doi:10.2533/chimia.2023.468 Chimia 77 (2023) 468–477

For the Sake of Making Molecules

Antonio Togni*

Paracelsus Prize 2022

Abstract: The aim of this article, while reviewing part of my research activities, is to illustrate the somewhat chaotic way leading from one specific topic to another – from *e.g.* ferrocenyl ligands for asymmetric catalysis, to asymmetric fluorination, to reagents for perfluoroalkylation, just to mention some of the most fruitful ones. That the way meandering through several areas of research in chemical synthesis can be described as chaotic is not primarily due to my inability to plan the work of my research group. In the contrary, it is argued that academic research, viewed as a means to educating and forming young researchers, should resist the temptation towards an increasing projectification, milestone mentality, the myth of societal relevance, and consciously aim for a more anarchical trait, much in the sense of Feyerabend's "anything goes".

Keywords: Academic research · Anything goes · Epistemological anarchism · Projectification

I was born in the Italian part of Switzerland (Misox) and I studied chemistry and obtained a PhD at ETH Zürich. After a postdoctoral stay at the California Institute of Technology (1983–1984), I joined the Central Research Laboratories of the former Ciba-Geigy Ltd. in Basel. In 1992, I took a risky move, leaving industry and returning to my alma mater as a non-tenure-track assistant professor. This choice paid out and I became a full professor in 1999. This is also about the time when I started slowly moving away from my original main research interests in organometallic chemistry and asymmetric catalysis towards fluorine chemistry. Since January 2021, I have been a happy retiree who quit research, but temporarily continues teaching. From 2016 until my retirement, I acted as the Vice Rector for the Doctorate at ETH. I also served as a member of the Research Council of the Swiss National Science Foundation from 2012 to 2016.

1. Introduction

The present article largely reflects the lecture I gave on September 8, 2022 at the Fall Meeting of the Swiss Chemical Society where I intended to express my personal attitude towards academic research in chemistry. Therefore, it has both a strong personal flavour and very much the character of an essay.

Everybody will agree that making molecules, *i.e.* synthesis, is at the heart of chemistry. However, is it appropriate for an academic researcher who originally started his career in industry to claim that the main aim of his work mainly consisted in just making molecules? This is what the title implies and it could be interpreted as an inaccurate over-simplification, reduction, or even belittlement of a complex and multi-faceted activity, such as chemical research is. On the other hand, some readers might even be irritated by such an attitude, which appears not to convey any justification as to why and to which purpose certain specific molecules have been made. Many would indeed expect the formulation of clear goals behind a molecule, in terms of its relevance, fundamental significance, and possible effective or at least potential applications. These are surely legitimate expectations, in particular in view of the fact that academic research is financed, if not totally, mostly to a large extent by public money. However, does reality truly reflect what I call a utilitarian attitude towards research, be it in chemistry, but also in other experimental disciplines? In other words, is there always an accountable rationale leading to a specific research effort, or, more in particular, behind the preparation of a certain new compound? What is the plan? Is there always a credible plan at all? I will come back to these points in the Conclusion.

The eight chosen molecules shown in Fig. 1 cover a period of more than three decades, from my first years at the Central Research Laboratories of the former Ciba-Geigy to the time already close to my retirement at ETH and will be presented in approximate chronological order. They have been chosen to illustrate my fascination for certain structures and properties as it kept moving and developing over the years. Some of them are related to one another in terms of structure and type of synthesis, others are connected by the effect of just simple inspiration, others again represent the departure from paths I deemed, more or less rationally, necessary to leave behind. Although some of these molecules have led to developments that could be dubbed as important, the molecules themselves as chemical objects remain in any case in the foreground of my considerations.

2. 4-Me-APPA, Ferrocenyl Ligands, and Au-Catalysis

4-Me-APPA (molecule **1**, CGP 37849, (*R*,*E*)-2-**a**mino-4-methyl-5-**p**hosphono**p**ent-3-enoic **a**cid) is a compound with an interesting history. When I joined Ciba-Geigy, it was already known as a competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist with potent anticonvulsant and neuroprotective properties.[1] Hence, it had been studied in the 1980s as a potential drug for the treatment of epilepsy, but it never made it to the pharmaceutical market. Nonetheless, it kept being mentioned in the literature and in patents until very recently.[2]

The then current retrosynthetic analysis and corresponding non-stereoselective synthesis comprised two key intermediates. One of them, a derivative of an unsaturated β-hydroxy amino acid, was amenable to be converted to the final product *via* a Michaelis-Arbuzov reaction by virtue of its allylic alcohol functionality. The

*Correspondence: Prof. em. Dr. A. Togni, E-mail: atogni@ethz.ch
Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 1, CH-8093 Zürich

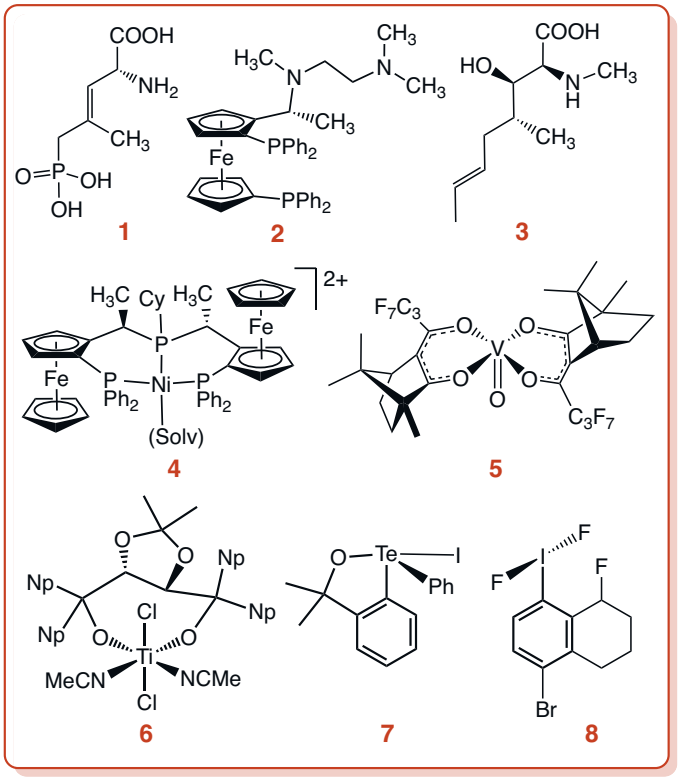


Fig 1. The eight chosen molecules representing 14 elements: C, H, N, O, P, Ni, Ti, V, Fe, Te, F, Cl, Br, I.

second one, a 4,5-disubstituted oxazoline, would afford the former upon hydrolysis and could be made by reacting an isocyanoacetate with an aldehyde. This latter approach was based on cyanide- or Cu_2O-assisted reactions, as independently developed by Schöllkopf[3] and Saegusa,[4] respectively, in the early 1970s.

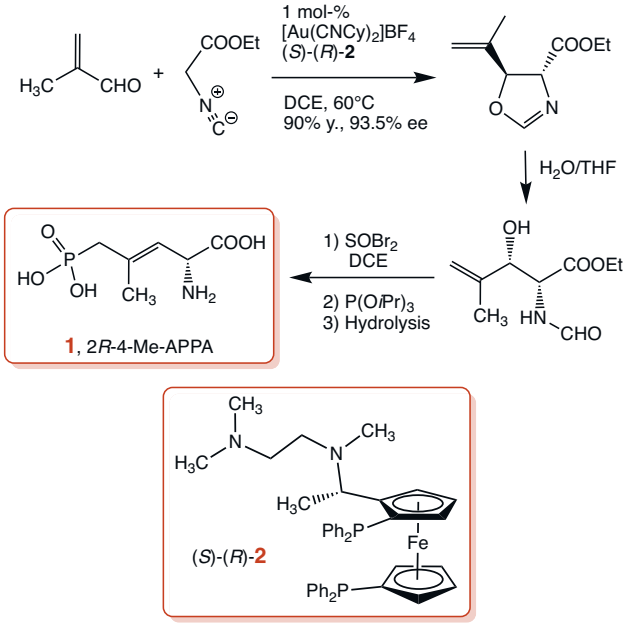
In 1986, Ito and Hayashi published a highly enantioselective synthesis of exactly the desired type of oxazolines by means of what they called an aldol reaction of typically ethyl isocyanoacetate and a relatively bulky aldehyde. The spectacular aspect of this reaction was its catalyst, *i.e.* a cationic Au(I) complex decorated with a ferrocenyl diphosphine bearing an amino side chain (molecule **2**). This was the very first example of an enantioselective reaction catalyzed by a gold complex. At Ciba-Geigy some of the colleagues had been aware of this work since May 1986 because Tamio Hayashi had presented it at the Bürgenstock Conference. Very soon after the corresponding Communication appeared in issue 21 of *JACS* in October of the same year,[5] I was asked to urgently look into this reaction, which seemed to represent the solution to a stereoselective synthesis of 4-Me-APPA. Given that I had been hired as an organometallic chemist, the prospective to work with ferrocenes and gold was extremely tempting. So I accepted the 'assignment', thereby leaving my initial Pd/sparteine chemistry[6] and unsuspecting that this decision was destined to shape my interests in chemistry, and hence my career, for years to come.

Reproducing and optimizing Hayashi's work was not difficult and I soon realized that both the syntheses of the catalyst precursor and the ligand, as well as the catalytic reaction itself were very robust processes, amenable to being scaled up to multi-kg quantities. Moreover, the stereoselectivity of the reaction (both diastereo- and enantioselectivity were consistently above 90%) were not influenced by the purity of the reagents, nor by the presence of oxygen. Additionally, the catalyst could be readily recovered by precipitation and possibly reused with almost no loss of activity and/or selectivity. The whole undertaking had also fun experimental aspects, such as dissolving a gold bar (bought at a local bank) in aqua regia at the kilo-lab in order to make the catalyst precursor as economically as possible, and culminated with the synthesis of 15 kg of *S*-4-Me-APPA for pharmaceutical testing. The synthesis, as described in detail in a patent,[7] is illustrated in Scheme 1.

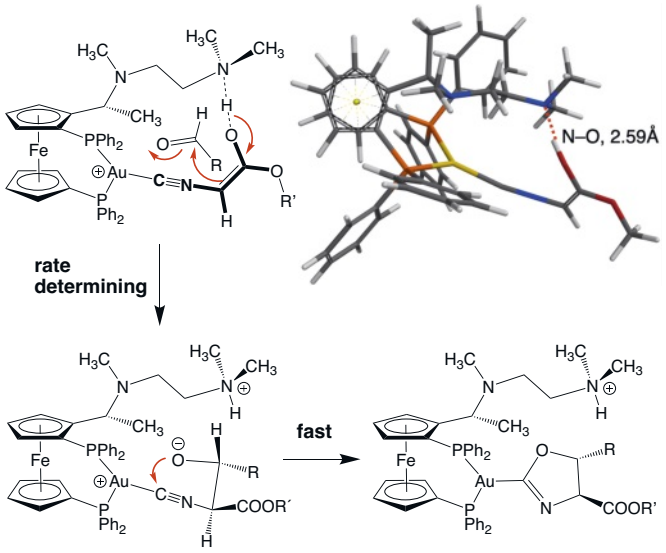
In a typical industrial setting I could now have moved on to different chemistry because I had fulfilled my task and reached the goal of that 'project', which consisted, for me personally, in optimizing the first crucial step of the 4-Me-APPA synthesis (note that I never carried out the whole synthesis myself). However, I would have never been satisfied as a researcher if I had had to stop studying this unique reaction and so I didn't. My attention, shared with colleague Steven Pastor, was then focused on 1) mechanistic aspects, 2) further synthetic applications, and 3) modifications of the original ligand **2**.

As postulated by Ito and Hayashi in their original paper, the diamino side chain of ligand **2** fulfills the important role of stabilizing the enol form of the coordinated isocyano acetate by the formation of a N-H-O hydrogen bond. Its length is therefore crucial and anything different from an ethylene moiety between the two N atoms leads to a drastic loss of selectivity. The formation of the enol is a rapid pre-equilibrium that also leads to a H/D scrambling at the methylene position, in the presence of *e.g.* D_2O. Scheme 2 shows the calculated structure of that intermediate,[8] which is a suited nucleophile attacking the aldehyde. Experiments I conducted with *p*-substituted benzaldehydes show a clear acceleration of the reaction for electron-withdrawing substituents giving a clean Hammett free-energy relationship $k_{rel} = 1.4 \cdot \sigma_{para}$. There is no detectable Au-O interaction and ring-closure is a very rapid process, as separately verified at low temperature with a sample of the highly reactive intermediate alcohol. The final step is then the fast protolytic release of the product.[9]

When looking for further synthetic applications of this remarkable reaction, my attention was caught by another very special β-hydroxy amino acid. MeBmt (molecule **3**, (4*R*)-4[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine) is the most complex amino acid contained in the cyclic undecapeptide Cyclosporine A (Scheme 3). This is a natural product originally isolated from fungi (*Trichoderma Polysporum*) and subsequently patented and commercialized by Sandoz Ltd. as one of the still most important immunosuppressives.[10] MeBmt was surely not of any relevant interest for Ciba-Geigy, as it was a compound from the 'other



Scheme 1. The stereoselective synthesis of 2*R*-4-Me-APPA.



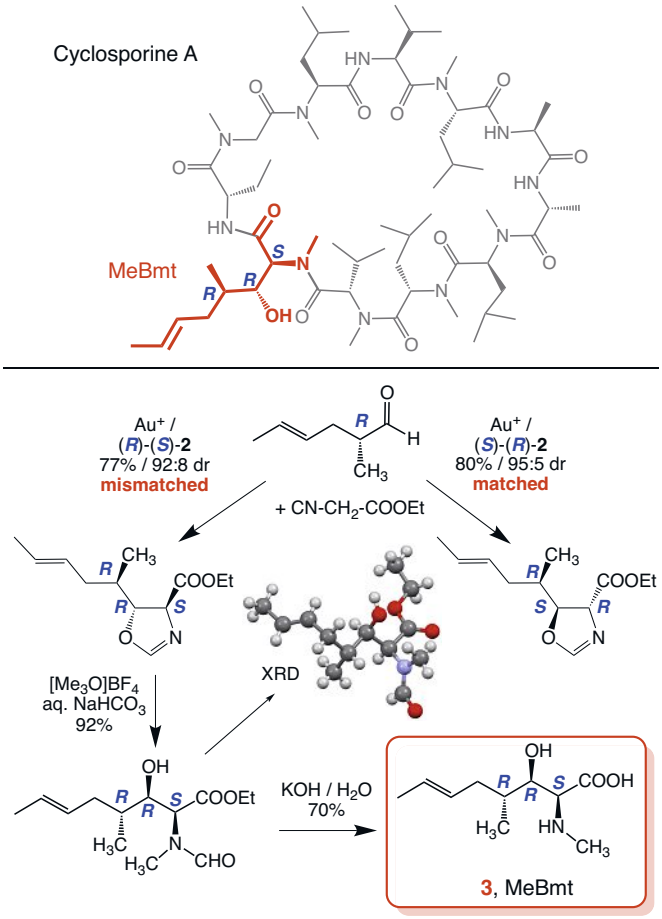
Scheme 2. Main mechanistic features of the Au-catalyzed aldol reaction between an isocyanoacetate and an aldehyde and the calculated structure of the catalyst/substrate adduct (DFT, ωB97X-D/6-311+G**).

side of the Rhine', so to speak. Because of the three adjacent stereogenic centers, it was nonetheless sufficiently interesting to me, in particular in view of investigating an example of double stereodifferentiation in the Au-catalyzed synthesis of oxazolines. The required chiral enantiopure aldehyde was a known compound previously reported by Evans.[11] As shown in Scheme 3, the desired absolute configuration of MeBmt required the use of the (*R*)-(*S*)-configured ferrocene ligand **2**, the combination of which with the *R*-aldehyde corresponds to the mismatched case, affording the two *trans* oxazolines in a dr of 92:8, as compared to an only slightly better dr of 95:5 for the matched case. This synthesis of MeBmt was at the time of its publication[12] the shortest known, much shorter than the first one reported by Wenger who started from tartaric acid.[13] Interestingly enough, MeBmt continued to attract the interest of synthetic organic chemists until recently.[14]

Ligand **2** has the peculiarity that the diamino side chain is introduced by an S_N1-type reaction allowing to connect the C-N bond at the pseudo benzylic position using the corresponding secondary amine as a nucleophile replacing acetate as the typical leaving group in a polar solvent. Looking into how to modify the side chain, it was soon discovered that also a dimethylamino group acts as a leaving group in the presence of a variety of nucleophiles when working in acetic acid solvent. The choice of this solvent was crucial and paved the way towards the synthesis of *Josiphos*,[15] the prototype of a new class of chiral ferrocenyl diphosphines that subsequently turned out to be extremely versatile. For the first time, it was possible to readily access chiral diphosphines having two different phosphino groups at wish, by a two-steps sequence starting from Ugi's amine (Scheme 4).

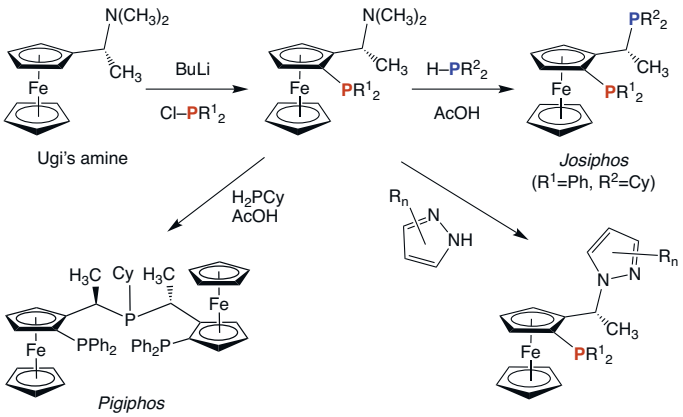
Anticipating that this could become important for future applications, a patent was first filed in 1992[16] and the first journal publication[17] came just after I left Ciba-Geigy and moved back to ETH where I kept working on ferrocenyl ligands, as well as many other ferrocene derivatives. Concomitantly, using a now proprietary *Josiphos* ligand, my Ciba-Geigy colleague and then labmate Felix Spindler was pivotal to the development of the enantioselective Ir-catalyzed imine hydrogenation process required for the manufacture of the herbicide *S*-Metolachlor (now Syngenta) on a scale of more than 10,000 tons per year.[18]

Dozens of further *Josiphos* derivatives have been made over the years, commercialized, and applied in academic and industrial laboratories worldwide. However, instead of elaborating more about *Josiphos* I prefer to mention *Pigiphos*.[19] This compound



Scheme 3. Cyclosporine A and the stereoselective synthesis of MeBmt.

constituted an only slight extension of the synthetic concept behind *Josiphos*. In fact, a primary phosphine, instead of a secondary, is able to engage twice as a nucleophile, thereby leading to an again easily accessible tridentate chiral ligand. *Pigiphos* was soon found to be a well-suited ligand for late-transition metals.[20] Correspondingly, molecule **4** is a dicationic Ni(II) *Pigiphos* complex, usually containing a nitrile solvent completing the slightly distorted square-planar coordination sphere. By virtue of the positive charge and the readily available coordination site *trans* to the central P atom of *Pigiphos*, this complex is a chiral Lewis acid, able to activate α,β-unsaturated nitriles and ketones. Fig. 2 shows examples of a variety of products obtained in enantioselective reactions catalyzed by this very complex. To be noted are the Michael-type additions of secondary amines and secondary phos-



Scheme 4. Two-steps synthesis of *Josiphos*-type ligands.

phines to methacrylonitrile, corresponding to a hydroamination[21] and a hydrophosphination[22] of this substrate, respectively. Hydrophosphinations of this kind were quite a novelty almost 20 years ago, but became more popular very recently. Transition-metal catalysis for asymmetric Nazarov[23] and 1,3-dipolar cycloadditions[24] with the observed levels of enantioselectivity were and remain a rarity.

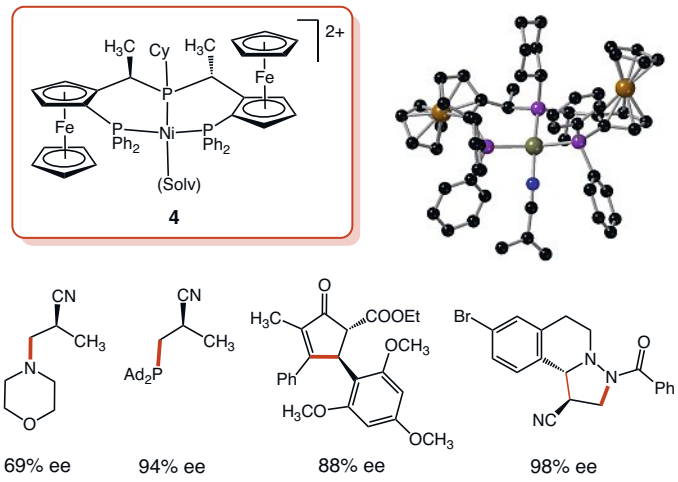


Fig. 2. Ni(II)(Pigiphos) as catalyst for a variety of reactions, including hydroamination and hydrophosphination of methacrylonitrile, a Nazarov and a 1,3-dipolar cycloaddition, and the crystal structure of the catalyst/methacrylonitrile adduct.

3. A Chiral Vanadium-based Lewis Acid as Catalyst for Hetero Diels-Alder Reactions

Given my general fascination – I admittedly don't know where it exactly came from – for chiral Lewis acids, carbon-heteroatom bond-forming and cyclization reactions, I embarked, while still at Ciba-Geigy, into some vanadium chemistry. The simple five-coordinate complex $VO(acac)_2$ was known for its ability to take up a sixth ligand (*e.g.* pyridine), thereby acting as a Lewis acid, but also to interact with main-group Lewis acidic compounds *via* the oxo ligand. Not only because of this interesting dichotomy, it was obvious for me to ask the question whether it would be possible to turn it into a chiral derivative to be used in asymmetric catalysis, more specifically for the activation of carbonyl compounds. Note that the use of vanadium in homogeneous catalysis was and still is largely confined to oxidation reactions. This didn't unsettle my firm intention to find a chiral V catalyst for a hetero Diels-Alder reaction. Thus, the 1,3-diketone Hhfbc (see Fig. 3), a derivative of the natural product camphor containing a heptafluorobutyryl substituent, had been used to form $Eu(hfbc)_3$, a chiral paramagnetic NMR shift reagent. However, it was essentially an unknown ligand in transition-metal chemistry, reason enough for me to make the corresponding vanadyl(IV) complex $VO(hfbc)_2$. This then (1990) new compound, molecule **5** in my present catalogue, turned out to be highly soluble even in unpolar solvents and very difficult to crystallize. The only way I found to luckily obtain single crystals was by slowly evaporating to dryness (!) a concentrated DCM solution.

As shown schematically in Fig. 3, the X-ray crystal structure of molecule **5** reveals its trimeric nature, as an expression, as just mentioned, of its Lewis-amphoteric character. Thus, the three oxo atoms act as bridging ligands. However, assuming that **5** very much likely exists in solution as a monomer, then three distinct configurational isomers are possible (Fig. 4). Though in 1990 I erroneously assumed that the *cis* isomer was the predominant one, I was also aware of the fact that five-coordination in V complexes

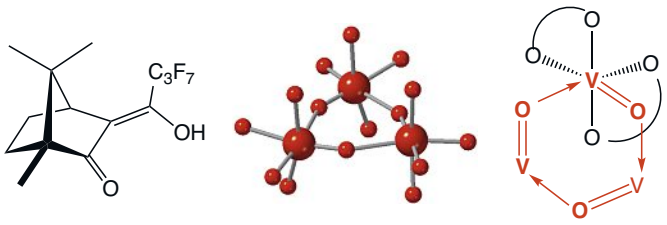


Fig. 3. Ligand precursor Hhfbc in its enol form, the V_3O_{15} core of $[VO(hfbc)_2]_3$ in the solid state, and a schematic representation of the coordination geometry of each V atom (Λ-configuration).

often implies stereochemical non-rigidity and rapidly interconverting configurational isomers.

However, I didn't make the effort to examine this very specific issue, also because of inherent experimental difficulties due to the paramagnetic nature of these compounds (d^1 electronic configuration). A thorough characterization of this system by EPR spectroscopy[25] was performed only after publishing its use in catalysis. Calculations carried out recently confirmed that the three isomers are very close in energy, the two essentially equally stable ones having a *trans* arrangement of the chelating ligands.[8]

Nevertheless, molecule **5** turned out to be an efficient catalyst for hetero Diels-Alder reactions of aldehydes with so-called Danishefsky's dienes, providing the corresponding substituted pyrones in up to 85% ee, as shown by the example in Scheme 5.[26]

Despite the relatively high catalytic activity of $VO(hfbc)_2$ in this unique reaction, its scope was unfortunately found to be rather narrow. Indeed, *e.g.* ketones and imines did not engage in hetero Diels-Alder reactions in the presence of this complex.

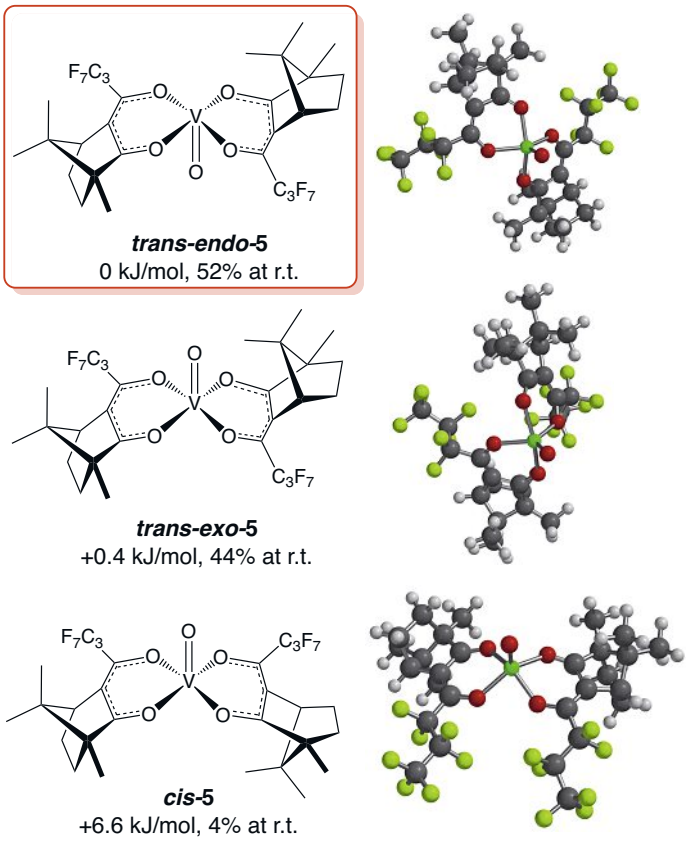
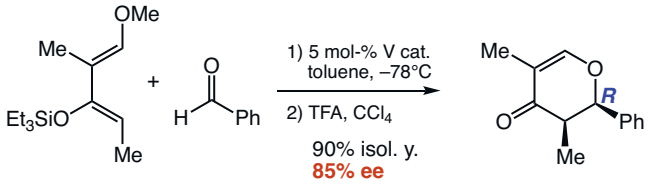


Fig. 4. The three possible isomeric forms of monomeric $[VO(hfbc)_2]$ as calculated by DFT (ωB97X-D/6-311+G**). Trans and cis refer to the relative position of the C_3F_7 substituents, *endo* and *exo* to the orientation of the oxo ligand with respect to the camphor scaffold.

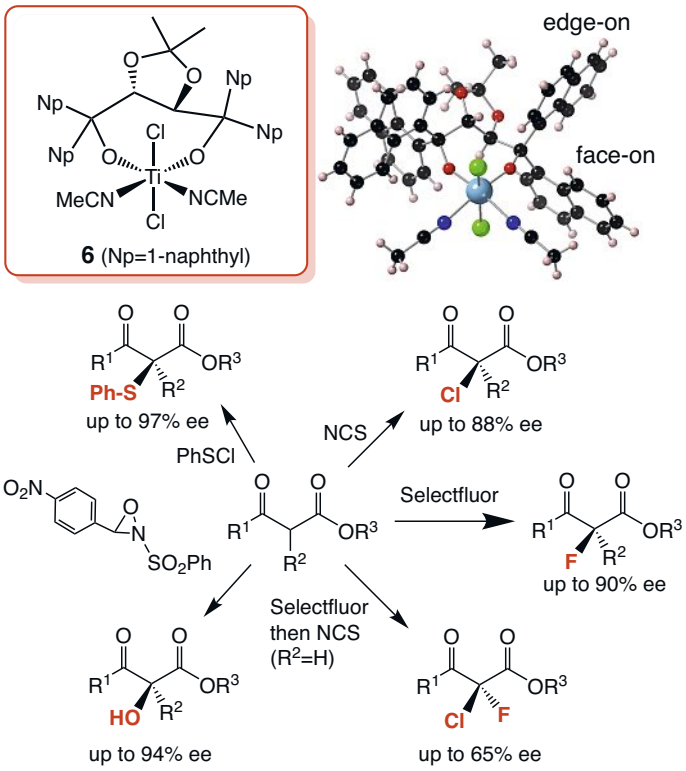


Scheme 5. V-catalyzed hetero Diels-Alder reaction of benzaldehyde with a Danishefsky's diene.

4. Developing the First Catalytic Asymmetric Fluorination and Serving Organofluorine Chemistry

After joining ETH at the end of 1992, part of my young research group was initially engaged in further developing ferrocenyl ligands, in particular combining a phosphine with a pyrazolyl donor[27] (see Scheme 4). Such ligands were found to be well-suited for Pd-catalyzed asymmetric allylic substitution reactions. When studying the effect of the counterion of the cationic Pd(II)(allyl) complexes used as catalyst precursors, a remarkable fluoride effect was found.[28] Surprisingly, when the intermediate Pd(allyl) complex was used as its PF_6^- salt, the enantioselectivity of the reaction of 1,3-diphenylallyl methyl carbonate with benzylamine was much lower than when the catalyst was generated *in situ* from a Pd(0) precursor and the ligand. However, the addition of an excess amount of a soluble fluoride salt, typically Bu_4NF, would restore the original selectivity. Moreover, the selectivity of the reaction conducted with a catalyst generated from the Pd(0) source was further improved upon adding fluoride. While I don't deem it necessary to discuss here the mechanistic background of this effect specifically due to the fluoride ion, it led to the idea of developing Pd-catalyzed asymmetric allylic fluorination, by using fluoride as a nucleophile. To make a long story short, we were not able to find the right reaction conditions that would lead to the formation of a chiral allylic fluoride.[29] At this point, it was decided with the involved doctoral student Lukas Hintermann to keep the goal of generating a new C-F stereogenic center by enantioselective catalysis as the only real fundamental incentive, but changing the strategy. Instead of 'going nucleophilic', we opted for an electrophilic fluorination using the reagent Selectfluor that was already known to react with *e.g.* 1,3-dicarbonyl compounds, in particular β-keto esters, undergoing a mono- or difluorination of the active methylene center. As to the catalyst, we then opted for Lewis-acidic Ti complexes, known to activate carbonyl compounds. It was soon realized that, indeed, a number of Ti(IV) complexes, including *e.g.* the simple $CpTiCl_3$, were able to catalyze the desired transformation. Turning to chiral derivatives, it was pretty obvious to examine Ti complexes with TADDOL ligands because these were well-known (and available!) in-house. In fact, Dieter Seebach's research group had already worked during several years with these derivatives of tartaric acid as chiral auxiliaries in a host of reactions.[30] Thus, molecule **6** (Scheme 6), bearing 1-naphthyl substituents, was one of the first Ti(TADDOLato) complexes to be made, isolated and characterized by X-ray crystallography. It provided high enantioselectivities in the α-fluorination of α-methyl-β-keto esters, the then first enantioselective and catalytic C-F bond-forming reaction. This was published in 2000[31] and since then many more enantioselective fluorinations have appeared in the literature. One could think that a new era in organofluorine chemistry had started!

The combination of molecule **6** as a catalyst with β-keto esters was found to be equally successful in chlorination,[32] thienylation,[33] and hydroxylation[34] reactions. In all three cases, a corresponding electrophilic reagent replaced Selectfluor: *N*-chlorosuccinimide, a sulfenyl chloride and, interestingly, an activated oxaziridine, respectively. In all these reactions the formation of the new C-heteroatom bond occurs from the same

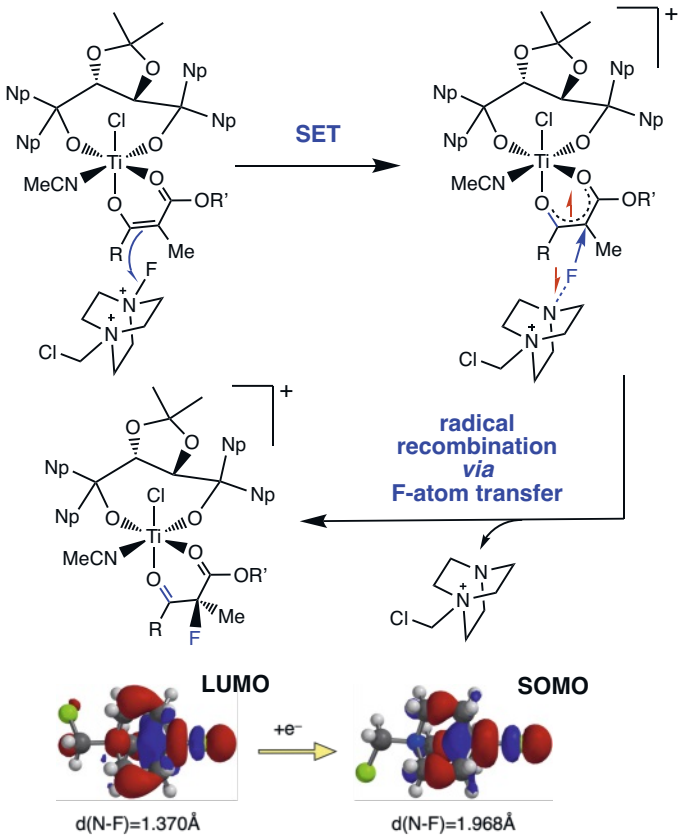


Scheme 6. Electrophilic, enantioselective Ti-catalyzed fluorination and further atom- or atom-group-transfer reactions of β-keto esters.

enantioface of the substrate enolate, preferentially. The opposite enantioface is very effectively shielded by one of the *face-on*-oriented 1-naphthyl groups of the ligand. Furthermore, the level of enantioselectivity in these reactions is also comparable, possibly indicating common mechanistic features. Combined experimental and quantum chemical studies were conducted early on for the fluorination reaction[35] and they clearly indicated a mechanistic feature that was then unexpected and new to me. Reagents such as Selectfluor can undergo single-electron-transfer (SET) processes. As shown in Scheme 7, the SET event takes one electron from the HOMO of the enolate complex to the LUMO of Selectfluor, which corresponds to the σ* orbital of the N-F bond. A singlet diradical is thereby generated, which is EPR-silent. The C-F bond-forming process subsequently occurs *via* radical recombination, thereby affording the product still coordinated to Ti in a κ^2 fashion. Its release closes the catalytic cycle.

The mechanistic characterization of the Ti-catalyzed fluorination inspired, besides the already mentioned extension to further electrophiles, two further developments. The very SET concept became for me relevant in comparison to and for the understanding of new pyridinium reagents for the direct radical trifluoromethoxylation of aromatic compounds[36] and for the pyridination of similar substrates,[37] as shown in Scheme 8. This advance took place thanks to the efforts of Benson Jelier, then postdoc, several years after the work concerned with Ti-catalyzed fluorination.

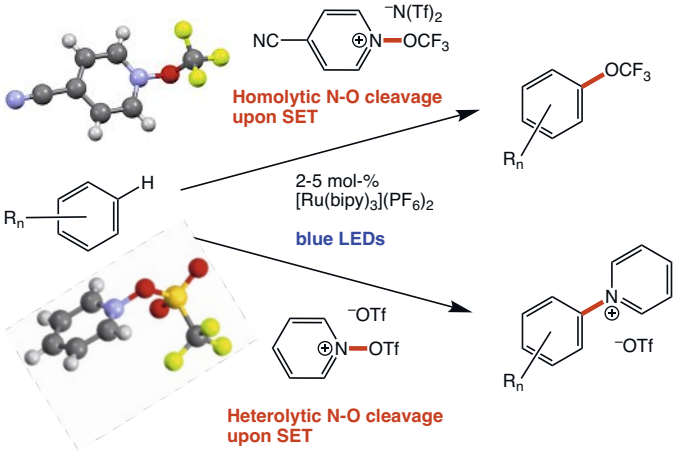
Yet, while still being concerned with atom- and atom-group transfer reactions, it occurred to me to think of a corresponding trifluoromethylation reaction, quite naively considering CF_3 as some kind of 'super halogen'. However, the then available reagents for electrophilic trifluoromethylation soon turned out to be unsuited for the desired reaction. This was the very trigger and impetus that led to conceiving new electrophilic trifluoromethylation reagents based on hypervalent iodine. For the first time in my career I have then been confronted with designing a molecule that would have a specific function as a reagent and not as a ligand or a catalyst. Patrick Eisenberger, the first doctoral student on this initially risky



Scheme 7. Main mechanistic features of the electrophilic, enantioselective Ti-catalyzed fluorination of β-keto esters.

topic, was able to convert my 'chemistry on paper' into feasible syntheses and substances with the desired reactivity.[38]

What I had initially considered to be a relatively narrow area that could have been exhausted by one or two doctoral dissertations, soon emerged as a wide playground for … making molecules. The scope of the new trifluoromethylation reagents kept widening and growing, also thanks to the interest and effort of many research groups worldwide applying these soon commercialized reagents to their specific synthetic problems in organofluorine chemistry.[39] It would be easy to dwell much longer on these compounds, but I prefer to limit my presentation to selected examples where the reagents shown in Fig. 5 have been used to address biomolecules by virtue of their high chemo-selectivity towards thiols, in particular cysteine residues in peptides.



Scheme 8. Pyridinium reagents for the photocatalytic trifluoromethoxylation and pyridination of aromatic compounds.

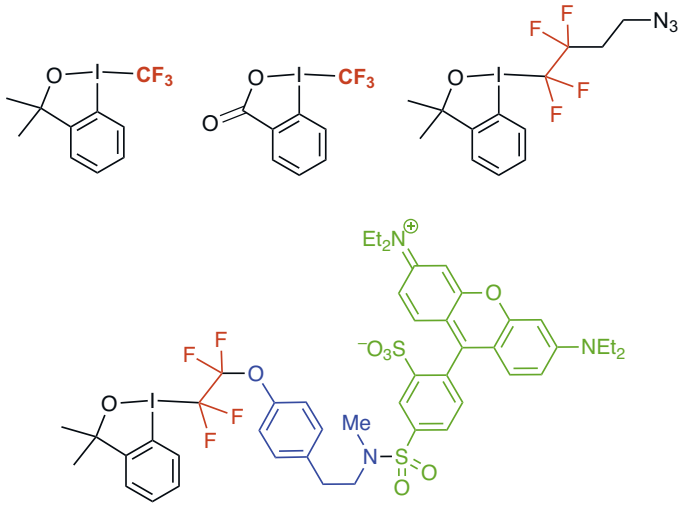


Fig. 5. Examples of hypervalent iodine reagents for trifluoromethylation and tetrafluoroalkylation.

Thanks to the initiative and suggestion of Dieter Seebach – who also provided the starting material – we first addressed the relatively simple cyclic octapeptide Sandostatin®.[40] Since Sandostatin contains a disulfide bridge connecting two cysteine residues, reducing this functionality was necessary before proceeding with the trifluoromethylation of the two thus formed thiols. This reaction could then be readily realized by Iris Kieltsch and later Katrin Niedermann affording the product shown in Fig. 6.[41] Analogously, Coenzyme A could also be selectively *S*-trifluoromethylated.[42]

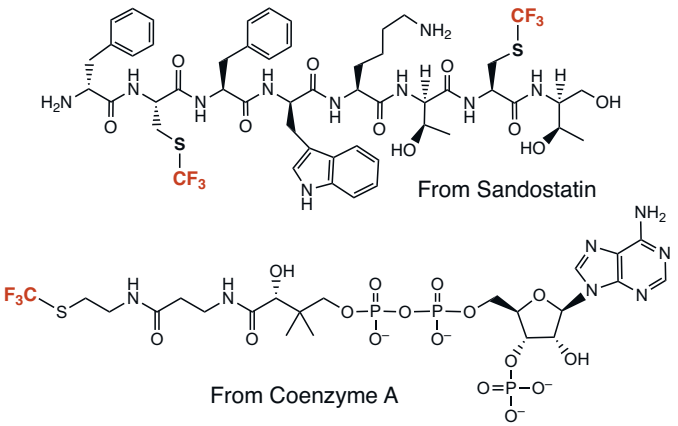


Fig. 6. The products deriving from the *S*-trifluoromethylation of Sandostatin and coenzyme A.

These reactions taught us that our hypervalent iodine reagents, despite their negligible solubility in water, could be used for the trifluoromethylation of complex molecules specifically requiring aqueous media. It was therefore obvious to call: Let's go for proteins! However, before getting to this for me potentially 'slippery' area – I am not a biochemist – I have to mention a further development due to Vasek Matoušek, another brilliant doctoral student who founded a spin-off, originally exploiting this chemistry.[43] In collaboration with the research group of Petr Beier in Prague, he demonstrated that new modular reagents based on a functionalized tetrafluoroethyl group instead of a CF_3 could be made, two examples of which are shown in Fig. 5. The more complex one of the two has subsequently been used for tagging a fluorescent dye to a synthetic retro-aldolase, a study realized in collaboration with

Don Hilvert.[44] This relatively small enzyme (34 kDalton) contains a single cysteine residue that is selectively *S*-fluoroalkylated. The more simple one, containing a clickable azide functionality, has been used quite recently by the Adibekian group for chemoproteomic profiling in live cells.[45]

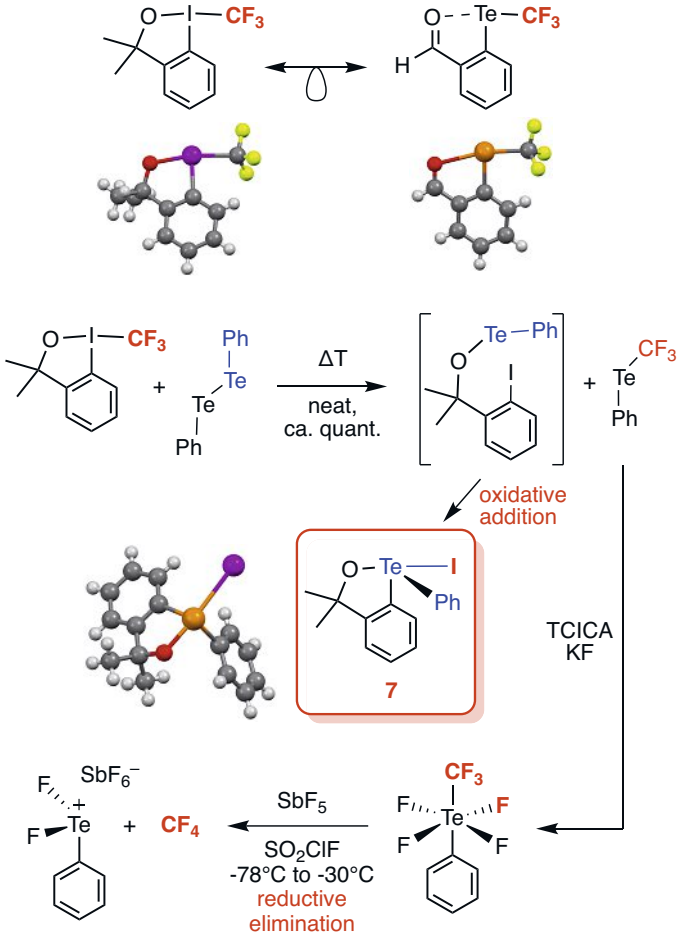
5. Exploring Tellurium Chemistry – Observing Transition-Metal-like Behaviour

Let me come back to small molecules. The broad reactivity scope of the hypervalent iodine reagents for trifluoromethylation, as I hinted to above, could not be anticipated. However, once it was clear that the exploration of further reactions of the same type would have been to a certain extent obvious and certainly productive, I realized that "doing more of the same" did not exactly correspond to my general research attitude. Thus, why not take iodine as an inspiration and investigate potentially analogous chemistry with its neighbour in the periodic table, Tellurium? After all, I had never 'touched' this element before! The idea was initially guided by structural considerations and by the isolobal concept. This led to the preparation of Te(II) compounds such as the one shown at the top of Scheme 9. While this kind of derivatives and the original iodine reagents show a pronounced structural-geometrical similarity, we have never been able to observe trifluoromethylation reactivity for the Te derivatives.[46] However, Ewa Pietrasiak and Amanda Baxter, the doctoral students in my group then in charge of Te chemistry, happened to discover a remarkable reaction. When equivalent amounts of the iodine trifluoromethylation reagent and 1,2-diphenyl-ditellane (PhTe-TePh) were heated together without solvent, besides the expected trifluoromethylation product PhTe-CF_3, a new Te(IV) derivative could be isolated in essentially quantitative yield.[47] The new compound (molecule **7**, Scheme 9) features now Te instead of iodine as part of the cyclic structure of the original CF_3 reagent. How could this happen? While we did not carry out any mechanistic studies of this reaction, it is plausible to assume that the second PhTe unit of the starting material forms an alkoxy(phenyl)tellane intermediate, which subsequently undergoes intramolecular oxidative addition of the phenyliodide moiety. While this would not have been surprising for a low-valent late transition-metal, such as Pd(0), it was certainly unexpected for tellurium, though some oxidative additions have been reported for this element.[48] In the following, we also discovered that organotellurium compounds such as PhTe-CF_3 undergo exhaustive fluorination under very mild conditions, affording the corresponding octahedral Te(VI) tetrafluoro derivative, using TCICA (trichloroiso-cyanuric acid) as an oxidant and excess KF.[49]

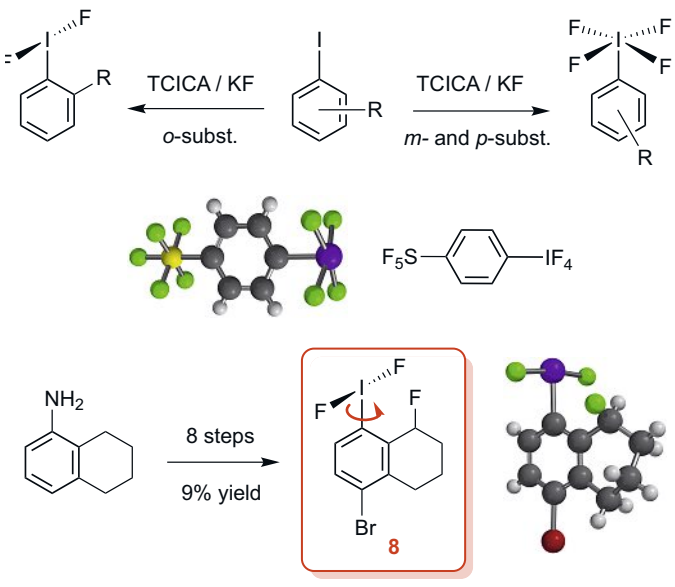
Polyfluorinations of main-group elements have been explored in my group mainly by Cody Pitts during his postdoc, together with Dustin Bornemann.[50] Cody has been interested in the reactivity of Te(VI) fluoro derivatives that was and still remains somewhat under explored (these compounds needed to be made using XeF_2 as an oxidant). Thus, he recently found that *trans*-$PhTeF_4CF_3$ undergoes reductive elimination of CF_4 upon fluoride abstraction with a strong Lewis acid at low temperature.[51] Such a reductive elimination stands in close analogy to the one observed for octahedral transition-metal complexes, *e.g.* of Pd(IV), but had never been observed before in this form for Te(VI). What started with the spontaneous wish to explore some new compounds of an element I have never been acquainted with, ended with the discovery of some unanticipated fundamental chemistry.

6. Polyfluoroiodanes and Their Dynamics

The oxidative polyfluorination relying on the reagents TCICA and KF emerged as a robust method not only for elements of groups 15 and 16, but also for iodine.[52] Thus, aryl iodides are smoothly converted either to their corresponding λ^3-difluoro- or λ^5-tetrafluoroiodanes, the difference between the two cases being connected to the substitution pattern of the aryl group (Scheme 10).[53] *Ortho*-substitution hampers the formation of the tetrafluoroiodane and the reaction stops at the stage of the difluoroiodane. This is quite a drastic steric effect on reactivity, exerted by even



Scheme 9. Isolobal analogy between iodine and tellurium trifluoromethyl derivatives; formation of a Te(IV) compound by oxidative addition and formation of CF_4 by reductive elimination from a Te(VI) derivative.



Scheme 10. Di- or tetrafluorination of aryl iodides, the X-ray structure of one example, and the probe molecule designed for the measure of the rotation barrier of the IF_2 group around the C-I bond.

just a methyl group or a halide. Subsequently, this raised the question whether *ortho*-substitution would also lead to a significant rotation barrier of the IF_2 group around the C-I bond. In order to measure such a rotation barrier in solution by NMR spectroscopic methods (line shape analysis), one needs to render the two fluorine atoms diastereotopic, thus becoming inequivalent below coalescence temperature. This requires the incorporation of a stereogenic center, at best in *ortho*-position and led to the design and synthesis of molecule **8** (Scheme 10), realized by Joel Häfliger as part of his MSc thesis. With this compound in hands, it was indeed possible to determine the rotation barrier amounting to 7.4 ± 0.9 kcal/mol, with a slightly lower calculated value of 5.9 kcal/mol. The computational study also confirmed that the barrier for the exchange of the two fluorine atoms does indeed concern rotation around the C-I bond, *i.e*. a *conformational* change, and is not related to any *configurational* change at iodine, a process with a prohibitive activation barrier.

7. Conclusions

I hope I was able to convey that the journey leading me from molecule **1** to molecule **8** was a fruitful and original learning experience about how to make them and about their properties and reactivity. This learning experience was very important for me and, possibly to an even larger extent, for my involved coworkers. During my time as an ETH professor I always tried to conceive research mainly as a vehicle to educate young researchers, be it at MSc, doctoral, or postdoctoral level, to become and behave as independent minds.

Given that the eight molecules reflect a chronological order, what is the nature of each transition, from one to the next? I already hinted at *e.g.* structural similarities as one important factor. The precursors of 4-Me-APPA and MeBmt, for example, are both very similar oxazolines. However, it would be very simplistic to claim that this was *the* reason for making **3** after having been exposed to the chemistry of **1**. As I mentioned, making **3** was also an excuse to look at the phenomenon of double stereodifferentiation in asymmetric catalysis, but this is just another crude 'factual reason'! MeBmt represented for me also the chance to realize my first total synthesis of a natural product (or part of a natural product), quite a simple one indeed, yet a matter of being involved in total synthesis in the first place. This could represent a reason for some pride for a chemist bearing the label 'organometallic/inorganic'. Additionally, since Cyclosporine A, hence MeBmt, 'belonged' to Sandoz and was not of any interest for Ciba-Geigy, there was also a spirit of innocently violating boundaries. Ultimately, though this is almost a common place, simple chemical curiosity has always certainly been a leading factor.

Similar considerations, as to why any of the subsequent molecules have been made, could be invoked. So the very transition from one to the next is a complex process and cannot be explained just by factual reasons, which are from case to case invariably different. In other words, the transition process from one molecule to the next has been neither linear, so to speak, nor very obvious or logical and could not have been predicted in advance. Every step was contingent to the immediate inspirations and mostly spontaneous ideas I had either myself or together with my coworkers. The only exceptions were molecules **1** and **2**. For these two there was the objective necessity to make them, dictated to an acceptable degree by my employer.

At this point, two more general aspects needs to be discussed briefly and both can be first formulated as questions: 1) Was it worth making the molecules I have presented? and 2) Could other molecules have been made *instead* of those presented?

While it is actually to be expected that I would positively answer the first question – why would I now say that *e.g*. **5** was not worth making? – this question hides a more subtle concern, *i.e*. the general issue of the *pursuitworthiness* of research ideas. As recently discussed for example by Jamie Shaw, a philosopher at the University of Toronto, many philosophers of science have thought about pursuitworthiness before,[54] one of them being Paul Feyerabend. As also quoted by Shaw, once Feyerabend said:[55]

"There is hardly any idea that is totally without merit and that might not also become the starting point of concentrated effort"

At least with respect to the microcosm of my own research, I could not agree more!

Furthermore, in the context of analyzing the reasons behind pursuitworthiness, Shaw makes a distinction between 'urgent science' and 'luxury science'. In the setting of my eight molecules, both **1** and **2** clearly represent an example of urgent science, whereas all others are rather to be classified as an expression of luxury science.[56] While for some readers this term might be affected by a negative connotation, I think that, in the contrary, it should definitely be attached to academic fundamental research, quite in general.

Concerning the second question, it is also clear that it must be answered with "yes". However, which other specific molecules could have been made instead of those presented? Possibly very many, similar or completely different ones, being part of the same chemical context or belonging to a totally new one, who knows! We are dealing here with the non-predictability of research ideas.

Paul Feyerabend is superficially known to many, not only in the philosophy of science, for his mostly criticized statement "*Anything goes*", often considered to be even infamous.[57] In the context of pursuitworthiness and luxury science, however, "*anything goes*" is not only a non-offending description of fundamental research, it is, from my point of view, even a rather accurate one. Again focussing just on the microcosm of my own research, molecules **3** to **8** can clearly be viewed from an anything-goes-perspective.

Feyerabend's stance towards how science works, as symbolically expressed by "*anything goes*", has been called epistemological anarchism,[58] in strong contrast to the philosophy of research programs (Lakatos and others). It is not my intention, nor I really have the expertise, to go here into the details of this debate. It is sufficient for me to recognize that an open, conscious, and positively anarchical trait in academic (fundamental) research is not only realistic but also recommendable, within reasonable ethical boundaries.

Finally, I want to mention the concept of *projectification*.[59] The term itself hints at an increasing granularity in the organization of research activities and it has consequences also concerning research practices. In this sense, a project is usually meant to be a well-defined unit of research work, mostly to be executed within rather short temporal boundaries, it includes the formulation of milestones, and *must* lead to at least one publication. Projectification has taken over very much in general and I have seen part of my younger generations of doctoral students uncritically succumbing to this new way of proceeding doing research, though this has never reflected my personal way of thinking and has never been part of my mentoring. Did I miss anything in terms of research developments? Am I some sort of old-fashioned scientist who refuses to go with the times? Maybe, maybe not. In any case, I have never thought about the work carried out towards the eight presented molecules in terms of eight separate projects. Lapidary, I should say, my only 'project' was chemistry!

Acknowledgements

I wish to acknowledge the contributions of all coworkers, MSc students, doctoral students (more than 70), postdocs, and collaborators at Ciba-Geigy and ETH who accompanied me since 1985 and whose names are partly mentioned in the text and in the references. Financial support came from ETH, the SNSF, Ciba-Geigy, Solvias, Lonza, and Bayer.

Received: June 9, 2023

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