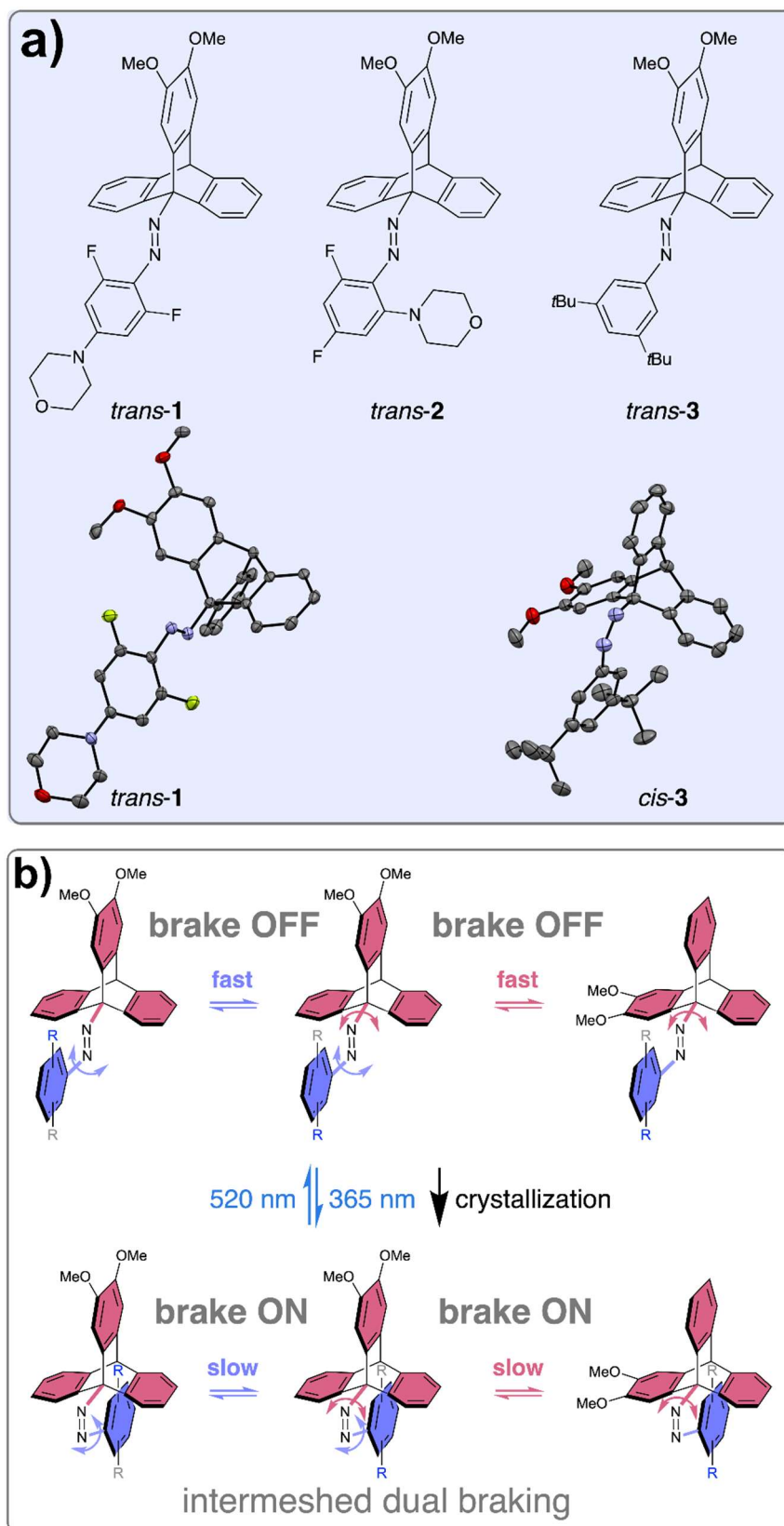


Figure 1. Azotriptycenes **1** to **3** enabling photoswitching of mechanical braking C-N single bond rotations. a) Schematic representation of azotriptycenes *trans*-1 to *trans*-3 and structures of *trans*-1 and *cis*-3 in the crystalline state. b) Two fast C-N single bond rotations of the triptycene fragment (red) and the phenyl ring (blue) are present in the *trans* isomers of azotriptycenes (top, brake OFF). Upon switching to the *cis* isomers the two single bond rotations are slowed down significantly (bottom, brake ON).

In this work we present a different photoswitchable molecular brake motive based on an azobenzene-triptycene hybrid, which we term azotriptycene (derivatives **1** to **3** are shown in Figure 1). Our system establishes reversible control over the rotation rate of two C-N single bonds connecting the diazobenzene and triptycene molecular fragments by up to five orders of magnitude. The behavior is scrutinized comprehensively by a combined low-temperature NMR and quantum chemical approach to gain detailed mechanistic insights into the inner workings of azotriptycenes.

4.3 Results and Discussion

The azotriptycene system consists of an azo compound with one aryl substituent and one alkyl-like triptycene at the other side (for a recent triptycene-based azobenzene connecting the diazo-moiety to one of the phenyl blades see ref. ²²). Azo compounds inheriting alkyl substituents are known for a long time but only few studies have addressed their photoisomerization behavior.²³ The implementation of a triptycene as alkane-moiety has also been reported before,²⁴ however the potential of such structures for molecular machines has not been explored so far. Azotriptycenes **1** and **3** were designed in such a way that dynamic NMR spectroscopy could be employed for directly quantifying the braking kinetics. For this reason, the triptycene rotor blades were desymmetrized by introducing two methoxy-substituents and the phenyl ring was substituted symmetrically with fluorine atoms at both *ortho*-positions (azotriptycene **1**) or *tert*-butyl groups at both *meta*-positions (azotriptycene **3**) as shown in Figure 1. In this way a splitting of fluorine or *tert*-butyl signals in the NMR experiments would signify conformational locking and thus allow kinetic measurements for phenyl-ring and triptycene rotations. Fluorine substitution in **1** serves as convenient structural probe enabling ¹⁹F-NMR spectroscopy as analytical tool with the combined benefits of high signal intensities and reduced number of signals that have to be analyzed. The morpholine substitution in *para*-position to the diazo-moiety in **1** serves the purpose of increasing electron density at the phenyl residue in order to optimize the intermeshing propensity with the triptycene. Compound **2** serves as control compound to distinguish dynamic exchange processes from nuclear Overhauser effects (NOEs) in azotriptycene **1**. In azotriptycene **3** the *tert*-butyl substitution leads to a strong stabilization of the *cis*-isomer, which can exclusively be trapped in the crystalline state (see Figure 1 and the ESI). This behavior is most likely owed to intrinsic stabilization by weak intramolecular forces, especially the accumulative effect of dispersion, similar to the ones observed in highly alkylated azobenzenes.²⁵ Crystallization can thus be used to revert back to the brake-ON state of *cis*-**3**.

First, we have undertaken a comprehensive theoretical analysis of the azotriptycene system to probe the geometries in the *trans*- and *cis*-isomeric states, assess the fast rotation kinetics of the *trans*-isomers, and predict the effectiveness of the braking process in the *cis*-isomers. To this end the different ground state minima and corresponding transition states associated with their interconversions were calculated at 165.15 K on the B3LYP-D3BJ/6-311G(d,p) PCM(CH₂Cl₂) level of theory for azotriptycene **1** and on the B3LYP/6-311G(d,p) PCM(CH₂Cl₂) level of theory for azotriptycene **3** (only explicitly omitting dispersive interactions delivered a theoretical description in agreement with the experimental data for azotriptycene **3**) as shown in Figure 2. azotriptycenes **1** and **3** can

essentially be described by three different energy minima in the *trans*- as well as the *cis*-isomeric states, two of which are enantiomers of each other and thus lie at the same energies. For this reason, only one enantiomer was taken into account in the theoretical description.

Rotations around the two C-N single bonds (phenyl and triptycene rotations) lead to a degenerate doubling for each of these three minima, resulting in a corresponding energy landscape containing six minima and six connecting transition states, four of which possess different energies in each case (Figure 2). Because rotations within the azotriptycenes interconvert states of rather similar energies across barriers of also similar energies two points need to be made for clarification. First, when discussing the theoretical description alone individual energies of minima and transition states are compared. However, to compare theoretically obtained values with values derived from experimental kinetic analysis, the equilibrium populations of the two involved minima need to be taken into account (see below and for details how to calculate Gibbs energies of activation differences $\Delta G^\ddagger$ and the corresponding rate constants k in equilibrium see ESI). Second, for the description of theoretical results involving rotations between two minima of different energies, we will only refer to calculated Gibbs energies of activation differences $\Delta G^\ddagger$ between the transition state and the corresponding minimum with higher energy as indicated with plus signs in Figure 2.

For *trans*-**1** the global minimum is the isomer with the methoxy-substituted triptycene blade and the fluorinated phenyl ring in a coplanar arrangement. The two other enantiomeric minima are 0.31 kcal/mol higher in energy and are similar to the structure of *trans*-**1** found in the crystalline state (compare to Figure 1a). The transition state with highest energy of 6.09 kcal/mol is encountered for the C-N rotation of the phenyl ring starting from the enantiomeric minima with the aryl moiety residing between the two different triptycene blades, which exchanges fluorine atoms of the phenyl residue with respect to the nonsymmetric triptycene pocket. The corresponding rotation of the phenyl ring starting from the respective global minimum encounter a barrier of $\Delta G^\ddagger = 5.38$ kcal/mol. These sizable barriers can be explained mainly by the broken conjugation between the diazo-moiety and the phenyl ring, which is clearly visible in the structure of the transition state. Significantly lower barriers are found for the triptycene rotation, where no conjugation is broken and also steric interactions are less pronounced compared to the above-described phenyl ring rotation. Triptycene rotation is fastest when the methoxy-substituted blade is passing the diazo moiety, which gives rise to a barrier of $\Delta G^\ddagger = 1.33$ kcal/mol. Nevertheless, also the second possibility (unsubstituted blades

are passing the diazo moiety) is a very fast process with an associated barrier of $\Delta G^\ddagger = 2.30$ kcal/mol.

A similar overall behavior is found for *trans*-**3**. Again, the symmetric minimum is the global minimum and the enantiomeric minima are found at only 0.24 kcal/mol higher energy. Thus, an almost statistical population of minima is expected for *trans*-**3**. As already observed for *trans*-**1**, triptycene rotations of *trans*-**3** are fastest encountering barriers of $\Delta G^\ddagger = 1.25$ and 2.23 kcal/mol. Phenyl rotations are significantly slower with barriers of $\Delta G^\ddagger = 6.18$ and 6.78 kcal/mol. Taken together, very different yet fast rotation speeds are present in *trans*-isomeric state of azotriptycenes, where the faster triptycene rotation rate is up to four to five orders of magnitude (corresponding to 5.53 kcal/mol difference in $\Delta G^\ddagger$ values) faster than the phenyl ring rotation.

For *cis*-**1** the enantiomeric global minimum is found with the phenyl ring located between two symmetric triptycene blades. The enantiomeric metastable states are only 0.30 kcal/mol higher in energy, which predicts a roughly equal population of the three minima. Importantly, in all minimum structures the fluorinated phenyl ring is well intermeshed within two rotor blades of the triptycene rotor fragment. When analyzing the rotations in *cis*-**1** again four motions need to be considered. Two represent rotations around the C-N single bond connecting to the phenyl ring (marked with blue arrows in Figure 2b) within either the symmetric triptycene pocket (metastable state, termed pocket I in the following) with an associated Gibbs energy of activation of $\Delta G^\ddagger = 8.43$ kcal/mol or the enantiomeric nonsymmetric pockets II/II' with a corresponding barrier of 7.97 kcal/mol. Two different rotations proceed around the C-N single bond connecting to the triptycene (marked in red in Figure 2b), either across an unsubstituted triptycene blade with $\Delta G^\ddagger = 8.01$ kcal/mol or across the methoxy-substituted triptycene blade with $\Delta G^\ddagger = 7.08$ kcal/mol. These transition states feature a perpendicular phenyl ring residing on top of the triptycene rotor blades as shown schematically in Figure 2b. In azotriptycene *cis*-**1** the rotation rates of the phenyl substituent and the triptycene are thus rather similar with the exception of the phenyl rotation in pocket I, which encounters a barrier 1.35 kcal/mol higher in energy compared to the fastest triptycene rotation.

For azotriptycene *cis*-**3** again a similar behavior is seen but with somewhat different energies for the particular transitions and minima overall. In this case the enantiomeric structures bearing the phenyl ring in pocket II/II' represent the global minimum. This minimum structure is also observed experimentally in the crystalline state of *cis*-**3** (compare to Figure 1a). For *cis*-**3** the metastable state is only slightly higher in energy (by 0.16 kcal/mol) as compared to the global minimum. Therefore, all minima are expected to be significantly populated. The transition states for *cis*-**3** rotations are lower

than the corresponding transition states in *cis*-**1** with the exception of the triptycene rotation across the methoxy-substituted blade. Overall, phenyl rotations within the triptycene pockets ($\Delta G^\ddagger = 7.68$ and 7.27 kcal/mol) are similarly decelerated as the triptycene rotations ($\Delta G^\ddagger = 7.81$ and 8.66 kcal/mol) in azotriptycene *cis*-**3**.

Taken together, the theoretical description predicts a significantly slowed down triptycene rotation in the *cis*-isomers of the azotriptycenes as compared to the *trans*-isomers. Deceleration can reach up to five orders of magnitude in rate differences (corresponding to 5.53 kcal/mol difference in $\Delta G^\ddagger$ values) for this motion in **1**, which is a significant speed change. Also in **3** the speed changes of triptycene rotation reach sizable numbers of up to five orders of magnitude (corresponding to 7.41 kcal/mol difference in $\Delta G^\ddagger$ values). The corresponding phenyl rotation is also slowed down in the *cis*-isomers but to a much lesser degree of maximal two orders of magnitude (corresponding to 3.05 kcal/mol difference in $\Delta G^\ddagger$ values) in *cis*-**1**. In the *trans*-isomers the triptycene rotation is theoretically predicted to be up to four-fold faster than phenyl rotation whereas in the *cis*-isomers both rotations are of similar rate. Thus, the braking effect is strongly localized to the triptycene moieties in the azotriptycene structures, which is important to note for future applications.

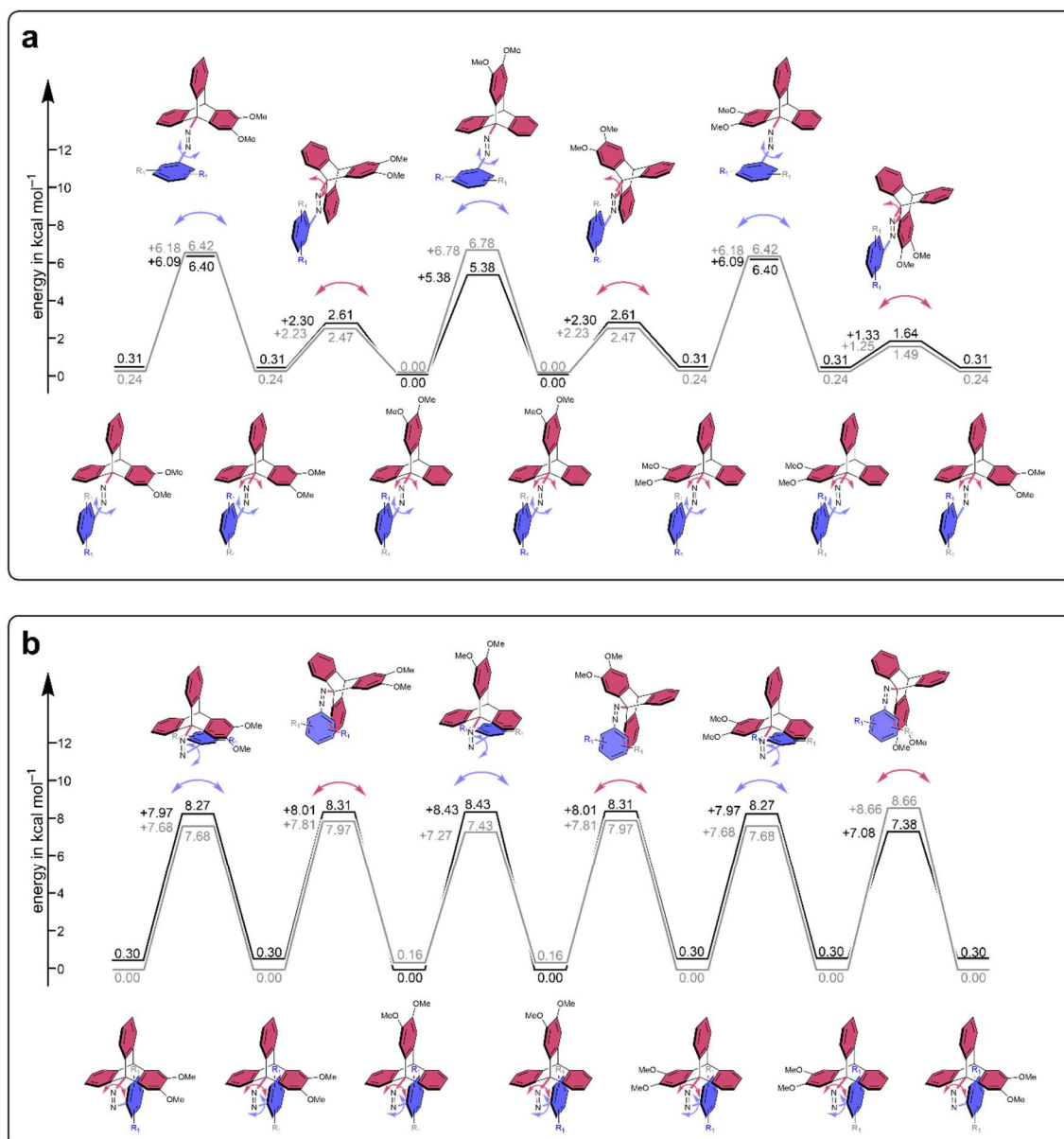


Figure 2. Calculated ground state energy profiles of azotriptycenes **1** (B3LYP-D3BJ/6311G(d,p) PCM(CH₂Cl₂) level of theory, black) and **3** (B3LYP/6-311G(d,p) PCM(CH₂Cl₂) level of theory, grey) at 165.15 K and associated motions. Schematic representations of the molecular minimum and transition state structures are shown (for actual structures calculated see ESI). Rotations around specific C-N single bonds are indicated by color coded arrows (blue for phenyl rotations, red for triptycene rotations). To guide the eye in the particular rotations, residues R are further color coded in grey and blue. In the transition states this color coding suggests a particular rotation direction, which is not the case as the enantiomeric rotation direction is present with equal probability but has been left out for clarity reasons. a) Energy profile of *trans*-azotriptycenes. b) Energy profile of *cis*-azotriptycenes. For clarity, phenyl residues R residing in the triptycene pockets I or enantiomeric II/II' are labeled R^I, R^{II}, R^{II'}, respectively. Energies correspond to calculated thermochemical data and thus ΔG and $\Delta G^\ddagger$ values.

Azotriptycenes **1** to **3** were synthesized in four steps starting from commercially available anthracene **4** and anthranilic acid **5** (for synthetic details see the ESI). After formation of diazonium salt **6**, heating generated the corresponding aryne *in situ* which furnished

tritycene **7** via a Diels-Alder reaction with **4**. Bromine-lithium exchange gave the lithiated triptycene **8**, which was reacted directly with diazonium salts **9** or **10** to yield azotriptycenes **1** and **2**, respectively, or with diazonium salt **11** to yield **3** in the final step. Crystals suitable for X-ray analysis were obtained for *trans*-**1** and *cis*-**3** evidencing the molecular structures and isomeric states directly (see Figure 1a).

After successful synthesis the photochemical properties as well as the braking behavior of azotriptycenes **1** and **3** were scrutinized experimentally. At elevated temperatures only the *trans*-isomers and no *cis*-isomer population is observed for **1** in solution. Azotriptycene **3** can be isolated as *cis*-isomer in the crystalline state, however this isomer slowly returns to the *trans*-isomer when dissolved at ambient temperature in CD₂Cl₂ or CDCl₃. The preferred crystallization as *cis*-isomer is probably due to a combination of pronounced dispersive interactions as lately studied in detail for alkyl-substituted azobenzenes while also crystal packing effects might play an important role.

Photoirradiation of **1** at ambient temperatures (22 °C) did not lead to a discernible population of the *cis*-isomer. However, at low temperatures (<−20 °C) a sizable population of up to 20% *cis*-isomer can be accumulated when irradiating with 365 nm light. Allowing the *cis*-**1** containing solution to warm up to 22 °C leads to full conversion to the *trans*-isomer within minutes. At low temperatures *cis*-**1** can also completely converted to *trans*-**1** by irradiation with 520 nm light. Photoirradiation of *trans*-**3** with 365 nm light allows accumulation of *cis*-**3** in up to 22% and also in this case irradiation with 520 nm light leads accumulation of 96% *trans*-**3**.

Variable temperature NMR spectroscopy was used as analytical tool for investigating the dynamics of motion for azotriptycenes **1** and **3**. At −48 °C averaged signals of both *cis*-**1** and *trans*-**1** are detected in the ¹⁹F NMR spectrum (see Figure 3a) after irradiation with 365 nm light. After coalescence at −78 °C, the previously averaged aromatic fluorine signal of *cis*-**1** is split into a total of four new signals. In contrast, for *trans*-**1** only a slight line broadening can be detected down to −108 °C, which evidences still very fast rotation around the C-N bonds even at this very low temperature (Figure 3a). For *cis*-**1** two sets of signals are well separated with intensities in a 1:2 ratio at −108 °C. Each set consists of two well separated fluorine signals. These two sets with a 1:2 ratio reflect the two intermeshed energy minima states with phenyl-occupied pockets I and II/II', which are distinguishable by NMR spectroscopy (Figure 3e, the two states with occupied pockets II and II' are enantiomers and give identical NMR signals). The splitting into a down- and upfield shifted ¹⁹F signal of the same intensity shows that at −108 °C the rotation around the phenyl C-N bond is substantially slowed down leading to distinct magnetic environments for the two fluorine atoms residing either outside or inside the triptycene

pockets (blue arrows in Figure 3a; note that for signal distinction the residues at the phenyl ring are termed R^I for isomers with pocket I occupancy and R^{II} and $R^{II'}$ for pocket II and II' occupancy and the * sign signifies residues pointing inside the triptycene pockets). At the same time rotation of the triptycene fragment *via* the other C-N bond is also severely slowed down at this low temperature. This is reflected in the 2:1 ratio of the two signal sets representing isomers with the phenyl ring residing in the triptycene pocket I or the two enantiomeric pockets II/II' with roughly equal population (red arrows in Figure 3a). This finding is in very good agreement with the theoretical description.

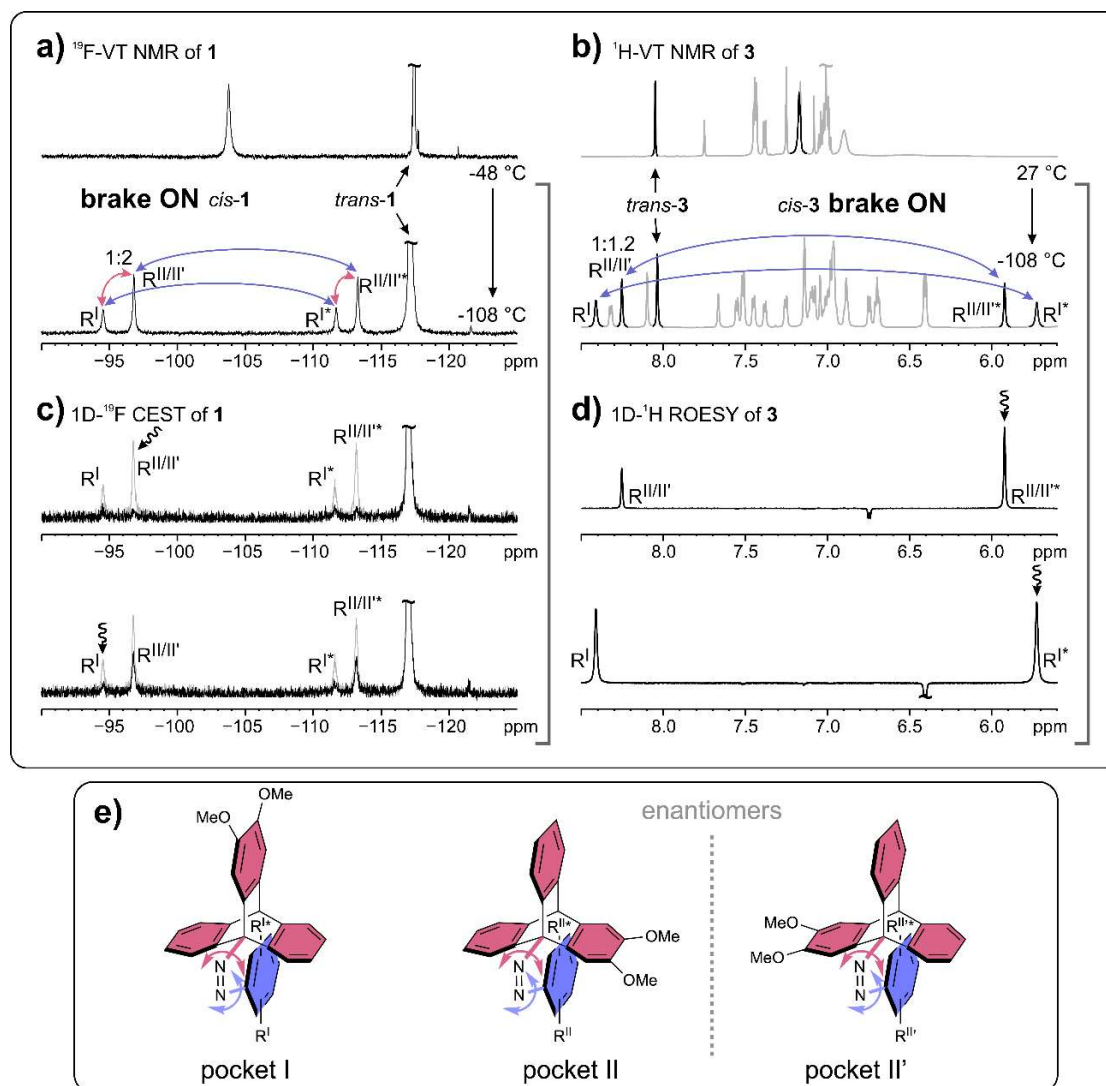


Figure 3. Variable temperature (VT)-NMR spectroscopic investigation of azotriptycenes **1** (left) and **3** (right) showing the split-up of *cis*-**1** (a) and *cis*-**3** (b) signals at $-108\text{ }^{\circ}\text{C}$ compared to the averaged *cis*-signal of *cis*-**1** at $-48\text{ }^{\circ}\text{C}$ and *cis*-**3** at $27\text{ }^{\circ}\text{C}$, respectively (a and b). Mixed *trans* and *cis* isomer compositions were obtained after irradiation of pure *trans*-**1** with 365 nm and of pure *cis*-**3** with 520 nm light. Rotational exchange (blue and red arrows) at $-108\text{ }^{\circ}\text{C}$ between the different intermeshed states with occupied pockets I and II/II' (e) was identified for *cis*-**1** *via* 1D- ^{19}F CEST; the grey spectra in the background correspond to control experiments without saturation (c). For *cis*-**3** 1D- ^1H ROESY was applied to detect rotational exchange (d). Residues R that point inside the respective pockets are labeled with * (e.g. R^{I*} or R^{II*}) while residues R pointing away from the pocket bear no further label.

Identical experiments of azotriptycene **3** show a very similar behavior. For the phenyl signals of *trans*-**3** no signal splitting is observed even at $-108\text{ }^{\circ}\text{C}$. For *cis*-**3** two sets of signals are received in a 1:1.2 ratio for pocket I and II/II' at low temperatures, which again shows concomitant slowed down rotation of both C-N single bonds (Figure 3b). The pocket, in which the phenyl ring is located (pocket I or II/II'; see Figure 3e) can easily be identified by the total number of signals in each signal set. For the signals R^I and R^{I*} only one subset of aromatic signals was found for the two unsubstituted triptycene blades. Therefore, R^I and R^{I*} can be assigned to the structure with pocket I occupied by the phenyl ring. Accordingly, for $R^{II/II'}$ and $R^{II/II'*}$ two subsets of aromatic signals were detected for the unsubstituted triptycene blades indicating the structure with pocket II/II' occupied by the phenyl ring (for further details see supporting information, chapter 4.5.6.2). The position of the phenyl rings inside the triptycene pockets within the intermeshed states was furthermore corroborated by 1D- and 2D- ^1H ROESY and ^1H nuclear Overhauser enhancement spectroscopy (NOESY) experiments (see e.g. Figure 3d; for further details see supporting information, chapter 4.5.6.2). All of these experiments reveal exclusive through space magnetization transfers between the two triptycene blades forming the pocket and the phenyl fragment. This reveals spatial proximity, which is only possible in intermeshed states. The most sensitive 1D- ^1H ROESY spectra even showed signals from the phenyl to the back side of the triptycene pockets underpinning the high degree of intermeshing. The increased population of the symmetric triptycene pocket I in *cis*-**3** indicates an impeded occupation of the enantiomeric pocket II/II' compared to azotriptycene *cis*-**1**. In the theoretical description of *cis*-**3** the occupied enantiomeric pocket II/II' is found to be the global minimum, however, sizable populations of all minima are predicted in the calculations because of the small energy differences (for a direct comparison of theoretically predicted and experimentally found minimum populations see ESI). Despite the crowded aromatic region, the protons in *ortho*-position of the phenyl fragment give better separated and also sharper signals than the *tert*-butyl-substituents in *meta*-position. Therefore, these signals were used for the analysis of the different rotational processes.

To evidence the particular motions that lead to signal interconversions at low temperatures, 1D- ^{19}F chemical exchange saturation transfer (CEST) and 1D- ^1H rotating frame Overhauser enhancement spectroscopy (ROESY) were conducted for *cis*-**1** and for *cis*-**3**, respectively (Figure 3c and d). Especially the more modern CEST method has been recently successfully applied to identify exchange processes in various systems.²⁶ In case of exclusive rotation of the phenyl ring within the same triptycene pocket, a specific saturation transfer in the CEST spectra or signal buildup in the ROESY spectra is expected. For example, saturation of one phenyl signal with lower intensity (e.g. R^I in

Figure 3a) would only affect the second signal with equally low intensity (R^{I*}) but not the other phenyl signals ($R^{II/III}$ and $R^{II/III*}$) as highlighted by the blue arrow between R^I and R^{I*} in Figure 3. In contrast, a coupled motion or gearing process would be discernible if saturation of one individual phenyl signal would lead to an analogous intensity change of all other three *cis*-signals. During such gearing process rotation of the phenyl fragment would occur concomitantly with changing the triptycene pocket and thus all four *cis*-signals should be interchanging with the same kinetics.

First, 1D- ^{19}F CEST experiments were conducted for azotriptycene *cis*-**1** at $-108\text{ }^\circ\text{C}$ (Figure 3c). Selective saturation of one *cis*-**1** ^{19}F NMR signal after another resulted in a signal decrease of all remaining three *cis*-signals but not of the signals of *trans*-**1** or *vice versa* (see e.g. saturation of R^I and $R^{II/III}$ in Figure 3c and for further details the supporting information, chapter 4.5.6.1). This explicitly verifies rotational exchange processes between all four *cis*-signals. At first glance this exchange profile would be also occurring in a gearing process. However, in a real gearing process the rates of rotation for the phenyl C-N bond and for the triptycene C-N bond must be identical. To differentiate between gearing and independent rotations and most importantly, to quantify the braking effect a reliable kinetic analysis of the rotational processes is required. The applied CEST experiments are only qualitative and so far there is only a single quantitative CEST analysis of a defined four side exchange published.²⁷ Therefore, 1D selective EXSY buildup experiments were selected to perform a kinetic analysis (see below). Before, the rotational exchange processes of azotriptycene **3** will be discussed (see Figure 3d). In contrast to azotriptycene **1**, azotriptycene **3** does not contain ^{19}F substituents, therefore a similar facilitated analysis using ^{19}F signals is not possible. For azotriptycene **3** a ^1H ROESY pulse sequence is the best choice instead, since two different and clearly distinguishable pieces of information can be obtained. First, selective excitation and chemical exchange yield signals with positive intensity. Second, possible additional negative signals would evidence spatial proximity between the two protons enabling efficient Overhauser effects. In response to excitation of R^{I*} and $R^{II/III*}$ signals of *cis*-**3** only the signals with same intensity (R^I and $R^{II/III}$, respectively) were detected as corresponding positive signals, but no magnetization transfer to the second set of phenyl-signals could be observed ($R^{II/III*} \nrightarrow R^{I*}$ or R^I and $R^{I*} \nrightarrow R^{II/III*}$ or $R^{II/III}$; see Figure 3d)). These experiments unambiguously show selective rotation of the phenyl groups within their respective triptycene pockets without detectable pocket interchange at a mixing time of 200 ms.

To obtain the rate constants and Gibbs energies of activation for both decelerated C-N single bond rotations of azotriptycene *cis*-**1** and *cis*-**3** experimentally, series of 1D selective EXSY spectra with incremented mixing time were recorded at $-108\text{ }^\circ\text{C}$. For rate

determination exclusively signals within the initial linear buildup were used, leading e.g. for the determination of the decelerated phenyl C-N bond rotation to extremely short maximal mixing times of 2.0 ms for azotriptycene *cis*-**1** and 12.5 ms for azotriptycene *cis*-**3** (see Figure 4). To receive reliable signal to noise ratio for the kinetic analysis the extremely small intensities of the resulting signals were compensated by up to 22,000 scans for azotriptycene *cis*-**1**. Furthermore, nuclear Overhauser effect (NOE) interactions may contribute to this EXSY buildup in *cis*-**1**. To exclude NOE interaction from potentially disturbing the EXSY buildup interpretation, model compound **2** was investigated. Compound **2** has among other important prerequisites an equal distance between the two fluorine substituents as found in **1** (for further details see supporting information, chapter 4.5.7.1). In **2** no magnetization transfer between the two fluorine atoms was observed under identical experimental conditions evidencing that exclusively rotational exchange has to be considered for the kinetic analysis of *cis*-**1**. Since the distances of *meta*-F-F for *cis*-**1** and *ortho*-H-H for *cis*-**3** are similar an absence of interfering NOE interactions is also assumed for quantifying the braking kinetics of *cis*-**3**.

Under the established experimental conditions now the initial linear buildup and the initial intensity of the selectively saturated signal (I_0) can be used to determine the rates for these intramolecular exchange processes classically applied for intermolecular exchange processes.^{26a,28} At $-108\text{ }^{\circ}\text{C}$ the respective kinetic analysis for *cis*-**1** delivers a rate constant of $k = 136\text{ s}^{-1}$ and an associated experimentally determined Gibbs energy of activation of $\Delta G^{\ddagger} = 7.85\text{ kcal/mol}$ for the phenyl rotation in the enantiomeric triptycene pockets (see Figure 4a and b). Due to the extremely low signal to noise ratio for R1 and R1' in combination with short mixing times no conclusive rate constant for the phenyl C-N bond rotation within the unsubstituted pocket I could be obtained. For triptycene rotation, leading to pocket I to pocket II/II' change for the phenyl ring, a rate constant of $k = 21.5\text{ s}^{-1}$ and an associated Gibbs energy of activation of $\Delta G^{\ddagger} = 8.46\text{ kcal/mol}$ was obtained; and for the corresponding triptycene rotation interchanging pockets II/II' and I the values are $k = 11.1\text{ s}^{-1}$ and $\Delta G^{\ddagger} = 8.68\text{ kcal/mol}$.

Care has to be taken when comparing theoretically obtained rate constants with experimentally obtained ones for rotations around the triptycene axis. (exchanging phenyl-occupation of pocket I with pockets II/II' and pockets II/II' with I, respectively). In this case one has to take into account that the experimentally obtained rate constant k describes the sum of triptycene rotations exchanging phenyl-occupation or pocket I with pockets II/II' and of pockets II/II' with I, but not the sub-process of individual interconversions of each pocket II to I and II' to I, and *vice versa*. Since the enantiomeric interconversions involving pockets II and II' proceed with the same rate constant, the

rate constants for individual sub-rotations can be obtained by dividing the experimentally measured rate constants for the sum-processes of pocket II/II' to I interconversion by a factor of two and by multiplying the rate constant for the net-processes of pocket I to II/II' interconversion with factor of two. For phenyl rotations theoretical and experimental values can be compared directly. The results are summarized in Table 1 (see also the supporting information, chapters 4.5.7.2 and ESI).

Table 1. Summary of the theoretically (B3LYP-D3BJ/6-311G(d,p) PCM (CH₂Cl₂) level of theory for **1** and (B3LYP/6-311G(d,p) PCM(CH₂Cl₂) level of theory for **3**) and experimentally obtained values of Gibbs energies of activation $\Delta G^\ddagger$ and rate constants k for the individual isomerization processes of azotriptycenes **1** and **3**. ^{a)} measured at -108°C .

		$\Delta G^\ddagger$ [kcal/mol]		k [s ⁻¹]	
azotriptycene		Theoretical	Experimental	Theoretical	Experimental
trans-1					
phenyl rot.	II/II' $\rightarrow$ II*/II'*	6.09	/	$3.00 \cdot 10^4$	/
	I $\rightarrow$ I*	5.38	/	$2.61 \cdot 10^5$	/
triptycene rot.	II $\rightarrow$ I / II' $\rightarrow$ $\rightarrow$ I	2.30	/	$6.22 \cdot 10^9$	/
	I $\rightarrow$ II / I $\rightarrow$ II'	2.61	/	$6.05 \cdot 10^8$	/
	II/II' $\rightarrow$ II'/II	1.33	/	$5.98 \cdot 10^{10}$	/
cis-1					
phenyl rot.	II/II' $\rightarrow$ II*/II'*	7.97	7.85 ^{a)}	97.70	135.94 ^{a)}
	I $\rightarrow$ I*	8.43	/	24.05	/
triptycene rot.	II $\rightarrow$ I / II' $\rightarrow$ $\rightarrow$ I	8.01	8.91 ^{a)}	172.98	5.56 ^{a)}
	I $\rightarrow$ II / I $\rightarrow$ II'	8.31	8.24 ^{a)}	17.34	43.00 ^{a)}
	II/II' $\rightarrow$ II'/II	7.08	/	$1.47 \cdot 10^3$	/
trans-3					
phenyl rot.	II/II' $\rightarrow$ II*/II'*	6.18	/	$2.28 \cdot 10^4$	/
	I $\rightarrow$ I*	6.78	/	$3.67 \cdot 10^3$	/
triptycene rot.	II $\rightarrow$ I / II' $\rightarrow$ $\rightarrow$ I	2.23	/	$7.71 \cdot 10^9$	/
	I $\rightarrow$ II / I $\rightarrow$ II'	2.47	/	$9.27 \cdot 10^8$	/
	II/II' $\rightarrow$ II'/II	1.25	/	$7.63 \cdot 10^{10}$	/
cis-3					
phenyl rot.	II/II' $\rightarrow$ II*/II'*	7.68	9.19 ^{a)}	236.41	2.40 ^{a)}
	I $\rightarrow$ I*	7.27	8.61 ^{a)}	824.55	13.38 ^{a)}
triptycene rot.	II $\rightarrow$ I / II' $\rightarrow$ $\rightarrow$ I	7.97	11.45 ^{a)}	195.40	0.0024 ^{a)}
	I $\rightarrow$ II / I $\rightarrow$ II'	7.81	/	79.54	/
	II/II' $\rightarrow$ II'/II	8.66	/	11.93	/

In general, a good agreement is achieved between the theoretically predicted and the experimentally measured absolute ΔG and $\Delta G^\ddagger$ values for *cis*-1. Experimentally it is seen however, that phenyl rotation within the triptycene pockets is fastest and proceeds with a factor of ca. 10 faster than the triptycene rotation. Theory predicts a slightly faster triptycene rotation instead. The corresponding energetic differences are however rather small and lie within the typical error of DFT calculations (within 3 kcal/mol). Because of the experimentally observed significant difference between individual rotations, gearing processes in which both phenyl and triptycene rotations occur simultaneously with the same rate, can be excluded for azotriptycene 1.

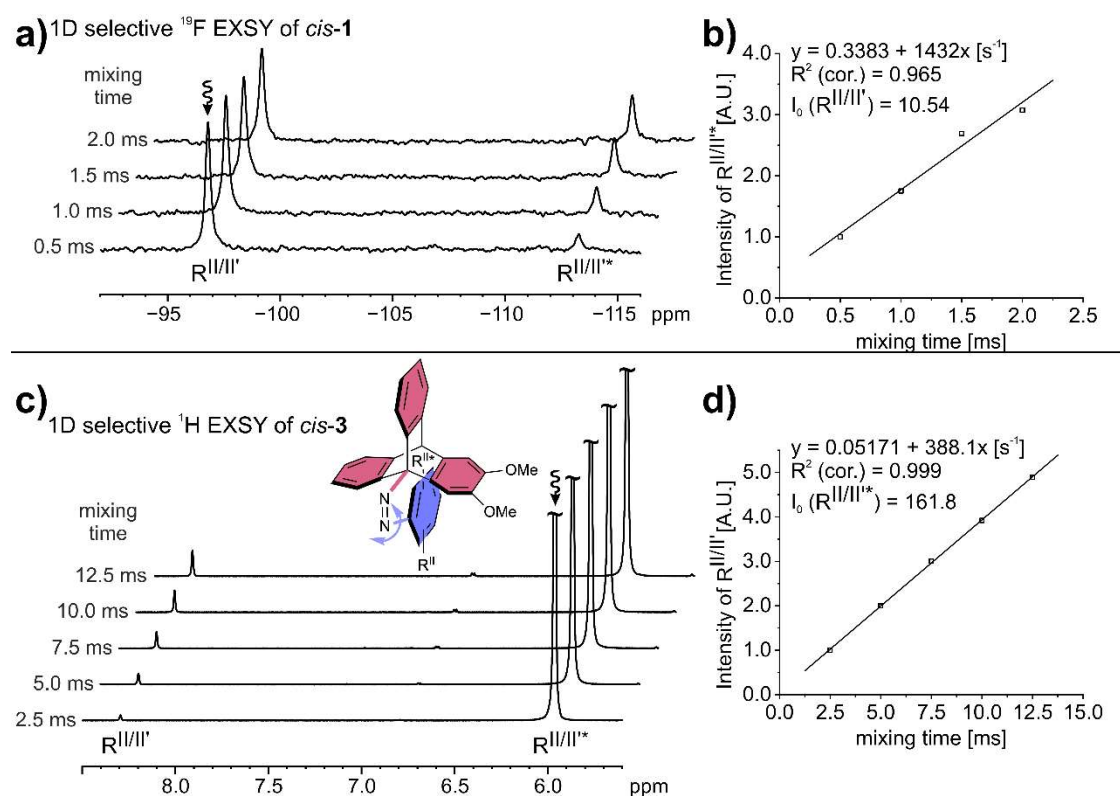


Figure 4. Stacked 1D selective EXSY spectra (a) and (c) at incremented mixing times and corresponding linear plot (b) and (d) to determine the rate constant of the phenyl C-N bond rotation (highlighted by the blue arrow) for *cis*-1 (top, R = *ortho*-F) and *cis*-3 (bottom, R = *ortho*-H) being intermeshed within the enantiomeric triptycene pocket II/II' at -108°C . For details of the kinetic analyses of the other decelerated rotations see supporting information, chapter 4.5.7.2. Residues R that point inside the respective pockets are labeled with * (e.g. $\text{R}^{\text{I}'}$ or $\text{R}^{\text{II}''}$) while residues R pointing away from the pocket bear no further label.

For *cis*-3 the rotation of the phenyl fragment inside the two different triptycene pockets could also be quantified (see Figure 4c and d and supporting information, chapter 4.5.7.2). 1D selective EXSY experiments established rate constants of $k = 2.09 \text{ s}^{-1}$ and $k = 13.4 \text{ s}^{-1}$ and an associated Gibbs energy of activation $\Delta G^\ddagger = 9.22 \text{ kcal/mol}$ and $\Delta G^\ddagger = 8.61 \text{ kcal/mol}$ for the phenyl rotation in pockets II/II' and I, respectively. The rotation of the phenyl C-N bond inside the enantiomeric pocket II/II' with one OMe-

substituted triptycene blade is decelerated by a factor of 6.4 in terms of rate constant compared to the rotation within the unsubstituted pocket I. This can be owed to the increased electron density at the methoxy-substituted triptycene blade and/or to increased steric hindrance with this blade. The 65-times (in terms of rate) stronger phenyl C-N bond deceleration inside pocket II/II' of *cis*-**3** in comparison to *cis*-**1** demonstrates high effectiveness of meta-substituted *tert*-butyl groups for efficient braking. Most likely a combination of repulsive steric and weak attractive interactions is responsible for this behavior. Also similar to *cis*-**1** no coupled gearing rotation is observed in *cis*-**3**. For the corresponding triptycene C-N bond rotation of *cis*-**3** no exchange signals were detected up to 250 ms mixing time. This correlates to a lower limit of $\Delta G^\ddagger = 11.45$ kcal/mol for this rotation (for further details see supporting information, chapter 4.5.7.2). When comparing theory and experimental values for *cis*-**3** again good qualitative agreement is achieved (see Table 1 for a direct numerical comparison). In this case theory also correctly predicts faster phenyl than triptycene rotation, however the absolute $\Delta G^\ddagger$ value for triptycene rotation is found to be higher by at least 3.48 kcal/mol in the experiment.

When linearly extrapolating the values measured at low temperatures to 25 °C, a similar braking efficiency is observed, however on a significantly faster time scale. For azotriptycene **3** the triptycene would thus be slowed down from a half-life of 46 ps (i.e. 2×23 ps, as two triptycene rotations out of three needed for one full rotation encounter very similar barriers and the third barrier is much smaller) in the *trans*-isomer to 0.9 μ s in the *cis*-isomer. Likewise, phenylrotation in **3** would be slowed down from 60 ns in the *trans*-isomer to 600 ns in the *cis*-isomer.

The experimental evaluation thus shows that a significant deceleration of triptycene rotation is achieved in azotriptycenes **1** and **3** when isomerizing from the *trans*- to the *cis*-configuration. A lesser braking effect on the phenyl rotation is also seen in both cases. Thus, braking of intrinsically hindered rotations (e.g. the conjugated phenyl-diazo single bond in azotriptycenes) is clearly less effective than of intrinsically unhindered rotations (e.g. the triptycene rotor in azotriptycenes).

When irradiating with 365 nm light about 20% of the *cis*-isomers can be accumulated in the photostationary state of both azotriptycene **1** and **3**. For azotriptycene **3** it is additionally possible to crystallize the *cis*-isomer and thus revert back to the brake-ON state. Conversely, almost quantitative *cis*- to *trans*-photoisomerization is achieved by irradiation with 520 nm light in both cases. Thus, reversible braking and accelerating of two C-N single bond rotations is possible within azotriptycenes **1** and **3**.

4.4 Conclusion

In conclusion, we present triptycyl-azobenzene based azotriptycenes as light-responsive molecular braking system. Within azotriptycenes **1** and **3** the thermally induced rotation of two molecular fragments, a phenyl and a triptycene rotor, can be decelerated up to five orders of magnitude when isomerizing from the *trans*- to the *cis*-configuration of the central N-N double bond. Braking efficiency is most pronounced for the triptycene rotation as compared to phenyl rotation. Reversible interconversion between the brake ON (*cis* isomer) and OFF (*trans*-isomer) state of azotriptycene **3** is achieved by crystallization and photoisomerization, respectively or by two photoisomerizations at different wavelengths of light. A comprehensive low-temperature NMR analysis directly quantifies the molecular braking and delivers detailed insights into the different molecular motions present in azotriptycenes. The corresponding theoretical analysis is in good agreement with the experiments and allows the design of effective molecular brakes based on azobenzene *in silico*. With the azotriptycene framework an effective molecular braking system is thus developed to serve as new building block for future molecular machinery.

4.5 Supporting Information

4.5.1 General

NMR experiments were performed on a Bruker Avance III HD 600 (600.03 MHz) spectrometer with a 5 mm fluorine selective TBIF probe and TopSpin 3.2. For NMR measurements employing standard NMR solvents 5 mm NMR tubes were used. For *in situ* illumination NMR spectroscopy the reported setup with 5 mm amberized thin wall NMR tubes was applied and for illumination at various peak-wavelengths the following LEDs were used and operated at 1.0 A: LG Innotek LEUVA66X00RV00 (365 nm), CREE XLamp XT-E Royal Blue (450 nm), Osram Oslon SSL 80 (520 nm).²⁹ NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software. ¹H- and ¹³C-NMR spectra were calibrated on the solvent residual peak of CD₂Cl₂ ($\delta(^1\text{H}) = 5.32$ ppm, $\delta(^{13}\text{C}) = 53.84$ ppm). Further plotting of the spectra was performed with Origin 2019 and Corel Draw 2020 software.

4.5.2 Chemicals

Commercially available chemicals were, unless otherwise stated, used without further purification. CD₂Cl₂ was distilled over CaH₂, degassed using the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve. CS₂ as solvent for NMR-spectroscopic investigations was degassed using the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask with 3Å molecular sieve.

4.5.3 NMR Sample preparation

4.5.3.1 Preparation of the NMR samples with standard NMR solvents

An oven dried 5 mm NMR tube, containing the azotriptycene (9 μmol for **1** and **2**, 15 μmol for **3**), was connected to a Schlenk line. For **1** and **2** a 3:1 mixture of anhydrous (anh.) and degassed (deg.) CS₂/CD₂Cl₂ (0.6 mL) was added *via* a syringe under argon atmosphere. **3** was either dissolved in pure anh. and deg. CD₂Cl₂ (0.6 mL) or in a anh. and deg. CS₂/CD₂Cl₂ 1:3 mixture (0.6 mL). The samples were stored at -80 °C in a freezer between the measurements.

4.5.3.2 Preparation of the NMR samples for *in situ* illumination NMR spectroscopy

An oven dried 5 mm amberized thin wall NMR tube, containing the azotriptycene (7.5 μmol for **1** and **3**), was connected to a Schlenk line and either anh. and deg. CD_2Cl_2 (0.3 mL) (**3**) or a 3:1 mixture of anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ (0.3 mL) (**1**) was added *via* a syringe under argon atmosphere. Lastly a *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μm core) was inserted into the NMR tube and fastened with parafilm.²⁹

4.5.3.3 *Ex situ* illumination of azotriptycene **1** NMR samples

An antimagnetic Dewar was filled with diethyl ether and the liquid was cooled to $-60\text{ }^\circ\text{C}$ using liquid nitrogen. The spinner turbine was attached on the prepared NMR sample and the NMR tube was placed in the precooled Dewar. A glass rod illumination setup with an LED emitting at a wavelength of 365 nm was positioned in the Dewar next to the NMR sample and the sample was illuminated for 60 min. After illumination, the illumination setup was removed and the NMR sample was directly transferred from the Dewar to the pre-cooled NMR spectrometer to avoid thermal *cis* to *trans* back-isomerization.

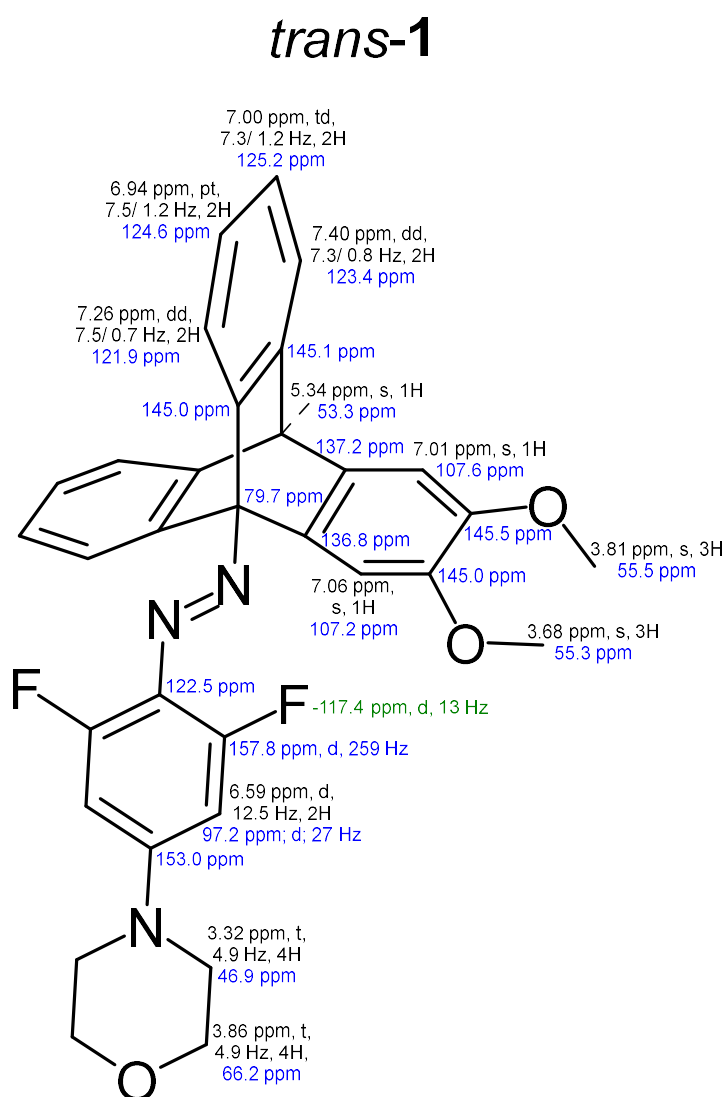


Figure S1. *Ex situ* illumination setup of NMR samples.

4.5.4 Structural elucidation of azotriptycene **1** and **3**

4.5.4.1 Structural elucidation of *trans*- and *cis*-isomer of **1** at $-48\text{ }^{\circ}\text{C}$

To assign the signals for the *trans*- and *cis*-isomer of azotriptycene **1** (Figure S2) a standard set of NMR experiments ($1\text{D-}^{19}\text{F}$; $1\text{D-}^1\text{H}$; $1\text{D-}^{13}\text{C}\{^1\text{H}\}$; $2\text{D-}^1\text{H}$, ^1H correlated spectroscopy (COSY); $2\text{D-}^1\text{H}$, ^{13}C heteronuclear multiple bond correlation (HMBC); $2\text{D-}^1\text{H}$, ^{13}C heteronuclear single quantum coherence (HSQC); Figure S3-S8) was performed at $-48\text{ }^{\circ}\text{C}$ after generating the *cis*-isomer in a ratio of *cis/trans* 13:87 using the *ex situ* illumination setup (Figure S1).



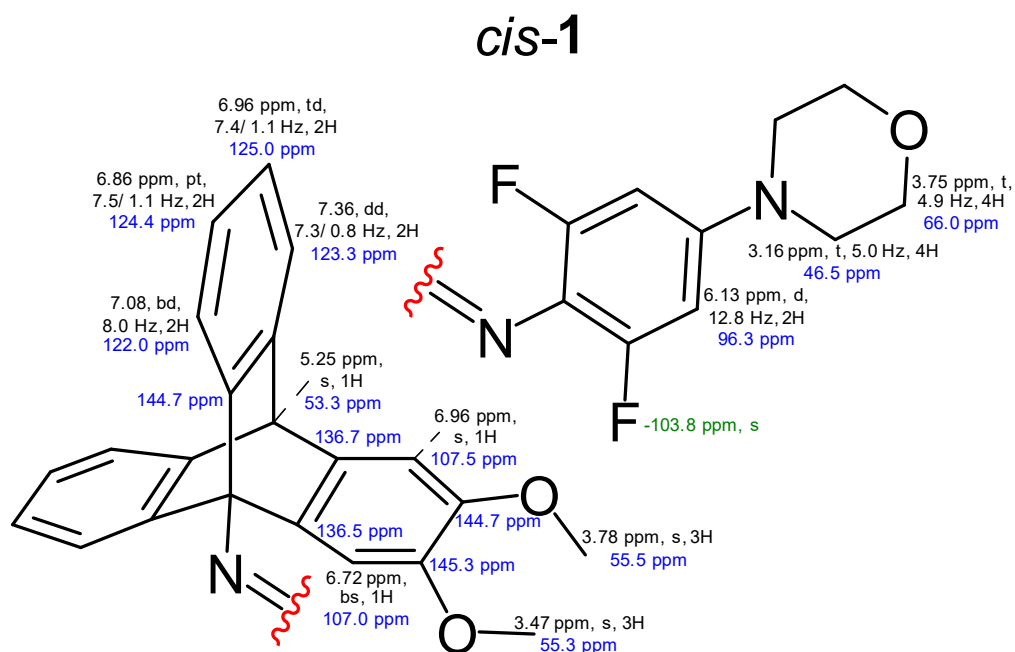


Figure S2. Assignment of *trans*- (top) and *cis*-isomer (bottom) of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. CS₂/CD₂Cl₂ 3:1 at -48 °C. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black, ¹³C blue and ¹⁹F green.

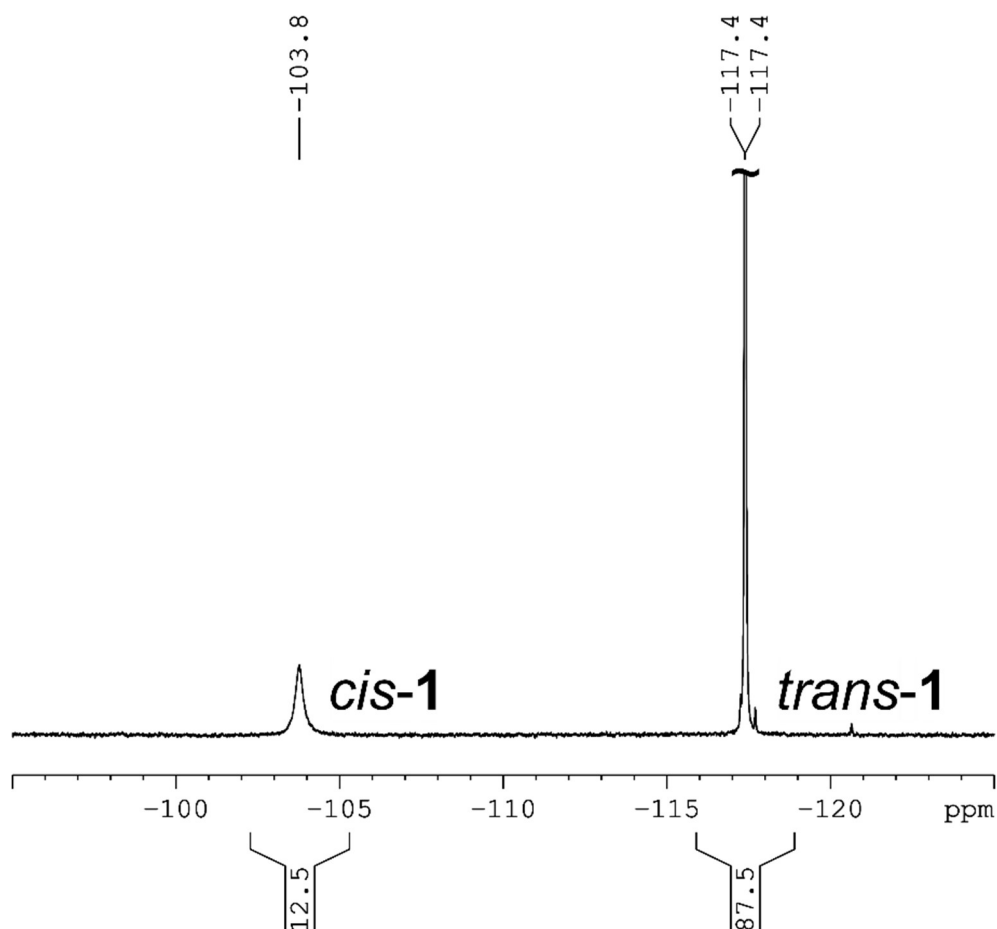


Figure S3. 1D-¹⁹F spectrum (ns = 1024) of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. CS₂/CD₂Cl₂ 3:1 (15 mM) measured at -48 °C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm showing a *trans/cis*-ratio of 87:13.

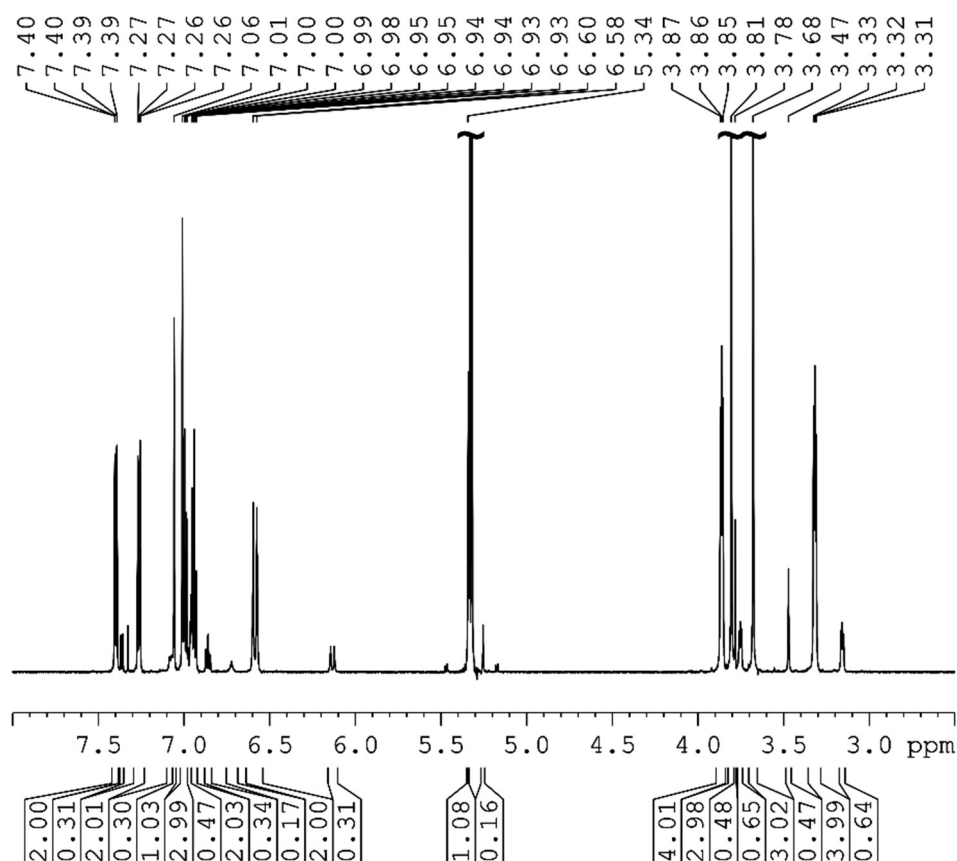


Figure S4. 1D- ^1H spectrum (ns = 16) of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -48°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

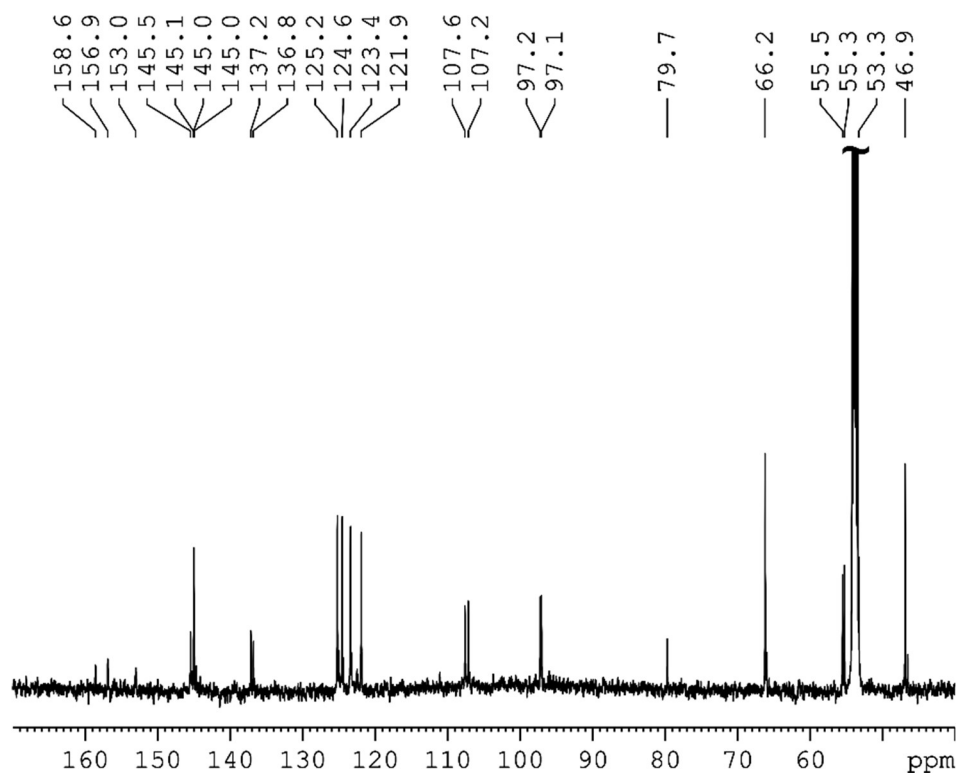


Figure S5. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 11264) of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -48°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

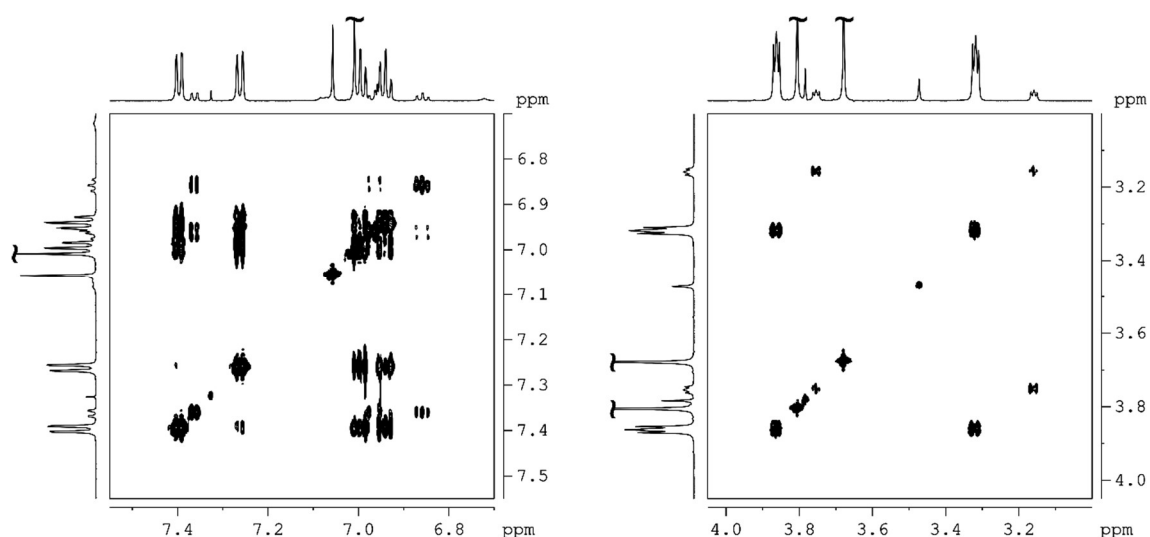


Figure S6. 2D- ^1H , ^1H COSY spectrum of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -48°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm. Left: Section of aromatic protons. Right: Section of aliphatic protons.

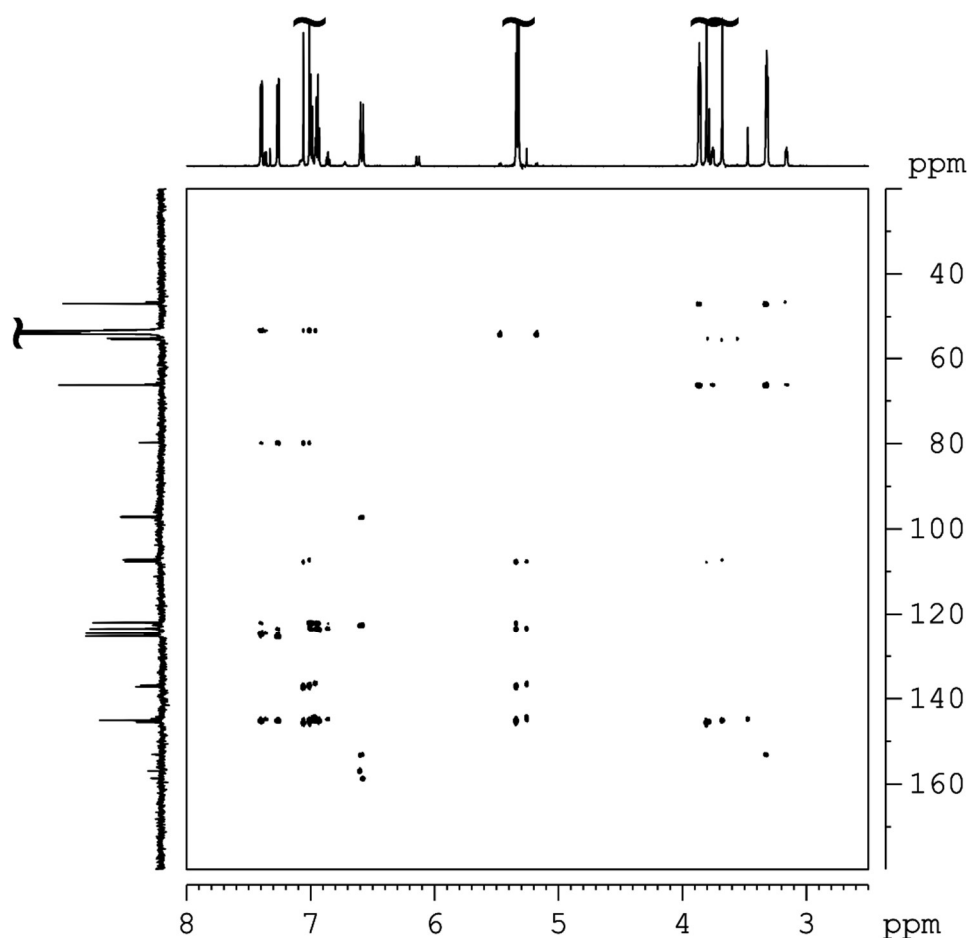


Figure S7. 2D- ^1H , ^{13}C HMBC spectrum of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -48°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

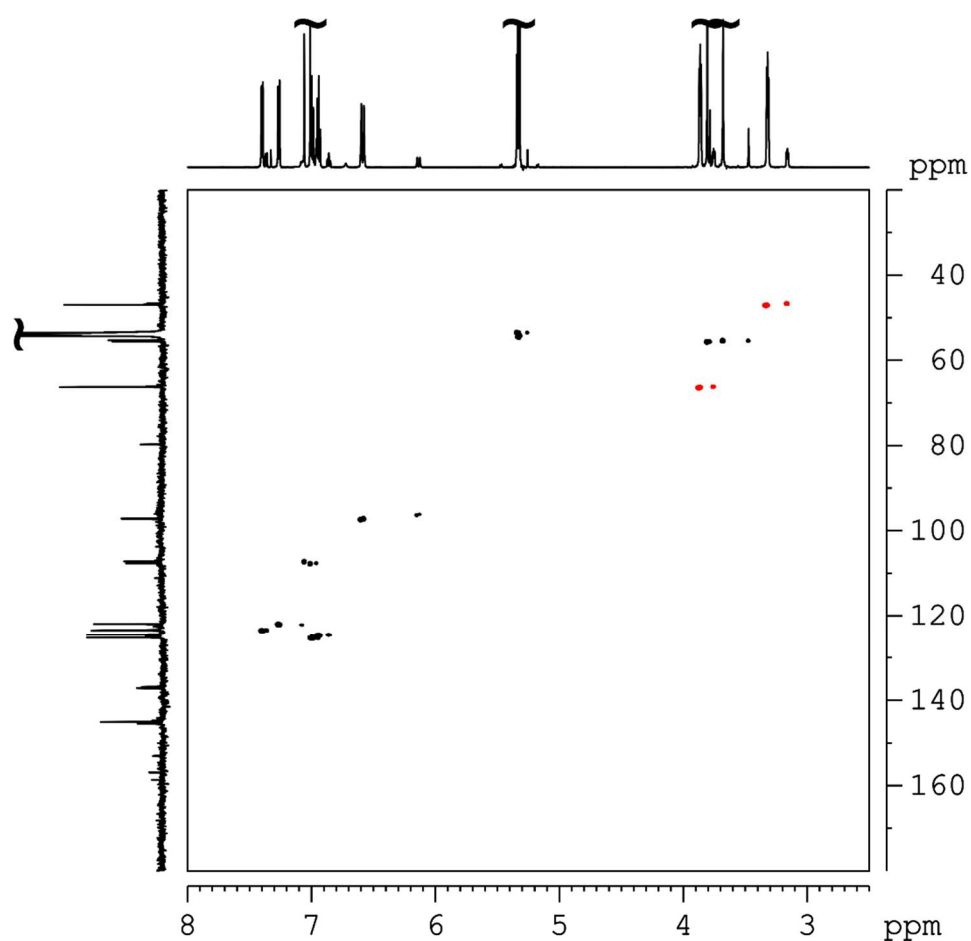
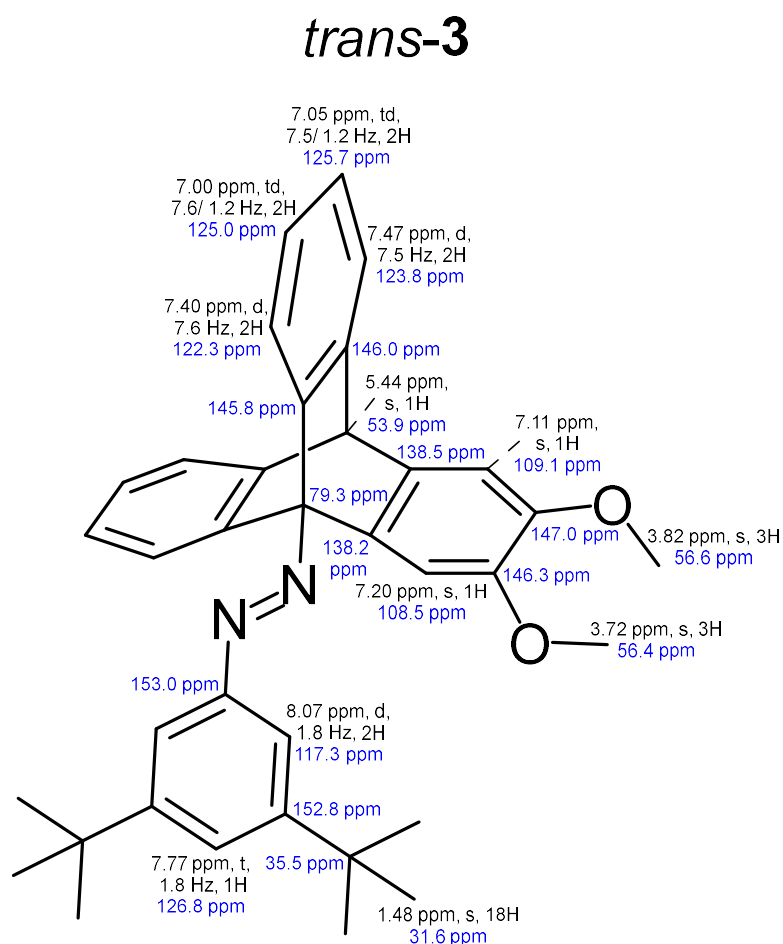


Figure S8. 2D- ^1H , ^{13}C HSQC spectrum of a *cis/trans* mixture of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -48°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

4.5.4.2 Structural elucidation of *trans*- and *cis*-isomer of **3** at 25 °C

To assign the signals for the *trans*- and *cis*-isomer of **3** (Figure S9) a standard set of NMR experiments (1D- ^1H ; 1D- $^{13}\text{C}\{^1\text{H}\}$; 2D- ^1H , ^1H COSY; 2D- ^1H , ^{13}C HMBC; 2D- ^1H , ^{13}C HSQC; Figure S10-S14) was performed at 25 °C. An isomer mixture with *cis/trans* ratio of 62:38 was obtained by *in situ* illumination of a highly *cis*-enriched sample (obtained from the synthesis) with 520 nm light (Figure S1).²⁹



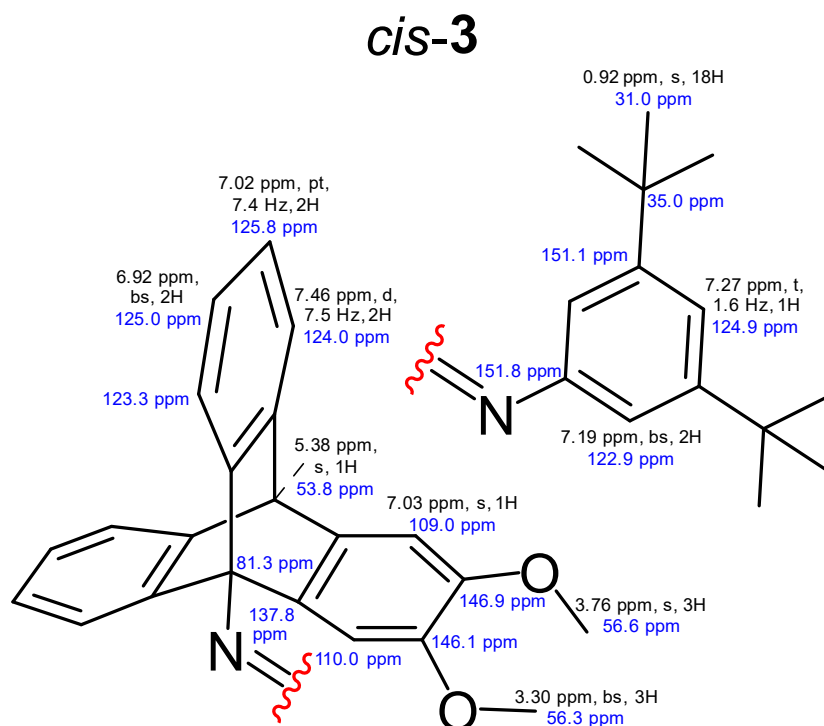


Figure S9. Assignment of *trans*- (top) and *cis*-isomer (bottom) of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD₂Cl₂ at 25 °C. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black and ¹³C blue.

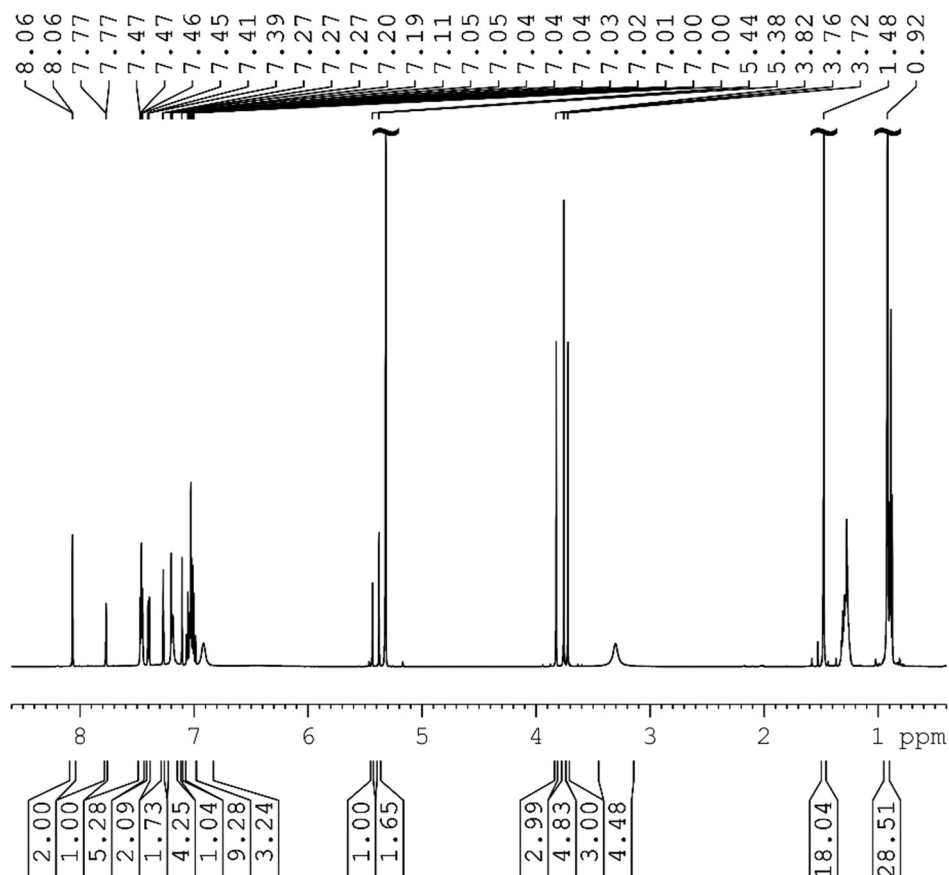


Figure S10. 1D-¹H spectrum (ns = 64) of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD₂Cl₂ (25 mM) measured at 25 °C after *in situ* illumination with an LED emitting at a wavelength of 520 nm showing a *trans/cis*-ratio of 38:62 ≈ 1:1.6.

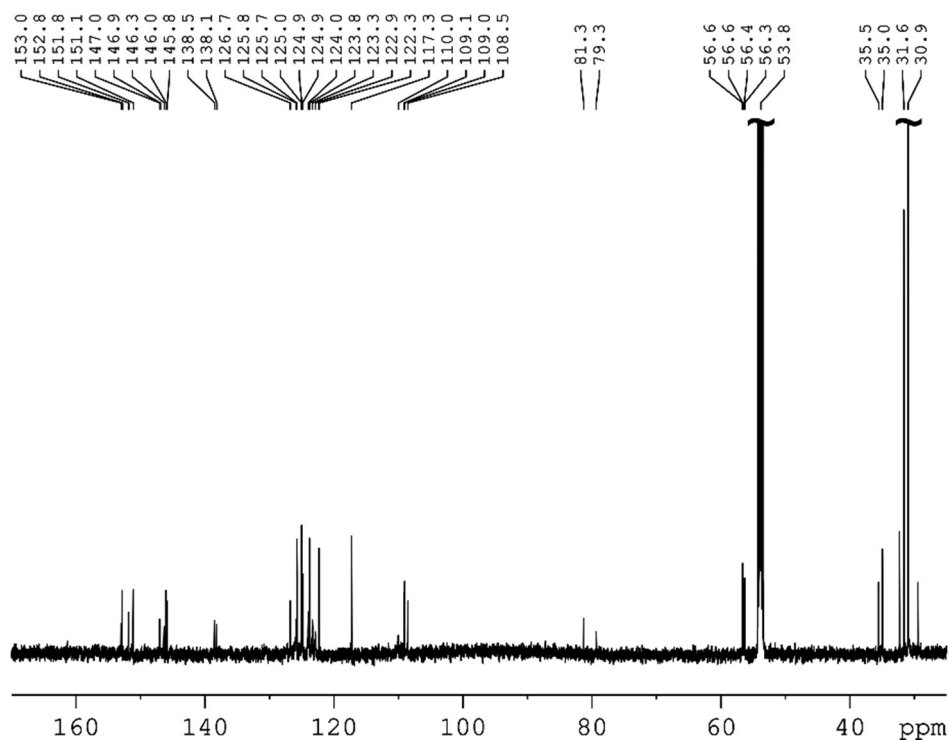


Figure S11. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 8192) of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD_2Cl_2 (25 mM) measured at 25 °C after *in situ* illumination with an LED emitting at a wavelength of 520 nm.

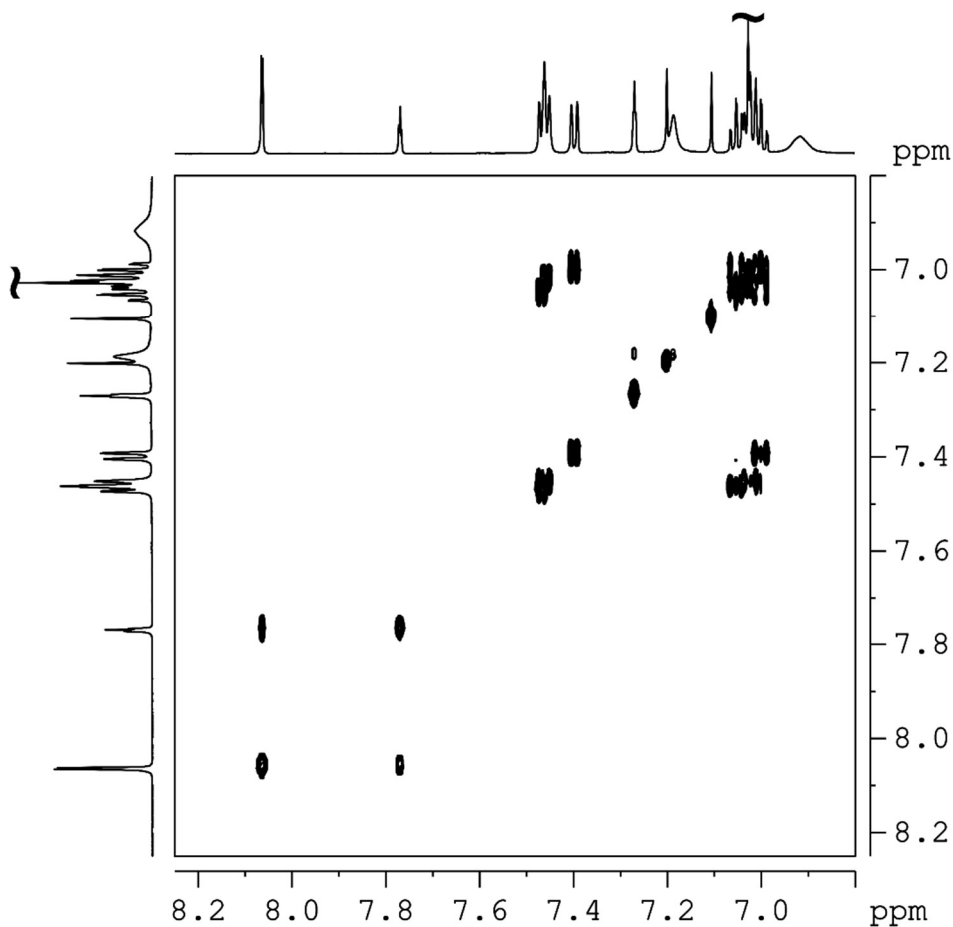


Figure S12. 2D- ^1H , ^1H COSY spectrum of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD_2Cl_2 (25 mM) measured at 25 °C after *in situ* illumination with an LED emitting at a wavelength of 520 nm.

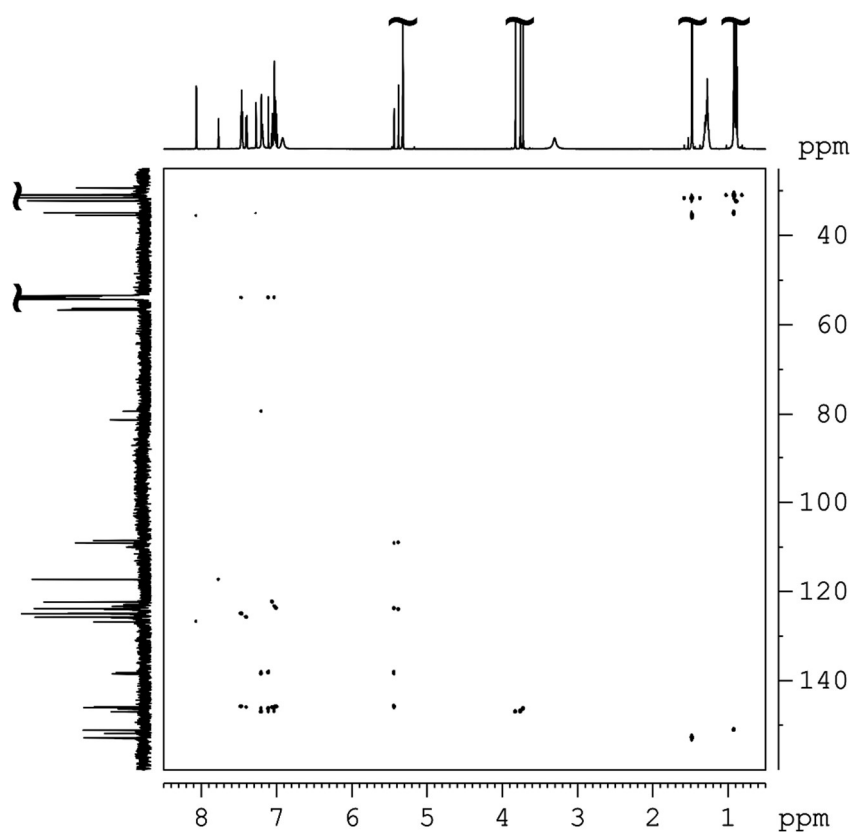


Figure S13. 2D-¹H, ¹³C HMBC spectrum of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD₂Cl₂ (25 mM) measured at 25 °C after *in situ* illumination with an LED emitting at a wavelength of 520 nm.

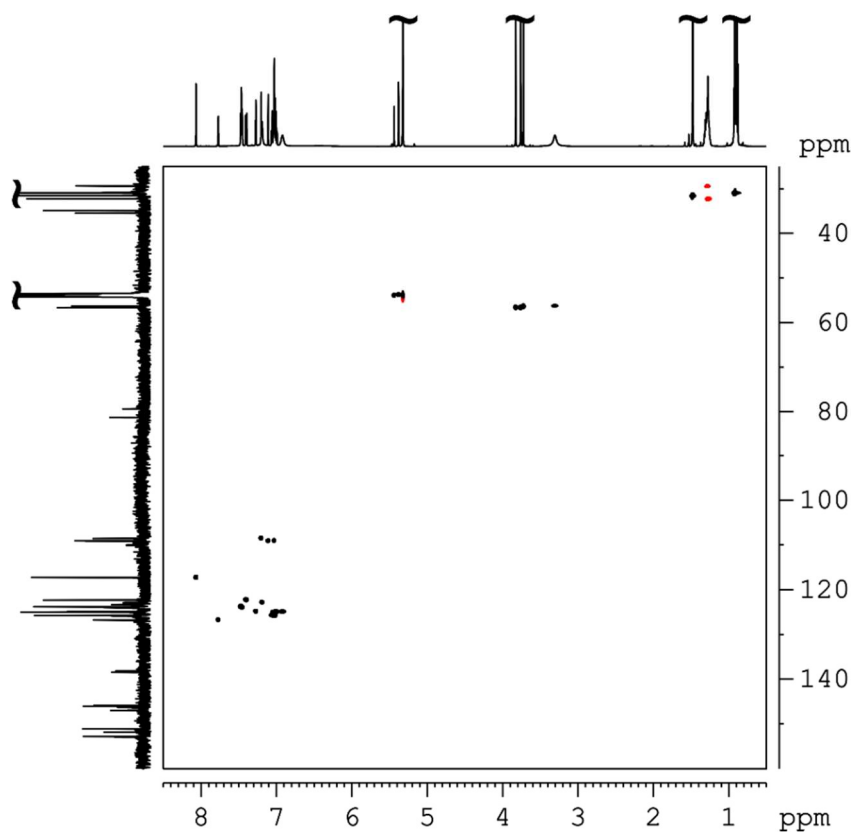


Figure S14. 2D-¹H, ¹³C HSQC spectrum of a *cis/trans* mixture of azotriptycene **3** in anh. and deg. CD₂Cl₂ (25 mM) measured at 25 °C after *in situ* illumination with an LED emitting at a wavelength of 520 nm.

4.5.5 Variable temperature NMR studies of azotriptycenes 1 and 3 and proposed braking mechanisms based on these studies

To gain insight in dynamic processes one must consider the NMR-timescale. At high temperature, dynamic processes like single bond rotations are typically too fast for NMR and yield one averaged signal. Upon decreasing the temperature and thus the rate of conformational exchange between the involved isomers, an averaged signal starts to broaden and splits into new signals, which are arranged equidistant from the averaged signal in case of equal population. This behavior can be easily demonstrated using variable temperature (VT) NMR.³⁰

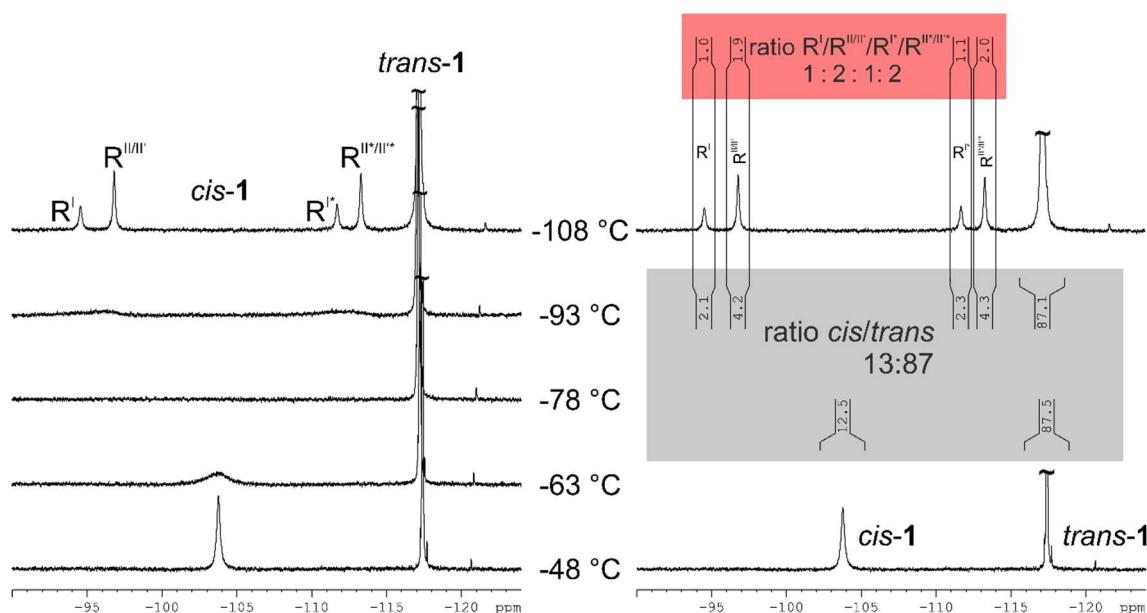


Figure S15. Stacked 1D-¹⁹F spectra (ns = 1024) of azotriptycene **1** in anh. and deg. CS₂/CD₂Cl₂ 3:1 (15 mM) measured at different temperatures (–48 °C – –108 °C) after *ex situ* illumination with an LED emitting at a wavelength of 365 nm. Left: With decreasing temperature, splitting of the averaged *cis*-signal into four new signals can be observed. Right: Similar *cis*/*trans* ratios at –48 °C and –108 °C underpin that the four new signals correspond to *cis*-configured isomers (grey box). A ratio of 1:2:1:2 for R^I/R^{II/III}/R^{I*}/R^{II*/III*} (red box) hints at the described intermeshing mechanism with II and II* being magnetic equivalent (see Figure S18). In contrast, *trans*-1 experiences no signal splitting even at the lowest temperature.

At –48 °C only one averaged *cis*-isomer signal is present for azotriptycene **1** due to fast rotation. Decreasing the temperature in 10 °C steps results, after coalescence at approximately –78 °C, in a set of four signals, on both sides of the averaged signal at –48 °C. Similar *cis*/*trans* ratios of 13:87 at –48 °C and –108 °C suggest that the four new signals correspond to *cis*-configured isomers (Figure S15 right, grey box). The four signals, with a ratio of 1:2:1:2 for R^I/R^{II/III}/R^{I*}/R^{II*/III*} (Figure S15 right, red box) hint at the described intermeshing mechanism (Figure S18). No splitting of the *trans*-1 signal could be detected within the investigated temperature range. Hence, this configuration isomer

does not experience pronounced braking of the phenyl or triptycene C-N bond rotation in contrast to *cis*-1.

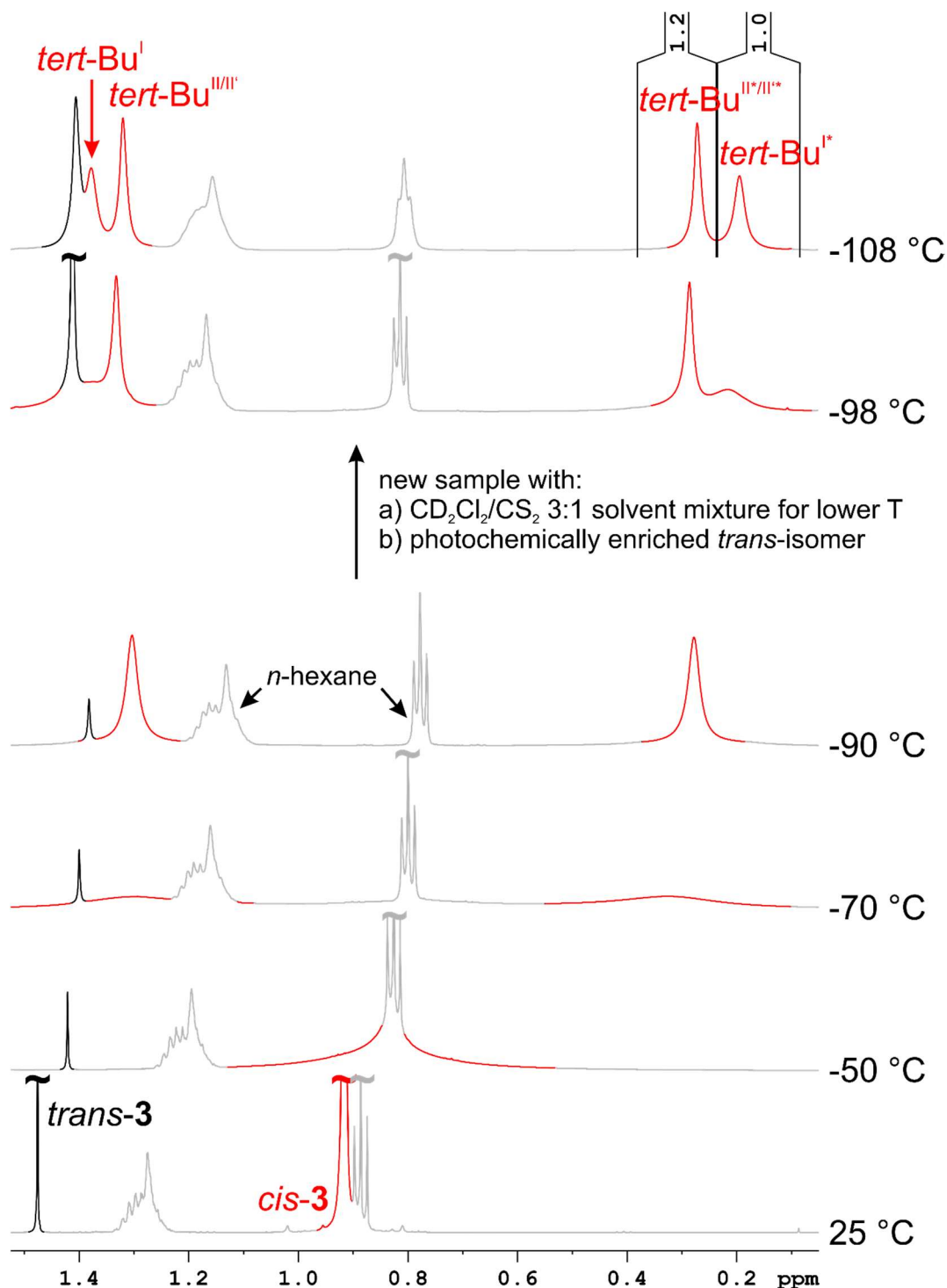


Figure S16. Stacked $1D-^1H$ spectra (ns = 16 - 64) of azotriptycene **3** in anh. and deg. CD_2Cl_2 (25 mM) (bottom) and anh. and deg. CD_2Cl_2/CS_2 3:1 (25 mM) (top) measured at different temperatures (25 °C - -108 °C). With decreasing temperature, splitting of the averaged *cis*-3 signal (highlighted in red) into at first two new signals can be observed. Further lowering of the temperature by applying a solvent mixture results in a second split-up in a total of four signals, which suggests a similar intermeshing based braking mechanism as for azotriptycene **1** (see Figure S18). No splitting could be observed for *trans*-3 (highlighted in black). The two grey signals belong to residual traces of *n*-hexane.

For azotriptycene **3**, also a splitting of the at 25 °C averaged *cis*-signal of the *meta-tert*-butyl substituents occurs at low temperatures (Figure S16). Lowering the temperature results first in a broadening of the *cis*-isomer signal. After a coalescence of the signal in the temperature range of –50 °C –70 °C, two new *tert*-butyl signals are obtained at –90 °C. They appear on both sides of the averaged *tert*-butyl signal at 25 °C. Applying a solvent mixture of anh. and deg. CD₂Cl₂/CS₂ 3:1 enables further cooling below –90 °C. Due to that an additional splitting can be observed at –108 °C. Similar to azotriptycene **1**, the *cis*-signal is now split into four new signals (highlighted red). The same intensities of one down- and one upfield-shifted signal (*tert*-Bu^I and *tert*-Bu^{I*} or *tert*-Bu^{III'} and *tert*-Bu^{II*/II*}) suggest also an intermeshing mechanism with the upfield-shifted substituent pointing into the triptycene pocket (see Figure S18). However, the ratio of *tert*-Bu^{II*/II*}/*tert*-Bu^{I*} 1.2:1 is not in accordance with evenly occupied triptycene pockets. The *trans*-**3** signal (highlighted black) remains as *trans*-**1** a singlet regardless of the applied temperature.

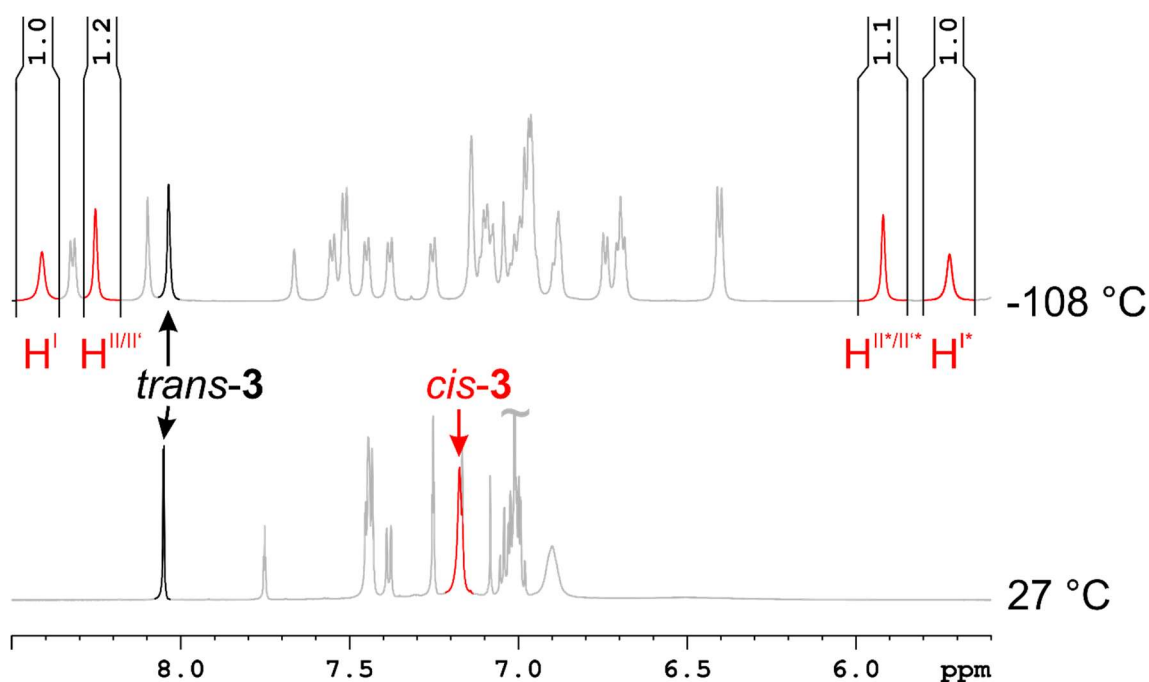


Figure S17. Stacked 1D-¹H spectra (ns = 64) of azotriptycene **3** in anh. and deg. CD₂Cl₂/CS₂ 3:1 (25 mM) measured at different temperatures (27 °C - –108 °C) showing the aromatic region. With decreasing temperature, splitting of the at 27 °C averaged *cis*-**3** signal (highlighted in red) into a total of four signals at –108 °C can be observed. For the *trans*-**3** signal (highlighted in black) only a slight line broadening could be detected. For better visibility of the relevant *cis* and *trans* signals, the remaining NMR spectrum was colored grey.

Similar splitting and ratios can be observed for the *ortho*-H substituents of *cis*-**3** (Figure S17). At 27 °C *cis*-**3** is present as one averaged signal. At –108 °C, on the other hand, it is split fourfold. Two signals are shifted downfield and two upfield compared to the averaged signal at 27 °C. The two outer (H^I and H^{I*}) and inner signals (H^{III'} and H^{II*/II*})

are of same intensity. The ratio within one downfield (H^I and $H^{II/III}$) or upfield shifted signal set (H^I and $H^{II/III}$) is ca 1:1.2. As for the *tert*-butyl signal of *trans*-**3** only a slight line broadening of the *ortho*-H signal (highlighted black) can be observed.

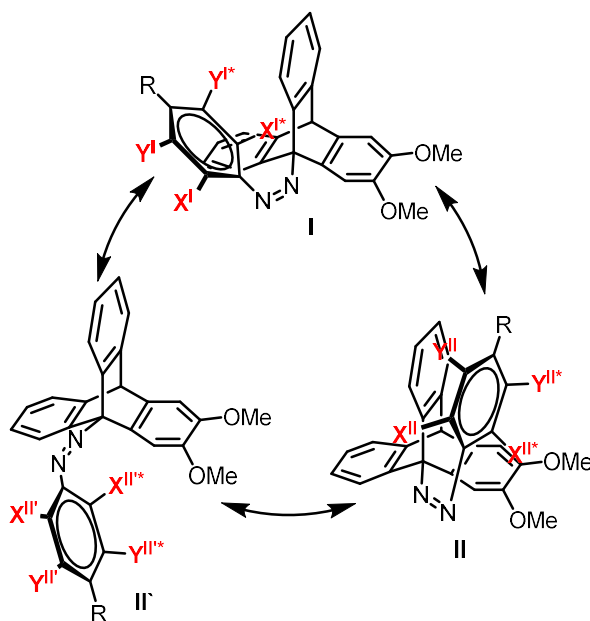


Figure S18. Proposed braking mechanism for *cis*-**1** ($X = F$; $Y = H$, $R = \text{morpholine}$) and *cis*-**3** ($X = H$; $Y = \text{tert-Bu}$, $R = H$). The phenyl fragment of the *cis*-isomers is positioned in such a way to the triptycene rotor blades that intermeshing inside the pockets is enabled. This decelerates the phenyl C-N and triptycene C-N bond rotations. The upfield shifted signal corresponds to the substituent pointing into the triptycene pocket (highlighted with a star *). An interconversion of the phenyl between the different triptycene pockets is also possible. The two structures II and II' (highlighted with an apostrophe) are enantiomers and hence yield the same NMR signals.

Within the *cis*-configuration of azotriptycene **1** and **3**, the phenyl ring is in close proximity to the triptycene backbone. This enables a pointing of the phenyl into one of the different triptycene pockets, called intermeshing. In this intermeshed state the phenyl can rotate within the same triptycene pocket along the phenyl C-N bond. This results in a splitting into two signals with same intensity (X and X^* or Y and Y^* , respectively) in case the rotation is sufficiently decelerated for NMR spectroscopy. The *ortho*- (= X) and *meta*-substituents (= Y) are no longer equivalent and two sets of signals with same intensity X and X^* or Y and Y^* are now detected with the same offset to the averaged *cis*-signal. The one substituent directed inward is shifted upfield and *vice versa*. Additionally, an interchange of the phenyl ring between the different triptycene pockets is possible. A slowed down rotation around the triptycene C-N bond is reflected by the number of signals of X and X^* resp. Y and Y^* . This additional interchange between three differently substituted triptycene pockets would result in six X signals and six Y signals, all of equal intensity and three of them shifted up and the other three shifted downfield. However, since the structures of II and II' represent enantiomers due to the same substitution

pattern of the triptycene pockets, II and II' result in the same NMR signals. A set of four X signals in a ratio of 2:1 (downfield) and 2:1 (upfield) for *cis*-**1** at $-108\text{ }^{\circ}\text{C}$ indicates evenly occupied triptycene pockets (see Figure S15 right, red box). Since no rate constants can be obtained based on these results, it is impossible to give any statement about a possible rotation mechanism, *i.e.* whether individual single bond rotations or simultaneous gearing motions occur. This is also true for of *cis*-**3**, however, the ratio of 1.2:1 of $\text{tert-Bu}^{\text{II*}/\text{III*}}/\text{tert-Bu}^{\text{I*}}$ (Figure S16) and $\text{H}^{\text{II*}/\text{III*}}/\text{H}^{\text{I*}}$ (Figure S17) indicates a favored intermeshing within pocket I for azotriptycene **3**.

4.5.6 Qualitative investigation of the rotational processes within the brake ON state of *cis*-1 and *cis*-3 at $-108\text{ }^{\circ}\text{C}$

4.5.6.1 1D- ^{19}F CEST Studies of azotriptycene **1** at $-108\text{ }^{\circ}\text{C}$

Using chemical exchange saturation transfer (CEST), chemical/conformational exchange between different signals can be detected in various systems.³¹ For this, a signal is selectively saturated leading *via* saturation transfer to a population and hence a signal-intensity decrease for the involved isomers. To get insight in the origin of *cis*-1 signal splitting a series of 1D ^{19}F -CEST experiments was measured by selectively saturating at different ppm values. If the splitting of the *cis*-isomer signals occurs only due to a deceleration of the phenyl C-N bond without a migration in between the triptycene pockets, a saturation of one of the four *cis*-signals should exclusively give a selective saturation transfer to the second signal of same intensity ($\text{R}^{\text{I}} \leftrightarrow \text{R}^{\text{I}*}$ and $\text{R}^{\text{II/III}*} \leftrightarrow \text{R}^{\text{II/III}}$, respectively). In contrast, a response of all three *cis*-signals to selective saturation of the fourth *cis*-signal would suggest gearing, where phenyl C-N and triptycene C-N bond rotations occur at the same rate.

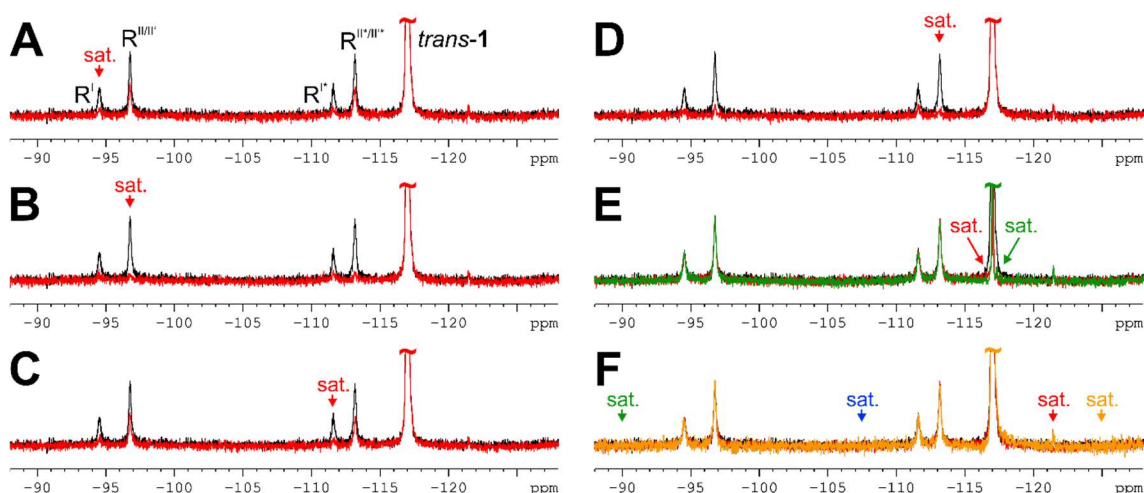


Figure S19. 1D- ^{19}F CEST experiments (ns = 256) of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at $-108\text{ }^{\circ}\text{C}$ with selective saturation at different ppm values. The black spectrum corresponds to the control experiment with saturation pulse power = 1000 $-\text{dBW}$ = 0 W, the overlayed colored spectra correspond to the actual CEST experiments (pulse power = 35 $-\text{dBW}$; puls length = 97.5 ms). **A:** Selective saturation at R^{I} (-94.51 ppm). **B:** Selective saturation at $\text{R}^{\text{II/III}}$ (-96.75 ppm). **C:** Selective saturation at $\text{R}^{\text{I}*}$ (-111.57 ppm). **D:** Selective saturation at $\text{R}^{\text{II/III}*}$ (-113.16 ppm). **E:** Selective saturation at *trans*-**1** (-116.96 ppm resp. -117.05 ppm). **F:** Selective saturation at different points of the baseline (-90.00 ppm, -107.50 ppm, -121.44 ppm, -125.00 ppm).

Selective saturation of one of the four *cis*-signals of **1** at $-108\text{ }^{\circ}\text{C}$ yields a saturation transfer and hence signal reduction of the other three ^{19}F *cis*-signals (Figure S19 A-D). This hints to a gearing process. However, due to a potential multiside exchange process no reliable information about the rate of rotational exchange can be obtained *via* these

CEST experiments, which is crucial to state the existence of gearing. Therefore, gearing is possible by the VT and CEST experiments but not evidenced (for quantitative studies of the rotational rate see chapter 4.5.7.2). The absence of exchange due to e.g. thermal isomerization at $-108\text{ }^{\circ}\text{C}$ between *cis*-**1** and *trans*-**1** is reflected by experiments **A-E**, where saturating one of the *cis*-signals does not yield a saturation transfer to the *trans*-signal (**A-D**) and *vice versa* (**E**). A high selectivity of the saturation pulse can be confirmed, since no intensity decrease of the *cis*- and *trans*-signals can be detected when the baseline is saturated in different areas of the ^{19}F spectrum with the same pulse profile (**F**).

4.5.6.2 Dynamic and structural elucidation of azotriptycene **3** isomers at $-108\text{ }^{\circ}\text{C}$

To investigate the rotational processes of *cis*-**3** within the brake ON state at $-108\text{ }^{\circ}\text{C}$ the rotating frame Overhauser enhancement spectroscopy (ROESY) pulse sequence was applied. Similar to the CEST experiments, exchange processes can be identified qualitatively with this method. Here, selective excitation of one signal yields a positive signal as response for all signals, which are in exchange with the excited signal.

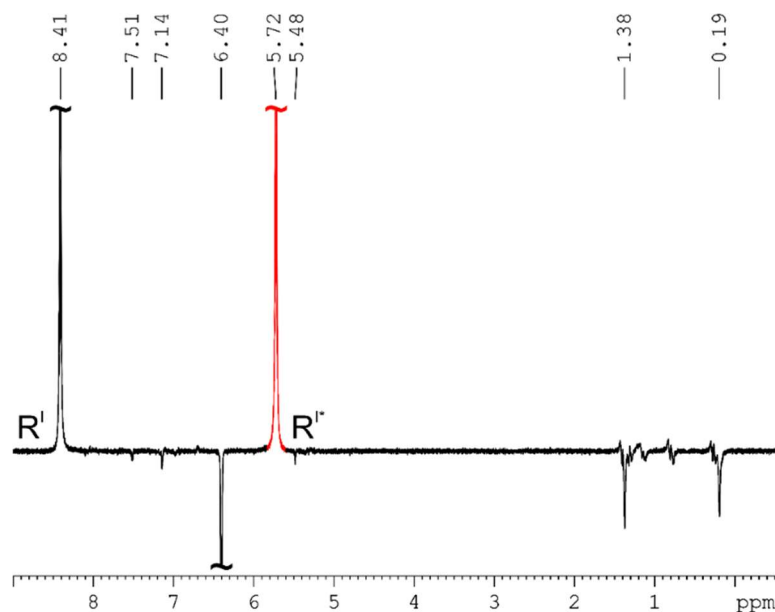


Figure S20. 1D- ^1H ROESY spectrum ($ns = 512$) of *cis*-**3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at $-108\text{ }^{\circ}\text{C}$. The selectively excited signal is highlighted in red (5.72 ppm). Signals with a positive phase are in conformational exchange with the selectively excited signal. In the case signals have a negative phase, there is an ROE to the selectively excited signal.

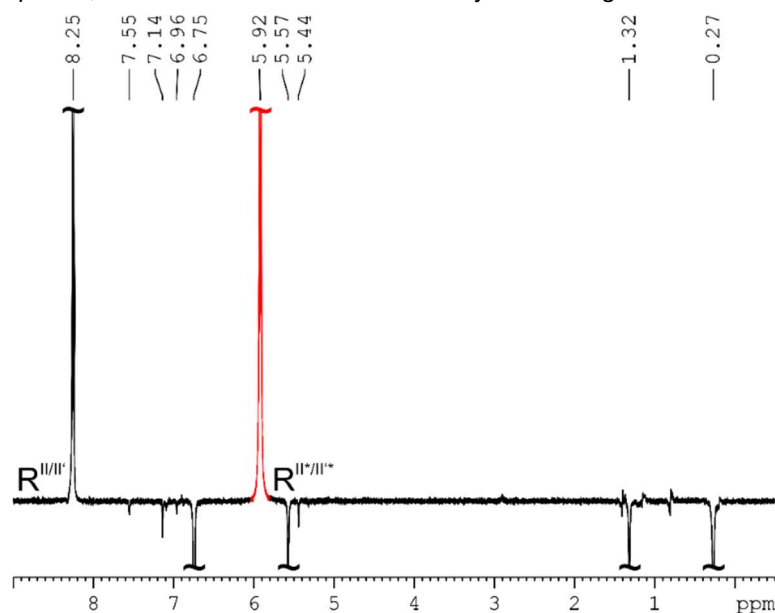


Figure S21. 1D- ^1H ROESY spectrum ($ns = 512$) of *cis*-**3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at $-108\text{ }^{\circ}\text{C}$. The selectively excited signal is highlighted in red (5.92 ppm). Signals with a positive phase are in conformational exchange with the selectively excited signal. In the case signals have a negative phase, there is an ROE to the selectively excited signal.

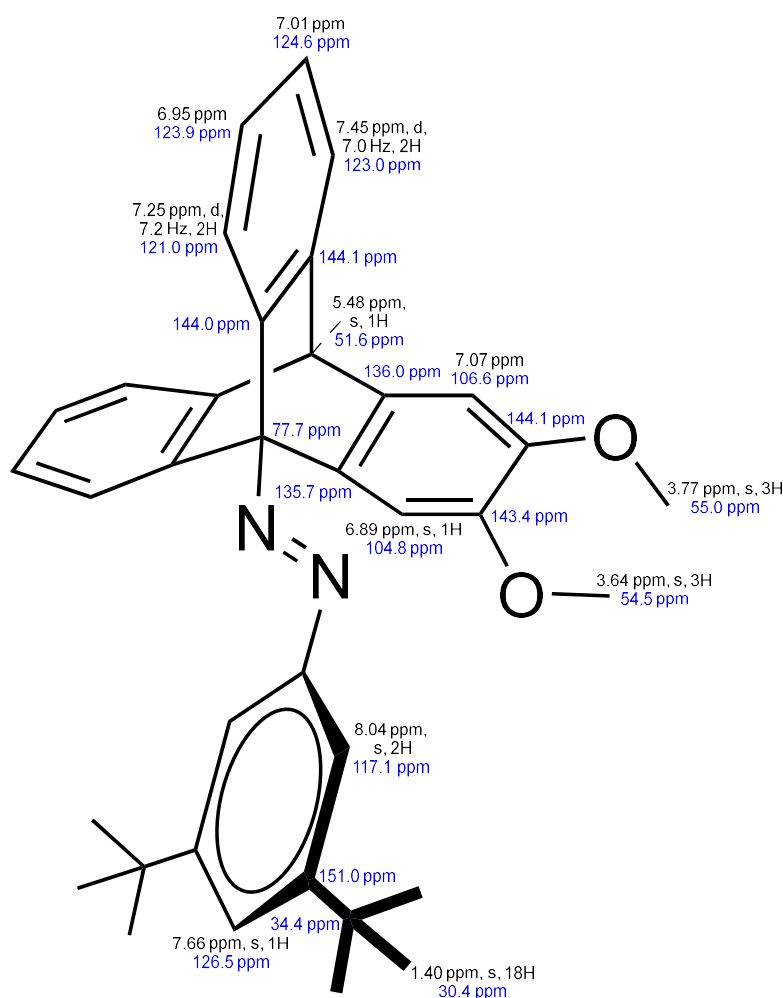
As for *cis*-**1**, one of the phenyl signals of *cis*-**3** was selectively excited, in this case the upfield shifted signals of the *ortho*-H pointing in the unsubstituted pocket I (R^* , see Figure S20) and enantiomeric pocket II/II' ($R^{II*/II'}$, see Figure S21), respectively. In both cases, an exchange to the downfield shifted signal of same intensity ($R^* \rightarrow R^I$ and $R^{II*/II'} \rightarrow R^{II/II'}$, respectively), but not to the second intermeshed state could be detected ($R^* \nleftrightarrow R^{II*/II'}$ and $R^{II/II'}$ or $R^{II*/II'} \nleftrightarrow R^*$ and R^I). This indicates a deceleration of the rotation around the triptycene C-N bond to such an extent, that no exchange is detectable any more.

Two special features of azotriptycene **3** enable a detailed structural elucidation of the intermeshed *cis*-isomer in contrast to **1**: First, *cis*-**3** can be present as the major-isomer. Up to 97% can be obtained, when the sample is freshly prepared and this amount stays reasonably constant as long as thermal *cis* to *trans* isomerization is prevented by sample-cooling. Second, the majority of the corresponding ^1H signals are received as non-overlapping, sharp and intense signals including multiplicity. For the structural elucidation, in addition to a standard set of NMR experiments ($1\text{D-}^1\text{H}$; $1\text{D-}^{13}\text{C}$; $2\text{D-}^1\text{H}$, ^1H COSY; $2\text{D-}^1\text{H}$, ^{13}C HMBC; $2\text{D-}^1\text{H}$, ^{13}C HSQC; Figure S23-S27), a routine $2\text{D-}^1\text{H}$, ^1H nuclear Overhauser enhancement spectroscopy (NOESY) experiment (Figure S28) was supplemented by a $2\text{D-}^1\text{H}$, ^1H ROESY (Figure S29) and for even more sensitivity also a series of $1\text{D-}^1\text{H}$ ROESY experiments (Figure S20 and S21) was performed at $-108\text{ }^\circ\text{C}$ to determine the position of the phenyl within the intermeshed states I and II/II'. Using the ROESY pulse sequence not only exchange processes can be identified, but also spatial proximity *via* Overhauser effects. In this case, signals with negative phase are obtained after selective excitation of another signal. The same information can be received, if the NOESY pulse sequence is applied. However, due to slow tumbling at the low temperatures of $-108\text{ }^\circ\text{C}$, exchange and nuclear Overhauser effect (NOE) signals yield in this case signals with the same phase and are therefore indistinguishable (see Figure S28 and S29 to compare $2\text{D-}^1\text{H}$, ^1H -NOESY and $2\text{D-}^1\text{H}$, ^1H -ROESY).

To identify next to the different intermeshed states of *cis*-**3** also the structure of the *trans*-**3** isomer at $-108\text{ }^\circ\text{C}$, *cis* to *trans* isomerization was triggered by illuminating the prepared NMR sample from the outside with an LED emitting at a peak wavelength of 520 nm until a sufficient amount of *trans*-**3** was present. In this case the *cis/trans* ratio was set to ca. 2.6:1. Three different sets of azotriptycene signals were found, which represent the two distinguishable intermeshing *cis*-**3** structures I and II/II' and also *trans*-**3** (Figure S22). *Trans*-**3** could be clearly assigned to the one azotriptycene signals set, where the opposed phenyl substituents (*ortho*-H and *tert*-butyl) still yield averaged signals due to insufficient deceleration of both C-N single bond rotations (Figure S22 **A**). The two intermeshed *cis*-**3** states can be differentiated by the number of signal sets for the unsubstituted triptycene rotor blades. If the phenyl is positioned in the unsubstituted

tritycene pocket I, both unsubstituted triptycene blades experience the same magnetic environment due to symmetry reasons and thus yield the same signal set (**B**). This symmetry is not present for the intermeshed state with the phenyl being located in the enantiomeric pockets II/II'. Here, the two unsubstituted triptycene blades yield separated sets of signals (**C**). This structural elucidation is further confirmed by distinct Overhauser effect patterns within the different azotriptycene signal sets. The *trans*-configuration could be verified by missing through space magnetization transfer between the phenyl and the triptycene backbone. In contrast, distinct NOEs and ROEs between the respective phenyl and the triptycene pocket forming blades evidence the spatial proximity within the intermeshed states of *cis*-**3** (see Figure S20, S21, S28 and S29).

A *trans*-**3** (free rotating)



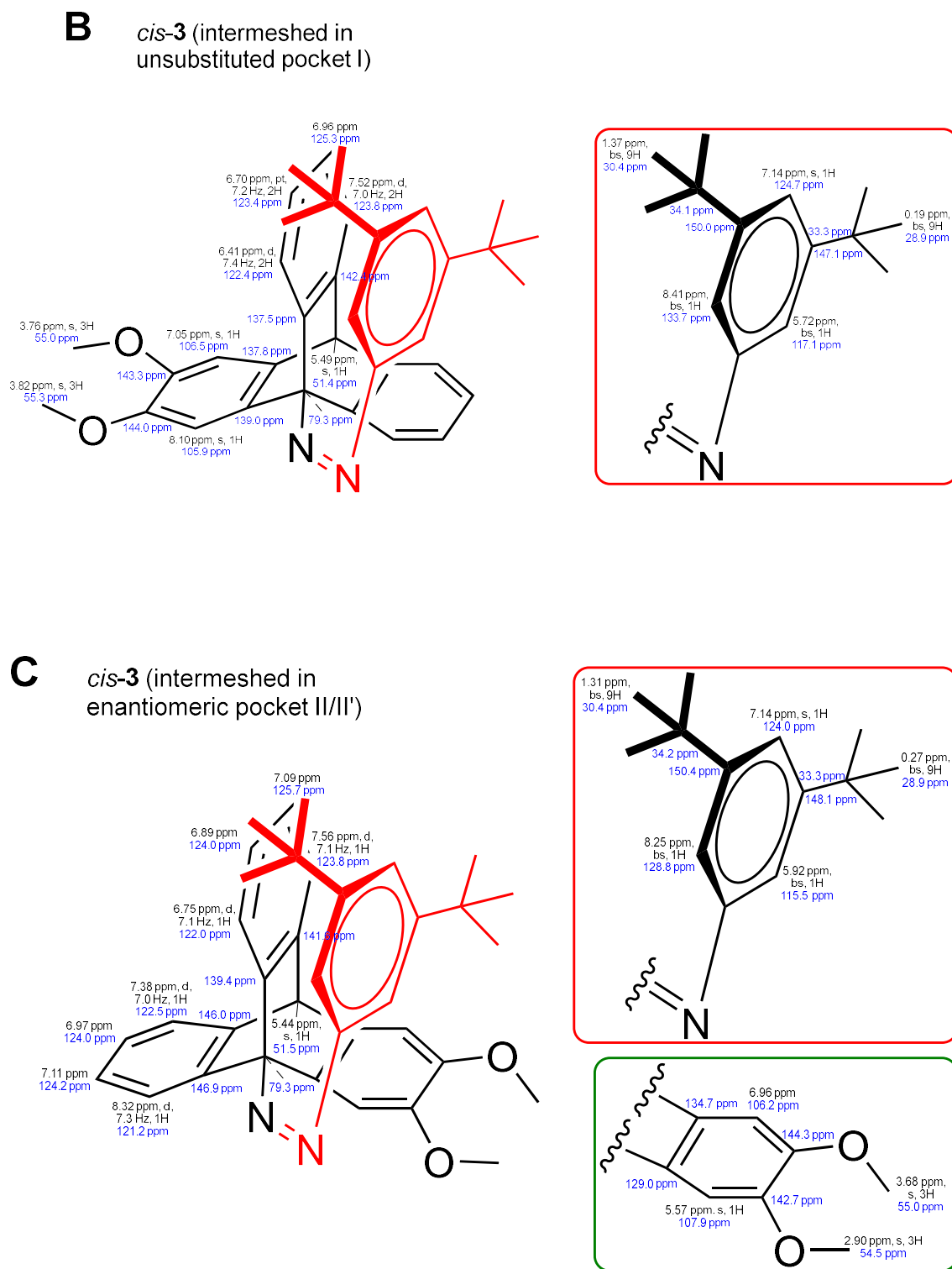


Figure S22. Assignment of the three different structural isomers of azotriptycene **3** in anhydrous and degassed $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) at -108°C . ^1H chemical shift, multiplicity, coupling constants and integral are highlighted black and ^{13}C blue. **A:** Structural assignment of the brake OFF *trans*-3 isomer. **B:** Structural assignment of brake ON *cis*-3 with the phenyl intermeshing in the unsubstituted triptycene pocket I. **C:** Structural assignment of brake ON *cis*-3 with the phenyl intermeshing in the enantiomeric triptycene pockets II/II'.

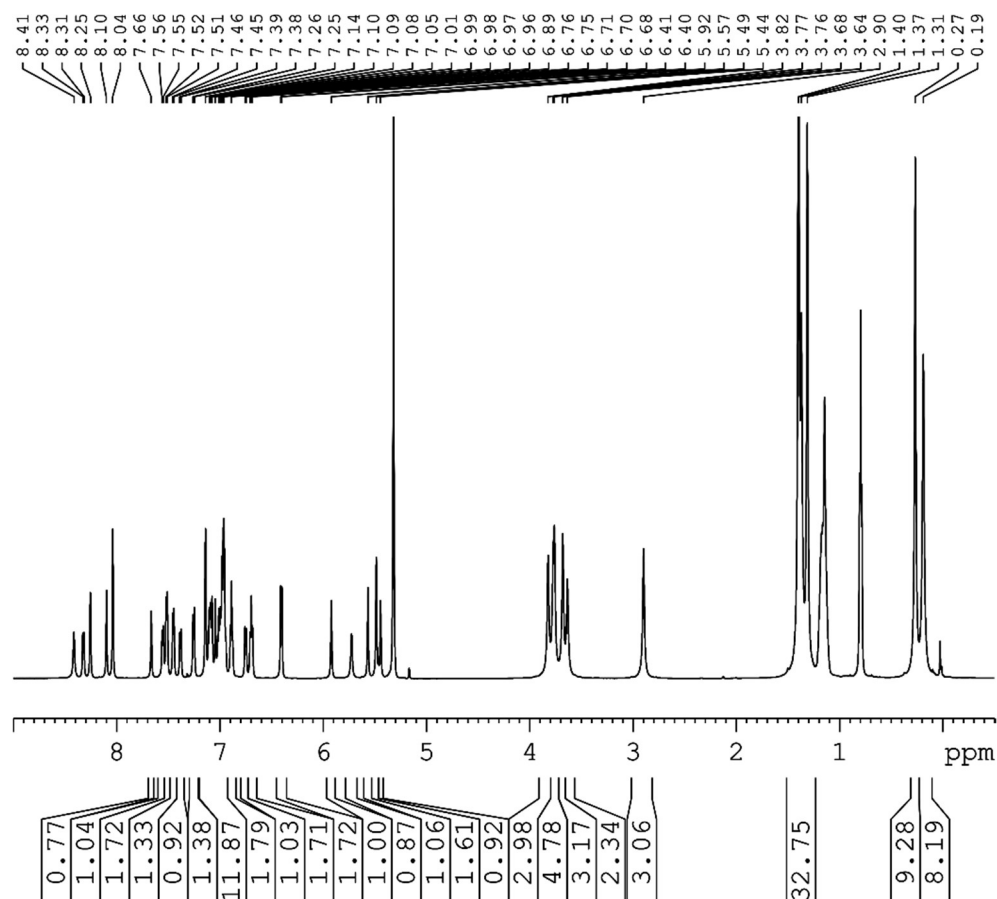


Figure S23. 1D- ^1H spectrum (ns = 64) of azotriptycene **3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at -108°C .

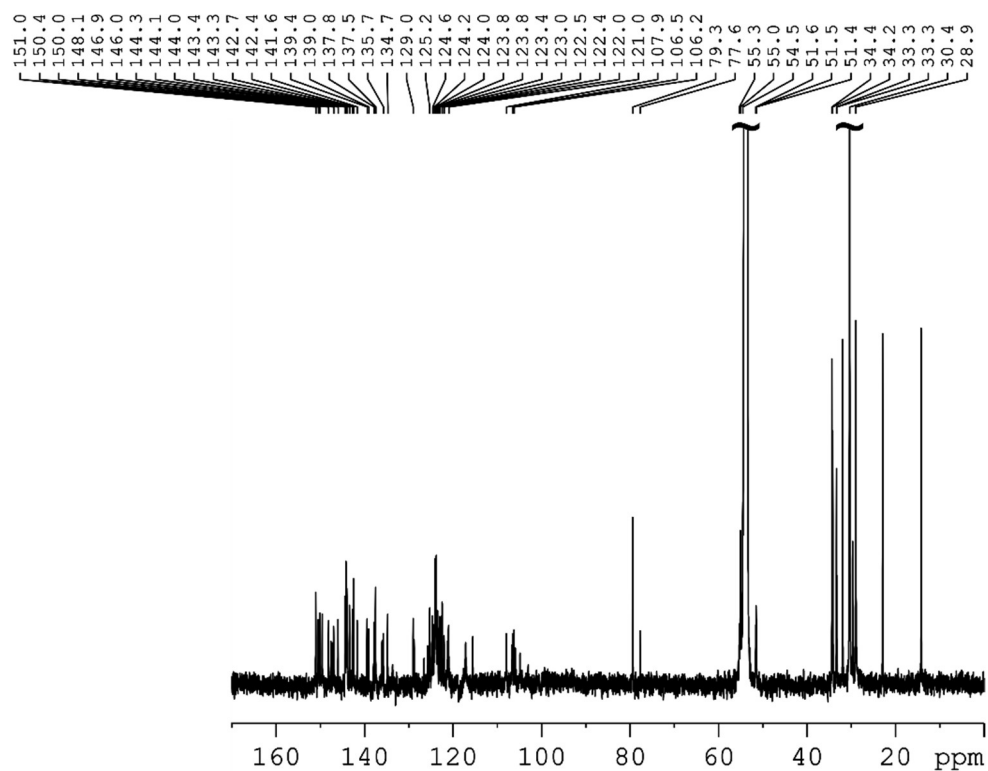


Figure S24. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 8192) of azotriptycene **3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at -108°C .

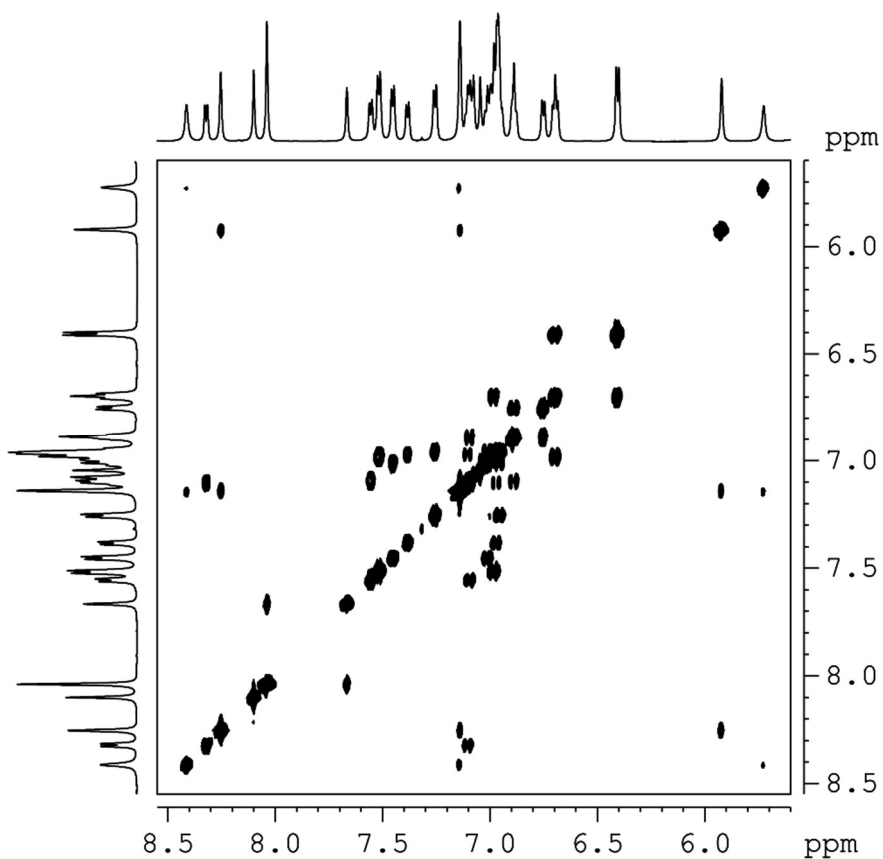


Figure S25. 2D-¹H, ¹H COSY spectrum of azotriptycene **3** in anh. and deg. CD₂Cl₂/CS₂ 3:1 (25 mM) measured at –108 °C.

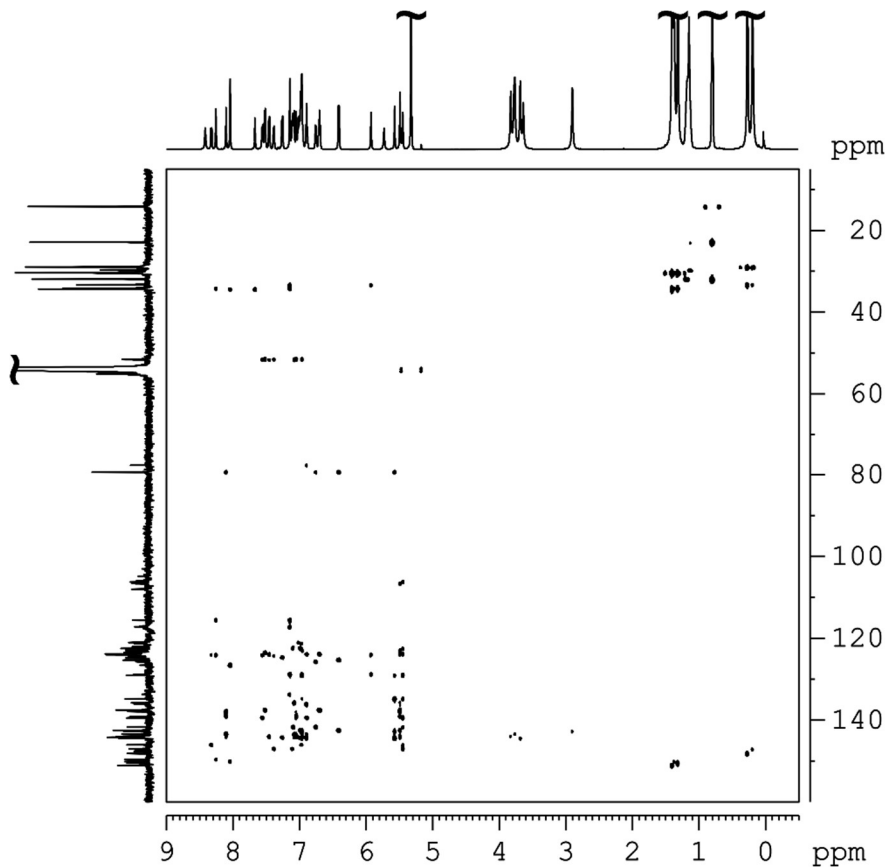


Figure S26. 2D-¹H, ¹³C HMBC spectrum of azotriptycene **3** in anh. and deg. CD₂Cl₂/CS₂ 3:1 (25 mM) measured at –108 °C.

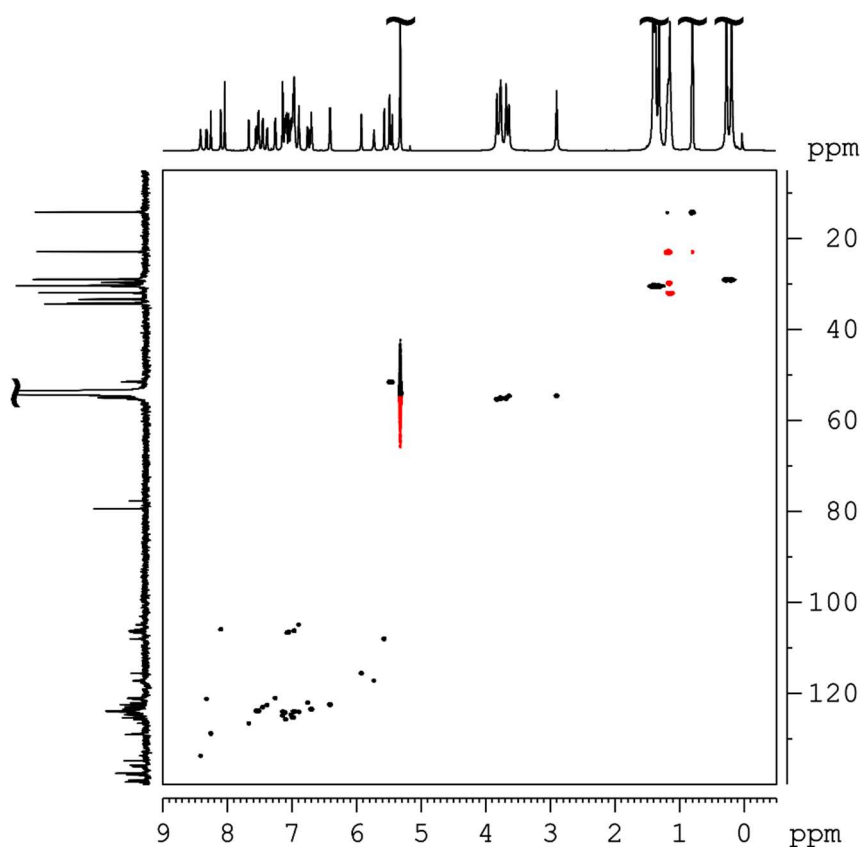


Figure S27. 2D- ^1H , ^{13}C HSQC spectrum of azotriptycene **3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at -108°C .

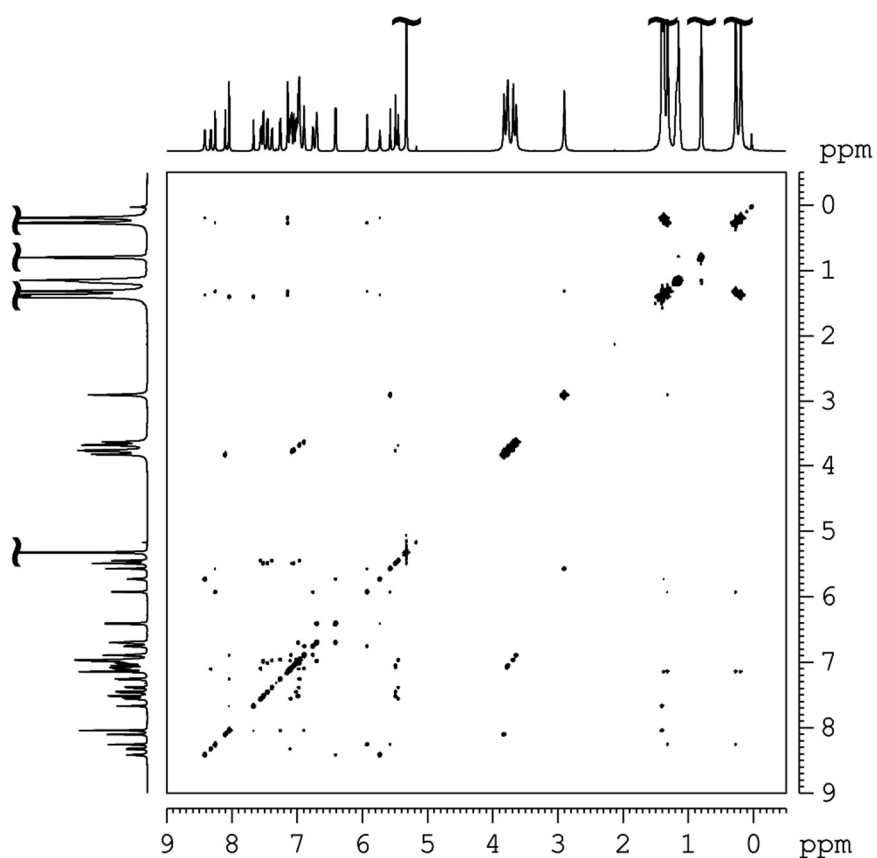


Figure S28. 2D- ^1H , ^1H NOESY spectrum (mixing time = 0.2 s) of azotriptycene **3** in anh. and deg. $\text{CD}_2\text{Cl}_2/\text{CS}_2$ 3:1 (25 mM) measured at -108°C . Due to slow tumbling at -108°C , the NOESY pulse sequence yields exchange and NOE signals of the same phase.

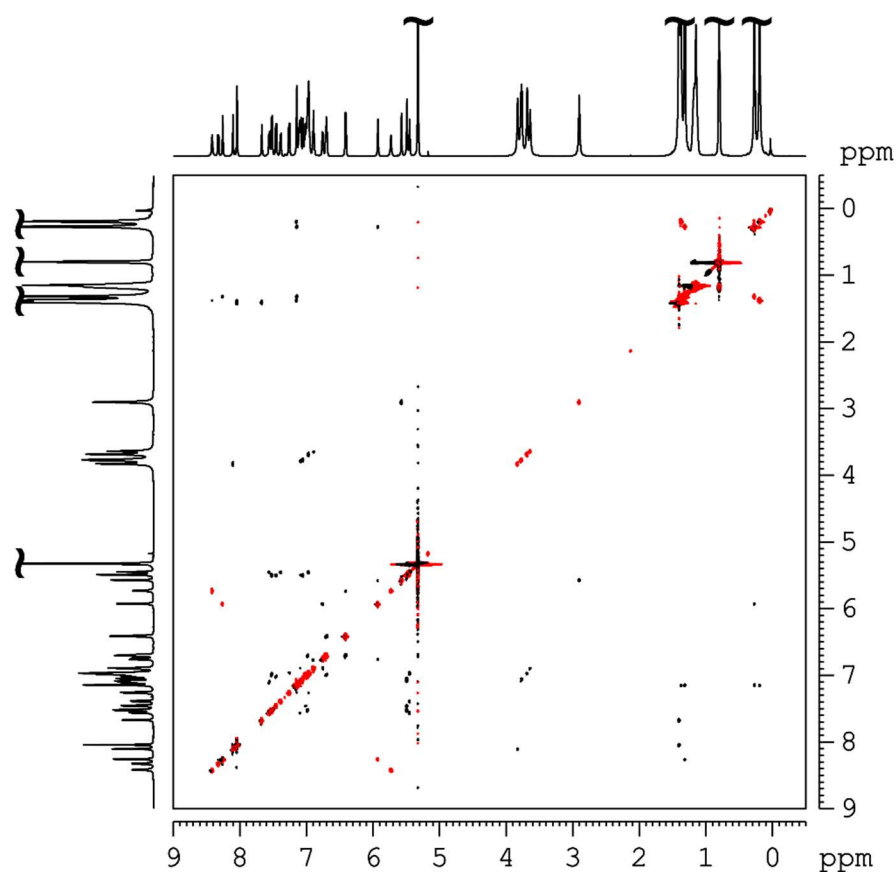


Figure S29. 2D-¹H, ¹H ROESY spectrum (mixing time = 0.2 s) of azotriptycene **3** in anh. and deg. CD₂Cl₂/CS₂ 3:1 (25 mM) measured at –108 °C with different phases for exchange- (negative) and NOE-signals (positive).

4.5.7 1D Selective EXSY studies of *cis*-1 and *cis*-3 for a kinetic analysis of the decelerated phenyl C-N and triptycene C-N bond rotations within the brake ON states at $-108\text{ }^{\circ}\text{C}$

4.5.7.1 External referencing of NOE contribution for azotriptycene **1** and **3** using **2** as reference at $-108\text{ }^{\circ}\text{C}$

Saturation transfer between two signals can be caused by chemical/conformational exchange as well as by NOE.³² For a reliable kinetic analysis of intramolecular exchange processes, in this case determination of rotational rate constants and Gibbs energies of activation, the contribution of NOE to the EXSY buildup must be known. For the quantification of the NOE between the two fluorine-substituents of **1**, an external referencing with a suitable reference molecule must be performed. This reference molecule must fulfill several conditions: First, the distance between the two fluorine-substituents must be the same in both, model system and test system. Second, the two fluorine-substituents must not result in one averaged signal as for **1**, but in two different ones. Third, the overall reference molecule must be as similar to **1** as possible. The reason for this is the correlation time τ_c , which determines the amount of NOE. This correlation time τ_c corresponds approximately to the inverse rate of molecular tumbling, which in turn depends most of all of molecular weight, shape and solvent viscosity. To reproduce the solvent viscosity, additionally the same solvent and temperature must be used for the reference measurements. Fourth, any disturbing contribution of chemical/conformational exchange while referencing the NOE must be excluded.

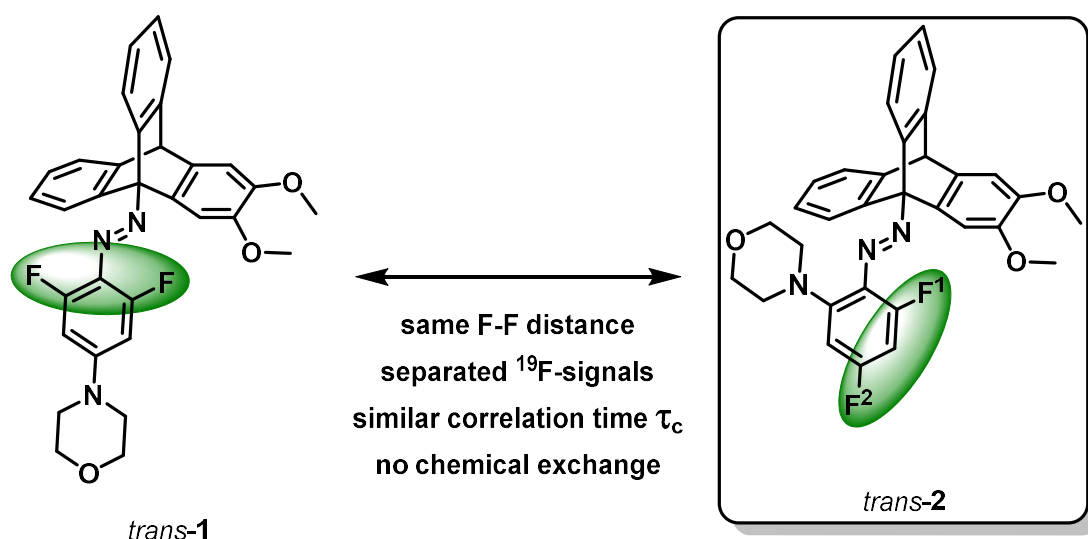


Figure S30. To quantify the NOE between the two fluorine substituents of **1**, an external referencing of the NOE using **2** as reference molecule must be performed. **2** fulfills all required conditions as a reference molecule: Same F-F distance, two separated ¹⁹F-signals, similar correlation time τ_c , but without any chemical/ conformational exchange between the two fluorine-substituents.

All these preconditions are fulfilled using *trans*-**2** (Figure 30). Because both fluorines are still in *meta*-position to each other, the fluorine-fluorine distance is unchanged (first condition). The two fluorines F¹ and F² are no longer in the *ortho*-position of the diazo-moiety, but in *ortho* and *para*. This breaks the symmetry of the phenyl-substituent and hence results in two different ¹⁹F-signals (second condition). The only difference of **2** compared to **1** is the varied order of the aryl-substituents, which does not change the molecular weight and only marginally the molecular shape. Therefore, a similar correlation time τ_c can be assumed (third condition). Last but not least, due to the varied substitution pattern also chemical/ conformational exchange – especially in *trans*-configuration – and hence a distorting contribution during the NOE quantification can be excluded.

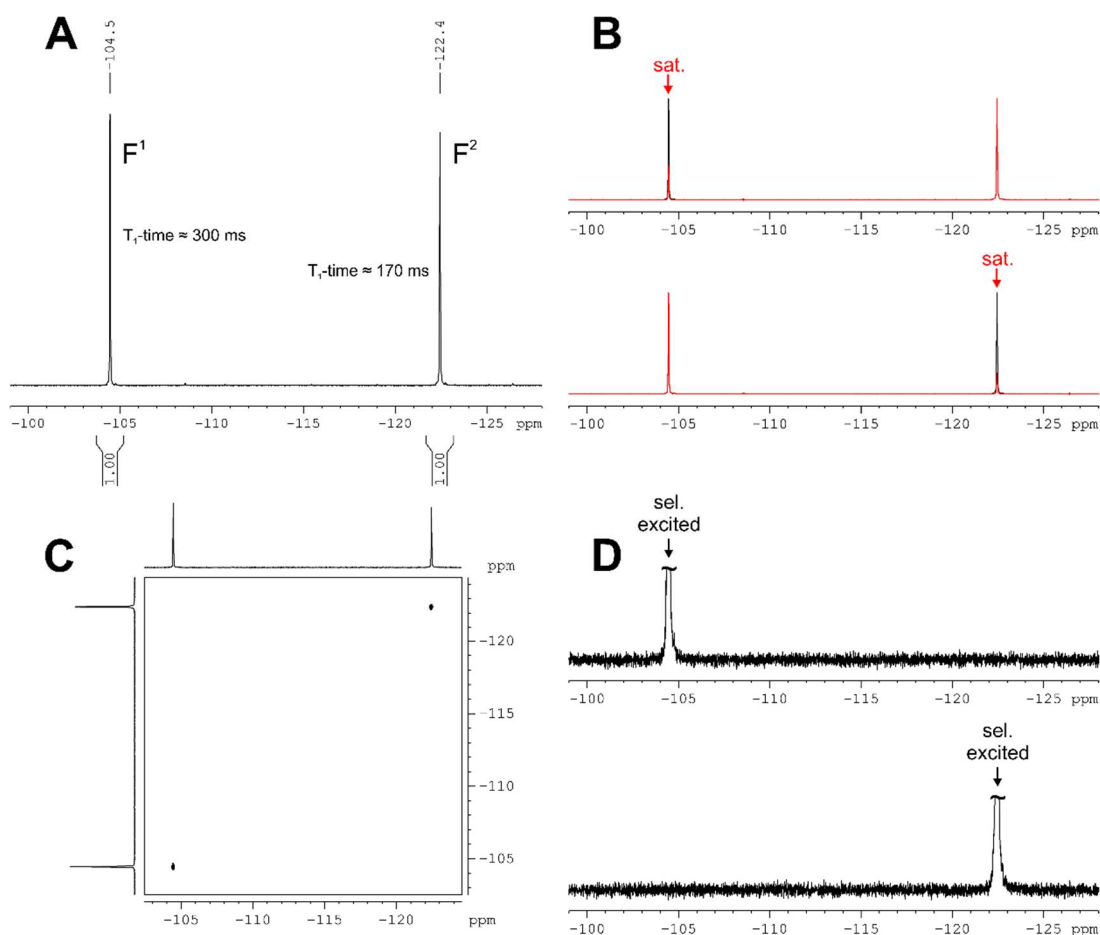


Figure S31: Different ¹⁹F experiments of *trans*-**2** measured in anh. and deg. CS₂/CD₂Cl₂ 3:1 (15 mM) at –108 °C to determine the NOE contribution to the overall magnetization transfer. **A:** 1D-¹⁹F spectrum (ns = 64) showing the two signals for the different fluorine-substituents F¹ and F² and the corresponding T₁-times. **B:** 1D-¹⁹F CEST experiments (ns = 64) with selective saturation at different ppm values. The black spectrum corresponds to the control experiment with saturation pulse power = 1000 -dBW = 0 W, the overlaid red spectrum corresponds to the actual CEST experiments (pulse power = 30 -dBW; pulse length = 50 ms) with selective saturation at -104.45 ppm (top) or at -122.45 ppm (bottom). **C:** 2D-¹⁹F, ¹⁹F NOESY with mixing time = 100 ms. **D:** 1D-¹⁹F NOESY (ns = 2048) with mixing time = 100 ms and selective excitation at -104.45 ppm (top) or at -122.45 ppm (bottom).

To determine the amount of NOE between F^1 and F^2 , a series of different ^{19}F -NMR experiments with through space magnetization transfers was applied (Figure S31). To maximize the amount of NOE, a mixing time similar to the T_1 -time of the observed signals was used. T_1 -times of 300 ms respectively 170 ms were determined for F^1 and F^2 , respectively (Figure S31 **A**). Using 1D- ^{19}F CEST experiments with in each case selective saturation at one of the two ^{19}F signals of **2**, only a decrease of the saturated signals, but no saturation transfer to the second signal is detected (**B**). Likewise measuring a 2D- ^{19}F , ^{19}F NOESY (**C**) and for an increased sensitivity also a 1D- ^{19}F NOESY (**D**) did not yield any sign of magnetization transfer. Based on this, NOE contribution to the overall saturation transfer can unambiguously be excluded. Therefore, also no disturbing NOE contribution during the determination of the different rate constants and Gibbs energy of activation for **1** must be considered.

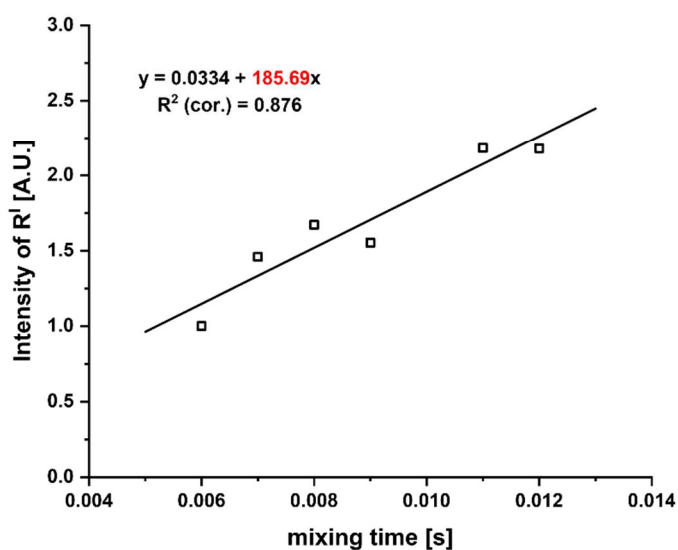
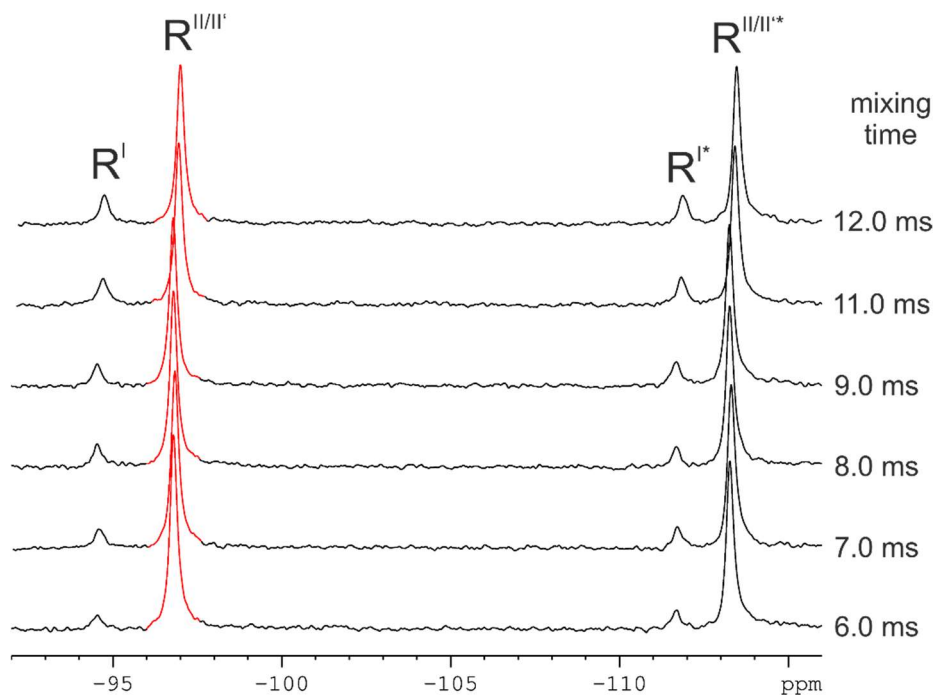
Due to similar *ortho*- ^{19}F - ^{19}F distances for azotriptycene **1** and *ortho*- ^1H - ^1H -distances for **3** also the absence of a disturbing NOE contribution for the quantification of the phenyl C-N bond rotation for the intermeshed *cis*-**3** is assumed.

4.5.7.2 1D EXSY Buildup studies of *cis*-1 and *cis*-3 to obtain rate constants and Gibbs free energy barriers for triptycene C-N and phenyl C-N bond rotations at -108 °C

The intensity of exchange signals usually increases with the applied mixing time. Based on the slope of this intensity gain within its initial linear EXSY buildup and the intensity of the selectively excited signal (I_0), the rate constant for this exchange process and also, using the Eyring equation, the corresponding Gibbs energy of activation $\Delta G^\ddagger$ can be calculated for the sum-process (note that for triptycene rotations the sum $\Delta G^\ddagger$ value needs to be dissected into the individual $\Delta G^\ddagger$ values for rotations leading to independent phenyl exchanges involving pocket I and pocket II or pocket I and pocket II').^{26b,28} Therefore, a series of 1D selective ^{19}F or ^1H EXSY experiments with incremented mixing time and selective excitation of one of the *cis*-1 or *cis*-3 signals was performed.

To obtain the rate constants and Gibbs energy of activation for the triptycene C-N bond rotation for *cis*-1, a process where conformational exchange between two intermeshed structures I and II/II' (see Figure S18) occurs, the buildup of the R^{I} signal intensity during selective excitation of $\text{R}^{\text{II/II'}}$ and *vice versa* was investigated (Figure S32 and S33). For *cis*-3 no such exchange between the triptycene pockets could be detected. The phenyl C-N bond rotation only leads to a conformational exchange between the opposed *ortho*- and *meta*-substituents within one intermeshed state. Therefore, the intensity buildup of $\text{R}^{\text{II*/II'*}}$ and $\text{R}^{\text{I*}}$ ($\text{R} = \text{F}$ for **1** and $\text{R} = \text{H}$ for **3**) during selective excitation of $\text{R}^{\text{II/II'}}$ or R^{I} for different mixing times was examined (Figure S34-S36).

$R^{II/III'} \rightarrow R^I$ (tritycene C-N bond rotation for *cis*-1)



$$k(R^{II/III'} \rightarrow R^I) = \frac{m}{I_0(R^{II/III'})} = \frac{185.69}{16.72} = 11.11 \text{ s}^{-1}$$

The Intensity I_0 ($R^{II/III'}$) is the relative intensity of the $R^{II/III'}$ signal at mixing time = 0 s

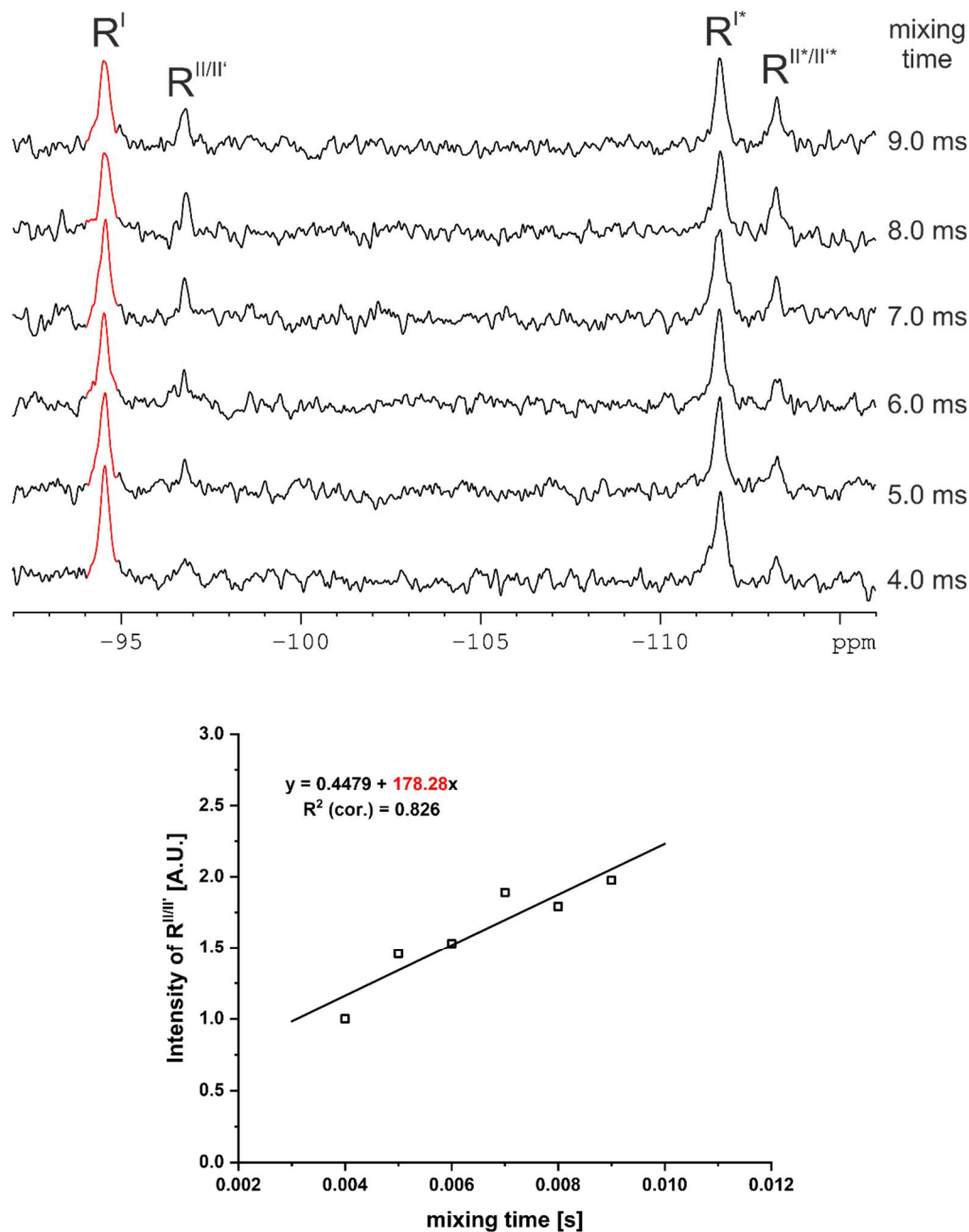
By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 11.11 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^{II/III'} \rightarrow R^I$ is

$$\Delta G^\ddagger = 36.30 \text{ kJ/mol} = 8.68 \text{ kcal/mol}$$

Figure S32. 1D selective ^{19}F EXSY experiments ($n_s = 20480$) with $R^{II/III'}$ as selectively excited signal (highlighted red) and incremented mixing time (6.0-12.0 ms) of *cis*-1 in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -108°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm. Based on the slope of the fitted curve of the initial linear EXSY buildup and I_0 , the rate constant and sum-Gibbs energy of activation for the decelerated triptycene C-N bond was calculated.

$R^I \rightarrow R^{II/III}$ (tritycene C-N bond rotation for *cis*-1)



$$k(R^I \rightarrow R^{II/III}) = \frac{m}{I_0(R^I)} = \frac{178.28}{8.29} = 21.50 \text{ s}^{-1}$$

The Intensity $I_0(R^I)$ is the relative intensity of the R^I signal at mixing time = 0 s

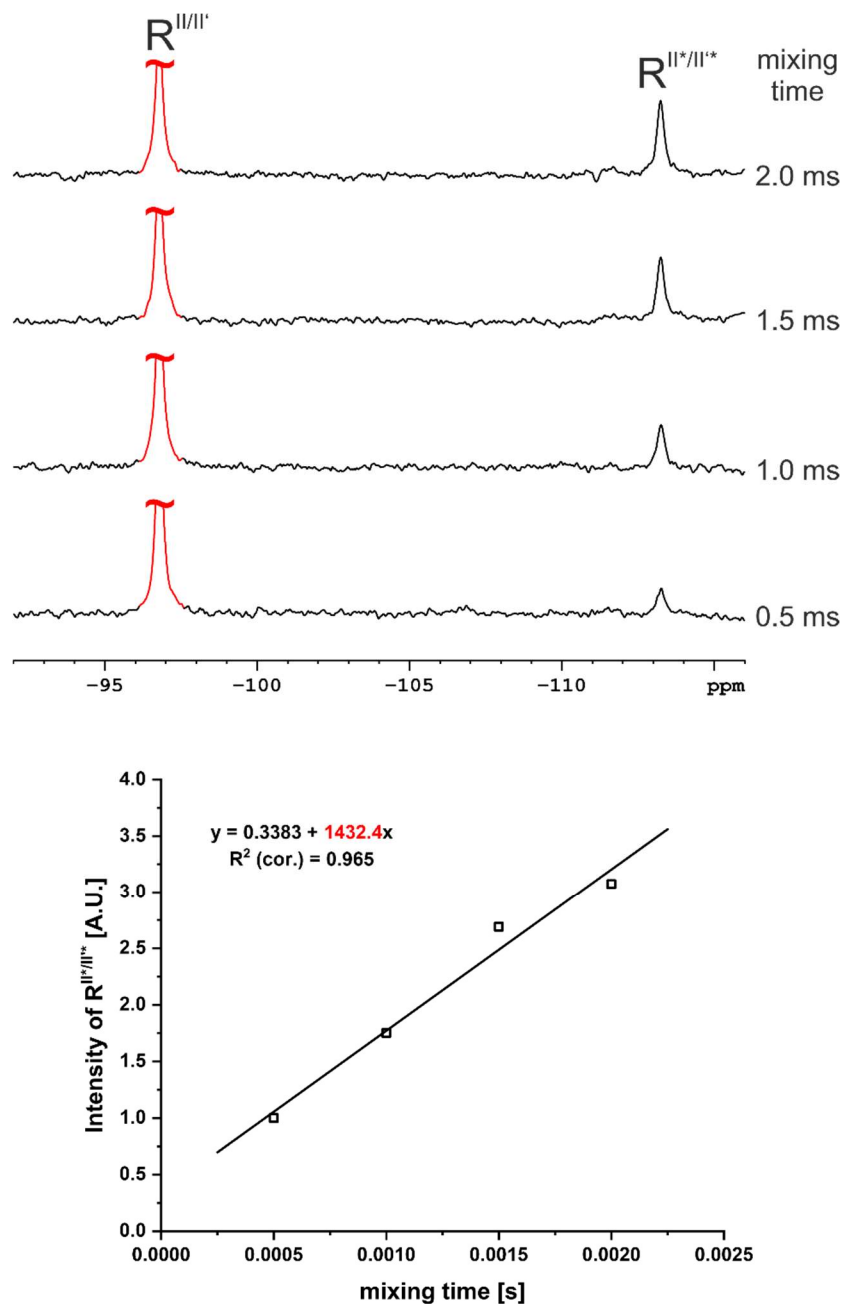
By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 21.50 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^I \rightarrow R^{II/III}$ is

$$\Delta G^\ddagger = 35.39 \text{ kJ/mol} = 8.46 \text{ kcal/mol}$$

Figure S33. 1D selective ^{19}F EXSY experiments (ns = 22528) with R^I as selectively excited signal (highlighted red) and incremented mixing time (4.0–9.0 ms) of *cis*-1 in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -108°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm. Based on the slope of the fitted curve of the initial linear EXSY buildup and I_0 , the rate constant and sum-Gibbs energy of activation for the decelerated triptycene C-N bond rotation was calculated.

$R^{II/III} \rightarrow R^{II*/III*}$ (phenyl C-N bond rotation for *cis*-1 in the enantio. triptycene pocket II/III')



$$k(R^{II/III} \rightarrow R^{II*/III*}) = \frac{m}{I_0(R^{II*/III*})} = \frac{1432.4}{10.54} = 135.94 \text{ s}^{-1}$$

The Intensity I_0 ($R^{II/III}$) is the relative intensity of the $R^{II/III'}$ signal at mixing time = 0 s

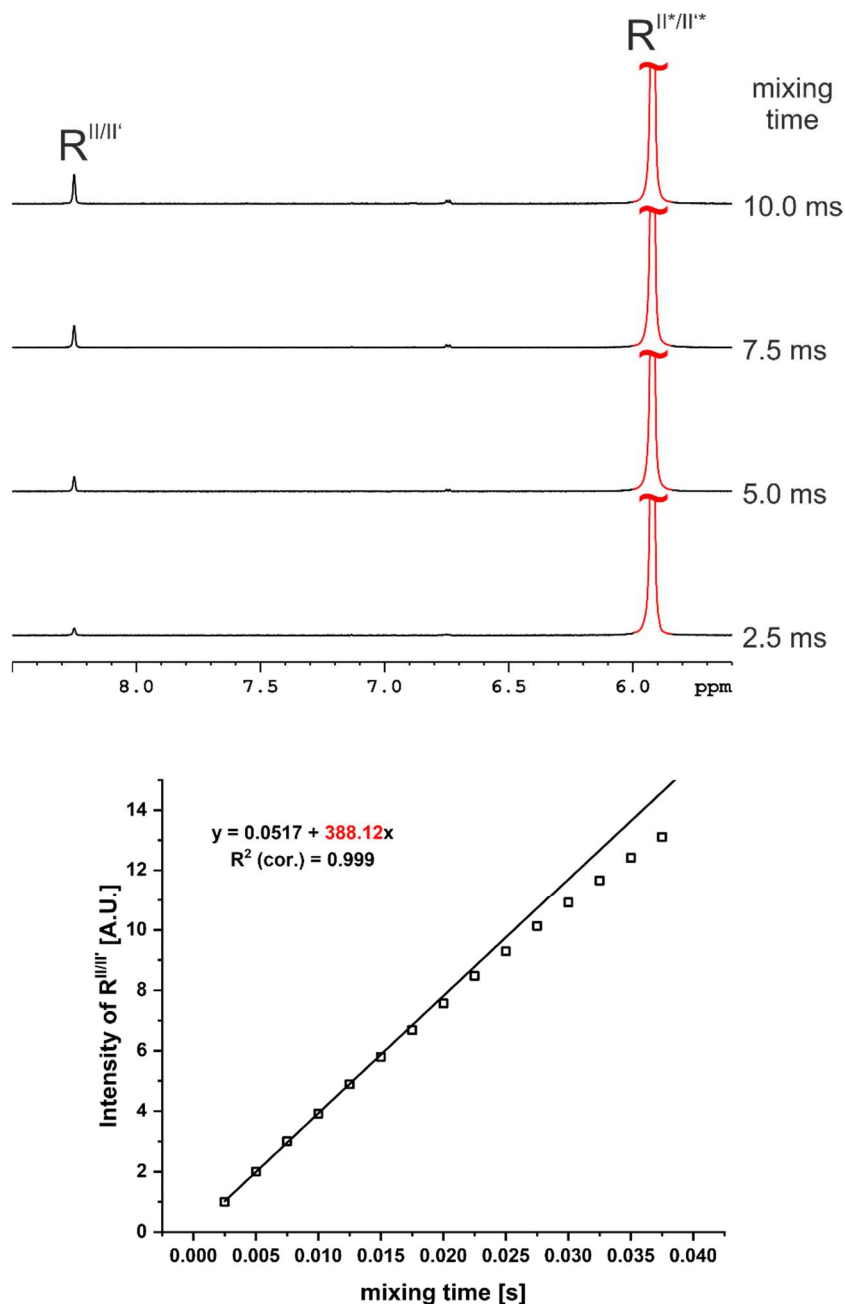
By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 135.94 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^{II/III} \rightarrow R^{II*/III*}$ is

$$\Delta G^\ddagger = 32.86 \text{ kJ/mol} = 7.85 \text{ kcal/mol}$$

Figure S34. 1D selective ^{19}F EXSY experiments (ns = 2048) with $R^{II/III'}$ as selectively excited signal (highlighted red) and incremented mixing time (0.5-2.0 ms) of *cis*-1 in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (15 mM) measured at -108°C after ex situ illumination with an LED emitting at a wavelength of 365 nm. Based on the slope of the fitted curve of the initial linear EXSY buildup and I_0 , the rate constant and sum-Gibbs energy of activation for the decelerated triptycene C-N bond was calculated.

$R^{II*/II*} \rightarrow R^{II/II'}$ (phenyl C-N bond rotation for *cis*-**3** in the enantio. triptycene pocket II/II')



$$k(R^{II*/II*} \rightarrow R^{II/II'}) = \frac{m}{I_0(R^{II*/II*})} = \frac{388.12}{161.83} = 2.09 \text{ s}^{-1}$$

The Intensity $I_0(R^{II*/II*})$ is the relative intensity of the $R^{II*/II*}$ signal at mixing time = 0 s

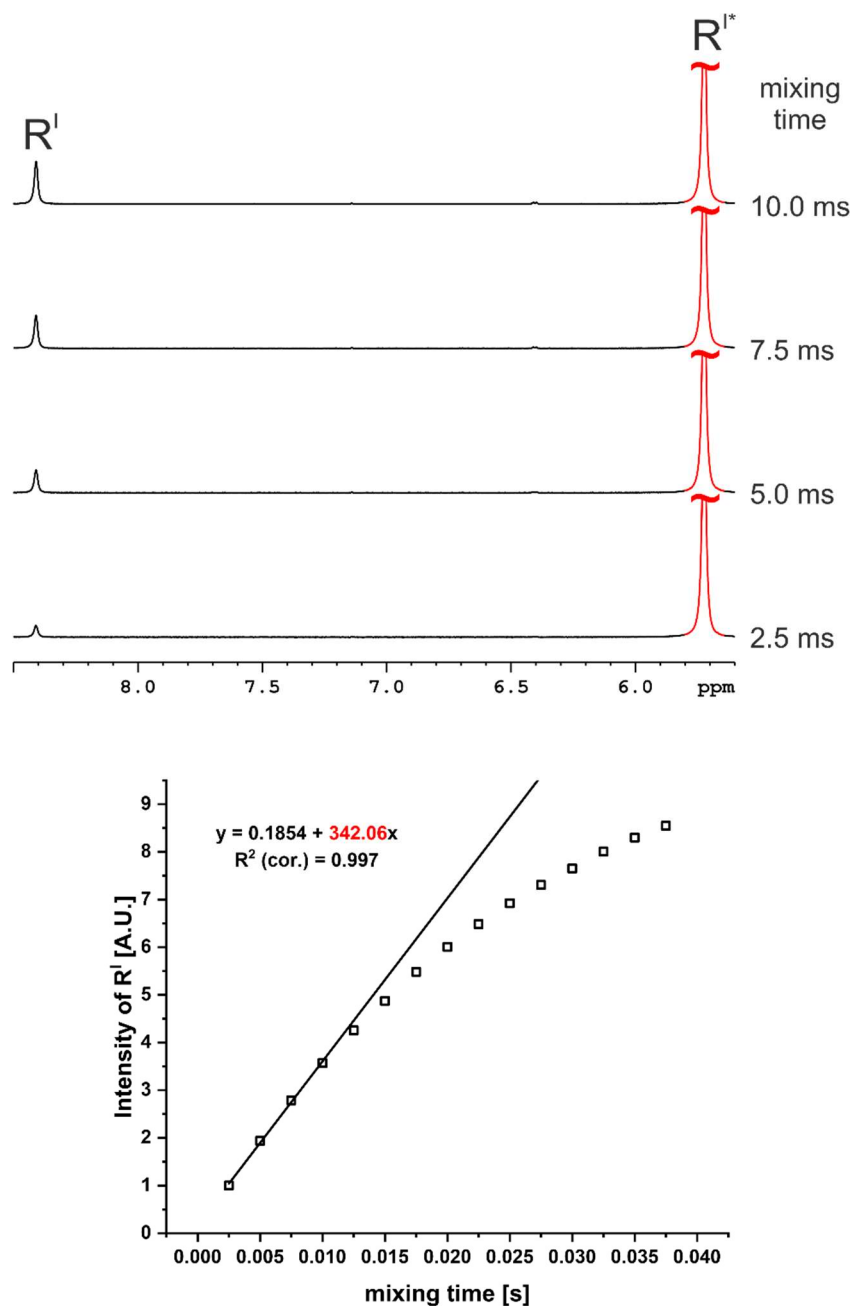
By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 2.09 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^{II*/II*} \rightarrow R^{II/II'}$ is

$$\Delta G^\ddagger = 38.59 \text{ kJ/mol} = 9.22 \text{ kcal/mol}$$

Figure S35. 1D selective ¹H EXSY experiments (ns = 256) with $R^{II*/II*}$ as selectively excited signal (highlighted red) and incremented mixing time (2.5–37.5 ms) of *cis*-**3** in anh. and deg. CS₂/CD₂Cl₂ 1:3 (25 mM) measured at –108 °C. Based on the slope of the fitted curve of the initial linear EXSY buildup and I_0 , the rate constant and sum-Gibbs energy of activation for the decelerated triptycene C-N bond was calculated. Only the 1D ¹H-EXSY spectra within the initial linear EXSY buildup are depicted.

$R^I \rightarrow R^I$ (phenyl C-N bond rotation for *cis*-3 in the unsubstituted triptycene pocket I)



$$k(R^{I*} \rightarrow R^I) = \frac{m}{I_0(R^{I*})} = \frac{342.06}{25.56} = 13.38 \text{ s}^{-1}$$

The Intensity $I_0(R^{I*})$ is the relative intensity of the R^{I*} signal at mixing time = 0 s

By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 13.38 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^{I*} \rightarrow R^I$ is

$$\Delta G^\ddagger = 36.04 \text{ kJ/mol} = 8.61 \text{ kcal/mol}$$

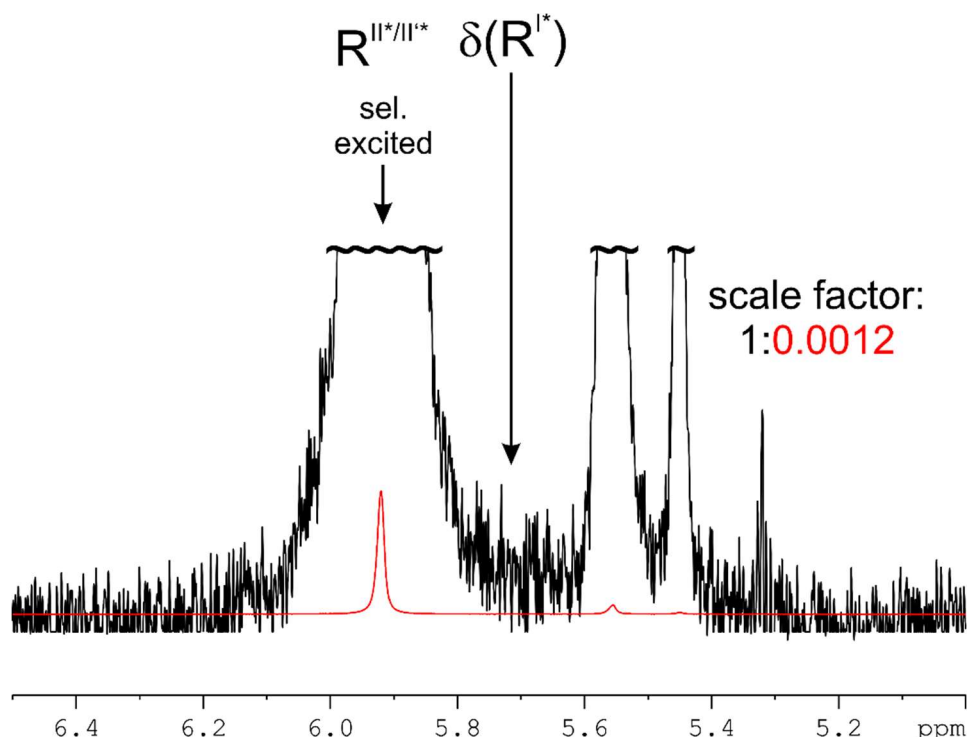
Figure S36. 1D selective ¹H EXSY experiments (ns = 256) with R^{I*} as selectively excited signal (highlighted red) and incremented mixing time (2.5–37.5 ms) of *cis*-3 in anh. and deg. CS₂/CD₂Cl₂ 1:3 (25 mM) measured at −108 °C. Based on the slope of the fitted curve of the initial linear EXSY buildup and I_0 , the rate constant and sum-Gibbs energy of activation for the decelerated triptycene C-N bond was calculated. Only the 1D ¹H-EXSY spectra within the initial linear EXSY buildup are depicted.

Based on the received buildup curves, rate constants of $k = 11.1 \text{ s}^{-1}$ ($R^{II/III'} \rightarrow R^I$, Figure S32) and $k = 21.5 \text{ s}^{-1}$ ($R^I \rightarrow R^{II/III'}$, Figure S33) were calculated for the sum-decelerated triptycene C-N bond rotation of *cis*-**1** at -108°C . These correspond to sum-Gibbs energies of activation of $\Delta G^\ddagger = 8.68 \text{ kcal/mol}$ and $\Delta G^\ddagger = 8.46 \text{ kcal/mol}$, respectively. The rate constants for the phenyl C-N bond rotation ($R^{II/III'} \rightarrow R^{II^*/III^*}$, Figure S34) of *cis*-**1** in the enantiomeric triptycene pocket II/II' is one order of magnitude faster. This rotation occurs with a rate constant of $k = 136 \text{ s}^{-1}$, which corresponds to a Gibbs energy of activation of $\Delta G^\ddagger = 7.85 \text{ kcal/mol}$. Since the rate constants of the phenyl and triptycene C-N rotation differ to such a degree, gearing must be excluded for *cis*-**1**.

For *cis*-**3** phenyl C-N bond rotation rate constants of $k = 2.09 \text{ s}^{-1}$ ($R^{II/III'} \rightarrow R^{II^*/III^*}$, Figure S35) for the enantiomeric pocket II/II' and $k = 13.4 \text{ s}^{-1}$ ($R^I \rightarrow R^I$, Figure S36) inside the unsubstituted pocket I were determined at -108°C , which relates to Gibbs energies of activation of $\Delta G^\ddagger = 9.22 \text{ kcal/mol}$ and $\Delta G^\ddagger = 8.61 \text{ kcal/mol}$, respectively. Compared to the rate of the phenyl C-N bond rotation of *cis*-**1** within the enantiomeric pocket, the same rotation is slowed down by a factor of ca. 65 for *cis*-**3**.

Lower limit for $R^{II*/III*} \rightarrow R^{I*}$ (tritycene C-N bond rotation for *cis*-3)

For the rotation along the triptycene C-N bond of *cis*-3 at $-108\text{ }^{\circ}\text{C}$, no clear rotational exchange signal could be detected between the different intermeshed states I and II/III' within the investigated mixing times (see Figure S37, black arrow). In order to estimate a lower limit for this process, it was first determined what intensity of the R^{I*} signal would be necessary compared to $R^{II*/III*}$ to be no longer distinguishable from the baseline noise. This is the case for a ratio of less than or equal to $R^{II*/III*}/R^{I*} = 1:0.0012$ (Figure S37). With this ratio, a rate constant and thus the Gibbs energy of activation for this rotational process can be calculated.³³



$$k(R^{II*/III*} \rightarrow R^{I*}) = \frac{1}{t_m \left(\frac{I_{R^{II*/III*}}}{I_{R^{I*}}} \right) + 1} = \frac{1}{0.25 \left(\frac{1}{0.00012} \right) + 1} = 0.0048 \text{ s}^{-1}$$

With t_m = mixing time

By Eyring equation we obtain the sum-Gibbs energy of activation $\Delta G^\ddagger$: $k = \frac{k_B T}{h} e^{\frac{-\Delta G^\ddagger}{RT}}$

For $k = 0.0048 \text{ s}^{-1}$ the sum-Gibbs energy of activation for $R^{II*/III*} \rightarrow R^{I*}$ is >

$$\Delta G^\ddagger = 46.92 \text{ kJ/mol} = 11.21 \text{ kcal/mol}$$

Figure S37. 1D selective ^1H EXSY experiment ($n_s = 256$) with $R^{II*/III*}$ as selectively excited signal and a mixing time of $t_m = 0.25 \text{ s}$ of *cis*-3 in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 1:3 (25 mM) measured at $-108\text{ }^{\circ}\text{C}$. Based on the scale factor it can be estimated from which intensity the R^{I*} signal starts to be indistinguishable from the baseline noise and would be therefore no longer detectable. Thus, a lower limit can be determined for the rotational rate constant and also for the Gibbs energy of activation for the decelerated triptycene C-N bond rotation.

Using the ratio of 1:0.0012 determined by the scale factor, an upper limit of $k = 0.0048 \text{ s}^{-1}$ and $\Delta G^\ddagger = 11.21 \text{ kcal/mol}$ for the decelerated rotation along the triptycene C-N bond is obtained ($R^{\text{II}^*/\text{III}^*} \rightarrow R^{\text{I}^*}$). This rotation of *cis*-**3** is thus slowed down by at least 2-3 orders of magnitude in terms of rate compared to the rotations along the phenyl C-N bond within the triptycene pockets (see Figure S35 and S36).

4.5.8 Investigations of the photoswitching behavior of azotriptycenes 1 and 3 in the brake OFF and brake ON state at different temperatures using *in situ* illumination NMR spectroscopy

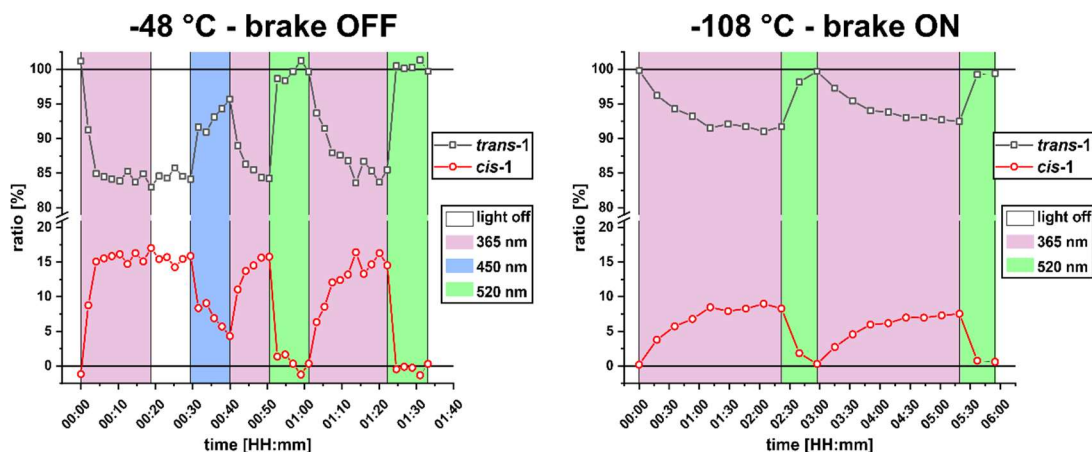


Figure S38. 1D- ^{19}F *in situ* illumination NMR kinetic (left: $n_s = 24$, right: $n_s = 1024$) of azotriptycene **1** in anh. and deg. $\text{CS}_2/\text{CD}_2\text{Cl}_2$ 3:1 (25 mM) measured at $-48\text{ }^\circ\text{C}$ (left) and $-108\text{ }^\circ\text{C}$ (right). Illumination with LEDs emitting at different wavelengths (365 nm, 450 nm, 520 nm) results in reversible *trans* $\rightarrow$ *cis* and *cis* $\rightarrow$ *trans* isomerization.

The performance of azotriptycene **1** as photoswitch was examined at two different temperatures: At $-48\text{ }^\circ\text{C}$ (Figure S38 left) and at $-108\text{ }^\circ\text{C}$ with the *cis*-isomer in the brake ON state (Figure S38 right). Illumination with 365 nm within approx. 5 min at $-48\text{ }^\circ\text{C}$ leads to a change in *trans/cis* from $>99:1$ in thermal equilibrium to $84:16$. With 450 nm moderate *cis* to *trans* isomerization can be achieved yielding a ratio of *trans/cis* $96:4$. Illumination with 520 nm is more effective and a ratio of *trans/cis* $>99:1$ is re-established within less than 2 min. A similar picture emerges at $-108\text{ }^\circ\text{C}$, however the isomerization rate and amount of generated *cis*-isomer are smaller. It takes 55 min of illumination with 365 nm until a photostationary state with *trans/cis* $92:8$ is reached and by illuminating for about 30 min with 520 nm a ratio of *trans/cis* $>99:1$ is established. Over the total of 5 cycles of photoswitching, no fatigue in performance was detected.

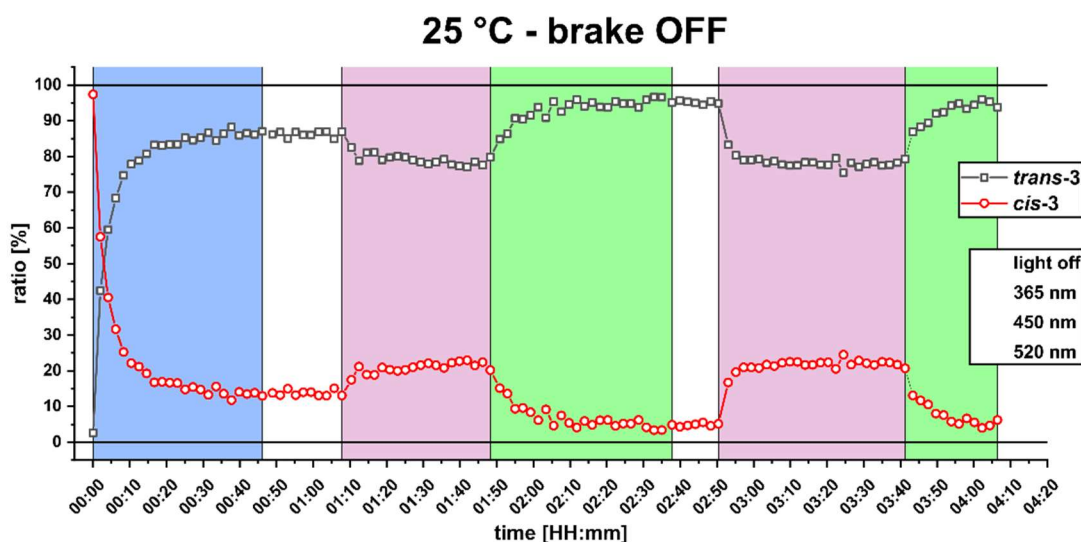


Figure S39. 1D- ^1H *in situ* illumination NMR kinetic ($n_s = 2$) of azotriptycene **3** in anh. and deg. CD_2Cl_2 (25 mM) measured at 25 °C. Illumination with LEDs emitting at different wavelengths (365 nm, 450 nm, 520 nm) results in reversible *trans* $\rightarrow$ *cis* and *cis* $\rightarrow$ *trans* photoisomerization.

The same experiments were performed for azotriptycene **3**, but only at elevated temperatures (Figure S39). Illumination with 450 nm enables a significant *cis* $\rightarrow$ *trans*-isomerization with a ratio of *trans/cis* 86:14 in the photostationary state, which is reached after approx. 30 min. With 520 nm this *cis* $\rightarrow$ *trans* isomerization can be further improved. After 10 minutes of irradiation a *trans/cis* ratio of 96:4 is achieved. By illumination with 365 nm the *cis*-isomer can be recovered in up to 22%. The photoswitching was examined over 2 cycles without any recognizable deterioration of performance.

4.6 Additional Findings

4.6.1 Discussion

During this project, we also investigated the photoswitching and braking capacity of a third azotriptycene (see Figure A1 **A**). This photoswitchable molecular brake **4** resembles **1** as this also contains two fluorine substituents in *ortho*-position of the diazobenzene fragment.

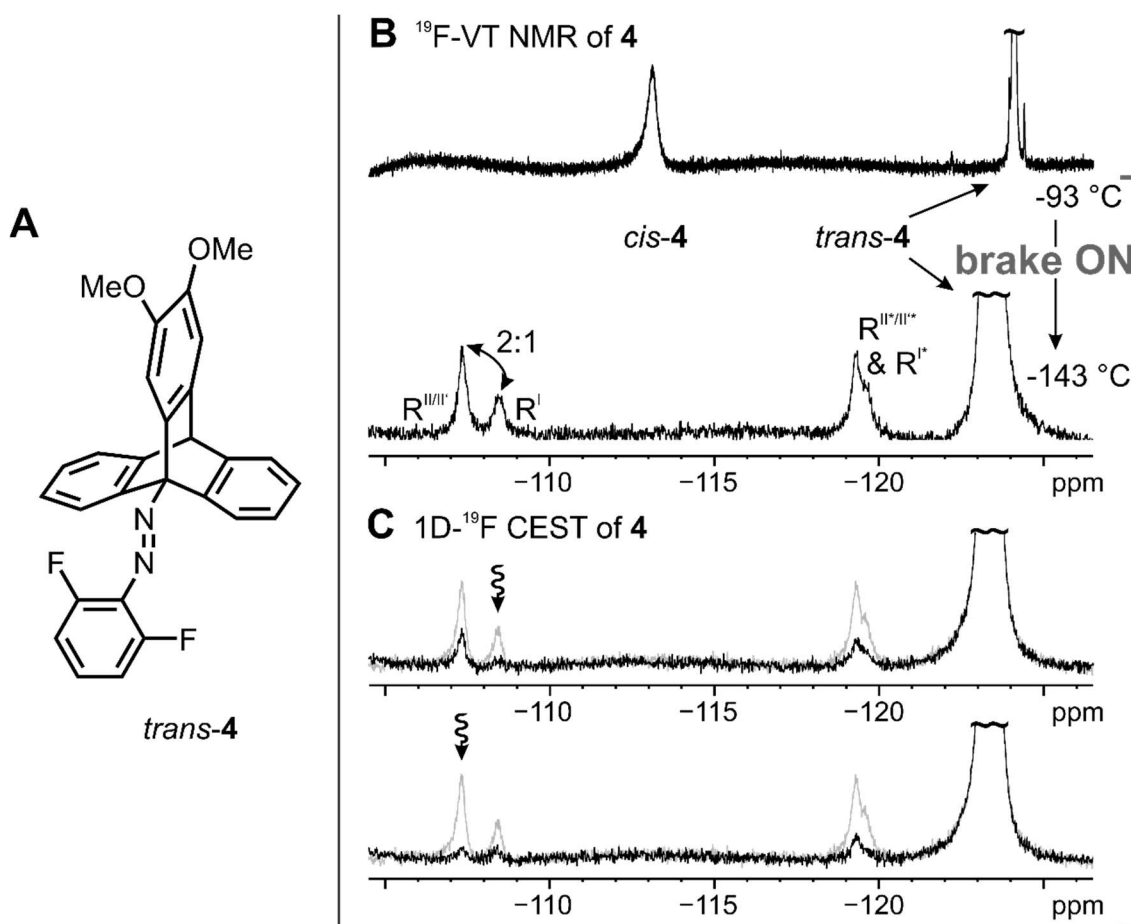


Figure A1. **A:** Schematic representation of azotriptycene *trans*-**4**. **B:** ^{19}F -VT NMR spectroscopic investigations of *cis*-**4** and *trans*-**4** showing *cis*-**4** signal splitting at a very low temperature of $-143\text{ }^{\circ}\text{C}$ compared to the averaged *cis*-**4** signal at $-93\text{ }^{\circ}\text{C}$. For *trans*-**4** only slight line broadening can be observed at $-143\text{ }^{\circ}\text{C}$. **C:** Rotational exchange processes between and within the different pockets I and II/II' were detected via 1D- ^{19}F CEST (the grey spectra in the background correspond to control experiments without saturation).

As expected, starting from *trans/cis* = >99:1 we found a similar UV-illumination (365 nm) induced *trans* $\rightarrow$ *cis* isomerization of up to 11% *cis*-**4** at a low temperature of ca. $-80\text{ }^{\circ}\text{C}$ (see chapter 4.6.2.8). While we obtained an averaged signal for the two *ortho*-positioned fluorine substituents of *cis*-**4** at $-93\text{ }^{\circ}\text{C}$, lowering the temperature to $-143\text{ }^{\circ}\text{C}$ resulted in a signal splitting similar to **1** (see Figure A1 **B** and chapter 4.6.2.6). Two sets of each two signals are obtained, one set shifted upfield ($R^{\text{II'}/\text{II'}}$ and $R^{\text{I'}}$; the two signals are partially

overlapping) and one downfield ($R^{II/II'}$ and R^I) compared to the averaged *cis*-**4** signal at $-93\text{ }^{\circ}\text{C}$. This signal splitting indicates the same intermeshing as already disclosed for **1** and **3** (see chapter 4.3). Therefore, the two upfield shifted ^{19}F signals can be assigned to fluorines pointing into the triptycene pocket, the two downfield shifted signals are pointing away. In both signal sets two signals in a 2:1 ratio are present ($R^{II/II'}/R^I$ and $R^{II^*/II'^*}/R^{I^*}$). This ratio indicates evenly occupied pockets I, II and II' with II and II' representing enantiomers and thus yielding identical NMR signals. In contrast, the *trans*-**4** signal only experiences slight line broadening at the low temperature of $-143\text{ }^{\circ}\text{C}$. However, compared to **1** an even lower temperature of $-143\text{ }^{\circ}\text{C}$ is required for an adequate resolution of the splitted ^{19}F -R signals, which is very close to the minimum allowed temperature for the used NMR spectrometer. We attribute the necessity of such low temperatures to the missing *para*-morpholine substituent. This substituent in azotriptycene **1** highly probably favors attractive dispersive interactions between the diazobenzene and triptycene molecular fragment and thus improves intermeshing and as consequence braking for *cis*-**1** compared to *cis*-**4**.

To evidence interchange motions between and within the different pockets I and II/II', we investigated possible exchange processes between the different ^{19}F -R signals *via* 1D- ^{19}F CEST (see Figure A1 C and chapter 4.6.2.7). Selective saturation of the different ^{19}F -R signals resulted in a significant intensity decrease of the remaining ^{19}F -R signals but not of the *trans*-**4** signal. This explicitly evidences rotational exchange processes between and within the different pockets I and II/II' for *cis*-**4**. However, the ^{19}F signals for R^{I^*} and R^{II^*/II'^*} are partially overlapping. Furthermore, the low temperature of $-143\text{ }^{\circ}\text{C}$ prohibits long lasting NMR experiments. Therefore, rate constants for the decelerated triptycene and phenyl C-N bond rotations of *cis*-**4** cannot be determined *via* 1D selective ^{19}F EXSY kinetics as an intensity change of only one of both partially overlapping signals cannot be quantified and similar experiments for **1** required up to 22,000 scans for obtaining one data point (ca. 4.5 h of measurement time). Nevertheless, despite a missing quantitative evaluation of the different rotational processes, we assume no gearing process for azotriptycene **4** as kinetic analyses for **1** and **3** excluded gearing for this type of molecular brake.

In situ illumination NMR spectroscopy at a temperature of $-83\text{ }^{\circ}\text{C}$ revealed reversible photoswitching between both configuration isomers of **4** (see chapter 4.6.2.8). Starting with a thermal equilibrium of *trans/cis* = >99:1, 11% of *cis*-**4** are obtained *via in situ* UV-illumination (365 nm). By illuminating with green light (520 nm) we could almost re-establish thermal equilibrium (*trans/cis* = 99:1). Heating to r.t. also restored the thermal equilibrium in a fast and effective manner.

4.6.2 Experimental part

4.6.2.1 General

NMR experiments were performed on a Bruker Avance III HD 600 (600.03 MHz) spectrometer with a 5 mm fluorine selective TBIF probe and TopSpin 3.2. For NMR measurements employing standard NMR solvents 5 mm NMR tubes were used. In the case where freonic mixtures were applied as solvents, 5 mm heavy wall NMR tubes equipped with J. Young valves from Norell were used. For *in situ* illumination NMR spectroscopy the reported setup²⁹ with 5 mm amberized thin wall NMR tubes was applied and for illumination at various peak-wavelengths the following LEDs were used and operated at 1.0 A: LG Innotek LEUVA66X00RV00 (365 nm), CREE XLamp XT-E Royal Blue (450 nm), Osram Oslon SSL 80 (520 nm). NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software. ¹H- and ¹³C-NMR spectra were calibrated on the solvent residual peak of CD₂Cl₂ ($\delta(^1\text{H}) = 5.32$ ppm, $\delta(^{13}\text{C}) = 53.84$ ppm). Further plotting of the spectra was performed with Origin 2019 and Corel Draw 2020 software.

4.6.2.2 Chemicals

Commercially available chemicals were, unless otherwise stated, used without further purification. CD₂Cl₂ was distilled over CaH₂, degassed using the freeze-pump-thaw method and stored under argon atmosphere in a Schlenk flask with 3 Å molecular sieve. Freonic mixtures were prepared from CCl₄ and SbCl₅/SbF₃ according to literature procedures and stored in a small lecture bottle.³⁴ The synthesized freonic mixtures composed of CDFCl₂/CDF₂Cl $\approx$ 10:1.

4.6.2.3 NMR Sample Preparation

Preparation of the NMR samples with freonic mixtures as solvent

4 (11.5 μmol) was added to a 5 mm heavy wall NMR tube and the NMR tube was closed with a J. Young valve. The sample was connected to a Schlenk line and the gas atmosphere was removed under reduced pressure. The NMR tube was frozen in a Dewar filled with liquid nitrogen and the freonic mixture was condensed through a column filled with KOH into the NMR tube. By judging the filling level of the freonic solution at r.t. (13 cm $\approx$ 475 μL), a concentration of 23 mM was determined. The NMR sample was stored at ca. 4 °C between the measurements.

Preparation of the NMR samples for *in situ* illumination NMR spectroscopy

An oven dried 5 mm amberized thin wall NMR tube, containing **4** (7.5 μmol) was connected to a Schlenk line and anh. and deg. CD_2Cl_2 (0.3 mL) was added *via* a syringe under argon atmosphere. Then an *in situ* illumination insert as described in literature²⁹ (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μm core) was inserted into the NMR tube and fastened with parafilm.

4.6.2.4 *Ex situ* illumination of the NMR sample

An antimagnetic Dewar was filled with diethyl ether and the liquid was cooled to $-80\text{ }^\circ\text{C}$ using liquid nitrogen. The spinner turbine was attached on the prepared NMR sample and the NMR tube was placed in the precooled Dewar. A glass rod illumination setup with an LED emitting at a wavelength of 365 nm was positioned in the Dewar next to the NMR sample and the sample was illuminated for 30 min. After illumination, the illumination setup was removed and the NMR sample was directly transferred from the Dewar to the pre-cooled NMR spectrometer to avoid thermal *cis* to *trans* back isomerization.



Figure A2. *Ex situ* illumination of NMR samples.

4.6.2.5 Structure elucidation of *trans*-4 and *cis*-4 at $-93\text{ }^{\circ}\text{C}$ in freonic mixtures as solvent

To assign the signals for the *trans*- and *cis*-isomer of azotriptycene **4** (Figure A3) a standard set of 1D- and 2D-NMR experiments (1D- ^{19}F ; 1D- ^1H ; 1D- $^{13}\text{C}\{^1\text{H}\}$; 2D- ^1H , ^1H correlated spectroscopy (COSY); 2D- ^1H , ^{13}C heteronuclear multiple bond correlation (HMBC); 2D- ^1H , ^{13}C heteronuclear single quantum coherence (HSQC); Figure A4-A9) was performed at $-93\text{ }^{\circ}\text{C}$ after generating the *cis*-isomer in a ratio of *cis/trans* 11:89 using the *ex situ* illumination setup (Figure A2).

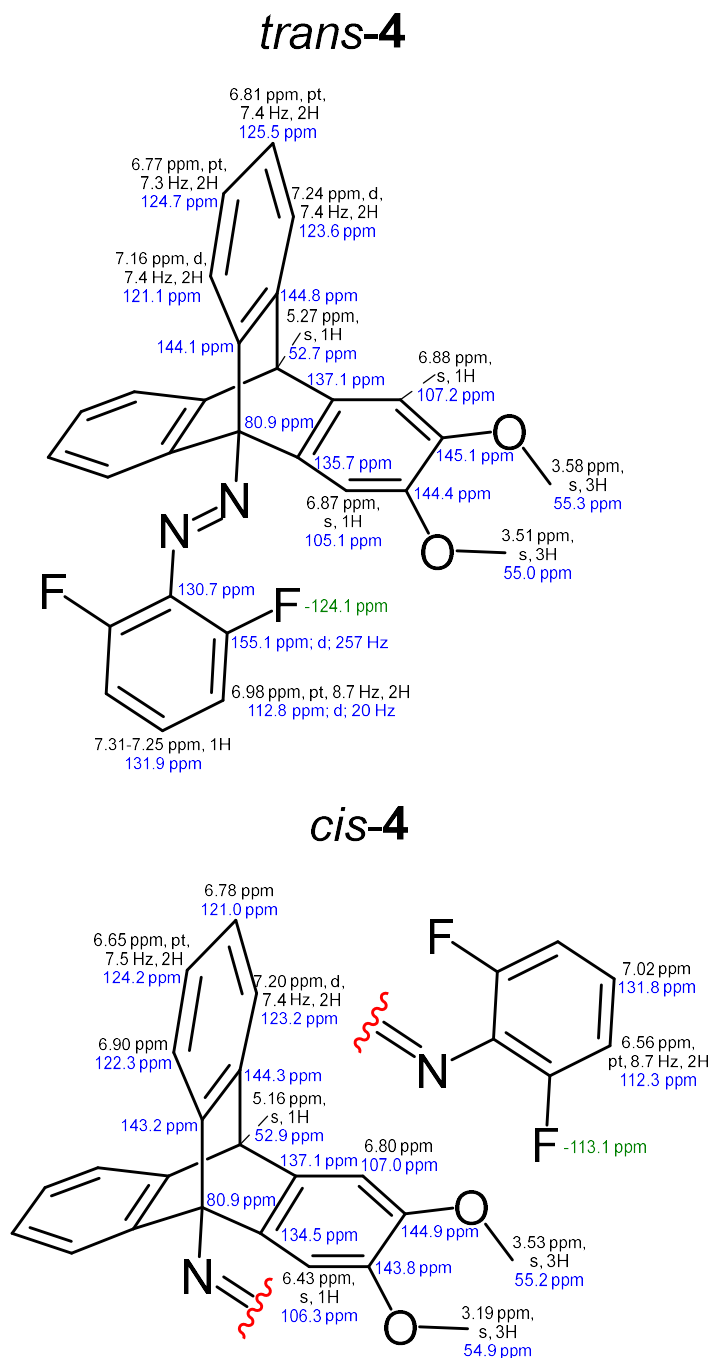


Figure A3. Assignment of *trans*- (top) and *cis*-isomer (bottom) of azotriptycene **4** in freonic mixtures at $-93\text{ }^{\circ}\text{C}$. ^1H chemical shift, multiplicity, coupling constants and integral are highlighted black, ^{13}C blue and ^{19}F green.

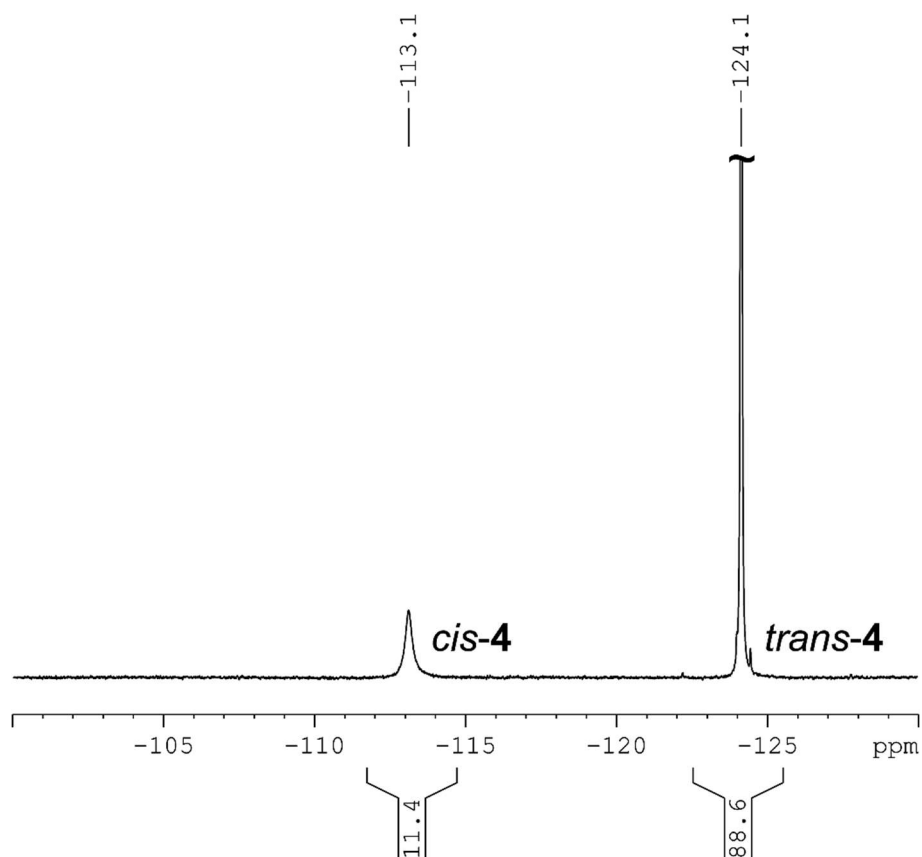


Figure A4. 1D ^{19}F -spectrum (ns = 1024) of azotriptycene **4** in freonic mixtures (23 mM) measured at $-93\text{ }^{\circ}\text{C}$ after *ex situ* illumination with an LED emitting at a wavelength of 365 nm showing a *trans/cis*-ratio of 89:11.

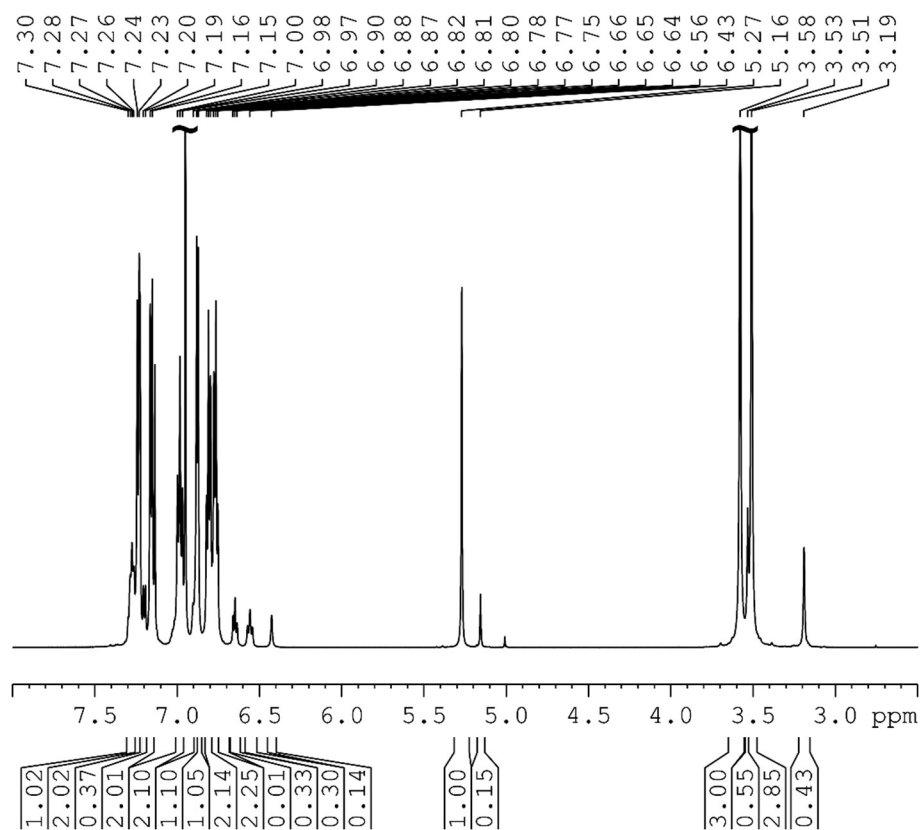


Figure A5. 1D ^1H spectrum (ns = 64) of azotriptycene **4** in freonic mixtures (23 mM) measured at $-93\text{ }^{\circ}\text{C}$ after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

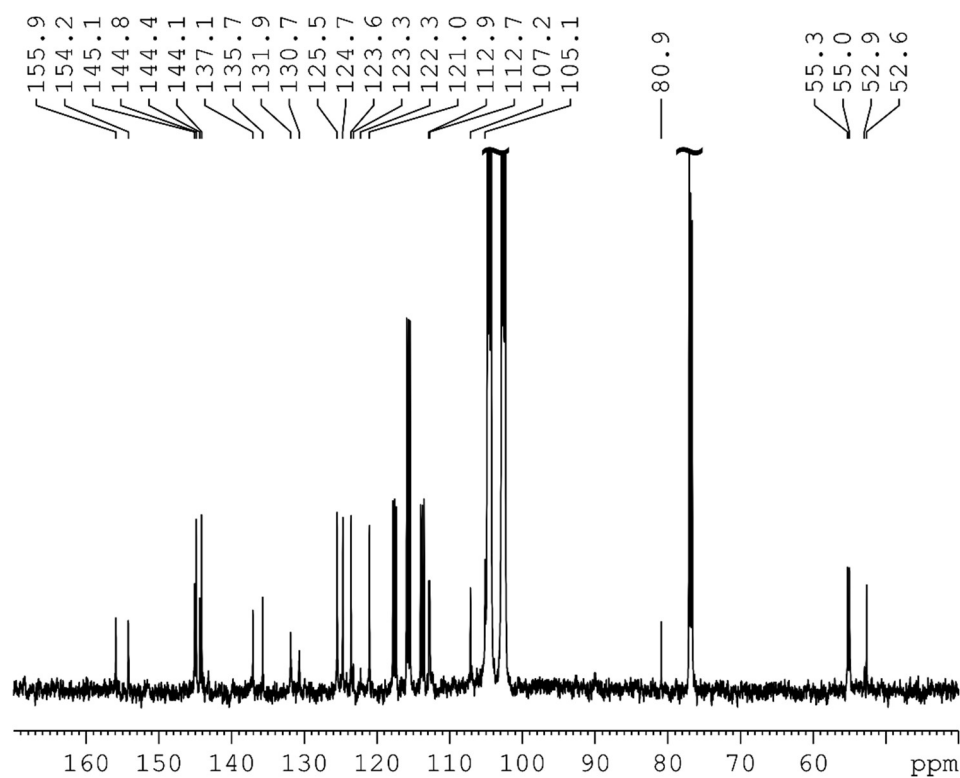


Figure A6. 1D- $^{13}\text{C}\{^1\text{H}\}$ spectrum (ns = 8192) of azotriptycene **4** in freonic mixtures (23 mM) measured at -93°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

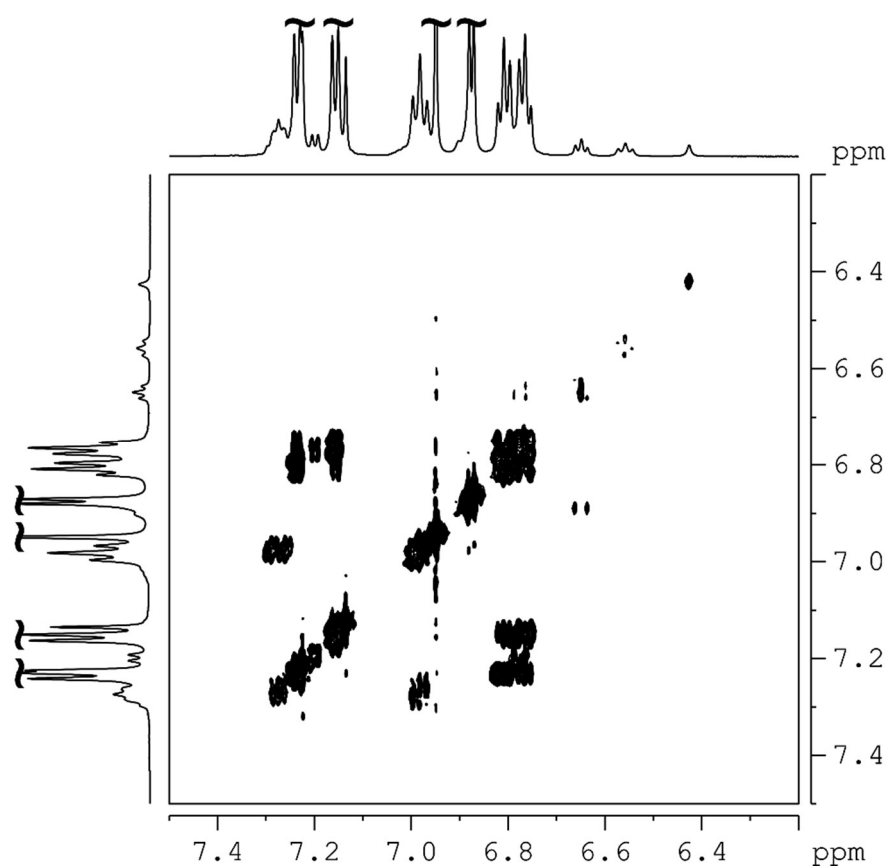


Figure A7. 2D- ^1H , ^1H COSY of azotriptycene **4** in freonic mixtures (23 mM) measured at -93°C after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

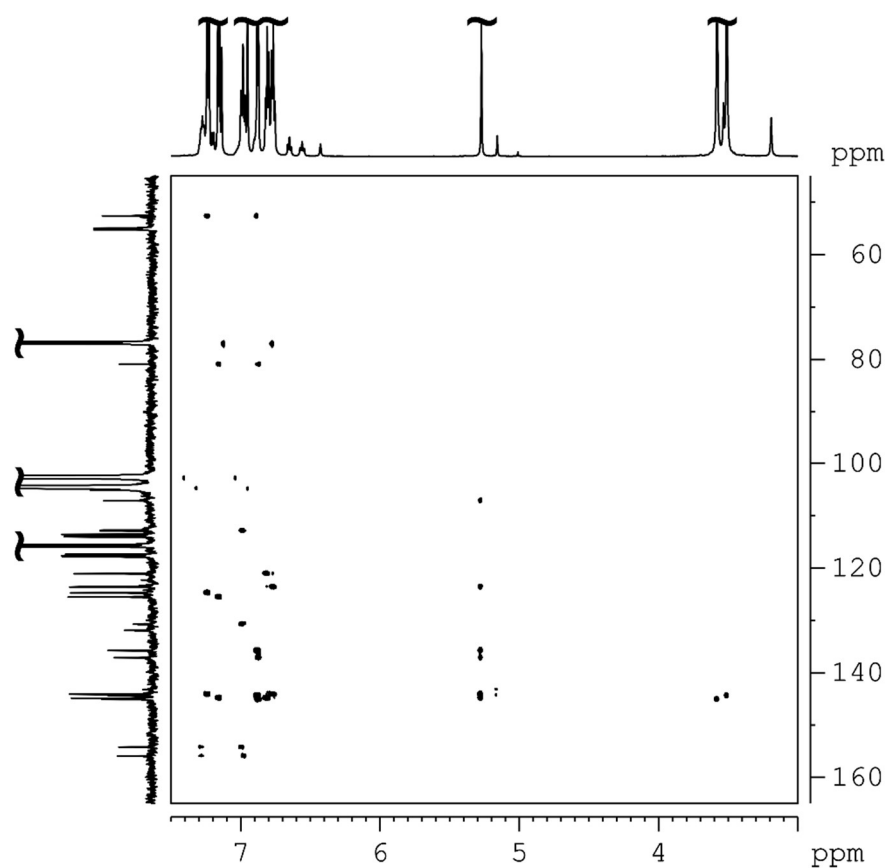


Figure A8. 2D- ^1H , ^{13}C HMBC of azotriptycene **4** in freonic mixtures (23 mM) measured at $-93\text{ }^\circ\text{C}$ after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

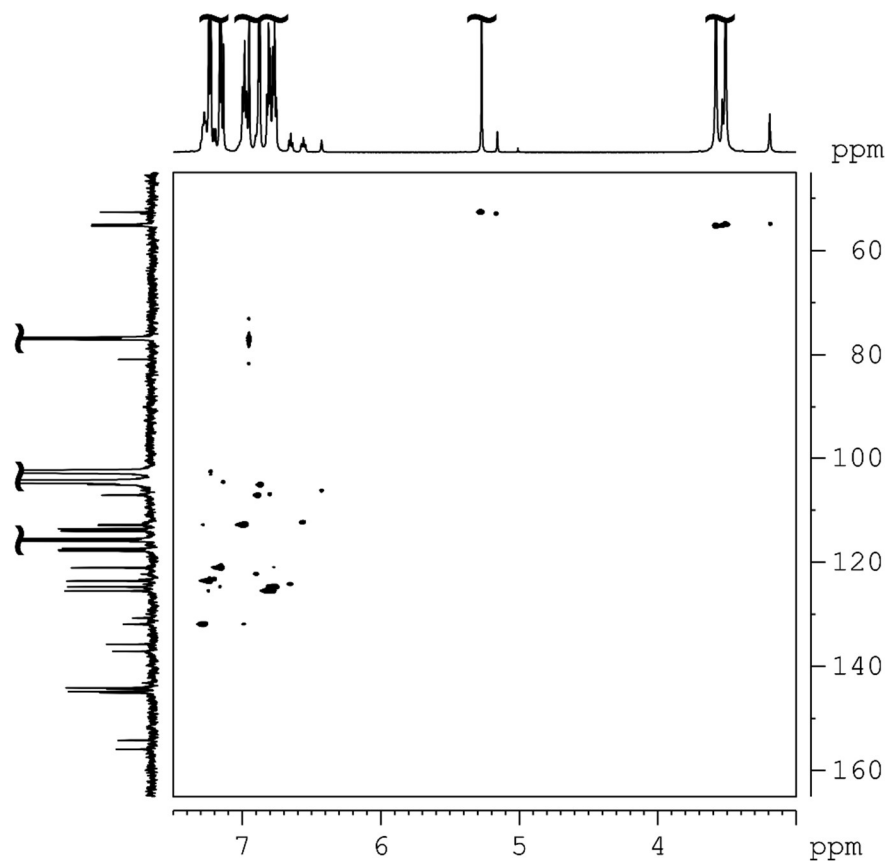


Figure A9. 2D- ^1H , ^{13}C HSQC of azotriptycene **4** in freonic mixtures (23 mM) measured at $-93\text{ }^\circ\text{C}$ after *ex situ* illumination with an LED emitting at a wavelength of 365 nm.

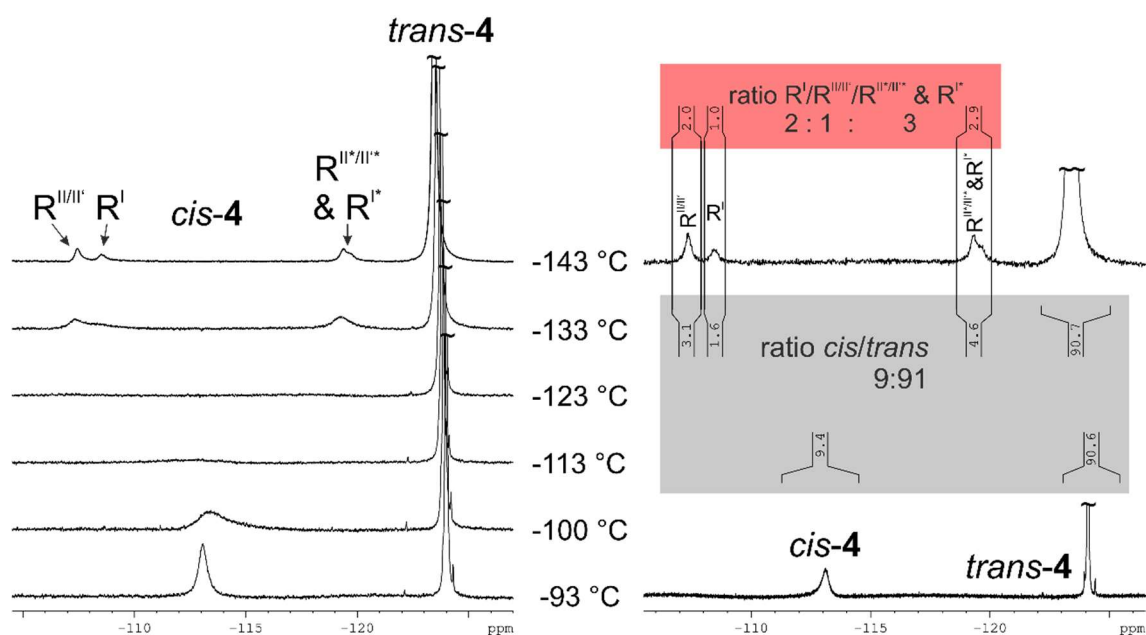
4.6.2.6 Variable temperature NMR study of azotriptycene **4**

Figure A10. Stacked 1D- ^{19}F spectra (ns = 512 - 2048) of azotriptycene **4** in freonic mixtures (23 mM) measured at different temperatures (-143 °C - -93 °C) after *ex situ* illumination with an LED emitting at a wavelength of 365 nm. Left: With decreasing temperature, splitting of the averaged *cis*-signal into four new signals can be observed. Right: Similar *cis*/*trans* ratios at -93 °C and -143 °C underpin that the four new signals correspond to *cis*-configured isomers (grey box). A ratio of 2:1:3 for $\text{R}^{\text{II'}/\text{II}'}/\text{R}^{\text{I}}/\text{R}^{\text{II}^*/\text{II}^*} & \text{R}^{\text{I}^*}$ (red box) hints at the described intermeshing mechanism with II and II' being magnetic equivalent (see chapter 4.5.5). In contrast, *trans*-**4** experiences no signal splitting.

At -93 °C due to still fast rotation along both C-N bonds only one averaged ^{19}F signal is present for *cis*-**4** (Figure A10). With decreasing the temperature in 10 °C steps a broadening of the *cis*-signal can be observed. The coalescence point is located in the temperature range from -113 °C to -123 °C. After further lowering the temperature a splitting into four new signals occurs (the two upfield shifted signals are partially overlapping). The new ^{19}F -R signals are located on both sides of the averaged *cis*-**4** signal. A matching *cis*/*trans* ratio of 9:91 for the averaged *cis*-signal at -93 °C and the set of four signals at -143 °C shows that the four new signals correspond to *cis*-configured states (Figure A10 right, grey box). The ratio of 2:1:3 of the four signals (Figure A10 right, red box) at -143 °C hints at the already described pocket interchanging mechanism (see chapter 4.5.5) with pockets II and II' representing enantiomers and thus yielding identical NMR signals.

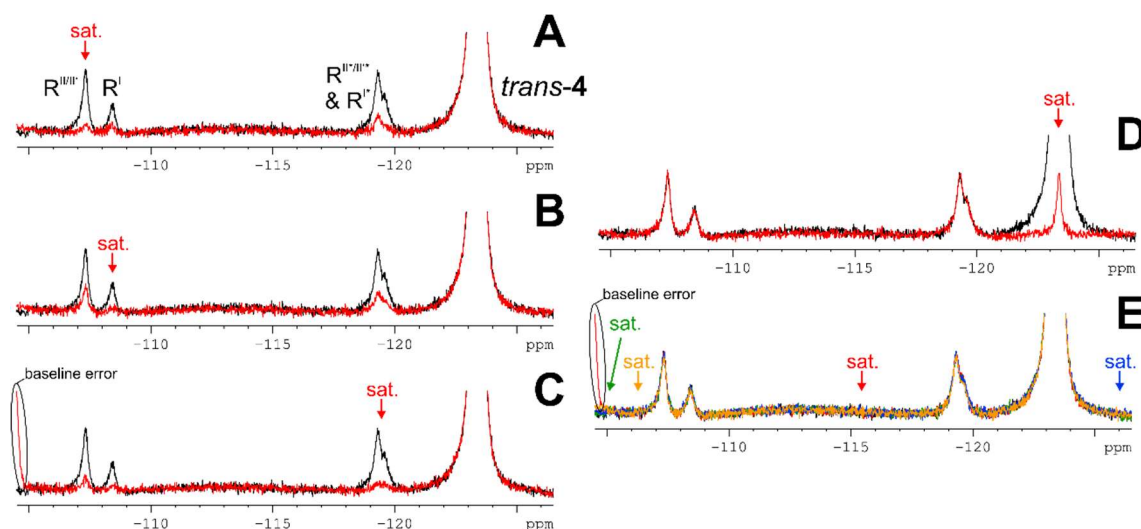
4.6.2.7 1D- ^{19}F CEST studies of azotriptycene **4** at $-143\text{ }^{\circ}\text{C}$ 

Figure A11: 1D- ^{19}F CEST experiments (ns = 256) of azotriptycene **4** in freonic mixtures (23 mM) measured at $-143\text{ }^{\circ}\text{C}$ after *ex situ* illumination with an LED emitting at a wavelength of 365 nm with selective saturation at different ppm values. The black spectrum corresponds to the control experiment with saturation pulse power = 1000 $-\text{dBW}$ = 0 W, the overlayed colored spectra correspond to the actual CEST experiments (pulse power = 35 $-\text{dBW}$; puls length = 100 ms). **A:** Selective saturation at $\text{R}^{\text{II/III'}}$ (-107.31 ppm). **B:** Selective saturation at R^{I} (-108.43 ppm). **C:** Selective saturation at $\text{R}^{\text{II*/III*}}$ & $\text{R}^{\text{I*}}$ (-119.40 ppm). **D:** Selective saturation at *trans-4* (-123.38 ppm). **E:** Selective saturation at different points of the baseline (-105.00 ppm, -106.21 ppm, -115.50 ppm, -126.00 ppm).

Selectively saturating one of the four ^{19}F -R signals assigned to different *cis-4* states at $-143\text{ }^{\circ}\text{C}$ results in a significant intensity decrease of the remaining ^{19}F -R signals (Figure A11 **A-C**). This clearly shows that all ^{19}F -R signals correspond to structures, which are in conformational exchange. These structures are highly probable *cis*-configured intermeshed states as shown for azotriptycenes **1** and **3**. There, the exchange between the different ^{19}F -R signals occurs *via* a decelerated rotation along the phenyl C-N bond within one triptycene pocket ($\text{R}^{\text{I}} \leftrightarrow \text{R}^{\text{I*}}$ or $\text{R}^{\text{II/III'}}$ $\leftrightarrow$ $\text{R}^{\text{II*/III*}}$) or *via* a decelerated rotation along the triptycene C-N bond between the different pockets ($\text{R}^{\text{I}} \leftrightarrow \text{R}^{\text{II/III'}}$ or $\text{R}^{\text{I*}} \leftrightarrow \text{R}^{\text{II*/III*}}$). The very low temperature of $-143\text{ }^{\circ}\text{C}$ required for signal splitting of *cis-4* limits the measurement time. Furthermore, the signals of $\text{R}^{\text{II*/III*}}$ and $\text{R}^{\text{I*}}$ are partially overlapping. Therefore, the kinetics for the exchange processes cannot be assessed *via* selective 1D EXSY experiments as for **1** and **3**. No saturation transfer to *trans-4* could be observed and *vice versa*, which excludes conformational exchange between these isomers (**A-D**). A high selectivity of the saturation pulse can be confirmed as the different R and *trans-4* signals preserve their intensity when the baseline is saturated in different areas of the ^{19}F spectrum with the same pulse profile (**E**).

4.6.2.8 Photoinduced and thermal isomerization between *trans*-4 and *cis*-4 at low temperatures

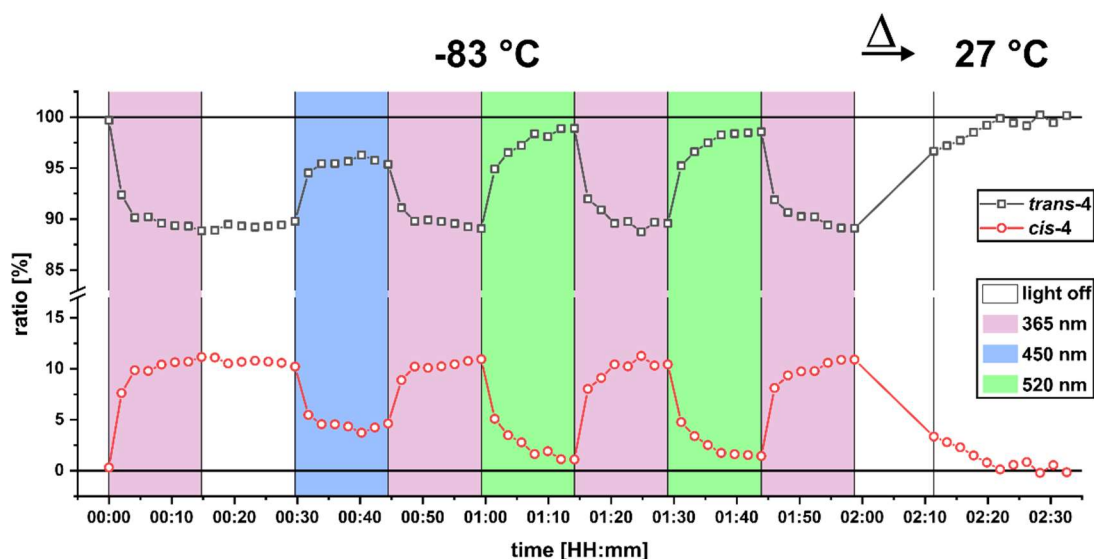


Figure A12. 1D- ^{19}F *in situ* illumination NMR kinetic (ns = 32) of azotriptycene **4** in anh. and deg. CD_2Cl_2 (25 mM) measured at $-83\text{ }^\circ\text{C}$. Illumination with LEDs emitting at different wavelengths (365 nm, 450 nm, 520 nm) results in reversible *trans* $\rightarrow$ *cis* and *cis* $\rightarrow$ *trans* isomerization. After investigating the photoswitching behavior at $-83\text{ }^\circ\text{C}$, the sample was heated to $27\text{ }^\circ\text{C}$ to obtain fast and effective thermal *cis* $\rightarrow$ *trans* back isomerization.

The reversible photoswitching capacity of azotriptycene **4** was investigated *via in situ* illumination NMR spectroscopy at $-83\text{ }^\circ\text{C}$ as an adequate population of *cis*-**4** could be obtained upon *ex situ* UV-illumination at this temperature. Furthermore, *cis*-**4** gives at this temperature a sufficiently sharp signal, which is necessary for a quantitative evaluation. Starting from the thermal equilibrium with >99% *trans*-isomer, illumination with 365 nm results within ca. 5 min in the photostationary state with a *trans/cis* ratio of 89:11. Illumination with 450 nm recovers a fraction of the *trans*-isomer. In the photostationary state a ratio of *trans/cis* = 95:5 could be obtained, which is reached after ca. 5 min. With 520 nm a *trans/cis* ratio of 99:1 is obtained after 10 min, which nearly resembles the ratio within the thermal equilibrium. The reproducibility of photoswitching was demonstrated over a total of four cycles without discernible losses. While *cis*-**4** seems reasonably stable towards thermal *cis* $\rightarrow$ *trans* isomerization at a low temperature of $-83\text{ }^\circ\text{C}$, heating-up to $27\text{ }^\circ\text{C}$ over a period of about 15 min and staying at this temperature for further 5 min re-establishes the thermal equilibrium of *trans/cis* >99:1.

4.7 References

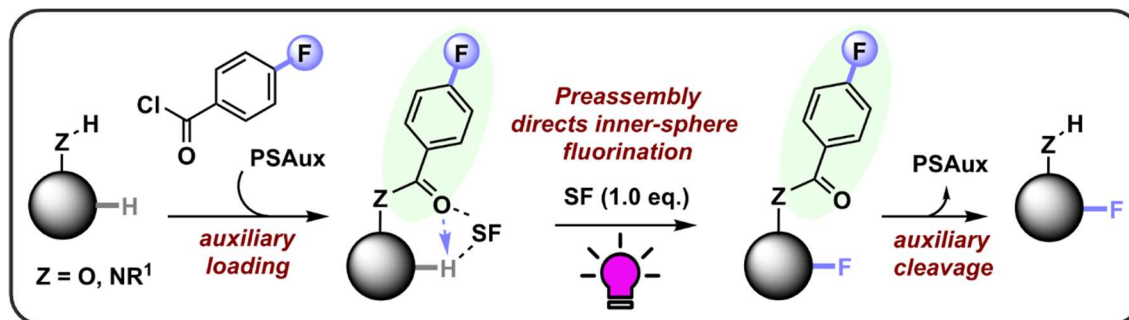
- 1 a) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem. Int. Ed.*, 2007, 46, 72–191; b) S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan and A. L. Nussbaumer, *Chem. Rev.*, 2015, 115, 10081–10206; c) R. Costil, M. Holzheimer, S. Crespi, N. A. Simeth and B. L. Feringa, *Chem. Rev.*, 2021, 121, 13213–13237; d) C. Pezzato, C. Cheng, J. F. Stoddart and R. D. Astumian, *Chem. Soc. Rev.*, 2017, 46, 5491–5507; e) V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines—Concepts and Perspectives for the Nanoworld*, Wiley-VCH, Weinheim, 2008.
- 2 a) B. L. Feringa, W. R. Browne, *Molecular Switches*, Vol. 1, Wiley-VCH, Weinheim, 2011; b) Z. Pianowski, *Molecular Photoswitches. Chemistry, Properties, and Applications*, Wiley-VCH, Weinheim, 2022.
- 3 a) G. S. Kottas, L. I. Clarke, D. Horinek and J. Michl, *Chem. Rev.*, 2005, 105, 1281–1376; b) A. Goswami, S. Saha, P. K. Biswas and M. Schmittel, *Chem. Rev.*, 2020, 120, 125–199.
- 4 a) S. Kassem, T. van Leeuwen, A. S. Lubbe, M. R. Wilson, B. L. Feringa and D. A. Leigh, *Chem. Soc. Rev.*, 2017, 46, 2592–2621; b) D. R. S. Pooler, A. S. Lubbe, S. Crespi and B. L. Feringa, *Chem. Sci.*, 2021, 12, 14964–14986.
- 5 Y. Feng, M. Ovalle, J. S. W. Seale, C. K. Lee, D. J. Kim, R. D. Astumian and J. F. Stoddart, *J. Am. Chem. Soc.*, 2021, 143, 5569–5591.
- 6 M. von Delius and D. A. Leigh, *Chem. Soc. Rev.*, 2011, 40, 3656–3676.
- 7 a) P. Štacko, J. C. M. Kistemaker, T. van Leeuwen, M.-C. Chang, E. Otten and B. L. Feringa, *Science*, 2017, 356, 964–968; b) E. Uhl, S. Thumser, P. Mayer and H. Dube, *Angew. Chem. Int. Ed.*, 2018, 57, 11064–11068; c) E. Uhl, P. Mayer and H. Dube, *Angew. Chem. Int. Ed.*, 2020, 59, 5730–5737; d) B. Regen-Pregizer and H. Dube, *J. Am. Chem. Soc.*, 2023, 145, 13081–13088.
- 8 a) Q. Li, G. Fuks, E. Moulin, M. Maaloum, M. Rawiso, I. Kulic, J. T. Foy and N. Giuseppone, *Nat. Nanotechnol.*, 2015, 10, 161–165; b) J. T. Foy, Q. Li, A. Goujon, J.-R. Colard-Itte, G. Fuks, E. Moulin, O. Schiffmann, D. Dattler, D. P. Funeriu and N. Giuseppone, *Nat. Nanotechnol.*, 2017, 12, 540–545; c) M. Kathan, S. Crespi, N. O. Thiel, D. L. Stares, D. Morsa, J. de Boer, G. Pacella, T. van den Enk, P. Kobauri, G. Portale, C. A. Schalley and B. L. Feringa, *Nat. Nanotechnol.*, 2021.
- 9 N. N. Bach, V. Josef, H. Maid and H. Dube, *Angew. Chem. Int. Ed.*, 2022, 61, e202201882.
- 10 a) K. Mislow, *Acc. Chem. Res.*, 1976, 9, 26–33; b) S. Perez-Estrada, B. Rodriguez-Molina, E. F. Maverick, S. I. Khan and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2019, 141, 2413–2420; c) B. Rodriguez-Molina, N. Farfan, M.

- Romero, J. M. Mendez-Stivalet, R. Santillan and M. A. Garcia-Garibay, *J. Am. Chem. Soc.*, 2011, 133, 7280–7283; d) D. K. Frantz, A. Linden, K. K. Baldrige and J. S. Siegel, *J. Am. Chem. Soc.*, 2012, 134, 1528–1535; e) C. Lemouchi, K. Iliopoulos, L. Zorina, S. Simonov, P. Wzietek, T. Cauchy, A. Rodriguez-Fortea, E. Canadell, J. Kaleta, J. Michl, D. Gindre, M. Chrysos and P. Batail, *J. Am. Chem. Soc.*, 2013, 135, 9366–9376; f) S. Abid, Y. Gisbert, M. Kojima, N. Saffon-Merceron, J. Cuny, C. Kammerer and G. Rapenne, *Chem. Sci.*, 2021, 12, 4709–4721.
- 11a) J. Chen, F. K. Leung, M. C. A. Stuart, T. Kajitani, T. Fukushima, E. van der Giessen and B. L. Feringa, *Nat. Chem.*, 2018, 10, 132–138; b) J. Boelke and S. Hecht, *Adv. Optical Mater.*, 2019, 7, 1900404; c) T. Orlova, F. Lancia, C. Loussert, S. Iamsaard, N. Katsonis and E. Brasselet, *Nat. Nanotechnol.*, 2018, 13, 304–308; d) S. Iamsaard, S. J. Aßhoff, B. Matt, T. Kudernac, J. J. L. M. Cornelissen, S. P. Fletcher and N. Katsonis, *Nat. Chem.*, 2014, 6, 229–235.
- 12a) J. Berna, D. A. Leigh, M. Lubomska, S. M. Mendoza, E. M. Perez, P. Rudolf, G. Teobaldi and F. Zerbetto, *Nat. Mater.*, 2005, 4, 704–710; b) R. Eelkema, M. M. Pollard, J. Vicario, N. Katsonis, B. S. Ramon, C. W. Bastiaansen, D. J. Broer and B. L. Feringa, *Nature*, 2006, 440, 163.
- 13 W. Danowski, T. van Leeuwen, S. Abdolazadeh, D. Roke, W. R. Browne, S. J. Wezenberg and B. L. Feringa, *Nat. Nanotechnol.*, 2019, 14, 488–494.
- 14a) T. R. Kelly, M. C. Bowyer, K. V. Bhaskar, D. Bebbington, A. Garcia, F. Lang, M. H. Kim and M. P. Jette, *J. Am. Chem. Soc.*, 1994, 116, 3657–3658; b) J.-S. Yang, Y.-T. Huang, J.-H. Ho, W.-T. Sun, H.-H. Huang, Y.-C. Lin, S.-J. Huang, S.-L. Huang, H.-F. Lu and I. Chao, *Org. Lett.*, 2008, 10, 2279–2282.
- 15 M. K. Ter Wiel, R. A. van Delden, A. Meetsma and B. L. Feringa, *Org. Biomol. Chem.*, 2005, 3, 4071–4076.
- 16 H. Ube, Y. Yasuda, H. Sato and M. Shionoya, *Nat. Commun.*, 2017, 8, 14296.
- 17 D. Roke, C. Stuckhardt, W. Danowski, S. J. Wezenberg and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2018, 57, 10515–10519.
- 18 A. Gerwien, F. Gnannt, P. Mayer and H. Dube, *Nat. Chem.*, 2022, 14, 670–676.
- 19a) K. Hirose, *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 2010, 68, 1–24; b) W. T. Sun, Y. T. Huang, G. J. Huang, H. F. Lu, I. Chao, S. L. Huang, S. J. Huang, Y. C. Lin, J. H. Ho and J. S. Yang, *Chem. Eur. J.*, 2010, 16, 11594–11604.
- 20 W. S. Tan, P. Y. Chuang, C. H. Chen, C. Prabhakar, S. J. Huang, S. L. Huang, Y. H. Liu, Y. C. Lin, S. M. Peng and J. S. Yang, *Chem. Asian J.*, 2015, 10, 989–997.

- 21 M. C. Basheer, Y. Oka, M. Mathews and N. Tamaoki, *Chem. Eur. J.*, 2010, 16, 3489–3496.
- 22 A. Kunz, N. Oberhof, F. Scherz, L. Martins, A. Dreuw and H. A. Wegner, *Chem. Eur. J.*, 2022, 28, e202200972.
- 23 M. Schmittl and C. Ruechardt, *J. Am. Chem. Soc.*, 1987, 109, 2750–2759.
- 24 a) W. Theilacker, K. Albrecht and H. Uffmann, *Chem. Ber.*, 1965, 98, 428–432; b) W. Theilacker and K.-H. Beyer, *Chem. Ber.*, 1961, 94, 2968–2977; c) Y. Kawada, H. Yamazaki, G. Koga, S. Murata and H. Iwamura, *J. Org. Chem.*, 1986, 51, 1472–1477.
- 25 L. Schweighauser, M. A. Strauss, S. Bellotto and H. A. Wegner, *Angew. Chem. Int. Ed.*, 2015, 54, 13436–13439.
- 26 a) N. Lokesh, A. Seegerer, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.*, 2018, 140, 1855–1862; b) C. Lorenz, F. Hastreiter, J. Hioe, N. Lokesh, S. Gartner, N. Korber and R. M. Gschwind, *Angew. Chem. Int. Ed.*, 2018, 57, 12956–12960; c) S. Wang, N. Lokesh, J. Hioe, R. M. Gschwind and B. König, *Chem. Sci.*, 2019, 10, 4580–4587; d) V. Ramanujam, C. Charlier and A. Bax, *Angew. Chem. Int. Ed.*, 2019, 58, 15309–15312; e) V. Guivel-Scharen, T. Sinnwell, S. D. Wolff and R. S. Balaban, *J. Magn. Reson.*, 1998, 133, 36–45; f) K. M. Ward, A. H. Aletras and R. S. Balaban, *J. Magn. Reson.*, 2000, 143, 79–87.
- 27 J. H. Overbeck, W. Kremer and R. Sprangers, *J. Biomol. NMR*, 2020, 74, 753–766.
- 28 a) M. H. Haindl, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.* 2015, 137, 12835–12842; b) S. Forsén and R. A. Hoffman, *J. Chem. Phys.*, 1963, 39, 2892–2901; c) I. D. Campbell, C. M. Dobson, R. G. Ratcliffe and R. J. P. Williams, *J. Magn. Reson.*, 1978, 29, 397–417; d) C. L. Perrin and E. R. Johnston, *J. Magn. Reson.*, 1979, 33, 619–626; e) S. N. Aski, Z. Takacs and J. Kowalewski, *Magn. Reson. Chem.*, 2008, 46, 1135–1140.
- 29 Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, 232, 39–44.
- 30 a) A. D. Bain, in *Encyclopedia of Spectroscopy and Spectrometry*, 2017, pp. 180–187; b) G. Binsch and H. Kessler, *Angew. Chem. Int. Ed.*, 1980, 19, 411–428; c) H. Kessler, *Angew. Chem.*, 1970, 82, 237–253; d) C. S. Johnson, *Chemical Rate Processes and Magnetic Resonance*; Academic Press Inc. 1965, Vol. 1.
- 31 a) V. Guivel-Scharen, T. Sinnwell, S. D. Wolff and R. S. Balaban, *J. Magn. Reson.*, 1998, 133, 36–45; b) N. Lokesh, A. Seegerer, J. Hioe and R. M. Gschwind, *J. Am. Chem. Soc.*, 2018, 140, 1855–1862; c) C. Lorenz, F. Hastreiter, J. Hioe, N. Lokesh, S. Gartner, N. Korber and R. M. Gschwind, *Angew. Chem.*

- Int. Ed., 2018, 57, 12956-12960; d) S. Wang, N. Lokesh, J. Hioe, R. M. Gschwind and B. König, *Chem. Sci.*, 2019, 10, 4580-4587; e) K. M. Ward, A. H. Aletras and R. S. Balaban, *J. Magn. Reson.*, 2000, 143, 79-87.
- 32 a) B. Choe, G. W. Cook and N. R. Krishna, *J. Magn. Reson.*, 1991, 94, 387–393; b) W. Lee and N. R. Krishna, *J. Magn. Reson.*, 1992, 98, 36–48; c) C. J. Szantay and A. Demeter, *J. Magn. Reson.*, 1995, 115, 94–105; d) J. L. Yan, X. A. Mao and L. F. Shen, *Chem. Phys. Lett.*, 1997, 272, 278–283.
- 33 H. Günther, *NMR Spectroscopy*, 3rd ed.; Wiley-VCH, Weinheim, 2013.
- 34 a) J. S. Siegel and F. A. L. Anet, *J. Org. Chem.*, 1988, 53, 2629–2630; b) I. G. Shenderovich, A. P. Burtsev, G. S. Denisov, N. S. Golubev, H.-H. Limbach, *Magn. Reson. Chem.*, 2001, 39, 91–99.

5. Benzoates as Photosensitization Catalysts and Auxiliaries in Efficient, Practical, Light-Powered Direct C(sp³)-H Fluorinations



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S. Yakubov discovered and optimized the photocatalytic and photochemical reaction conditions, synthesized most substrates, synthesized and purified all products, performed synthetic experimental mechanistic studies, measured UV-visible spectra and grew crystals for XRD. **Willibald J. Stockerl** conducted all studies on NMR kinetics and DOSY experiments and discovered the induction period and different aggregation states of SF. **Willibald J. Stockerl** assisted with 2D NMR structural assignments of complex fluorinated products. X. Tian synthesized several substrates and scientifically guided and supervised S. Yakubov throughout the project. A. Shahin measured luminescence spectroscopy of SF and MFB. M. J. P. Mandigma performed DFG and TD-DFT calculations and calculated triplet energies. J. P. Barham conceptualized the project, guided and supervised S. Yakubov, X. Tian, M. J. P. Mandigma and A. Shahin in their contributions. R. M. Gschwind guided and supervised **Willibald J. Stockerl**, who together wrote the NMR spectroscopic parts of the manuscript and ESI. S. Yakubov and J. P. Barham wrote all other sections of the manuscript and ESI and addressed peer review additions and corrections. All authors contributed to proofreading the manuscript.

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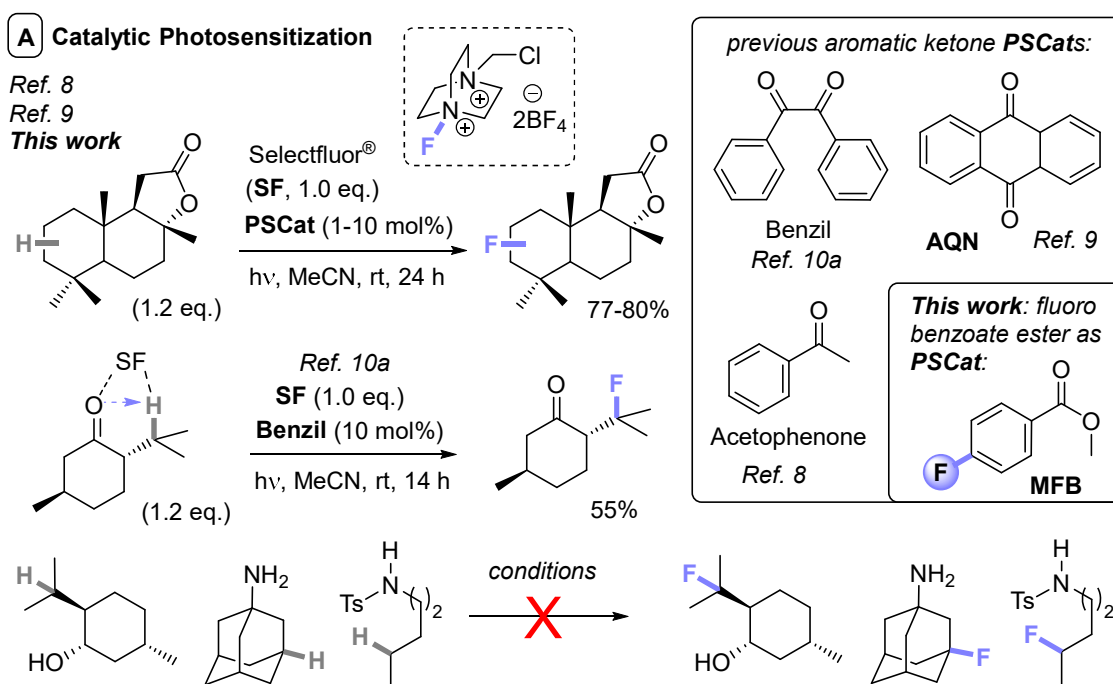
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5.1 Abstract

Of the methods for direct fluorination of unactivated C(sp³)-H bonds, photosensitization of SelectFluor is a promising approach. Although many substrates can be activated with photosensitizing catalysts, issues remain that hamper fluorination of complex molecules. Alcohol- or amine-containing groups are unsuccessful, fluorination regioselectivity follows factors endogenous to the substrate and cannot be influenced by the catalyst, and reactions are highly air-sensitive. We report that benzoates serve as highly efficient photosensitizers which, in combination with SelectFluor, enable visible light-powered direct fluorination of unactivated C(sp³)-H bonds. Compared to previous photosensitizer architectures, the benzoate has versatility to function both i) as a photosensitizing catalyst for simple substrate fluorinations ii) as a photosensitizing auxiliary for complex molecule fluorinations that is easily installed and removed without compromising yield. Our auxiliary approach i) substantially decreases the reaction's induction period, ii) enables C(sp³)-H fluorination of many substrates that fail under catalytic conditions, iii) increases kinetic reproducibility, iv) promotes reactions to higher yields, in shorter times, on multigram scales, and even *under air*. Observations and mechanistic studies suggest an intimate 'assembly' of auxiliary and SelectFluor prior/after photoexcitation. The auxiliary allows other E_nT photochemistry *under air*. Examples show how auxiliary placement proximally directs regioselectivity, where previous methods are substrate-directed.

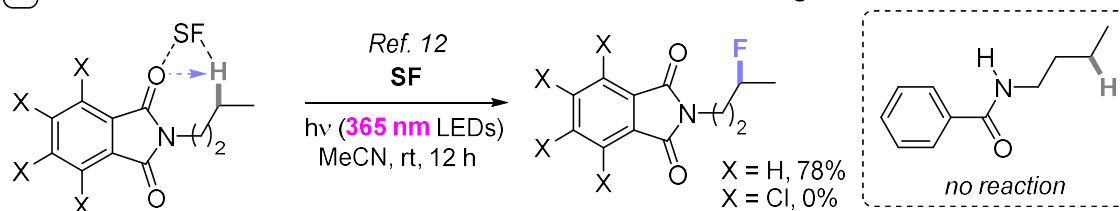
5.2 Introduction

Although numerous methods have been developed for fluorination reactions of C–H bonds, such as the fluorination of carbanions,¹ arylpalladium complexes,² and the addition of electrophilic fluorine to alkenes,³ few methods permit the direct fluorination of unactivated C(sp³)–H bonds.⁴ Such a transformation is particularly advantageous for the late-stage functionalization (LSF) of complex molecules, especially since F atoms as H atom bioisosteres impart vastly different - and usually favorable - properties (physical, ADME, lipophilicity) in a pharmaceutical/agrochemical context.⁵ Of these, methods that involve photosensitization of SelectFluor (**SF**) are particularly attractive for their mild conditions and use of light as a sustainable, uncontaminating energy to drive reactivity.⁶ Here, **SF** functions as both a fluorine source and an activator of C(sp³)–H bonds; since quinuclidinium-type radical cations are powerful and selective hydrogen atom transfer (HAT) agents.⁷ Pioneering studies by Chen⁸ and Tan⁹ demonstrated photocatalytic, direct fluorinations of unactivated C(sp³)–H bonds by employing acetophenone or anthraquinone (**AQN**) as photosensitization catalysts (**PSCats**, Figure 1A). Fluorination regioselectivity was governed by thermodynamic factors endogenous to the substrate; the most electron-rich C(sp³)–H bond that forms a stable 2° radical intermediate is fluorinated. Lectka used benzil as an alternative **PSCat** for the late-stage photocatalytic fluorination of complex molecules,¹⁰ including steroid derivatives, and found that ketones/enones innate to the substrate could direct regioselective C(sp³)–H fluorination in a proximal or distal fashion (Figure 1A).



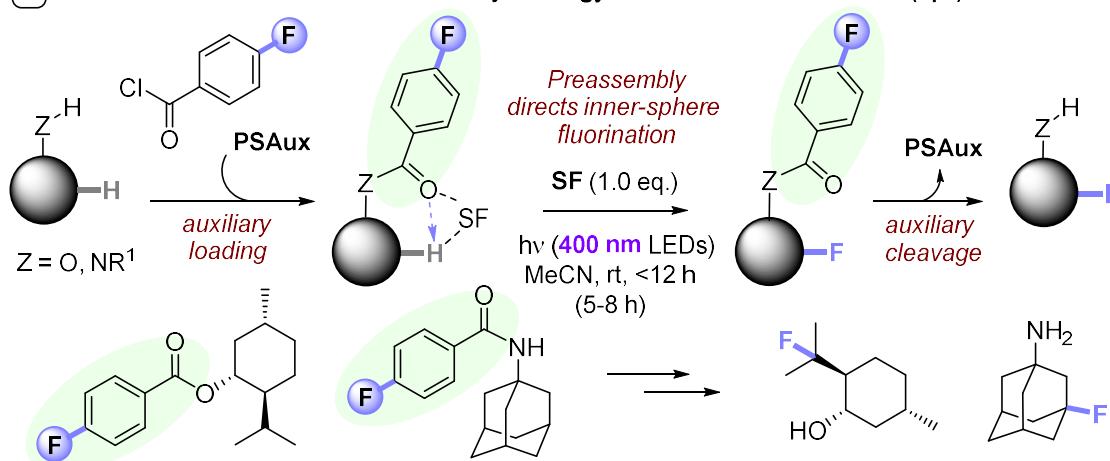
Catalytic method drawbacks: No unprotected 1°/2° alcohols/amines, only 3° alcohols
No protected 1° amines Long times Air sensitive (freeze-pump-thaw/Ar)

B Previous work: Phthalimide as a Photosensitization and Directing Handle



Drawbacks: Limited substrate scope UV-A light Not applicable to alcohols and amines

C This work: Photosensitization Auxiliary Strategy Accelerates and Directs C(sp³)-H Fluorination



Generality:

1°, 2°, 3° alcohols and amines ✓
Shorter reaction times, higher yields ✓
Late-stage fluorination of complex molecules ✓

Practicality:

Multigram scales, no freeze-pump-thaw/Argon ✓
Accessible loading/cleavage in >95% yields ✓
Visible light irradiation ✓ Works under air! ✓

Figure 1. Photochemical direct fluorination of unactivated C(sp³) –H bonds. **A)** Previous uses of catalytic aryl ketone photosensitizers and discovery herein of a catalytic benzoate photosensitizer. **B)** Phthalimides as a photosensitization handle. **C)** A general, efficient, selective, and rapid photosensitization auxiliary strategy.

Further examples of photosensitized C(sp³)-H fluorination have successfully engaged benzylic positions of simple substrates^{10a} or complex peptides,^{10c} as well as ketal substrates.^{10e} In most cases, **PSCats** belonged to the family of aryl ketones as a privileged architecture for photosensitization, whose success has been attributed to the matching of triplet energies with **SF₆**.^{9a} While the utilized aryl ketone catalysts alone do not absorb visible light, their assembly with **SF₆** affords a charge transfer complex with a tailing absorption >400 nm.^{9b} However, in all cases fluorinations of molecules containing 1°/2° alcohols or amines were unsuccessful (only 3° alcohols were tolerated), likely due to competing nucleophilic destruction of **SF₆** when the photochemical reaction is kinetically slow.¹¹ This severely hampers applications to complex bioactive molecules such as pharmaceuticals. Recently, Egami and Hamashima¹² found molecules with *N*-alkylphthalimides underwent directed photochemical C(sp³)-H fluorination of their alkyl chains (Figure 1B). However, both an *N*-alkyl tetrachlorophthalimide and an *N*-alkyl benzamide derivative were unsuccessful, leading authors to suggest a key role for the

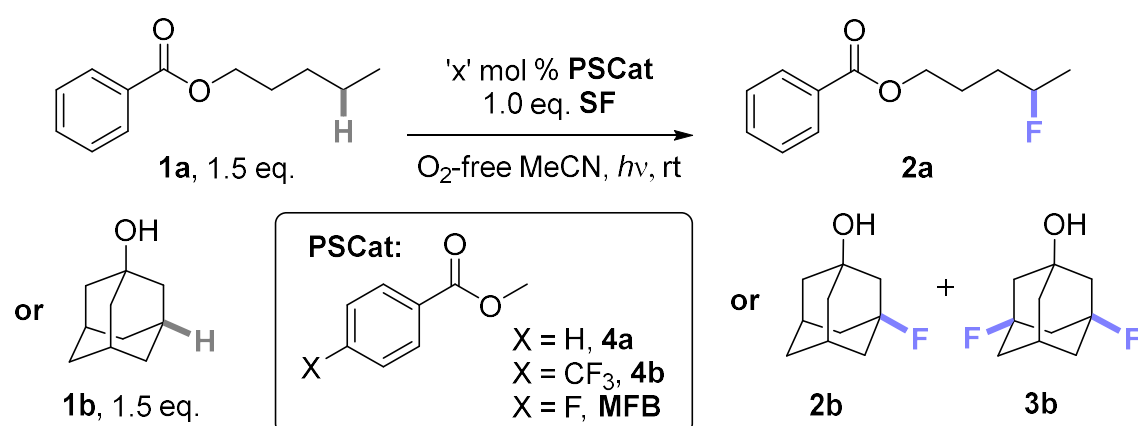
phthalimide's triplet energy. The phthalimide could be considered as a 'photosensitization auxiliary' (**PSAux**) that can be cleaved to reveal a fluorinated 1° amine, though this was not realized and would typically require toxic, explosive hydrazine.

We envisioned a **PSAux** that is easily incorporated and removed could increase the generality and rapidity of photochemical C(sp³)-H fluorinations. The **PSAux** may form an intimate assembly with **SF** for inner-sphere photochemistry, increasing reaction efficiency. Moreover, an appropriately designed **PSAux** (e.g. containing a C=O group^{10a}) may even provide a user handle to direct regioselectivity, where all previous reports follow factors endogenous to the substrate. Herein, we report the discovery of benzoate esters as novel, versatile photosensitizer architectures. Methyl 4-fluorobenzoate serves as a photosensitizing catalyst for fluorination of simple substrates, while the 4-fluorobenzoyl group serves as a **PSAux** for the fluorination of complex molecules containing alcohols and amines and can be easily installed and removed without compromising product yields. The **PSAux** strategy i) markedly increases the efficiency, rapidity, reliability and practicality of C(sp³)-H fluorination reactions; ii) enables reactions of substrates that cannot be engaged with photocatalysis (alcohols and amines, where previous catalytic methods were only applicable to 3° alcohols); iii) allows reactions to succeed under air atmosphere and iv) offers promise to direct fluorination regioselectivity (Figure 1C).

5.3 Results and Discussion

Discovery. When examining the C(sp³)-H fluorination of amyl benzoate **1a** to **2a** as reported by Tan and co-workers^{9a} (Table 1, entries 1-2) with **AQN** and derivatives, we found that no catalyst was necessary; the reaction proceeded in its absence at 365 and 400 nm (entries 3-4). The **PSCat**-free reaction did not proceed at 451 nm or in the absence of light (entries 5-6). Assuming that **1a** was acting as a photosensitizer for its own self-fluorination, we reasoned that arylbenzoate esters may function as exogenous **PSCats** in the C(sp³)-H fluorination of 1-adamantanol **1b** to **2b** and **3b**. However, **1a** was an ineffective **PSCat** (entry 7). Assuming that self-fluorination of **1a** may deactivate its catalysis of the fluorination of **1b**, methyl benzoate (**4a**) was attempted but was similarly unsuccessful (entry 8). While other *para*-substituted benzoate esters (**4**, where X = Cl, Br, CF₃, entry 9) were also ineffective (see ESI), methyl 4-fluorobenzoate (**MFB**) was a surprisingly effective **PSCat** (entry 10), delivering a 46% yield of **2b**(+**3b**) compared to an ineffective control reaction without **PSCat** (entry 11). Employing 10 mol% of **MFB** provided **2b**+**3b** in an improved 71% yield (entry 13). Doubling the overall concentration of **1b** to 0.31 M and decreasing catalyst loading at this higher overall concentration also improved the yield (entry 15). For both the low and high concentration conditions, a higher power LED further increased the yield of **2b**+**3b** in a shorter reaction time (entries 14 and 17, termed ‘conditions A’ and ‘conditions B’, respectively), although 6 h was here insufficient for full conversion (entry 16). Air, protic additives and using an equimolar ratio of SelectFluor (vs substrate) were all detrimental to the reaction (for full investigations, see ESI).

Table 1. Initial Investigations and Optimization of Conditions.

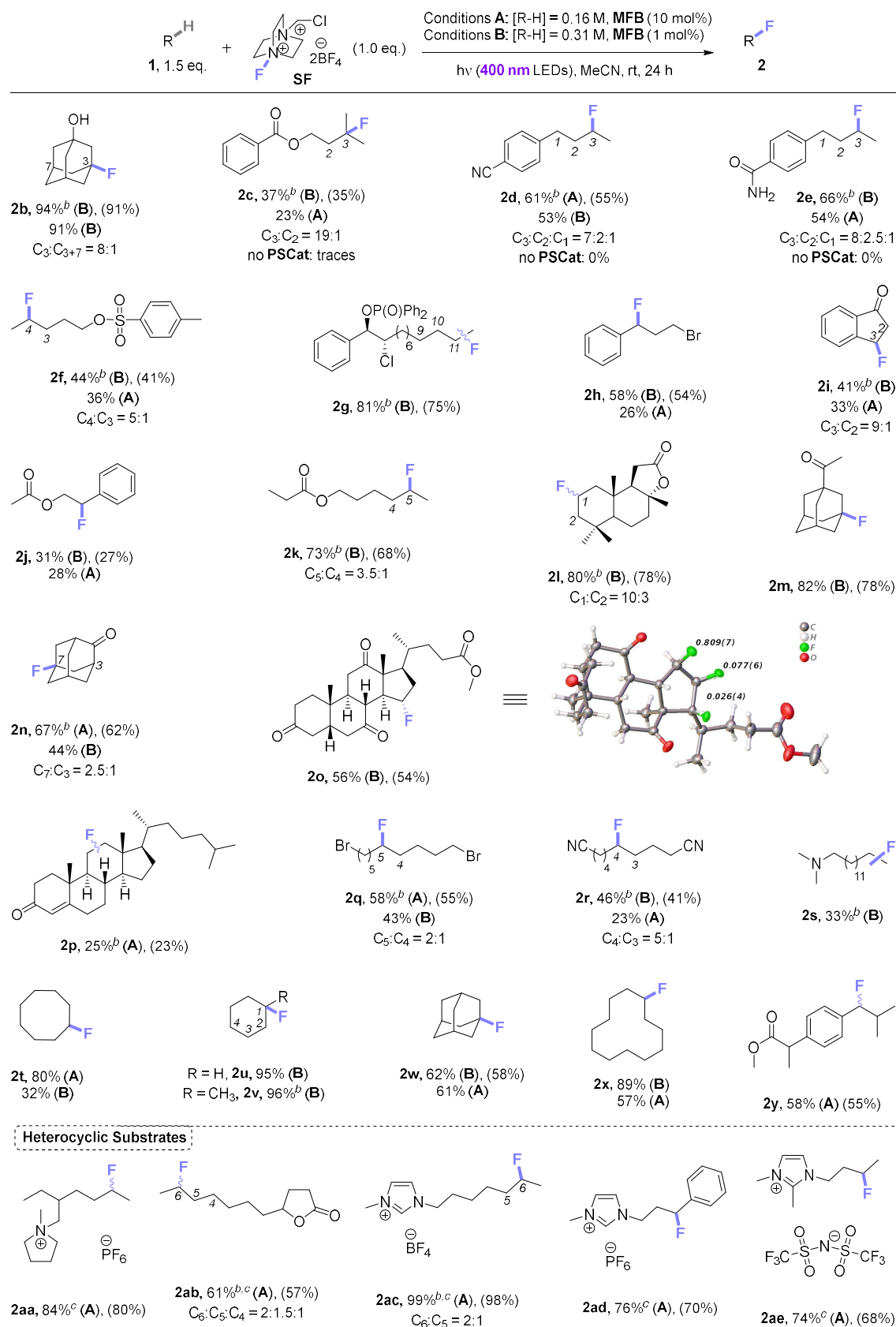


entry	substrate ^a	PSCat, 'x'	λ [nm]	t [h]	product, yield
1	1a	AQN , 2%	365	48	2a , 46% ^b
2	1a	AQN , 2%	400	48	2a , 46% ^b
3	1a	-	365	48	2a , 55% ^b
4	1a	-	400	48	2a , 44% ^b
5	1a	-	451	24	2a , n.d.
6	1a	-	-	24	2a , n.d.
7	1b	1a , 5%	400	24	2b , <5%; 3b , n.d.
8	1b	4a , 5%	400	24	2b , n.d.; 3b , n.d.
9	1b	4b , 5%	400	24	2b , <5%; 3b , n.d.
10	1b	MFB , 5%	400	24	2b , 43%; 3b , 3%
11	1b	-	400	48	2b , <5%; 3b , n.d.
12	1b	MFB , 5%	400	48	2b , 53%; 3b , 5%
13	1b	MFB , 10%	400	48	2b , 65%; 3b , 6%
14 ^{c,d}	1b	MFB , 10%	400	24	2b , 75%; 3b , 6%
15	1b	MFB , 1%	400	48	2b , 60%; 3b , 12%
	[0.31 M]				
16 ^c	1b	MFB , 1%	400	6	2b , 28%; 3b , 3%
	[0.31 M]				
17 ^{c,e}	1b	MFB , 1%	400	24	2b , 84%; 3b , 10%
	[0.31 M]				
18 ^f	1b	MFB , 1%	400	24	2b , <5%; 3b , n.d.
	[0.31 M]				

n.d., not detected; ^aUnless otherwise specified, substrate concentration was [0.16 M] and a 0.35 W 400 nm LED was employed. ^bYields determined by ¹⁹F NMR spectroscopy with trifluorotoluene as an internal standard and correspond to combined fluorinated regioisomers. ^cA 3.8 W LED was employed. ^dHereafter termed conditions **A**. ^eHereafter termed conditions **B**. ^fPrepared under air.

Synthetic Scope of PSCat method. Under these photocatalytic conditions, the C(sp³)-H fluorinations of a variety of small molecules was achieved in modest to excellent (31-94%) yields (Table 2). Though electronically bearing resemblance to amyl benzoate, substrates **1c-1e** did not fluorinate in the absence of **MFB**. Substrates **1c-1g** underwent fluorination not at their benzylic nor terminal positions but at the most electron rich C(sp³)-H bond that involves a 2° radical intermediate. Substrates **1h-1j** underwent benzylic fluorination likely due to their benzylic C(sp³)-H bonds being the least electron-deficient. Aliphatic esters **1k**, **1l** (Sclareolide), **1y** (Ibuprofen methyl ester) – and aliphatic ketone **1m** – were all fluorinated at their most electron-rich C(sp³)-H bonds remote from the carbonyl group.

Table 2. Scope of photocatalytic C(sp³)-H fluorination method.

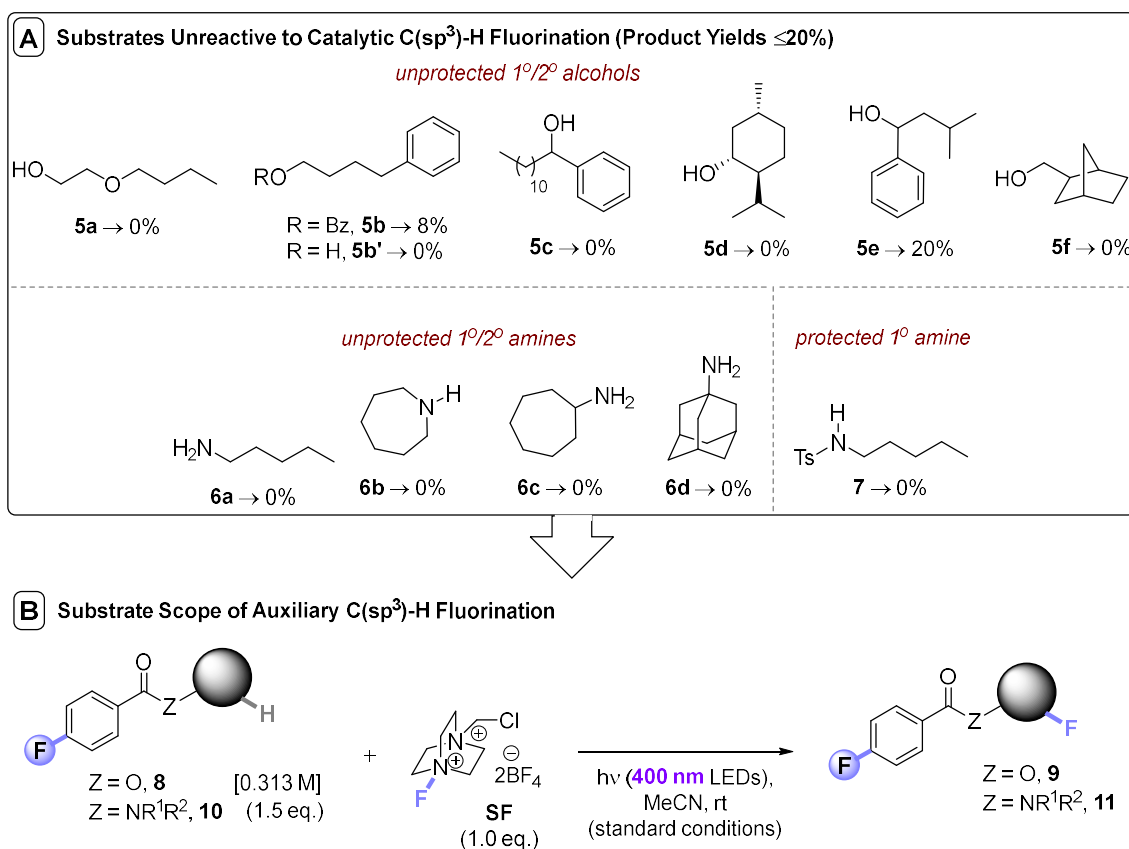


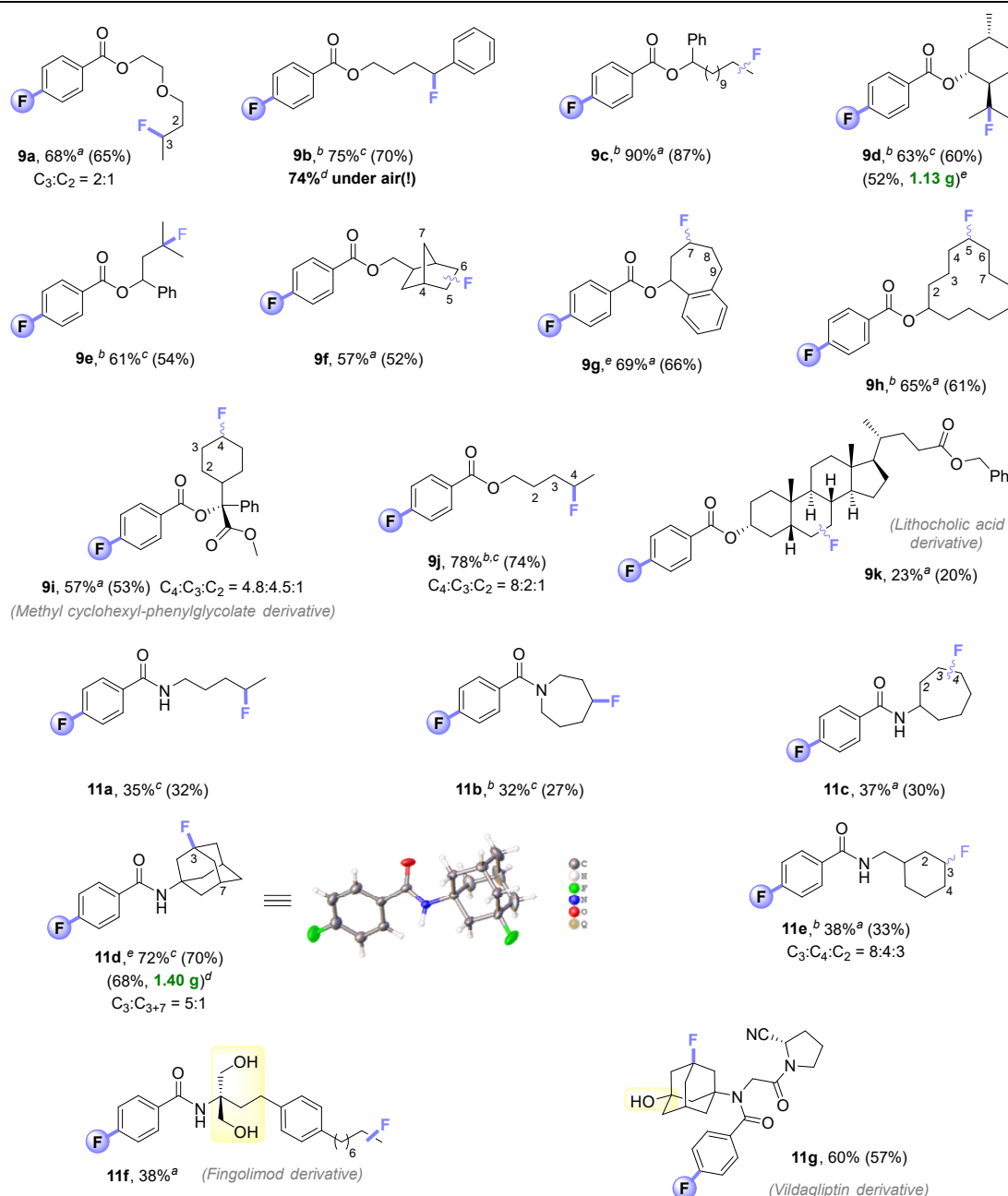
For substrates with more than one regioisomer, the major isomer is depicted. NMR yields were determined by ¹⁹F NMR with trifluorotoluene as internal standard (IS). Unless explicitly defined, yields correspond to a single regioisomer. Isolated yields in parenthesis. ^aYield corresponds to a mixture of regioisomers. ^b2.0 eq. of SF used.

Steroidal derivatives **1o**, cholest-4-en-3-one (**1p**) were successfully fluorinated. Bromoalkane **1q**, cyanoalkane **1r** and trialkylamine **1s** were fluorinated at their most electron rich C(sp³)-H positions. When unactivated hydrocarbons **1t-1x** were subjected to the reaction, C(sp³)-H was selective for 3° positions > 2° positions (when present). Both pyrrolidinium and imidazolium-type ionic liquids (**1aa**, **1ac-1ae**) and a common food flavor additive (Undecanoic g-lactone, **1ab**) were fluorinated in good to excellent (61-99%) yields demonstrating i) the tolerance of heterocyclic motifs (also see **1l**) and ii) synthetic utility of the method for ‘real-world’ molecules.

Despite a reasonably broad scope of applications of this catalytic method, we noticed that apart from 3° alcohols (e.g. **1b**), free alcohols (**5a,5c-5e,5g**) and free amines (**6a-6d**) all failed under photocatalytic C(sp³)-H fluorinations (Table 3). We note that in the earlier reports of Chen,⁸ Tan,^{9a} and Lectka,¹⁰ free 1° or 2° alcohols were never reported, only hindered 3° alcohols were tolerated. Neither were free 1°/2°/3° amine moieties; 1° and 2° amines always required protection.

Table 3. Scope of photosensitization auxiliary C(sp³)-H fluorination method. **A)** Unreactive, unprotected substrates. **B)** Scope of photosensitization auxiliary method.^a





For substrates with more than one regioisomer, the major isomer is depicted. NMR yields were determined by ¹⁹F NMR with trifluorotoluene as internal standard (IS). Unless explicitly defined, yields correspond to a single regioisomer. Isolated yields in parenthesis. ^bYield corresponds to a mixture of regioisomers. ^cCompleted in 10 h. ^dIsolated yields of gram scale reactions. ^eReaction complete in 5 h.

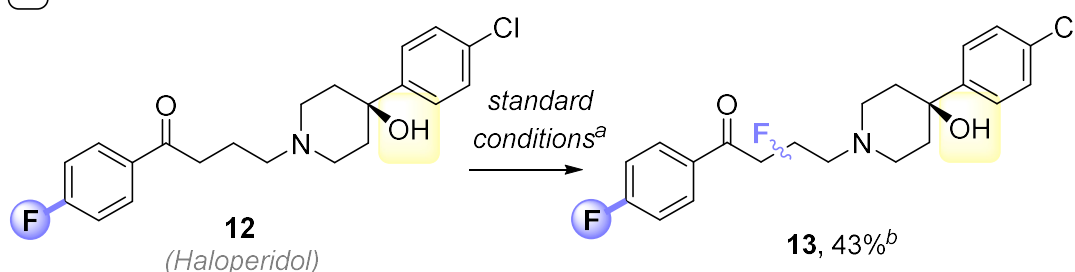
Even protected 1° amide **7** did not fluorinate in this case. One explanation could be that if the desired reactivity is too slow, nucleophilic destruction of SelectFluor (known to occur with 1° and 3° amines)¹³ may emerge as a competitive thermal reaction, arising lower yields or no reactivity. The steric hinderance of 3° alcohols – the only class of free alcohols that worked in the previous reports – may explain their tolerance. However, since nucleophilic 3° amines did proceed (**1s**, **1z**) albeit in low (33%, 18%) yields, there

may be other factors responsible for the failure of 1° and 2° alcohols/amines/amides. **SF**'s known interactions with a wide range of functional groups in ground state chemistry – such as Lewis acid interactions with C-O bonds and fluorinations of nucleophilic (S,N) atoms¹⁴ – are likely detrimental to its use in photocatalytic C(sp³)-H fluorinations. Another explanation is that hydrogen bonding networks around alcohol/water-solvated **SF** prohibit its non-covalent assembly with the aromatic **PSCat** that is needed for successful photochemistry (*vide infra*).^{9b} Interestingly, although **5b** has no unprotected alcohol and contained a privileged benzylic C(sp³)-H bond, it also reacted poorly (8% yield).

Synthetic Scope of PSAux method. At this juncture, we considered that a key advantage of our 4-fluorobenzoate photosensitizer compared to previously-employed aryl ketone **PSCats** was the ability to reversibly attach it to alcohol and amine substrates and cleave after photochemical fluorination: a 'photosensitization auxiliary' (**PSAux**) approach. Not only would this enable C(sp³)-H fluorinations that were catalytically inefficient or impossible (such as complex molecules), it would accelerate reaction kinetics and improve reproducibility (*vide infra*). Moreover, it would improve practicality by decreasing atmospheric sensitivity and simplify purification of otherwise highly polar unprotected substrates. Thus, a variety of alcohols **8** and amines **10** were loaded with the 4-fluorobenzoate **PSAux** in near-quantitative yields. To our delight, auxiliary-loaded alcohols **8a-i** all underwent C(sp³)-H fluorination (Table 3), generally in good to excellent (57-90%) yields. Interestingly, where benzoate ester **5b** provided only 8% yield, its 4-fluorobenzoate derivative **8b** was fluorinated to afford **9b** in 75% yield, highlighting the benefit of the **PSAux** in improving efficiency even when unprotected alcohols/amines are absent. Moreover, while the catalytic fluorination affording **2k** was completely ineffective under air, the yield of **9b** (74%) was unaffected by setting up *under air*. Although, the reaction of **1a** without catalyst gave a 44% yield of **2a** (Table 1, entry 4), however, it's **PSAux** derivative, amyl 4-fluorobenzoate, provided 78% yield of **9j** indicating beneficial effect of **PSAux** method. Though Lithocholic acid derivative **8k** only afforded a 23% yield of **9k**, the C(sp³)-H fluorination of steroid derivatives was only possible previously with in-built enone/ketone/ketal protecting/directing groups.¹⁰ Gratifyingly, the C(sp³)-H fluorination of amines was also enabled *via* their auxiliary-loaded amide forms **10a-10e**, affording **11a-11e** in moderate to very good (32-72%) yields. The profound increase in reactivity from having the fluorine in the 4-position of the benzoate group was apparent here. Substrate **10a** was successfully engaged, while the previously attempted photochemical fluorination of *N*-butylbenzamide (Figure 1B)¹² gave no reaction. Although phthalimides¹² offer the potential to serve as a **PSAux**, the 4-fluorobenzoyl **PSAux** is both more effective and generally applicable since i) phthalimides can only function in

this way for 1° amines and ii) benzoates undergo straightforward deprotection (*vide infra*). To our surprise, the auxiliary loaded amide derived from Fingolimod **10f** did not require any subsequent protection of its two free alcohols. In summary, incorporation of a **PSAux** accelerates the rate of C(sp³)-H fluorination to a point that it i) outcompetes the catalytic method, ii) outcompetes degradation of **SF**, iii) allows energy transfer (E_nT) photosensitization reactions to succeed *under air*. This renders the **PSAux** an attractive strategy for C(sp³)-H fluorination of complex, bioactive molecules like active pharmaceutical ingredients, exemplified by the successful fluorination of phenylcyclohexylglycolic acid (**8i**), lithocholic acid (**8k**) and multiple sclerosis active pharmaceutical intermediate (API) Fingolimod (**10f**) and anti-diabetic API vildagliptin (**10g**).

A 4-Fluoroaryl Ketone as Photosensitization Handle



B Auxiliary C(sp³)-H Fluorination of Dextromethorphan

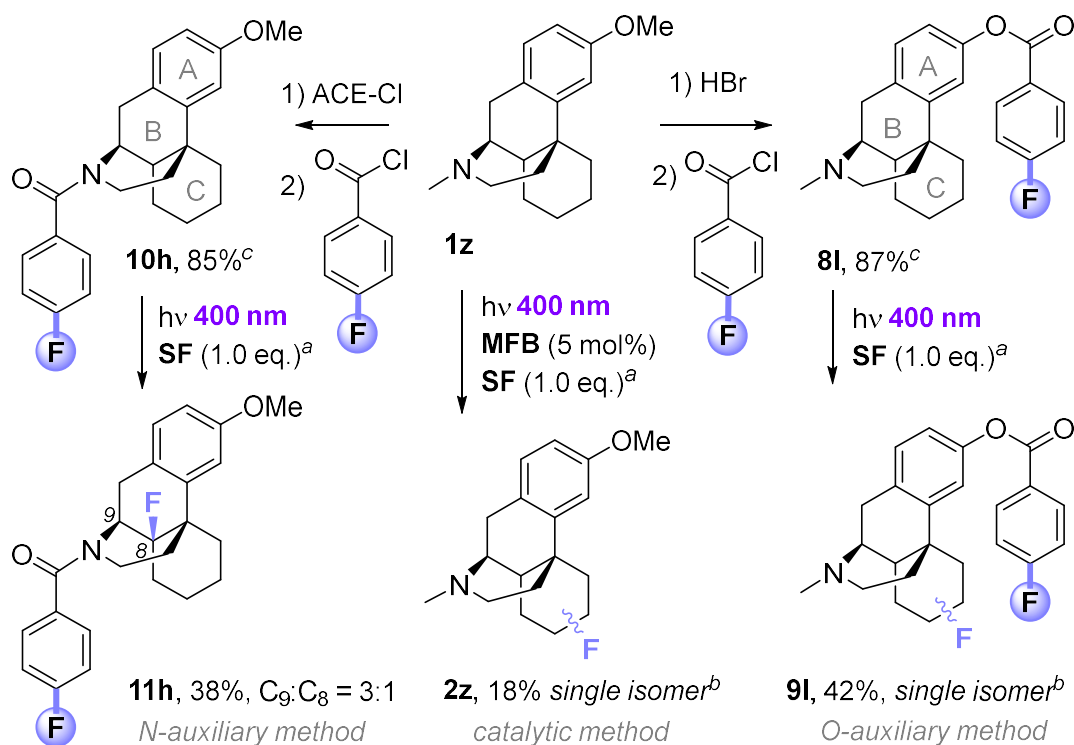


Figure 2. Applications of photosensitization auxiliary concept. ^aUnless otherwise stated, standard conditions in Table 3B were used, with 1.5 eq. substrate and 1.0 eq. **SF**. Isolated yields given unless stated otherwise. ^bYield determined by ¹⁹F NMR with trifluorotoluene as IS. ^cOverall yields over two steps.

Noticing that antipsychotic API Haloperidol **12** contains a 4-fluoro acetophenone moiety, we reasoned its photochemical C(sp³)-H fluorination may occur without *any* catalyst or auxiliary. Indeed, its reaction successfully gave **13** in 43% yield (Figure 2A). Haloperidol and Fingolimod feature in the top 200 pharmaceuticals by retail sales in 2020¹⁵ and their late-stage fluorination opens avenues to new chemical space and pharmacological activities. Finally, we investigated the impact of **PSAux** location on C(sp³)-H fluorination selectivity by the late-stage fluorination of Dextromethorphan **1z** (Figure 2B). The photocatalytic method with **MFB** was inefficient, affording an unsatisfactory (18%) yield of **2z**. Following attachment of the **PSAux** to **1z** by tandem *N*- or *O*-demethylation/**PSAux** loading - affording **10h** and **8l** in high yields over 2 steps (85 and 87%, respectively) - their photochemical C(sp³)-H fluorinations afforded **11h** and **9l** in satisfactory yields (42 and 48%, respectively). Interestingly, **11h** was afforded as two fluorinated regioisomers on the 'B' ring (possibly owing to a fluorine gauche effect)¹⁶ while **9l** was a single regioisomer on the 'C' ring. Therefore, our **PSAux** auxiliary strategy offers future promise as an attachable handle to direct late-stage C(sp³)-H fluorination selectivity which i) is not possible by previous catalytic methods and ii) allows fluorination to be exogenously directed by the chemist, rather than endogenously directed by the molecule *via* its inherent functionality.^{9a,10,12} Of key importance and justifying the use of a **PSAux** strategy, the 4-fluorobenzoate auxiliaries can be cleaved by known methods¹⁷ to give alcohols or amines in near-quantitative (93-98%) yields (Figure 3).

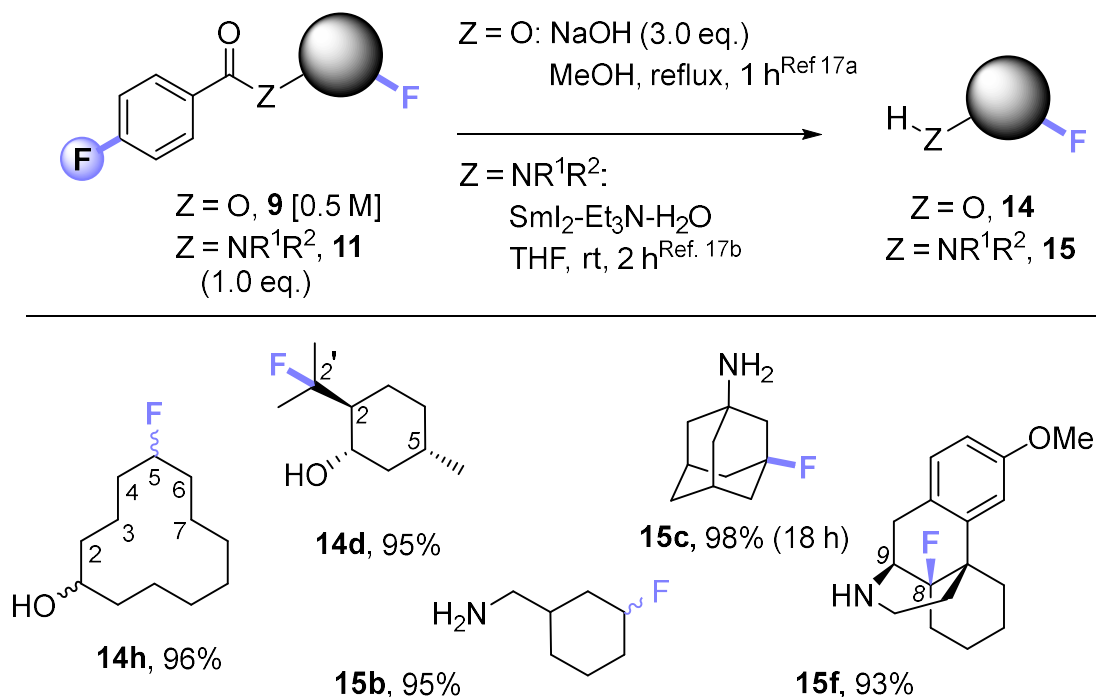


Figure 3. Cleavage of auxiliaries. Isolated yields are given. See Table 3 for regioselectivity.

Mechanistic Studies of PSCat method. Luminescence spectra of the reaction components were measured at their representative excesses (conditions B, 10x diluted to ensure **SF** would fully dissolve). While **MFB** showed no change at all after repeated excitations at $\lambda = 375$ nm (Figure 4, A), **SF** underwent a slow photodecomposition over 6-18 min (Figure 4, B; for photodecomposition rates, see ESI). Upon mixing **MFB** (12.5 mol% w.r.t. **SF**) with **SF** (8 eq. w.r.t. **MFB**), the peak at $\lambda = 434$ nm decreased in intensity by 42% (Figure 4, C). Its shape did not resemble **SF** (no peak at $\lambda = 467$ nm) and even after 5 min of repeated excitations the intensity barely decreased.

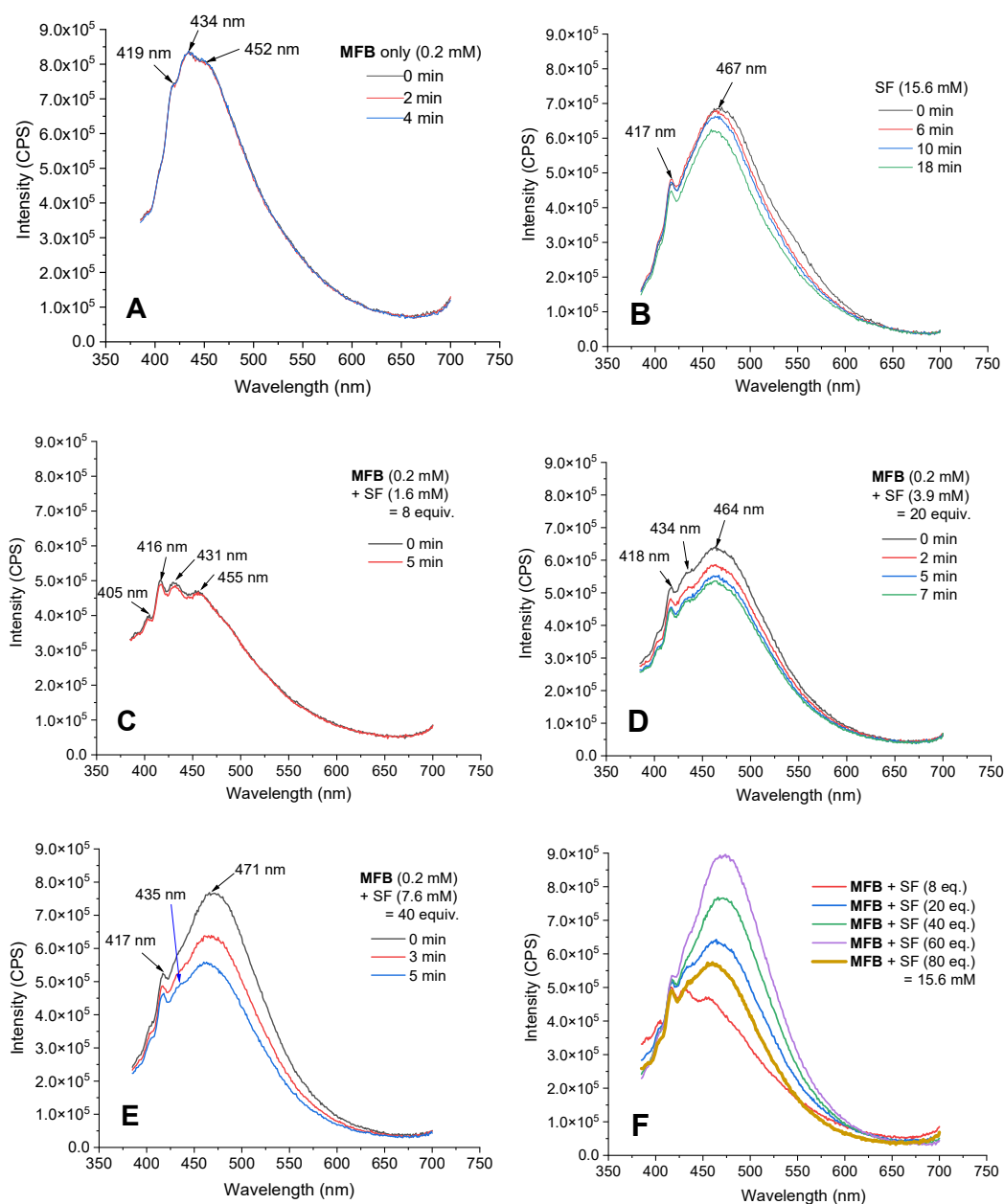


Figure 4. Luminescence of **MFB** and **SF**. **A)** **MFB** only (0.2 mM), repeated measurements. **B)** **SF** only (15.6 mM), repeated measurements. **C)-E)** **MFB** (0.2 mM) with increasing concentrations of **SF**, repeated measurements. **F)** **MFB** (0.2 mM) with increasing concentration of **SF**.

Lu, Soo, Tan and co-workers also observed that the emission peak shape of **AQN** differed in the presence of **SF**.^{9b} Mixing **MFB** with larger excesses of **SF** (Figure 4, C→E) led to buildup of a peak at $\lambda = 467$ nm that more closely resembled **SF**. Interestingly, the presence of **MFB** led to faster photodecomposition of the **SF** peak compared to **SF** alone (Figure 4, E vs B). The measured lifetime of **SF** also decreased in the presence of **MFB** (see ESI). These data corroborate an energy transfer between **MFB** and **SF**, in line with that proposed for previous arylketone catalysts.^{9,10} This suggests ³**MFB*** is the excited state involved, and its T₁ energy is well matched with that of **SF** (see Table 4, *vide infra*).

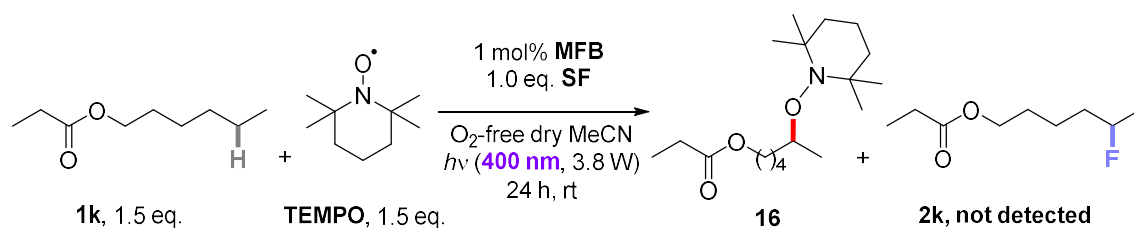


Figure 5. Radical trapping reaction of **1k** with TEMPO.

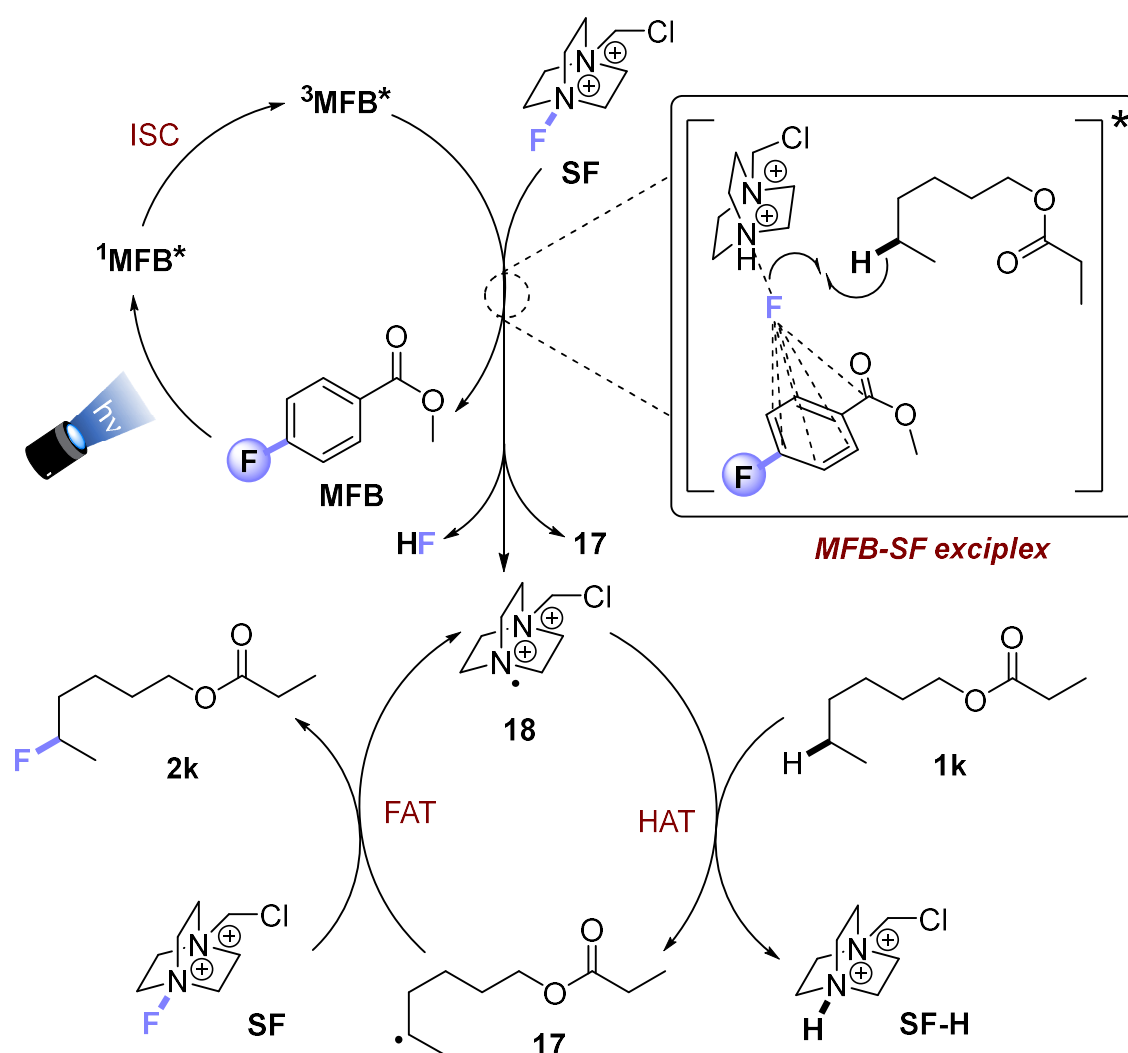


Figure 6. Proposed reaction mechanism for PSCat method.

A radical trapping experiment with 1.5 eq. of TEMPO was performed. As clear evidence of the alkyl chain radical intermediate, a product was detected by LC-MS which matched the TEMPO-bound **16** and no fluorinated product (**2k**) was detected (Figure 5). Therefore, the mechanism of the **MFB**-catalyzed reaction mirrors that previously proposed and elegantly investigated in the literature for **AQN** (Figure 6).^{9b,12} Upon photoexcitation and intersystem crossing, ³**MFB*** undergoes E_nT with **SF**. An exciplex is formed involving substrate molecule (**1k**) which facilitates the N–F bond cleavage and HAT process.^{9b} Intermolecular HAT occurs between the radical cation of **SF** (**18**) and the most hydridic C(sp³)–H bond of the substrate (**1k**) that affords the more stable 2° alkyl radical **17** and **SF–H**. Once **17** is generated, fluorine atom transfer (FAT) with **SF** affords **2k**. This may propagate a chain reaction, but a previously reported quantum yield of ca. 0.12 seems to oppose this (or suggests an inefficient chain propagation).^{9b}

Mechanistic Studies of PSAux method. The majority of efforts were directed at understanding (i) the pronounced benefit of the **PSAux** method over the catalytic method, and (ii) the promoting role of the 4-fluorine atom in the **PSAux**. The first observation was that compounds **1c**, **1d** and **1e** all gave no fluorination in the absence of **MFB** (Table 2), despite electronically resembling amyl benzoate (**1a**) and **MFB**. The lack of reactivity of **1e** in the absence of **PSCat** is consistent with the previously reported lack of reactivity of *n*-butylbenzamide (Figure 1B).¹² The triplet energies (T₁) for directly related compounds are summarized in Table 4. Time-dependent Density Functional Theory (TD-DFT) calculations were used to calculate T₁ for **MFB** (78.3 kcal mol^{–1}, see ESI). Although the T₁ values for all these compounds^{18,19} lay above that reported for **SF** (61.4 kcal mol^{–1}),^{9a} no correlation exists between the T₁ values and the efficiencies of the photochemical fluorinations of **1a–1d**, confirming other factors lie behind successful reactivity. To probe further, we examined substrate **5b** for which the catalytic method was ineffective, giving product **21** in only 8% yield (Table 5, entry 1). A control experiment without catalyst (entry 3) revealed this trace reactivity derived from photochemical self-fluorination, akin to amyl benzoate **1a** but in very low efficiency. When a stoichiometric amount (150 mol%) of **MFB** was employed (entry 4), activity of the **PSCat** method was observed, affording product **21** in 47% yield. That the reaction of **8b** without catalyst gave almost double (75%) the yield of **9b** (entry 7) confirmed the **PSAux** provides a beneficial effect beyond simply higher ‘effective’ catalyst loading. It supports the notion that a preassembly co-locating substrate and **SF** in close proximity sets up a more efficient inner-sphere photochemical process. This is further supported by the fact that the synthetic reactions work equally well under the **PSAux** method without degassing (entry

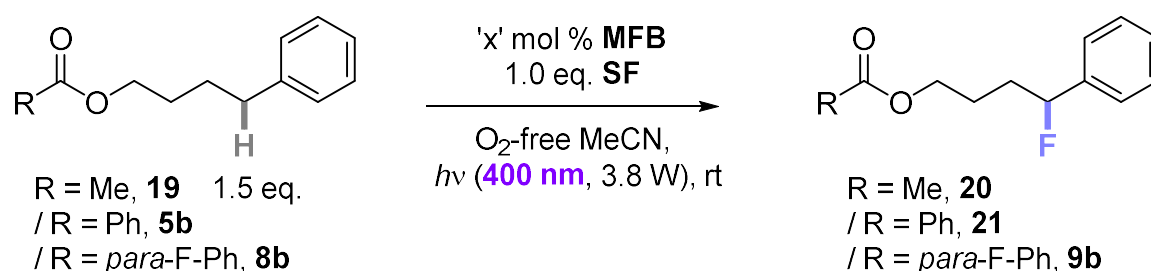
7 vs. 8), but not under the **PSCat** method (entry 4 vs. 6) which requires strict freeze/pump/thaw cycling (**2k**).

Table 4. Triplet energies of reaction components.

entry	Substrate (→ surrogate of)	T ₁ [kcal mol ⁻¹] ^a
1	Methyl benzoate (→ 1a , 1c)	77.9
2	Benzonitrile (→ 1d)	76.8
3	Benzamide (→ 1e)	79.3
4	MFB	78.3

^aCalculated using Time Dependent-Density Functional Theory (see ESI for details).

Table 5. Control reactions with different **MFB** loading



entry	R (Substrate)	MFB 'x' [mol%]	Yield ^a (Product)
1	Ph (5b)	1	8% (21)
2	Me (19)	1	19% (20)
3	Ph (5b)	0	10% (21)
4	Ph (5b)	150	47% (21)
5	Me (19)	150	30% (20)
6	Ph (5b)	150 ^b	35% (21)
7	<i>para</i> -F-Ph (8b)	0	75% (9b)
8	<i>para</i> -F-Ph (8b)	0 ^b	74% (9b)
9	<i>para</i> -F-Ph (8b)	0 ^c	23% (9b)

^aNMR yield, based on ¹⁹F NMR and trifluorotoluene as IS. ^bunder air. ^cInstead of SelectFluor, NFSI was used as a fluorine source.

NFSI as a different fluorinating source gave results that were i) far inferior to **SF** (entries 8 and 9) and ii) similar with **PSCat** and **PSAux** methods, suggesting a different, unrelated mechanism operates here. UV-vis spectroscopy of the reaction mixtures of **5b** and **8b** revealed, in both cases, an absorption band at ca. 400 nm (Figure 7, see ESI for details). This absorption was notably higher than any individual reaction component and was accessible at the synthetic experiments' LED wavelength, suggesting a charge-transfer complex²⁰ forms between the **PSAux** and **SF**. However, the peak shape and absorption intensity

was no different in the case of **5b**'s and **8b**'s reaction mixtures. Given the drastic difference in the efficiency of **5b**'s and **8b**'s reactions, the promoting role of the F atom in the **PSAux**'s clearly does not involve chromophoric changes.

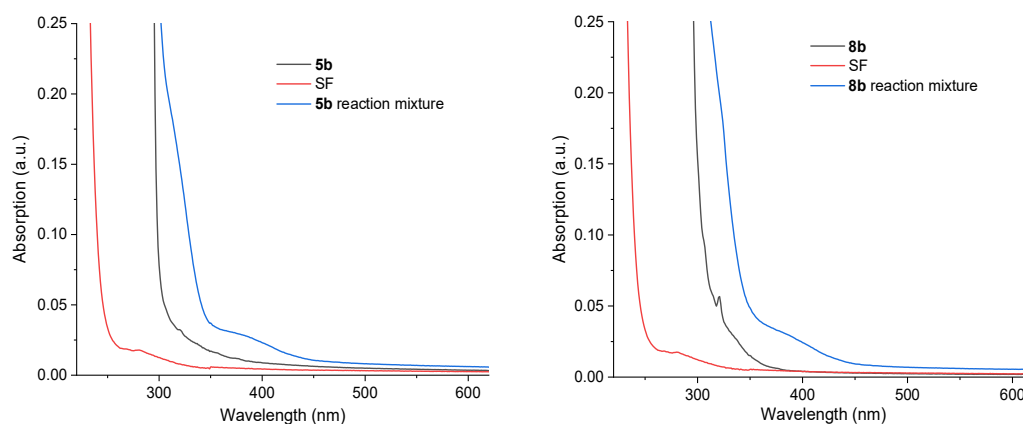


Figure 7. UV-visible spectroscopy of benzoate esters, **SF** and their reaction mixtures. Left: for benzoate **5b**; Right: for 4-fluorobenzoate **8b**.

Given the inability to determine the origin of the promoting effect of the **PSAux**'s F atom by optical spectroscopy, we turned to examine reaction kinetics. The kinetics of **8b**'s reaction were examined by a photoirradiation probe allowing on-line LED irradiation within the NMR spectrometer (for details see supporting information, chapter 5.5.4).²¹ Consumption of all starting materials and formation of all products could be tracked by time-resolved ¹H{¹⁹F} NMR. Samples were compared at the synthetic reaction concentration (0.31 M) to be as representative as possible. **SF** is not fully dissolved under these conditions, meaning unagitated reactions in NMR tubes could not reach yields/conversion rates as high as the synthetic reactions. Nonetheless, this approach was deemed sufficient to observe relative effects. Interestingly, an induction phase is apparent where scarcely any product forms. When repeating the reaction with different amounts of substrate, a clear trend emerges: the induction phase shortens as the loading of **8b** increases. This occurs even in spite of the decreasing (measured) solubility of **SF** as the overall mixture becomes more non-polar with increasing [**8b**]. While the standard reaction with 1.5 eq. of substrate **8b** has an induction phase of 9.2 h, when 3 eq. **8b** are used it only takes 1.9 h until product formation begins with a profile typical of a first-order reaction. In summary, by doubling the amount of substrate **8b**, the induction phase can be shortened by 79% (Figure 8A). The rates of product formation within the linear build-up and the overall yield were, however, independent of substrate loading (Figure 8B). This may be due to (i) the lack of stirring (an inevitable drawback of *in situ* NMR kinetics), meaning only traces of undissolved **SF** are available for the ongoing reaction, and/or (ii) lower light intensity of the *in situ* irradiation setup (see Table 1, entry 15 vs 17).

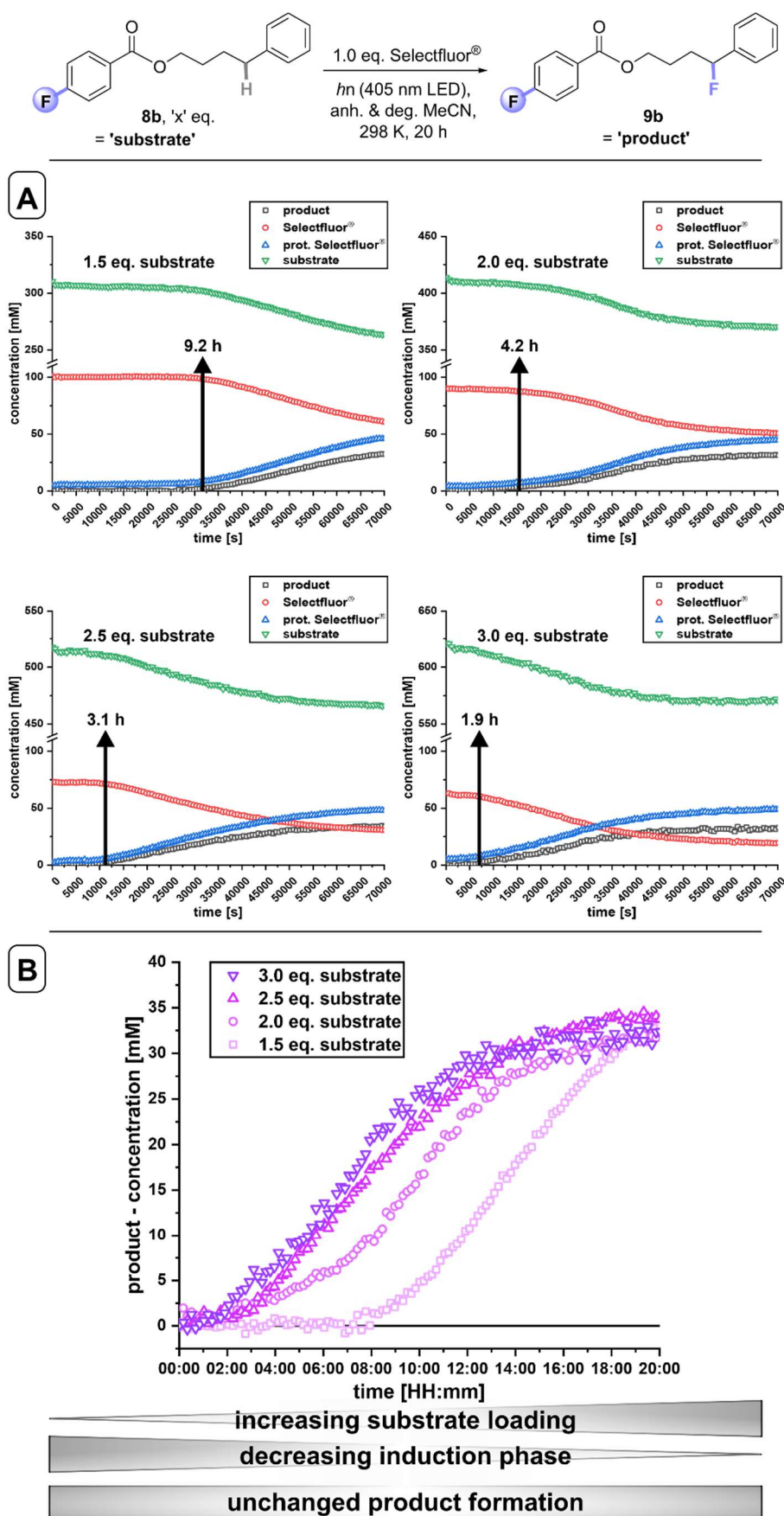


Figure 8. $^1\text{H}\{^{19}\text{F}\}$ *In situ* illumination NMR reaction monitoring of **PSAux**. **A)** Kinetic profiles of photosensitization auxiliary method with different amounts of **8b**. **B)** Detailed comparison of product formation of **9b** depending on different substrate loadings.

We hypothesized that a de-aggregation of **SF** may rationalize the induction period. Therefore, diffusion ordered spectroscopy (DOSY) was performed. The volume of **8b** hardly changed as a function of its concentration (431.4 Å for 0.62 M and 410.1 Å for 0.31 M; Table 6, entry 1-2) and was unchanged in the presence of **SF** (entry 4-6). In contrast, a volume reduction of **SF** by 13% from 952.2 Å (entry 3) to 825.3 Å (entry 7) in the presence of 1.5 eq **8b** and by 12% to 836.9 Å with 3 eq. **8b** (entry 5) compared to pure **SF** with the same concentration (952.2 Å, entry 3) occurred, which confirms the role of **8b** as a de-aggregation agent. According to the estimated (spherical) molecular volume of **SF** (see supporting information, chapter 5.5.6.2), such a change would suggest a change in aggregation from 3 to 2 **SF** molecules. We then examined the size of the **SF** aggregate in the presence of **5b**. The volume of **5b** alone (413.9 Å) was very similar to that of **8b**, consistent with the fact that the fluorine atom is a known bioisostere for H.⁶ However, **5b** only de-aggregates **SF** by 4% (entry 9) - a de-aggregating effect 73% smaller than **8b**. Therefore, the F atom in the **PSAux** clearly plays a role in de-aggregating **SF**. This could be explained by a halogen- π interaction as suggested by calculations (see ESI). However, we note that i) after this initial de-aggregation with 1.5 eq. **8b**, the volume of components remain unchanged during the reaction and ii) doubling the concentration of **8b** does not further de-aggregate **SF**. Thus, while de-aggregation of **SF** can explain **8b**'s success vs **5b**'s failure, the substrate concentration benefit on induction period shortening (see Figure 8) cannot be explained by de-aggregation. Further studies are ongoing.

Taking together the synthetic results of the **PSAux** strategy (ability to direct regioselectivity, remarkable tolerance to O₂, ability to engage molecules with unprotected functionality), our mechanistic studies suggest that the **PSAux** plays two key roles. Firstly, the benzoate **PSAux** engages **SF** in an intimate charge-transfer preassembly (Figure 9) that absorbs 400 nm (see Figure 7). The second key role of the **PSAux** is to de-aggregate **SF** (Figure 9), for which the 4-fluoro atom is especially effective. Moreover, calculated quantum yield of the **PSAux** reaction for **8b** ($\Phi < 0.01$) rule out a radical chain mechanism. The downstream mechanism then resembles that of the **PSCat** method (Figure 6) and that proposed in the literature,^{9,12} however we propose subsequent steps all occur within the exciplex/solvent cage. E_nT from ³**MFB*** to **SF** leads to N-F bond cleavage and the benzoate directs the dication radical to the locally most hydridic C(sp³)-H bond(s) for HAT that forms a stable (2°, 3°) radical to be fluorinated. We propose that the beneficial role of de-aggregation is not related to the success of charge-transfer complex formation (see Figure 6 and the poor reactivity of **5b** vs **8b**), but rather it increases the efficiency of the E_nT step following photoexcitation.

Table 6. Volumes of different compounds, pure and in reaction, measured by DOSY NMR.

entry	compound	composition	c [M]	average volume ^a with SD [Å ³]
1	8b	pure	0.62	413.4 ± 5.37
2			0.31	410.1 ± 7.44
3	SF		0.21 ^b	952.2 ± 6.44
4	8b	3.0 eq. 8b	0.62	425.6 ± 8.83
5	SF	reaction	0.21 ^b	836.9 ± 17.95
6	8b	1.5 eq. 8b	0.31	412.5 ± 6.27
7	SF	reaction	0.21 ^b	825.3 ± 16.40
8	8b	1.5 eq. 5b	0.31	413.9 ± 13.24
9	SF	reaction	0.21 ^b	917.5 ± 8.86

^aWeighed in concentration. ^bVolumes correspond to the mean values of several measurements carried out at different reaction states. For more details see supporting information, chapter 5.5.6.2.

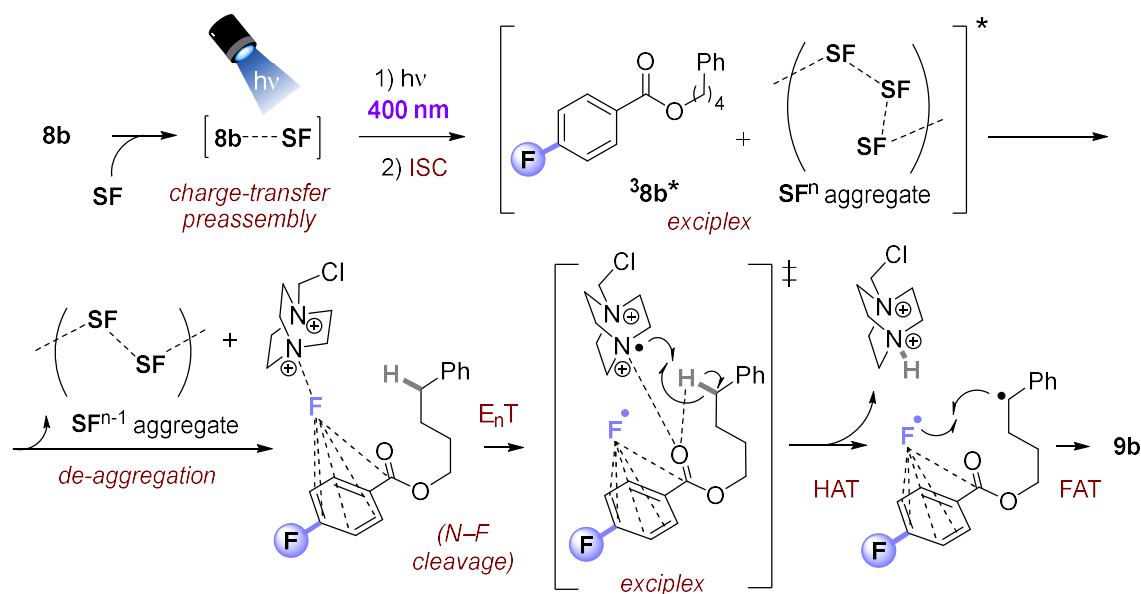


Figure 9. Proposed reaction mechanism for **PSAux** fluorination by **SF** de-aggregation.

We cannot rule out that the C=O of the $^3\text{PSAux}^*$ engages in photochemical HAT²² with the C(sp³)-H bond, but this seems inconsistent with (i) the catalytic lack of reactivities of other *para*-substituted or unsubstituted benzoyl groups (**4b**, **5b**) in **PSCat** or **PSAux** fluorinations and (ii) the clear promotion of **SF**'s photodecomposition as seen in the emission spectra. The ability to conduct photochemical C(sp³)-H fluorination reactions in shorter overall reaction times is highly attractive to practitioners, and useful for achieving high yields since **SF** undergoes a competing (photo)decomposition process.

Application of benzoyl auxiliary in other E_nT photochemistry. While the main purpose of our study targeted applications to (and understanding of) C(sp³)-H fluorinations, we found that the 4-fluorobenzoyl photosensitizer could successfully deliver E_nT [2+2]-photocycloadditions *in air*. The 4-fluorobenzamide derivative of cinnamyl amine (**22**) delivered cyclobutane **23** (31%) in exclusive head-to-head regioselectivity, but as a mixture of ‘all-*trans*’ and ‘all-*cis*’ diastereomers (5:1). In contrast, 4-fluorobenzoylated cinnamyl alcohol **24** underwent [2+2]-photocycloaddition to give exclusively the head-to-head, ‘all-*trans*’ diastereomer of **25** (87%). The previously reported direct UV excitation of cinnamyl alcohol (10 mM in MeCN, 450 W Hg bulb) affords a 2:1 mixture of *cis*-/*trans*- isomers and only traces of the cyclobutane (<5%).^[23a] Previously, high yield and selectivity for the cyclobutane was only possible by an iterative (2-step) covalent tethering of two cinnamyl alcohols by di-*iso*-propyldichlorosilane (compared to which, 4-fluorobenzoyl chloride is ~2.5× cheaper) under UV-light and strict degassing.^[23] Herein, this is achieved non-covalently, presumably *via* π-stacking of the photoactive 4-fluorobenzoyl motifs under milder visible-light conditions. Where contemporary photocatalytic [2+2]-cycloadditions require degassing due to redox or E_nT quenching of the photocatalyst by O₂,^[24] the 4-fluorobenzoyl photosensitization auxiliary provides an alternative strategy than can be run *open to air* (Figure 10).

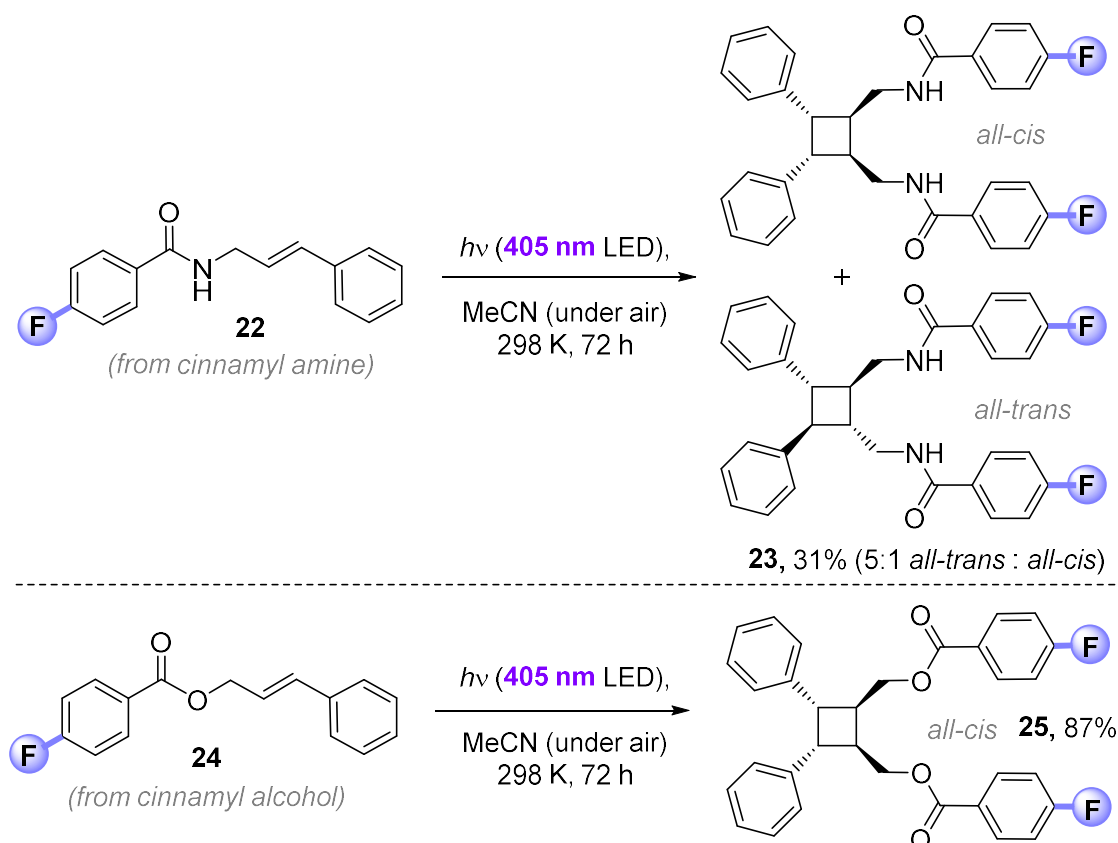


Figure 10. Application of 4-fluorobenzoyl photosensitizer to [2+2]-photocycloadditions.

5.4 Conclusion

In conclusion, we report the discovery of a highly efficient visible-light harvesting photosensitizer architecture for the direct fluorination of unactivated C(sp³)-H bonds. Our new photosensitizing (4-fluorobenzoyl) group was successfully used both as photosensitizing catalyst and photosensitizing auxiliary. Both catalytic and auxiliary methods were successfully applied to the late-stage functionalization of complex molecules. While a reasonably broad substrate scope of fluorinated products was accessible with catalytic method, the photosensitization auxiliary strategy was found to be far superior in scope and practicality. Substrates that for which the catalytic method was inefficient or ineffective were successfully engaged in higher yields and shorter reaction times, furnishing a general platform for photosensitized fluorination that even tolerates free alcohols/amine functionality and works under air. Mechanistic studies reveal the auxiliary's promoting effects derive from two angles, i) harnessing **SF** in an intimate charge transfer assembly with **SF** and ii) in de-aggregating **SF**. The 4-fluorobenzoyl auxiliary allows other E_nT photochemistries to occur in air, where its non-covalent π -stacking interactions alter mechanism and selectivity.

Assemblies between photocatalyst and substrate such as EDA complexes,²⁰ hydrogen bonding,^{22c,d} non-covalent interactions,²⁵ and ordering of solvent²⁶ attract ever more attention to uncover the next generation of photocatalytic transformations and provide new frontiers in selectivity and efficiency. This study highlights the emerging importance of how changes in aggregation states of photocatalysts can profoundly influence photochemical reaction mechanisms.²⁷ Further studies into the structural nature of the charge transfer assembly and the origins of the induction period in photochemical C(sp³)-H fluorination reactions are ongoing.

5.5 Supporting Information

5.5.1 General

NMR experiments were performed on a Bruker Avance III HD 600 (600.03 MHz) spectrometer with a 5 mm fluorine selective TBIF probe and TopSpin 3.2 or TopSpin 3.6. For *in situ* illumination NMR spectroscopy the reported setup with 5 mm amberized thin wall NMR tubes was applied.^{21d} NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software. ¹H- and ¹³C-NMR spectra without TMS as internal reference were calibrated on the solvent residual peak of CD₃CN ($\delta(^1\text{H}) = 1.94$ ppm) or CDCl₃ ($\delta(^1\text{H}) = 7.26$ ppm, $\delta(^{13}\text{C}) = 77.16$ ppm); otherwise on TMS ($\delta(^1\text{H}) = 0.00$ ppm). Further plotting of the obtained data was performed with Origin 2019 and Corel Draw 2020 software.

5.5.2 Chemicals

Commercially available chemicals were, unless otherwise stated, used without further purification. CD₃CN and CH₃CN were distilled over CaH₂, degassed using the freeze-pump-thaw method and stored in a flask with 3Å molecular sieve inside the glove box. TMS was degassed using the freeze-pump-thaw method and stored in a Schlenk-flask with 3Å molecular sieve.

5.5.3 Method for quantitative reaction monitoring by *in situ* illumination-NMR spectroscopy

For illumination of the NMR sample inside the NMR spectrometer an illumination setup as described in literature with a Seoul UV CA3535 series (CUN0GF1A) LED, emitting at a peak wavelength of 405 nm, was applied.^{21d} The LED was operated with maximum forward current (1.4 A). The kinetic studies were performed at r.t. (25 °C) as the standard reaction. The starting point of each kinetic (t = 0 s) was measured without illumination and during illumination, ¹H- and ¹⁹F-spectra were recorded alternately. The NMR experiments were measured as following to obtain spectra for quantitative evaluation: Due to the high concentration of the NMR samples (see NMR sample preparation), a S/N of > 250:1 was already achieved in single scan experiments. Additional S/N enhancement was achieved by removing heteronuclear ¹H-¹⁹F-coupling using a zgig pulse program (inverse gated decoupling). A relaxation delay d1 = 300 s was applied to ensure full relaxation of all signals before every scan and pulse lengths for ¹H-experiments were calibrated.

5.5.4 Reaction monitoring of photosensitization auxiliary method

5.5.4.1 NMR sample preparation

The entire NMR sample preparation was executed under inert gas conditions. The actual preparation was done inside glove box, the glass fiber insert for *in situ* illumination was inserted following Schlenk line technique. Selectfluor[®] (22.0 mg, 62.1 μ mol, 1.0 eq.) was weighed in an oven dried amberized 5 mm thin wall NMR tube. A 300 μ L aliquot of substrate **8b** in anhydrous and degassed CD₃CN (500 μ L) (amount of substrate **8b**: see Table S1) and pentafluorobenzene (2.9 μ L, 18.6 μ mol, 0.3 eq.) as internal standard were added to the NMR tube. In order to maximize the amount of dissolved Selectfluor[®] and to ensure a homogeneous sample, the sample was shaken intensively. Lastly an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μ m core) was inserted into the NMR tube and fastened with enough parafilm to prevent oxygen and moisture from penetrating the sample.^{21d}

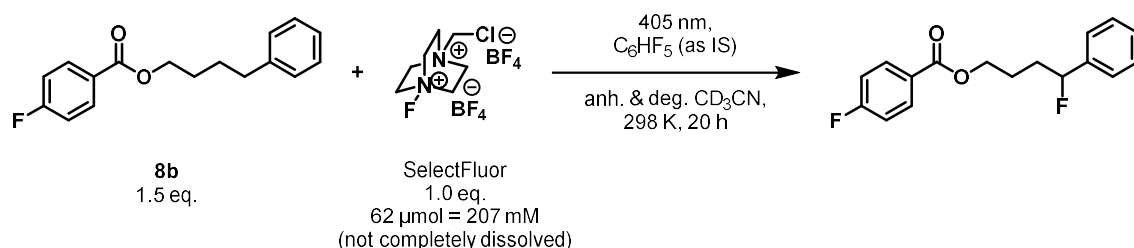
Table S1. Different amounts of substrate for reaction monitoring of photosensitization auxiliary method.

entry	equivalents	concentration [mM]	amount of substrate [μ mol] ^a	mass [mg] ^a
1	1.5	310.5	155.3	42.3
2	2.0	414.0	207.0	56.4
3	2.5	517.5	258.8	70.5
4	3.0	621.0	310.5	84.6

^aThe amounts are based on the 500 μ L stock solution.

5.5.4.2 Reaction monitoring of photosensitization auxiliary method applying different substrate equivalents

For a first insight in the reaction kinetic of the photosensitization auxiliary method, a reaction from the synthetic part of this work with the same concentrations was investigated (Scheme S1).



Scheme S1. Model reaction for reaction monitoring by *in situ* illumination-NMR spectroscopy of photosensitization auxiliary method.

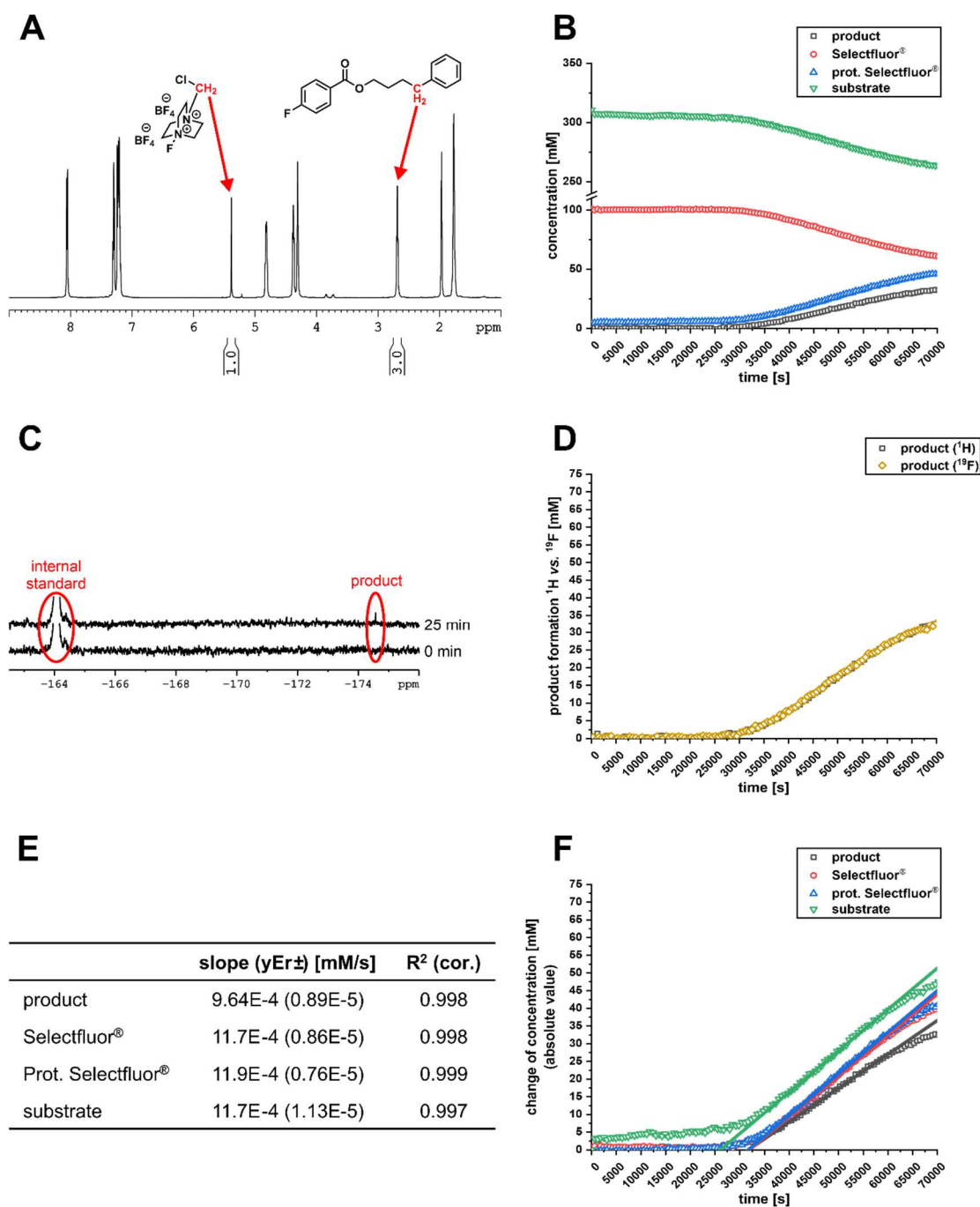


Figure S1. Data from the model reaction for *in situ* illumination NMR spectroscopy shown in scheme S1. **A:** Due to the high concentration and moderate solubility of Selectfluor®, it is not completely dissolved. Therefore, substrate **8b** and Selectfluor® are present in a ratio of 1.0:3.0 instead of 1.0:1.5. **B:** The reaction does not occur over a typical reaction profile. Instead, an induction phase of 9.2 h is required before the reaction begins with a first-order rate. **C:** The first traces of product, however, can be detected after just 25 minutes. **D:** Product build-up curves were followed *via* ¹H{¹⁹F} and ¹⁹F{¹H} spectroscopy without discernible difference. **E:** Rates for the linear build-up of the different reagents and products. The substrate and Selectfluor® are consumed at the same rate as the protonated Selectfluor® is formed. The product forms at a slightly slower rate. **F:** For a better comparison of the different processes, the absolute values of concentration changes are shown.

Due to the high concentration and moderate solubility of Selectfluor[®] in CD₃CN, it has not completely dissolved. Therefore, substrate **8b** and Selectfluor[®] were not in a ratio of 1.5:1.0 as weighed in, but in a ratio of 1.0:3.0 (Figure S1, **A**). The reaction shows a very long induction phase of approximately 9.2 h. Afterwards product forms with a build-up curve typical for a first-order reaction (Figure S1, **B**). Interestingly however, the first traces of product can be detected in the ¹⁹F{¹H} spectra after 25 minutes (Figure S1 **C**). These provide the same kinetic profile as the ¹H measurements (Figure S1, **D**). Looking at the rates for the different reagents and products during the linear build shows a similar consumption of substrate (11.7E-4 mM/s) and Selectfluor[®] (11.7E-4 mM/s) as the fluorinating agent. Protonated Selectfluor[®] (11.9E-4 mM/s), a stoichiometric by-product, also forms at the same rate. The monofluorinated product is obtained at a somewhat slower rate (9.64E-4 mM/s). This indicates that, in addition to the monofluorination, other reactions such as multiple fluorination or elimination reactions must take place to a small component (Figure S1, **E** and **F**).

For further studies the effect of substrate loading on the kinetic profile has been examined. For this, 1.5, 2.0, 2.5 and 3.0 equivalents of substrate **8b** were investigated.

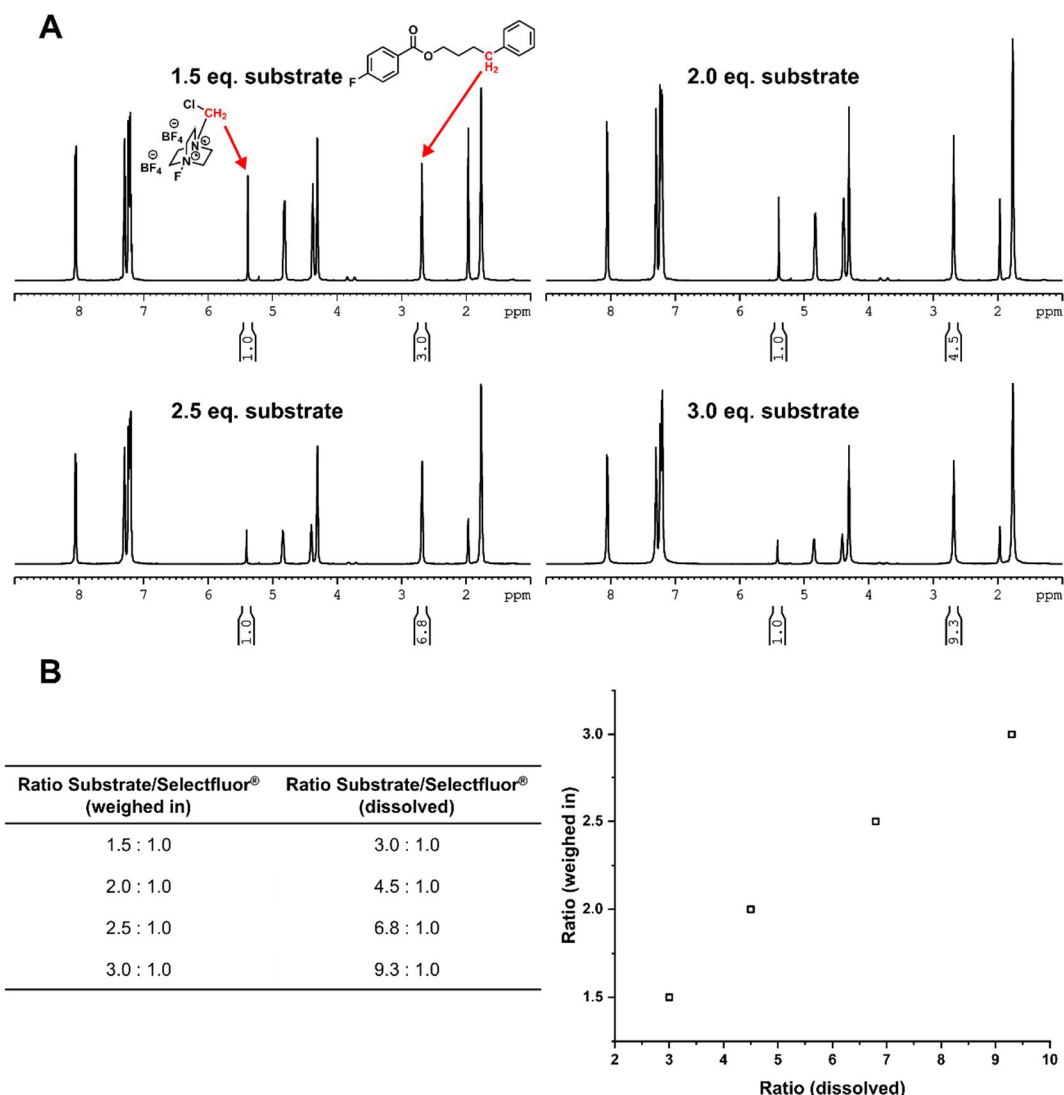


Figure S2. Comparison of the ratios of substrate **8b** and Selectfluor® weighed in vs. in solution for different amounts of substrate **8b**. **A:** Based on the integrals of Selectfluor®- and substrate-signals, the ratio of the two reagents in solution can be determined. **B:** Evaluation of the different ratios shows that the solubility of Selectfluor® decreases as the amount of substrate increases.

The NMR spectra of the different reaction mixtures (Figure S2, **A**) show that the ratios of Selectfluor® to substrate **8b** in solution do not correspond to those weighed in. This is highly due to the moderate solubility of Selectfluor®. There is a clear trend that the solubility of Selectfluor® continues to decrease as the substrate equivalents increase. While 50% of Selectfluor® are dissolved at the beginning of the reaction with 1.5 eq. of substrate **8b**, it is only 32% when 3.0 eq. substrate are applied.

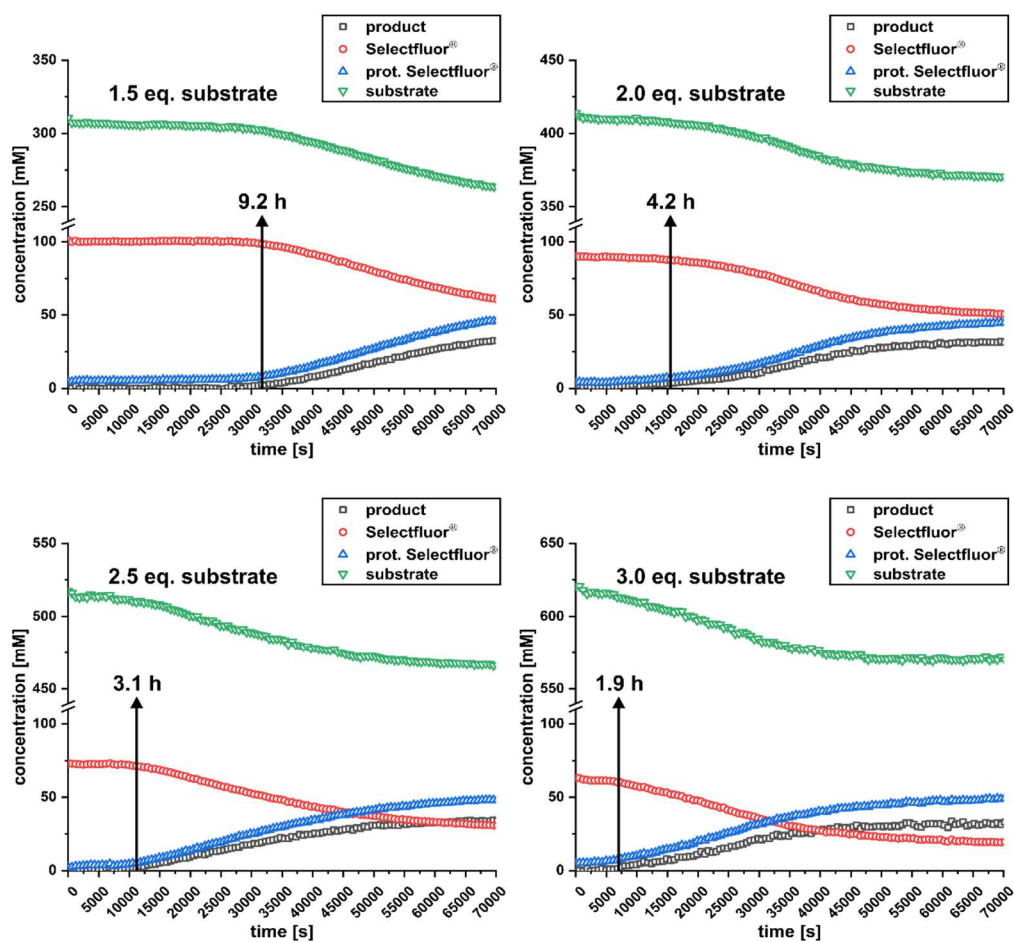


Figure S3. Kinetic profiles of the photosensitization auxiliary reaction with different substrate loadings. As the amount of substrate **8b** increases, the induction phase becomes shorter. Apart from that, the reaction profiles are very similar.

When repeating the reaction with different amounts of substrate (Figure S3), a clear trend emerges: The induction phase with scarcely any product formation becomes shorter as the substrate loading increases. While the standard reaction with 1.5 eq. of substrate **8b** has an induction phase of 9.2 h, it takes ca. 4.2 h with 2 eq. of substrate **8b**. With 2.5 eq. ca. 3.1 h are necessary and when 3 eq. substrate **8b** are applied only ca. 1.9 h expire until product formation with a profile typical of a first-order reaction can be observed. In summary, by doubling the amount of substrate **8b**, the induction phase can be shortened by 79%.

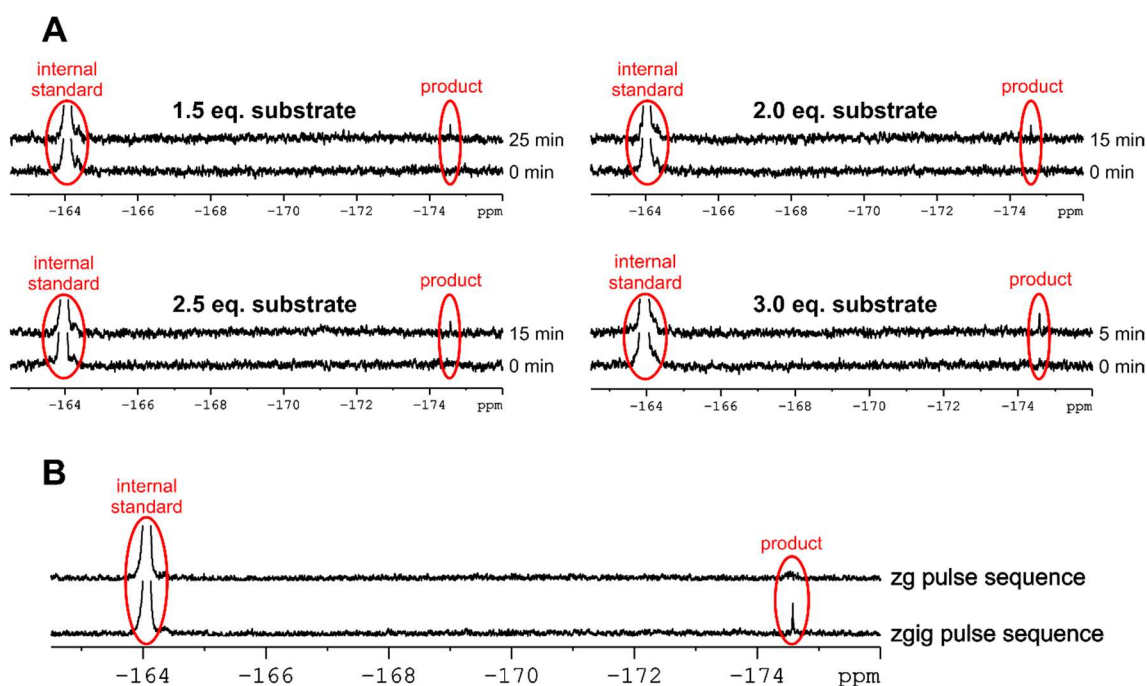


Figure S4. A: Despite the long induction phases, first traces of product can be detected after a significantly shorter time independent of the amount of substrate **8b**. However, the first-order type product formation begins much later. **B:** By applying a zgig pulse sequence instead of the standard zg pulse sequence, traces of product can be identified which would otherwise be almost indistinguishable from baseline noise.

Even if it takes more than 9 h for significant product formation to begin, the first traces of product can be detected much earlier. In the standard reaction with 1.5 eq. of substrate **8b**, a small product signal can be detected after just 25 minutes. Increasing the amount of substrate also reduces the time until an initial, small amount of product starts to form. With 2.0 and 2.5 eq. substrate, product generation can be observed after just 15 minutes. With 3.0 eq. substrate, a clear product signal is already obtained in the first spectrum after the illumination has been started (Figure S4 **A**). This also shows the clear advantage of the zgig pulse sequence. When using a zg pulse sequence for routine NMR measurements, the product signal is obtained as a multiplet due to the heteronuclear ¹H-¹⁹F coupling. Due to the low concentration of the product at the beginning of the reaction and hence a low signal intensity, this is hardly distinguishable from the baseline noise of the ¹⁹F-spectrum (Figure S4 **B** top). In contrast, inverse gated decoupling, which is implemented in the zgig pulse sequence, suppresses the heteronuclear ¹H-¹⁹F coupling. As a result, the product signal appears as a more intense singlet, which clearly stands out from the baseline noise (Figure S4 **B** bottom). However, since there is no signal enhancement through NOE as it is with power gated decoupling (zgpg pulse sequence) the obtained spectra are still quantitative.

To gain insight in the role of product, the reaction with 1.5 eq. substrate was repeated with additional 10 mM product.

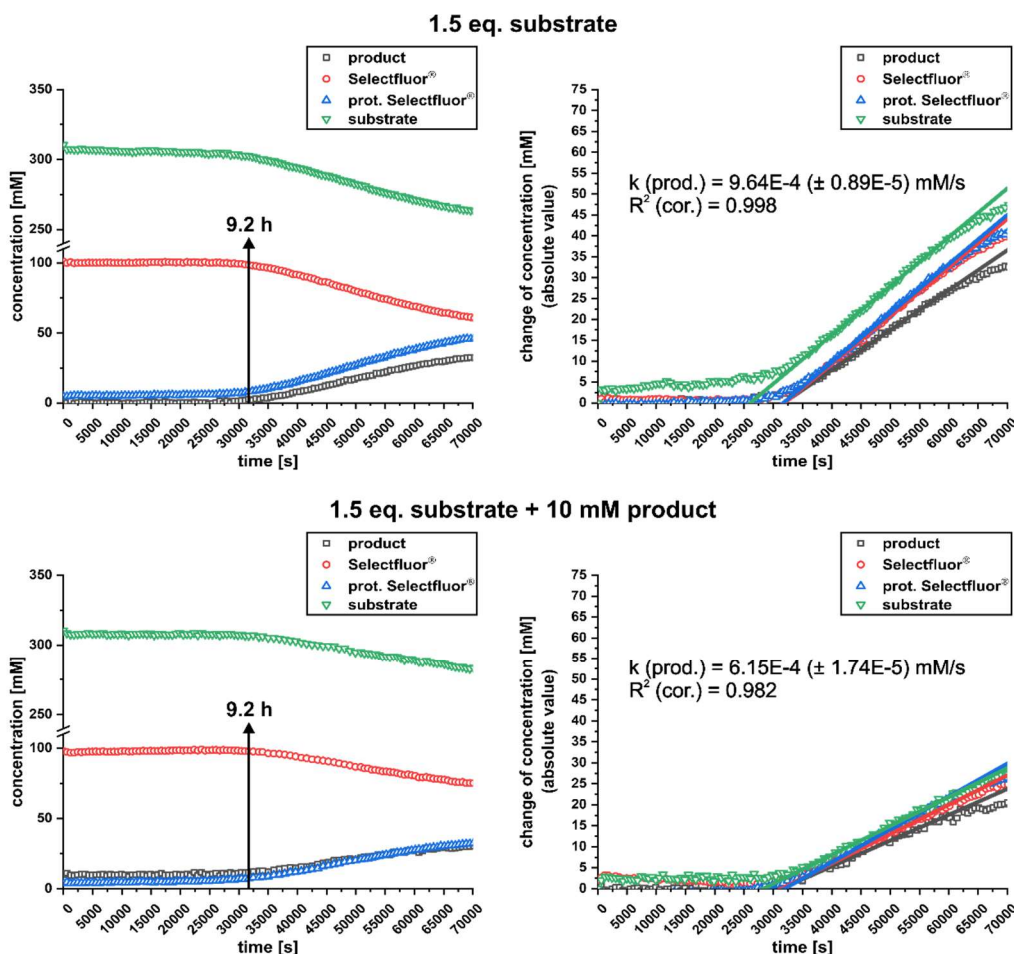
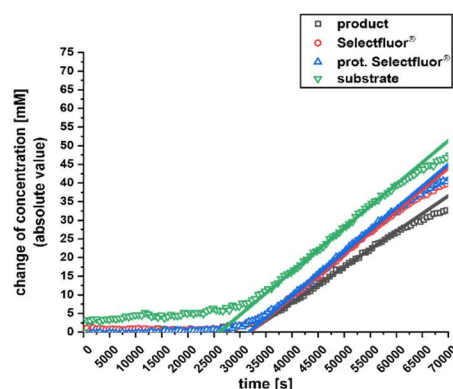


Figure S5. Kinetic profiles of the photosensitization auxiliary reaction with 1.5 eq. substrate **8b** (top) and additional 10 mM product **8b** (bottom). Since the additional product whether shortens the induction phase nor increases the rate for product formation an autocatalytic effect of the product can be excluded.

Comparison of the reaction profiles of the standard reaction (Figure S5 top) and the one with additional 10 mM product **8b** (Figure S5 bottom) shows that the length of the induction phase remains unchanged. In both reactions, it takes ca. 9.2 h before a distinct product formation occurs. A positive contribution of the product to the reaction mechanism can also be ruled out when looking at the rate of product formation. The additional product even reduces the reaction rate for product formation in the linear build-up by 36% from 9.64E-4 mM/s to 6.15E-4 mM/s.

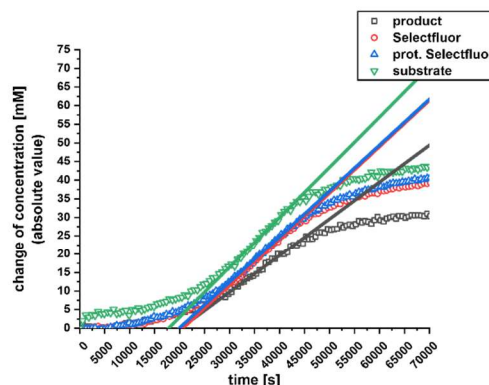
1.5 eq. substrate

	slope (yEr±) [mM/s]	R ² (cor.)
product	9.64E-4 (0.89E-5)	0.998
Selectfluor®	11.7E-4 (0.86E-5)	0.998
Prot. Selectfluor®	11.9E-4 (0.76E-5)	0.999
substrate	11.7E-4 (1.13E-5)	0.997



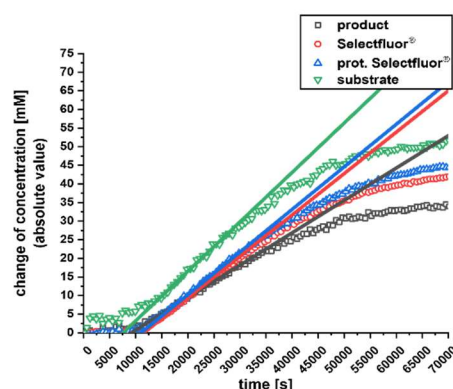
2.0 eq. substrate

	slope (yEr±) [mM/s]	R ² (cor.)
product	9.92E-4 (2.55E-5)	0.986
Selectfluor®	12.4E-4 (1.56E-5)	0.997
Prot. Selectfluor®	12.3E-4 (1.30E-5)	0.998
substrate	13.5E-4 (2.47E-5)	0.993



2.5 eq. substrate

	slope (yEr±) [mM/s]	R ² (cor.)
product	8.46E-4 (1.27E-5)	0.994
Selectfluor®	10.2E-4 (1.02E-5)	0.997
Prot. Selectfluor®	10.8E-4 (1.29E-5)	0.996
substrate	11.4E-4 (2.43E-5)	0.988



3.0 eq. substrate

	slope (yEr±) [mM/s]	R ² (cor.)
product	9.70E-4 (2.37E-5)	0.983
Selectfluor®	11.6E-4 (1.06E-5)	0.998
Prot. Selectfluor®	11.7E-4 (1.25E-5)	0.997
substrate	13.7E-4 (3.18E-5)	0.985

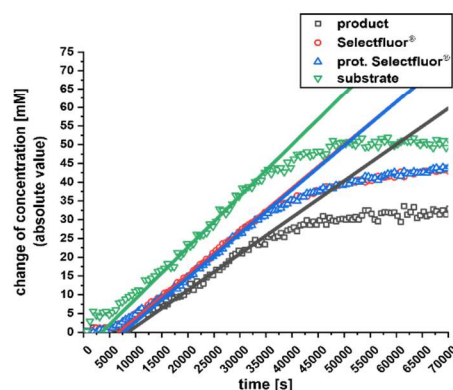


Figure S6. Rates and reaction kinetics (plotted as absolute changes) for photosensitization auxiliary reactions with different substrate loadings. With an increasing amount of substrate **8b**, the induction phase shortens. The rate at which the concentrations of the different species change is unaffected.

Plotting the absolute values of the concentration changes of all species involved, *i.e.* reagents (substrate **8b** and Selectfluor[®]) and products (product and protonated Selectfluor[®]), enables to read the transformation into each other out directly from the course of the curve. Overall, an increased substrate loading primarily affects the induction phase of the reaction. As in Figure S3, a shortening of the induction phase with increasing amount of substrate **8b** is observable. However, the amount of product that is generated and the rate at which this happens remains unchanged. The situation is similar with the other three species shown. The fact that everything of consumed Selectfluor[®] is transformed into its protonated form is reflected by the almost identical curves. The slightly smaller amount of generated product in all reactions indicates side reactions taking place in parallel, such as multiple fluorination and elimination reactions. A possible explanation for the shortening of the induction phase as the substrate loading increases can be found in the initial curve of the substrate kinetics. From almost the first spectrum, substrate **8b** is consumed up to a concentration of 5 mM. This process begins earlier and more pronounced as the amount of substrate increases. This fact in combination with the traces of product, which can also be detected from the beginning (see Figure S4), possibly indicates a so far unknown pre-aggregate, which is required for effective product formation. Further studies are ongoing to uncover the nature of aggregation changes.

5.5.5 Reaction monitoring of photocatalytic C(sp³)-H fluorination

5.5.5.1 NMR sample preparation

The NMR samples were prepared as for reaction monitoring of photosensitization auxiliary method under inert gas conditions (see chapter 5.5.4.1).

For monitoring the influence of catalyst loading a stock solution of **MFB** (16.6 mM in anhydrous and degassed CD₃CN) was prepared, which was stored inside a glove box refrigerator. Depending on the catalyst loading to be examined (see Table S2), the corresponding amount was transferred from the stock solution to an NMR tube loaded with Selectfluor® (22.0 mg, 62.1 μmol, 1.0 eq.) and then diluted with enough anhydrous and degassed CD₃CN to reach a volume of 300 μL. Afterwards, substrate **1k** (14.7 mg, 16.8 μL, 93.2 μmol, 1.5 eq.) and pentafluorobenzene as internal standard (2.9 μL, 18.6 μmol, 0.3 eq.) were added. The sample was shaken intensively to ensure a homogeneous and saturated Selectfluor® solution. Lastly an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μm core) was inserted into the NMR tube, which was fastened with enough parafilm to prevent oxygen and moisture from penetrating the sample.^{21d}

Table S2. Different catalyst loadings for reaction monitoring of photocatalytic C(sp³)-H fluorination.

entry	Catalyst loading [mol%]	amount of stock solution [μL]
1	1	37.5
2	5	188
3	5	188
4	8	300

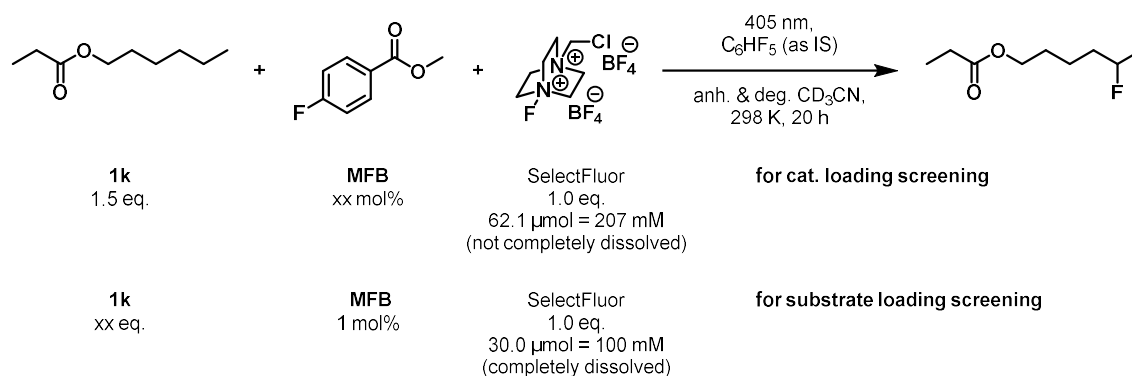
To investigate the influence of substrate loading a stock solution of catalyst **MFB** and pentafluorobenzene as internal standard (1.0 mM or 7.5 mM in anhydrous and degassed CD₃CN/ CH₃CN 1:1) was prepared, which was stored inside glove box refrigerator. Depending on the substrate loading to be examined (see table S3), the corresponding amount of substrate **1k** and a 300 μL aliquot of the catalyst/ internal standard stock solution were added to the with Selectfluor® (10.6 mg, 30.0 μmol, 1.0 eq.) loaded NMR tube. To ensure a homogenous sample, the NMR tube was shaken intensively and finally an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μm core) was inserted into the NMR tube and fastened with enough parafilm to prevent oxygen and moisture from penetrating the sample.^{21d}

Table S3. Different substrate loadings for reaction monitoring of photocatalytic C(sp³)-H fluorination.

entry	equivalents	volume [μL]	amount of substrate [μmol]
1	1.5	8.1	45
2	2.0	10.8	60
3	2.0	10.8	60
4	3.0	16.3	60

5.5.5.2 Reaction monitoring of photocatalytic C(sp³)-H fluorination with different catalyst and substrate loadings

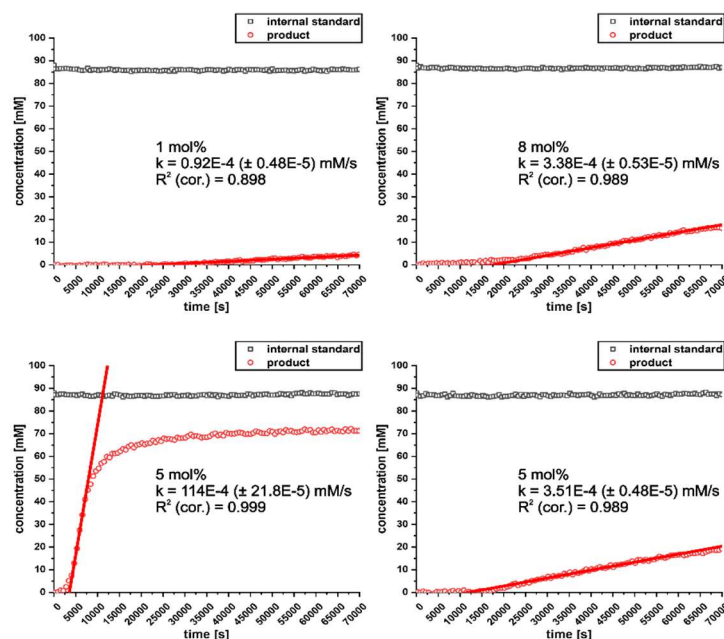
To gain information about the reaction kinetic of photocatalytic C(sp³)-H fluorination, the following reaction from the synthetic part of this work was chosen.



Scheme S2. Model reaction for reaction monitoring of photocatalytic C(sp³)-H fluorination by *in situ* illumination NMR spectroscopy.

As with the photosensitization auxiliary fluorination reaction, it was investigated how the kinetics of the reaction change by varying the catalyst loading or the amount of substrate **8b**. The same concentrations as in the synthetic part of this work were used to screen for the influence of catalyst loading. To investigate the influence of the substrate, however, the concentrations of all involved reagents were decreased until all Selectfluor[®] weighed in was also completely dissolved, which was the case at c = 100 mM. So this time the weighed-in conditions correspond precisely to the dissolved ones.

A Screening of catalyst-loading



B Screening of substrate-loading

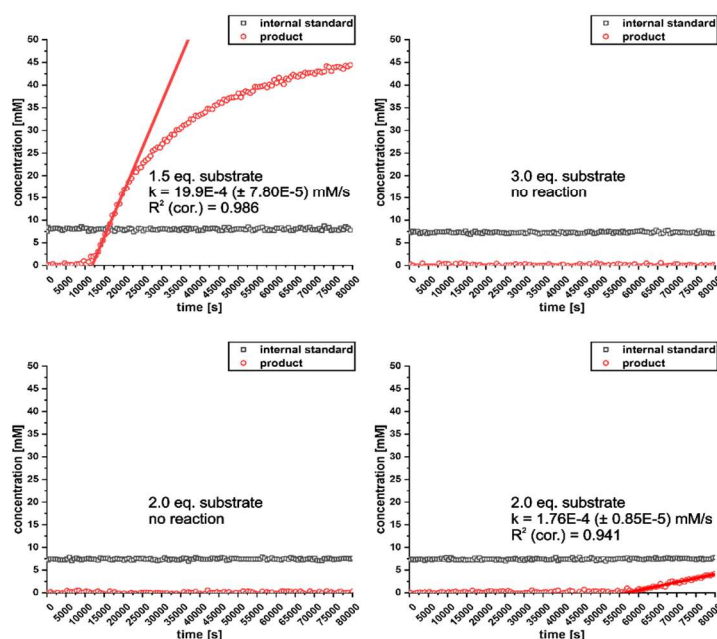


Figure S7. Reaction monitoring of photocatalytic C(sp³)-H fluorination reaction with different catalyst- and substrate loadings. Similar to the photosensitization auxiliary fluorination reactions an induction phase occurs before the reaction proceeds *via* a first order reaction profile. **A:** Product curves with different catalyst loadings: The reaction with 5 mol% was performed twice, one yielding product with a very high reaction rate and one with a rate comparable to the other catalyst loadings. **B:** Reaction profiles showing the product formation with different substrate loadings: While the reaction with 1.5 equivalents of substrate **1k** gave the product in a very good rate and conversion, no product was obtained with increasing the amount of substrate. The reaction with 2.0 eq. was done twice, once product was generated, but after a very long induction phase and with a rate, similar to those from catalyst loading screening.

Performing photocatalytic C(sp³)-H fluorination reaction with 1 mol% catalyst loading, product was generated after an induction phase of 8.3 h at a rate of 0.92E-4 mM/s. Increasing the catalyst loading to 5 or 8 mol% improved the product formation in a similar way. In both cases the induction phase is shortened by 41% to about 4.9 h and the product is formed at a rate almost 4 times higher than with 1 mol% catalyst loading (3.51E-4 mM/s for 5 mol% and 3.38E-4 mM/s for 8 mol%). In one example with 5 mol% catalyst loading, product was generated after approximately 40 min with a rate of 119E-4 mM/s. As with the screening of catalyst loading (Figure S7 **A**), different substrate loadings gave results that were difficult to classify (Figure S7 **B**): In contrast to the 1.5 eq. reaction of catalyst loading screening, here a by far more pronounced product formation could be observed. Product was yielded after an induction phase of 3.1 h with a rate of 19.9E-4 mM/s. When increasing the substrate loading, however, no product was obtained. Only in one example product was generated after a very long induction phase of 15.6 h and a rate comparable to that from the catalyst loading studies (1.76E-4 mM/s). Despite the generally less pronounced and slower product formation, “catalytic” PS fluorination nevertheless shows a reaction behavior like photosensitization auxiliary fluorination, consisting of an induction phase followed by first-order reaction type product generation.

In summary, the photocatalytic C(sp³)-H fluorination reaction kinetics were poorly reproducible. This emphasizes the importance of agitation of the slurry reaction mixture (in the NMR tube experiments, Selectfluor[®] sediments at the bottom of the tube). Moreover, it highlights a key advantage of the “auxiliary” PS fluorination in terms of robustness and reliability. The reason for the high robustness and generally better performance of “auxiliary” PS fluorination compared to the “catalytic” method, however, is the subject of further investigations.

5.5.6 Method for aggregate-investigations by diffusion ordered spectroscopy (DOSY) in photosensitization auxiliary fluorination

For DOSY measurements the dstebpgp3s pulse program, a convection suppressing DSTE (double stimulated echo) pulse sequence developed by Jerschow and Müller was applied in a pseudo 2D mode.²⁸ The diffusion time delay was set to 100 ms and a gradient pulse of 1350 μ s was applied. Sine.100 as gradient program and a linear gradient ramp with 20 increments between 10% and 95% of the maximum gradient strength were used. For z-only gradients 100 %, -13.17%, -17.13% and -15.17% were used. NMR data were processed and evaluated with TopSpin 3.2 (Topspin T1/T2 Module). Diffusion coefficients and average volumes were obtained according to Jerschow and Müller.²⁸

5.5.6.1 NMR sample preparation

The entire NMR sample preparation was executed similar as for reaction monitoring of photosensitization auxiliary fluorination under inert gas conditions (see chapter 5.5.4.1). The actual preparation was done inside glove box, anhydrous and degassed TMS and in case of the DOSY reaction monitoring also the glass fiber insert for *in situ* illumination were added following Schlenk line technique. To examine the pure components, depending on the concentration, they were weighed directly into the NMR tube or a dilution series was used to achieve the respective concentration (see Table S4). The sample preparation for investigating the reaction mixtures (1.5 eq. respectively 3.0 eq. substrate **8b**) was carried out as for the reaction monitoring of “auxiliary” PS fluorination (see Table S1) but without additional pentafluorobenzene as internal standard.

Table S4. Different amounts of substrate and Selectfluor® for DOSY studies of the pure compounds in anhydrous and degassed CD₃CN at 25 °C.

entry	compound	concentration [mM]
1		621.0
2	substrate 8b	310.5
3		1.0
4	Selectfluor®	207 ^a
5		1.0

^aWeighed in concentration. Due to moderate solubility, the concentration in solution is lower.

5.5.6.2 DOSY studies of photosensitization auxiliary fluorination using pure compounds at different concentrations and reaction mixtures with different substrate loadings and substrates

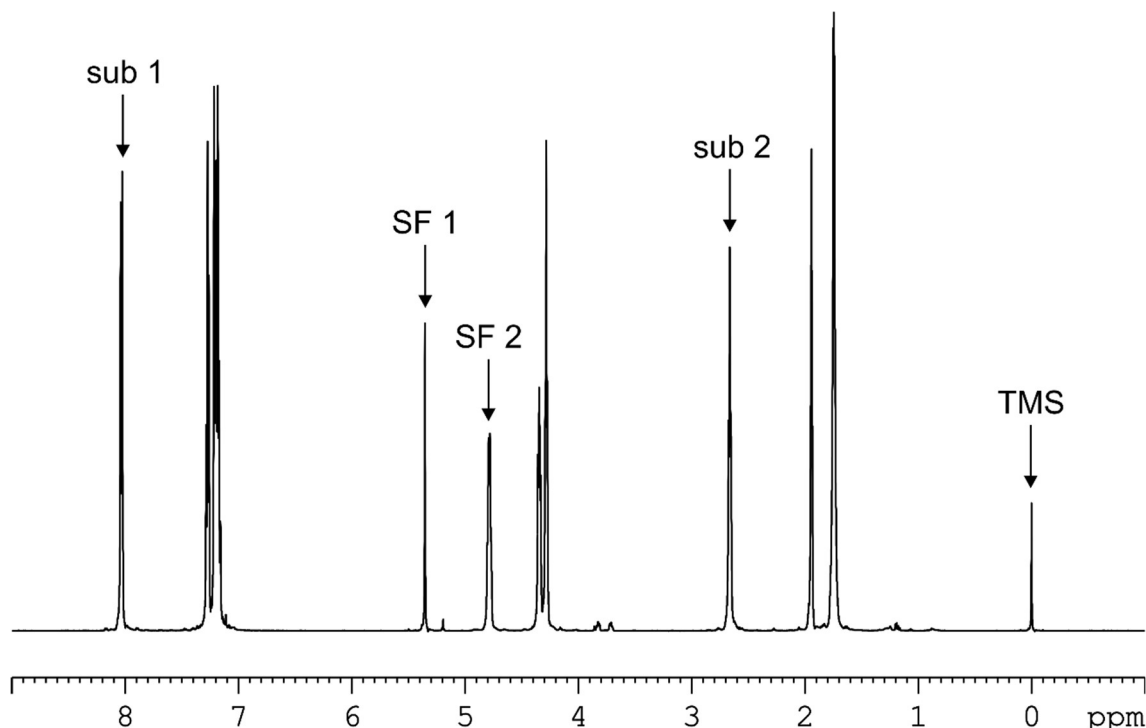


Figure S8. Representative ¹H-NMR spectrum of the photosensitization auxiliary fluorination of substrate **8b** measured in anhydrous and degassed CD₃CN at 25 °C. The volumes given in tables S5 to S7 correspond to mean values with standard deviation (SD). In the investigations of both, the pure compounds (Table S5) and the reaction mixtures (Table S6 and S7), the intense and non-overlapping signals sub 1 and sub 2 were used for substrate **8b** and the signals SF 1 and SF 2 for Selectfluor®.

To obtain the volumes of the pure reagents at the concentrations present in the reaction, they were first examined as pure samples (Table S5).

Table S5. Mean diffusion coefficients and average volumes of substrate **8b** and Selectfluor® as pure compounds at different concentrations in anhydrous and degassed CD₃CN at 25 °C.

entry	compound	concentration [mM]	mean diffusion coefficient [E-9m ² /s] with SD	average volume [Å ³] with SD
1	substrate 8b	621.0	6.48 ± 0.0291	431.4 ± 5.371
2		310.5	7.33 ± 0.0493	410.1 ± 7.44
3		1.0	8.52 ± 0.0375	390.0 ± 5.019
4	Selectfluor®	207 ^a	5.03 ± 0.0128	952.2 ± 6.439
5		1.0	6.61 ± 0.104	714.4 ± 29.06

^aWeighed in concentration. Due to moderate solubility, the concentration in solution is lower.

At the concentrations found in the standard reaction with 1.5 eq. substrate **8b**, the substrate **8b** has a volume of $410.1 \pm 7.44 \text{ \AA}^3$ (Table S5 entry 2) and Selectfluor[®] of $952.2 \pm 6.439 \text{ \AA}^3$ (Table S5 entry 4). At a concentration of 621 mM (Table S5 entry 1), which is present in the reaction with 3.0 eq, the volume of substrate **8b** increases slightly by 5.2%. If the concentration is significantly reduced to 1 mM (Table S5 entry 3), the volume diminishes by a similar amount to $390.0 \pm 5.019 \text{ \AA}^3$. When Selectfluor[®] is diluted to a concentration of 1 mM (Table S5 entry 5), the volume is also reduced, but by 25%. To check whether substrate **8b** and Selectfluor[®] are already present as monomers in the 1 mM samples, the monomer-volumes were calculated based on the known intermolecular van der Waals radii of the corresponding functional groups and atoms.²⁹ A volume of $247.23 \text{ \AA}^3$ for substrate **8b** and $332.27 \text{ \AA}^3$ for Selectfluor[®] was received. Since the calculated volumes, which are in general good approximations, differ significantly from the ones received by DOSY, this suggests that the two reagents are still aggregated even at such low concentrations.

Next, mixtures of substrate **8b** and Selectfluor[®] with 1.5 eq. substrate (Table S6) and 3.0 eq. (Table S7) were examined before and during the reaction.

Table S6. Mean diffusion coefficients and average volumes of substrate **8b** and Selectfluor[®] in a reaction mixture with 1.5 equivalents substrate **8b** at different times (reaction states) in anhydrous and degassed CD₃CN at 25 °C.

entry	compound	Reaction status	mean diffusion coefficient [E-9m ² /s] with SD	average volume [Å ³] with SD
1	8b	No illumination	6.74 ± 0.0131	423.8 ± 2.671
2		Illumination started	6.80 ± 0.0694	408.6 ± 10.63
3		Distinct product formation starts	6.81 ± 0.029	409.0 ± 4.151
4		Reaction finished	6.75 ± 0.047	408.5 ± 7.612
5	Selectfluor [®]	No illumination	5.13 ± 0.0713	845.4 ± 30.77
6		Illumination started	5.16 ± 0.0183	816.3 ± 7.574
7		Distinct product formation starts	5.15 ± 0.041	822.3 ± 17.09
8		Reaction finished	5.13 ± 0.0243	817.1 ± 10.15

Table S7. Mean diffusion coefficients and average volumes of substrate **8b** and Selectfluor[®] in a reaction mixture with 3.0 equivalents substrate **8b** at different times (reaction states) in anhydrous and degassed CD₃CN at 25 °C.

entry	compound	Reaction status	mean diffusion coefficient [E-9m ² /s] with SD	average volume [Å ³] with SD
1	8b	No illumination	6.07 ± 0.0244	428.6 ± 4.765
2		Illumination started	6.16 ± 0.0786	417.2 ± 13.71
3		Distinct product formation starts	6.17 ± 0.0284	429.2 ± 5.378
4		Reaction finished	6.11 ± 0.0633	427.5 ± 11.48
5	Selectfluor [®]	No illumination	4.64 ± 0.0498	846.0 ± 23.74
6		Illumination started	4.73 ± 0.0239	810.0 ± 10.70
7		Distinct product formation starts	4.70 ± 0.0439	852.3 ± 20.81
8		Reaction finished	4.67 ± 0.0352	839.2 ± 16.53

In order to determine whether there is a change in the volumes of the reagents involved during photosensitization auxiliary fluorination, their volume was identified for certain reaction states. It turns out, that in both reactions (1.5 eq substrate **8b**, Table S6 and 3.0 eq. substrate **8b**, Table S7), the volume of the two reagents, substrate **8b** and

Selectfluor[®], remains almost unchanged. The average volume of the substrate in the 1.5 equivalent reaction ($412.5 \pm 6.266 \text{ \AA}^3$) and 3.0 equivalent reaction ($425.6 \pm 8.833 \text{ \AA}^3$) do not differ from those, when substrate **8b** is present as a pure compound (see Table S5). The average volume of Selectfluor[®], however, is reduced to $825.3 \pm 16.40 \text{ \AA}^3$ for the 1.5 eq. reaction and $836.9 \pm 17.95 \text{ \AA}^3$ for the 3.0 eq. reaction. This corresponds to a reduction of 13% (1.5 eq. reaction) respectively 12% (3.0 eq. reaction) compared to Selectfluor[®] as a pure compound of the same concentration (see Table S5 entry 4).

To check the origin of the Selectfluor[®] de-aggregation inside the reaction mixture with substrate **8b**, the unreactive substrate **5b** without the fluorine in *para*-position was selected.

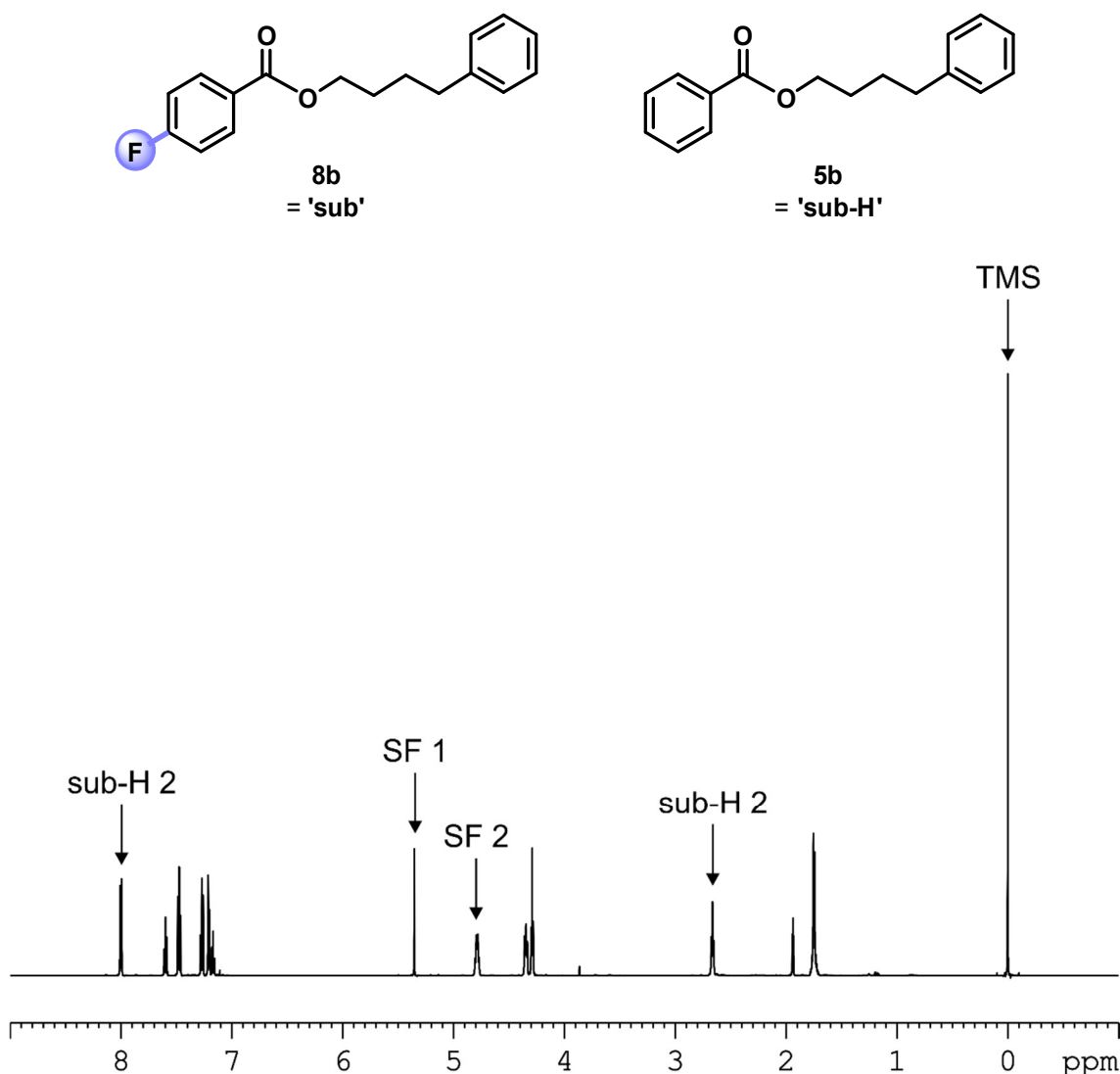


Figure S9. ¹H-NMR spectrum of substrate **5b** (1.5 eq., 310.5 mM) and Selectfluor[®] (1.0 eq., not completely dissolved) measured in anhydrous and degassed CD₃CN at 25 °C. The volumes given in Table S8 correspond to mean values with SD. For this, the intense and non-overlapping signals sub-H 1 and sub-H 2 were used for substrate **5b** and the signals SF 1 and SF 2 for Selectfluor[®].

Table S8. Mean diffusion coefficients and average volumes of substrate **5b** and Selectfluor[®] in a mixture with 1.5 eq. substrate **5b** and 1.0 eq. Selectfluor[®] in anhydrous and degassed CD₃CN at 25 °C.

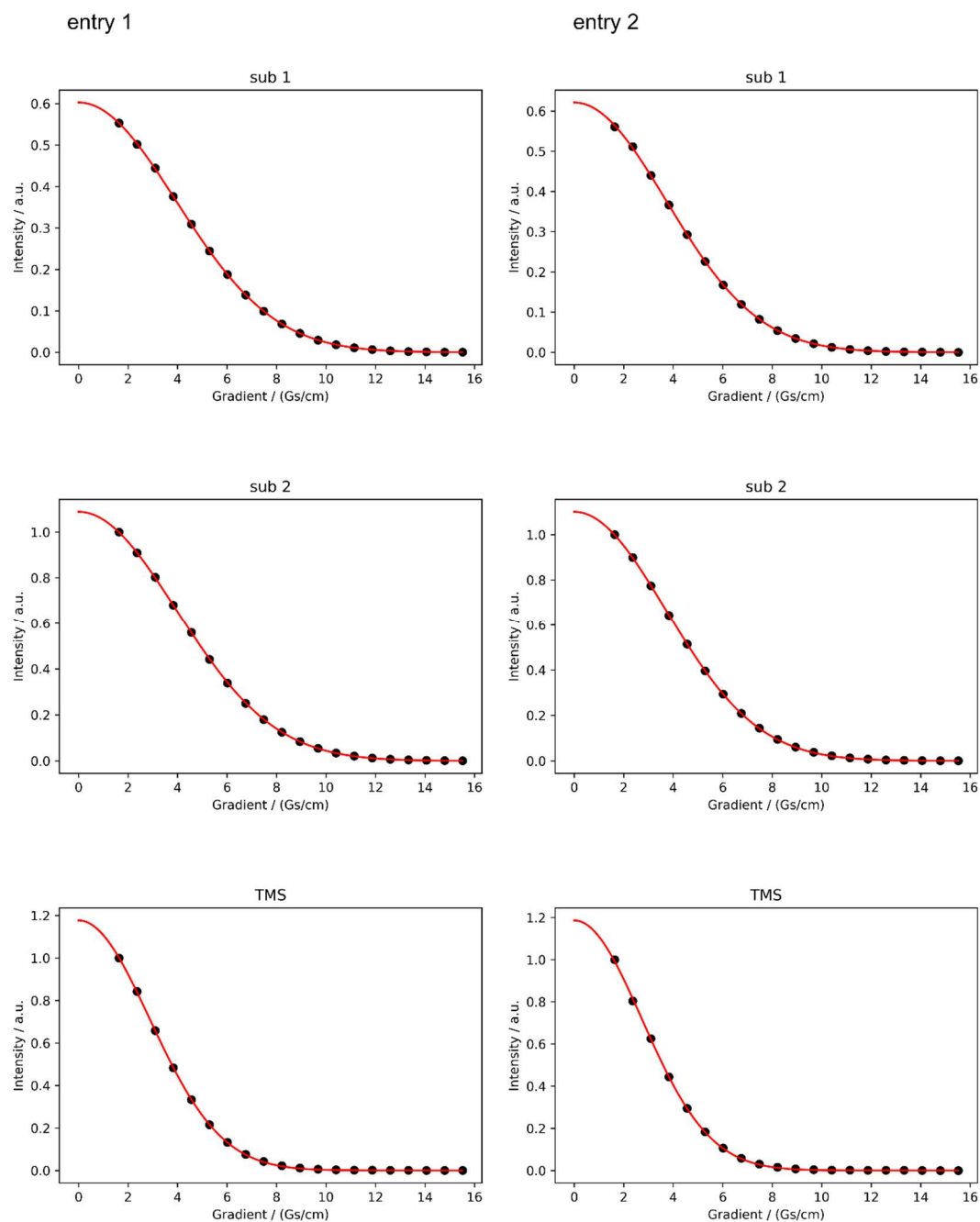
entry	compound	concentration [mM]	mean diffusion coefficient [E-9m ² /s] with SD	average volume [Å ³] with SD
1	substrate 5b	310.5	6.78 ± 0.0839	413.9 ± 13.24
2	Selectfluor [®]	207 ^a	4.95 ± 0.0181	917.5 ± 8.864

^aWeighed in concentration. Due to moderate solubility, the concentration in solution is lower.

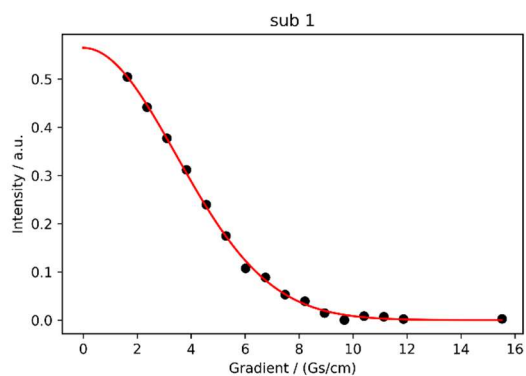
Similar to the previous investigations, a sample containing 1.5 eq. substrate **5b** and 1.0 eq. Selectfluor[®] was prepared. With 413.9 ± 13.24 Å³, the volume of substrate **5b** is very similar to that of substrate **8b** (412.5 ± 6.266 Å³, see Table S6). This is not surprising given that only the fluorine in the *para*-position has been replaced by a hydrogen atom. On the other hand, looking at the volume of Selectfluor[®] shows a clear effect of substrate **8b** compared to **5b**. While Selectfluor[®] mixed with 1.5 eq. **8b** was de-aggregated by 13% compared to its volume as pure compound with the same concentration (see Table S5 entry 4), its volume only decreases by 3.6% upon mixing with **5b**. Considering the good reactivity of **8b** vs **5b**, it is suggested that the ability of the **PSAux** F atom to de-aggregate Selectfluor[®] may play a key role in initiating reactivity.

5.5.6.3 DOSY plots

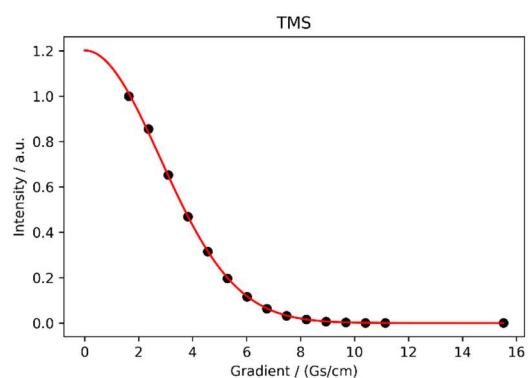
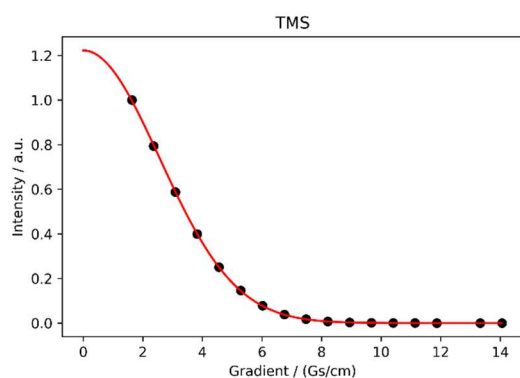
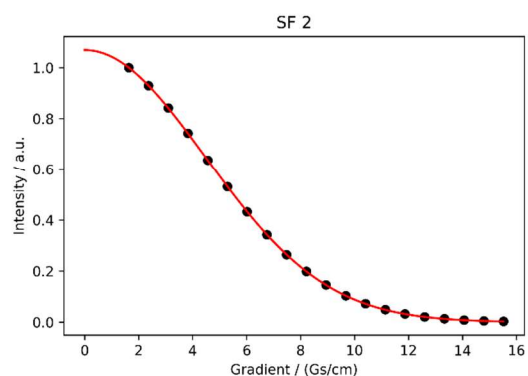
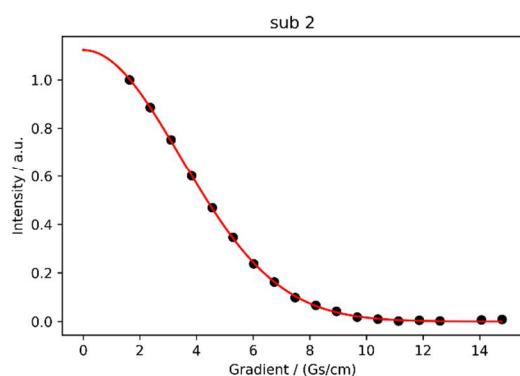
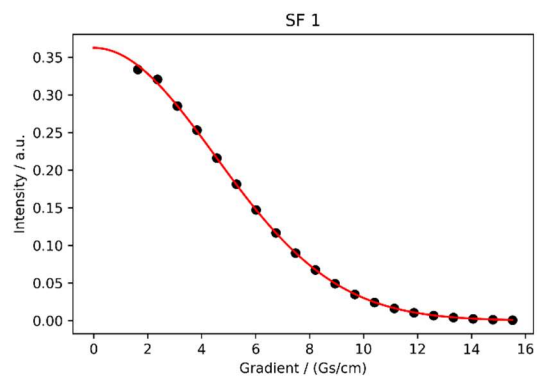
Pure compounds (Table S5)



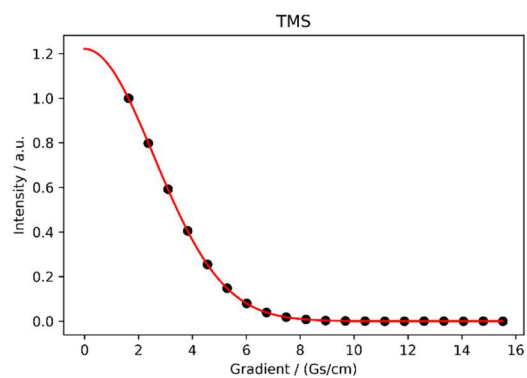
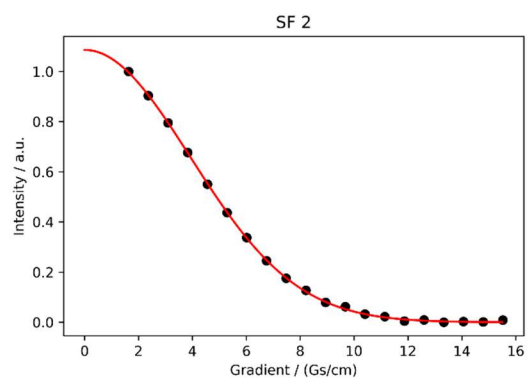
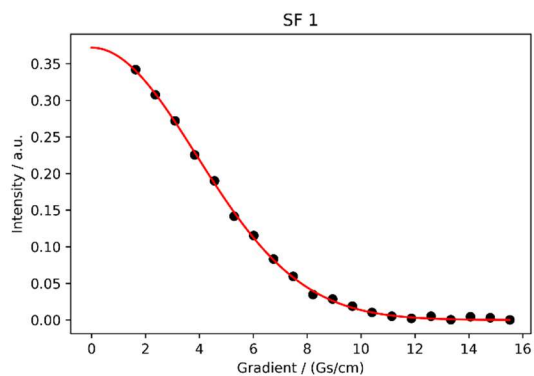
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entry 4

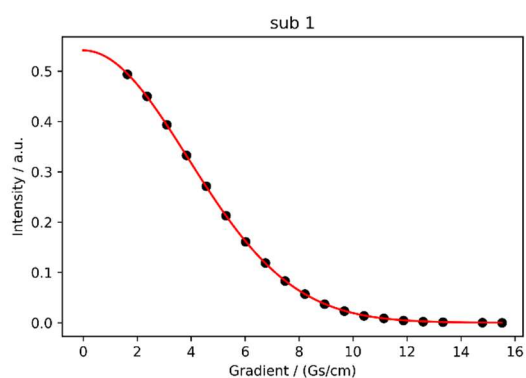


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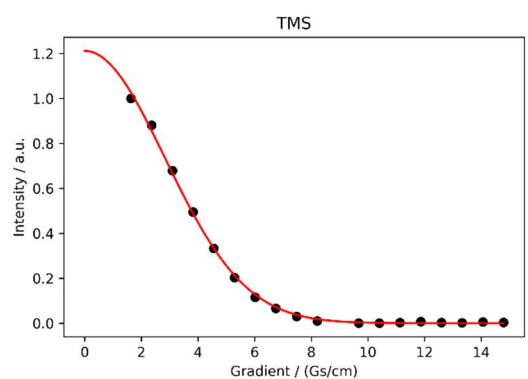
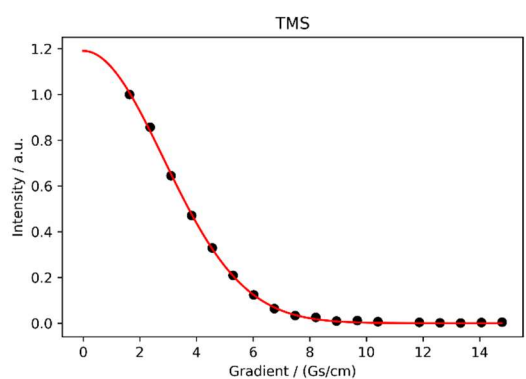
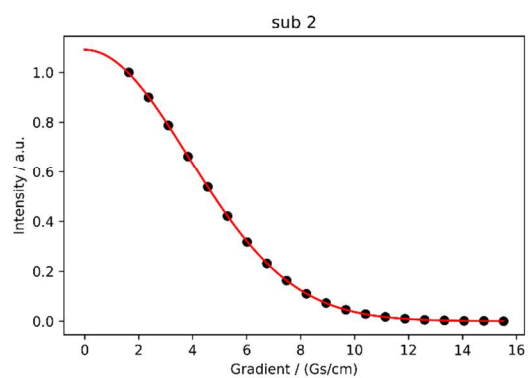
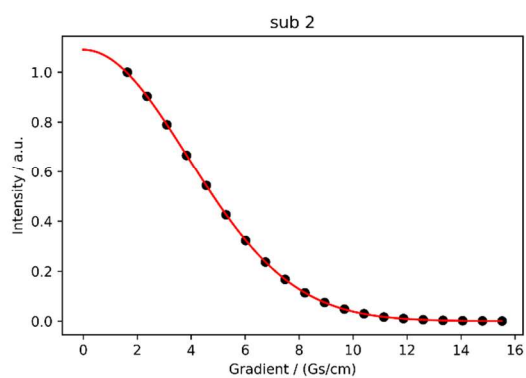
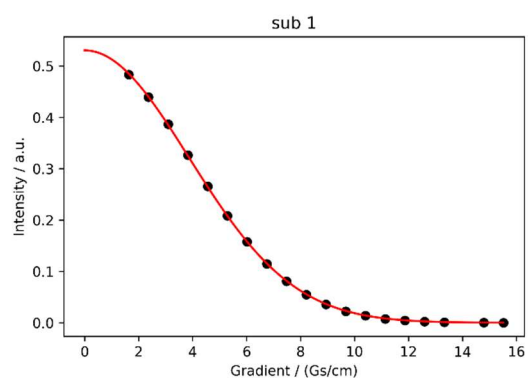


1.5 eq. reaction (Table S6)

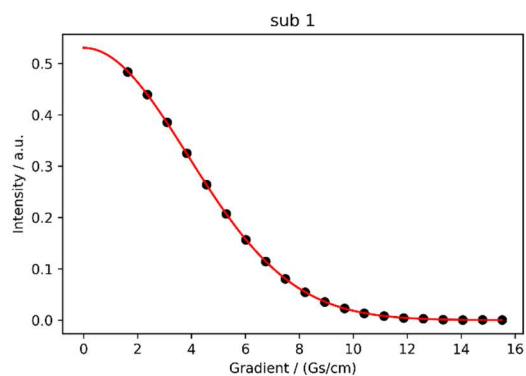
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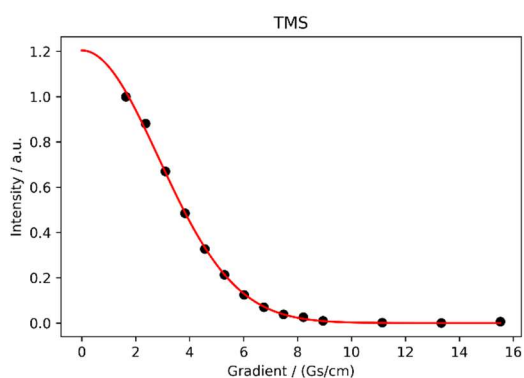
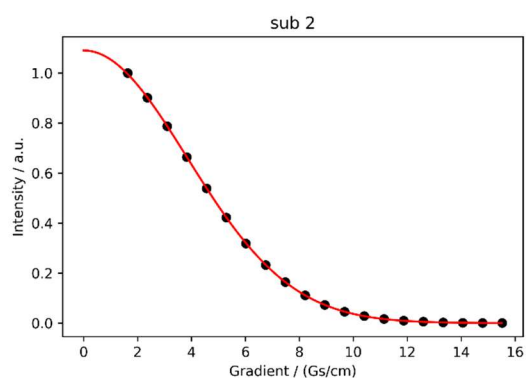
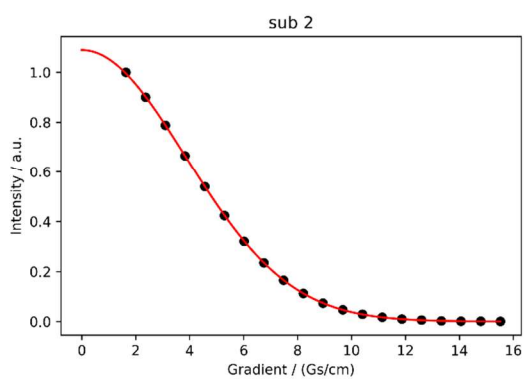
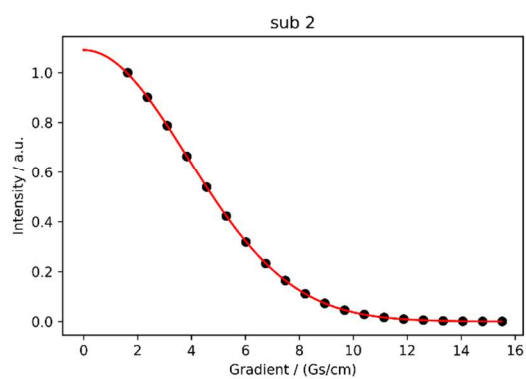
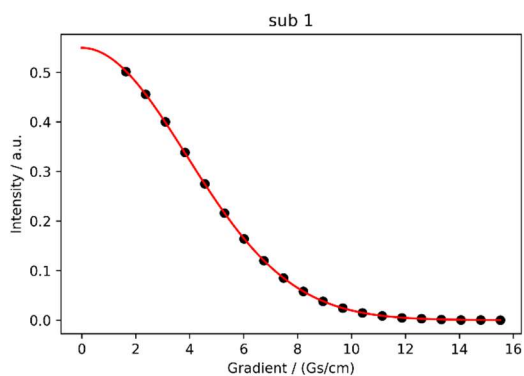
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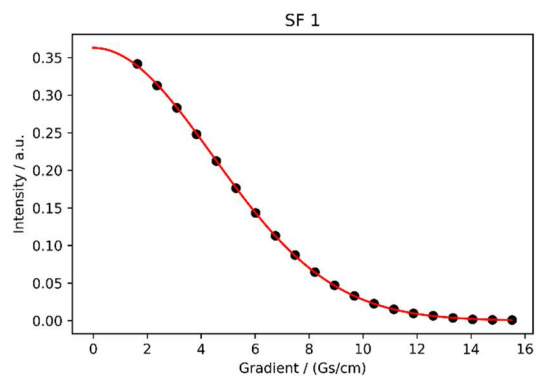
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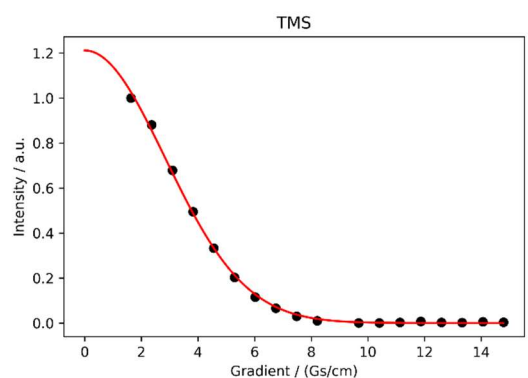
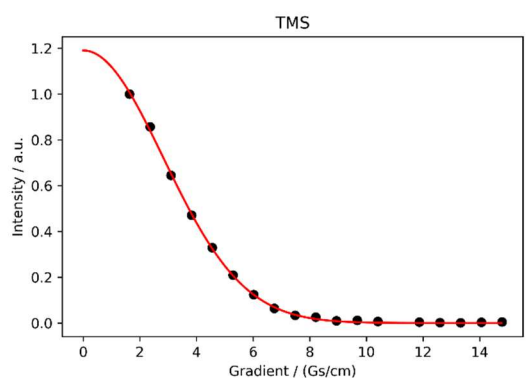
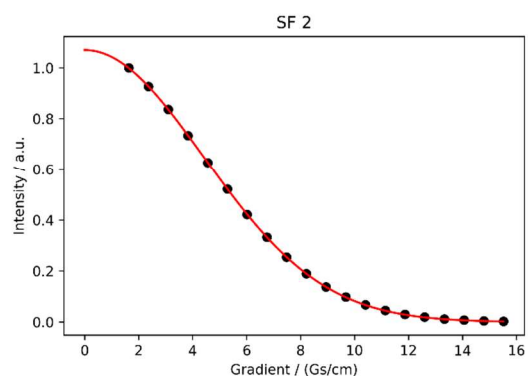
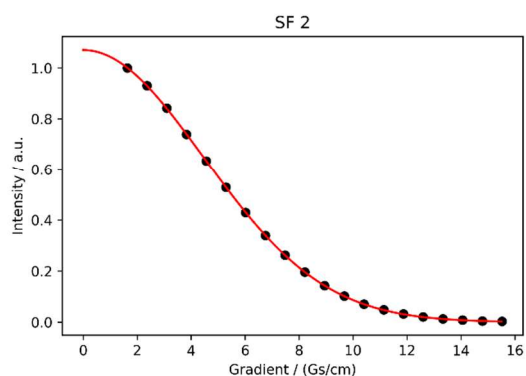
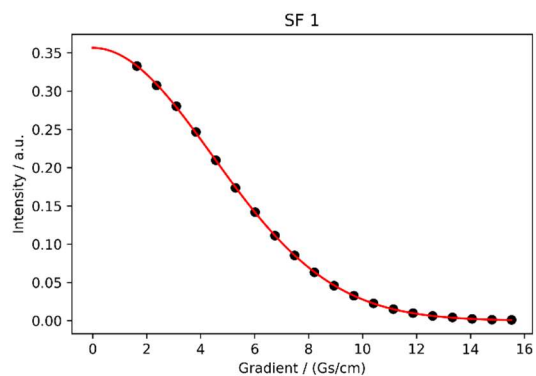
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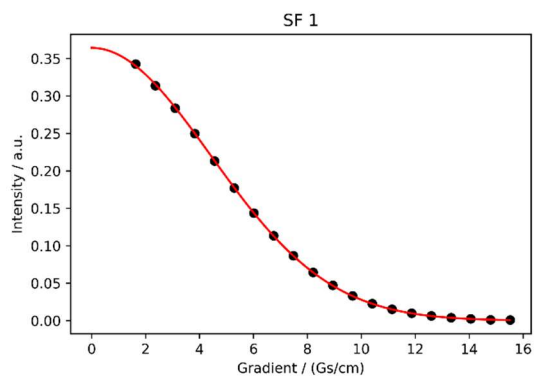
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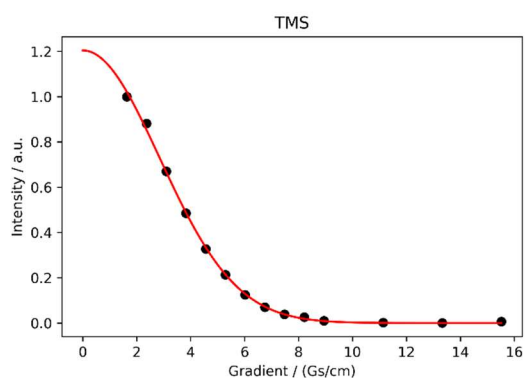
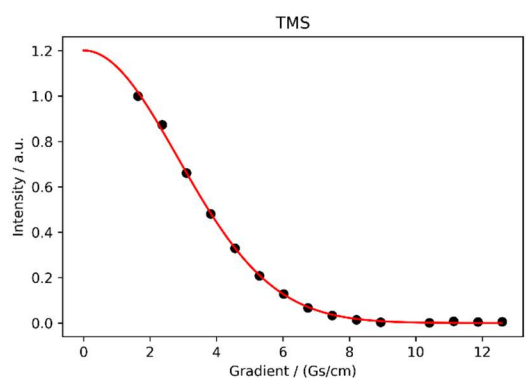
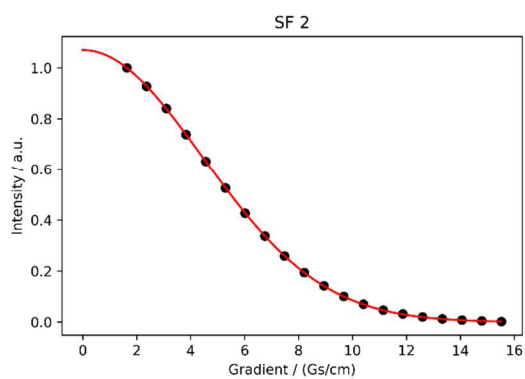
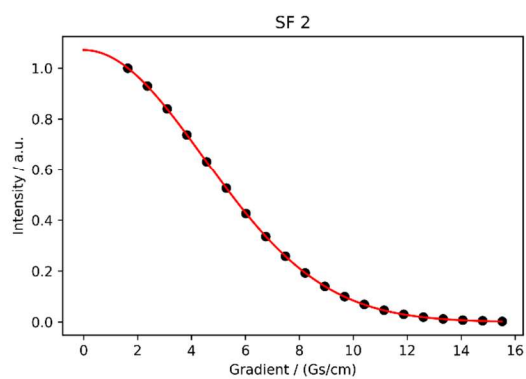
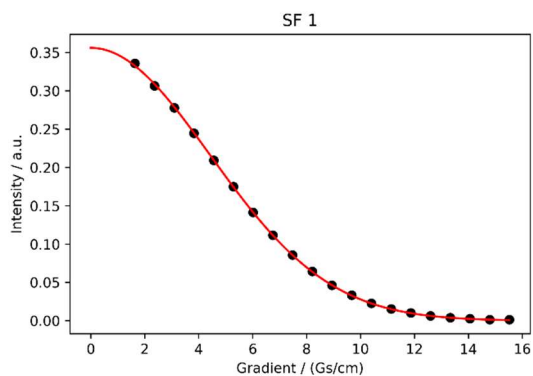
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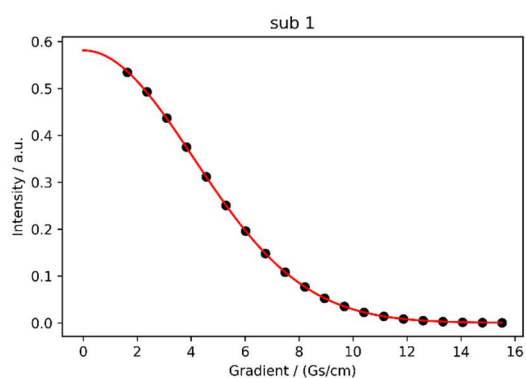


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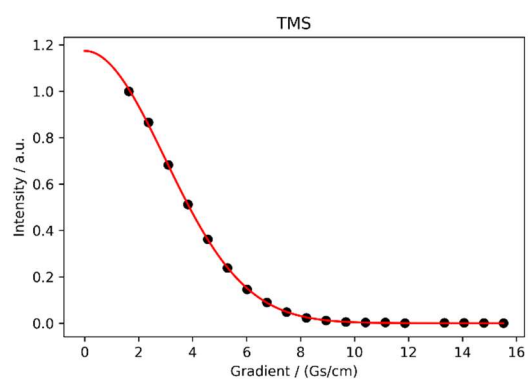
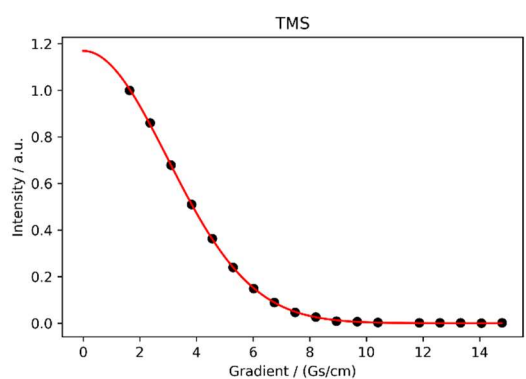
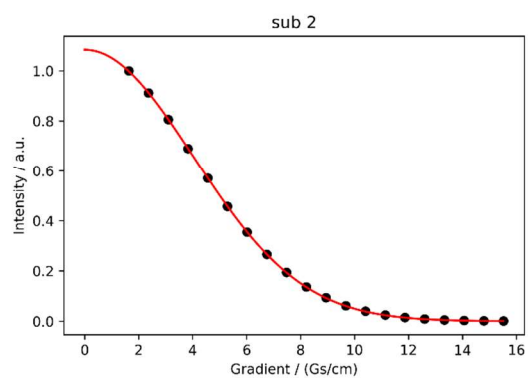
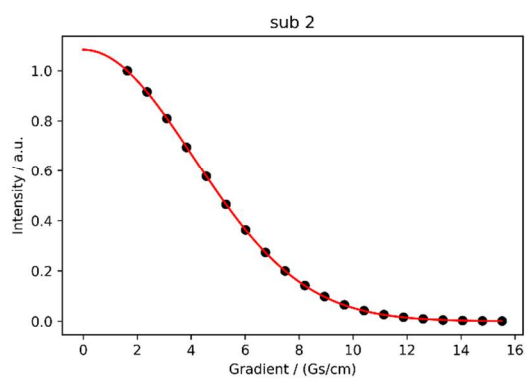
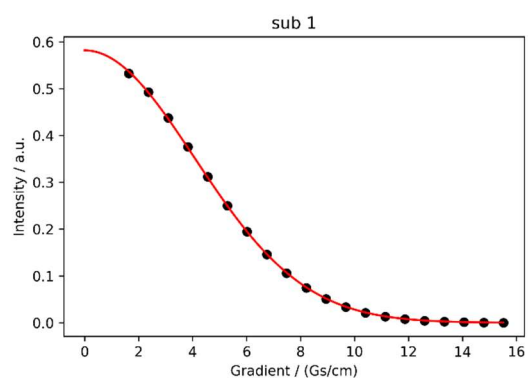


3.0 eq. reaction (Table S7)

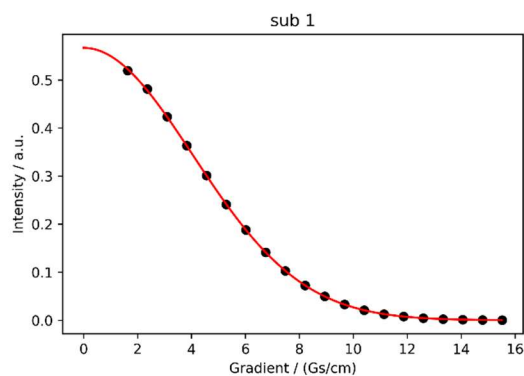
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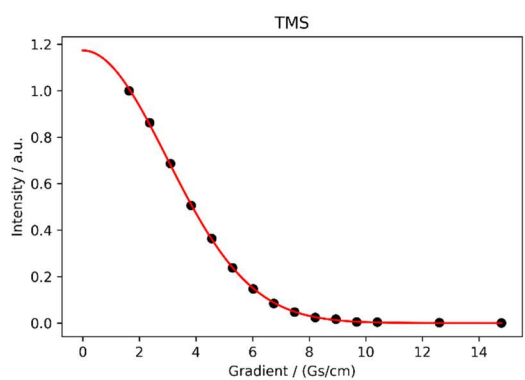
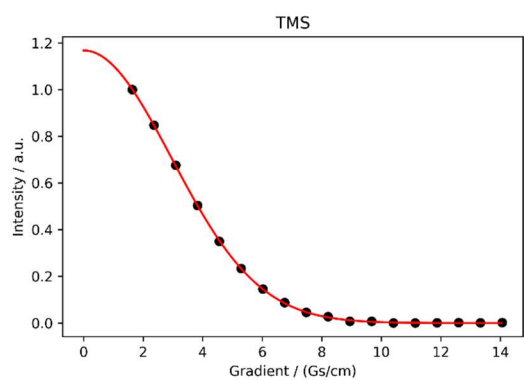
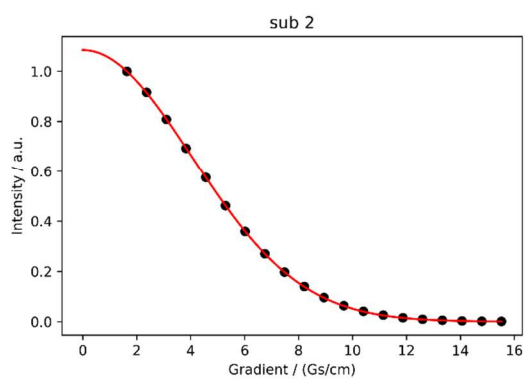
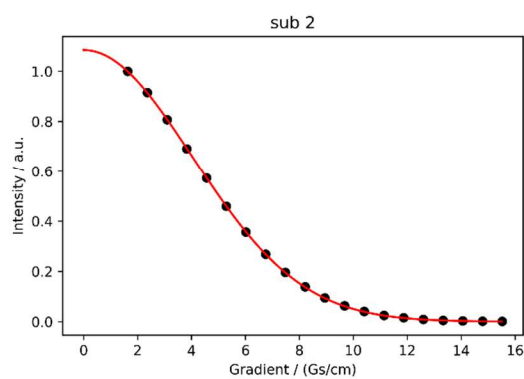
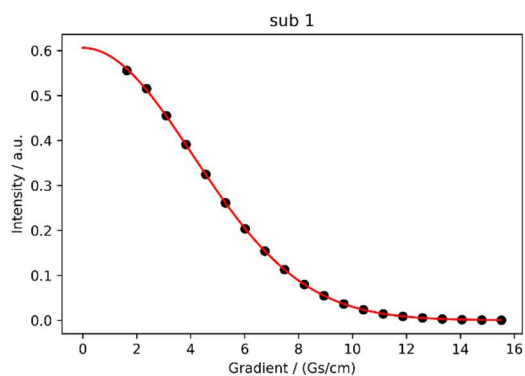
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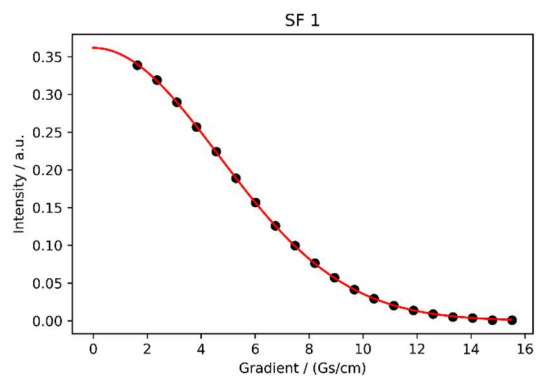
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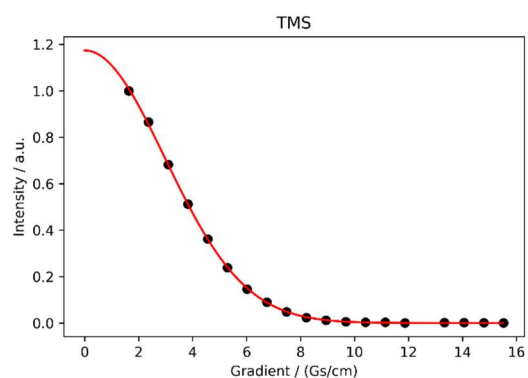
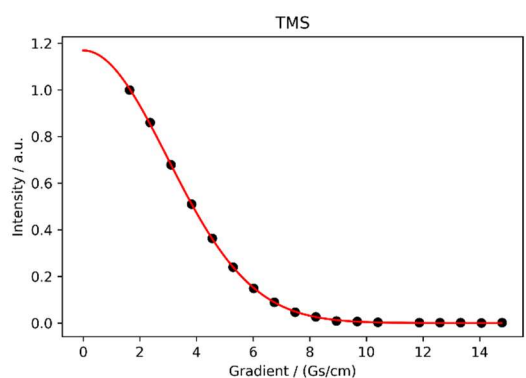
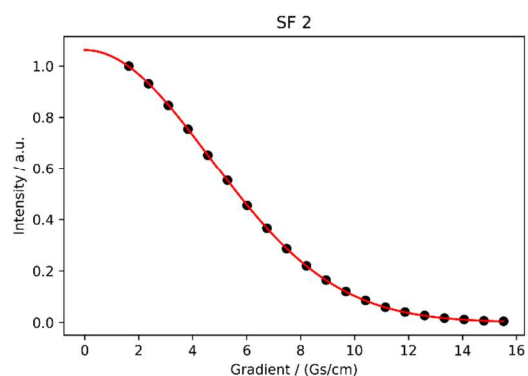
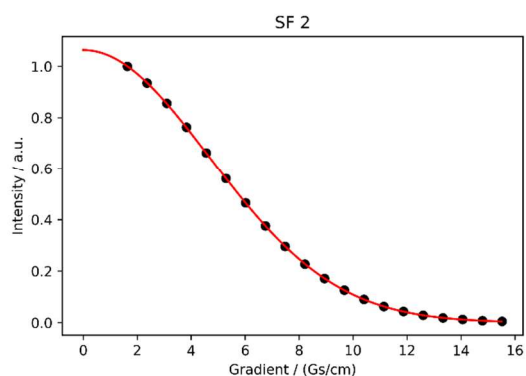
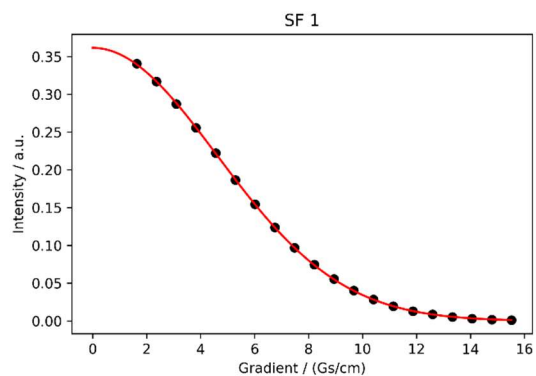
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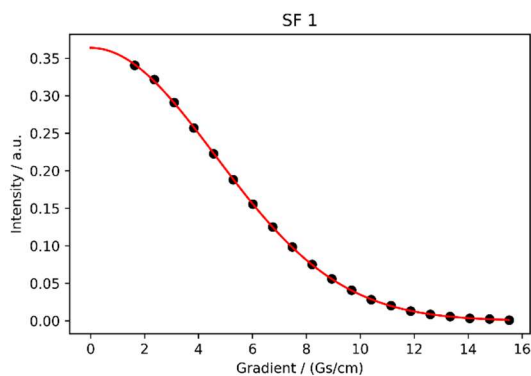
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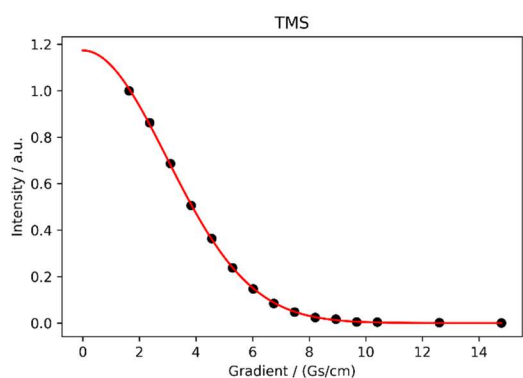
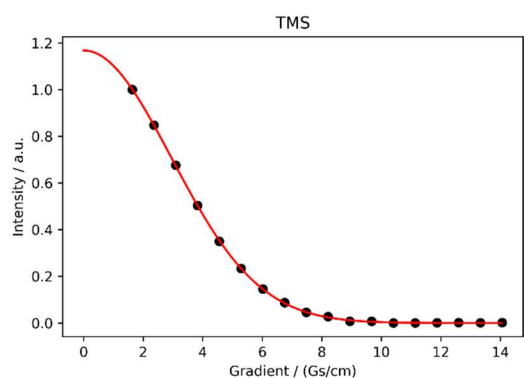
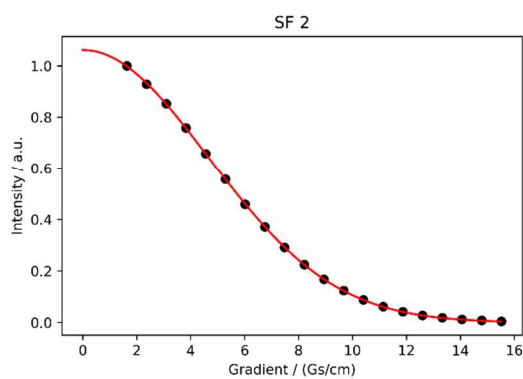
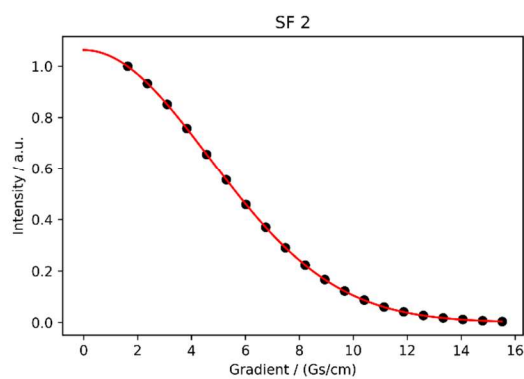
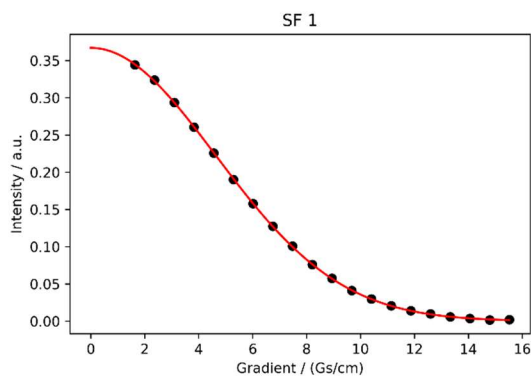
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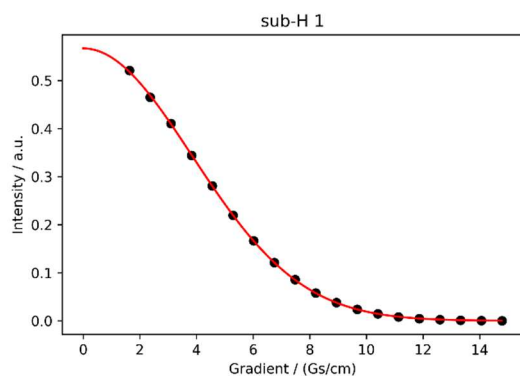


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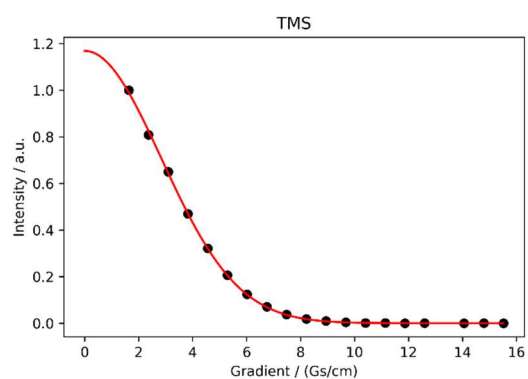
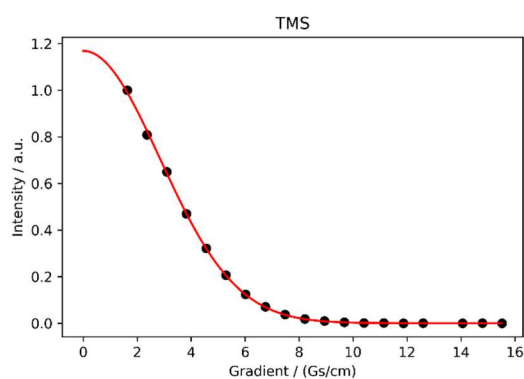
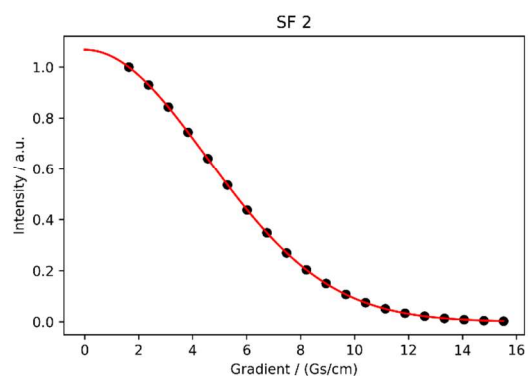
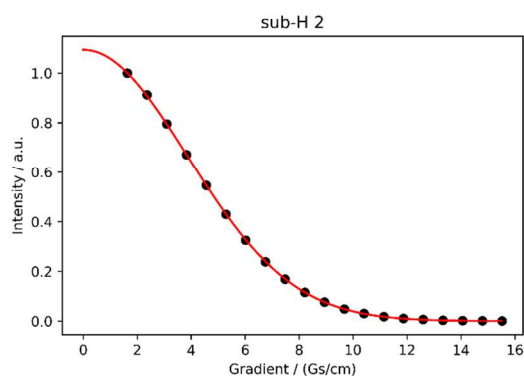
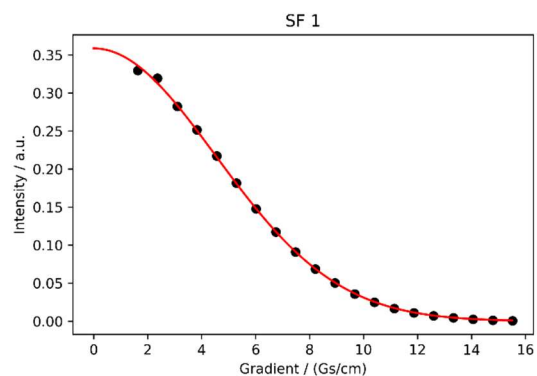


1.5 eq. substrate **5b** + 1.0 eq. Selectfluor® (Table S8)

entry 1



entry 2



5.5.7 Structural elucidation of **2o** in CDCl₃ at 25 °C

To assign the signals for **2o** in CDCl₃ (saturated solution) at 25 °C (Figure S10) a series of 1D and 2D NMR experiments (1D-¹H; 1D-¹⁹F{¹H}; 1D-¹³C{¹H}; 2D-¹H, ¹H correlated spectroscopy (COSY); 2D-¹H, ¹H nuclear Overhauser enhancement spectroscopy (NOESY), 2D-¹H, ¹³C heteronuclear multiple bond correlation (HMBC); 2D-¹H, ¹³C heteronuclear single quantum coherence (HSQC)) was measured (Figure S11-S17). Next to the routine 1D-¹³C{¹H} a 1D-¹³C{¹H,¹⁹F} with additional ¹⁹F-decoupling was measured. By comparing the two NMR spectra the carbons next to the fluorine substituent can explicitly be identified and assigned via the associated ¹³C-¹⁹F coupling constants (¹J_{CF} – ³J_{CF}). (Figure S18).

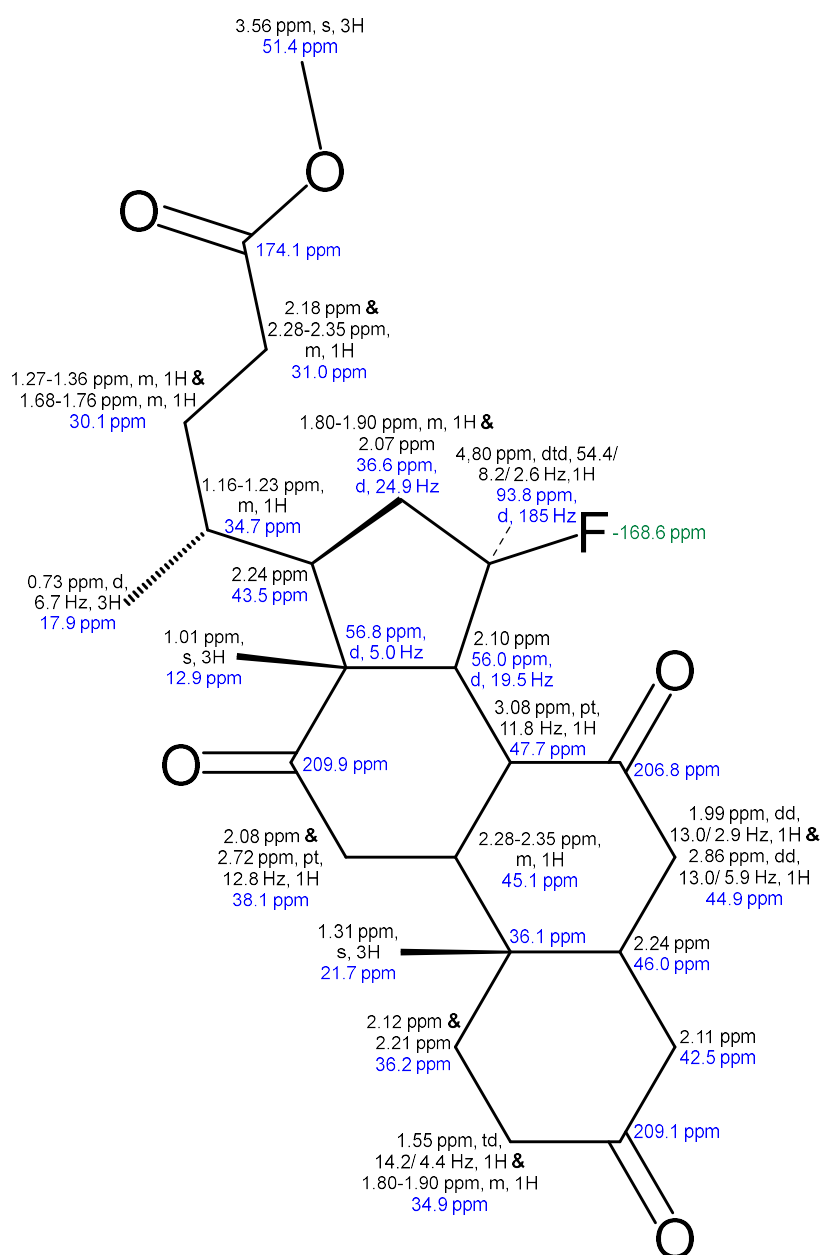


Figure S10. Assignment of **2o** in CDCl₃ (saturated solution) at 25 °C. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black, ¹³C blue and ¹⁹F green.

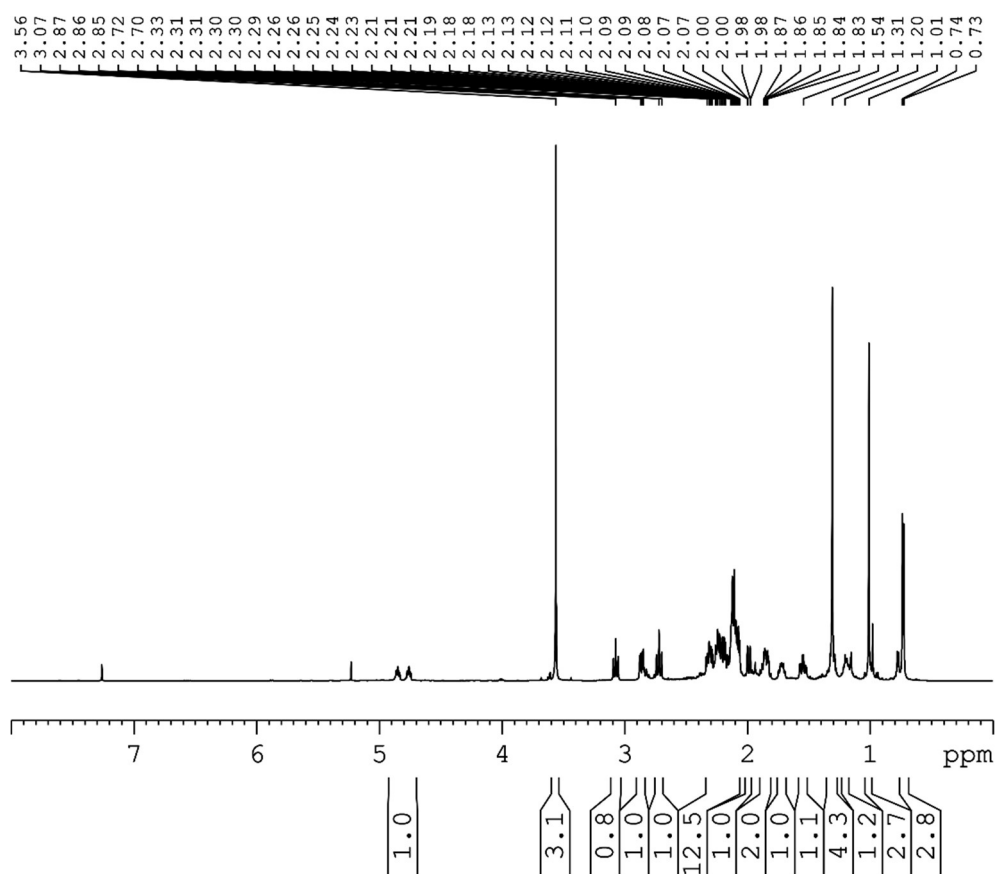


Figure S11. 1D-¹H spectrum (ns = 16) of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

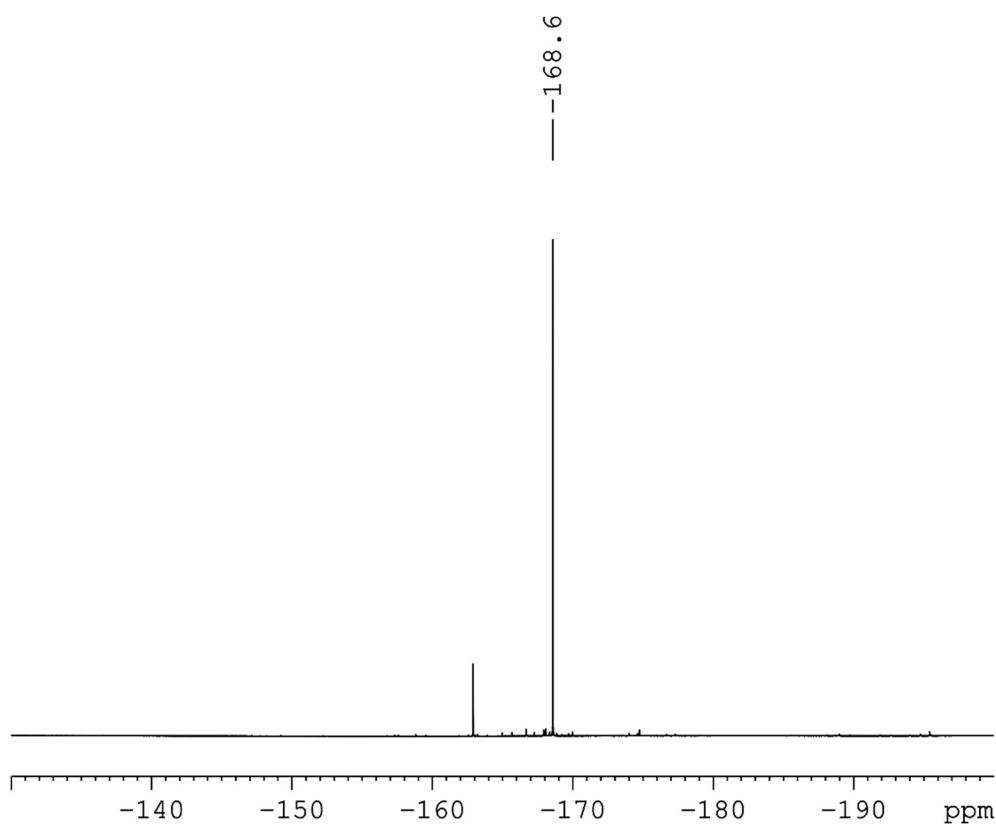


Figure S12. 1D-¹⁹F{¹H} spectrum (ns = 8) of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

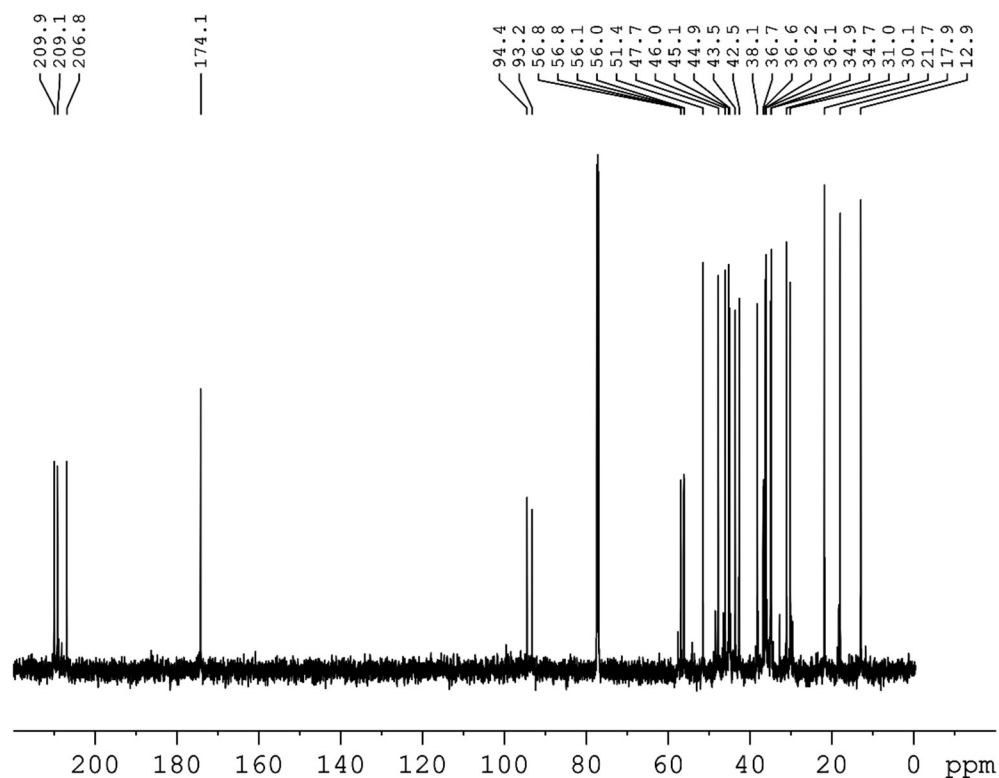


Figure S13. 1D-¹³C{¹H} spectrum (ns = 1024) of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

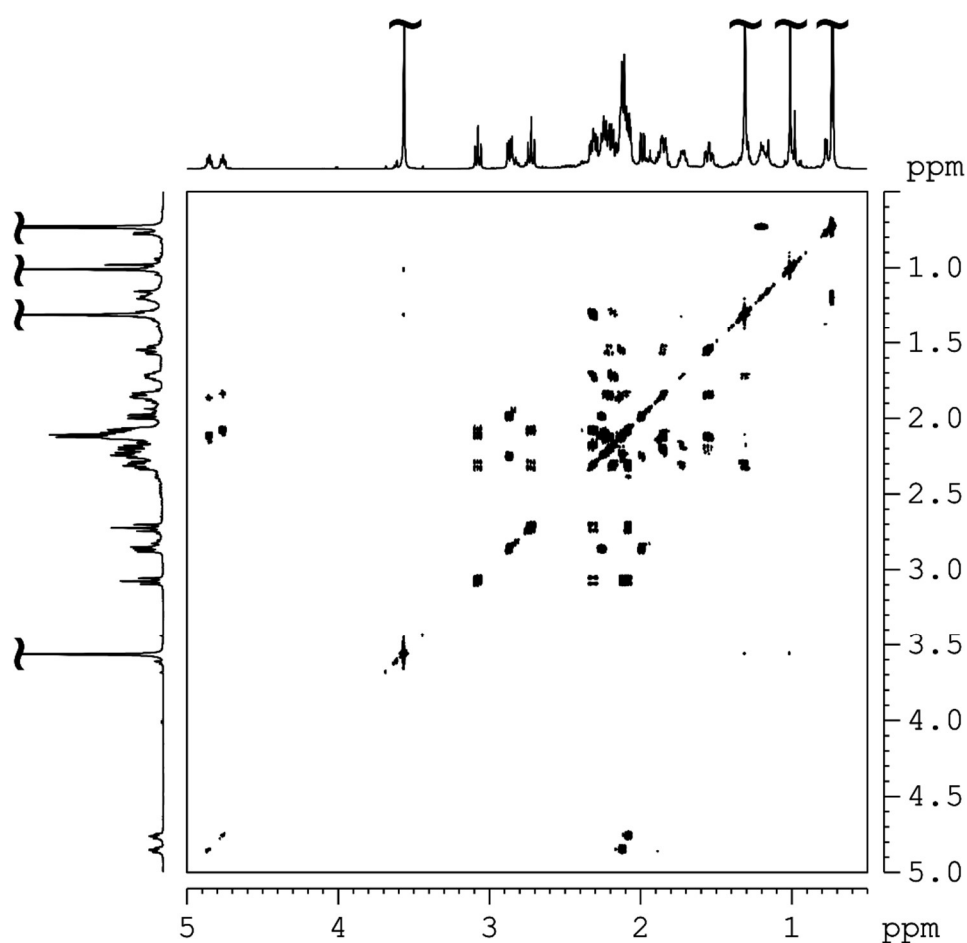


Figure S14. 2D-¹H, ¹H COSY spectrum of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

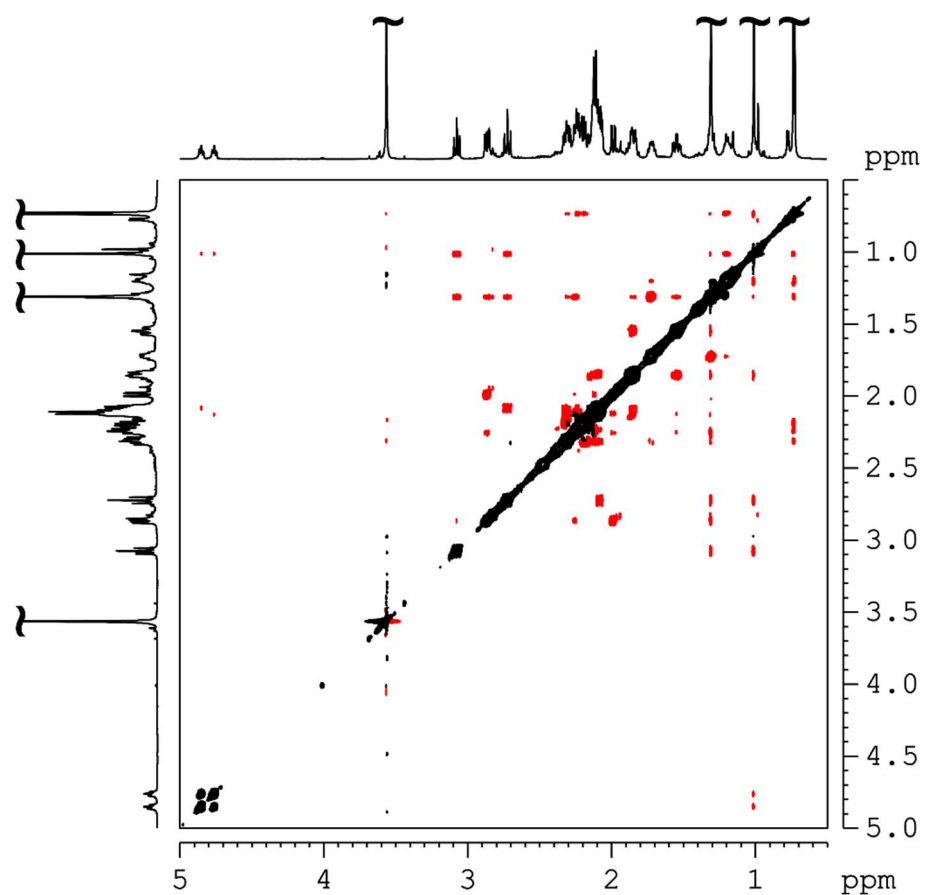


Figure S15. 2D-¹H, ¹H NOESY spectrum (mixing time = 0.7 s) of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

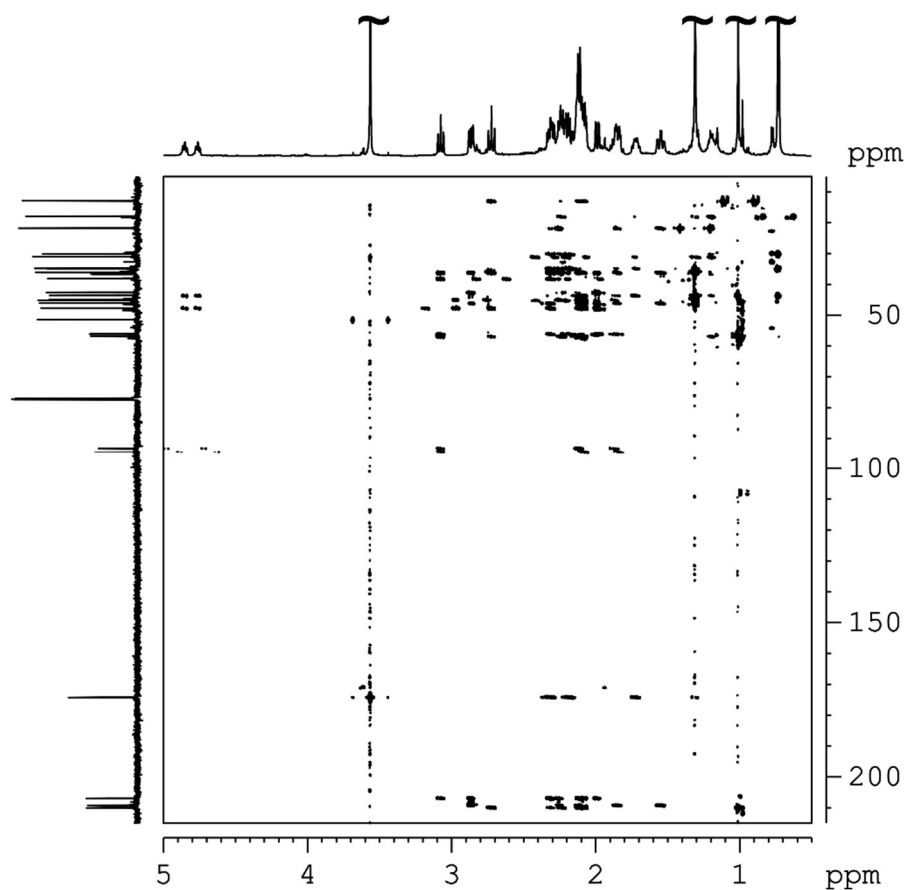


Figure S16. 2D-¹H, ¹³C HMBC spectrum of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

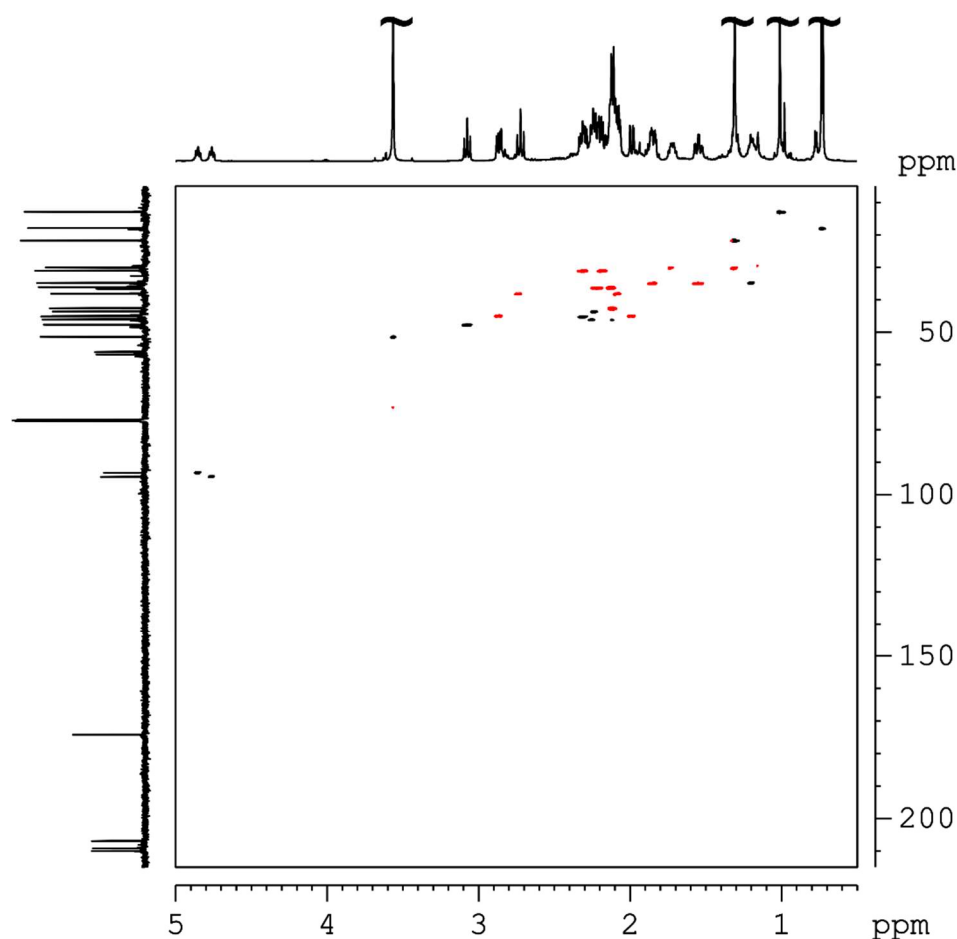


Figure S17. 2D-¹H, ¹³C HSQC spectrum of **2o** in CDCl₃ (saturated solution) measured at 25 °C.

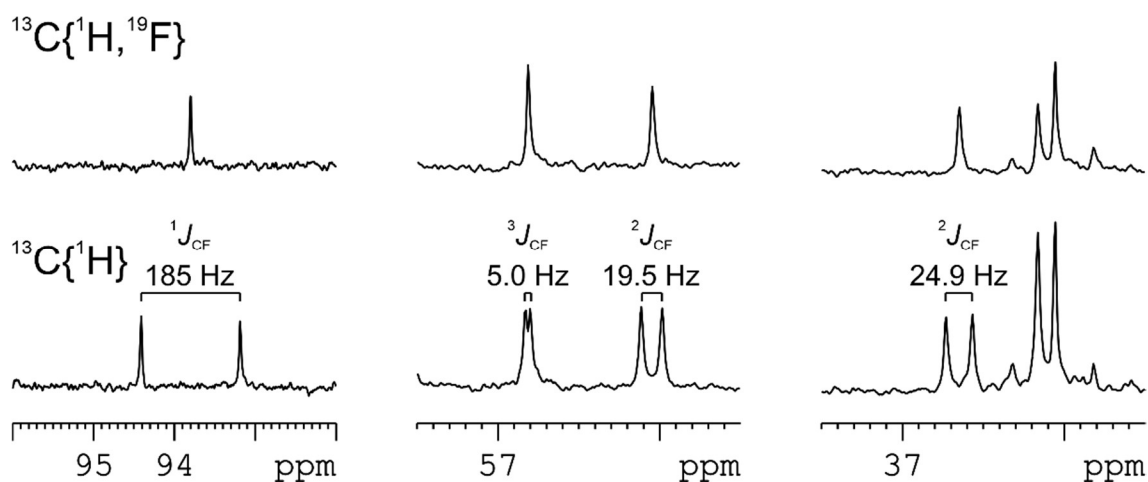


Figure S18. Sections of a routine 1D-¹³C{¹H} spectrum (ns = 1024) (bottom) and a 1D-¹³C{¹H,¹⁹F} spectrum (ns = 1024) (top) with additional ¹⁹F-decoupling. Because the adjacent ¹³C signals merge to one signal with additional ¹⁹F-decoupling, these signals must correspond to one carbon close to the fluorine substituent. The magnitude of *J*-coupling provides information on the number of bonds between in this case carbon and fluorine. In general, the smaller the coupling constant, the more bonds are between the coupled nuclei.

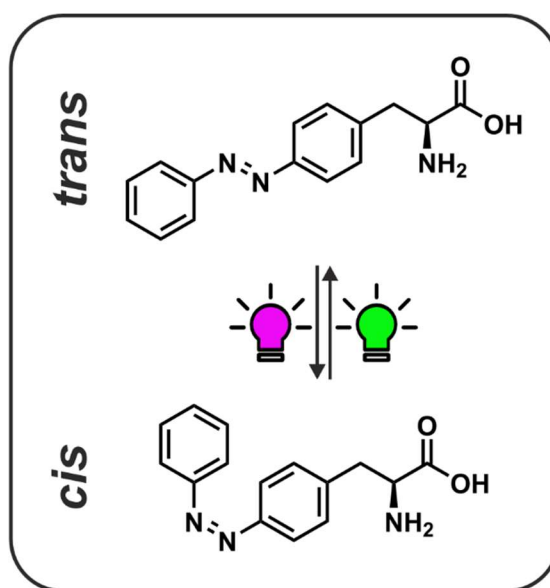
5.6 References

- 1 W. E. Barnette, *J. Am. Chem. Soc.* 1984, **106**, 452.
- 2 Selected examples: a) K. L. Hull, W. Q. Anani and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 7134; b) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, **334**, 639; c) M. G. Braun and A. G. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 12990.
- 3 Selected examples: a) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214; b) M. Y. Chang, M. F. Lee, C. H. Lin and N. C. Lee, *Tetrahedron Lett.*, 2011, **52**, 826.
- 4 For selected representative examples, see: a) R. Szpera, D. F. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, *Angew. Chem. Int. Ed.*, 2019, **58**, 14824; b) A. Lin, C. B. Huehls and J. Yang, *Org. Chem. Front.*, 2014, **1**, 434; c) M. Rueda-Becerril, C. C. Sazepin, J. C. Leung, T. Okbinoglu, P. Kennepohl, J. F. Paquin and G. M. Sammis, *J. Am. Chem. Soc.*, 2012, **134**, 4026; d) A. Vasilopoulos, D. L. Golden, J. A. Buss and S. S. Stahl, *Org. Lett.*, 2020, **22**, 5753; e) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III, J. T. Groves, *Science* **2012**, **337**, 1322-1325; f) W. Liu, X. Huang, M. S. Placzek, S. W. Krska, P. M. Quade, J. M. Hooker, J. T. Groves, *Chem. Sci.* **2018**, **9**, 1168-1172; g) Y. Zhang, N. A. Fitzpatrick, M. Das, I. P. Bedre, H. G. Yayla, M. S. Lall, P. Z. Musacchio, *Chem. Catal.* **2022**, **2**, 292-308.
- 5 Selected reviews: a) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; b) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; c) T. Fujiwara and D. O'Hagan, *J. Fluor. Chem.*, 2014, **167**, 16.
- 6 S. Yakubov, J. P. Barham, *Beilstein J. Org. Chem.*, 2020, **16**, 2151.
- 7 Selected examples: a) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim and T. Lectka, *Angew. Chem. Int. Ed.*, 2012, **51**, 10580; *Angew. Chem.*, 2012, **124**, 10732; b) M. H. Shaw, V. W. Shuftleff, J. A. Terrett, J. D. Cuthbertson and D. W. C. MacMillan, *Science*, 2016, **352**, 1304; c) J. P. Barham, M. P. John and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 15482; d) Y. Takahira, M. Chen, Y. Kawamata, P. Mykhailiuk, H. Nakamura, B. K. Peters, S. H. Reisberg, C. Li, L. Chen, T. Hoshikawa, T. Shibuguchi and P. S. Baran, *Synlett*, 2019, **30**, 1178. Selected reviews: d) F. J. A. Troyano, K. Merckens and A. Gómez-Suárez, *Asian J. Org. Chem.*, **2020**, **9**, 992; e) J. Kaur and J. P. Barham, *Synthesis*, 2022, **54**, 1461.
- 8 Selected examples: a) J. B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494; b) J. B. Xia, C. Zhu and C. Chen, *Chem. Commun.*, 2014, **50**, 11701.
- 9 Selected examples: a) C. W. Kee, K. F. Chin, M. W. Wong and C. H. Tan, *Chem. Commun.*, 2014, **50**, 8211; b) J. W. Kee, H. Shao, C. W. Kee, Y. Lu, H. S. Soo and C. H. Tan, *Catal. Sci. Technol.*, 2017, **7**, 848.

- 10 Selected examples: a) D. D. Bume, C. R. Pitts, F. Ghorbani, S. A. Harry, J. N. Capilato, M. A. Siegler, and T. Lectka, *Chem. Sci.* 2017, **8**, 6918; b) D. D. Bume, S. A. Harry, C. R. Pitts and T. Lectka, *J. Org. Chem.* 2018, **83**, 1565; c) D. D. Bume, C. R. Pitts, R. T. Jokhai and T. Lectka, *Tetrahedron* 2016, **72**, 6031; d) C. R. Pitts, D. D. Bume, S. A. Harry, M. A. Siegler and T. Lectka, *J. Am. Chem. Soc.*, 2017, **139**, 2208; e) J. N. Capilato, C. R. Pitts, R. Rowshanpour, T. Dudding and T. Lectka, *J. Org. Chem.*, 2020, **85**, 2855.
- 11 S. P. Vincent, M. D. Burkart, C. Y. Tsai, Z. Zhang and C. H. Wong, *J. Org. Chem.*, 1999, **64**, 5264.
- 12 H. Egami, S. Masuda, Y. Kawato and Y. Hamashima, *Org. Lett.*, 2018, **20**, 1367.
- 13 Selected examples: a) M. S. Chauhan, G. D. Yadav, F. Hussain and S. Singh, *Catal. Sci. Technol.*, 2014, **4**, 3945; b) P. Sharma and R. K. Sharma, *Chirality*, 2019, **31**, 91.
- 14 K. Yang, M. Song, A. I. Ali, S. M. Mudassir and H. Ge, *Chem. Asian J.*, 2020, **15**, 729.
- 15 N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348.
- 16 a) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; b) C. Thiehoff, Y. P. Rey and R. Gilmour, *Isr. J. Chem.*, 2016, **57**, 91.
- 17 a) J. F. Wu, M. M. Liu, S. X. Huang and Y. Wang, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3251; b) M. Szostak, M. Spain, A. J. Eberhart and D. J. Proctor, *J. Am. Chem. Soc.*, 2014, **136**, 2268.
- 18 D. R. Arnold, J. R. Bolton, G. E. Palmer and K. V. Prabhu, *Canad. J. Chem.*, 1977, **55**, 2728.
- 19 Y. Kanda, R. Shimada and Y. Takenoshita, *Spectrochimica Acta*, 1963, **19**, 1249.
- 20 Selected reviews: a) C. G. S. Lima, T. de M. Lima, M. Duarte, I. D. Jurberg and M. W. Paxiã, *ACS Catal.*, 2016, **6**, 1389; b) G. E. M. Crisenza, D. Mazzearella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461; c) selected example: during the review of this manuscript, a decarboxylative benzylic fluorination involving a charge transfer complex of SF and DMAP was reported, see: A. Madani, L. Anghileri, M. Heydenreich, H. M. Möller, B. Pieber, *Org. Lett.* **2022**, *24*, 5376-5380.
- 21 Previous examples of photochemical reaction kinetics: a) K. Chen, N. Berg, R. Gschwind and B. König, *J. Am. Chem. Soc.*, 2017, **139**, 18444; b) H. Bartling, A. Eisenhofer, B. König and R. M. Gschwind, *J. Am. Chem. Soc.*, 2016, **138**, 11860; c) S. Wang, N. Lokesh, J. Hioe, R. M. Gschwind and B. König, *Chem. Sci.*, 2019, **10**, 4580; d) C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39.
- 22 Selected reviews on photochemical HAT using arylketones: a) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, **2017**, 2056; b) S. Wu, J. Kaur, T. A. Karl, X. Tian and J. P. Barham, *Angew. Chem. Int. Ed.* 2021, **61**, e202107811; Selected examples:

- c) N. Berg, S. Bergwinkl, P. Nuernberger, D. Horinek and R. M. Gschwind, *J. Am. Chem. Soc.*, 2021, **143**, 724; d) F. Burg and T. Bach, *J. Org. Chem.* 2019, **84**, 8815.
- 23 a) S. A. Fleming, S. C. Ward, *Tetrahedron Lett.* **1992**, 33, 1013-1016; (b) S. C. Ward, S. A. Fleming, *J. Org. Chem.* **1994**, 59, 6476-6479.
- 24 Selected examples: J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, 131, 14604-14605; A. Törster, R. Alonso, A. Bauer, T. Bach, *J. Am. Chem. Soc.* **2016**, 138, 7808-7811; D. M. Flores, M. L. Neville, V. A. Schmidt, *Nat. Commun.* **2022**, 13:2764.
- 25 Selected examples: a) S. Wu, J. Žurauskas, M. Domański, P. S. Hitzfeld, V. Butera, D. J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer and J. P. Barham, *Org. Chem. Front.*, 2021, **8**, 1132; b) X. Tian, T. A. Karl, S. Reiter, S. Yakubov, R. de-Vivie Riedle, B. König and J. P. Barham, *Angew. Chem. Int. Ed.*, 2021, **60**, 20817; c) A. Bhattacharyya, S. De Sarkar and A. Das, *ACS Catal.*, 2021, **11**, 710.
- 26 Selected examples: a) M. Giedyk, R. Narobe, S. Weiß, D. Touraud, W. Kunz and B. König, *Nat. Catal.*, 2020, **3**, 40; b) J. Kaur, A. Shahin and J. P. Barham, *Org. Lett.*, 2021, **23**, 2002.
- 27 a) L. Zeng, T. Liu, C. He, D. Shi, F. Zhang and C. Duan, *J. Am. Chem. Soc.*, 2016, **138**, 3958; b) M. J. P. Mandigma, J. Žurauskas, C. I. MacGregor, L. J. Edwards, A. Shahin, L. d'Heureuse, P. Yip, D. J. S. Birch, T. Gruber, J. Heilmann, M. P. John and J. P. Barham, *Chem. Sci.*, 2022, **13**, 1912.
- 28 A. Jerschow and N. Müller, *J. Magn. Reson.*, 1997, **125**, 372.
- 29 a) A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441; b) M. Mantina, A. C. Chamberlin, R. Valero, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. A*, 2009, **113**, 5806.

6. Appendix: *In Situ* Illumination NMR Spectroscopic Investigations of a Photoresponsive Unnatural Amino Acid



Willibald J. Stockerl and Ruth M. Gschwind

This project was conceptualized by the working groups of A. Kneuttinger, R. Sterner and B. König. The working groups of R. Sprangers and R. M. Gschwind contributed to this project with various NMR spectroscopic insights either on the protein containing the photoresponsive unnatural amino acid AzoF or on the isolated amino acid. **Willibald J. Stockerl** performed all the *in situ* illumination NMR spectroscopic investigations presented in this appendix, which he wrote with input from R. M. Gschwind.

6.1 Abstract and Introduction

Photocontrol of proteins is of growing interest and different strategies have been developed over the last decades for enabling photoregulated cellular processes.¹ Applying photoxenoprotein engineering is one well-known method. Here, photoresponsive non-canonical amino acids (ncAAs) are incorporated into the desired protein.² One example for protein photocontrol *via* ncAAs is phenylalanine-4'-azobenzene (AzoF) **1** with its central N-N double bond, which can be reversibly switched between *trans* and *cis* configuration by illumination with different wavelengths $h\nu(1)$ and $h\nu(2)$ (Figure 1).³

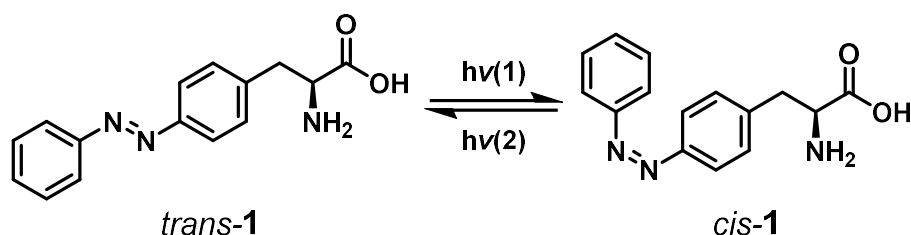


Figure 1. *Trans* and *cis* configuration of photoswitchable ncAA AzoF **1**.

Placing **1** at strategic positions of protein HisF successfully demonstrated the importance of this research field by yielding a reversible 10-fold regulation of enzyme activity upon photoisomerization.⁴ This regulation of enzyme activity could be even increased by changing from continuous illumination with either $h\nu(1)$ or $h\nu(2)$ to fast pulsing between both wavelengths.⁵ Therefore, the enhanced enzyme activity is assumed to base upon photoinduced isomerization being locally translated into vibrational energy. To prove that photoswitchable amino acids serve as a means of locally bringing in energy and thus increasing enzyme activity would be very interesting. One way to characterize such vibrational motions within proteins are NMR relaxation studies.⁶ However, a site-selective incorporation of photoresponsive ncAAs in proteins *via* photoxenoprotein engineering and additionally labelling for complex NMR spectroscopic investigations on proteins is very challenging. Furthermore, understanding the photoisomerization capacity of **1** is crucial for correctly interpreting possible motions of the protein amino acid side chains, obtained *via* NMR relaxation studies.

Therefore, in this study initial investigations on the photostability and photoswitching efficiency of **1** were performed on the isolated amino acid.

6.2 Results and Discussion

The photostability of isolated **1** was investigated *via* illuminating alternately with 380 nm and 460 nm (0.5 Hz switching rate) for more than 55 hours at 25 °C (see Figure 2). These two wavelengths were selected according to the major absorption bands of *trans*-**1** at ca. 365 nm and of *cis*-**1** at ca. 420 nm, which were determined by the Kneuttinger group (see chapter 6.4.5). **1** was dissolved in the same buffer (H₂O (25 mM NaP, 25 mM NaCl, pH 6.8)/D₂O 95:5), which is also applied for the corresponding **1**-containing proteins. However, **1** shows a poor solubility in this solvent mixture. To therefore increase signal to noise ratio, the solvent signal was suppressed using pre-saturation pulses and 4096 scans were accumulated per spectrum.

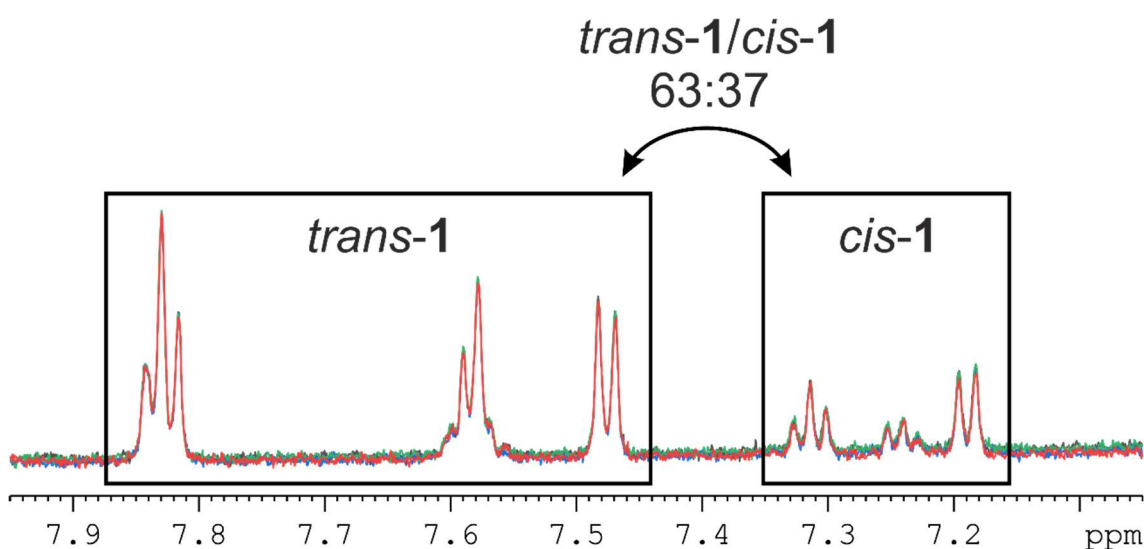


Figure 2. Investigation on the photostability of **1** (20 μ M in H₂O (25 mM NaP, 25 mM NaCl, pH 6.8)/D₂O 95:5) at 25 °C using the illumination setup for alternating illumination (1W light power, 0.5 Hz switching rate, see chapter 6.4.3.2). The signal intensities of *trans*-**1** and *cis*-**1** remain constant over a period of more than 55 hours. The depicted spectra were recorded after 13.8 h (red spectrum), 27,6 h (green spectrum), 41.4 h (blue spectrum) and 55.2 h (grey spectrum).

We obtained two sets of signals, which were assigned to *trans*-**1** and *cis*-**1** (see chapter 6.4.4 for structure elucidation of **1**). In each spectrum, equally intense signals with a ratio of *trans*-**1**/*cis*-**1** = ca. 63:37 could be observed. This reflects a high stability of **1** towards continuous photoillumination and also that alternately illuminating gives a stable mixture of *trans*-**1** and *cis*-**1**.

Next, we aimed to analyze photoswitching between *trans*-**1** and *cis*-**1** (see Figure 3). For this, we switched to DMSO-*d*₆ as solvent to measure higher concentrated samples and thus measure more sensitive spectra in shorter intervals.

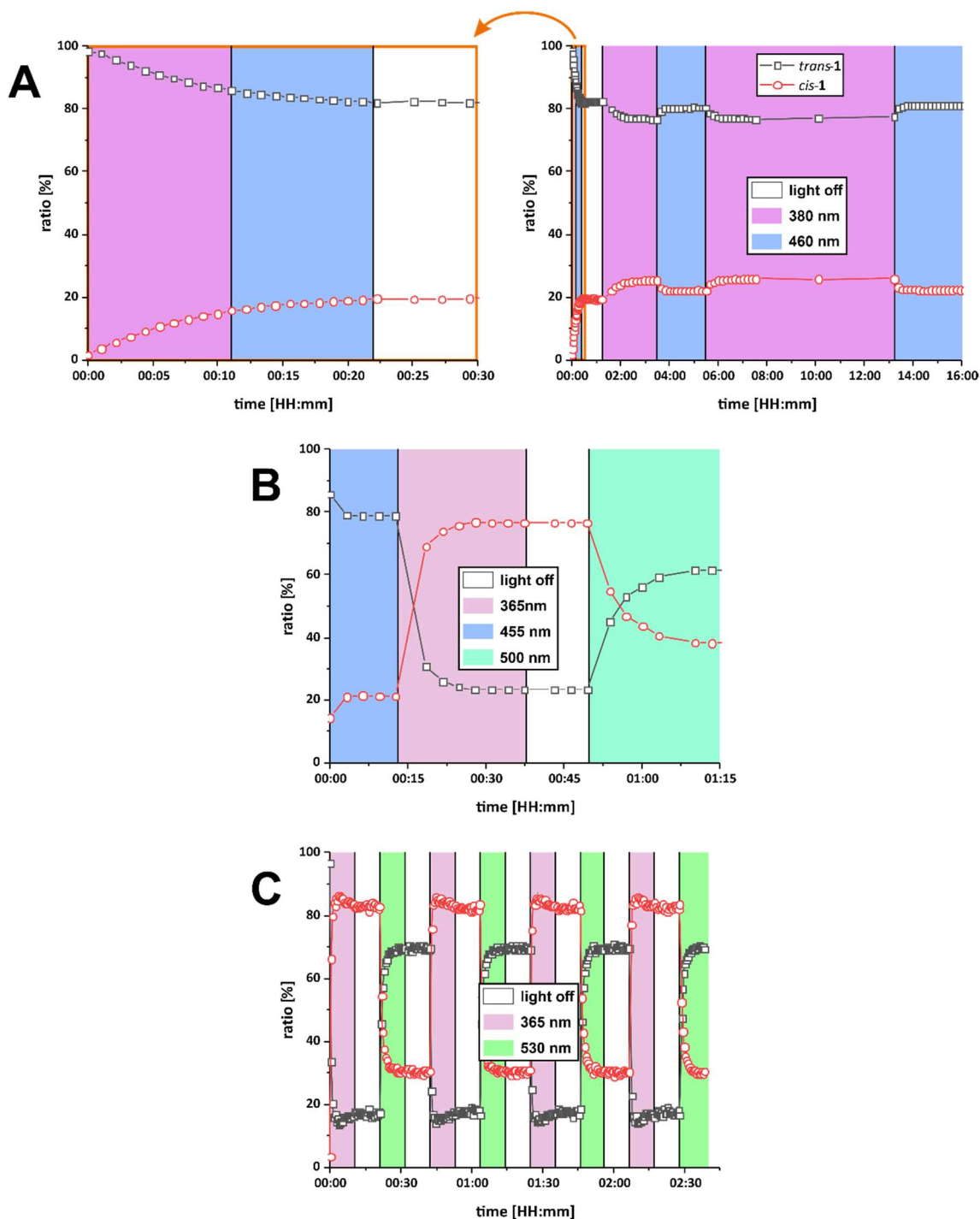


Figure 3. 1D- ^1H *in situ* illumination NMR kinetic (ns = 1) of **1** in DMSO- d_6 (10 mM) measured at 25 °C. Illumination with LEDs emitting at different wavelengths (365 nm, 380 nm, 455, 460 nm, 500 nm, 530 nm) results in different *trans* $\rightarrow$ *cis* and *cis* $\rightarrow$ *trans* isomerization profiles. For **A** the illumination setup according chapter 6.4.3.2 was used in continuous mode. For **B** and **C** the illumination setup according chapter 6.4.3.1 was used.

The photoswitching investigations were started by using the illumination setup for alternating illumination, *i.e.* the same setup as for analyzing the stability of **1** towards

longlasting illumination. The only difference is that not alternating, but continuous illumination was performed (Figure 3A). To our surprise, illumination with 460 nm increases *cis*-1 population in case only a minor fraction of *cis*-1 is present (see Figure 3A left) , although the major absorption band of *trans*-1 is at ca. 365 nm and of *cis*-1 at ca. 420 nm. The same could be observed while illuminating with a different illumination with an LED emitting at 455 nm (see blue section of Figure 3B) We assume this is due to an overlap of the broad *trans*-1 absorption band and the broad emission profile of the applied LED. Therefore, for subsequent investigations we applied for triggering *cis* → *trans* isomerization less energetic light (500 nm) to exit the overlapping wavelength area. Furthermore, as 380 nm illumination yielded only a moderate *trans* → *cis* isomerization from *trans*-1/*cis*-1 = ca. 99:1 in thermal equilibrium to ca. 74:26 in PSS, we switched for this isomerization process to higher energetic light (365 nm) to similarly improve *trans* → *cis* isomerization. As expected, with these new excitation wavelengths *trans* → *cis* isomerization and *vice versa* could be significantly improved (Figure 3B). By illuminating with 365 nm, a *trans*-1/*cis*-1 ratio of ca. 23:77 was obtained in PSS. Illumination with 500 nm resulted in a *trans*-1/*cis*-1 ratio of ca. 62:38, i.e. depending on the applied wavelength either *trans*-1 or *cis*-1 represents the higher populated isomer. However, more than 15 min are required to reach both PSS. Therefore, the illumination power of the 365 nm LED was further increased by raising the applied current from 1.0 A to 1.5 A and the 500 nm LED was replaced with an LED emitting at 530 nm. This further improved the photoswitching capacity of 1 (Figure 3C). After ca. 2 min of illumination with 365 nm a *trans*-1/*cis*-1 ratio of ca. 16:84 was obtained, 4 min of illumination with 530 nm were required to achieve the second PSS with a *trans*-1/*cis*-1 ratio of ca. 69:31. Over a total of 4 cycles of photoswitching, no fatigue in performance was detected. In case light was switched off, no thermal isomerization processes could be observed within the observed periods.

6.3 Conclusion

In conclusion, we scrutinized the photoswitching capacity of isolated, photoresponsive, unnatural amino acid **1**, called AzoF. Photoinduced switching between the *cis*- and *trans*-configuration of **1** is assumed to locally induce vibrational motions, which then enhances the activity of the corresponding **1** containing protein. To determine the photostability of **1** and furthermore to illustrate photoswitching between the *trans*- and *cis*-configuration *in situ* illumination NMR spectroscopic investigations were performed. Very good photostability over more than 55 hours was proven and depending on the applied wavelength moderate to good isomerization results were achieved. Based on these results, good photoswitching of **1** can similarly be assumed when incorporated in an protein.

6.4 Supporting Information

6.4.1 General

Detailed NMR spectroscopic investigations were performed on a Bruker Avance III HD 600 (600.03 MHz) with a 5 mm fluorine selective TBIF probe or on a Bruker Avance NEO 600 (600.03 MHz) with a 5 mm CryoProbe Prodigy BBO. For *in situ* illumination NMR spectroscopic investigations the reported setup with 5 mm amberized thin wall NMR tubes was used (see chapter 6.4.3.1).⁷ Here, the following LEDs were used and operated at 1.0 A: LG Innotek LEUVA66X00RV00 (365 nm), CREE XT-E (455 nm), NICHIA NCSE119 A (500 nm), unknown LED (530 nm). For alternating illumination, the setup shown in chapter 6.4.3.2 was applied. NMR data were processed, evaluated and plotted with TopSpin 3.2 and 4.0 software. All spectra are referenced to the solvent residual signal: DMSO-*d*₆: $\delta(^1\text{H}) = 2.50$ ppm, D₂O: $\delta(^1\text{H}) = 4.79$ ppm. Further plotting of the spectra was performed with Origin 2019 and Corel Draw 2020 software.

6.4.2 Preparation of the NMR samples for *in situ* illumination NMR spectroscopy

In case H₂O (25 mM NaP, 25 mM NaCl, pH 6.8)/D₂O 95:5 was applied as solvent a stock solution of **1** (1 mM in the respective solvent mixture) was prepared. The corresponding amount was transferred from the stock solution in an oven dried 5 mm amberized thin wall NMR tube and then diluted with H₂O (25 mM NaP, 25 mM NaCl, pH 6.8)/D₂O 95:5 to reach a volume of 0.3 mL. In case DMSO-*d*₆ was applied as solvent, an oven dried 5 mm amberized thin wall NMR tube was charged with **1** and the respective solvent (0.3 mL) was added *via* a syringe.

6.4.3 Illumination setup for *in situ* illumination NMR spectroscopy

6.4.3.1 Illumination setup for continuously illuminating with one wavelength

After preparation of the NMR sample (see chapter 6.4.2) an *in situ* illumination insert as described in literature (glass fiber: Thorlabs; fiber type: MM, FP1500URT, 0.50 NA, 300 - 1200 nm, 1500 μm core) was inserted into the NMR tube using the Schlenk line technique and fastened with parafilm. For illumination, the glass fiber was connected to a light source as described in literature.⁷

6.4.3.2 Illumination setup for alternately illuminating with two wavelengths

Alternating illumination was performed using a specially designed setup for two light sources. Here, the two LEDs are connected with the *in situ* illumination insert as reported in chapter 6.4.3.1 using a bifurcated glass fiber (Thorlabs; fiber type: BFY1000HS02, 0.39 NA, 300 - 1200 nm, 1000 μm core) and the corresponding SMA adapters to maximize the light coupling to the NMR sample. The light source, a two

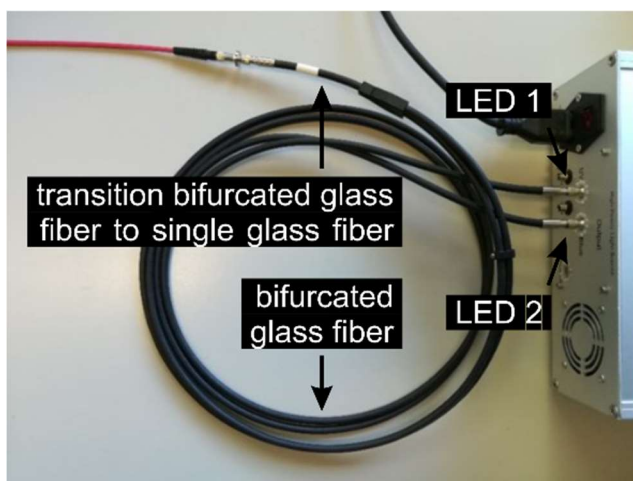


Figure S1. Photo reactor setup for alternate illumination with two wavelengths.

channel pulse generator, was designed in cooperation with HK Testsysteme GmbH. It allows a switching frequency from < 1 Hz to several kHz and a light output from 1 W to 7 W can be adjusted. Also continuous illumination with one wavelength is possible. For the presented investigations a radiant flux 5-6.5W LED (380 nm) and a radiant flux 5W LED (460 nm) were applied. Different LEDs can be installed by replacing the complete LED board.

6.4.4 Structure elucidation of **1** at 25 °C

To assign the signals for *trans*-**1** and *cis*-**1** in DMSO-*d*₆ (10 mM) at 25 °C (Figure S2) different NMR experiments (1D-¹H; 2D-¹H, ¹H correlated spectroscopy (COSY); 2D-¹H, ¹³C heteronuclear multiple bond correlation (HMBC); 2D-¹H, ¹³C heteronuclear single quantum coherence (HSQC)) were measured (see Figures S3-S6). Before performing these NMR experiments, the NMR sample was illuminated using the *in situ* illumination setup (see chapter 6.4.3.1, λ = 365 nm) until a photostationary state (PSS) with a *trans*-**1**/*cis*-**1** ratio of ca. 66:34 was reached. Illumination was switched off while recording the NMR experiments.

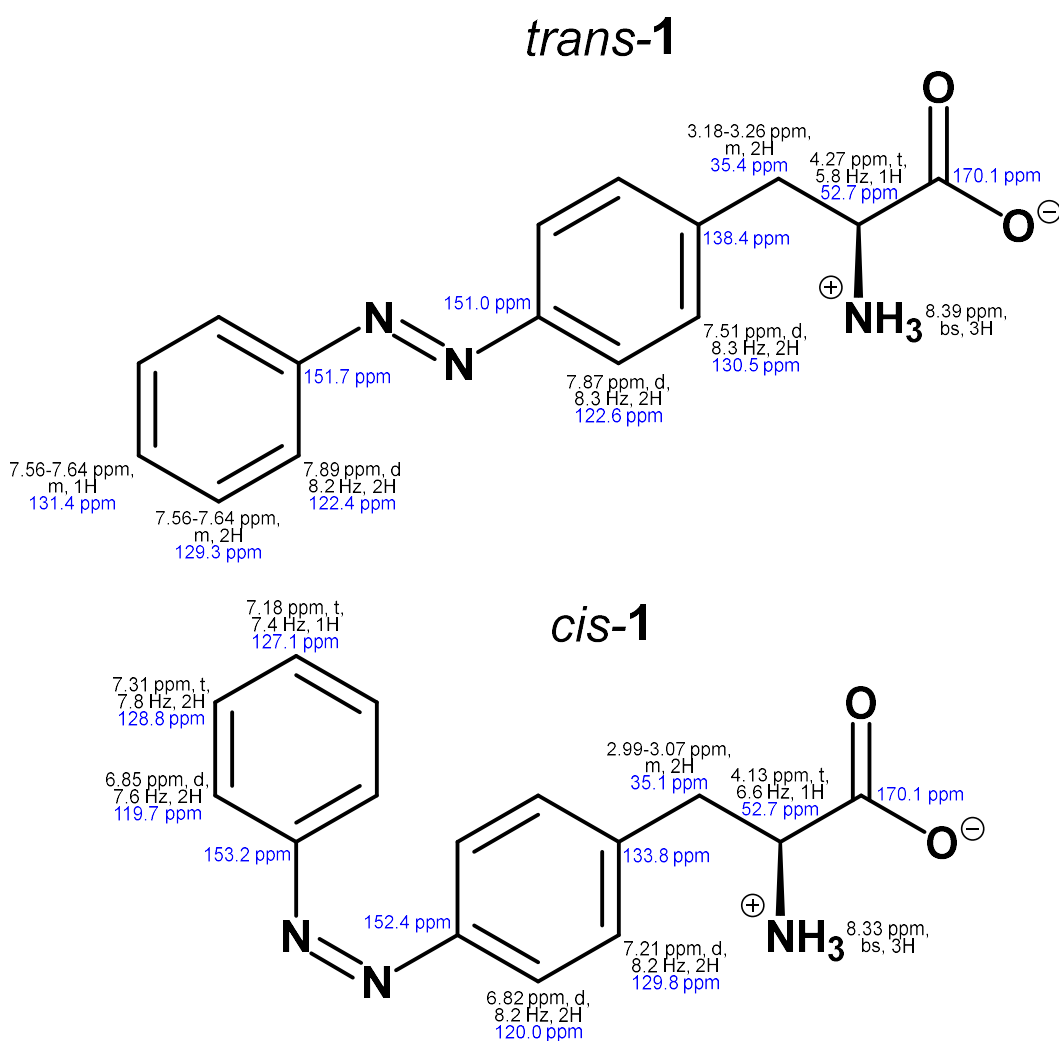


Figure S2. Structure determination of the two configuration-isomers *trans*-**1** and *cis*-**1** in DMSO-*d*₆ at 25 °C. Here, a sample of **1** in DMSO-*d*₆ (10 mM) was illuminated at 25 °C with an LED emitting at 365 nm until PSS was reached. The different NMR experiments were performed while light was switched off. ¹H chemical shift, multiplicity, coupling constants and integral are highlighted black and ¹³C blue. While measuring the different NMR experiments without additional illumination (ca. 11 h) the *trans*-**1**/*cis*-**1** ratio slightly decreased from ca. 66:34 to 67:33.

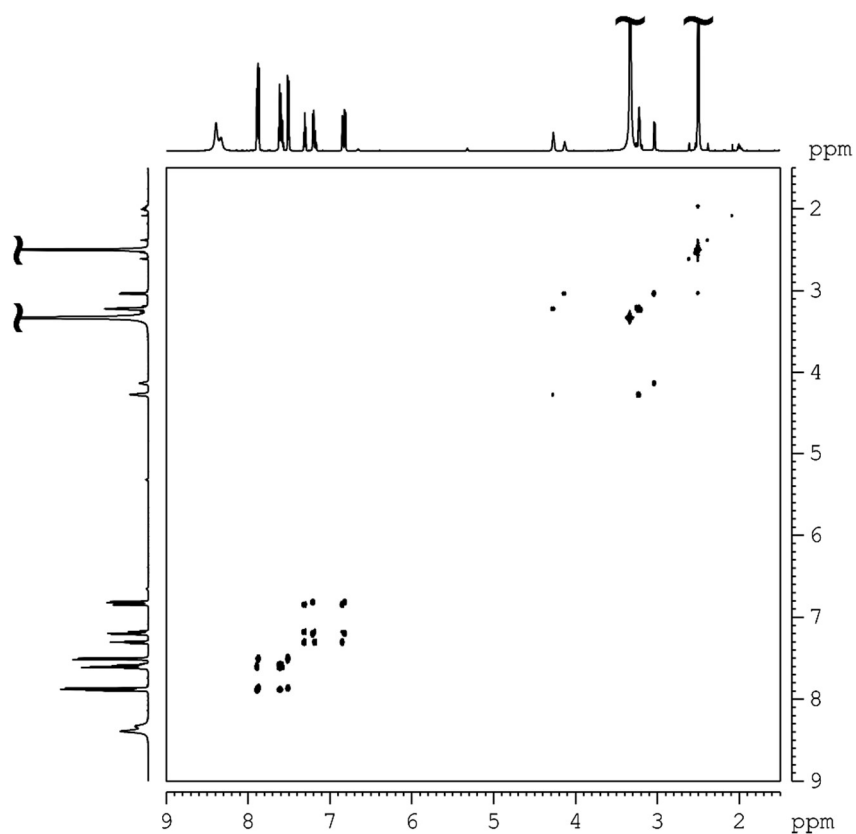


Figure S4. 2D- ^1H , ^1H COSY spectrum of **1** in DMSO- d_6 (10 mM) measured at 25 °C.

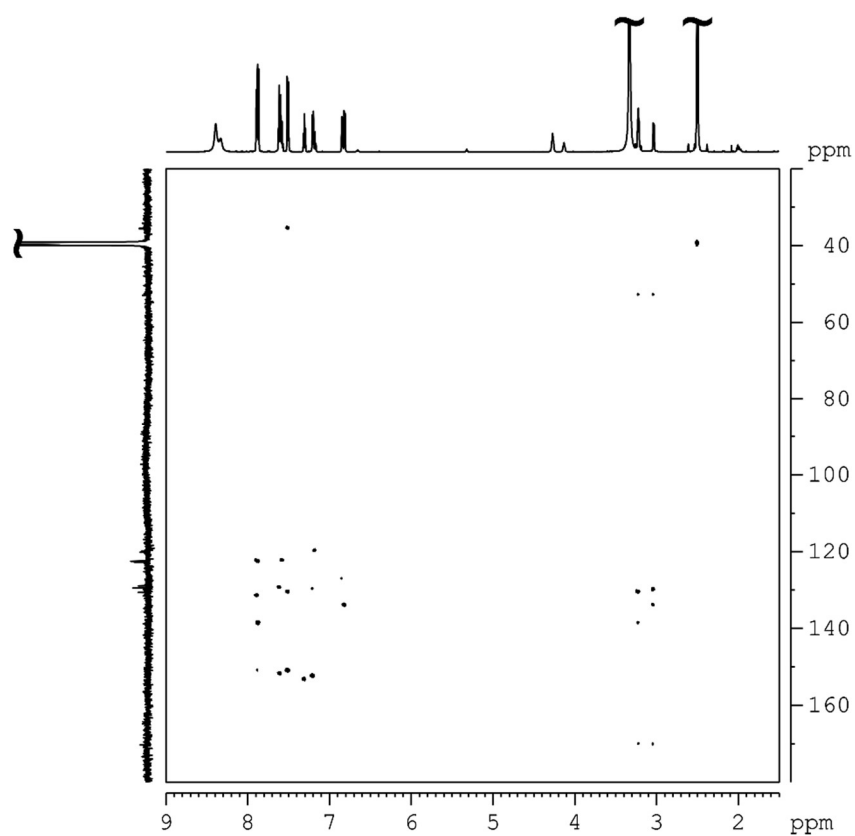


Figure S5. 2D-¹H, ¹³C HMBC spectrum of **1** in DMSO-*d*₆ (10 mM) measured at 25 °C.

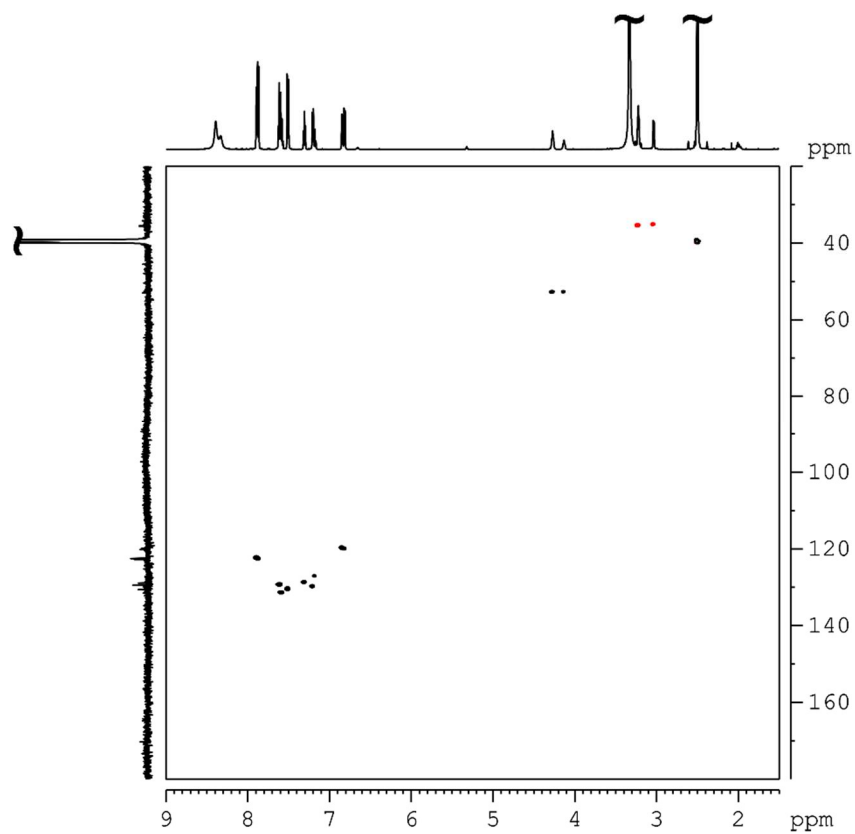


Figure S6. 2D-¹H, ¹³C HSQC spectrum of **1** in DMSO-*d*₆ (10 mM) measured at 25 °C.

6.4.5 UV/Vis spectrum of **1**

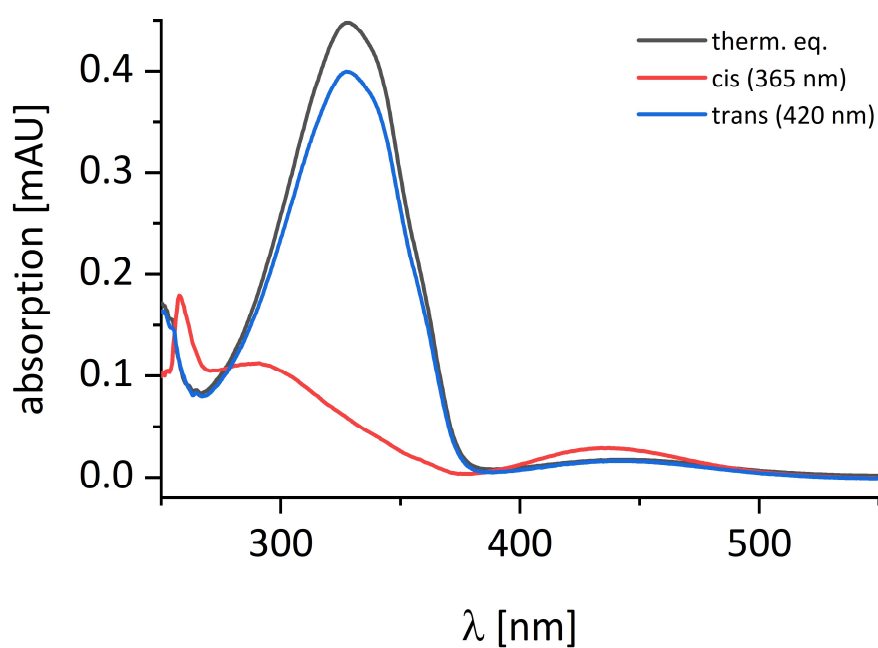


Figure S7. UV/Vis spectra of **1** (in thermal equilibrium (grey curve), *cis*-**1** enriched (red curve), *trans*-**1** enriched (blue curve)) in DMSO (50 μ M) measured at ambient temperature by the Kneuttinger group.

6.5 References

- 1 A. C. Kneuttinger, *Biol. Chem.*, 2022, **403**, 573–613.
- 2 C. Hiefinger, S. Mandl, M. Wieland and A. Kneuttinger, *Rational design , production and in vitro analysis of photoxenoproteins*, Elsevier Inc., 1st edn., 2023, vol. 682.
- 3 M. Bose, D. Groff, J. Xie, E. Brustad and P. G. Schultz, *J. Am. Chem. Soc.*, 2006, **128**, 388–389.
- 4 A. C. Kneuttinger, K. Straub, P. Bittner, N. A. Simeth, A. Bruckmann, F. Busch, C. Rajendran, E. Hupfeld, V. H. Wysocki, D. Horinek, B. König, R. Merkl and R. Sterner, *Cell Chem. Biol.*, 2019, **26**, 1–14.
- 5 F. Zeqiri, Master thesis, University of Regensburg, 2021.
- 6 a) T. I. Igumenova, K. K. Frederick and A. J. Wand, *Chem. Rev.*, 2006, **106**, 1672–1699; b) P. J. Sapienza and A. L. Lee, *Curr. Opin. Pharmacol.*, 2010, **10**, 723–730.
- 7 C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39–44.

7. Conclusion

With the aim to render chemistry more sustainable and efficient, photochemistry with light as overall environmentally friendly energy source has evolved to one of the major research fields in chemistry over the past decades. However, for developing new or improving existing photochemical applications understanding the underlying reaction mechanism and processes is pivotal. In various research fields NMR spectroscopy has already proven its enormous power for comprehensively scrutinizing reaction mechanism as this analytical tool not only provides information about the structures and dynamics of reaction intermediates and products but also about the corresponding populations. *In situ* reaction monitoring of photochemical processes *via* NMR spectroscopy is however not straightforward and therefore for NMR spectroscopy tailored illumination principles had to be developed to allow detailed *in situ* investigations of the reaction pathways proceeding downstream to the photoexcitation event. To demonstrate the omnipresence of light-driven systems in organochemistry and the power and versatility of state-of-the-art *in situ* illumination NMR spectroscopy this thesis dealt with investigating in detail the reaction mechanism in diverse photochemical applications within organic chemistry.

In chapter two, the reactive species of asymmetric iminium ion catalysis served as example to demonstrate that photoisomerization can be applied to detect and assign intermediates, which are otherwise below the detection limit of routine NMR spectroscopy. The α,β -unsaturated model iminium ion consisted of the in catalysis frequently applied MacMillan's 1st generation catalyst and cinnamaldehyde; and perchlorate as counter ion to stabilize this usually highly reactive intermediate. So far only (*E,E*) and (*Z,E*) configuration isomers of such for catalysis most relevant chiral imidazolidinone based iminium ions were disclosed in solution and as crystal structures. But applying photoillumination enabled to sufficiently populate and thus assign the structures of two additional double bond configuration isomers, namely (*E,Z*) and (*Z,Z*). Furthermore, by exploiting its explicit response to UV-illumination the high energetic (*E,Z*) isomer could also be explicitly determined under general synthetic conditions. Therefore, this isomer should be considered for future mechanistic investigations or synthetic applications in asymmetric iminium ion catalysis. A further focus of this work was to reveal ways to stabilize such high energetic intermediates after photoinduced isomerization as this is the key prerequisite for their investigation. Accordingly, the competitive thermal (*Z*) $\rightarrow$ (*E*) back isomerization was monitored and quantitatively analyzed. Three factors were identified, which contribute to an increasing stability: Low temperature, a high concentration of the iminium ion and a low nucleophilicity of the

solvent. This is because the thermal (Z) $\rightarrow$ (E) back isomerization highly probable occurs *via* a solvent based nucleophilic catalyzed mechanism. However, low temperature and especially a high concentration of the iminium ion promote ion pair aggregation, which results in effective shielding of the high energetic (Z)-configured double bonds from the solvent molecules.

In chapter three, it was illustrated step-by-step how to develop a model system to investigate experimentally a possible influence of the iminium ion double bond configuration on the stereoselective outcome of a frequently applied asymmetric iminium ion catalyzed β -functionalization strategy *via* the DTS- $h\nu$ approach. In general, the key idea of this mechanistic tool is to perform the same reaction with different amounts of the configuration isomer on suspicion. For this, the population of the desired isomer is selectively changed *via* photoisomerization. In this case the key for a successful application of DTS- $h\nu$ was to increase the amount of the (Z,E) iminium, but upstream to the actual addition reaction. Otherwise, another undesired light-induced reactivity of the iminium ion gets promoted. Thus, the major challenge was to find conditions to stabilize the *via* photoinduced isomerization increased (Z,E) population for the nucleophilic addition event. To find the ideal model iminium ion, stabilized iminium ions derived from MacMillan's 1st and 2nd generation catalyst were investigated at low temperature. Scrutinizing how the differently substituted imidazolidinone moieties influence the stabilities of the (Z)-configured isomers revealed a strong influence of sterics on the stability of the (Z)-C=N and (Z)-C=C double bond. Furthermore it was investigated how different basic additives influence the stability of the (Z,E)-isomer. Such an additive was required to mimic the in catalysis applied co-catalyst and thus maintain kinetic asymmetric control. Again a decreasing stability of the high energetic (Z)-configured isomers was observed with increasing relative nucleophilicity of the basic additive. This further supports the already in chapter two suggested nucleophilic catalyzed thermal back isomerization pathway. Based on this it was expected to hold all requirements for successfully applying DTS- $h\nu$. Unfortunately, all needed stability measures results in lacking reactivity of this model system, which remains up to now a major challenge.

Chapter four was created in cooperation with the group of Prof. Dr. Henry Dube. Here, azotriptycenes as a molecular framework for a photoswitchable molecular brake were comprehensively scrutinized. While keeping the same triptycene backbone, the effect of differently substituted phenyl rotors on the performance of this molecular braking system was studied. In *ortho*-position of the phenyl rotor either fluorine substituents were installed as convenient structural probe enabling ^{19}F NMR spectroscopy or *tert*-butyl groups to further stabilize the corresponding brake ON state by additional attractive intramolecular dispersive forces. By photoillumination *trans* $\rightarrow$ *cis* isomerization can be

triggered. This means, the molecular brake switches from the brake OFF to the brake ON state resulting in a deceleration of up to five orders of magnitude for the two rotations along the central azo double bond. These quantitative analyses were performed *via* a low temperature NMR approach and corroborated by theoretical calculations yielding results in good agreement to the ones obtained experimentally. Therefore, an *in silico* approach to design effective molecular brakes based on the illustrated framework seems very feasible. By identifying exclusive through space magnetization transfers between the two triptycene blades forming the pocket and the phenyl fragment the proposed braking *via* intermeshing could also be confirmed. Reversible decelerating and accelerating was achieved by crystallization or by photoillumination with different wavelengths.

In chapter five, which was done in collaboration with the group of Dr. Joshua-Philip Barham, new highly efficient light-powered fluorination strategies of unactivated C(sp³)-H bonds were elaborated using SelectFluor as already well-known fluorination source. Two different approaches were developed with a photosensitizing (4-fluorobenzoyl) group either employed as catalyst or as auxiliary. Especially the photosensitization auxiliary approach seems very promising. Here, upstream to the actual fluorination reaction the auxiliary is attached to otherwise interfering alcohol- or amine-groups and released afterwards without compromising the yield. This allows fluorination of complex for example pharmaceutically active molecules. Furthermore, it enables regioselectivity exogenously directed by the chemist based on the placement of the auxiliary. This is because the auxiliary attached to the substrate and SelectFluor form a charge transfer assembly. The role of the substrate was especially investigated *via* NMR spectroscopy. Measuring quantitative *in situ* illumination NMR kinetics, an induction period upstream to the fluorination reaction was discovered. By increasing the substrate loading this induction period could be shortened by up to 79%. Additionally, de-aggregation of SelectFluor seems a key prerequisite for successful fluorination reaction as the smallest SelectFluor-aggregate could be observed in presence of very reactive substrates.

In an appendix, *in situ* illumination NMR spectroscopic investigations on an isolated, photoresponsive, unnatural amino acid are presented. This study was created as part of a collaborative project with the working groups of Dr. Andrea Kneuttinger, Prof. Dr. Reinhard Sterner, Prof. Dr. Burkhard König und Prof. Dr. Remco Sprangers. Herein, the photoswitching between the *cis*- and *trans*-configuration of the photoresponsive unnatural amino AzoF was investigated to evaluate a potential influence of photochemically induced configuration switching on the activity on an enzyme containing AzoF. In this regard, next to an already reported illumination setup a specially designed

light source for *in situ* illumination of a NMR sample with two alternating wavelengths was applied.

In summary, the different studies presented in this thesis aim to demonstrate two main points: First, the power of *in situ* illumination NMR spectroscopy and especially the extraordinary versatility of the in this work applied illumination principle consisting of an LED as light source and an optical fiber as light guide. Second, the importance of comprehensive mechanistic investigations to understand the ongoing reactions and thus lay the foundation for future developments in all kinds of chemical research.

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9. Curriculum Vitae

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Education

Since Nov.2018	Ph. D. in the group of Prof. Dr. Ruth M. Gschwind, University of Regensburg Dissertation: "NMR Spectroscopic Investigations in Diverse Light-Driven Systems"
Oct.2016 – Sep.2018	Master of Science Chemistry , University of Regensburg Master thesis: "NMR Spectroscopic Investigations in Organocatalysis"
Oct.2013 – Sep.2016	Bachelor of Science Chemistry , University of Regensburg Bachelor thesis: "Synthese von 2-isopropyl-4,5-disubstituierten Cyclopent-2-en-1-onen"
Sep.2005 – May.2013	Abitur , Joseph von Fraunhofer Gymnasium, Cham

Attended conferences and scientific presentations

Feb.2020	"4th G-NMR school" in Göttingen, Germany
Sep.2019	"SMASH Small Molecule NMR Conference" in Porto, Portugal
Mar.2019	"Praktische Probleme der Kernresonanzspektroskopie" in Halle (Saale), Germany

10. List of Publications

- (1) S. Yakubov, W. J. Stockerl, X. Tian, A. Shahin, M. J. P. Mandigma, R. M. Gschwind and J. P. Barham, “Benzoates as Photosensitization Catalysts and Auxiliaries in Efficient, Practical, Light-Powered Direct C(sp³)-H Fluorinations”, *Chem. Sci.*, **2022**, *13*, 14041–14051. **DOI:** 10.1039/d2sc05735b
- (2) W. J. Stockerl and R. M. Gschwind, “Photo Enhancement Reveals (*E,Z*) and (*Z,Z*) Configurations as Additional Intermediates in Iminium Ion Catalysis”, *Chem. Commun.*, **2023**, *59*, 1325–1328. **DOI:** 10.1039/d2cc05976b
- (3) W. J. Stockerl, L. Reißenweber, A. Gerwien, N. N. Bach, S. Thumser, P. Mayer, R. M. Gschwind and H. Dube, “Azotriptycenes: Photoswitchable Molecular Brakes”, *Chem. Eur. J.*, **2023**, *29*, e202302267 (1–11). **DOI:** 10.1002/chem.202302267

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