Photocatalysis Beyond Conventional Precious Metal Complexes

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“My solitude doesn’t depend on the presence or absence of people; on the contrary, I hate who steals my solitude without, in exchange, offering me true company.”

Friedrich Nietzsche

“The stirring up of conflict is a Luciferian virtue in the true sense of the word. Conflict engenders fire, the fire of affects and emotions, and like every other fire it has two aspects, that of combustion and that of creating light. On the one hand, emotion is the alchemical fire whose warmth brings everything into existence and whose heat burns all superfluities to ashes (*omnes superfluitates comburit*). But on the other hand, emotion is the moment when steel meets flint and a spark is struck forth, for emotion is the chief source of consciousness. There is no change from darkness to light or from inertia to movement without emotion.”

Carl Jung

”An intellectual says a simple thing in a hard way. An artist says a hard thing in a simple way.”

Charles Bukowski

”It would be unfair to expect other people to be as remarkable as oneself.”

Oscar Wilde

”Ignorance is bliss.”

Thomas Gray

”Bildningstillägnelsens första förutsättning: att ”de bildade” håller sej utom syn-, lukt- och hörhåll.”

Nikanor Teratologen

Abstract

Precious metals, e.g. Ru and Ir, are expensive, scarce and non-renewable resources. As oppose to many renewable resources, these cannot be deliberately produced wherever one wishes. The mining of these metal ores is limited to their natural abundance which is restricted to only a few places of the world. In addition to their high price, the metals - which the modern world technology is dependent on - are associated with the risk of a potential supply cutoff related to any momentary global geopolitical instabilities. Many modern-day chemical methods, among them photoredox catalysis, has become dependent on Ru and Ir. The price, scarcity and instability of the supply chain calls for a state-of-the-art update of the research field's toolbox.

The two factors substitutability and recycling rate of the relative supply risk index (RSR) have been investigated within the context of Ru and Ir as applied to photoredox catalysis. Specifically, earth abundant Fe as an alternative and heterogenization of Ir were studied as potential elements of the future toolbox of photoredox catalysis.

A protocol for an oxidative fragmentation of ethers and acetals to ketones and esters was developed using a simple Fe(III) photocatalyst. Fe and its complexes generally have much lower excited state life-times than those of Ru and Ir, and a high value is often assumed to be required for any reactions to occur. However, the results disclosed here question that assumption.

A similar transformation was also developed that addressed the shortcoming of pre-synthesis of acetals by enabling an *in situ* formation from aldehydes. Furthermore, this visible light promoted reaction proceeded without any added photocatalyst.

Lastly, the reaction scope of a heterogenized Ir catalyst was investigated. The reusable catalytic material could be applied to a range of different classes of photoredox reactions and in addition catalyzed the reactions faster than the corresponding homogeneous catalyst.

In summary, the results show that the go-to catalysts in photoredox catalysis are not essential. Inexpensive and short excited state life-time Fe(III) photocatalysts and heterogenized constructs constitute, conceptually, two attractive alternatives worthy of further research.

Keywords: Iron photocatalysis, Heterogenization

Sammanfattning på Svenska

I den episka romansviten Dune av Frank Herbert får man följa Paul Atreides och hans kamp för att förhindra den ondskefulle Baron Harkonnen från att ta över planeten Arrakis. Där finns nämligen 'spice', en psykoaktiv substans som höjer människors medvetande, vilket krävs för att kunna göra interstellära rymdfarter. I den fiktiva världen finns flera imperier som önskar ha tillgång till den högt eftertraktade substansen spice och man är beredd att starta krig för att säkra sin egna tillgång. Sensmoralen i berättelsen, åtminstone en av många, kan sägas vara att vem som än styr produktionen kan i mångt och mycket härska över hela världen.

Dune må vara fiktion, men kanske är fiktiv fantasy ett medvetet val för att skildra den universella maktkampen gällande de för ett samhälle oumbärliga råvaror? Vårt högteknologiska samhälle är bland annat beroende av många olika metaller. De två metallerna rutenium och iridium är några av de mest sällsynta metallerna på jorden, och gruvor för utvinning finns endast i ett par få länder i världen. Man skulle kunna säga att de som styr över produktionen av vissa metaller härskar de också, om de så vill, över hela världen.

Fotoredoxkatalys är ett forskningsfält som har utvecklats till att idag ses som ett av de mest attraktiva och lovande alternativen för att skapa nya bindningar i organiska molekyler. Genom att nyttja synligt ljus som energikälla via så kallade fotokatalysatorer kan man skapa radikaler som reagerar med andra organiska molekyler och förädla dem till exempelvis läkemedel. Fotokatalysatorerna man använder sig av i reaktionerna består oftast av just rutenium och iridium. Förutom som fotokatalysatorer används både rutenium och iridium även inom den elektroniska industrin. Att metallerna är sällsynta reflekteras även i priset vilket gör att industriella processer som kräver metallerna i form av katalysatorer blir väldigt dyra.

I denna avhandling sammanfattas tre artiklar som på ett eller annat sätt utvecklat nya typer av ljusdrivna organiska reaktioner på sätt som inte kräver konventionella fotokatalysatorer. I en av artiklarna används i stället en järnkatalysator, som dessutom visar att betydligt kortare livslängder hos exciterade tillstånd än vad som vedertaget anses vara möjligt kan användas, och i en annan hur man kan designa så kallade heterogena katalysator av iridium vilka enkelt går att återanvända. Sammanfattningsvis har forskningen bidragit till att finna mer hållbara alternativ för fotoredoxkemisk syntes utan att kompromissa på effektivitet.

List of Papers

Publications discussed in the thesis

I. Lindroth, R.; Ondrejková, A.; Wallentin, C-J. Visible-Light Mediated Oxidative Fragmentation of Ethers and Acetals by Means of Fe(III) Catalysis.
Organic Letters, **2022**, 24(8) 1662-1667.

II. Lindroth, R.; Bryce-Rogers, H.; Merke, T.; Wallentin, C-J. Highly efficient direct visible-light-mediated oxidative esterification of aldehydes.
Photochemical & Photobiological Sciences, **2022**, 21, 819-824.

III. Lindroth, R.; Materna, K.; Hammarström, L.; Wallentin, C-J. Sustainable Ir-Photoredox Catalysis by Means of Heterogenization.
ACS Organic & Inorganic Au, **2022**, 2(5), 427-432.

Publications not included in the thesis

IV. Ondrejková, A.; Lindroth, R.; Hilmersson, G.; Wallentin, C-J. Utilizing a needle as a source of iron in synergistic dual photoredox catalytic generation of alkoxy radicals.
Chemical Communication, **2022**, 58, 10241-10244.

Contribution Report

I. Took part in defining and planning the project. Carried out the majority of experiments, the majority of interpretation of data. I wrote the manuscript.

II. I proposed the project. Carried out some initial optimization. Supervised two students, now co-authors, working on the project. Carried out the mechanistic experiments. Interpreted data and wrote the manuscript.

III. Took part in defining the project. Carried out about half the experiments and interpreting the data. Wrote parts of the manuscript.

IV. Contributed to the experiments regarding applications. Proposed the role of the needle and interpretation of results.

The contribution report is hereby approved by Carl-Johan Wallentin, supervisor and corresponding author of all papers included in the thesis.

Content

Abbreviations

acac	Acetyl acetonate
bpy	Bipyridine
CV	Cyclic Voltammetry
DCE	Dichloroethane
DCM	Dichloromethane
DMF	N,N'-Dimethylformamide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
EDA	Electron-Donor-Acceptor (Complex)
EDG	Electron Donating Group
Eq.	Equivalents
EtOAc	Ethyl acetate
EWG	Electron Withdrawing Group
HAT	Hydrogen Atom Transfer
HOMO	Highest Occupied Molecular Orbital
ISC	Intersystem Crossing
LMCT	Ligand-to-Metal Charge-Transfer
LUMO	Lowest Unoccupied Molecular Orbital
MeCN	Acetonitrile
MeOH	Methanol
MLCT	Metal-to-Ligand Charge-Transfer
MO	Molecular Orbital

MRI	Magnetic Resonance Imaging
NBS	N-bromosuccinimide
NMR	Nuclear Magnetic Resonance (spectroscopy)
OTf	Triflate (trifluoromethanesulfonate)
ppy	2-phenylpyridine
RSR	Relative Supply Risk
rt	Room temperature
SCE	Saturated Calomel Electrode
SOMO	Singly Occupied Molecular Orbital
SET	Single Electron Transfer
THF	Tetrahydrofuran

1 Introduction

There is a continual call for new methods with regards to the construction of organic molecules. A method in this context refers to a set of reaction conditions enabling a certain transformation. Thus, with this definition, there are more methods than transformations. Research in this field serves a dual purpose. On the one hand, we have method development that aims at replacing existing methods for a specific transformation that in one way or another could be argued to have some benefits over the previous one(s). Benefits could refer to a broad set of considerations such as price, hazard/safety, waste production or energy consumption to mention a few typical perspectives for evaluation. On the other hand, research aims at uncovering new reaction patterns, or chemical species, and explore the unknown mechanistic space that opens up with such findings. The two approaches are, of course, not independent of one another and are oftentimes pursued together.

Photoredox catalysis is a subfield of method development which has the past two decades grown to become one of the largest and most promising new field of research within organic chemistry[1–7]. It has earned the position as the state-of-the-art radical chemistry by offering replacement of traditional methods as well as disclosing unprecedented chemical reactivity. By utilizing absorption of visible light as a gentle form of energy input, photocatalysts convert the photonic energy into the creation of radicals, a process that was previously accomplished with rather harsh methods.

Despite all the promise, few photoredox catalytic methods find their way to industrial applications[8]. One can discuss two – but by no means claiming to be the only - reasons for this. First, industrial application implies an enormous upscaling of the reactions, and photoreactors at that scale have previously not been demanded meaning that such technology is not available. It is, however, a solvable problem for the engineers. A second factor that goes into this is that the most commonly applied photocatalysts are based on rather expensive precious metals, i.e. ruthenium and iridium. Economy generally works as such that a method using either more toxic/explosive chemicals or is associated with whatever hazardous risk but provides the desired product at a lower cost will then, nonetheless, be the approach most likely to be adopted. The use of inherently expensive materials is something the engineers cannot affect, whereas the necessity of such materials can, and indeed should, be questioned by the research community and by doing so instigate the search for alternatives. Because if not, the promising field of photoredox catalysis risks the prospect of becoming nothing more but an *academica curiositas*.

All metals on earth are so called non-renewable resources, i.e. natural resources whose rate of consumption far exceeds the rate of replenishment. And many metals, of course, do not replenish at all. Both Ru and Ir are two of the least abundant metals on earth[9–13], which partly accounts for its price. In an ideal world, non-renewable resources would be fully recycled but, currently, the recycling rate of Ru and Ir is estimated to be >30%[12,13]. If recycling rate is not improved upon, while the precious metal reserves dwindle with continued mining, the price will increase even more in the future. On top of that, there are other industries with an increasing interest in Ru and Ir that the chemical industry - if failing to find alternatives – will have to compete with for the metals. This in turn means that the demand goes up with the consequence that yet a further increase in price will take place on account of that competition of resources. An index taking several of the above-mentioned considerations into account is the relative supply risk (RSR), a scale ranging from 1 to 10. Factors going into the index is crustal abundance, reserve distribution, production concentration, substitutability, recycling rate and political stability[12,13]. An index of 10 means there is great risk that supply cannot meet the demand. For instance, rare earth metals – an unfortunate name since some indeed are relatively speaking very abundant - have a RSR of 9.5; the dominating supplier being China. For platinum group metals, which includes Ru and Ir, the score is 7.6. The supply comes from, in decreasing order, South Africa, Russia and Zimbabwe[12,13]. The factor called reserve distribution simply means how widespread both actual and potential mining sites are. Then, obviously, with a low distribution, as is the case for Ru and Ir, any political instability quickly alters the RSR which affects the ability of that part of the world which is dependent on the metals to maintain their current living standard. One should, for instance, take lessons from an event earlier this year that it is a rather foolish idea to make the crucial energy demand dependent on certain non-renewable resources, such as gas, without consideration to either resource distribution or political stability of the supplying countries.

As a last concern, the pharmaceutical industry accounts for one of the largest applications of organic synthesis. Since the products are going into the human body, the industry has strict demands regarding trace levels of metal impurities in the final products[14–16]. There is not much data indicating a significant toxicity of Ru or Ir as such, except for some of their specific compounds, but the history of pharmaceuticals is such that fewer risks are nowadays tolerated and must be a point of consideration in developing synthetic routes.

Lastly, scarce as it may be, it seems there is enough Ru and Ir for generations to come. Apocalyptic narratives should always be avoided for the best of humanity. With that said, if alternatives can be found, or recycling improved, there is no reason not to pursue such an ambition.

2 Aim

Photoredox catalysis has arrived at the stage of development where the new mechanistic space enabled by the ingenious utilization of photocatalysts is well explored. For that purpose, there is no immediate concern using expensive metals at small academic scales. However, to further advance the development, i.e. to enable large scale applications, a state-of-the-art adaptation of the general methodology is required.

Substitutability and recycling rate are two factors going into the RSR that can be explored by research in the context of photoredox catalysis. Thus, the projects, *vide infra*, were aimed at developing a set of original visible-light mediated radical reactions that anywise undertake the effort of advancing contemporary photoredox catalysis to allow for methodologies beyond conventional homogeneous ruthenium- and iridium photocatalysts. The overall goal, therefore, is to contribute to the aforementioned field by means of expanding the platform available today.

Paper I - The engagement of cyclic ethers, in particular the THF-core, in oxidative fragmentations are rare. The few examples that exist generally proceed by ionic mechanisms and rely on ring strain for efficiency. Thus, exploring if a radical approach, by means of photoredox catalysis, could provide an easier manipulation of the THF-core than current methods were pursued.

Paper II - Based on the results of Paper I, the shortcoming of having to synthesize acetals was addressed by investigating the possibility of a one-pot approach by *in situ* formation from aldehydes.

Paper III - Investigate the performance of a new heterogenized Ir-catalyst in terms of reaction compatibility, stability, efficiency and reusability.

3 Photochemistry and Radicals

Photochemistry is the scientific field investigating light's ability to effect chemical transformations[17–19]. It encompasses mankind's desire to invent new ways of doing so, as well as seeking out a greater understanding of nature's already many examples. At present, it is no challenge to argue that nature is superior to man with regards to photochemical skills. The prototypical example in nature is the process termed photosynthesis, where plants convert CO_2 and water into carbohydrates. In the process, plants do not only store the energy coming from light in the biomaterial it is made up of but also produce oxygen as a byproduct which the animal kingdom, in turn, thrives on. In other words, nature uses photochemistry to synthesize herself. Another prototypical example is the photochemistry taking place in our eyes which converts photons into perceived images of the world around us. Hence, reading this would be impossible without one's autonomous skills in photochemistry.

3.1 Light Matter Interactions

Light can be described in several different ways depending on what best serves the problem at hand. Classically, light is described as propagating electromagnetic waves – i.e. synchronized oscillations of electric and magnetic fields – and is characterized by its frequency[20]. However, all systems touched upon in this work are microscopically small, down to the molecular level, and then the classical descriptions are insufficient. Hence, the quantum mechanical description is in this case more suitable where light instead is described as consisting of elementary particles called photons[21]. Besides the intrinsic properties of charge, mass and spin - which is beyond the scope of this discussion - photons are conveniently characterized by their energy, E, according to the equation $E=h\nu$, where h is Planck's constant and ν the frequency of light. One can simply swap between the two abstractions by recognizing that light viewed as a wave with a certain frequency corresponds uniquely to photons of a certain energy, ignoring any quantum mechanical uncertainties regarding "certain" frequency or energy.

Light has the intriguing, and utmost important, property of interacting with matter in various ways[22,23]. The kind of interaction possible depends largely on the energy of the photons. The topic is incomprehensively large and cannot be undertaken in an all-encompassing manner despite the infotainment value of such an exposition and, therefore, only interactions with molecules alone is deemed to suffice. The interactions are generally speaking of the kind that allows a molecule to undergo a transition from one state to another state of higher energy by absorbing a photon whose energy matches the difference between the two molecular states. The following paragraph exemplifies the principle.

Photons of relatively low energy, those belonging to the region termed radio waves, have an energy that matches the transitions of nuclear spins that are subjected to a strong external magnetic field[24]. This light-matter interaction is the foundation of nuclear magnetic resonance (NMR) spectroscopy, the indispensable technique to determine chemical structure, and magnetic resonance imaging (MRI) to produce images of the interior of human bodies. Photons of higher energy, those found in the range of microwaves to infrared radiation, instead match the energy difference of vibrational- and rotational transitions and, thus, are also utilized in various spectroscopical techniques as well as for efficient heating[23]. The visible light, consisting of wavelengths in the range 400-700 nm, is the most interesting region for contemporary photochemistry and is the focus for the rest of the discussion. Photons of higher energy have their uses too, but tend to be rather destructive to the larger classes of molecules of interest[25]. Only for a limited set of structures are ultraviolet light useful and, in addition, if being used carelessly can put the chemist at risk. And yet higher energy radiation, e.g. x-rays or γ-rays, usually ionize the molecules by expelling electrons entirely.

Visible light consists of photons with appropriate energy for effecting transitions of electrons within atoms and molecules. Since chemical reactions are a result of redistribution of the outermost electrons, such transitions are what enable chemical change and form the foundation for nearly all photochemistry. This is basically a reformulation of the first law of photochemistry, which is also called the Grotthuss-Draper law[26–28],

> *Light must be absorbed by a compound in order for a photochemical reaction to take place.*

which in turn does not only have one popular formulation quoted in the scientific literature. This law might from the perspective of contemporary chemists look superfluous, but can be genuinely appreciated once seen from the perspective of chemists in the early 19th century being unaware of current models of electrons, photons and quantum mechanical states.

The properties of molecules in electronically excited states differ remarkably from those in the ground state and usually, perhaps always, are more prone to chemical change, i.e. the excited state is more reactive[25,29]. The fate of the excited state depends on the molecular structure, its environment and, if chosen wisely, can be ingeniously utilized to drive chemical change. A crucial requirement for any chemical change to occur upon absorption of a photon is that the life-time of the excited state is long enough to have the opportunity to proceed with any of the kinetically possible pathways available to it[18,19]. If it is too short, or no feasible reaction pathways exist, the molecule relaxes back to its ground state. Worthwhile to point out is that reality is always, no matter how much someone wish to grasp its entirety, a couple of steps more complex than any model. Regarding the life-time, the case is such that it is nothing but an extracted number from a whole population. Thus, individual molecules in any solution have different life-times following a distribution from which that number is derived. This means that a seemingly low life-time, perhaps even anomalously low, in fact have, by means of probability, a small number of molecules that, nevertheless, have a longer life-time than the statistical average and can engage in a chemical transformation. If such a transformation in turn initiate a propagation chain, that itself does not depend on either absorption of photons or any excited states, chemical change could, nevertheless, occur at an useful rate.

3.2 Radicals and Their Properties

Radicals are defined as any species with unpaired electrons, or equivalently, having half-filled orbitals. In what follows, the attention will be on organic molecular radicals only. Organic radicals as a group treated together display dichotomous behavior in that they can act both as nucleophiles and electrophiles. Many radicals are neutral and despite not being electrically polarized show reactive behavior and, thus, radical reactions, therefore, are often governed by orbital interactions while coulombic interactions play a lesser role[29]. The unpaired nature of these species gives them properties quite different from species having all electrons paired. The orbital containing an unpaired electron is termed singly occupied molecular orbital (SOMO) and has an energy close to that of a non-bonding orbital. Organic radicals are unstable species which render them – exceptions always exist – transient and always on the look for something to pair up with. Thus, contrary to plenty of molecules with all-paired electrons, radicals are in general highly reactive. For this reason, radical reactions often necessitate *in situ* formation of the radicals.

Radicals can, however, be stabilized by neighboring groups[29,30]. In a simplified manner; a radical is stabilized by spreading out the unpaired electron over a larger region in space by means of orbital interactions. Stabilized radicals are easier to form and, compared to non-stabilized radicals, are less reactive. But they are reactive enough and offer greater control over selectivity, a requirement to be deemed useful in chemistry.

Stabilizing vicinal groups that simply enable spreading out the unpaired electron - i.e. resonance stabilization - are π-bonds in conjugation with the SOMO e.g. an allylic system (*i*), systems of multiple conjugated C-C π-bonds (*ii*) or aromatic systems (*iii*), see Figure 1. A second type of stabilizing group are the electron withdrawing ones such as carbonyl (*iv*), cyano (*v*) or nitro (*vi*) groups etc. They resemble the allylic system but also contains a more electronegative heteroatom which has the effect of shifting the electron density somewhat to that side. A third common type is heteroatoms that contain a lone pair that interacts with the unpaired electron by means of orbital overlap. Such an interaction can also be viewed, considering molecular orbital thus formed, as spreading out the unpaired electron over a larger region.

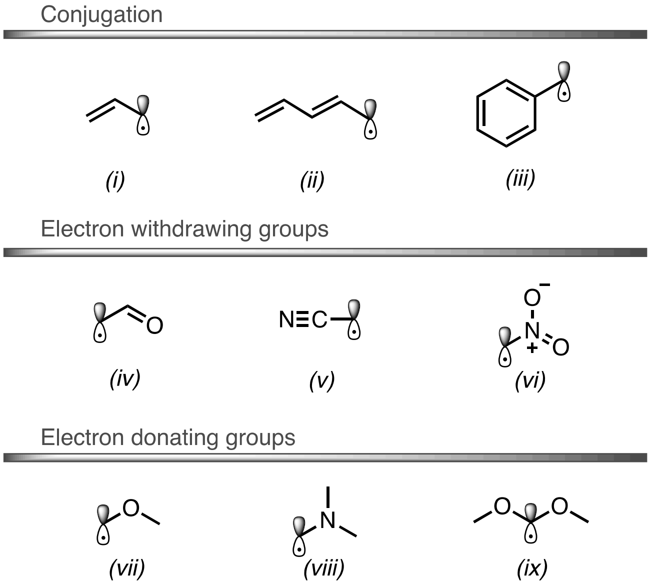


Figure 1. Various modes of stabilization of organic radicals.

The nucleophilicity or electrophilicity of a radical correlates well with the energy of the SOMO. Using the frontier orbital theory one can state that in general, the better the overlap of the two orbitals interacting in a bond forming scenario, the faster the reaction is likely to be[25,29]. And orbital overlap tends to be maximized when the energies of the two orbitals are similar in magnitude. LUMO is considered in this case a high energy orbital, and good electrophiles have LUMOs of low enough energy to participate in reactions. Therefore, LUMOs interacts most favorably with high energy SOMOs than low energy SOMOs since they are closer in energy. A nucleophilic radical then, in general, has relatively high energy SOMOs. Reversing the argument, one arrives at electrophilic radicals generally have relatively low energy SOMOs, see Figure 2. Electron donating groups forces the unpaired electron to occupy an anti-bonding orbital and is therefore of higher energy, thus, radicals with stabilizing heteroatoms - or equivalently - having electron donating groups, tend to be nucleophilic. In case of confusion, one must not forget that two electrons also occupy a bonding orbital in this case so the overall effect of an EDG is stabilizing even if the unpaired electron (the SOMO) is raised in energy. And conversely, EWGs put the unpaired electron in a bonding orbital which lowers the energy of the SOMO and, thus, tend to be electrophilic.

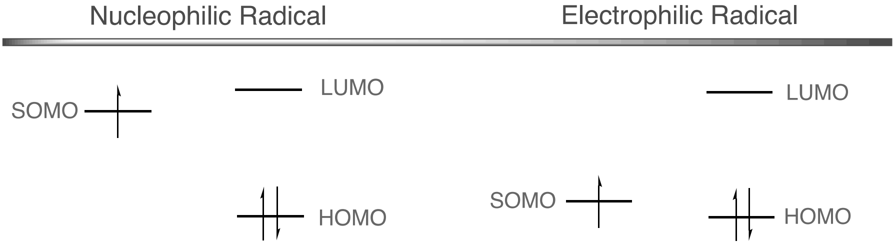


Figure 2. MO diagrams illustrating the energetic condition dictating the philicity of radicals.

When a molecule absorbs a photon, an electron from the HOMO is promoted to the LUMO[29]. What happens at this point is a whole book in itself and will not be dealt with. In a way, the molecule has become a radical since it now has, not only one, but two unpaired electrons. Let us term the orbital having the excited electron as $\mathrm{SOMO_{LUMO}}$ and the electron staying behind as $\mathrm{SOMO_{HOMO}}$. Since, by molecular energy standards, a photon contains a great deal of energy that gets trapped in the excited state, the $\mathrm{SOMO_{LUMO}}$ is generally higher in energy than the SOMOs of typical nucleophilic radicals. In fact, provided the life-time is long enough for bimolecular collisions to occur by means of diffusion, excited states can be so nucleophilic that rather than sharing the electron with an electrophile donate the electron all together. Reversely, the unpaired electron left in what used to be the HOMO is in a moderate to low energy orbital and, rather than sharing, can sometimes confiscate an electron entirely from a nucleophile. Thus, the excited state is both a stronger reductant and oxidant than the ground state. These single electron transfers (SET) between excited states and molecules form the foundation of photoredox catalysis.

3.3 Radicals and Their Reactions

At first sight, the number of radical reactions might look enormous and near impossible to gain an overview of. Fortunately, there is an underlying structure to it. But of course, there are a lot of subtleties and a fully thorough discussion of each class would rather distort than clarify the otherwise very elegant simplicity. Therefore, inclusion of all exceptions - however interesting - will be avoided to bring about as coherent a fundamental picture as possible.

Most radical reactions – which also holds true for two-electron chemistry – are variants and combinations of a small set of characteristic elementary reactions. One such radical elementary reaction was mentioned above, namely, redox reactions. The following sections go through the other three main types of reactions, as well as commenting on the reverse of each which constitute yet another set. One will then notice that more complicated radical reactions are simply a sequential combination of the these elementary types.

3.3.1 Abstraction – The Radical Counterpart to Substitution

A general formula for an abstraction is as shown in Figure 3,

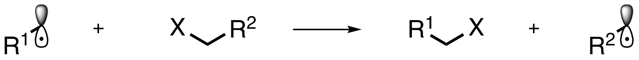


Figure 3. A general reaction formula for an atom abstraction.

where X usually is, but not limited to, a hydrogen or halogen atom[29]. The reverse of an abstraction reaction is essentially the same, just that the other atom or group will be transferred instead. In general, the rates of abstractions correlate well with the thermodynamics of the reaction, i.e. the lower the energy of the formed radical the faster the reaction. The subset of abstractions where X=H has a name of its own: the hydrogen atom transfer reaction, or HAT reaction. It represents one of the most common and interesting abstraction reaction since it enables manipulation of the relatively inert C-H bond[5,31,32]. Several rather different radicals can act as HAT reagents provided there is a thermodynamic drive for it. However, it is somewhat more difficult to simply list the identity of some, since, whether or not a radical acts as a HAT depends on the substrates in the environment, i.e. a radical is a HAT reagent in some circumstances and in others not[29].

3.3.2 Radical Addition to π-bonds

This section will limit the discussion to non-aromatic systems only. A general formula for a radical addition to a π-bond is as shown in Figure 4,

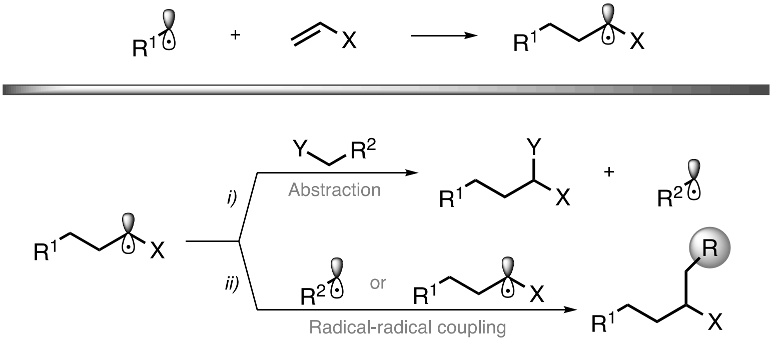


Figure 4. A general reaction scheme for radical addition reactions.

where X (and Y) could be anything that makes sense[29,30]. The nature of X, however, determines what kind of radicals it can engage with. If X is an EDG, then the HOMO of the alkene is rather high in energy and, thus, preferentially reacts with electrophilic radicals. Conversely, with an EWG, the reaction is favorable with nucleophilic radicals. The regioselectivity is generally as depicted in Figure 4, the least substituted carbon is the site of reaction regardless of the identity of X since any such X stabilize a radical and, thus, will provide the thermodynamically preferred radical intermediate.

After the reaction, another radical is formed that will react further. In polymerizations it will proceed to add to another alkene and so forth[33]. Usually, exception being when coupled together with transition metal catalysis[34], the so formed radical abstracts an atom Y (*i*) which in turn could be the start of a propagating chain. Alternatively, radical coupling (*ii*) occur which also constitute the so called termination step for propagation based mechanisms.

The reverse of a radical addition to π-bonds is a fragmentation. Common to all is a radical intermediate that splits into two distinct entities which create another radical and a new π-bond[29].

3.3.3 Radical Coupling

The last type of elementary reaction is the simple radical coupling, i.e. two radicals combine to form a σ-bond[29], see Figure 5.

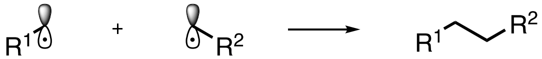


Figure 5. A general reaction formula for a radical-radical coupling.

The reverse of this reaction is perhaps more important; the homolysis of a single bond.

3.4 Traditional Radical Generation

So far, the discussion has centered around properties and reactions of radicals and it remains to comment on their formation since, as previously pointed out, they are generally transient and require *in situ* formation. Generation á la photoredox catalysis will be dealt with separately, *vide infra*, as that constitutes the core principle of this work. There are more methods of generating radicals than are useful for synthesis, so again, restriction will be made to those widely used in synthesis.

Weak bonds enable facile cleavage. Homolysis, the process of cleaving a single bond with an equal share of one electron, can be induced by energy coming from either photons or heat. Typical compounds that easily undergo homolysis are molecular halogens, peroxides and azo compounds. The latter two are common examples of radical initiators[30,35]. Radical initiators operate by first absorbing a suitable source of energy to yield two radicals that typically proceed to initiate - in some cases a fragmentation expelling gaseous molecules precedes the event - parallel propagating chains by engaging in either an abstraction or addition. As such, it can be used in substoichiometric amounts.

Stoichiometric amounts of one electron oxidants, e.g. cerium ammonium nitrate[36], or reductants, e.g. alkali metals[37], are alternative methods of generation.

A very old method, which also has seen a resurgence the past decade, is radical generation by means of electrochemistry[38]. Similar to stoichiometric oxidants/reductants; running a current through a solution can promote one electron oxidizations or reductions – or sometimes both – of organic molecules creating radicals. It has the advantage of better control over the redox events compared to stoichiometric reagents in addition to increased safety.

3.5 Photoredox Catalysis

The field of photoredox catalysis has the past two decades emerged as a competitive alternative to the traditional methods for generating radicals[1–7]. Besides offering alternative protocols for performing traditional radical reactions it has also opened up to unprecedented reactions inconceivable with traditional modes of radical generation. And it does all this under rather mild conditions which is a ubiquitous but, unfortunate as it is, hard to define term. Many of the traditional methods, although competent in performing reactions and synthesizing molecules difficult or impossible with ionic chemistry, suffer from less than ideal reaction conditions.

Homolysis usually require UV light which is a rather harsh treatment of molecules and the applicability space for that reason becomes narrow. Homolysis with visible light is instead limited to a small number of options with, again, a narrow applicability space. Furthermore, the peroxides often used as initiators are frequently criticized for their somewhat explosive properties under some conditions rendering large scale applications riskier than ideal[39]. On top of that, many other reagents traditionally used are very toxic, e.g. organotin reagents[40], or flammable, e.g. alkali metals.

Photoredox catalysis for these very reasons is nowadays considered a highly attractive field. The core principle is the application of a photocatalyst that absorbs light to reach an excited state that is then utilized to generate radicals from organic molecules, directly or indirectly, via a set of few basic quenching mechanisms.

3.5.1 Photocatalysts

Although there are nowadays many different photocatalysts available, the majority are still based on ruthenium and iridium where $Ru(bpy)_3^{2+}$ and $Ir(ppy)_3$ represent two prototypical photocatalyst structures, Figure 6. The reason these structures are so prevalent is due to both history and their properties. Long before these coordination complexes became photocatalysts for organic synthesis they were studied in other research fields[41]. As a consequence, the synthetic procedures were well established, their photophysical properties in both ground and excited state well characterized and so were their redox properties which naturally led to these being among the first ones applied to organic synthesis. The reason, however, these coordination complexes also started to find appreciation elsewhere is no coincidence, the same properties that were appreciated in other fields also make them good catalysts for photoredox catalysis.

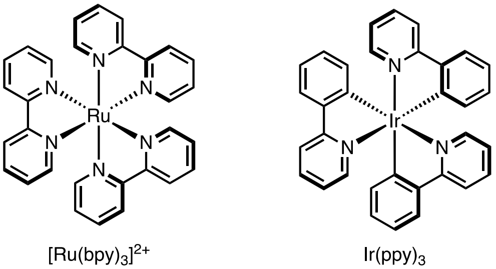


Figure 6. Structure of the two most prevalent photocatalyst scaffolds.

Photocatalysts are characterized by being able to efficiently absorb light, and typically visible light in the blue region is employed. This constitutes, generally, a very selective excitation if LEDs with rather narrow emission spectra are used since the small organic molecules typically used in reactions rarely absorb visible light. Usually, these coordination complexes undergo a metal-to-ligand charge-transfer (MLCT) e.g. an electron in a metal centered *d*-orbital upon absorption of a photon is promoted to an empty LUMO of the ligand[19,41], see Figure 7.

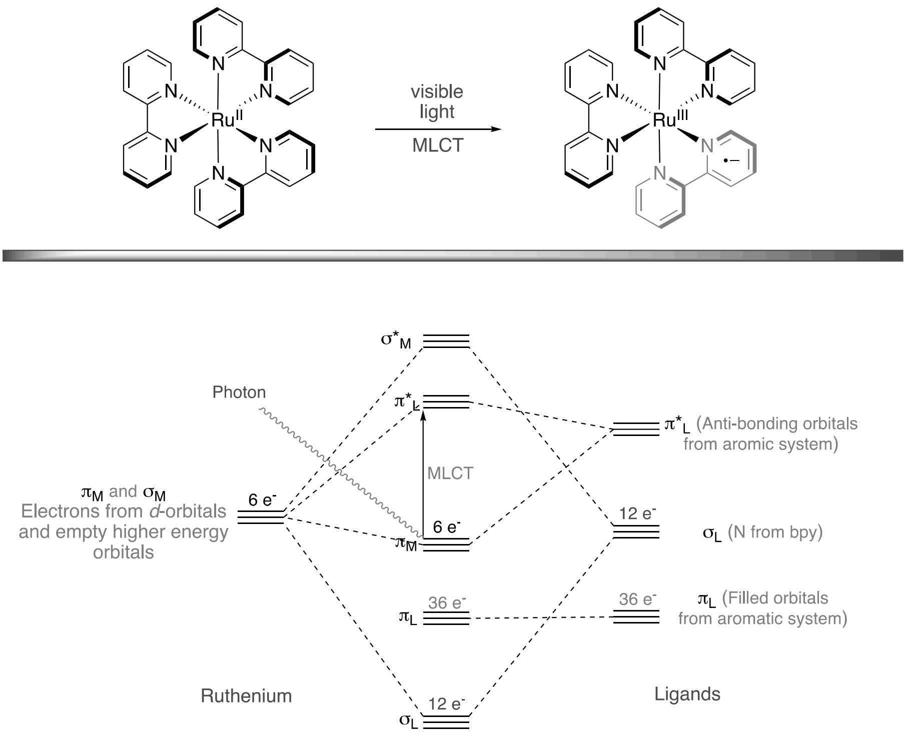


Figure 7. At the top is illustrated the photophysical process taking place when Ru(bpy)$_3^{2+}$ absorbs a photon. Below is a *much* simplified MO diagram of Ru(bpy)$_3^{2+}$ since e.g. several metal-ligand orbital interactions are not explicitly shown. Of particular importance is the interactions of the non-bonding metal centered orbitals, π_M, with the empty anti-bonding orbitals of the bpy ligands, π^*_L, generating a new set of π-orbitals essentially localized at the ligand. It is in one of these orbitals that an excited electron – if visible light was used - ends up in during the MLCT process.

Once excited, these complexes tend to rapidly undergo a process called intersystem crossing (ISC) from where any further relaxation to the ground state in slowed down by the spin-'forbidden' transition. Thus, their excited state life-times are relatively long compared to most organic molecules. Often, such final relaxations occur by emitting a photon - i.e. phosphorescence - which enable studying many processes involving these complexes[18]. The relaxation is a first-order kinetic process, i.e. an exponential decay of the excited states is observed. The inverse of the observed rate constant - the constant within the exponential function - is defined as the life-time τ_0[19]. For any reaction to occur, τ_0 must be long enough in order to not relax before colliding with another molecule. Collisions happen as a result of diffusion, and diffusion coefficients together with concentration determines the rate of collision. Thus, the life-time needs to be comparable in magnitude to the rate of diffusion. However, it is not necessary that every excited state collides with another molecule, that is merely desirable from an energy efficiency point of view. The fraction of productive collisions to the number of photons absorbed is a quantity closely related to the quantum yield, a measure that instead is defined by the amount of product formed[42]. But one should bear in mind the conceivable possibility that even if only a small fraction of the excited states engages in productive collisions, such an event could initiate a long chain reaction by means of propagation and, nonetheless, constitute a reaction with practical and acceptable efficiency.

Whether or not a SET can occur between a photocatalyst, in either excited or ground state, and another molecule is dictated by the reduction potentials of both species[1,19]. In general - electrochemical potential data is notorious for their confusing definitions and terminology - the preferred convention of tabulation is to report the value for the reduction potential for all species. The higher, more positive, value the reduction potential, $E_{1/2}^{red}$ (A/A^-), the more favorable that reduction is in comparing any two such half reactions. The oxidation potential is simply the negative of the reduction potential. The values for ground state potentials are measured with cyclic voltammetry, CV, and usually reported against the saturated calomel electrode reference (SCE). Excited state redox potentials are problematic to measure directly why they are usually instead estimated based on ground state potentials and excitation energies, both of which can be experimentally measured[43]. Photocatalysts based on ruthenium and iridium can access a wide range of redox potentials by ligand modifications, enabling one-electron reduction or oxidation of a huge number of organic molecules[19]. In general, EWGs introduction to ligands render coordination complexes easier to reduce and, conversely, EDGs render them easier to oxidize.

When a substrate in one way or another deactivates the excited state and itself absorbs some of its energy we speak of a quenching of the excited state by that substrate. In photoredox catalysis, this normally proceeds by one of three typical quenching mechanisms[19]. If the substrate receives an electron from the excited state photocatalyst, the photocatalyst undergoes an oxidization and, thus, such a process is term oxidative quenching. Conversely, if a quencher donates an electron to the excited state photocatalyst the process is termed reductive quenching. There is also a third mechanism, which does not involve any SET, termed energy transfer. In such a process, the photocatalyst transfers its excited state energy to the substrate that in turn gets promoted to an excited state.

3.5.2 Photocatalysts Beyond Ru and Ir

There are of course plenty of protocols reported using photocatalysts of earth abundant metals such as Cu, Cr, Co, V, W, Zn, Ni, Ce, Mo, Ti, U and Fe[44–47]. Nevertheless, those based on Ru and Ir are still the go-to catalysts in the method development community. Presumably because of convenience considering their reliability for such matters and, furthermore, they do indeed have many desirable properties. Among the earth-abundant alternatives Cu, stands out as the most studied metal with many examples. Cu-photocatalysts generally possess strong reducing power but, compared to Ru and Ir, suffer from being rather weak oxidants in the excited state limiting their applicability[19]. Besides photocatalysts based on earth-abundant metals there are also many examples of purely organic photocatalysts, or dyes[48–50]. Some dyes, e.g. Fukuzumi's catalyst or DDQ (Figure 8), are, as opposed to Cu, very strong oxidants in the excited state, also when compared to Ru and Ir, and can access radical generation from, seen from the perspective of Ru and Ir, inert molecules. However, they often suffer from the opposite limitations to those of Cu and, furthermore, tend to be more prone to degradation and, therefore, requires somewhat higher catalyst loadings.

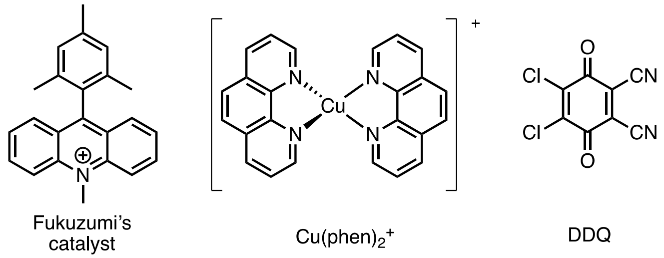


Figure 8. Structure of some common photocatalysts not based on precious metals.

As of today there are only a few examples of Fe(II) or Fe(III) as photocatalysts[51,52]. The reason is often attributed to the low life-times of such complexes. However, Wärnmark and co-workers recently disclosed an Fe(II) catalysts with life-times approaching those of traditional photocatalysts[53,54]. On the other hand, the papers that do exist on simple iron coordination complexes suggest that the assumption that life-times on the order of ns to μs to be strictly necessary for efficient reactions could, and indeed should, be questioned.

As an example (Figure 9), Cozzi and Ceroni reported[55] that $Fe(bpy)_3^{2+}$ could catalyze the enantioselective dual organo- and photoredox catalytic α-alkylation of aldehydes reported by MacMillan[56]. The original procedure used $Ru(bpy)_3^{2+}$ that has a $\tau \in [500,1000]$ ns while $Fe(bpy)_3^{2+}$ has a life-time of only ca. 650 ps.

Despite a three order of magnitude difference in life-time, $Fe(bpy)_3^{2+}$ replicated the scope with only slightly lower yields. Some insights into this seemingly anomalous result can be gained from the mechanistic studies by Yoon[57] who studied the reaction by MacMillan, along with his own reactions, and concluded that a significant chain propagation is present. Thus, many times, these photocatalysts might operate to a larger extent as initiators and, even though probably most excitations of Fe(II) relax back, it is enough with occasional quenching to set off a fast and long propagating chain that ultimately does not affect the practicality of the process.

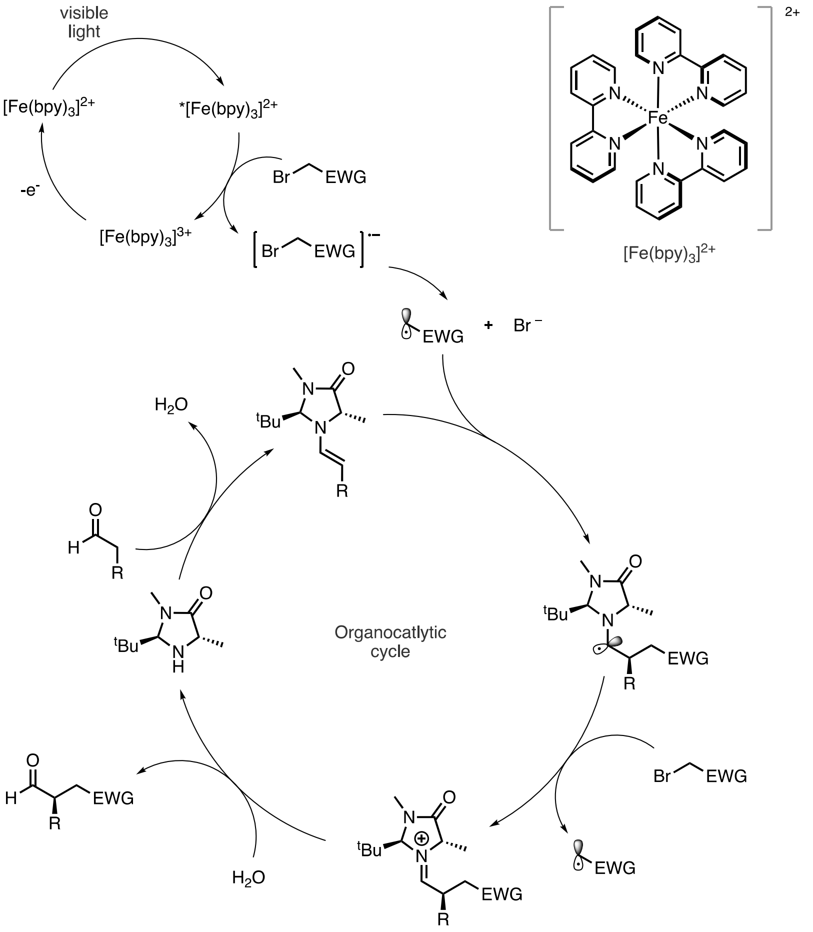


Figure 9. Proposed mechanism for the dual organo- and photoredox catalytic enantioselective α-alkylation of aldehydes.

The only difference between this mechanism and the one proposed by MacMillan, besides the indication of a propagating mechanism, is an oxidative quenching instead of a reductive quenching of the photocatalyst. Thus, when $Fe(bpy)_3^{2+}$ absorbs a photon an electron is promoted to a higher energy level (MLCT) resulting in a relatively short lived excited state that, nevertheless, is quenched by the alkyl halide bearing an EWG. The radical anion is unstable and undergoes a mesolytic cleavage to yield an alkyl radical, which is electrophilic due to the EWG, as well as an expelled bromide ion. Hence, the radical reacts most efficiently with nucleophiles, i.e. electron rich species. Meanwhile, the aldehyde condenses with the organocatalyst to form an electron rich enamine. Should come as no surprise then that the radical adds - enantioselectively due to the enantiomeric steric hindrance - to the enamine forming an intermediate radical that is nucleophilic due to the neighboring nitrogen atom, an EDG. This intermediate radical can either get oxidized by another alkyl halide or by $Fe(bpy)_3^{3+}$ which would close the iron catalytic cycle. The iminium ion formed upon oxidation hydrolyses by the water formed in the condensation to give the alkylated aldehyde as product as well as reforming the organocatalyst. True magic!

There are also interesting examples of Fe(III) in photoredox catalysis that often affords a complementary mechanism[58–67]. For Fe(III), it is more common to have an excitation of the kind ligand-to-metal charge-transfer (LMCT). A very well-known example of this process - for which it becomes surprising that applications to organic synthesis came only in very recent years – is the photolysis of ferric oxalate, $Fe(C_2O_4)_3$[68]. Upon absorption of a photon, an irreversible LMCT from the oxalate ligand to the iron center occurs which generates a radical that decarboxylates, a process extensively used in actinometry[69,70], see Figure 10. The same principle has enabled oxygen-centered radicals from simple iron halides. In solution, the carboxylates or alcohols substitute the halides and coordinate to iron. Upon absorption of a photon, an oxygen-centered electron is promoted to an iron-centered orbital forming either carboxyl radicals that decarboxylates to alkyl radicals that can be engage with other substrates or, from alcohols, oxygen-centered radicals that either proceed with HAT or β-fragmentation.

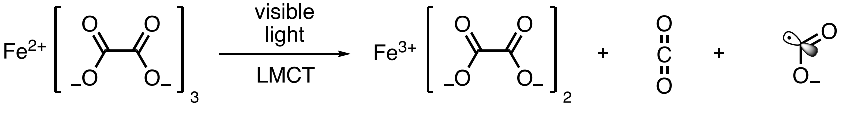


Figure 10. Photolysis of ferric oxalate.

In the following chapter an example of a very short-lived excited state Fe(III) catalyst that mimics typical SET events following LMCT will be presented. Enjoy!

4 Iron(III) as photocatalyst (Paper I)

This paper describes an oxidative fragmentation of ethers and acetals with $Fe(acac)_3$ acting as a photocatalyst[71], see Figure 11. The transformation in which a cyclic ether or acetal is turned into a ketone or ester has been reported before but only a handful of protocols exist and, generally, give very poor yields and are associated with narrow substrate scopes[72–80]. The products obtained in Paper I are for the most part distally brominated ketones. Such structures do not find direct applications, nor are they ubiquitous in nature. However, they are recognized as valuable synthetic intermediates for synthesis of molecules of greater complexity, which do, indeed, have important applications as pharmaceuticals. The two prescribed pharmaceuticals Fexofenadine[81,82] and Haldol[83] are both accessed via γ-bromo ketones. A more efficient access to these structures via such a transformation was attempted by means of a photoredox catalytic radical strategy.

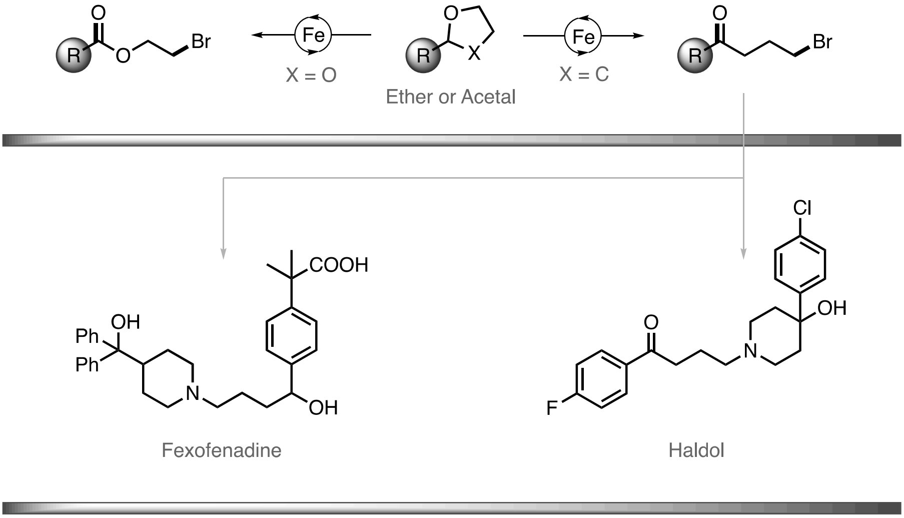


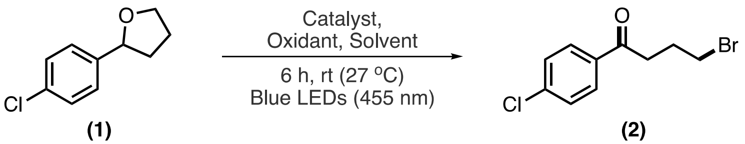
Figure 11. On top, a general reaction formula summarizing the chemistry of Paper I. At the bottom, two important pharmaceuticals accessible via γ-bromoketones and of which the Fexofenadine intermediate was synthesized in Paper I.

Ethers are rarely considered useful synthons in chemistry[30]. Their status as starting materials for transformations is far inferior to all the structures showing greater reactivity. It is precisely for this reason they instead are viewed as excellent solvents; they are relatively speaking inert molecules. However, that inertness is questioned by highly reactive radical species. For instance, in the presence of good HAT reagents the hydrogen alpha to the ether oxygen is easily abstracted since the so formed carbon centered radical is stabilized by the electron donating oxygen atom. Indeed, many reactions involving ethers proceed by an initial HAT event[5,31,84]. Thus, it was suspected that HAT reagents formed under photocatalytic conditions would enable oxidation of ethers to ketones via fragmentation of an unstable intermediate.

In the literature it is well known that $BrCCl_3$ is a precursor to the excellent HAT reagent, the trichloromethyl radical[1,85]. By accepting an electron from the excited state of a photocatalyst an unstable radical anion is formed which mesolytically fragments into a bromide ion and a trichloromethyl radical. Initial results showed that the conventional photocatalyst $Ru(bpy)_3^{2+}$ promoted the formation of trichloromethyl radicals that, presumably, abstracted the α-hydrogen that reacts further to give γ-bromoketones. While carrying out an optimization on the system, the true charm of science got revealed when, by a mere coincidence, it was discovered that $Fe(acac)_3$ with a life-time of some tens of picoseconds[86] promoted the reaction even more efficiently.

4.1 Optimization

The optimization was carried out on the cyclic ether 2-(4-chlorophenyl)tetrahydrofuran (**1**), a THF-derivative, see Table 1. At the start of the optimization, the results were rather scattered and no clear trend was observed. One should be cautious, however, in interpreting entry 1 since, in addition to the parameters shown, different setups and procedures were varied in search for reproducibility. But the real puzzle came when a control experiment removing $Ru(bpy)_3^{2+}$ showed that product formation, in some cases, were as good as the best results. However, as before, that control experiment lacked the quality of proper reproducibility with a statistical outcome of roughly 50% success rate. The whole story is very long and the reproducibility issue went on for about three good months. In the end, the only factor not yet investigated was that of trace metal impurities responsible for the different outcomes under seemingly identical reaction conditions, both with or without $Ru(bpy)_3^{2+}$.



Entry	Catalyst	$BrCCl_3$	Solvent	Yield (%)[a]
1	$Ru(bpy)_3(PF_6)_2$ (1-5 mol%)	2-10 eq.	Solvents	0-quant[b]
2	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	3 eq.	DCE	31(full conv.[c])[g]
3	$Fe(acac)_3$ (1 mol%)	5 eq.	DCE	76
4	**$Fe(acac)_3$ (1 mol%)**	**3 eq.**	**DCE**	**89 (90[d])**
5	$Fe(acac)_3$ (1 mol%)	1.2 eq.	DCE	59
6	$Fe(acac)_3$ (1 mol%)	0 eq.	DCE	No reaction
7	$Fe(acac)_3$ (1 mol%)	3 eq.	Toluene	52
8	$Fe(acac)_3$ (1 mol%)	3 eq.	MeCN	41
9	$Fe(acac)_3$ (1 mol%)	3 eq.	EtOAc	66
10	$Fe(acac)_3$ (1 mol%)	3 eq.	DMF	Trace
11	$Fe(acac)_3$ (1 mol%)	CBr_4, 3 eq.	DCE	64
12	$Fe(acac)_3$ (0.1 mol%)	3 eq.	DCE	64
13	$FeBr_3$ (1 mol%)	3 eq.	DCE	55
14[e]	$Fe(acac)_3$ (1 mol%)	3 eq.	DCE	Trace
15[f]	$Fe(acac)_3$ (1 mol%)	3 eq.	DCE	No reaction
16[g]	No catalyst	3 eq.	DCE	0-trace

Table 1. [a] Isolated yields conducted at 0.1 mmol scale. [b] Note, irreproducible yields were consistently obtained also when keeping all parameters constant. Yields were determined by ^{1}H-NMR using dimethyl sulfone or ethylene carbonate as internal standard. [c] Reaction run for 18 h. [d] Average isolated yield of two runs at 0.2 mmol scale. [e] Heat control (80 °C). [f] Control experiment in the dark. [g] Reaction conducted either in a brand new vial or a vial cleaned with aqua regia.

Thus, a screening of various metals was therefore performed, see Table 2. Before those experiments, all reaction vials were soaked in aqua regia for about two weeks with the additional effect of extreme corrosion of all the stands in the fume hood. The choice of metals are to some extent arbitrary, they reflect what were available in the storage room which, though, can be argued is a scientifically justified approach since any metal impurities present would, in fact, come from chemicals in that storage room.

Entry	Metal additive (1 mol%)	Conversion (%)
1	$Ce(SO_4)_2$	0
2	$Co(ClO_4)_2$	100
3	$Sc(OTf)_3$	0
4	$Pd(CF_3COO)_2$	0
5	$Gd(OTf)_3$	0
6	$La(OTf)_3$	0
7	$Bi(OTf)_3$	0
8	$AgBF_4$	0
9	$Rh_2(CH_3COO)_4$	0
10	$MnCl_2$	0
11	$RuCl_3$	0
12	$Ni(acac)_2$	29
13	CuCl	17
14	$CuCl_2$	0
15	$Fe(acac)_3$	100
16	$In(OTf)_3$	100

Table 2. 1 mol% of metal additive, and 2-(4-chlorophenyl)tetrahydrofuran (**1**) as substrate were used in each reaction and subjected to the optimized conditions. All vials and stir bars were carefully cleaned with aqua regia before reaction.

This screening, with two exceptions, displayed very definite results in that either nothing happened, or it proceeded to full conversion. The fact that so many zero-conversions were obtained this time while, previously, 50% without any metal added gave some to full conversion suggests that trace metal impurities indeed were present in the vials and removed by that long aqua regia treatment. Furthermore, three rather interesting results were discovered, $Co(ClO_4)_2$ (entry 2), $Fe(acac)_3$ (entry 15) and $In(OTf)_3$ (entry 16) all catalyzed the reaction to completion. None of these metal compounds are viewed as conventional photocatalysts, and $In(OTf)_3$ is the most peculiar result as it is white and do not absorb visible light. These results were reproducible, and examined also in brand new vials. However, at this point, any mechanism is unknown and it remained to determine whether they do operate as photocatalysts or not. Besides, an interesting side note is that $In(OTf)_3$ were used extensively in a previous project which likely explains the mystery encountered. As iron is an earth abundant metal and $Fe(acac)_3$ is a cheap and simple compound it became the preferred choice for further study. Thus, in the end, optimization led to the reaction condition of 1 mol % $Fe(acac)_3$, 3 eq. $BrCCl_3$ in DCE which afforded the product γ-bromoketone (**2**) after 6 h of irradiation in 90 % isolated yield (Table 1, entry 4).

4.2 Scope

In the first part of the scope the THF-core was kept constant while varying the aromatic group, see Figure 12. For the scope, the reaction time was extended to 18 h as it was noted early on that some substrates converted at a lower rate. With the extended reaction time the reaction of all substrates bearing a substituted benzene ring reached practically full conversion. The various fluctuations seen around a mean yield of ca. 80 % should not be interpreted as inherent to the specific structure but reflects an earnest report on the isolation skills.

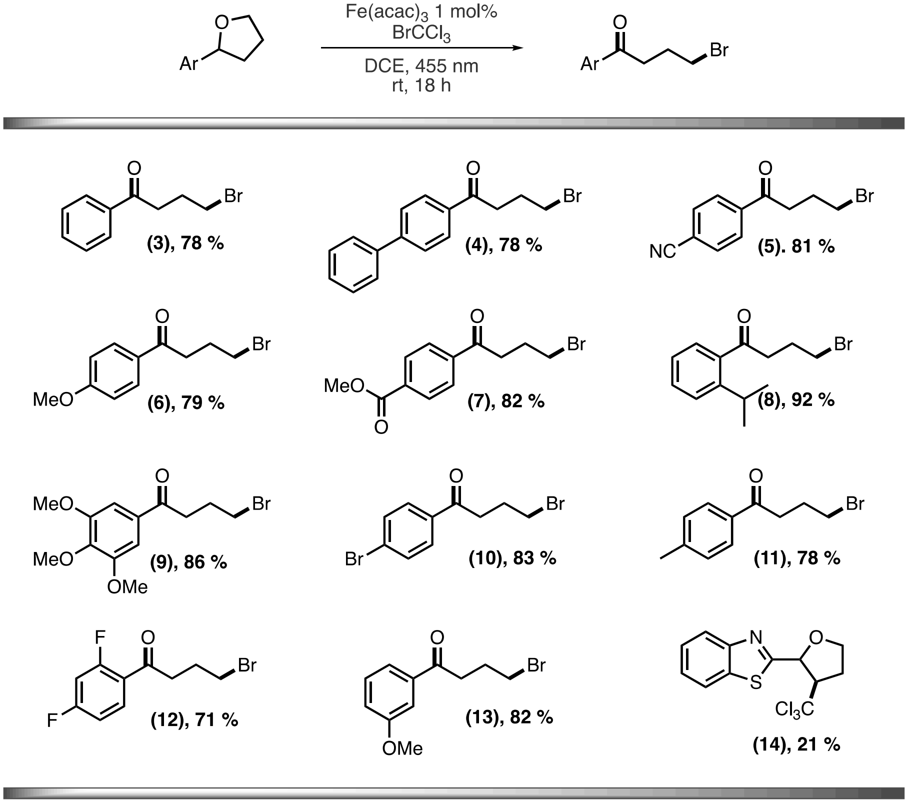


Figure 12. The scope with respect to the aromatic group.

The reaction turned out to not be very sensitive to either electronic or steric effects. Going from a nitrile group (**5**) on one hand to a methoxy group (**6**) on the other gave more or less identical result. Also, putting an *iso*-propyl group (**8**) near the reaction center did not inhibit the reaction the slightest. The odd one out is with a benzothiazole core (**14**), here probably the nitrogen acted as a base to force an elimination with the formation of an electron rich double bond to which the electrophilic trichloromethyl radical added.

The second part of the scope looked into moieties beyond the THF-core, see Figure 13. The reaction behaved similarly with a methyl group (**15**) on the THF-core or if the ring was enlarged to a pyran core (**16**). However, a complete inhibition of reaction was observed with a dioxane core (**17**). The reaction was attempted four times to make sure this really was the case but always gave all starting material left unchanged. The reason for this is not understood.

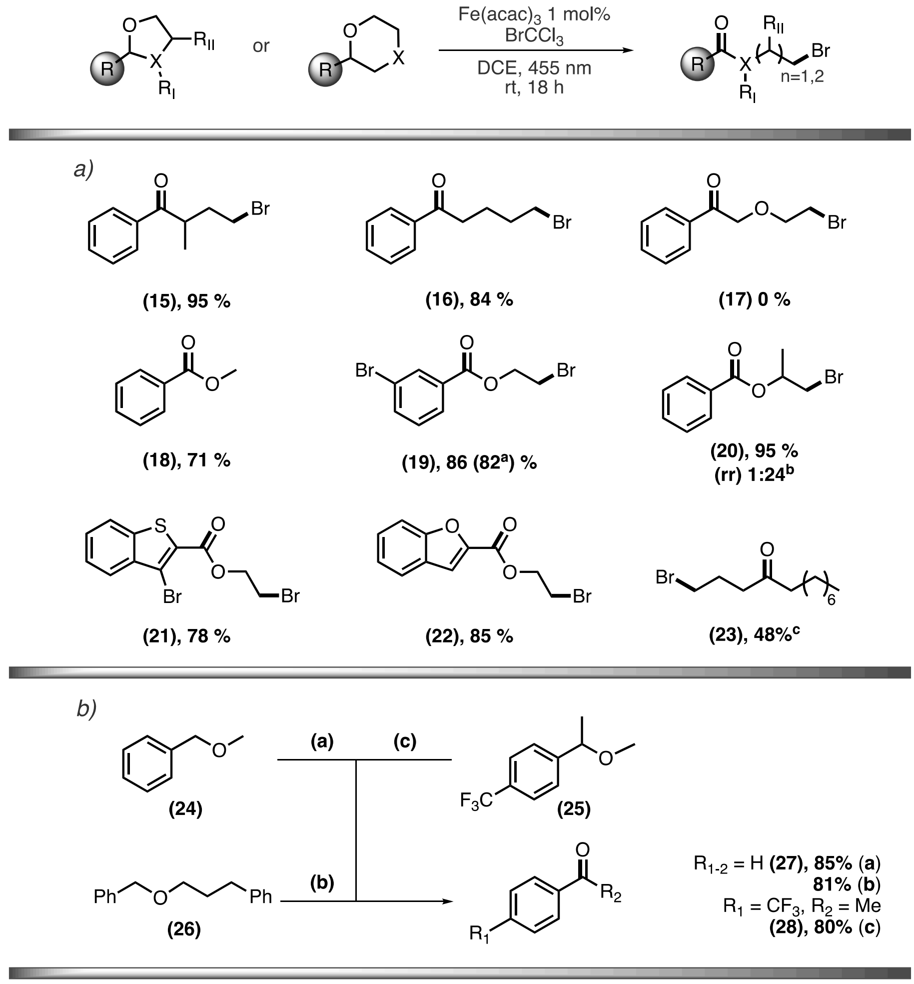


Figure 13. Scope concerning the reacting moiety i.e. cyclic/acyclic ethers and acetals. [a]Reaction conducted at 1 mmol scale. [b]Regioisomeric ratio. [c]Conversion by ^{1}H-NMR. 10 eq. BrCCl$_3$.

Having looked into various ethers the question of whether the protocol could be applied to acetals, which instead would yield esters, was investigated. Here there are two possibilities; for acyclic acetals a dealkylation by a bromide ion should take place rather than a ring-opening which, instead, would be the case for cyclic acetals. And indeed, acetals (**18**-**22**) turned out to be suitable substrates under these conditions. An attempt at a non-aromatic THF-derivative (**23**) was also done which required a bit more forcing conditions, i.e. 10 eq. $BrCCl_3$, but then some byproducts started to form and on top of that the product and starting material mixture was virtually inseparable. Lastly, acyclic ethers were investigated which afforded aldehydes or ketones as products in good yields (**27**-**28**).

4.3 Mechanistic Investigations

$Fe(acac)_3$ does not fluoresce nor phosphoresce, hence, the typical experiments to elucidate the mechanism for photoredox reactions are not viable in this case. Generally, in such experiments - i.e. Stern-Volmer plots - one can decide what species in a reaction mixture quench the excited state. That data combined with redox potentials can suggest what kind of quenching is operating[19]. Since $Fe(acac)_3$ in the eyes of the photoredox community has a provocatively low life-time it is worthwhile to spend some time going through the experiments that underly the claim that it, nevertheless, acts as a photocatalyst.

It was mentioned before that in the initial state of the project the hypothesis was always that a trichloromethyl radical is responsible for the initial engagement with the THF-derivative. However, with $Fe(acac)_3$ taking the place of $Ru(bpy)_3^{2+}$ that can no longer be assumed. Because in addition to such a mechanism the possibility of extruded acac radicals taking the place of trichloromethyl radicals cannot be ruled out. There are indications in literature that upon absorption of a photon, $Fe(acac)_3$ undergoes a LMCT followed by a release of an acac radical and leaving behind an Fe(II) species[87–89]. There is no literature suggesting that an acac radical acts as a HAT reagent whereby it was necessary to probe for that possibility.

If acac radicals would act as a HAT reagent in the reaction, then engagement of a THF-derivative would occur also in the absence of $BrCCl_3$. Two experiments were devised (Figure 14); equimolar amount of $Fe(acac)_3$ and no $BrCCl_3$ was used in both, and in one of them a Michael acceptor was also added. In the first case (*i*), no specific product is envisioned but rather a degradation of the THF-derivative or a possible dimerization would likely be observed but the result was a full recovery of the starting material. In the latter (*ii*), with addition of a Michael acceptor full recovery was again obtained. Thus, it was deemed unlikely that acac radicals initiate any engagement of the THF-substrate. In addition, for the sake of rigor, the possibility of an ionic mechanism (*iii*), e.g. by a hydride transfer which would generate a highly stabilized carbocation, was probed for by adding bromide ions, NBu_4Br, to the reaction but this too gave negative result.

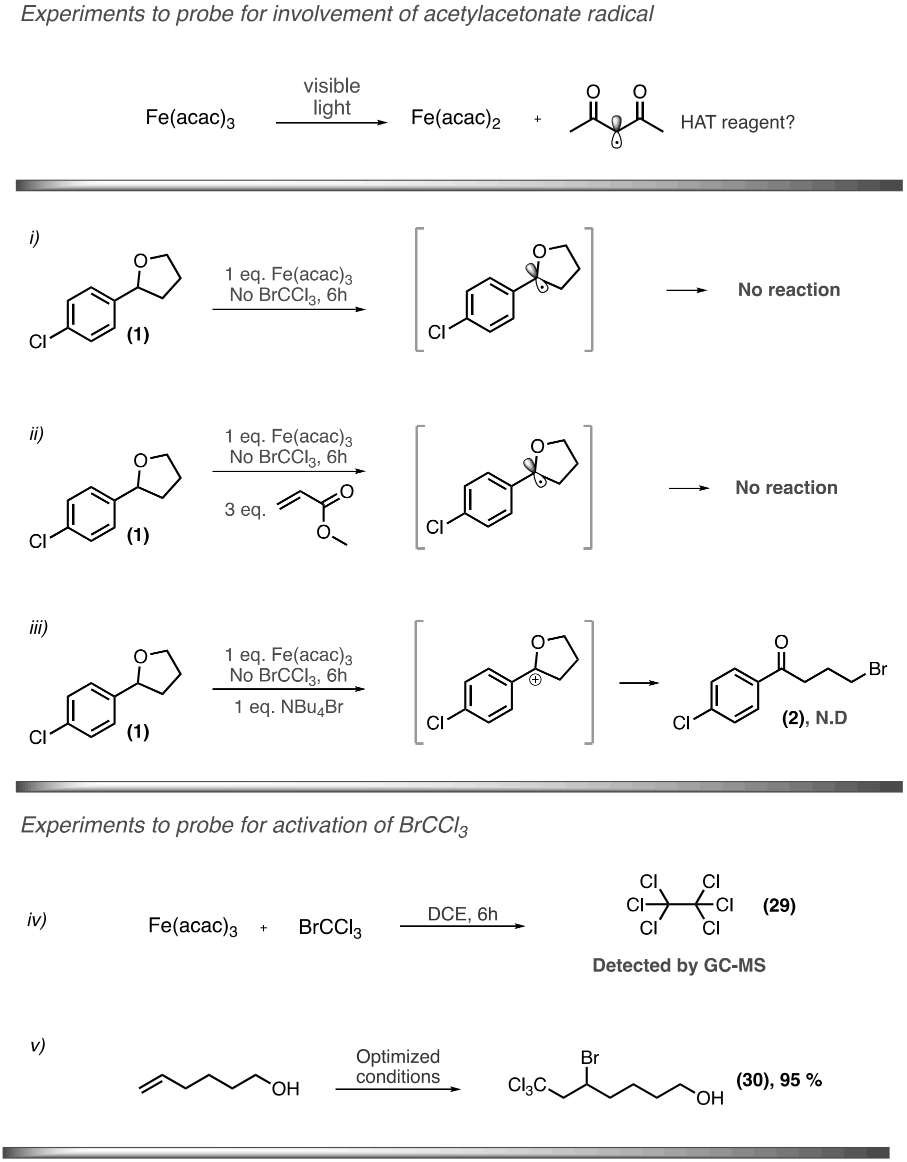


Figure 14. Mechanistic experiments by means of product analysis.

With this at hand, the hypothesis that trichloromethyl radicals act as HAT reagents rebecame the center of attention. To probe for this possibility two experiments were devised. In the first experiment Fe(acac)$_3$ and BrCCl$_3$ were irradiated in the absence of THF-derivatives or any other reaction partners (*iv*). Thus, if Fe(acac)$_3$ can turn BrCCl$_3$ into trichloromethyl radicals one should find the dimerization product hexachloroethane (**29**) and indeed that was observed. Since trichloromethyl radicals are known to also add to carbon-carbon double[90] bonds attempts at making an atom transfer radical addition (ATRA) reaction with 5-hexene-1-ol was also done (*v*). Interestingly, that reaction was published with Ru(bpy)$_3^{2+}$ but this control experiment proved that one could instead use Fe(acac)$_3$. Thus, the experiments suggest that Fe(acac)$_3$ by a yet unknown mechanism produce trichloromethyl radicals from BrCCl$_3$.

It remains to find support for the precise mechanism by which trichloromethyl radicals are formed. One conceivable possibility is that of an EDA-complex between Fe(acac)$_3$ and BrCCl$_3$ which, perhaps, could cause an electron transfer to BrCCl$_3$, the prelude to mesolytic cleavage. For this UV-vis experiments were performed with 300 eq. and 600 eq. BrCCl$_3$ with respect to Fe(acac)$_3$. However, no visible changes in spectral appearance, i.e. no new bands indicative of EDA-complex formation in the visible region or shifts of existing bands, see Figure 15. The only slight deviation in the spectra compared to pure Fe(acac)$_3$ is the absorbance which, however, correlates with the dilution upon addition of BrCCl$_3$.

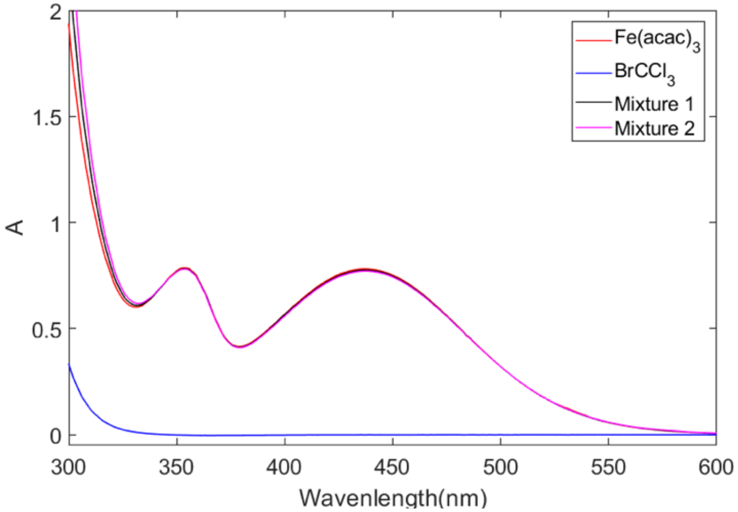


Figure 15. UV-vis absorbance spectroscopy experiments. No shifts of bands were observed indicating there is no formation of an EDA-complex. Fe(acac)$_3$ was measured at 0.2 mM, Mixture 1 includes addition of 300 eq. BrCCl$_3$, Mixture 2 contains 600 eq. BrCCl$_3$.

One quenching mechanism would be that of energy transfer. Here, there is no electron going into $BrCCl_3$ but an excitation of $BrCCl_3$ takes place which then would likely fragment homolytically. However, based on calculated transition energies of $BrCCl_3$[71] together with reported data on excitation energies of $Fe(acac)_3$[86] such an energy transfer would be strongly endergonic and was therefore ruled out.

The last conceivable possibility is that of a SET from $^*Fe(acac)_3$ to $BrCCl_3$. The redox potential for $^*Fe(acac)_3$ is not reported in literature but was estimated based on reported values on quenching studies[86] and CV measurements[91,92]. The quenching studies used $Fe(acac)_3$ as a quencher for the excited triplet states of molecules with known energies. From the data it became apparent that different excited states exist associated with different redox potentials. Thus, two estimated reduction potentials, $^*E_{1/2}^{red}$=-0.68 V vs SCE and $^*E_{1/2}^{red}$=-0.22 V vs SCE, allow for an exergonic SET to $BrCCl_3$ ($^*E_{1/2}^{red}$=-0.18 V vs SCE)[1]. Thus, despite the low life-time, acquired experimental data together with literature data points to a SET from the excited state $Fe(acac)_3$ to $BrCCl_3$.

Based on the aforementioned discussion the following mechanism was proposed, see Figure 16. An electron is transferred from $^*Fe(acac)_3$ to $BrCCl_3$ forming the unstable radical anion that fragments into a bromide ion and a trichloromethyl radical. The radical abstracts the α-hydrogen of the ether or acetal to form a radical intermediate. From here a propagation mechanism opens up; the radical intermediate abstracts a bromine atom from $BrCCl_3$ forming another trichloromethyl radical. The brominated intermediate is in equilibrium with the carbocation, but when the bromide ion instead attacks the carbon atom the irreversible formation of the final product γ-bromo ketone take place. There is also the possibility of returning the oxidized $[Fe(acac)_3]^+$ back to an active catalyst by oxidizing the intermediate benzylic radical to the highly stabilized carbocation. It should be pointed out that there is no direct evidence of a SET as an elementary reaction but is indicated indirectly. Thus, it is possible that it is a *formal* SET; a black box containing multiple elementary steps with the net effect of that of a SET.

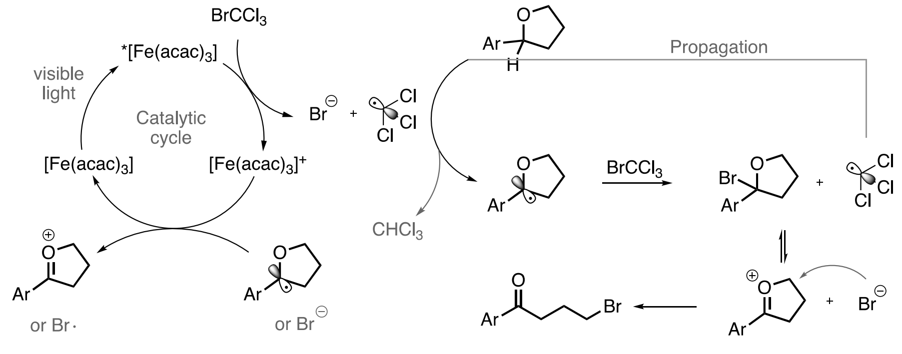


Figure 16. Proposed mechanism for the oxidative fragmentation. To the left a catalytic cycle for Fe(acac)$_3$ is drawn showing the excited state engaging in a SET event with BrCCl$_3$ and at the bottom a potential pathway for returning to the original form.

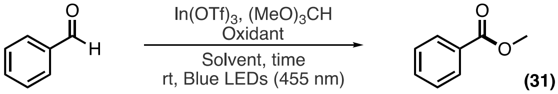
5 Photocatalyst-free conditions (Paper II)

This project grew out of paper I as a complement to the chemistry as well as for the opportunity of demonstrating a novel mechanistic pathway. As mentioned in section 4.1, $In(OTf)_3$, despite being a white solid, mediated the reaction with the same efficiency as $Fe(acac)_3$. The mechanism by which $In(OTf)_3$ catalyzes the reaction seems strange from a visible light driven point of view. But precisely for that reason, i.e. the allusion to some peculiar and potentially truly novel mechanism at work, it was deemed interesting enough to explore further in a separate project. Furthermore, acetals as starting material has the drawback of, in many cases, the need to be synthesized in a separate step. Graham reported a synthesis of acetals from aldehydes and orthoesters (or alcohols) using $In(OTf)_3$ as a very efficient catalyst completing the reaction for many substrate within 5 min and, in addition, no removal of any water was necessary[93]. It was then rather straightforward to propose this project as a combination of that article with paper I. Thus, the hypothesis was that two reactions, i.e. acetalization of aldehydes and oxidative fragmentation to esters, could be performed in one-pot by forming the acetal *in situ*[94].

5.1 Optimization

The optimization was carried out on benzaldehyde to give methyl benzoate (**31**), see Table 3. Initially, similar conditions as in Paper I was used but $In(OTf)_3$ was added instead of $Fe(acac)_3$ together with trimethyl orthoester used for the acetalization step. The yield seemed anomalous as the best yield obtained was 32 % (entry 1) but the crude mixture showed no signs of significant aldehyde, acetal or other species present. When using *p*-methoxybenzaldehyde yields were reaching near quantitative. Hence, it was suspected that methyl benzoate forms an azeotrope with $BrCCl_3$ while substituted aromatic rings were not. This was also, albeit less extreme, observed in Paper I. For optimization, the crude reaction mixture was filtered through a short silica plug and concentrated under reduced pressure where residues, or byproducts, of $BrCCl_3$ are mixed with the product while in Paper I a column on the substrate was performed which seemed to reduce the volatility.

Next, a screening of oxidants was performed which revealed the superiority of NBS (entry 5) over $BrCCl_3$. The results with NBS support the hypothesis of $BrCCl_3$, or perhaps hexachloroethane, forming an azeotrope as the yields increased towards 80 %. Control experiments performed on $BrCCl_3$ and NBS alludes to a change of mechanism accompanying the change of oxidant. For instance, a dark control experiment showed that for NBS the reaction still proceeded to some extent (entry 8) although with worsen efficiency, but with $BrCCl_3$ no reaction occurred at all. Furthermore, if one instead of aldehyde starts with a benzaldehyde dimethyl acetal, NBS alone still carried out the transformation to the ester while $BrCCl_3$ required $In(OTf)_3$ for any conversion to be observed. Contrary to Paper I, all reagents added was not necessary for reaction to occur - one could omit both light and $In(OTf)_3$ when using NBS – but, on the other hand, the addition significantly speeded up the rate of reaction.



Entry	Oxidant	Solvent	Time	Yield (%)[a]
1	$BrCCl_3$	DCE	18 h	32
2	$BrCCl_3$	DCM	18 h	26
3	$BrCCl_3$	MeCN	18 h	14
4	$BrCCl_3$	EtOAc	18 h	3
5	NBS	DCE	18 h	76
6	NBS	DCM	18 h	60
7	NBS	MeCN	18 h	66
8	NBS	DCE	18 h	41[b]
9	NBS	DCE	18 h	13[c]
10	NBS	DCE	8 h	74
11	NBS	DCE	4 h	75
12	NBS	DCE	2 h	75
13	NBS	DCE	1 h	82
14	**NBS**	**DCE**	**5 min**	**91**
15	NBS	DCE	2 min	88
16	NBS	DCE	10 s	82

Table 3. Reaction conditions: Benzaldehyde (0.2 mmol), $In(OTf)_3$ (1 mol%), oxidant (1.2 – 2.0 eq.), solvent (0.5 mL) and trimethyl orthoformate (1.0 eq.) under blue LED irradiation at rt for 10 s – 18 h under argon atmosphere. [a]Yield determined by ^{1}H-NMR using dimethyl sulfone or methyl 3,5-dinitrobenzoate as internal standard. [b]Reaction in the dark. [c]Reaction without $In(OTf)_3$.

Lastly, the reaction time was successively reduced which revealed an unexpected quality; the transformation of benzaldehyde to methyl benzoate via a (hemi)acetal with NBS as oxidant yielded the product in 82 % after only 10 s irradiation (entry 16). It seems, scrutinizing the literature, that this is the fastest protocol for such a transformation. Put it differently: a world record.

5.2 Scope

When moving on to the substrate scope, investigating the aromatic group firstly, it turned out that only benzaldehyde converted with impressive yields in 10 s. It could, perhaps, be rationalized by considering the electron density around the carbonyl carbon throughout the transformation. First, EDG or EWG have less dramatic effects on the rate of reaction for radical reactions taking place at the benzylic position so it is fair to assume that any difference in rate of reaction seen for such electronics are due to polar elementary steps. Thus, in Paper I, one should expect a slower expulsion of the bromide ion from the brominated intermediate (Figure 16 or 20) to form the cation if the aromatic ring contain an EWG. The opposite should hold true for acetalization of aldehydes as the carbonyl carbon is more electrophilic with EWGs. So what favors the acetalization step disfavors the expulsion of the bromide and vice versa. It is possible then that the mere electronically neutral benzaldehyde does not discriminate any of those steps and therefore the only substrate for which 10 s is enough. However, for the majority of the scope a reaction time of 5 min was enough which is still very fast in this context. As in Paper I, the reaction does not seem to be strongly dependent on electronic effects and functional group compatibility is similar, see Figure 17. In addition, with one carboxylic acid on the ring (**40**) a diester was formed under these conditions. In this paper, the effect of a nitro group (**37**-**38**) could be investigated on the reaction. The typical protocol to make THF-derivatives[95] in Paper I did not allow for nitro substituents why this was not investigated there. Despite the very strong electron withdrawing nitro group, the reaction still proceeded albeit the reaction time in this case needed extension to 1 h, indicating a much slower dissociation of bromide.

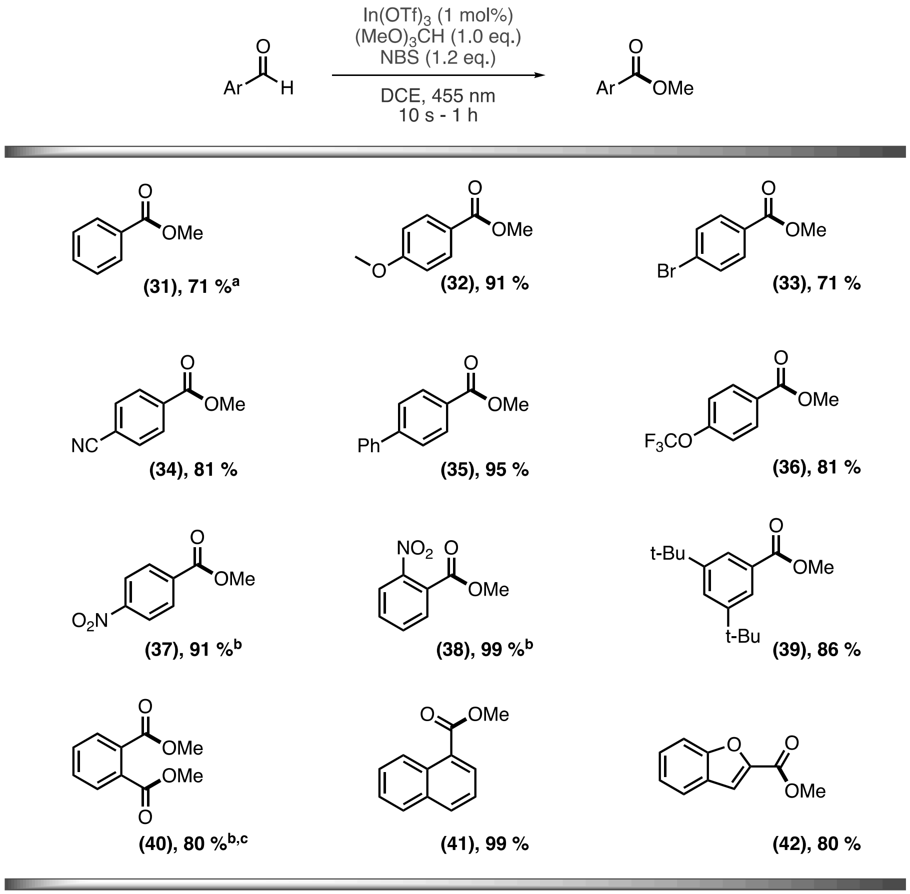


Figure 17. The scope with respect to the aromatic group. Reactions were irradiated with blue LEDs for 5 min unless otherwise specified. [a]Reaction time 10 s. [b]Reaction time 1 h. [c]2 eq. NBS.

Next, whether esters beyond methyl ester could be formed as well as if alcohols in place of ortho esters is viable was explored, see Figure 18. Indeed, triethyl orthoformate performed with similar efficiency (**43**). It was noted early on that acetalization only using alcohols in place of ortho esters proceeded slower. However, with optimized conditions established it was reinvestigated and both isobutyl alcohol (**44**) and *tert*-butanol (**45**) converted to the corresponding ester when extending the reaction time to 4 h and using 2 eq. NBS. The possibility of engaging diols to form brominated esters via cyclic acetals was less successful; not only did they give lower yields but tended to form an ester linkage on both alcohol groups which indicates that, probably, reaction also proceeds via hemiacetals.

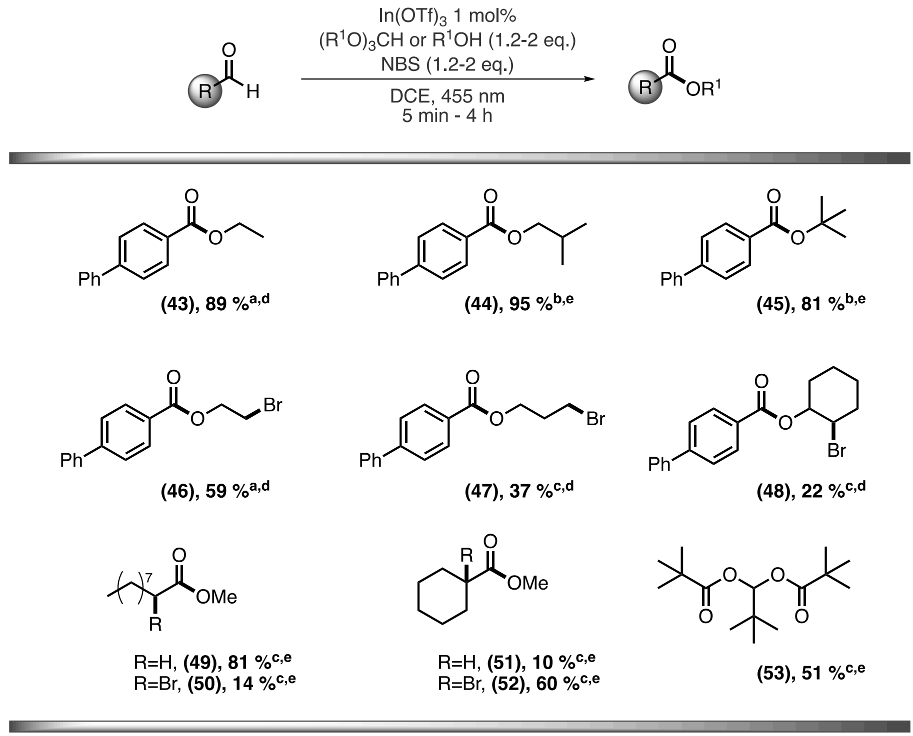


Figure 18. Scope continuation. [a]Reaction time = 5 min, [b]Reaction time = 4 h, [c]Reaction time = 1 h. [d]1.2 eq. NBS, [e]2 eq. NBS.

As in Paper I, aliphatic substrates suffered, in part, from the same problem of bromination at the alpha-position. It did, however, require less forcing conditions (2 eq. vs 10 eq. oxidant). Using greater amounts of NBS caused greater α-bromination and decreasing prevented full conversion of starting material. Thus, the procedure can only be considered useful for aromatic substrates, unless one also wishes to brominate the α-position, in which case it can be accomplished by simply adding more NBS.

5.3 Mechanism

It is tempting to assume that the mechanism for this reaction, which was designed as a combination of two reactions, is simply the mechanism of the first followed by the mechanism of the second. And sometimes, perhaps, that is the case but it cannot be assumed here which the following reasoning will convey. The mechanism for the In(OTf)$_3$ catalyzed acetalization was not addressed at all by Graham[93]. Brønsted acid catalyzed acetalization using trimethyl orthoformate is generally considered to proceed via formation of MeOH[96] which cannot, however, be formed with Lewis acids as no protons can be provided. Attempts at drawing a Lewis acid catalyzed mechanism analogous to that of a Brønsted acid catalyzed mechanism for this reaction will fail at rationalize the formation of the acetal without proposing highly speculative peculiar pathways. Furthermore, the results presented by Graham support the idea that the mechanism for acetalization with alcohols proceed by a different mechanism. These matters will not be elaborated any further since, *vide infra*, the second reaction taking place in the reaction produces a Brønsted acid which complicate things even further and in the end there are likely multiple mechanistic pathways taking place simultaneously. As a last note, the acetalization for the purpose of this protocol could in principle stop halfway, i.e. to the hemiacetal, as there is no obvious reason why HAT could not occur already from the hemiacetal.

An application of the first law of photochemistry[28] to this reaction states that blue light needs to be absorbed in order for this photochemical reaction to take place. This simple matter became puzzling as nothing added in the reaction, nor the initial reaction solution, were colored. So what then is the role of blue light which is proven to increase the reaction rate so staggeringly much? Furthermore, a reaction time of 10 s suggests that the reaction is predominately operating via a propagating mechanism as not so many photons could be absorbed in only 10 s. It was noted, however, that immediately upon irradiation the reaction turned brown indicating formation of molecular bromine. Once bromine is formed it is straightforward to propose a homolytic cleavage upon absorption of a photon yielding two bromine radicals - which are known HAT reagents[97–99] - that would act analogously to the trichloromethyl radical in Paper I with the rest of the propagating mechanism being similar. If, as is popular to hypothesize when NBS is on the table[100], it contains trace amounts of molecular bromine then a plausible mechanism could be proposed. Once that trace amount of bromine absorbs photons, followed by dissociation and abstraction of hydrogens, HBr is formed which, according to Goldfinger's mechanism[100], would shift the equilibrium towards more bromine and this would be enough for a proposal. The problem is, when UV-vis of a solution of NBS in DCE - even as concentrated as in the reaction - was recorded no signs of molecular bromine was ever detected. Hence, one should look into other possible hypotheses as this one relies on an assumption that cannot be supported with standard techniques. Important to point out though, UV-vis does not disprove trace amounts of bromine, all it can say is that the concentration of bromine is less than the detection limit. So, in the end, trace amount of bromine could nevertheless be there and responsible for the initial reaction. However, further experiments were performed to gain a greater insight.

Since the reaction mixture turns brown within seconds upon irradiation various parameters and their effect on bromine formation were investigated separately. When $In(OTf)_3$ was added to a solution of NBS in DCE and irradiated with blue light followed by UV-vis no bromine was detected. When instead adding a Brønsted acid, HBr, UV-vis was superfluous as the solution instantly turned brown. On the other hand, adding either MeOH or $(MeO)_3CH$ and irradiating with blue light turned the solutions brown within a few seconds. Note that without light, even for extended periods of time, no formation of bromine took place in any of the abovementioned cases. In addition, when $In(OTf)_3$ was added on top of alcohols an even greater amount of bromine was formed, see Figure 19. Thus, from the experiments one can conclude that bromine is rapidly formed from NBS by the combination of alcohol - ortho esters were confirmed to contain minor amounts of the corresponding alcohol - and light. This result was reconfirmed when such solutions were irradiated in a totally dark room with blue LEDs equipped with a 400 nm short pass filter.

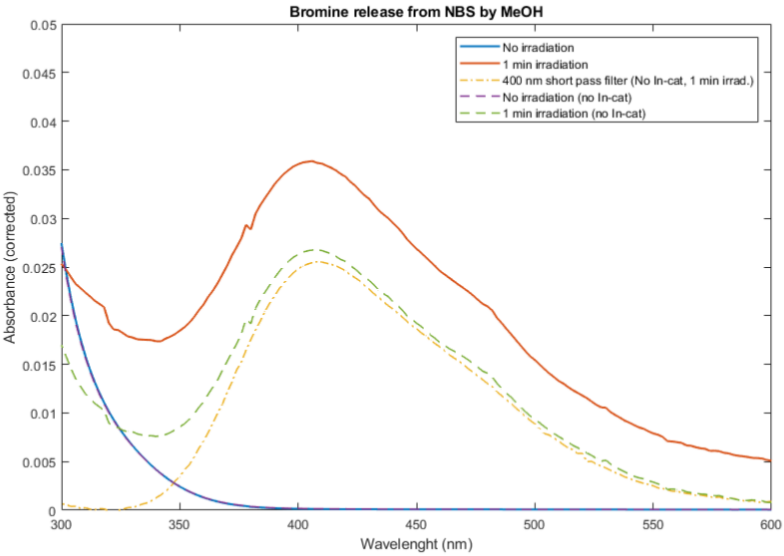


Figure 19. UV-vis spectra recording formation of elemental bromine under different conditions.

Note, none of the experiments give any definite answers to the question whether trace amount of bromine is present at start or formed first by the conditions proven to produce large amounts of bromine. One cannot conclude that the experiments producing bromine would do so also in the case where any trace amounts have been completely eliminated. In any case, one can on the other hand account for the rapid formation observed by the combination of alcohols and light. With bromine present, it dissociates into bromine radicals upon absorption of blue light. Bromine radicals can abstract hydrogens from hydrocarbons[101], so in the case of methanol, which provides a stabilizing oxygen to the carbon centered radical, abstraction proceeds even easier. The product of abstraction is HBr which shifts the equilibrium further towards bromine, which absorbs another photon and so on. The first bromine molecules absorbing photons are either present in trace amounts or formed, that part of the mechanism is still somewhat speculative at this stage.

Finally, both how (hemi)acetals and bromine are formed under the conditions employed have been discussed thoroughly, and the remaining mechanism is nearly identical to that in Paper I. A bromine radical first abstracts the α-hydrogen forming a stabilized electron rich radical that abstracts a bromine from molecular bromine giving the brominated acetal intermediate and a new HAT reagent. The intermediate collapses by expulsion of a bromide ion that demethylates the cationic intermediate forming the ester (Figure 20).

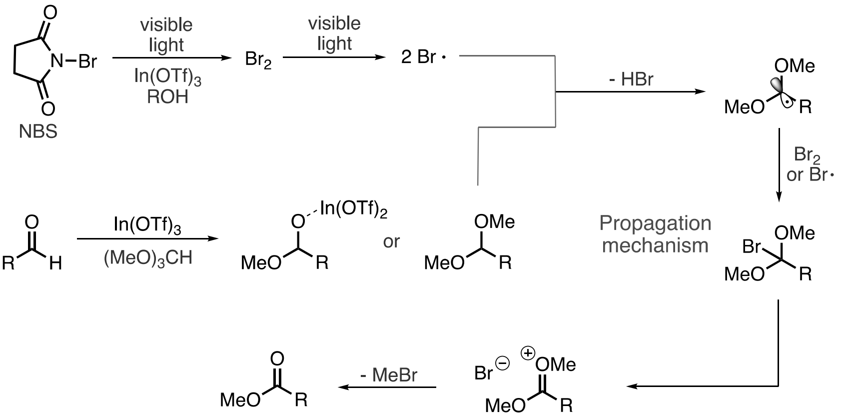


Figure 20. Proposed mechanism. The possible pathways discussed in the text for producing acetals are omitted for clarity.

6 Heterogenized Ir catalysis (Paper III)

Paper I-II looked into alternatives to Ru and Ir aiming at increasing the substitutability of those metals in the context of photoredox catalysis. Paper III makes no apologies for using Ir since the project instead looks at the other pursued aspect of RSR, the recycling rate. The insistence to use Ir is motivated by the fact that one cannot ignore the inherent favorable properties. What is meant with recycling in the context of RSR is simply that the metal itself is being recovered from whatever it was used for. Recycling in the context of Paper III is different, but related, in that one is not concerned with recovering the Ir metal but the whole catalytic material. The distinction makes a difference; a homogeneous Ir catalyst can rarely, if ever, be recovered as a catalytic material after a reaction. Furthermore, any such attempts are confronted with the problem of appropriately separating the catalyst from everything else in the end of the reaction which itself constitutes a burdensome and economically suboptimal process. And that is itself based on the assumption that the structure of the homogeneous Ir catalyst is retained. Furthermore, if one is content with simply recovering the Ir metal, rather than the catalyst, there is still a whole process of turning that Ir into a catalyst that can reenter a reaction vessel and reconduct its purpose.

The method of heterogenization of homogeneous photocatalysts aims at improving recycling of the catalytic material[102–111]. If heterogenization properly enables reusage of such a catalyst then the advantageous properties of precious metals can be utilized without the drawbacks inherent to the realm of homogeneity. A heterogenized catalyst, i.e. a solid, can be recovered by simple filtration or centrifugation, two processes appreciated by industry due to their economic aspects[112], provided the recovered material is still catalytically active. Heterogenization can take many architectural forms, and the form used in Paper III consists of an Ir catalyst, $Ir(dcabpy)(ppy)_2^+$, covalently bonded to an Al_2O_3 support via so called anchoring groups, see Figure 21. The anchoring group in this case are carboxylic acids pendent on one of the ligands of the catalyst. The catalytic material as such is an insoluble powdered solid.

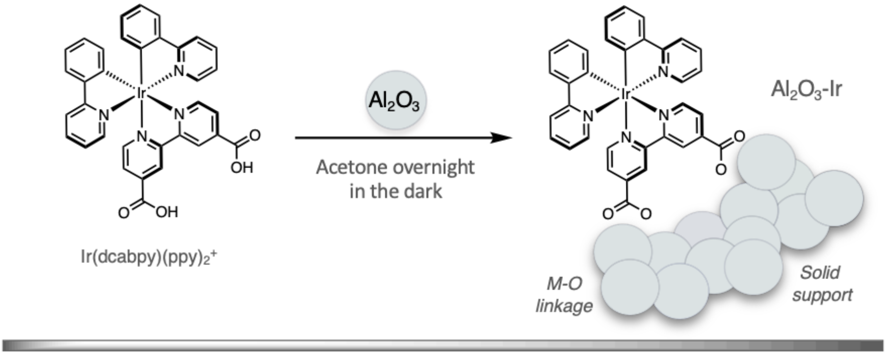


Figure 21. Heterogenization of Ir(dcabpy)$(ppy)_2^+$.

This work is based on a previous study by Hammarström et al[103]. where the design and properties of Al_2O_3-Ir, together with other catalyst variants, were developed. In that study, Al_2O_3-Ir demonstrated its potentially usefulness as a catalyst by the successful engagement in a dehalogenation reaction of bromoacetophenone. The purpose in Paper III, therefore, was to systematically explore the broader reaction scope, the recyclability and kinetics in relation to homogeneous catalysts. The rationale for choosing reactions for this study was to test Al_2O_3-Ir on examples that has been proposed to engage the catalyst in all three modes, i.e. reductive- and oxidative quenching and energy transfer. In the following, the focus of discussion will be on the reactions performed in Paper III since that constitutes the laboratory contribution by the author of this thesis which, by virtue of the literary form, should not be referred to by the pronouns me or I.

6.1 Reaction Scope

In what follows, the catalyst loading was always strived for being as low as possible. A compromise between catalyst loading and reaction time was therefore needed, a trade-off that was judged on a case-by-case basis. As will be apparent below, different catalyst loadings have been used and, interestingly, turned out to always be much lower than those in the reported procedures. Sure, the reaction times in most cases had to be increased as well, but not to the same extent as the catalyst loading was reduced.

6.1.1 Reductive Dehalogenation

The reaction conditions for this reaction were adopted from the reported procedure for dehalogenation of bromoacetophenone that also used a heterogenized strategy; a Ru-catalyst incorporated into a MOF matrix[111]. The protocol necessitates a stoichiometric electron donor, triethanolamine, which, depending on the redox potentials involved for both catalysts and substrates, could serve either by means of closing the catalytic cycle for the oxidized catalyst or as a reductive quencher of the excited state to enable electrons of high enough energy for reduction of substrates.

Using as little as 0.1 mol %, with respect to Ir, of Al_2O_3-Ir gave full conversion of bromoacetophenone to acetophenone (**54**), see Figure 22, and 93 % isolated yield. Also the two malonates (*iii*) and (*iv*) proceeded smoothly giving (**56**) in 99 % and (**57**) in 85 % respectively. When using benzyl bromide a dimer (**55**) was formed in 41 %. The dimerization is hypothesized to be due to the so often observed unique reactivity of the benzylic position and not the catalyst Al_2O_3-Ir.

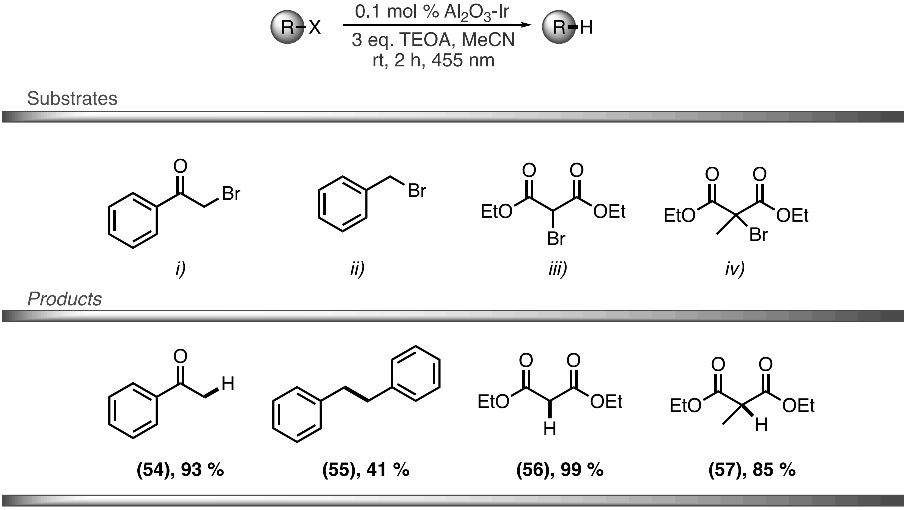


Figure 22. Reductive dehalogenation.

6.1.2 Atom-Transfer Radical Addition (ATRA)

The three reactions chosen here, see Figure 23, is reported previously using homogeneous Ru or Ir catalysts in their original form represented examples of both oxidative and reductive quenching pathways[90]. For the perfluoro alkylation of alkenes an electron donor, sodium ascorbate, was added in a substoichiometric amount, indicating that it is needed as a form of initiator and thereafter a propagating mechanism operates independently. This reaction was successfully replicated using Al_2O_3-Ir without any need for modification other than being able to employ a hundredth the catalyst loading, 0.01 mol %, without loss in efficiency, thus after 30 min irradiation the ATRA product (**58**) was obtained in 91 % yield. Furthermore, when conducted at a gram scale (**58**) was isolated in 99 %.

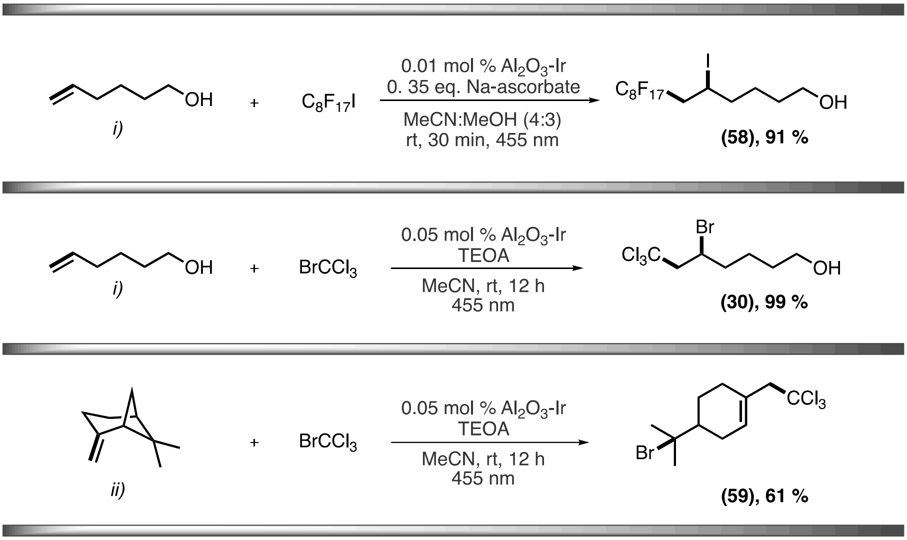


Figure 23. Atom transfer radical addition (ATRA).

The ATRA of $BrCCl_3$ onto alkenes, which would constitute an oxidative quenching, could not be replicated directly. Optimization regarding time, catalyst loading and solvents did not promote any reactivity. When adding an electron donor, triethanolamine, the reaction proceeded without any difficulties. Also in this case, an acceptable reaction rate was obtained by adding no more than 0.05 mol % Al_2O_3-Ir. ATRA of $BrCCl_3$ onto 5-hexene-1-ol afforded (**30**) in 99 % yield. For β-pinene, upon addition of a trichloromethyl radical onto the alkene a fragmentation take place to relieve the ring strain in the four membered ring giving the cyclohexene derivative (**59**) in 61 %, along with unidentified byproducts.

6.1.3 Aerobic Oxidative Hydroxylation of Boronic Acids

This reaction utilize N,N-diisopropylethylamine as an electron donor and quenches $Ru(bpy)_3^{2+}$ reductively which enables a one-electron reduction of molecular oxygen to form the highly reactive superoxide radical anion that in a series of steps oxidizes arylboronic acids to phenols[113]. When using Al_2O_3-Ir, no modification of the reported reaction conditions were necessary but, on the other hand, a lower catalyst loading was used, 0.1 mol % vs 2 mol %, albeit, in this case, at the cost of a three- to fourfold increase in reaction time. But that time has to be viewed from the perspective of using only a twentieth of the reported Ru(bpy)$_3^{2+}$ loading. All reactions (Figure 24), from methoxy (**60**) to chloro (**62**) substituents in para position as well as the more electronically neutral methyl group (**61**) converted to the corresponding phenols with similar efficiency. The lower yield of *p*-methyl phenol (**61**) is attributed to the lower boiling point since, after all, it has to be separated from residues of DMF.

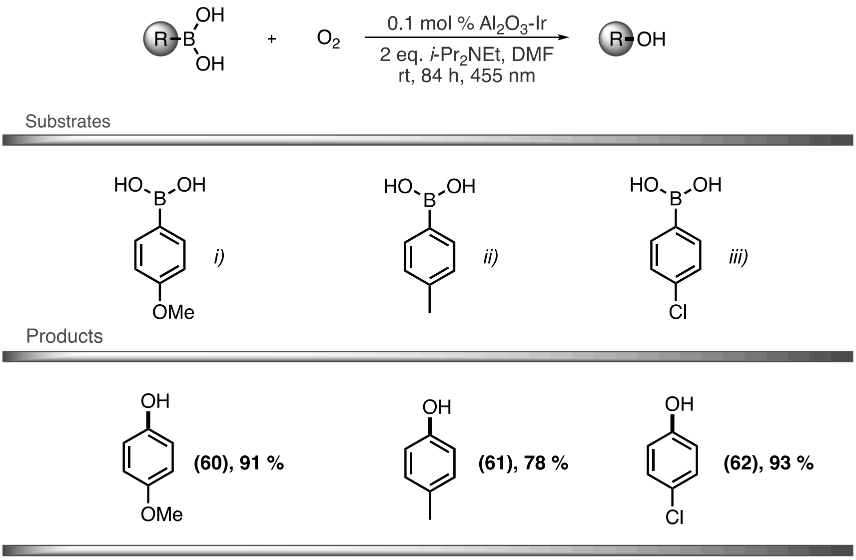


Figure 24. Aerobic oxidative hydroxylation of boronic acids.

6.1.4 Oxidative Fragmentation of Ethers and Acetals

The title reaction does not need much introduction as it has already been discussed at length[71]. Without any additional modifications, 0.05 mol % Al_2O_3-Ir catalyzed the reaction with similar efficiency as for 1 mol % Fe(acac)$_3$, see Figure 25. Ketones (**3**) and (**16**) was isolated in 89 % and 92 % respectively and, satisfyingly, methyl benzoate (**18**) was isolated in 99 % showcasing that one's evaporation skills has improved in dealing with this notoriously volatile compound. However, with these wonderful results came a puzzling and ostensible contradiction namely that no addition of an electron donor was necessary. $BrCCl_3$ is postulated, either with Fe(acac)$_3$ or various Ru and Ir catalysts, to form trichloromethyl radicals following a one-electron reduction by a photocatalyst. It then becomes tricky to rationalize why that can be achieved by the Al_2O_3-Ir alone in this case but not for the two ATRA reactions, described above, using $BrCCl_3$. Even when ATRA was attempted in DCE, i.e. identical conditions besides the reacting substrate, no reaction occurred why any solvent effects can be ruled out. Thus, the difference then has to, albeit uncertain exactly how, be attributed to the starting material. It is important to point out that the results cannot be sloppily accused of deriving from human mistake as the results are reproducible. Under no conditions did the ATRA work without an electron donor using Al_2O_3-Ir while that works perfectly fine with various homogeneous Fe, Ru and Ir catalysts. And furthermore, under no conditions does the oxidative fragmentation occur without addition of either Fe, Ru or Ir for which the only sensible mechanism proceeds via initial one electron reduction of $BrCCl_3$. Contradicting as it may, the experiments speak their crystal clear provocative language.

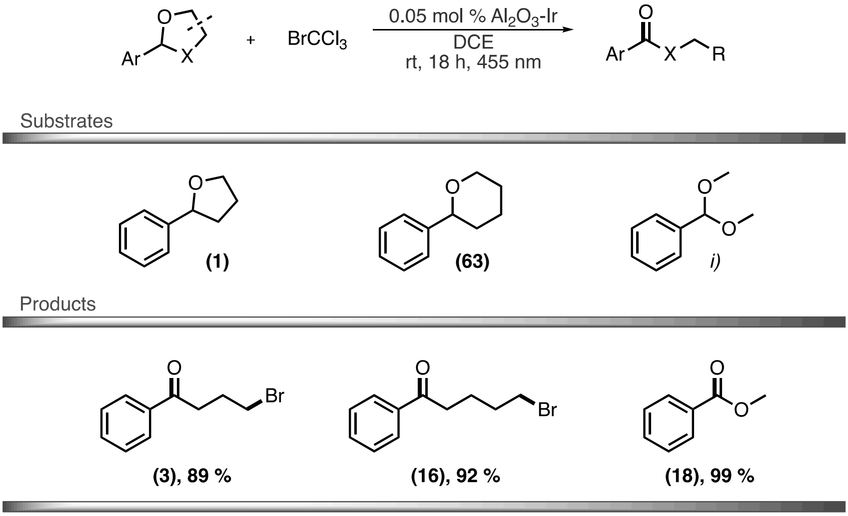


Figure 25. Oxidative fragmentation of ethers and acetals.

6.1.5 *E-Z* Isomerization

As a last example, the performance of the heterogenized construct was evaluated in a mechanism postulated to proceed via energy transfer. When cinnamaldehyde and its derivatives interact with the excited state of $Ir(ppy)_3$ the energy is absorbed by them and in doing so are promoted to the excited triplet state. In the triplet state the barrier for rotation about the sigma bond is lowered which enables a rotation before relaxation to form the opposite isomer. It so turns out, that the *Z*-isomer quenches the photocatalyst at a lower rate than does the *E*-isomer causing an accumulation of the *Z*-isomer[114]. As such, one will reach a state, depending on the specific substrate, where the rate of conversion of the two is the same in both directions causing an equilibrium to establish which puts an upper bound on the yield.

When irradiated for 48 h using 0.1 mol % Al_2O_3-Ir ethyl cinnamate (*i*) and cinnamaldehyde (*ii*) was isomerized to (**64**) in 56 % and (**65**) in 56 % yield respectively. With a hydroxyl group in the *o*-position the possibility of a lactonization opens up, which also would shift any equilibrium towards product which perhaps explain the excellent yield of 94 % for the coumarin (**66**).

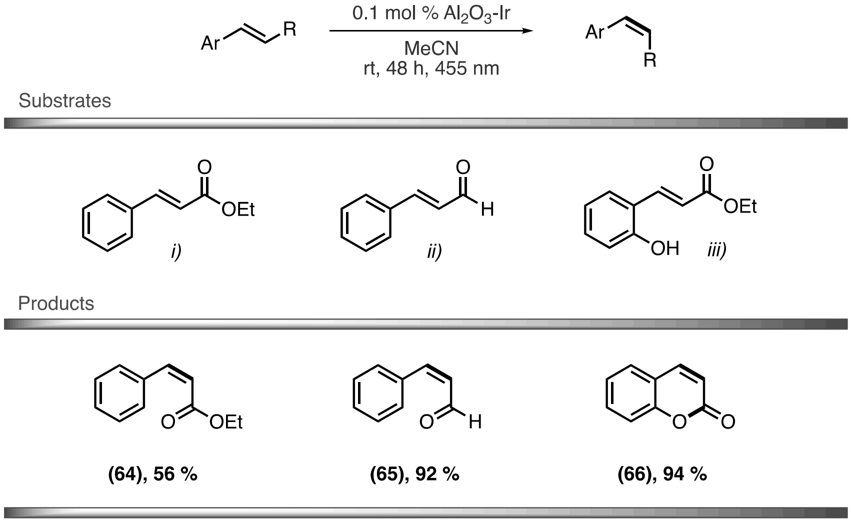


Figure 26. *E* to *Z* isomerization.

In summary, Al_2O_3-Ir could be engaged in all three common modes of quenching mechanisms. However, for many reactions, published and non-published, the homogeneous catalyst could not be simply substituted for the heterogenized catalyst. Seemingly anomalous results were sometimes obtained for which a rationalization is yet to be made. In other cases, differences in reaction outcome can be attributed by taking the reactivity of Al_2O_3 into account. Thus, Al_2O_3-Ir needs to be evaluated in its own right and not assumed to simply be a heterogeneous version with otherwise identical properties.

6.1.6 Reusability and Reaction Rates

An interesting aspect of the heterogenized catalyst is that it performs any reaction among the ones that has been investigated faster than the corresponding homogeneous Ir(dcabpy)(ppy)$_2^+$. The rate enhancement is not dramatic but significant still. However, one should be somewhat careful in interpreting the results in Paper III when comparing with the corresponding results in the literature. When compared, though, a seemingly astonished rate enhancement is observed which might to some extent be attributed to the design but before any such definite claims can be made it would be necessary to try the exact same amount of Al_2O_3-Ir as used in the literature procedures as well as conducting it in parallel in one's own hands, and multiple times to gather statistics, and with a sample of Al_2O_3-Ir with a confirmed homogeneity of distribution of Ir onto the Al_2O_3 support to ensure equality of loading. Because, of course, one cannot assume that the literature procedures necessitated either the reported catalyst loading or time to achieve full conversion.

In any case, the rate enhancement observed when compared to $Ir(dcabpy)(ppy)_2^+$ could be rationalized by the following contributing factors: 1) Al_2O_3 is often used as support material for the very reason of its ability to adsorb reactants[115], thus, increasing the local concentration 2) Al_2O_3 also has Lewis acidic sites which might assist reactions by e.g. altering the reduction potential of a substrate. The very same Lewis acidity, however, could also prevent other reactions 3) any self-quenching of photocatalysts is suppressed by the immobilization.

Lastly, the whole project relates to recycling so worth mentioning is the results of reusing the recovered catalyst. For dehalogenation of 2-bromoacetophenone the catalyst was reused five times dropping from 93 % to 62 % yield. For oxidative hydroxylation of 4-chloroboronic acid and isomerization of ethyl cinnamate the catalyst was reused three times with a drop in yield from 93 % to 50 % and 56 % to 25 % respectively. The greater drop in yield for the two latter reactions is partly due to longer reaction times which gradually deteriorate the catalyst. When the stability of Al_2O_3-Ir was investigated in various solvents under irradiation some desorption was observed in MeCN and DMF, the two solvents used in these reactions. Thus, the longer the reaction times the greater the desorption which leads to a less efficient recovered catalytic material. Nevertheless, reusage was possible in all cases. Although not investigated here, one should expect a greater reusability when applied to systems where the catalyst is more stable. The stability of heterogenized catalysts, which increases their relevancy, in certain systems can be improved upon in future work.

7 Conclusion and Outlook

The substitutability of Ru or Ir was addressed in Paper I and to some extent in Paper II. The two represent examples of chemical transformations that can be performed using conventional photocatalysts but were here demonstrated either with an Fe(III) catalyst (Paper I) or under photocatalyst-free conditions (Paper II).

In Paper I, a method for an easy manipulation of the ether functionality, in particular the THF-moiety, to yield distally brominated ketones was developed using a radical strategy by means of photoredox catalysis. This methodology outperformed previous similar transformations in terms of both yields and substrate scope. In addition, acetals turned out to be suitable starting materials for yielding esters. Unfortunately, the protocol was limited to substrates bearing an aromatic group in the alpha-position to the reacting center. Alkyl substrates could be converted but produced inevitable byproducts under the conditions employed.

The catalyst used for the transformation was $Fe(acac)_3$, a much simpler metal complex than the catalysts traditionally used in photoredox catalysis. Furthermore, although not investigated in any dept, Paper I disclosed that other comparatively simple metal salts also proved viable.

A most important aspect regarding $Fe(acac)_3$ concerns the low life-time, which is on the order of picoseconds. That questions the range traditionally conceived as necessary. It would be informative to conduct a study selecting a set of reactions and analyzing the rate of reaction as a function of life-time for a series of photocatalysts with appropriate reduction potentials. As discussed in both the theory and result sections, life-times of several orders of magnitudes produce only a small difference in reaction rate. Does a relationship between reaction rate and life-time exist? What is lower limit of life-times?

Since $Fe(acac)_3$ is a rather novel choice of photocatalyst the question arises whether this reaction constitutes an exception or if it is the initial discovery of something larger and more significant yet to be discovered. It is of great interest exploring what other substrates than $BrCCl_3$ can quench the excited state of $Fe(acac)_3$, e.g. other alkyl halides or aryl halides. Can reduction potentials alone predict if a SET will occur or not? Furthermore, it is admitted that in reality the mechanism is a bit of a black box, the details of the SET needs further investigation. Such detailed understanding in turn would contribute answering the question of generality concerning $Fe(acac)_3$ as a photocatalyst.

With that said, one is encouraged to dare to go beyond the conventional box of understanding in photoredox catalysis and try something truly novel. One never knows what one could discover.

In Paper II, the inconvenience of having to synthesize the acetals in Paper I was addressed by developing a one-pot procedure, i.e. a direct oxidative esterification of aldehydes. The scope of the reaction displayed similar trends as in Paper I. Furthermore, the employment of NBS as oxidant in place of $BrCCl_3$ removed the necessity of any photocatalyst and decreased the reaction time to only 10 s for the optimization substrate.

In addition to the highly efficient chemistry disclosed in Paper II, some interesting reactivity of NBS was found. NBS is known to release elemental bromine under various conditions; in Paper II it was shown that the combined condition of blue light and methanol effected a very rapid release of bromine which could be a useful general approach for e.g. bromination reactions in those cases a low concentration of bromine is not a requirement.

As for the recyclability of precious metal photocatalysts; Paper III demonstrated the possibility of increasing the recycling rate by means of heterogenization. Such a catalyst does not, however, have identical properties to the homogeneous congener. In fact, such a catalyst was proven to provide a greater reaction rate, although accompanied with a somewhat narrower reaction applicability.

The heterogenized construct could be reused with an efficiency correlating with the stability of the catalyst in the reaction environment. For relatively fast reactions, i.e. when the catalyst is exposed to the reaction environment for only a short period of time (here 2 h), the catalyst could be reused five times with a loss in yield of no more than ca. 30 %. The current instability, however, is an issue if a broad appreciation of the design is ever going to manifest in the chemistry community. Fortunately, there are multiple ways of designing heterogenized catalysts. Since desorption is the main cause of instability, the bond strength to the support material needs to be improved upon. That could be achieved by e.g. different linker identity, support material or by atomic layer deposition. Looking beyond the powder construct, further research into the film construct with particular attention to the incorporation into transparent tubes for flow chemistry setups constitutes an attractive future direction. Thus, heterogenization has proven to have potential, but it remains to discover an ‘optimal’ construct for a more general use.

Acknowledgement

I have noticed while reading through the acknowledgement section of many other doctoral theses that they tend to take the form a commentary list; a list of friends, and colleagues - which by the existence of the two distinct words are not the same thing - and then relatives get acknowledged too. Basically a list of everyone one happens to know. While my interpretation of this section is that no more than those people who I can argue in one way or another has provided an actual contribution to its finalization should get a special mentioning. Thus, if I know you, and you are not mentioned here, don't worry! You are not alone. It simply means I consider your contribution to this thesis to be insignificant to say the least. If even that. So consequently, "everyone at floor 8" - the standard last item on such a typical acquaintance list - has not earned an acknowledgment in a thesis that I wrote. Let's not be pretentious here, because, you know, that's one of those things I'm truly allergic to, alongside uninformed criticism, intentional misunderstandings and a whole bunch of other stuff, all too common stuff. In any case, I do acknowledge, of course, that it is not only about writing this thesis that this section is here for. No, rather, it should include all those contributions that has helped me finalize the entire PhD with all its ups and downs. And then it turns out to be trickier to define 'a contribution'. It becomes more personal. Does that, for instance, include people that has contributed turning a down to an up? So, perhaps then, in order not to forget even the slightest contribution, I might as well just write "everyone I know" as the last item too…

First of all, as is custom, I would like to direct my attention to my supervisor. Oh, Calle! Dear old Calle, Calle, Calle... When I first started my PhD in your group - and thanks for giving me that opportunity btw - I viewed your role in our relationship as some kind of father. Now I wonder if not I have become the father of our relationship? I bet you disagree, but let's leave it at that. There are two things that comes to my mind. First of all, I am very grateful, it has been encouraging indeed, that you have allowed me, with your non-dictatorial way of conduct, to try out my own ideas. Sometimes they got published, other times scooped. Whatever. Secondly, the biggest help has always been your fountain of ideas that, whenever I felt stuck in research, always gave me new directions to explore. What would I have done without your constantly squirting fountain? Many thanks.

I will try to make things shorter now, I realize I could go on forever with this…

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Lastly, a big thank to everyone I know. Including all students I've had in courses, the cashiers at ICA, the staff on the boat taking me to work oh sorry I mean taking me to my education as Calle is often eager to point out it really is, and my neighbors playing loud music when I'm trying to think as well as all the regular visitors in the gym. And perhaps my piano too, who offers me great company, perhaps the best (?)

Love you all, peace out.

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