Solvent-Free Visible-Light Photocatalysis and Synthesis in Deep-Eutectic Solvents

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Meiner Familie gewidmet

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1 Organic synthesis without conventional solvents

This chapter gives an overview about synthetic approaches that are performed in the absence of conventional solvents. This includes solvent-free methods in solids (mechanochemistry and solid-state photochemistry), and in liquids, as well as the application of unconventional solvents (ionic liquids and deep-eutectic solvents). The different approaches are briefly presented and examples illustrating their specific advantages are shown, followed by a critical discussion of their limitations. It is concluded that all methods bear the intrinsic advantages of solvent-free operation, such as the avoidance of solubility problems and side-reactions with the solvent. Additional advantages depend on the method, which should be selected according to a specific application in synthesis.

1.1 Introduction

The choice of a suitable solvent is an essential prerequisite for organic synthesis and industrial processes, as most of them occur in solution. The three main functions a solvent fulfils is to a) enable diffusion of reactants and catalysts, thereby achieving homogeneous conditions, b) receive, store and transfer thermal energy required for a chemical transformation, and c) stabilize transition states. The solvent controls the reactivity, thereby influencing the rate and outcome of a reaction.[1] Even though the use of a solvent is standard in synthetic organic chemistry, there have always been solvent-free approaches. Due to the toxicity, risks, possible harms on the environment, and low sustainability of most conventional solvents, the need to reduce their application or replace them by "green" alternatives became obvious in the last decades.[1–3] On the one hand, this lead to the development of a variety of new reaction media such as deep-eutectic solvents. On the other hand, there has been increasing research effort regarding solvent-free methodologies, such as mechanochemistry and solid-state photochemistry. Next to the "environmental" aspect, it became clear that the replacement of conventional solvents may be also quite promising from a synthetic point of view. For example, in mechanochemistry, high concentrations of reactants and catalysts are achieved, the atom economy is improved, and quantitative conversions can facilitate the work-up significantly.[4,5]

Herein, we give an overview about the different approaches that have been taken for organic synthesis without classical, e.g. conventional solvents. In this context, we define "conventional solvents" as uncharged compounds with a molecular weight below 150 g/mol, a boiling point below 200 °C, and a viscosity below 5 mPa s, which do not form covalent bonds with the reactants. We do not aim to be comprehensive in our survey, but we show the main directions, which have been explored, discuss them critically in a larger context and elucidate their advantages and challenges. Namely, we focus on solvent-free reactions in the solid state, which are driven by mechanical energy (mechanochemistry) and light energy (solid-state photochemistry and photocatalysis). Furthermore, we discuss solvent-free reactions in liquid mixtures, driven by thermal and light energy. As a third area, we explain reactions in unusual, non-conventional solvents, namely deep-eutectic solvents and ionic liquids.

It must be noted that the definition of a “solvent-free” reaction is not trivial. Whereas mechanochemical reactions, occurring in the solid state, are generally accepted as solvent-free, this is not the case for reactions containing a liquid reactant since this may also act as solvent, especially when it is present in large excess with respect to another solid component. The terms “solvent-free”, “solid-state”, and “mechanochemical” are often used as synonyms, leading to confusion. Even the application of ionic liquids or deep-eutectic solvents is sometimes called “solvent-free”.[6] To clarify, in this overview, we do not focus only on approaches that are entirely solvent-free, but also include new, “unconventional” reaction media.

1.2 Solid-state reactions

1.2.1 Mechanochemistry

Among all the fields of solvent-free approaches discussed in this review, mechanochemistry is certainly the oldest. Since ancient times, chemical transformations of solid compounds have been performed, usually in a pestle and mortar. Systematic studies started in the 19th century by M. Carey Lea, who decomposed silver- and mercury halogenides to the elements by the application of mechanical forces. The term “mechanochemistry” was first introduced in 1919 by Wilhelm Ostwald, one of the pioneers of physical chemistry.[7] Since then, mechanochemistry became a well-established methodology for the conversion of solid reactants. In the last decade, research effort in this field has strongly increased, corresponding to a variety of reports for all types of conversions in synthetic organic chemistry.[3,4; 8–11]

1.2.1.1 Definition and mechanism

The term “mechanochemistry” denotes a chemical reaction of solid reactants, which is induced by mechanical energy. Usually, this is realized by milling the reaction mixture in a vibrational or planetary ball mill. Since the processes caused by the input of mechanical energy are rather complex, the mechanisms involved in a mechanochemical reaction are not fully understood. A variety of models has been proposed, most importantly the “Magma-Plasma model” and the “Hot-spot model”,

both models stating the occurrence of high local temperatures. According to the "Magma-Plasma-Model", deformation leads to energy accumulation in a limited region, which causes the formation of a high-energetic plasma with temperatures higher than 10^4 °C. Therein, electronically excited states and the release of free electrons lead to a chemical reaction.[3] The "Hot-spot model" states that the friction between to surfaces is responsible for high temperatures. However, mechanochemical processes are not explained by these models alone; possibly, dissipation of the local thermal energy over a larger area occurs. Furthermore, the strong influence of temperature on many mechanochemical reactions questions both models. A general problem in understanding these processes is caused by the fact that organic and inorganic materials behave rather different under the input of mechanical energy, also depending on their mechanical properties, like crystallinity, brittleness, and flexibility. Furthermore, traces of liquids, which are present in the reactants or are released during the reaction can have a significant impact. For mechanochemical reactions in co-crystals, other models have been developed. Therein, the increase in reactivity by mechanical energy is assigned to the formation of liquid eutectic states and amorphous phases, which are caused by a decrease of particle size, the formation of defects, heating, and mixing. In this context, liquid eutectic states also exist in most mechanochemical covalent bond formation reactions, but not exclusively; several reactions are reported to occur in entirely solid phases. To conclude, in a simplified understanding, the milling effects the reaction both directly, that is *mechanically* (amorphization) and indirectly, that is *thermic* (heating caused by friction).[3,4]

To influence the reactivity and increase the rate of a mechanochemical reaction, small amounts of an additive can be used. This can be a liquid ("Liquid-assisted grinding", LAG) or a solid. In LAG, organic solvents can be used, such as acetonitrile, methanol, or toluene. The effects in LAG are still unclear, however it is proposed that the reactants are partially dissolved and their mobility is increased. Solid additives, such as inorganic salts, mostly work as inert milling aids, preventing an agglomeration of solid particles and making the reaction mixture more powder-like. They can also influence the reaction in a chemical way, working as an acid or base catalyst.[12]

1.2.1.2. Apparatus

The pestle and mortar are amongst the oldest tools used by humans and the first mechanochemical reactions were performed therein. However, this setup has several drawbacks, making it rather impractical for scientific research. For example, the reaction strongly depends on the milling frequency (which depends on the operator) and the shape and surface of both pestle and mortar, resulting in bad reproducibility.[4] Nowadays, mechanochemistry uses ball mills, usually the vibrational ball mill or the planetary ball mill. The milling jar contains several milling balls, which, upon rapid movement of the milling jar, grind the solid reaction mixture. Figure 1 shows a schematic representation of both ball mill types.

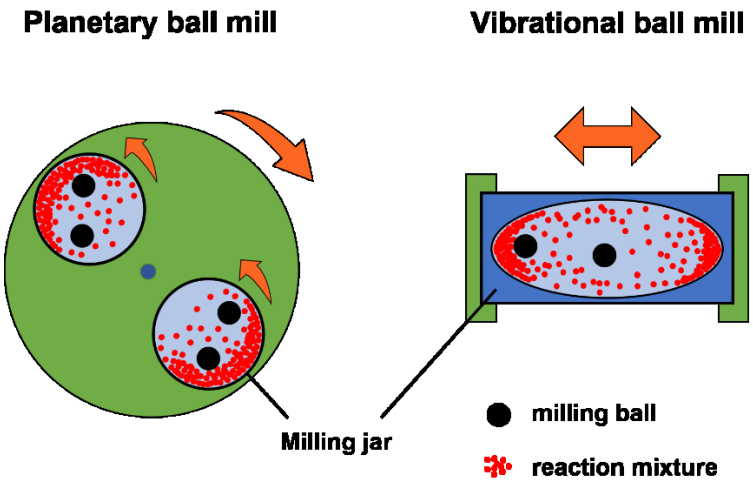


Figure 1. Schematic representation of planetary ball mill and vibrational ball mill (for simplification, only two milling balls are shown).

In a planetary ball mill, the milling jar (installed on a rotating disk) rotates around its own axis and contrariwise around a central axis, similar to the movement of the planets around the sun. The milling is induced by the centrifugal force of the milling balls. Typically, a planetary ball mill contains two or four milling jars. Depending on the amount of milling balls and reaction mixture as well as the rotation speed, the balls show different behavior upon milling, namely cascading, cataracting, and rolling. In the vibrational ball mill, the milling jar is shaken around its idle position. Both setups allow an exact adjustment of the milling parameters, like the size and number of milling balls (at a constant amount of reaction mixture), the milling frequency (in the range of 5 Hz to 60 Hz), and the milling time. For example,

increasing the frequency of disk rotation in planetary ball mills can lead to higher conversion due to improved mixing and more collisions of the milling balls.[4,13]

Whereas vibrational ball mills are suitable for small-scale synthesis, typically 50 mg to 5 g, planetary ball mills are used for the conversion of larger amounts of reaction mixture in the kilogram scale.[4]

The milling jars and balls should be hard and inert (minimizing abrasion during the milling process) and consist of materials like aluminium, polymers (polycarbonate, for example), zirconia, teflon, and tungsten carbide. Even though steel is very common as well, it bears the risk of contaminating the reaction mixture with metals, complicating the isolation of the product. The extent of abrasion depends on the hardness of the milling balls, milling frequency, and milling time, which is why the milling time must be limited to keep abrasion as small as possible.

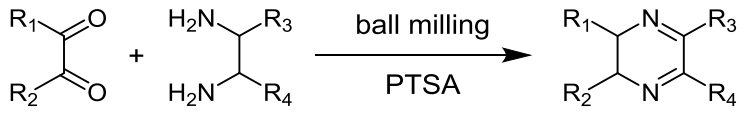
However, there are also approaches, which make use of abrasion, for example the synthesis of iron silicates by milling quartz powder with steel balls.[4,9,13] It was also shown that milling balls made from copper can act as catalyst, namely in the coupling of tetrahydroisoquinolines with nitroalkanes or the azide-alkyne-cycloaddition; in the latter case, also the copper milling jar was catalytically active.[14,15]

1.2.1.3 Mechanochemistry in organic synthesis

Due to the variety of reports on mechanochemical organic syntheses, it is impossible to discuss all approaches comprehensively. Useful summaries can be found in recent reviews.[3,4; 8-11] There are numerous reports on mechanochemical syntheses (stoichiometric and catalytic), which work already efficiently in solution and where mechanochemistry does not introduce a significant “synthetic” benefit, apart from avoiding the solvent. Therefore, without the intention to limit the value of these works, we restrict our discussion to a few reports, which illustrate the specific advantages and limitations of mechanochemistry.

A general advantage of mechanochemistry is an increase of reactivity of the reactants. It was found that many reactions occur much faster as in solution, they can be performed under milder conditions, and the product is isolated in higher yields, compared to the corresponding reaction in solution. For example,

heteroacenes were synthesized by cyclocondensation of diaminoarenes and dicarbonyl compounds with *para*-toluenesulfonic acid (PTSA) as a catalyst in a ball mill (Scheme 1). The reactions were over in 4 h, yielding the products in very good to excellent yield (76–95%). In pyridine, the reactions required harsh conditions (120 °C or reflux) for 3 days and the products were isolated in 32–40% yield only.[16]

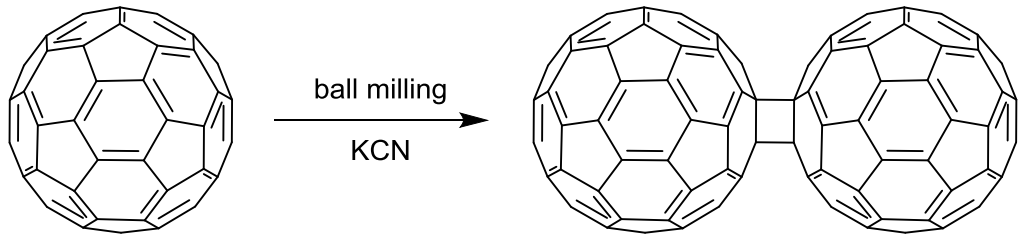


Scheme 1. Mechanochemical synthesis of heteroacenes.[16]

Similar process improvements under mechanochemical conditions were achieved for a variety of reactions, for example the amidation of aldehydes,[17] the fluorination of 1,3-diketones,[18] the Michael addition,[19,20] the Knoevenagel condensation,[21] and the Morita-Baylis-Hillman reaction.[22]

Furthermore, the handling of air- and moisture sensitive reactions can be facilitated, which was especially shown for Palladium-catalyzed C-C-couplings, such as the Heck, Suzuki, and Sonogashira coupling. Whereas conventional methods require drying of the solvent and an inert atmosphere, ball milling allows the reaction to be performed in an aerobic environment.[23–25]

Mechanochemistry can also enable reactions, which do not proceed in solution or give the product in very low yield. An example is the dimerization of fullerene (C_{60}) by milling with 20 eq. KCN (Scheme 2).

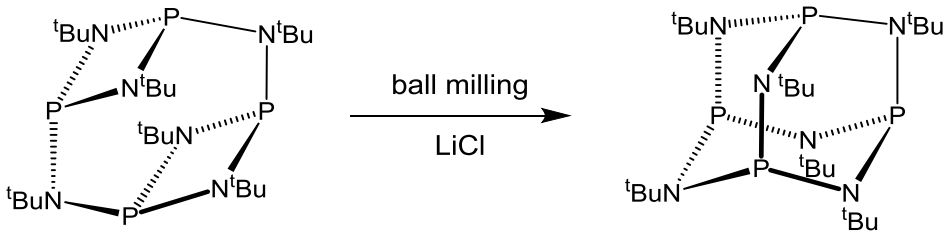


Scheme 2. Mechanochemical dimerization of fullerene.[26]

The milling was performed under nitrogen and the product was formed in 18% yield. In toluene/DMF, no dimerization, but cyanation occurred; this behaviour is attributed to a difference in nucleophilicity of the cyanide anion in the solid state and in solution. It is proposed that the cyanide first adds to the fullerene, resulting in a negative

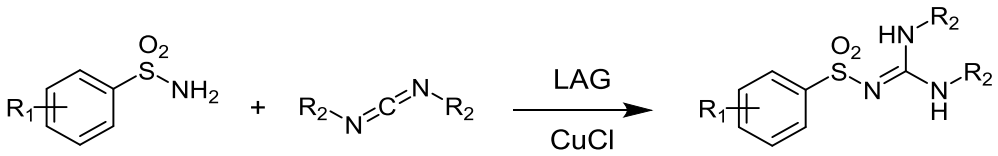
charge, which attacks a second fullerene and forms a bond between the two fullerenes. Subsequent ring closure gives the product, cleaving off the cyanide.[26]

Another example for a reaction enabled by mechanochemistry is the synthesis of an adamantoid cyclophosphazene. All attempts to prepare this compound in solution failed; a variety of solvents was tested at high temperature. However, milling the starting material in the presence of LiCl (20%) for 90 min resulted in the formation of the product in 53% isolated yield (Scheme 3). Furthermore, the synthesis of the isopropyl analogue could also be performed under the same conditions; in solution, high temperatures and long reaction times are necessary. In both cases, the milling jar had to be dried before the reaction and loaded in a glove box under inert atmosphere.[27]



Scheme 3. Mechanochemical synthesis of adamantoid cyclophosphazene.[27]

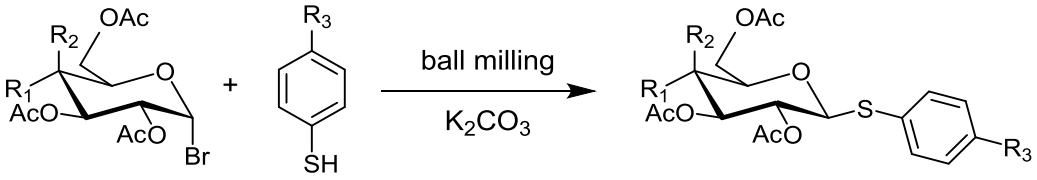
The coupling of arylsulfonamides with carbodiimides, which does not work in solution or gives only very low conversion due to the low nucleophilicity of the sulfonamide, is also enabled by mechanochemistry. Liquid-assisted grinding (nitromethane) with CuCl as a catalyst yielded a broad scope of products (Scheme 4).[28]



Scheme 4. Mechanochemical reaction of arylsulfonamides with carbodiimides.[28]

An intrinsic advantage of mechanochemistry is the avoidance of solubility problems. In solution, the different polarity of the reactants or the catalyst often impedes the application of a common solvent or requires toxic polar-aprotic solvents, which is a challenge for saccharides and other polar natural products. For example, the reaction of acylated glycosides with thiophenols to yield thioglycosides in an organic solvent requires the presence of a phase transfer catalyst. This is avoided by

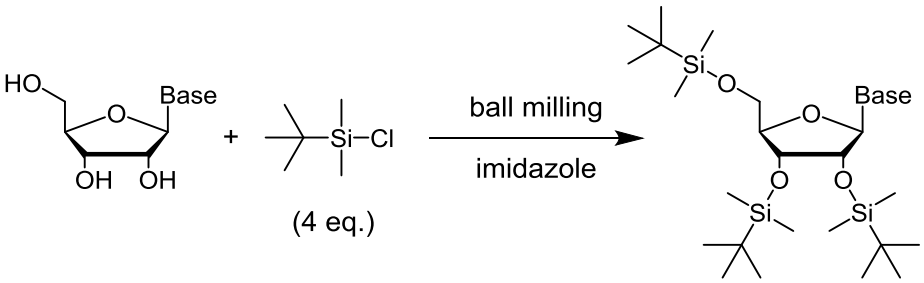
performing the reaction in a ball mill and the products are formed in excellent yield in 30 min, applying K_2CO_3 (Scheme 5).[29]



$R_{1,2}$ = OAc, H; R_3 = H, CH_3, NO_2

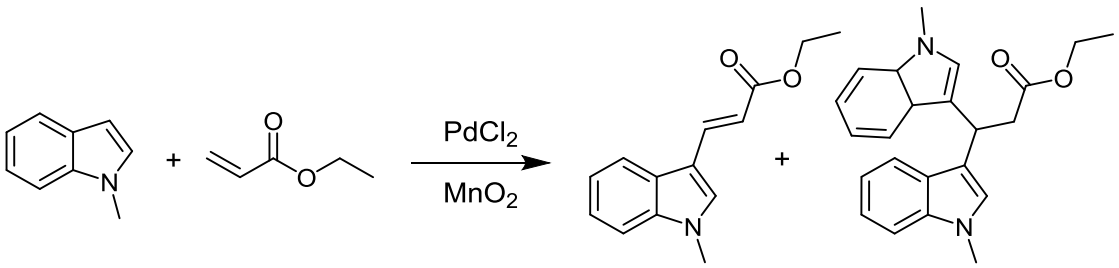
Scheme 5. Mechanochemical synthesis of thioglycosides.[29]

Another example is the persilylation of nucleosides, which is usually performed in DMF or pyridine. This reaction can be performed by milling as well, avoiding the application of these toxic solvents. Milling of a mixture of the nucleoside, *tert*-butyldimethylsilyl chloride (4 eq.), and imidazole (8 eq.) for 1–3 h resulted in the products in quantitative yields (Scheme 6). Remarkably, inosine (a nucleoside with uracil as a base), which shows poor solubility in DMF, also reacted under these conditions.[30]



Scheme 6. Mechanochemical persilylation of nucleosides (Base = cytosine, guanine, uracil, adenine, hypoxanthine).[30]

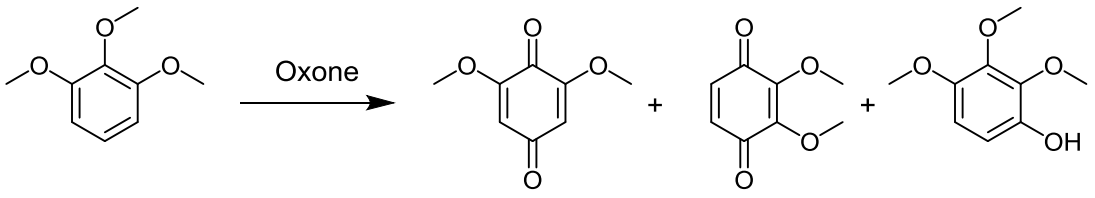
Mechanochemistry allows product formation with different selectivity patterns compared to the corresponding reaction in solution.[10] For example, the coupling of 1-methylindole with ethyl acrylate was performed in a ball mill with $PdCl_2$ as catalyst and MnO_2 as oxidizing agent. Silica gel and acetic acid were applied as milling additives and the product consisting of two 1-methylindoles attached to one ethyl acrylate was formed predominantly. When the reaction was performed in DMF, the 3-vinylindole was obtained exclusively, inverting the selectivity (Scheme 7). This difference was explained by the existence of dimeric palladium species, which are labile in the presence of a solvent. Besides, the product yield was 87% by milling (30 Hz, 20 min) and only 42% in solution (100 °C, overnight).[31]



solution (DMF)	100%	0%
ball milling	10%	90%

Scheme 7. Coupling of 1-methylindole with ethyl acrylate by ball milling and in solution.[31]

Another example is the oxidation of 1,2,3-trimethoxybenzene with potassium peroxymonosulfate (Oxone). In solution (90% water and 10% of a co-solvent), a mixture of three products was obtained, their amount depending on the equivalents of Oxone (2-4) and the co-solvent (acetonitrile, methanol, or acetone). In contrast, oxidation of the substrate by ball milling (applying a rock tumbler) resulted in the exclusive formation of 2,6-dimethoxybenzoquinone, which was isolated in 81% yield (Scheme 8). This procedure also circumvents the problem caused by the low solubility of the inorganic salt (Oxone) in organic solvents, which necessitated the application of a water-organic solvent mixture. However, the milling time was quite long (7d) and the application of a commercial ball mill or a pestle and mortar resulted in low isolated yields (about 20%), which was explained by evaporation of the substrate and the product, caused by the heat within the milling jar.[32]

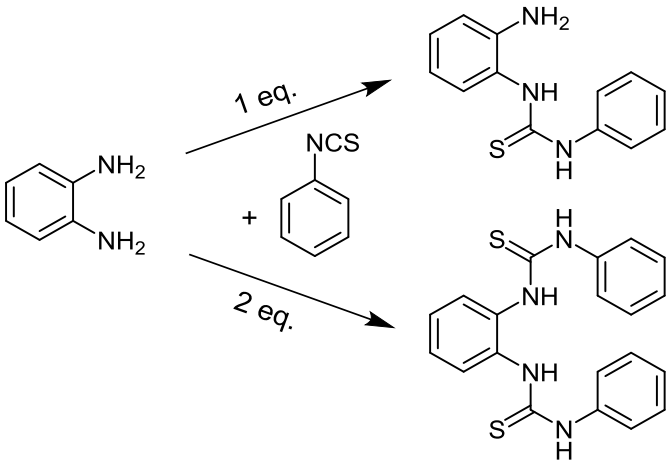


solution (H_2O/co-solvent)	3-9%	2-6%	24-49%
ball milling	100%	0%	0%

Scheme 8. Oxidation of 1,2,3-trimethoxybenzene with Oxone by ball milling and in solution; numbers indicate conversion.[32]

The quantitative reaction of two molecules under milling conditions enables a stoichiometric control of many reactions, which is often not achieved in solution and avoids the application of a reactant in excess. For example, milling of *ortho*-

phenylenediamine with one equivalent of phenylisothiocyanate resulted in the formation of the mono-thiourea, whereas the application of two equivalents gave the bis-thiourea (Scheme 9). Both products where isolated in more than 95% yield. In solution, a mixture was obtained, containing the unreacted diamine, mono-thiourea, and bis-thiourea. A broad scope of thiourea derivatives was prepared and isocyanates were also reacted, resulting in urea derivatives. This methodology allows the synthesis of both symmetrical and non-symmetrical aromatic urea and thiourea derivatives.[33,34]



Scheme 9. Mechanochemical synthesis of thiourea derivatives.[33,34]

One of the newest discoveries of mechanochemistry are reactions that are catalyzed by enzymes. Due to the pressure and high local temperatures in a ball mill, which may lead to denaturation, it seems impossible that an enzymatic reaction could occur under these conditions. In fact, it was shown that lipase B from the yeast *Candida Antarctica* is inactivated by milling. However, when a mixture of racemic 1-phenylethanol and isopropenyl acetate was milled in the presence of the immobilized enzyme, the (R)-acetate was formed in 47% conversion with an ee of more than 99%, the enzyme distinguishing between the (R)- and the (S)-1-phenylethanol and leaving the (S)-enantiomer unreacted. The enzyme could be recycled, but the conversion of the racemic 1-phenylethanol decreased by 20% in four cycles.[35] The concept of mechanochemical enzyme catalysis was also applied in the formation of amide bonds catalysed by papain.[36]

1.2.1.4 Conclusion

To conclude, mechanochemistry is nowadays a very useful tool in organic synthesis, being superior to conventional synthesis in solution in several aspects. In many cases, faster reactions and higher product yields are achieved and the reactions are performed at mild reaction conditions, often avoiding strong acids and bases. Control of the stoichiometry can avoid an excess of one reactant (which is often necessary in solution), improving the process regarding efficiency and atom-economy and reducing waste. Solubility problems, caused by the different polarity of the reactants and resulting in insolubility of one reactant in a solvent, do not play a role in mechanochemistry, as shown in the synthesis of thioglycosides. Furthermore, mechanochemistry can offer new synthetic pathways (enabling reactions impossible in solution) and give another selectivity compared to procedures in solution.

However, mechanochemistry also bears various intrinsic limitations. Above all, up-scale in the milling apparatus is a problem, the amount of reactants being limited to several hundred grams in planetary ball mills. Although continuous ball mills are used in industry for the crushing of materials, e.g. in mining or recycling, their application in mechanochemistry was not demonstrated yet. These mills are usually operated by rotation of the milling jar and the high-frequent vibration or planet-like movement is hard to realize in a continuous mode. Furthermore, in ball mills, temperature control is difficult, which may cause problems, especially for compounds which are thermally labile or volatile. Due to the complex processes occurring under mechanochemical conditions, a cooling or heating jacket around the milling jar cannot ensure a defined temperature in the entire reaction mixture. To overcome these limitations of mechanochemistry in ball mills, Twin Screw Extrusion (TSE), which is frequently used in industry, was recently examined as a technique to convert solid reaction mixtures. It allows both an up-scale (working in flow) and temperature control. Recently, the Knoevenagel condensation between several aldehydes and barbituric acid or malononitrile as well as the Michael addition and the Aldol condensation were successfully performed by TSE.[37] However, temperatures higher than the melting point of at least one reactant were necessary (except for the Aldol condensation) and the reactions are proceeding in a melt. Certainly, the grinding in TSE transfers mechanical energy to the reaction

mixture and leads to proper mixing. However, this is not the primary cause for the reaction in this case. Therefore, regarding organic synthesis, we believe that there is not enough evidence to call TSE a technique for mechanochemistry so far. Though, investigations in the future may justify such an assignment. In this review, we will focus on TSE in more detail later, when we discuss solvent-free reactions occurring in the liquid state.

Moreover, in mechanochemistry, the transformation of air-, or moisture sensitive compounds can be problematic and requires loading of the milling jar in a glove box. Furthermore, monitoring of the reaction course in the milling jar is challenging and was limited to periodic interruption of the milling, followed by sampling and analysis. As this procedure may influence the reaction, is too slow and often unreliable, and hinders an appropriate understanding of the mechanisms responsible for the reaction, new techniques for online-analytics were recently established, such as powder x-ray diffraction (PXRD). Therein, the milling jar oscillates perpendicular to an X-ray beam, which interacts with the sample and is detected outside the milling jar, the diffraction pattern enabling an in-situ monitoring of the reaction. Though, this technique is not applicable for amorphous solids; Raman spectroscopy turned out to be a useful tool to follow organic reactions in the amorphous state and to understand the mechanisms involved.[38] However, compared to the analysis of solutions, both techniques are more complicated, requiring appropriate instruments (e.g., for PXRD, a synchrotron source is necessary), which are usually not available in a synthetic laboratory.

It is often argued that the absence of a solvent during the reaction makes the process more environmentally friendly. This is true, namely for reactions which occur in the absence of a catalyst, show a 1:1 stoichiometry, and yield the product in quantitative conversion. However, many procedures require purification of the product by column chromatography (in case of incomplete conversion) or removal of a metal catalyst by washing, both methods consuming large amounts of solvent, decreasing the benefit, which was achieved by performing the reaction without a solvent.[12] Furthermore, the argumentation regarding the environmental impact often forgets that the solvent is recycled in many industrial processes. To compare different methodologies regarding their environmental impact, the so-called “E-factor” was defined, which takes into account the waste generated in a reaction. It is calculated by subtracting the mass of product from the mass of reactants and

dividing this difference by the mass of product.[39] Therefore, the higher the E-factor, the more waste is produced. Obviously, the E-factor is low for reactions, which proceed quantitatively and avoid excesses of one reactant, which is often the case in mechanochemistry. However, when comparing mechanochemistry with solution chemistry, the difference of the E-factor for both methods is only large if the solvent and reactants are not recycled in the latter case. Recycling of solvent and reactants in a solution reaction minimizes this difference of the E-Factor, not considering the energy required for the recycling. On the other hand, energetic studies on organic syntheses, such as the Knoevenagel condensation, oxidation with $KMnO_4$, or the Suzuki-Miyaura coupling revealed that the energy consumption by ball milling (required energy per mole of product) is lower than in microwave irradiation or classical heating, making these mechanochemical reactions more environmentally friendly from an energetic point of view.[4] However, these studies were performed for only a few reactions. In short, the discussion whether one process is more environmentally friendly than another is quite complicated and must consider many factors carefully.

1.2.2 Photochemistry

The term “solid-state photochemistry” describes the chemical transformation of crystalline compounds which is driven by light energy. The required energy is directly absorbed by the compound, usually in the UV region of the electromagnetic spectrum. Therefore, no photocatalyst or sensitizer is necessary. Due to the structural information of the crystal, the reaction strongly depends on the substitution pattern, isomer, and polarity of the starting material; this is called the “topochemical principle”.[40] Light-driven syntheses in the solid state make use of several types of photoreactions, including cycloaddition, cyclization, rearrangement, isomerization, and decarbonylation reactions.[41]

1.2.2.1 Setup and mechanism

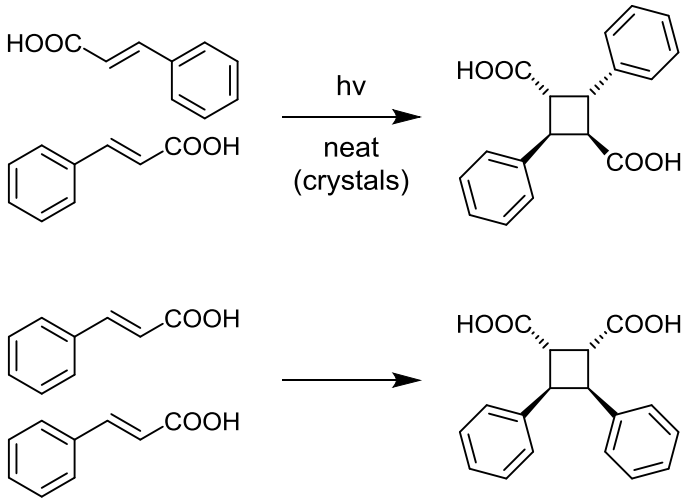
In principle, solid-state photoreactions can be performed by exposing the crystals to sunlight upon continuous turning and the first photoreactions were performed in this way. Furthermore, suspensions of the crystals in water were formed and irradiated.

It is also possible to simply spread the crystals on a glass plate. More advanced methods transform the starting material into a thin film. Irradiation is performed with a xenon or mercury lamp, for example. To irradiate the film with a defined wavelength region of the light spectrum, filters are used.[42–46] The most common photoreactions in the solid state are dimerization reactions, especially [2+2] cycloadditions, such as the dimerization of cinnamic acid. The course of these photoreactions strongly depends on the spectrum of irradiation: when a broadband light source (covering the absorption maximum of the substrate) is used, the photoreaction occurs heterogeneously, starting from the surface of the crystal. As the dimerization product shows only low absorption, light can pass the product layer and initiate reactions in the inner crystal, which was not reached by light before due to the absorbance by surface molecules. Obviously, this “nucleation and growth” process strongly depends on the shape and size of the crystal. Atomic force microscopy was applied to follow the changes on the crystal surface of trans-cinnamic acid upon irradiation and revealed that clods and craters are formed, which is due to phase separation of unreacted and reacted molecules.[42,47] In contrast, irradiation with light outside the absorption maximum (“absorption-tail” irradiation) leads to a homogeneous photoreaction since the light is absorbed to low extend only, resulting in comparable light intensity in the whole crystal. Therefore, during the photoreaction, the product molecules are distributed statistically within the crystal.[42,48,49]

According to the „topochemical rule“, the regio- and stereochemistry of the [2+2] cycloaddition product is determined by the contact geometry of two neighbouring molecules and the reaction occurs only if the distance of two parallel double bonds is in the order of 4 Å to allow overlap of the p_z orbitals. For example, while α-and β-trans-cinnamic acid dimerize under irradiation, γ-trans-cinnamic acid is stable because the double bonds lie too far from each other in this crystal modification.[50-52] A fundamental of this rule is that the molecules show no or very small movement. However, several exceptions are reported; some crystals, for example anthracene, show photodimerization even though the distance of the molecules is larger than 4 Å. This indicates that anisotropic material transfer occurs, caused by crystal disintegration during the reaction.[47,53,54]

1.2.2.2 Photochemistry in organic synthesis

Since the beginning of the 20th century, it is known that crystals of α-trans-cinnamic acid undergo a [2+2] cycloaddition when irradiated with sunlight, resulting in α-truxillic acid. The metastabile modification β-trans-cinnamic acid dimerizes to β-truxinic acid instead (Scheme 10). In the α form, the molecules show head-to-tail orientation, whereas they lay parallel (head-to-head) in the β form. Therefore, the crystal modification controls the regioselectivity of the product. In solution, no dimerization, but isomerization occurs.[44,45,48,51] In this solid-state reaction, temperature control is crucial since a thermal transformation from β-trans-cinnamic acid to α-trans-cinnamic acid occurs at higher temperature, resulting in a mixture of α-truxillic acid and β-truxinic acid.[45] This can be achieved using a dichroic filter, which prevents infrared light from reaching the crystals.[48] Furthermore, high purity of the crystalline starting material must be ensured.

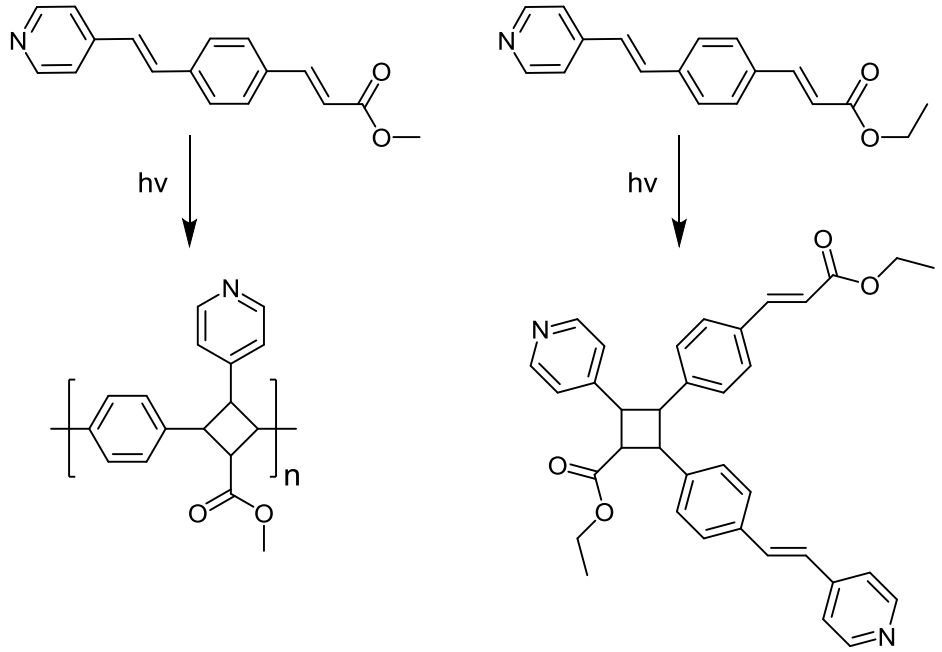


Scheme 10. Solid-state photodimerization of α-, β-trans-cinnamic acid, resulting in α-truxillic acid (top) and β-truxinic acid (below).

Until now, solid-state light-induced cycloadditions were reported for a variety of substances, including cinnamic acid derivatives,[43,45] stilbenes,[40] *para*-quinones,[55] anthracenes, acenaphthylene,[50] coumarins,[51] and thiocoumarin.[56]

The fact that the outcome of photodimerizations is determined by the relative geometry and orientation of the molecules within the crystal, which is controlled by electronic and steric effects as well as hydrogen bonds and π-π stacking, is used for crystal engineering and chemo- as well as enantioselective synthesis.[50,52,57,58] Therein, the key is to obtain a well-defined crystal structure of the starting material

by making use of all non-covalent interactions between the molecules to allow one defined photoreaction, leading to the desired product. For example, increasing polarity in heterostilbenes favours head-to-tail orientation, leading to photodimerization. In some derivatives, the ratio of head-to-head and head-to-tail dimerization product is determined by the presence of electron withdrawing substituents, which lower the overall polarity.[40] Similarly, chlorine substitution of the aromatic moiety of cinnamic acids and coumarins leads to head-to-head orientation.[51] Minor changes in the molecular structure can have a significant influence on the photoreactivity, which is not observed in solution: upon irradiation of a methyl cinnamate ester, polymerization occurs, whereas a dimer is formed from the ethyl ester (Scheme 11).[43]

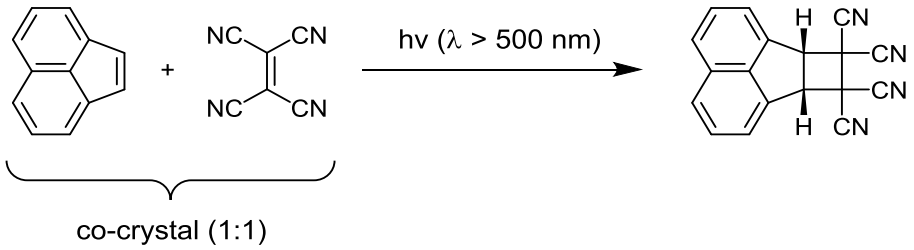


Scheme 11. Solid-state photopolymerization and photodimerization of methyl and ethyl pyridyl ethenyl cinnamate esters.[43]

Furthermore, it was found that *para*-methylcinnamic acid photodimerizes, whereas ortho-methylcinnamic acid is stable under irradiation. Crystal engineering also includes the application of template molecules, which form co-crystals with the starting material, such as resorcinol.[58]

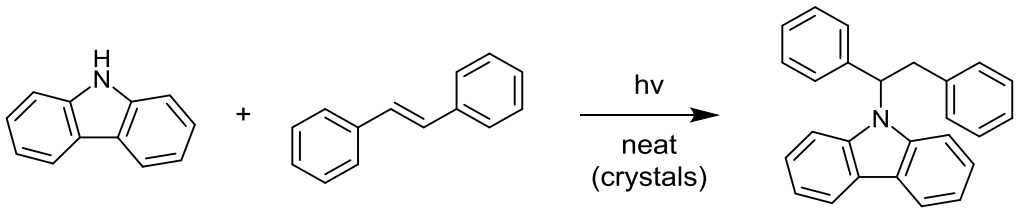
The fact that solid-state [2+2] cycloadditions can also occur between two different molecules opens the way to organic synthesis. First, a co-crystal out of the two reactants is formed, containing the reactants in the stoichiometric amounts required for the reaction. On the one hand, this can be achieved by mixing two solutions

(each containing one of the reactants), followed by slow evaporation of the solvent, leading to crystallization. Alternatively, a stoichiometric mixture of both reactants is molten and subsequent solidifying leads to the co-crystal. The co-crystal is than irradiated, leading to the product.[59] For example, by irradiation of a (1:1) co-crystal consisting of acenaphthylene and tetracyanoethylene, the [2+2] cycloaddition product was formed (Scheme 12). Interestingly, the product was not formed when a solution containing the two reactants was irradiated. When a (1:1) mixture of the reactants was ground and the resulting powder was irradiated, about 10% of homo-coupling product of acenaphthylene was observed next to the product shown in Scheme 12, showing a clear advantage of photochemistry in the crystal over amorphous reaction mixtures.[60]



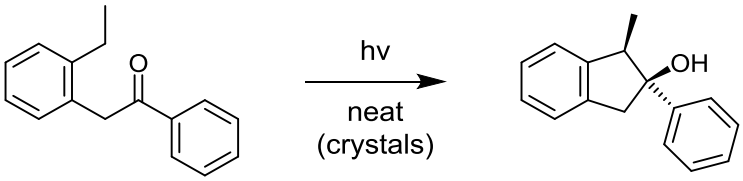
Scheme 12. Solid-state cycloaddition of acenaphthylene and tetracyanoethylene in a (1:1) co-crystal.[60]

Next to cycloadditions, a variety of other reaction types can be used for synthesis in the solid state: by irradiation of a (1:1) co-crystal formed by carbazole and trans-stilbene, photoaddition occurs (Scheme 13).[61]



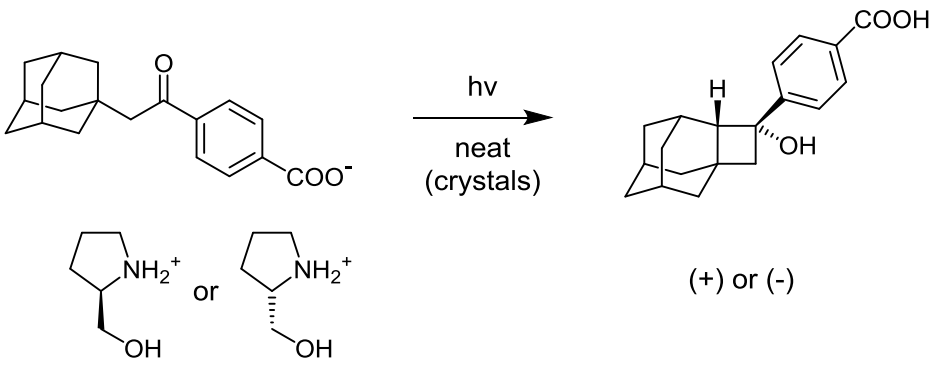
Scheme 13. Photoaddition of carbazole and trans-stilbene.[61]

Further reactions occurring in the solid state are isomerization, rearrangement, decarbonylation, and cyclization reactions.[41] For example, irradiation of crystals of acetophenone derivatives leads to cyclization, resulting selectively in the cis-product (Scheme 14). In solution, the trans-product is partially formed in varying amounts, depending on the solvent, proving the better selectivity of the solid-state photo-chemistry in this case.[62]



Scheme 14. Solid-state photocyclization.[62]

There are various methods for chiral light-driven synthesis in the solid state, including the application of chiral host molecules, forming an inclusion crystal with the achiral substrate, or the transformation of achiral substrates in their chiral crystals. In the latter case, the molecules in the crystal are arranged in a chiral space group, resulting in a chiral photoaddition product, as observed for cinnamic acid esters and phenylenediacrylate derivatives.[41] The transformation of a non-chiral substrate into a chiral crystal can be achieved by the presence of a chiral auxiliary. For example, chiral prolinols form a salt with carboxylic acids and irradiation leads to the formation of a cyclobutanol derivative, the stereochemistry of the product being determined by the prolinol (Scheme 15).[63]



Scheme 15. Photocyclization of carboxylic acid derivatives.[63]

1.2.2.3 Conclusion

Next to the general advantages of solvent-free operation (like the absence of toxic solvents), solid-state photochemistry is a unique possibility to synthesize tailored crystal structures, making use of the “topochemical rule”.[50] In the crystal reaction, the formation of byproducts is excluded and one product with defined stereo- and regiochemistry can be obtained. The fact that some achiral molecules form chiral crystal structures enables their transformation to chiral products. Several examples show the superiority of solid-state photoreactions over the same reactions in

solution, which often result in the formation of a variety of stereoisomers.[41] However, the strength of this methodology also defines its limitations: crystalline samples with high purity are necessary, which may be laborious or difficult to obtain; when two molecules are supposed to react, a co-crystal must be formed beforehand, increasing the workload. Molecules, which do not form crystals, cannot be reacted by this methodology. Even though various photochemical solid-state syntheses are reported, the overall number of accessible pathways and products is rather low compared to mechanochemistry or conventional solution chemistry. Moreover, the temperature during irradiation must be controlled very carefully to prevent thermal transitions of one crystal structure to another. Above all, the prediction of the outcome of the photoreactions can be challenging and requires accurate and comprehensive analysis of the crystal structure of the starting materials by X-ray diffraction. Another challenge is that the mechanisms involved in the topochemical photoreactions are not yet fully understood since several exceptions from the topochemical rule exist, which is due to material transport occurring in the crystal, impeding a precise prediction as well.[47,54]

1.2.3 Photocatalysis

The transformation of light energy into chemical energy, applying a photocatalyst, is nowadays a well-established methodology in synthesis. This is mainly due to mild reaction conditions (most reactions are performed at room temperature), high selectivity and high functional group tolerance. Upon irradiation with visible light, the photocatalyst is excited and subsequent electron transfer leads to a chemical transformation.[64-67] In contrast to photochemistry, the application of visible-light absorbing photocatalysts avoids the irradiation with high-energetic UV light, which can lead to decomposition of the substrate or undesired side-reactions.[68] A variety of metal-containing and metal-free photocatalysts with well-known redox potential and spectroscopic properties is available and has been used for various transformations, for example the oxidation,[69] reduction,[70] and amination,[71] of aromatic compounds, C-C couplings,[70,72,73] and cycloadditions.[74,75]

Most photocatalytic syntheses are performed in solution. The solvent enables diffusion of the substrate and the catalyst and thereby the transfer of energy and electrons. Furthermore, dilution of the reaction mixture allows an efficient excitation

of the photocatalyst. Therefore, it seems self-evident in photocatalysis to use a solvent, which is why the number of reports on solvent-free photocatalysis is rather small. Initially, our work in this field was motivated by the aim to combine photocatalysis with mechanochemistry, making use of the advantages of both fields. Therefore, we envisaged to transform solid starting materials to solid products by the application of a photocatalyst. The main challenge is the low penetration depth of light into solids: the inner reaction mixture is shielded from light, due to scattering and absorption of light by the photocatalyst in the outer part of the solid reaction mixture. This excluded the majority of the photocatalyst from excitation. Hence, neither an apparatus for mechanochemistry (e.g. ball mills), nor classical photoreactors were suitable for such transformations. We addressed this problem by the design of a novel reactor. In this “rod mill reactor”, the solid reaction mixture is ground between the inner side of a test tube and the outer side of a glass rod, thereby forming a thin film, allowing an efficient excitation of the photocatalyst with LEDs from the outside (Figure 2). Applying this reactor, we could oxidize several benzylic alcohols with riboflavin tetraacetate (RFTA) as photocatalyst under blue light irradiation. As both the starting materials and the products were solid and no product was observed when the reaction mixture was cooled, we assume that the oxidation occurs via the molten state of starting material and product. Most likely, small droplets are formed, caused by heating due to the intense blue light irradiation. Even though the RFTA catalyzed alcohol oxidation works already efficiently in solution and the solvent-free methodology does not improve the process from a synthetic point of view, it is an interesting alternative to homogeneous photocatalysis and shows that photocatalysis can in principle be performed under “entirely” solvent-free conditions. However, performing reactions on larger scale in such a reactor may be technically chalenging.[76]

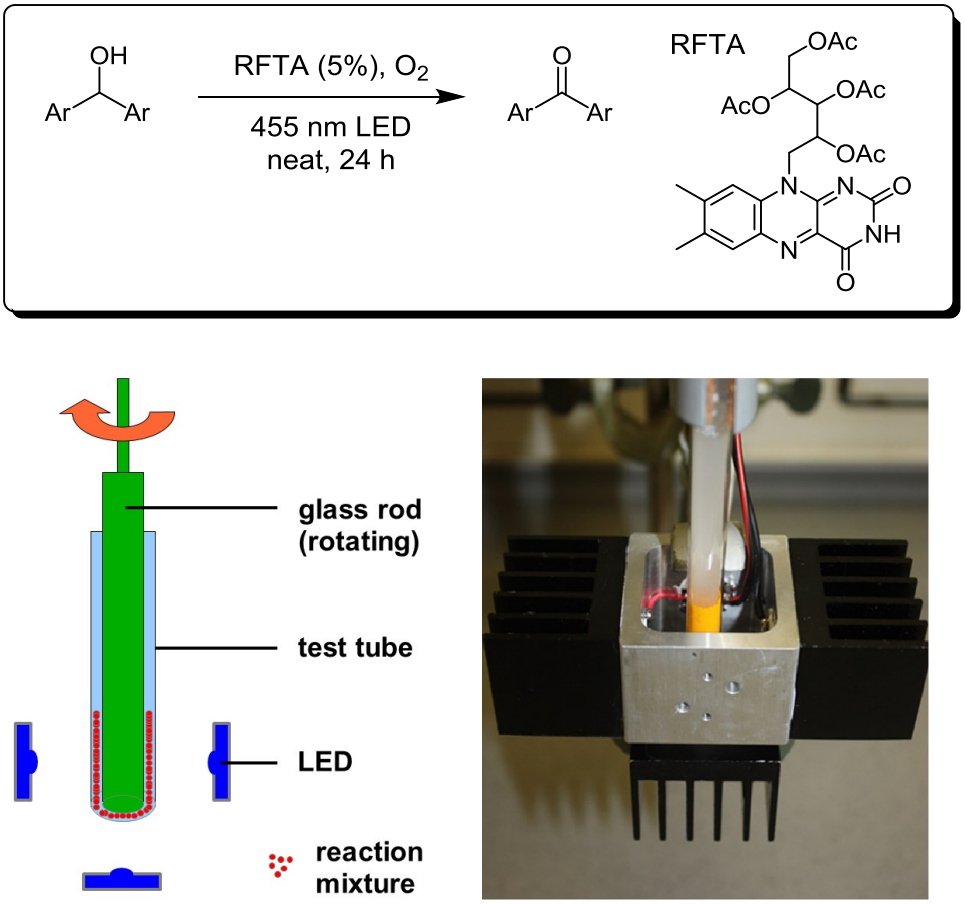


Figure 2. Solvent-free oxidation of benzylic alcohols with RFTA as photocatalyst in rod mill reactor (schematic and photograph).[76]

1.3 Reactions in liquids

1.3.1 Reactions driven by thermal energy

1.3.1.1 Setup

In contrast to mechanochemistry and solid-state photochemistry, solvent-free synthesis in neat liquids, realized by heating, does often not require special setups. The reactants are simply mixed in a vessel and heated (e.g. in an oil bath) under magnetic stirring. However, a challenge in solvent-free reactions in neat liquids is the removal of heat, which is generated in the reaction. In conventional syntheses, heat dissipation is mediated by a solvent. Strongly exothermic reactions under solvent-free conditions may result in decomposition of the reactants or even explosions. Microreactor technology can overcome this limitation. Therein, the reaction mixture flows in small channels and the high surface-to-volume ratio

enables an efficient heat transfer to the surrounding material.[6,77] Applying a microreactor, the exothermic Paal-Knorr pyrrole synthesis could be performed without a solvent.[78] Besides, the use of microreactors facilitates the mixing significantly.[79]

Solid reactants can also be converted thermally under solvent-free conditions; the reaction proceeds in a melt. In this context, Twin Screw Extrusion (TSE) is a unique methodology as it allows both temperature control and up-scale. A twin screw extruder consists of two screws between which the reaction mixture is pressed. By rotation of the intermeshing screws, the reaction mixture is transported from the feed to the outlet, alternating sections conveying or kneading. As mentioned above, TSE was applied in the solvent-free Knoevenagel condensation between several aldehydes and barbituric acid. Furthermore, the Michael addition between veratraldehyde and dimedone, which gives only low conversion in a ball mill, could also be performed by TSE.[37]

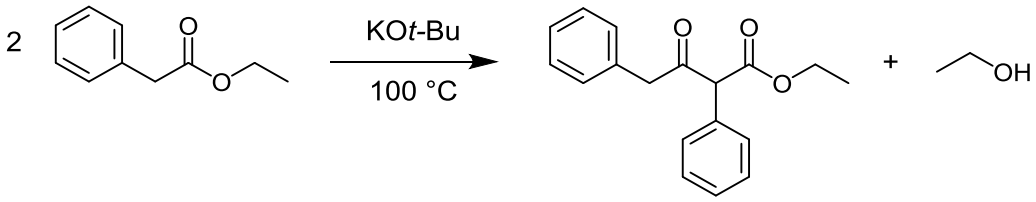
Next to conventional heating, microwave irradiation proved to be a very efficient method to perform reactions under solvent-free conditions. The microwaves induce rotation of molecules possessing a dipole moment, which results in heating. Compared to heating in an oil bath, the heat is generated within the reaction mixture homogeneously and is not transferred from the outside. Due to the high viscosity in solvent-free systems and incomplete mixing, the latter may lead to different temperatures within the reaction mixture. Several examples of solvent-free reactions in liquids show a significant increase in yield by microwave irradiation compared to conventional heating; in fact, the application of microwaves is a standard methodology in solvent-free synthesis performed in liquids.[80–82]

1.3.1.2 Organic synthesis

From the variety of reported solvent-free reactions in liquid mixtures (e.g. the synthesis of heterocycles,[81,82] the Wittig,[83] Claisen,[84] and Cannizzaro reaction,[85] and the oxidation of alcohols,[86] thiols, and amines[87]), we selected a few examples, which demonstrate the advantages of solvent-free operation.

Solvent-free conditions avoid side-reactions of the reactants with the solvent, which may lead to by-products. An example is the Claisen condensation of neat ethyl

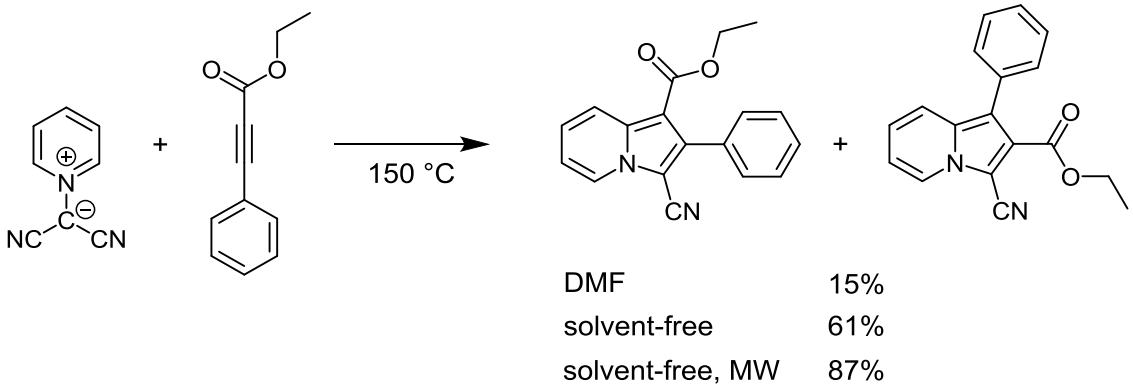
phenylacetate, mediated by potassium *tert*-butoxide. The two reactants were mixed with a spatula, followed by heating to 100 °C for 30 min, resulting in the product in 80% yield (Scheme 16).[84]



Scheme 16. Solvent-free Claisen condensation of phenylacetate.[84]

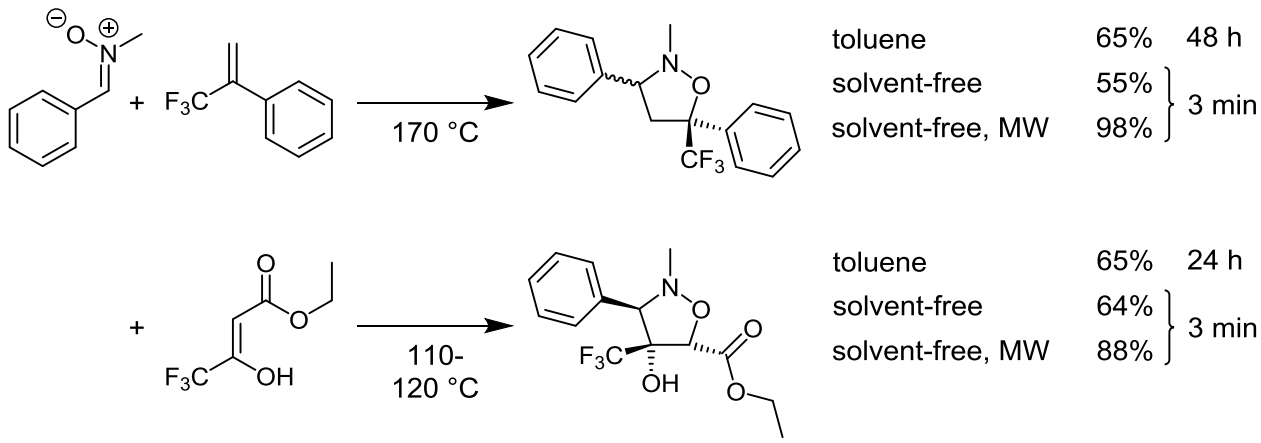
In solution, the ester, metal alkoxide, and solvent must bear the same alkoxy group to exclude exchange of this group between the three components and the formation of by-products. Solvent-free operation overcomes this limitation.[84]

The high concentration of the reactants in solvent-free systems can increase the rate and product yield of a reaction significantly. For example, in DMF, the reaction of pyridinium N-dicyanomethylide with ethyl phenylpropiolate gave the products in 15% yield at 150 °C after 25 min, whereas heating without the solvent resulted in 61% yield. Interestingly, heating in a microwave further increased the yield to 87% (Scheme 17). However, the ratio of the two products was not influenced, being 88/12 in all cases.[88]



Scheme 17. Reaction of pyridinium N-dicyanomethylide with ethyl phenylpropiolate (MW = microwave).[88]

Similar effects were observed for the 1,3-dipolar cycloaddition of *N*-methyl-*C*-phenyl nitrone and trifluoroethylenes, leading to isoxazolidines (Scheme 18): Under solvent-free conditions, the reaction is much faster, higher yields are achieved and microwave irradiation is superior to conventional heating (Scheme 18).[80]



Scheme 18. Synthesis of isoxazolidines.[80]

1.3.1.3 Conclusion

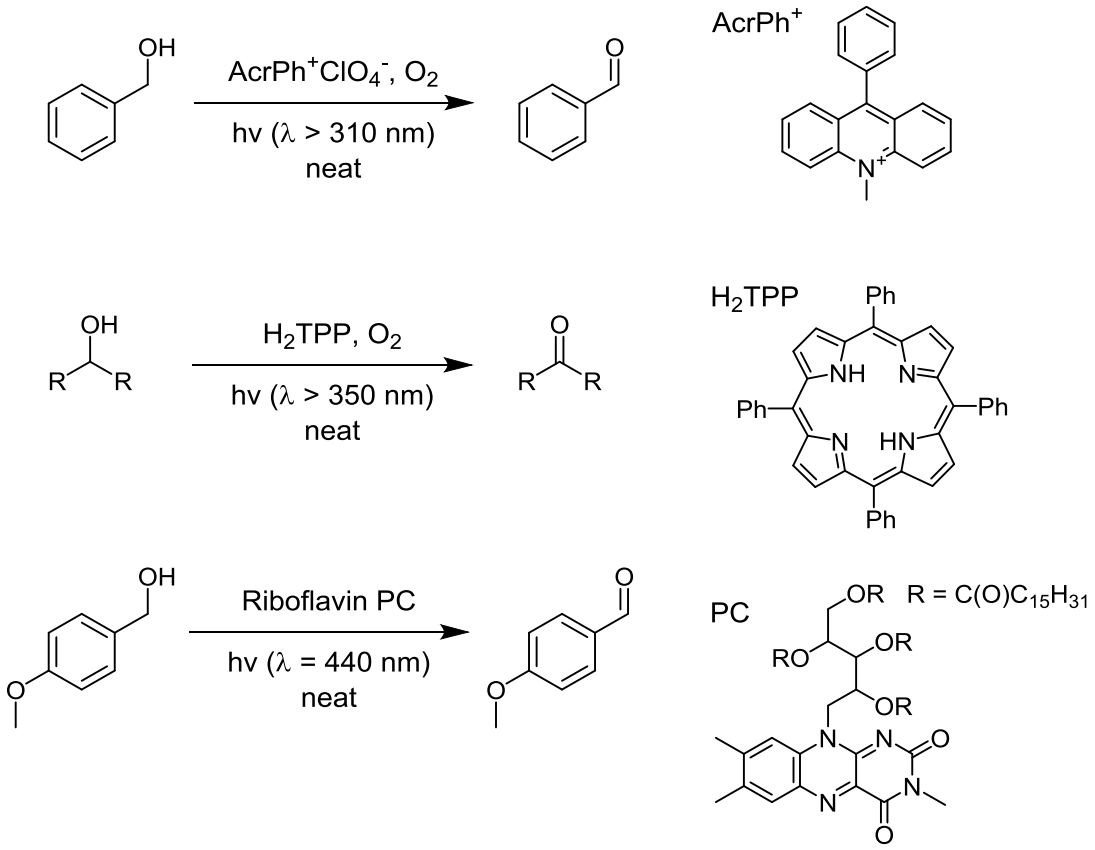
In contrast to solid-state photochemistry and mechanochemistry, the advantages of solvent-free synthesis in neat liquid mixtures are mostly limited to process improvement, i.e. increasing the yield and avoiding side-reactions. Many examples show that the outcome of a reaction (e.g. stereo- and regiochemistry of the product, selectivities) are not changed significantly by switching to solvent-free conditions. This may be due to the fact that the mechanisms involved in solvent-free liquid mixtures are not fundamentally different from these occurring in a solvent. Although conventional heating in an oil bath allows an efficient solvent-free synthesis in many cases, the application of microreactors and TSE enables control of the temperature and heat transfer, which is crucial for exothermic reactions. Furthermore, heating by microwaves can improve the process significantly, corresponding to higher yields and decreased reaction times.[80–82]

1.3.2 Photocatalysis

One field of solvent-free photocatalysis in liquid mixtures is the application of heterogeneous photocatalysts, which will not be discussed in detail, although there are several reports about solvent-free, light-driven transformations applying semiconductors containing TiO_2 and other metal oxides. Therein, either the substrate itself acts as solvent, resulting in low conversion and requiring very long

reaction times[89–92] or one reagent is used in large excess.[93] An exception is the reduction of nitrobenzene to aniline applying a Au/TiO_2 photocatalyst.[94]

Applying organic photocatalysts, the solvent-free oxidation of benzylic and aliphatic alcohols was achieved by visible light irradiation with oxygen as terminal oxidant (Scheme 19). Benzyl alcohol was oxidized to benzaldehyde with 9-phenyl-10-methylacridium perchlorate as photocatalyst. A mercury lamp was used as light source. Since the photocatalyst is soluble in benzyl alcohol, a homogeneous solution was formed. Even though considerable amounts of benzaldehyde were formed after 15 h (800% relative to the photocatalyst), the conversion was only around 1.6%.[95] In another approach, tetraphenylporphyrin (H_2TPP) was used as photocatalyst for the oxidation of benzyl alcohols and cycloalkyl alcohols to their corresponding carbonyls under LED irradiation. For most substrates, only moderate conversions were observed. However, in comparison to the same reaction in solvent (acetonitrile), more than three-fold turnover numbers and frequencies were achieved.[96,97] Similar effects were observed for the solvent-free oxidation of *para*-methoxybenzyl alcohol with a riboflavin photocatalyst immobilized on silica gel, which resulted in very high turnover numbers.[98] These observations clearly show that a high molar substrate-to-catalyst ratio (like it is achieved in solvent-free conditions) favors an efficient reaction and that the addition of a solvent is not necessary and can even slow down the reaction.



Scheme 19. Solvent-free photocatalytic oxidation of alcohols to carbonyls.[95,96,98]

We envisaged to perform photocatalytic reactions in a liquid-or paste-like state under solvent-free conditions. In contrast to the two solvent-free approaches discussed above, where the substrate acts as solvent (resulting in a homogeneous solution), our approach excluded the application of conventional setups for irradiation due to the limited penetration depth of light in solvent-free systems. Therefore, we constructed a “rotating film reactor”. Therein, fast rotation of the reaction mixture, resulting in a centrifugal force, leads to the formation of a film on the inner side of the reaction vessel. Irradiation is achieved with LEDs from the outside (Figure 3).[99] We applied this reactor to the solvent-free coupling of aryl halides with pyrroles and phosphites with rhodamine 6G as photocatalyst under blue light irradiation. This methodology has been reported by our group before and the reactions are performed in DMSO.[72] The mechanistic hypothesis proposes a fast trapping of the intermediate aryl radical by the pyrrole as crucial step, since competing hydrogen transfer from the solvent may occur resulting in the reduced benzene derivative as a side product. Therefore, a high trapping reagent-to-aryl radical ratio is desirable.

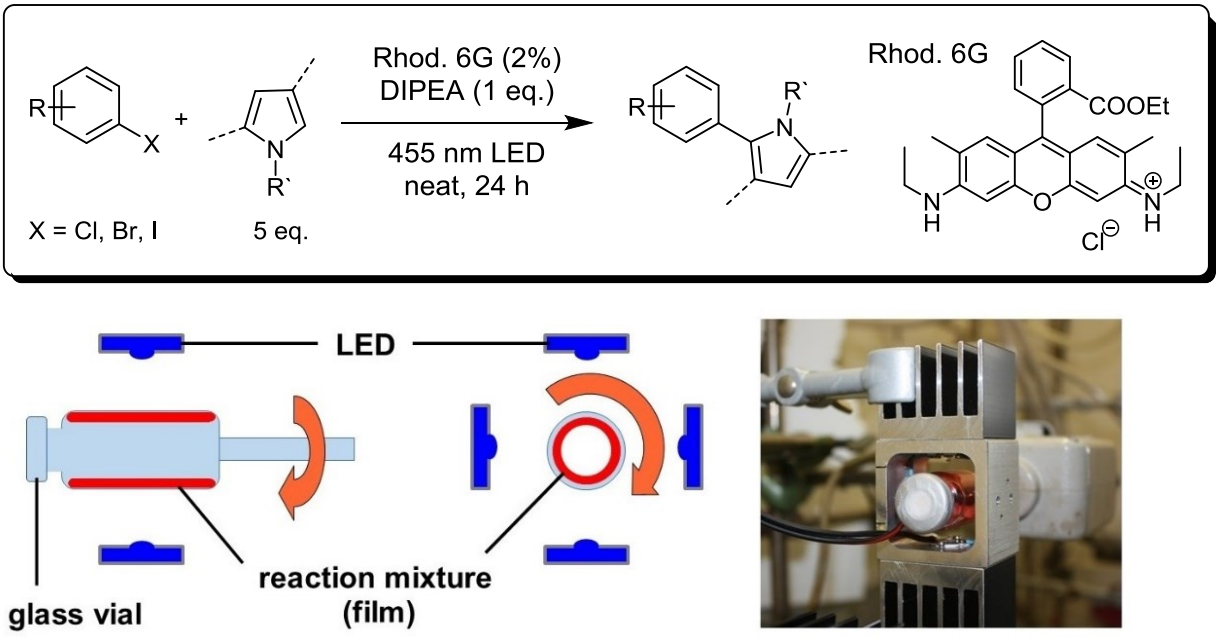


Figure 3. Solvent-free coupling of aryl halides with pyrroles with rhodamine 6G as photocatalyst in rotating film reactor (schematic and photograph).[99]

In solution, high amounts of the trapping reagents were necessary, usually 13 to 26 equivalents relative to the substrate.[72] By leaving out the solvent, the mole fraction of the trapping reagent in the reaction mixture is much higher compared to solution; keeping the amounts of all the other reactants and catalyst constant, a high trapping reagent-to aryl-radical ratio is achieved. Therefore, solvent-free operation offers a unique opportunity to achieve high molar fractions of the trapping reagent, which should favor an effective trapping and prevent the formation of side products. Furthermore, the high mole fraction of DIPEA as the electron donor may facilitate the reduction of the excited state of rhodamine 6G.

Interestingly, under solvent-free conditions, we obtained the coupling products in comparable yields like in solution, but with significantly lower amounts of trapping reagent (5 eq. vs. 13–26 eq.). In addition, the amount of electron donor was reduced to 1 equivalent (in solution: 1.4 eq. DIPEA) and only 2% of rhodamine 6G was necessary (in solution: 10%). In fact, increasing the amount of rhodamine 6G in our system decreased the yield, indicating an increasing excitation efficiency with decreasing concentration of photocatalyst. To summarize, in this photocatalytic coupling reaction, solvent-free operation proved to be more efficient and atom-economic than the procedure in solution.[99]

To conclude, although reports on solvent-free photocatalysis are quite limited, this approach is very promising, because high concentrations in liquid mixtures favor the trapping of reactive intermediates and increase the efficiency of the reaction due to a high substrate-to-photocatalyst ratio, resulting in high turnover numbers. The addition of a solvent decreases this ratio, thereby decelerating the reaction. On the one hand, the substrate itself can act as solvent, forming a homogeneous solution, which results in low overall conversions. Whereas conventional vials used for homogeneous photocatalysis are sufficient for this approach, solvent-free photocatalysis in paste-like reaction mixtures (being entirely solvent-free) is not possible in these reactors, which is why we developed the “rotating film reactor”. Applying this reactor for the rhodamine 6G-catalyzed C-C coupling, we could achieve significant improvements under solvent-free conditions compared to the reaction in solution. However, both scale-up and temperature control are difficult to realize. In solution photocatalysis, scale-up is simply achieved by the application of flow reactors.[100]

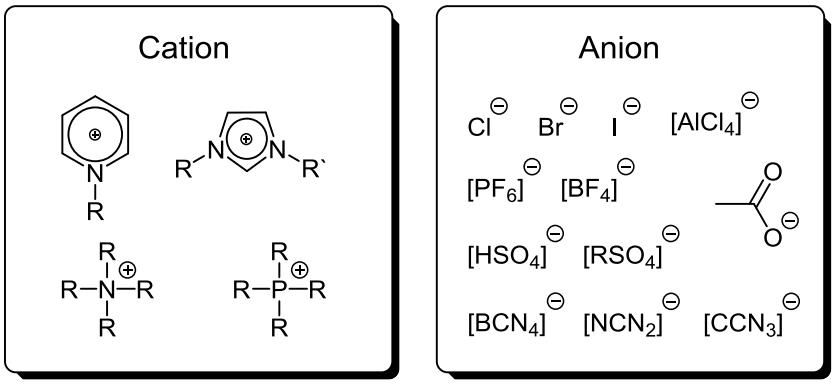
1.4 Reactions in unconventional solvents

In the previous paragraphs, we showed that solvent-free reactions in the solid or liquid state can have advantages in organic synthesis. Leaving the undeniable benefits of solvent-free synthesis untouched, the exclusion of a solvent can also lead to complication, such as a difficult heat transfer, incomplete mixing and the formation of side-products due to the very high reactant concentrations. Therefore, in the last decades, there have been enormous efforts to establish new reaction media, which are more sustainable and less toxic and volatile than conventional organic solvents. In this context, ionic liquids and deep-eutectic solvents are particularly interesting due to their unique chemical and physical properties, which is why we focus on these two types of solvents. We discuss properties and preparation and show representative examples for their application in organic synthesis.

1.4.1 Ionic liquids

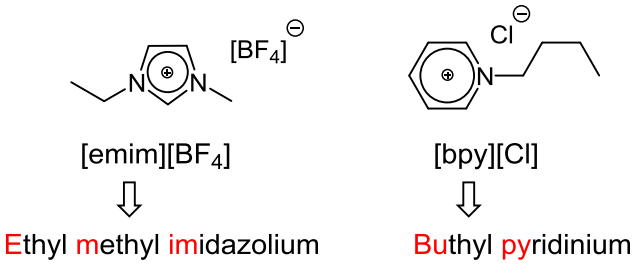
1.4.1.1 Definition and preparation

Ionic liquids (ILs) are organic salts with a melting point lower than 100 °C. Due to charge delocalization and steric effects, no solid crystals are formed. A very low vapor pressure and flammability, stability against air and heat, a high heat capacity, and electric conductivity are typical properties characterizing ILs. ILs consist entirely of ions and are formed by an organic cation typically based on nitrogen or phosphorous atoms (such as alkylammonium or dialkylimidazolium) and by an anion, which can be organic or inorganic.[101–103] Scheme 20 gives an overview about common cations and anions.



Scheme 20. Examples for cations and anions forming ILs.[102,103]

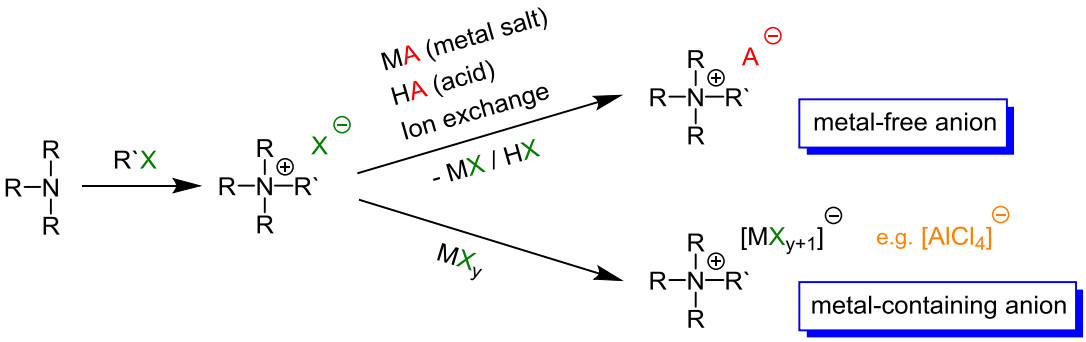
For simplification, ILs are named by abbreviating the cation (e.g., “ethyl methyl imidazolium” gives “emim”), followed by the formula of the anion, in square brackets (Scheme 21).



Scheme 21. Examples explaining IL nomenclature.

Furthermore, ILs can be named by abbreviation of the alkyl chain as “C_x “together with the core amine. In this nomenclature, ethyl methyl imidazolium is written as [C_2C_1im].[104]

Most ILs are prepared by quaternization of an amine or a phosphane with a halogenalkane (Scheme 22). The product of this reaction can be already an IL. However, it may be necessary to exchange the anion, which is achieved by the addition of a metal salt or acid or an ion exchange. If a metal-containing anion is required, such as $[AlCl_4]^-$, a metal salt with the same anion as the quaternization product is added.[101]



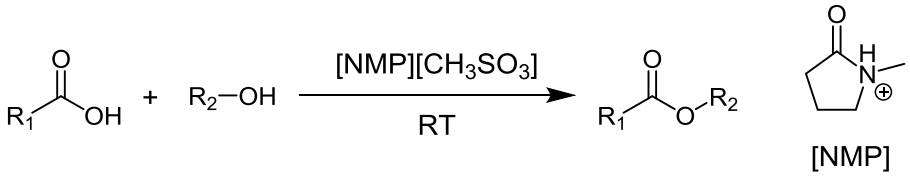
Scheme 22. Synthesis of ILs.[101]

1.4.1.2 Application in organic synthesis

For more than twenty years, ILs are considered as a replacement for conventional solvents and a variety of organic transformations has been performed in ILs, including name reactions such as the Knoevenagel condensation, the Fischer Indole synthesis, the Mannich, Diels-Alder, Henry, and Baylis-Hillman reaction, and, in general, substitution, elimination, addition, esterification, dehydration, and C-C coupling reactions. This is due to the unique physical properties of ILs mentioned above and the fact that their chemical properties can be fine-tuned by varying the structure of the cation and the anion, influencing organic reactions in a different way than conventional solvents, acting not only as a solvent, but also as a catalyst. Overall, an IL can be applied as a) inert solvent, b) solvent and catalyst simultaneously, and c) catalyst. Several reviews summarize the application of ILs in organic synthesis.[103–106]

Facilitation of the work-up, the possibility of catalyst recycling, and the achievement of mild reaction conditions are among the major motivations to perform syntheses in ILs. Many approaches make use of the “untypical” polarity of ILs, dissolving several components of a reaction mixture selectively, and the immiscibility of ILs

with many organic solvents, enabling an easy extraction of the product. An example is the esterification of carboxylic acids and alcohols. Whereas standard procedures in organic solvents use activated acids like acyl chlorides or acyl imidazoles, generating stoichiometric waste (or require removal of water, if the free acid is reacted), the application of an IL (N-methyl-2-pyrrolidonium methyl sulfonate) allows the esterification of the free acid at room temperature in excellent yields (Scheme 23). Remarkably, only 25% of the IL relative to the substrates were used and the IL takes the role of a catalyst rather than a solvent. Due to the insolubility of the ester in the IL, it forms a separate layer upon reaction and the equilibrium is shifted towards the product, which can be simply separated from the reaction mixture by decantation. Water is miscible with the IL, remaining in the reaction mixture. The IL could be recycled five times without a significant decrease of the yield.[107]

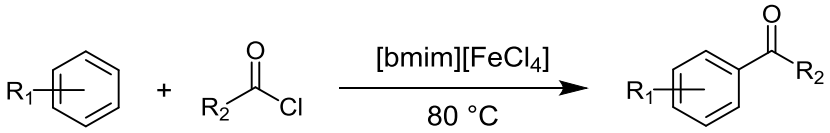


Scheme 23. Esterification with N-methyl-2-pyrrolidonium methyl sulfonate.[107]

In general, the Brønsted acidity of imidazolium-based ILs enables their application as a recyclable catalyst and solvent for a variety of acid-catalyzed reactions. Thereby, the use of strong and corrosive acids, such as H_2SO_4 or HCl, is avoided and the reactions are often performed at room temperature. For example, N-methyl imidazolium was applied in the Mannich reaction,[108] the dehydration of fructose and sucrose to 5-hydroxymethylfurfural,[109] and the reductive amination[110] and protection[111] of carbonyls.

Lewis-acidic ILs containing a metal in the anion, such as $[AlCl_4]^-$, are promising catalyst-solvent systems as well. An example is the Friedel-Craft acylation of benzene derivatives applying [bmim][$FeCl_4$] at 80 °C (Scheme 24). In comparison to solvent-free reactions of benzene with benzoyl chloride applying solid catalysts, such as $GaCl_3$/kaolin, higher yields were achieved in a shorter reaction time. Furthermore, solution-based procedures using Lewis acids like $AlCl_3$ and $FeCl_3$ require hydrolysis of the product, followed by neutralization of the reaction mixture; in the IL, the product was simply extracted with cyclohexane, facilitating the work-up significantly. Recycling of the IL was possible, but the yield decreased from >80%

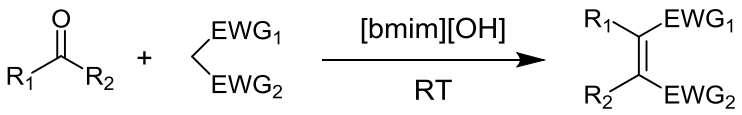
to <30% in the fourth run, which was attributed to a loss of $FeCl_3$ due to accumulation of water and other effects; addition of fresh $FeCl_3$ resulted in a yield comparable to the first value. In general, this observation shows that the catalytic activity of metal-containing ILs may be sensitive to traces of impurities, which can decrease the amount of the catalytic species.[112]



Scheme 24. Friedel-Craft acylation of benzene derivatives in [bmim][$FeCl_4$].[112]

Interestingly, the Lewis acid-base behavior of ILs can be changed by varying the amount of the metal component, thereby influencing the selectivity of a reaction. This was shown for the Diels-Alder reaction of cyclopentadiene with methyl acrylate, which was performed in [bpy][$AlCl_4$] and [emim][$AlCl_4$] acting as catalyst and solvent. By switching the IL from basic (48% $AlCl_3$) to acidic (51% $AlCl_3$), the endo/exo ratio of the product increased by the factor of 4.[113] The Diels-Alder reaction was also performed in [bmim][PF_6] with scandium triflate as a catalyst, resulting in a strong increase in reaction rate and yield compared to the reaction in dichloromethane and a >99% selectivity of the endo product.[114]

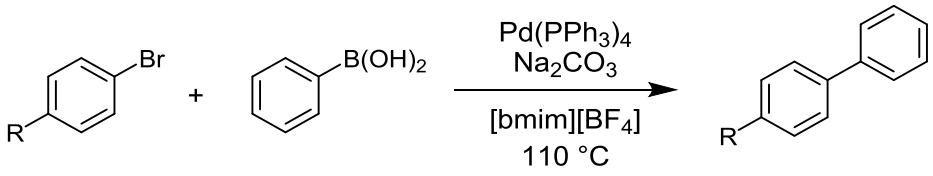
The concept of using an IL as a recyclable catalyst was also applied in base-catalyzed reactions. An example is the Knoevenagel condensation of carbonyls with activated methylene compounds. Therein, the application of [bmim][OH] in 20% resulted in very good yields of the product alkenes at room temperature and in short reaction times, usually 10–30 min (Scheme 25). The products were isolated from the reaction mixture by distillation or extraction with ethyl acetate and the IL could be recycled four times.[115]



$R_{1,2}$ = Alkyl, Aryl, H
$EWG_{1,2}$ = CN, CO_2Et, COOH

Scheme 25. Knoevenagel condensation in [bmim][OH].[115]

Next to the application of an IL acting as solvent and/or catalyst, significant improvements are achieved when the IL acts as an inert solvent, for example in Suzuki couplings catalyzed by $Pd(PPh_3)_4$ (Scheme 26). Performing these reactions in [bmim][BF_4] dramatically increased the reaction rate, compared to conventional solvents: Whereas the reaction of bromobenzene with phenylboronic acid in toluene-water-ethanol (4:2:1) gave the product in 88% after 6h, 93% were obtained in 10 min for this reaction in [bmim][BF_4]. Furthermore, the catalyst loading in the IL could be reduced from 3% (as applied in toluene-water-ethanol) to 1.2%. Isolation of the product was possible by extraction with diethyl ether, sublimation *in vacuo* or the addition of water, which leads to precipitation of the product. Sodium salts formed as by-products were simply removed from the reaction mixture by washing with water, enabling the recycling of the catalyst.[116]

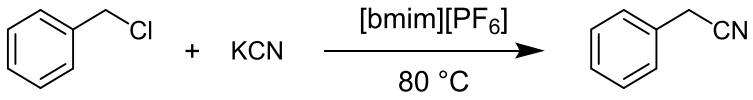


R = H, CH_3, $COCH_3$, OCH_3

Scheme 26. Suzuki coupling in [bmim][BF_4].[116]

Furthermore, performing the Heck olefination of chlorobenzene with styrene in [NBu_4][Br] instead of DMF resulted in both a higher activity and thermal stability of the palladium catalyst, corresponding to increased yields.[117]

Another important motive for the application of ILs is the fact that solubility problems can be avoided. Usually, the reaction of an inorganic salt with an organic compound requires the application of a phase transfer catalyst, due to the insolubility of the salt in an organic solvent. However, ILs can dissolve inorganic salts, making ILs a rather promising solvent class for this kind of reactions. For example, the synthesis of phenylacetonitrile from benzyl chloride and KCN via nucleophilic substitution was performed in [bmim][PF_6] at 80 °C (Scheme 27). The reaction was found to be highly temperature-dependent, the conversion at 40 °C increased much slower than at 80 °C. KCN was used in excess, not dissolving completely in the IL; at lower temperature, the transfer of the solid KCN into the IL is the rate-limiting step due to the higher viscosity of the IL.[118]



Scheme 27. Synthesis of phenylacetonitrile in [bmim][PF_6].[118]

1.4.1.3 Conclusion

The above examples show that ILs are a promising alternative to conventional organic solvents, improving organic syntheses in many ways. This includes "technical" advantages, e.g. facilitation of the work-up, recycling of the catalyst-solvent system, mild reaction conditions, and the avoidance of solubility problems, as well as "synthetic" advantages, namely the achievement of higher yields, an enhancement of the reaction rate, and the possibility to influence selectivities. Moreover, the high thermal stability and low flammability allows reactions to be performed at high temperatures, which is not possible in volatile solvents. However, there are also several drawbacks associated with ILs. First, their preparation can be complicated and requires the strict exclusion of air and moisture. Furthermore, the quaternization reaction is exothermic, which may lead to elimination instead of substitution; therefore, the temperature must be controlled very carefully. For example, the application of a "microstructured reactor" allows an efficient cooling of solvent-free exothermic IL syntheses.[119] Since small amounts of impurities in the IL may change the chemical and physical properties dramatically, a high purity is crucial. On the other hand, purification of IL is challenging due to difficult distillation, which is why a high purity of the starting materials must be ensured to exclude impurities from the beginning of the preparation. Due to the high hydrophilicity of many ILs, they must be handled in an inert atmosphere to prevent contamination by moisture. ILs containing a Lewis acidic anion can be sensitive to water, resulting in a loss of the catalytic activity.[103]

The fact that a volatile organic solvent is replaced by an ionic liquid does not necessarily make the process "greener". The preparation of ionic liquids may require several energy-consuming steps, extensive purification and the application of conventional organic solvents. A recent attempt to improve this is the efficient synthesis of [bmim][Cl] by nucleophilic substitution reaction in [bmim][Cl], the solvent being identical to the product.[120] Furthermore, the starting materials for IL synthesis

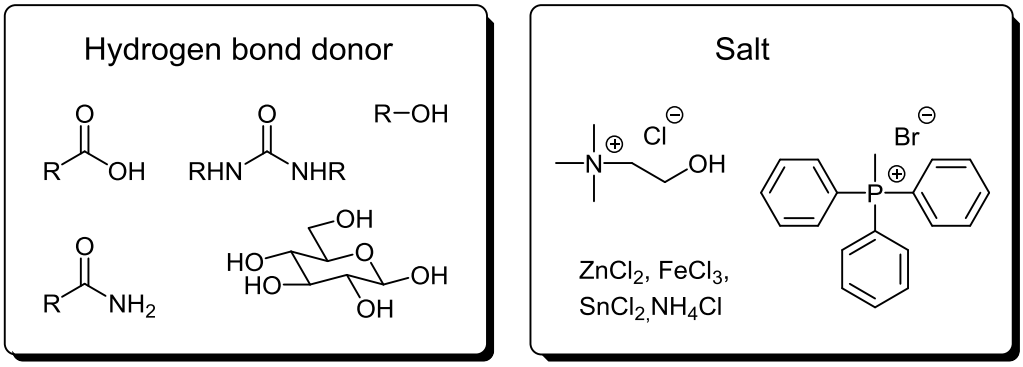
are often derived from petroleum. Recently, research effort increased regarding the preparation of ILs from renewable resources, namely polysaccharides, proteins, and lignin. The combination of these resources with simple and sustainable procedures for preparation and purification should decrease the environmental impact of ILs, making them a thoroughly “green” medium for synthesis.[121]

Although ILs are often seen as a non-toxic alternative to cancerogenic and teratogenic solvents, such as chloroform, dichloromethane, or DMF, they are not harmless per se, their toxicity strongly depending on their structure. For example, ILs containing fluoride in the anion (e.g. $[BF_4]^-$ or $[PF_6]^-$) can release HF when exposed to moisture. Admittedly, the very low vapor pressure of ILs decreases the risk of inhalation. On the other hand, ILs derived from saccharides or amino acids are mostly non-toxic. Comprehensive studies of the toxicological properties of ILs are necessary to evaluate their biological safety and compare them with conventional solvents. Until now, knowledge on the effects of ILs on humans and environment is still limited; however, some general trends have been observed, e.g. an increasing toxicity with increasing alkyl chain length.[103,122]

1.4.2 Deep-eutectic solvents

1.4.2.1 Definition and preparation

A deep-eutectic solvent (DES) is a mixture of at least two components, possessing a lower melting point than each of the pure components, typically below 100 °C; some DES are even liquid at room temperature. DES consist of a hydrogen bond donor and a salt, which can be organic or inorganic, the formation of hydrogen bonds between the two components being responsible for DES formation. Hydrogen bond donors can be carboxylic acids, amides, urea derivatives, alcohols, and saccharides. Typical organic salts are based on nitrogen atom containing compounds (e.g. choline chloride, ChCl) or phosphorous atom containing compounds (e.g. methyltriphenylphosphonium bromide); mostly, inorganic salts are metal salts, such as $ZnCl_2$, $FeCl_3$, or $SnCl_2$, the metal cation coordinating to the hydrogen bond donor (Scheme 28).[1,2,123]



Scheme 28. Examples for hydrogen bond donors and salts forming DES.[1,2,123]

The difference between ILs and DES is that ILs consist entirely of ions. Like ILs, DES possess a very low vapor pressure and flammability and are stable against air. However, DES often have a lower thermal stability.[1,2] DES can be simply prepared by mixing the solid components and heating under stirring until a clear, homogeneous mixture occurs.[2] While this procedure is quite convenient for the preparation of a DES in gram-scale in the laboratory, it is challenging for larger amounts as applying heat to a huge volume of solids may be difficult due to incomplete heat conduction, requiring the time-consuming addition of the solids to the liquid phase. Heating for a long time can also lead to decomposition of the material. Therefore, planetary ball milling was recently established as a method for DES preparation up to 80 g, decreasing the required time significantly. Furthermore, as a continuous method, TSE was applied for the efficient preparation of ChCl–$ZnCl_2$ and ChCl–fructose DES with a throughput rate of about 6 kg/h. In the case of ChCl–fructose, caramelization, as usually observed by long-time heating, could be avoided, showing a clear advantage of this method over conventional heating in batch.[124]

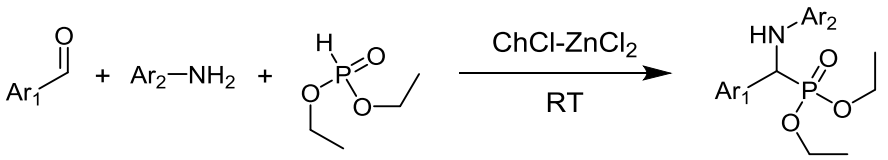
1.4.2.2 Application in organic synthesis

Since the first report on a DES based on quaternary ammonium salts and urea,[125] DES were in the focus of intense research. A typical application is the use as solvent for organic transformations. Due to their biodegradability and availability from renewable materials, they are often seen as “bio-ILs”, justifying considerable efforts to establish them in synthesis as an alternative to conventional solvents and even ILs. Thus, similar to ILs, there is a variety of reports on the application of DES in

standard reactions. Therein, DES can act as a) inert solvent, b) solvent and catalyst simultaneously, c) catalyst, and d) catalyst, solvent, and reactant simultaneously.

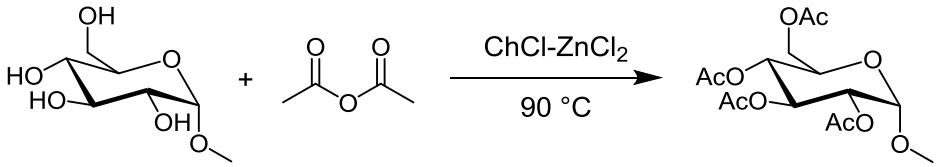
DES containing a metal halide are Lewis acidic and therefore, they were applied as recyclable catalyst system in many transformations. Especially ChCl–$ZnCl_2$ (1:2) was used extensively, for example in esterification,[126] the Biginelli reaction,[127] the Kabachnik-Fields reaction,[128] the Fischer Indole synthesis,[129] the acetylation of monosaccharides,[130] the Friedel-Craft-Acylation[131] and alkylation,[132] the Mannich reaction,[133] the synthesis of aromatic amides,[134] and the Diels-Alder reaction.[135]

The Kabachnik-Fields-reaction is the Lewis-acid catalyzed reaction between an aromatic aldehyde, an amine, and a phosphite, leading to an α-aminophosphonate. Due to the presence of the amine and the formation of water during the reaction, expensive and toxic metal catalysts are often necessary. Furthermore, conventional procedures require long reaction times and usually result in low yields. To overcome these problems, ChCl–$ZnCl_2$ was successfully applied as catalyst (15%) in the Kabachnik–Fields reaction (Scheme 29). The reactions were performed at room temperature for 1 h and the products were isolated in very good yields by extraction; washing of the residual DES with diethyl ether enabled its recycling for five cycles.[128]



Scheme 29. Kabachnik–Fields reaction in ChCl–$ZnCl_2$ (1:2).[128]

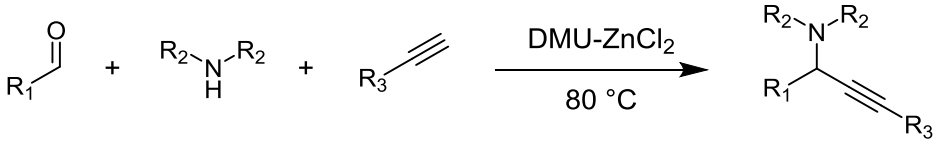
Another example illustrating the efficiency of ChCl–$ZnCl_2$ as a Lewis acidic catalyst is the acetylation of monosaccharides (Scheme 30). Applying one equivalent of acetic anhydride per alcohol functionality in ChCl–$ZnCl_2$ (acting as catalyst and solvent) resulted in the exclusive formation of the per-acetylated product in excellent yield. In contrast, when the reaction is performed in THF (with $ZnCl_2$ as a catalyst) or pyridine, a mixture of partially acetylated monosaccharides is obtained. Interestingly, the alcohol functionality of ChCl was not acetylated, despite its large excess as a DES component. After isolation of the product by extraction with ethyl acetate, the DES could be recycled three times; however, the stepwise accumulation of impurities in each reaction lead to a significant decrease of the yield after the fourth cycle.[130]



Scheme 30. Acetylation of monosaccharides in ChCl–$ZnCl_2$ (1:2), shown for α-1-methoxyglucose.[130]

As mentioned above, the Diels-Alder reaction was performed in Lewis-acidic ILs, namely [bpy][$AlCl_4$] and [emim][$AlCl_4$].[113] However, the sensitivity of these chloroaluminate ILs to water may lead to deactivation. Remarkably, the application of ChCl–$ZnCl_2$ as solvent and catalyst in this reaction was possible in the presence of water, which is particularly useful because it allows a decrease of the DES viscosity by water addition. Due to insolubility of the product, it formed a separate layer and could be simply isolated by decantation. Recyclability of the DES and short reaction times at room temperature are additional advantages of this methodology.[135]

Next to carbonyls, $ZnCl_2$ can also activate alkynes, transforming them to more nucleophilic acetylides. Thus, among other metal salts, it is used as catalyst in the reaction of an aldehyde, an amine, and an alkyne, leading to a propargyl amine ("A^3-coupling"). Therefore, we applied DMU–$ZnCl_2$ (7:2) acting as catalyst and solvent in the A^3-coupling (Scheme 31). The products were isolated in moderate to very good yields and the DES could be recycled two times. Further hydrogen bond donors forming a DES with $ZnCl_2$, including ChCl, acetamide, and urea, resulted in low conversion or trace amounts, partly due to limited solubility of the substrates.[136]

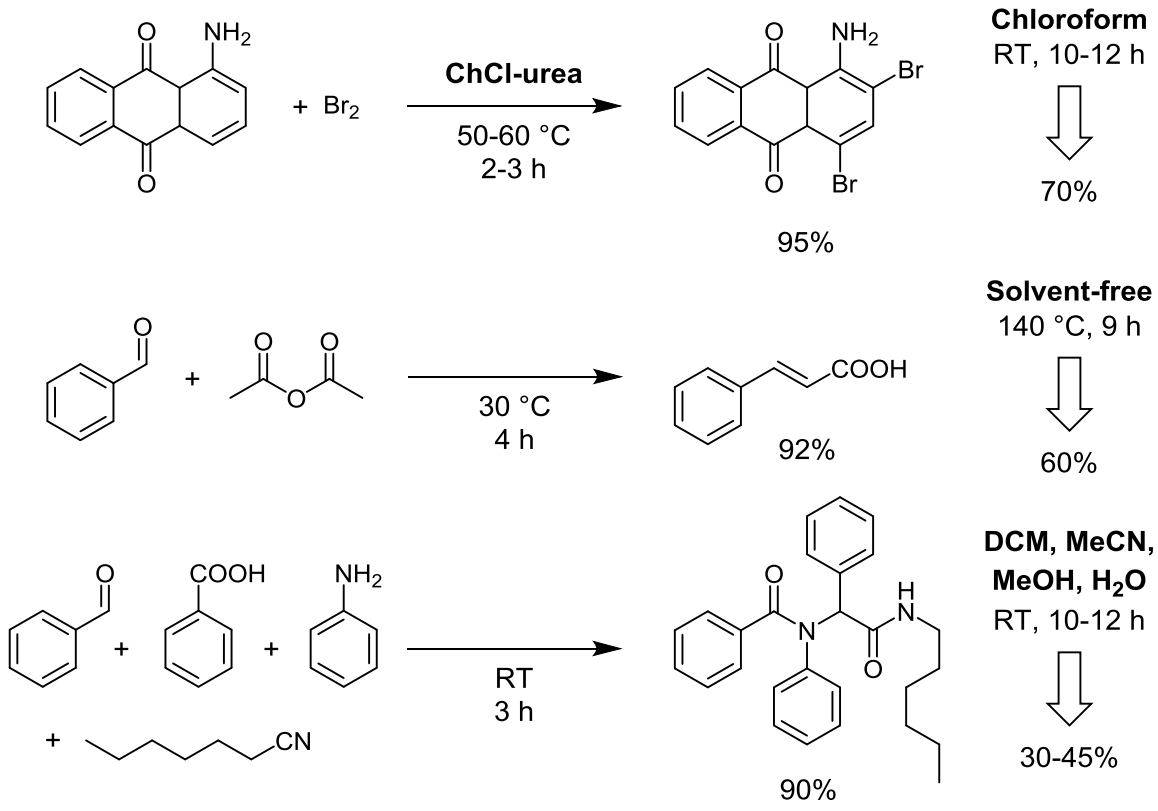


R_1 = aryl, alkyl
R_2 = morpholine, piperidine, alkyl
R_3 = aryl, alkyl

Scheme 31. Synthesis of propargyl amines in DMU–$ZnCl_2$ (7:2).[136]

ChCl–urea (1:2) is another versatile, recyclable catalyst acting as solvent simultaneously and was applied in a variety of transformations, including bromination,[137] the Paal-Knorr synthesis,[138] the Perkin[139] and Ugi[140] reaction and

the synthesis of imines[141] and aurones.[142] The low freezing point (-12 °C), allowing its application at room temperature, and giving higher yields in shorter reaction times compared to conventional procedures are the main advantages of this DES. Especially, this was shown for the bromination of aminoanthraquinones, the Ugi, and the Perkin reaction (Scheme 32). Moreover, in the Ugi and Perkin reaction, the pure product was easily obtained by precipitation in water and washing.[137,139,140]

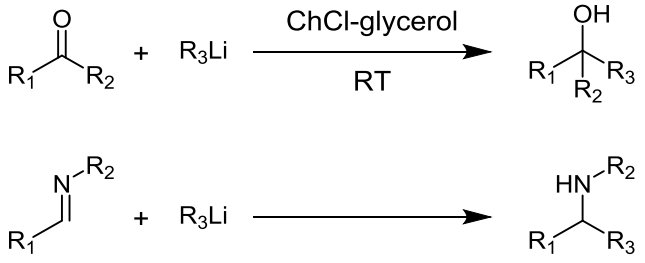


Scheme 32. Bromination, Perkin, and Ugi reaction in ChCh–urea (1:2) and comparison with conventional procedures.[137,139,140]

Furthermore, whereas the conventional synthesis of aurones from an aldehyde and a coumaranone requires the addition of an acid or base, this reaction could be performed in ChCl–urea under neutral conditions, resulting in moderate to good yields. However, the reaction times were quite long (12–48 h).[142]

The application of DES as a solvent in organometallic chemistry can facilitate the synthetic procedure significantly. In synthesis, the addition of organolithium and Grignard compounds to electrophiles is a standard to build C-C bonds. However, the high reactivity of these compounds usually requires low temperatures and the strict exclusion from water and air to prevent side-reactions or explosion. Therefore, it seems unreasonable to run such reactions in a protic DES. Nevertheless, the

addition of organolithium compounds to ketones and imines could be performed in ChCl–glycerol (1:2) DES in open air at room temperature (Scheme 33). The reactions were very fast (3 s), giving access to a variety of alcohols and amines in very good to excellent yields without the formation of by-products. This indicates that the competing protonation of the organolithium compound is much slower than its addition to the electrophile. In fact, the organolithium compound was found to be relatively stable in the DES for at least 15 s; when it was stirred in the DES for 60 s, followed by the addition of an imine, the corresponding amine was still isolated in good yield. Furthermore, the addition of Grignard compounds to ketones under these conditions was performed as well. The surprising reactivity was explained by activation of the organometallic compounds by ChCl, forming an intermediate with increased nucleophilicity.[143,144]



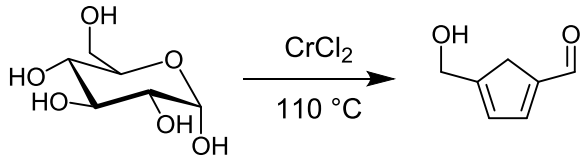
$R_{1,2,3}$ = Alkyl, Aryl

Scheme 33. Addition of organolithium compounds to ketones and amines in ChCl–glycerol (1:2). [143,144]

Furthermore, palladium catalyzed C-C coupling reactions were performed in DES based on saccharides and DMU or urea, including the Stille,[145] Heck, Sonogashira,[146] and Suzuki[147] coupling.

The high saccharide concentration in a DES (up to 50% by weight) allows the efficient conversion of this DES component itself. This was shown for the synthesis of 5-hydroxymethylfurfural (HMF) by saccharide dehydration in a DES formed with ChCl.[148] Made from renewable resources, HMF is often seen as a platform chemical to replace petroleum-based materials. However, conventional methods for HMF synthesis require the application of high-boiling solvents like DMSO, DMF, and water, impeding HMF isolation. Furthermore, the presence of an acidic catalyst in water can lead to rehydration and condensation of DMF, resulting in unwanted by-products. Therefore, ChCl-based DES were investigated as reaction medium, and

D-fructose, D-glucose, sucrose, and inulin could be converted to HMF, resulting in moderate to good yields (45–67%) in 30–60 min. As catalysts, *para*-toluenesulfonic acid and $CrCl_2$, were applied, depending on the saccharide used. The addition of water and extraction with ethyl acetate after the reaction gave the pure HMF. Remarkably, in case of sucrose and inulin, hydrolysis into the monosaccharides and dehydration occurred simultaneously in one step. As an example, Scheme 34 shows the synthesis of HMF from D-glucose.[148]

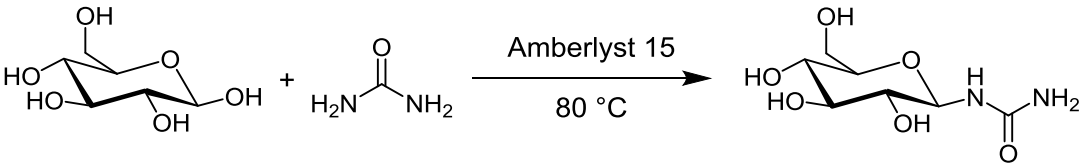


(glucose-ChCl 4:6)

Scheme 34. Dehydration of D-glucose in a ChCl–glucose (6:4).[148]

Similarly, 5-(a-D-glucosyloxymethyl)furfural (GMF) was synthesized in ChCl–isomaltulose (1:1) applying several acidic catalysts.[149]

The concept of applying a saccharide DES component as a reactant was also extended to the reaction of two components. For example, heating D-glucose–urea–NH_4Cl (3:7:1) at 80 °C in the presence of Amberlyst 15 as an acidic catalyst resulted in β-D-glycosyl urea in 81% yield after 2 h (Scheme 35). Several saccharides were converted this way, such as D-glucose, D-mannose, and D-galactose; the urea component was varied as well. Conventional procedures for the reaction of aldoses with urea, applying water or water mixtures as solvent, require very long reaction times, usually days, and result in moderate yields only (30–50%).[150]

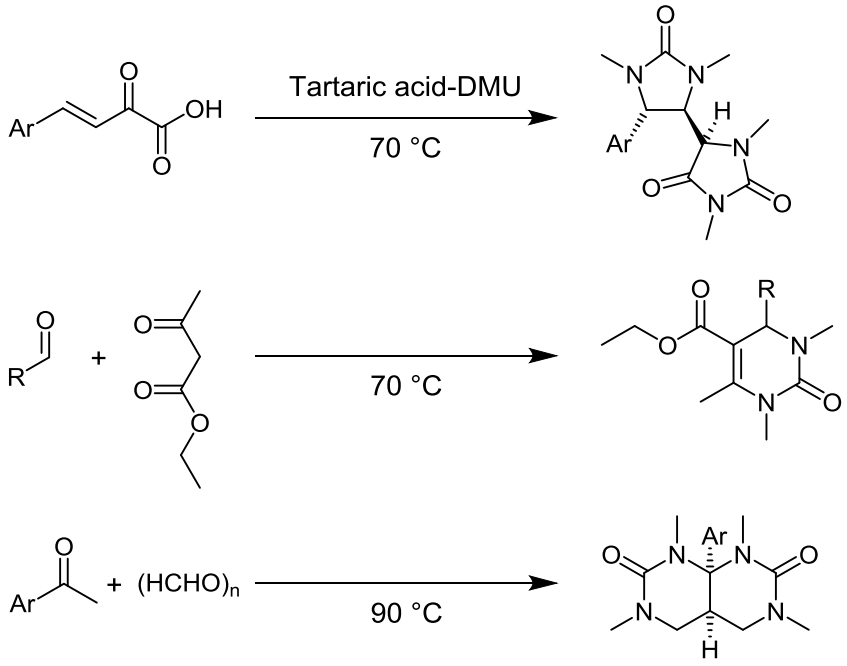


(glucose-urea-NH_4Cl 3:7:1)

Scheme 35. Synthesis of β-D-glycosyl urea in D-glucose–urea–NH_4Cl (3:7:1).[150]

The DES can even fulfill a triple role as reactant, solvent, and catalyst. An illustrative example is a DES composed of tartaric acid and dimethylurea (3:7), which was applied in the synthesis of hydantoins,[151] dihydropyrimidinones,[152] and pyrimido-pyrimidinediones[153] (Scheme 36). Due to its Brønsted acidity, this DES acts an

efficient catalyst for carbonyl activation, avoiding the use of strong and corrosive acids, which are often required in conventional reactions. Under these mild reaction conditions, most functional groups were found to be stable. Interestingly, in pyrimidopyrimidinedione synthesis, the DES could be recycled two times, although dimethylurea was consumed.[153]



Scheme 36. Synthesis of hydantoins, dihydropyrimidinones, and pyrimido-pyrimidinediones in tartaric acid–DMU (3:7).[151–153]

It is worth mentioning that the Brønsted acidity of DES allows their application as an inert catalyst as well. For example, ChCl–oxalic acid (1:1) catalyzes the synthesis of hydrazones from carbonyls and phenylhydrazine, resulting in high yields and short reaction times.[154]

Another example for a DES acting as reactant, catalyst, and solvent is the synthesis of bisamides from aromatic aldehydes and urea in ChCl–urea (1:2) at 80 °C. The products precipitated from the reaction mixture and were isolated in very good yields after 15 min. In conventional solvents, including ethyl acetate, acetonitrile, toluene, DMF, THF, and water, only moderate yields (10–48%) were observed.[155]

1.4.2.3 Conclusion

Similar to ILs, the application of a DES possesses several advantages over conventional organic solvents. DES acting as a recyclable catalyst-solvent system often result in higher yields and shorter reaction times and the reaction can be performed at mild conditions, including lower temperature, the exclusion of corrosive acids and bases or toxic and expensive catalysts. Furthermore, in DES, reactions of organometallic compounds (namely organolithium and Grignard compounds), which usually require low temperatures and the exclusion of air and moisture, can be simply performed without these precautions. Remarkably, the conversion of one or two of the DES components within a saccharide-based DES is a very promising alternative to the corresponding reactions in solution due to the high concentration of the reactants, resulting in improved yields, shorter reaction times, and higher selectivity.

The ability to fine-tune the chemical and physical properties by variation of the components is an advantage that DES share with ILs. However, in contrast to ILs, most DES are easily available from renewable feedstock, are biodegradable, cheap, and non-toxic. Furthermore, while the preparation of ILs require multi-step organic synthesis, DES can be simply prepared in high purity by mixing together the components and heating. Therefore, DES combine the remarkable physical properties of ILs, such as non-volatility, flammability, thermal stability, and high heat capacity, with a higher sustainability, which makes them a real “green” alternative to conventional solvents. While it is true that ILs can be obtained from renewable materials as well, their preparation still requires a chemical modification, whereas a DES can be prepared in one step by melting. Moreover, compared to some ILs, DES are not sensitive to water. However, DES often have a lower thermal stability than ILs, especially when one of the components is a saccharide; on the other hand, these DES mostly have high melting points of more than 60 °C, both characteristics decreasing the possible temperature range for an application in synthesis. Another challenge is the high viscosity of some DES. Furthermore, in contrast to most ILs, DES are not chemically inert and can interfere with the reaction. Though, while this is problematic when the DES is supposed to act as an inert solvent or catalyst, many approaches make use of the reactivity by converting the DES components itself, as explained above.[1,2,156,157]

1.5 Comparison of specific advantages and disadvantages

The individual advantages and limitations of the methods have been already discussed in the conclusion sections of the review. We summarize these again in Table 1 to allow a complete overview and highlight similar advantages in the same color. It must be noted that a direct comparison of the different methods is difficult. Each approach has its specific advantages and disadvantages and none of the approaches can be selected being superior over conventional reactions in organic solvents or in comparison with each other. The specific advantage of a solvent-free or unconventional solvent method comes with its specific application. Furthermore, the advantages and disadvantages given in Table 1 cannot be generalized; for each method, there may be examples refuting a given assignment. The comparison in Table 1 necessarily simplifies the specific issues of the different methods. In general, the absence of a conventional solvent brings several intrinsic benefits: solubility problems are avoided, side-reactions with the solvent cannot occur, and high concentrations often result in an increased reactivity. In addition, each method possesses typical advantages, but certain drawbacks as well. In this overview, we aimed to show where the use of a method is promising and where challenges and difficulties may emerge.

Table 1. Advantages and disadvantages of the methods discussed.

	Method	Advantages	Challenges
Solid	Mechano-chemistry	high reactivity no side-reactions with solvent no solubility problems new selectivities and pathways simple work-up (if quant. conv.) stoichiometric control	• up-scale • temp. control • online-analytics difficult for air,-moisture-sensitive reactions
	Photo-chemistry	no side-reactions with solvent simple work-up (if quant. conv.) stoichiometric control no solubility problems chemo-,stereoselective	crystals with high purity necessary temperature control is crucial
Liquid	Thermal	high reactivity no side-reactions with solvent no solubility problems simple work-up (if quant. conv.)	difficult temperature control (may require special equipment) challenging for viscous mixtures
	Photo-catalysis	high reactivity no side-reactions with solvent no solubility problems	special setups necessary difficult up-scale
New solvents	Ionic liquids	high reactivity no side-reactions with solvent may avoid solubility problems new selectivities and pathways may facilitate work-up simple catalyst recycling high reaction temperature possible	complicated preparation difficult purification may be moisture-sensitive may be toxic not biodegradable
	Deep-eutectic solvents	high reactivity may avoid solubility problems new selectivities and pathways may facilitate work-up simple catalyst recycling simple preparation insensitive to water non-toxic, biodegradable	lower thermal stability than ILs sometimes high viscosity and high melting points possible side-reactions reactant-DES

1.6 References

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2 Solvent-free, visible-light photocatalytic alcohol oxidations applying an organic photocatalyst

A method for the solvent-free photocatalytic conversion of solid and liquid substrates was developed, using a novel rod mill apparatus. In this setup, thin liquid films are realized, which is crucial for an effective photocatalytic conversion due to the low penetration depth of light in heterogeneous systems. Several benzylic alcohols were oxidized with riboflavin tetraacetate as photocatalyst under blue light irradiation of the reaction mixture. The corresponding carbonyl compounds were obtained in moderate to good yields.

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2.1 Introduction

According to a classification made by Wilhelm Ostwald, one of the pioneers in the field of physical chemistry and Nobel Prize laureate 1909, chemistry can be divided into the four sub-disciplines thermochemistry, electrochemistry, photochemistry, and mechanochemistry, depending on the kind of energy involved in a chemical process.[1] Among these, mechanochemistry is nowadays a well-established method for the solvent-free conversion of solid reactants. The reaction is driven by mechanical energy, which is for instance realized by grinding in ball mills or pestle and mortar. Obviously, this method possesses several advantages compared to reactions, which are performed in solution: toxic solvents and wastes are avoided, making the process more environmentally friendly and sustainable. Furthermore, quantitative yields can be achieved, avoiding work-up and laborious purification.[2] Moreover, solubility problems, like insolubility of one reactant or the different polarity of two reactants, are solved. Examples for mechanochemical syntheses include stoichiometric reactions such as the Knoevenagel condensation and the Wittig reaction, but also reactions catalyzed by metal catalysts, like the Sonogashira coupling and the Suzuki coupling.[1]

Photocatalysis, as a part of Ostwald's sub-discipline photochemistry, is a rather new field of great academic interest. Namely, visible-light photocatalysis applying an organic, redoxactive catalyst allows mild and efficient transformations. By exciting the photocatalyst, which then exchanges electrons with the substrate, light energy is converted into chemical energy.[3] This approach avoids expensive reagents and harsh reaction conditions, which are improvements compared to conventional processes. Considering that, we envisaged combining photocatalysis with mechanochemistry, thereby making use of the advantages of both disciplines. In such an approach, solid substrates would be grinded under visible light irradiation. In contrast to mechanochemistry, the process would be driven by light energy and not by mechanical energy, but profit from the absence of toxic solvents, high concentrations of the substrate, and easy work-up. Furthermore, undesired effects of the solvent like hydrogen-atom transfer or the formation of byproducts could be excluded.

For liquid substrates, some examples for photocatalytic, solvent-free conversions are reported, such as the oxidation of benzyl alcohol to benzaldehyde[4] and the

oxidation of benzenes to phenols.[5] Another field of solvent-free photocatalysis is the application of heterogeneous, semiconducting photocatalysts, often based on titanium dioxide and other metal oxides.[6–8] However, to the best of our knowledge, no solvent-free visible-light driven transformation of a solid substrate applying an organic photocatalyst has been reported yet.

In this work, we present a novel milling apparatus, which we developed especially for the conversion of solid substrates. Applying this apparatus, the solvent-free oxidation of various benzylic alcohols to their corresponding carbonyl compounds using riboflavin tetraacetate as photocatalyst under blue light irradiation was performed. Furthermore, the oxidation of a liquid benzylic alcohol is presented as well.

2.2 Results and Discussion

For our investigations on solvent-free photocatalytic conversions, we chose riboflavin tetraacetate (RFTA) as photocatalyst. RFTA and flavin derivatives in general are well-known blue light absorbing photocatalysts, which can oxidize a variety of substrates under aerobic conditions with oxygen as terminal oxidant. Flavins were studied extensively for the oxidation of alcohols, amines, methylbenzenes, styrenes, and phenylacetic acids.[9–12] Some derivatives were also immobilized on silica gel and applied in the oxidation of benzyl alcohols.[13] Furthermore, it was shown that the oxidation power of RFTA can be increased by coordination to scandium triflate.[14] Recently, the E/Z-isomerization of olefins with riboflavin as catalyst was reported,[15] which was also used for cyclization to form coumarins.[16]

In this work, we focus on benzylic alcohols as substrates since their oxidation to the corresponding carbonyl compounds can be simply performed in acetonitrile/water mixtures. Thus, they are suitable model substrates for the investigation of our solvent-free principle.

In mechanochemistry, reactions are performed by grinding the reaction mixture in ball mills, such as the vibrational ball mill or the planetary ball mill, or with a pestle and mortar. In preliminary studies, we tested a vibrational ball mill for photocatalytic oxidations with RFTA, using a transparent milling chamber. However, this reactor

proved to be unsuitable: the solid reaction mixture prevented light to reach the photocatalyst, both by attachment of small amounts of solid to the inner side and shielding within the milling chamber. The low penetration depth of light led us to the conclusion that thin interfaces of reactants, combined with continuous grinding, are necessary. Based on these considerations, we constructed a rod mill, consisting of a test tube which contains the reaction mixture, a glass rod, which is fixed to a stirrer, and an LED frame with 5 LEDs (λ = 455 nm). Figure 1 shows a schematic representation and photographs. Before reaction, the solid substrate and photocatalyst are gently homogenized with a spatula, followed by grinding with pestle and mortar. The reaction mixture is then filled into the test tube. Subsequently, the rotating glass rod is pressed into the test tube, which leads to vertical migration of the reaction mixture and the formation of a film between the inner wall of the test tube and the glass rod. The reaction is carried out by rotation and irradiation with the LEDs from the outside.

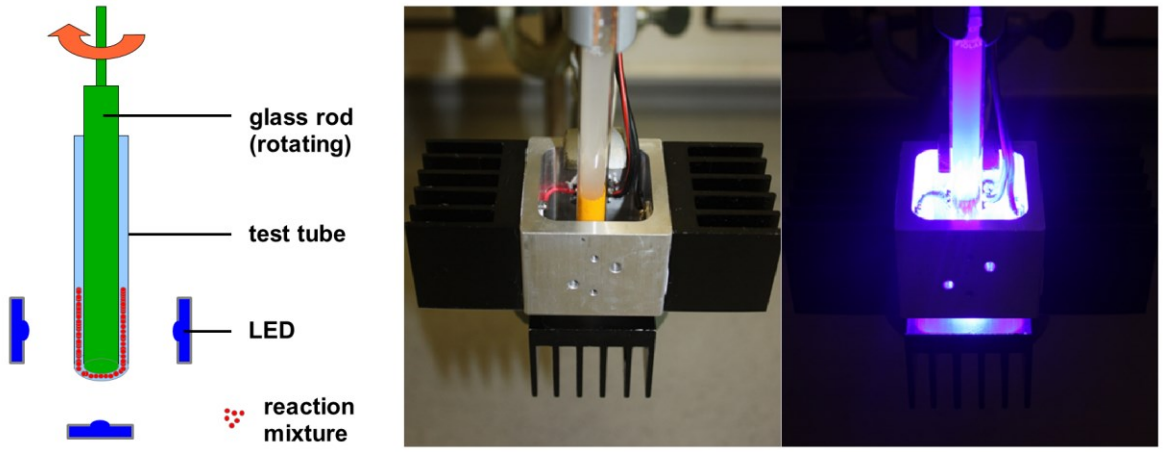
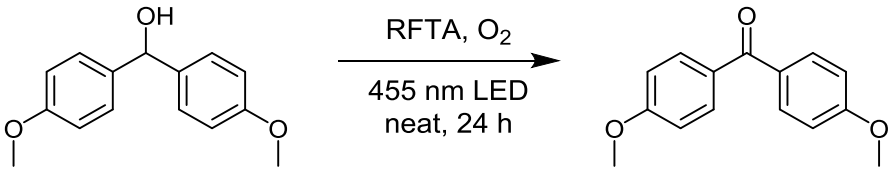


Figure 1. Rod mill, schematic (left) and photographs (middle and right).

We started our investigations with the oxidation of 4,4'-dimethoxybenzhydrol (**1a**) to 4,4'-dimethoxybenzophenone (**1b**), applying 10% RFTA (Scheme 1).

In this initial trial, the product could be obtained in 72% yield (entry 1, Table 1). Subsequently, we varied the amount of RFTA. Lowering the catalyst concentration from 10% to 5% does not significantly influence the yield (entry 2, yield in average of four trials). Even a further decrease to 2% (entry 3) causes no essential decline. However, at a RFTA concentration of 1% (entry 4), the isolated yield was only 61%; very low catalyst concentrations are problematic due to inactivation of a certain portion of the catalyst, which might be due to burning.



1a **1b**

Scheme 1. Oxidation of 4,4'-dimethoxybenzhydrol (**1a**) to 4,4'-dimethoxybenzophenone (**1b**).

No product was formed in the dark (entry 5) and only traces were obtained without photocatalyst (entry 6). However, in this control reaction, melting of the substrate was observed. All reaction mixtures containing RFTA appeared solid.

Table 1. Conditions and yields for the oxidation of 4,4'-dimethoxybenzhydrol (**1a**).

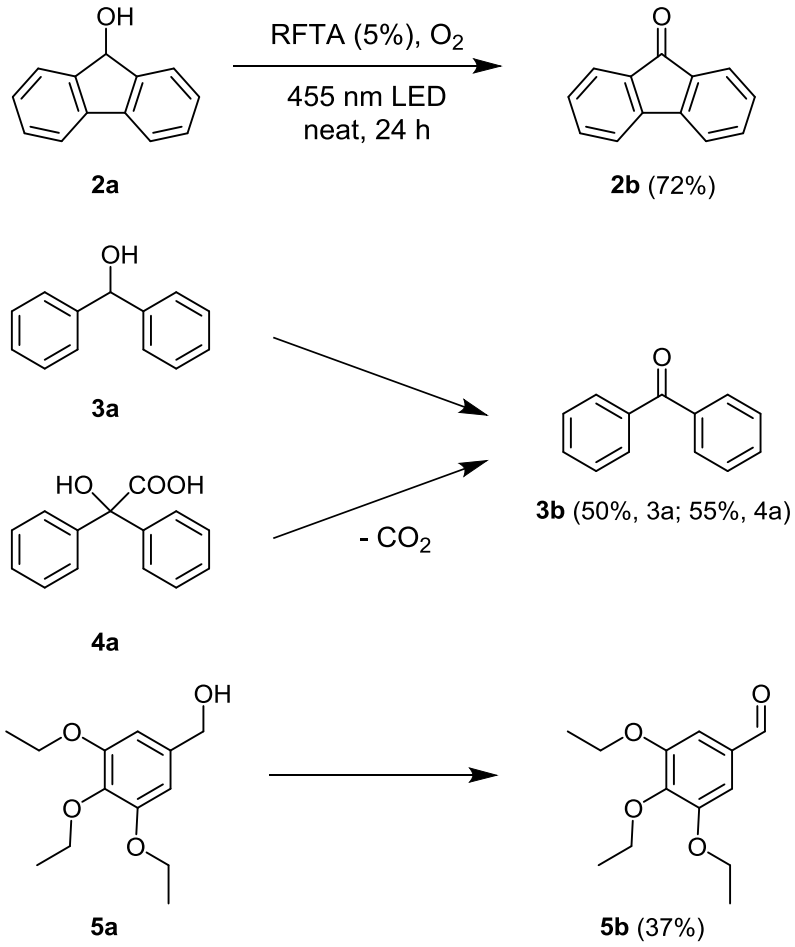
Entry	RFTA (%)	Yield (%)
1	10	72
2	5	74
3	2	69
4	1	61
5[a]	10	0
6	–	traces
7[b]	5	traces
8[c]	5	traces
9[d]	5	78

[a] in the dark; [b] in the dark at 85 °C; [c] with cooling; [d] no rotation.

The fact that the substrate was molten without RFTA leads to the conclusion that the blue light irradiation was heating the substrate and temperatures higher than its melting point (67–70 °C) occurred. The temperatures of the reaction mixtures were measured using an IR thermometer. Though, values not higher than 42 °C were obtained. This could be explained by the fact that the IR thermometer records only the surface temperature of the test tube; the temperature within the reaction mixture might be above this value. When the reaction mixture was heated to 85 °C in the dark, melting was observed (entry 7) and only traces of product were formed, showing that the oxidation of the substrate is not only due to heating. For further investigation, the reaction was performed within a continuous water cooling (entry 8). In this setup, no product was formed. Therefore, the heating effect of the blue

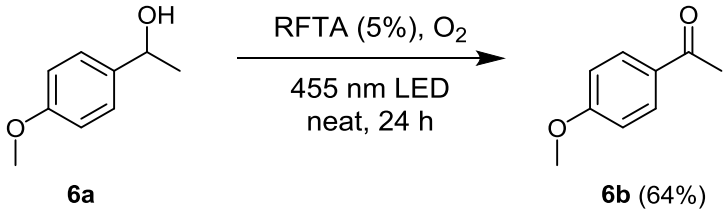
light was found to be necessary to perform the reaction: melting of the substrate leads to mobility of the substrate and catalyst molecules, ensuring the occurrence of the catalytic cycle. When the rotation was switched off after the formation of the solid film (2 min), followed by LED irradiation (entry 9), the product was obtained in similar yield compared to the reactions performed under grinding (entry 2), indicating that the grinding does not contribute to the essential heating. Hence, light irradiation fulfils a double function: the excitation of the photocatalyst and melting of the substrate, inducing mobility of the molecules. As mentioned above, the reaction mixtures containing RFTA appeared solid. Possibly, small droplets of molten substrate were formed; due to the presence of RFTA, no homogeneous liquid phase was observed. In mechanochemistry, the formation of hot spots by friction heating with high local temperatures and the existence of liquid eutectic states are believed to be responsible for chemical transformations.[1] In contrast, in our rod mill apparatus, heating is not induced by mechanical but by electromagnetic energy input, realized by blue light irradiation. Furthermore, the heat input is not the primary cause for the reaction, but its prerequisite.

Subsequently, the scope of the benzylic alcohol oxidation was investigated, applying 5% of RFTA. Four solid alcohols were oxidized to their corresponding ketones or aldehydes, including fluorenol (9-hydroxyfluoren), benzhydrol, benzilic acid, and 3,4,5-triethoxybenzylalcohol (**2a**–**5a**). Scheme 2 shows the products and isolated yields, which are in the range from 37% to 72%. In contrast to 4,4'-dimethoxybenzhydrol, a liquid paste was observed in all cases, indicating melting of the substrate or the product, which maintains mobility. The oxidation of benzilic acid and benzhydrol was also performed using an LED setup containing only 4 LEDs instead of 5 LEDs like in the frame rod mill. Here, the obtained yields were significantly lower (36% and 30% vs. 55% and 50%). This shows that the amount of energy reaching the reaction mixture plays a crucial role.



Scheme 2. Scope for benzylic alcohol oxidation and obtained yields.

Furthermore, the suitability of the rod mill for the conversion of liquid substrates was tested. 1-(4-Methoxyphenyl)ethanol was oxidized applying 5% of RFTA (Scheme 3).



Scheme 3. Oxidation of 1-(4-methoxyphenyl)ethanol (**6a**) to 4-methoxyacetophenone (**6b**).

The crude ^{1}H NMR spectrum recorded after the reaction shows a quantitative conversion of the starting material and no visible by-product formation (see Experimental). In general terms, this shows the potential of this method for an efficient synthesis with direct product formation, facilitating work-up. However, the isolated yield of the product **6b** was only 64% (average of two trials), indicating loss

in the column purification process and decomposition of a part of the product in the reaction mixture.

2.3 Conclusion

We have developed a method for the solvent-free photocatalytic conversion of solid and liquid substrates using a novel rod mill apparatus. The applicability of the rod mill was shown for the oxidation of benzylic alcohols with riboflavin tetraacetate as photocatalyst under blue light irradiation; the products were isolated in moderate to good yields. In case of the solid benzyl alcohols, the reactions were found to proceed via the molten state of the substrates or products, which enables mobility of the substrate and catalyst molecules and the occurrence of the catalytic cycle. Thus, light fulfils the double function of both the excitation of the photocatalyst and heating of the reaction mixture.

To summarize, the new combination of photocatalysis and mechanochemistry, realized in a simple rod mill apparatus is an alternative to conventional reaction setups. It may provide advantages for the conversion of starting materials or catalysts with no or low solubility in the same solvent and reactions benefitting from high substrate concentrations.

2.4 Experimental

2.4.1 Materials and methods

NMR spectra were recorded on a Bruker Avance 300. 4,4'-Dimethoxybenzhydrol was purchased from Alfa Aesar, 9-hydroxyfluoren, benzhydrol, and 3,4,5-triethoxybenzaldehyde from Sigma-Aldrich, benzilic acid from Merck Schuchardt and 1-(4-Methoxyphenyl)ethanol from Fluorochem. Riboflavin tetraacetate was synthesized from riboflavin (Acros Organics) according to a procedure reported in the literature.[17]

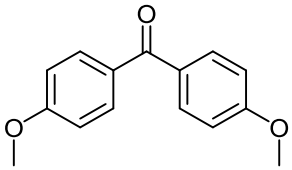
Technical data of the rod mill apparatus: 4 LEDs (455 nm, 700 mA) on a square aluminium frame (inner diameter 35 mm) and one LED below the test tube were

used. The distance of each LED to the test tube was 10 mm. The diameter of the glass rod was 8 mm and the inner diameter of the test tube was 9 mm.

2.4.2 Synthesis

General procedure: The substrate and riboflavin tetraacetate were weighed into a mortar in stoichiometric amounts and gently homogenized with a spatula, followed by grinding with a pestle. The reaction mixture was filled into the rod mill test tube and the mass was determined. Subsequently, the rotating glass rod was pressed into the test tube, forming a film between the test tube and the glass rod. The reaction was carried out by rotation of the glass rod (80 rpm) and parallel irradiation with the 455 nm LEDs for 24 hours. After the reaction, the product was isolated by flash column chromatography (gradient of ethyl acetate in petroleum ether).

4,4'-Dimethoxybenzophenone (1b)

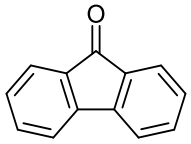


^{1}H NMR (300 MHz, $CDCl_3$): 7.84–7.73 (m, 4H), 7.01–6.91 (m, 4H), 3.88 (s, 6H). EI-MS m/z calculated for $C_{15}H_{14}O_3$ $[M]^+$: 242.0943, found: 242.0924.

Entry*	Amount, weighed (mg/mmol)		(trial)	Total mass for reaction (mg)	Yield (%)
	substrate	RFTA			
1	85.5/0.35	19.1/0.035	–	77.2	72
2	85.5/0.35	9.5/0.018	1	76.7	70
			2	76.3	79
			3	81.4	70
			4	83.2	76
3	97.7/0.4	4.4/0.008	–	83.5	69
4	97.7/0.4	2.2/0.004	–	76.6	61
9	85.5/0.35	9.5/0.018	–	81.9	78

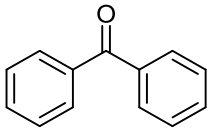
*In Table 1.

9-Fluorenone (2b)



9-Hydroxyfluorene (82.0 mg, 0.45 mmol) and RFTA (12.3 mg, 0.023 mmol) were weighed and 70.6 mg of the mixture was used for reaction. Yield: 72%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.66 (d, 2H), 7.54–7.47 (m, 4H), 7.30 (td, J = 7.3, 1.3 Hz, 2H). EI-MS m/z calculated for $C_{13}H_8O$ $[M]^+$: 180.0575, found: 180.0579.

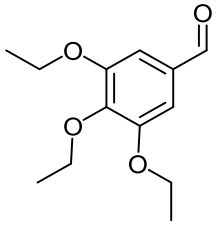
Benzophenone (3b)



3b from **3a**: Diphenylmethanol (73.3 mg, 0.40 mmol) and RFTA (10.9 mg, 0.020 mmol) were weighed and 74.0 mg of the mixture was used for reaction. Yield: 50%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.83–7.79 (m, 2H), 7.62–7.57 (m, 2H), 7.51–7.46 (m, 4H). EI-MS m/z calculated for $C_{13}H_{10}O$ $[M]^+$: 182.0732, found: 182.0730.

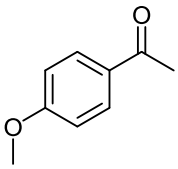
3b from **4a**: Benzylic acid (91.3 mg, 0.40 mmol) and RFTA (10.9 mg, 0.020 mmol) were weighed and 89.2 mg of the mixture was used for reaction. Yield: 55%.

3,4,5-Triethoxybenzaldehyde (5b)



3,4,5-Triethoxybenzyl alcohol (96.1 mg, 0.40 mmol) and RFTA (10.9 mg, 0.020 mmol) were weighed and 82.3 mg of the mixture was used for reaction. Yield: 37%. ^{1}H NMR (300 MHz, $CDCl_3$): 9.82 (s, 1H), 7.08 (s, 1H), 4.17–4.09 (m, 6H), 1.45 (t, 6H), 1.36 (t, 3H).

4-Methoxyacetophenone (6b)



Riboflavin tetraacetate was ground with pestle and mortar before use. 1-(4-Methoxyphenyl)ethanol and riboflavin tetraacetate were weighed into the rod mill test tube and the mixture was sonicated for 1 min. The rotating glass rod was pressed into the test tube, forming a film between the test tube and the glass rod. The reaction was carried out by rotation of the glass rod (80 rpm) and parallel irradiation with the 455 nm LEDs for 24 hours. After the reaction, the product was isolated by flash column chromatography (gradient of ethyl acetate in petroleum ether). Trial 1: 1-(4-Methoxyphenyl)ethanol (82.2 mg, 0.54 mmol) and RFTA (14.0 mg, 0.03 mmol) were used. Yield: 63%. Trial 2: 1-(4-Methoxyphenyl)ethanol (178.5 mg, 1.17 mmol) and RFTA (31.9 mg, 0.06 mmol) were used. Yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$): 8.01–7.82 (m, 2H), 6.96–6.85 (m, 2H), 3.87 (s, 3H), 2.55 (s, 3H). CI-MS m/z calculated for $C_9H_{10}O_2$ $[MH]^+$: 151.0759, found: 151.0771.

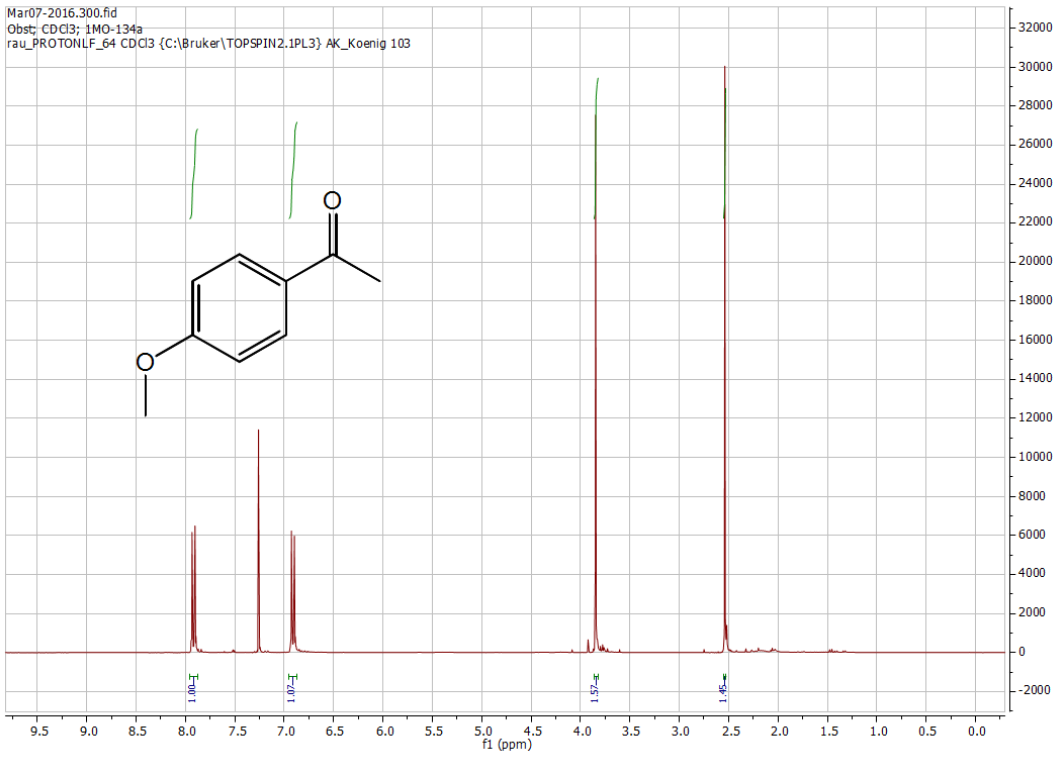


Figure 2. ^{1}H NMR (crude) of 4-methoxyacetophenone **6b**.

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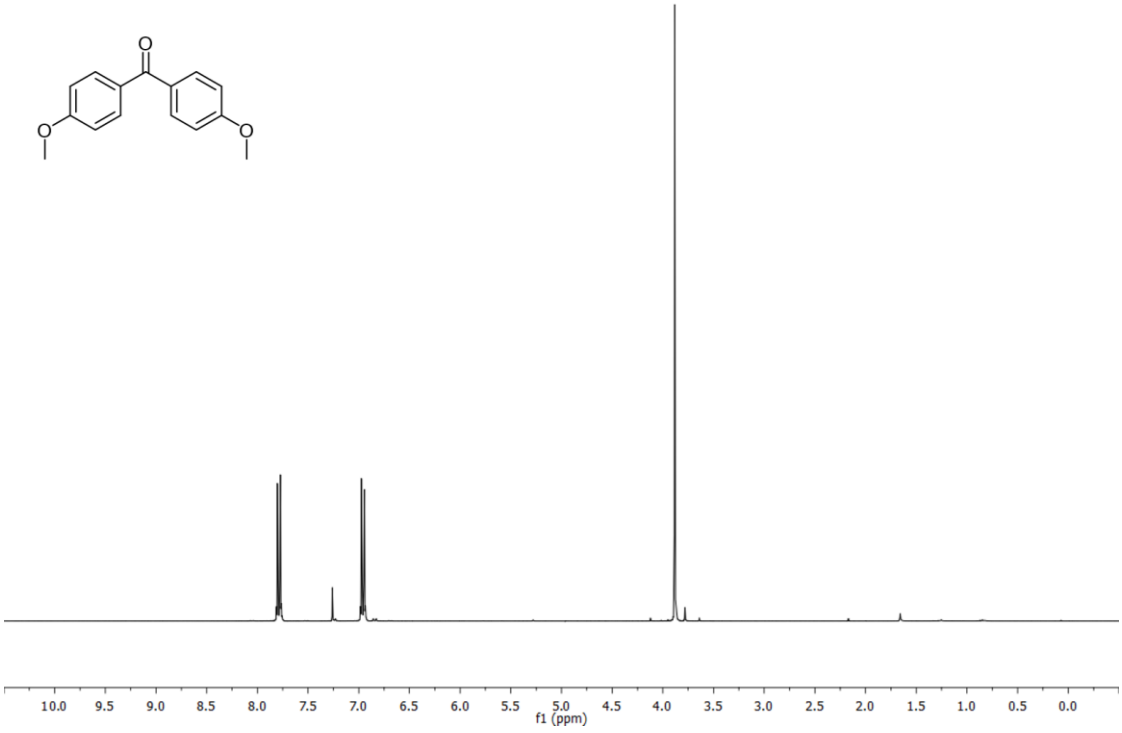
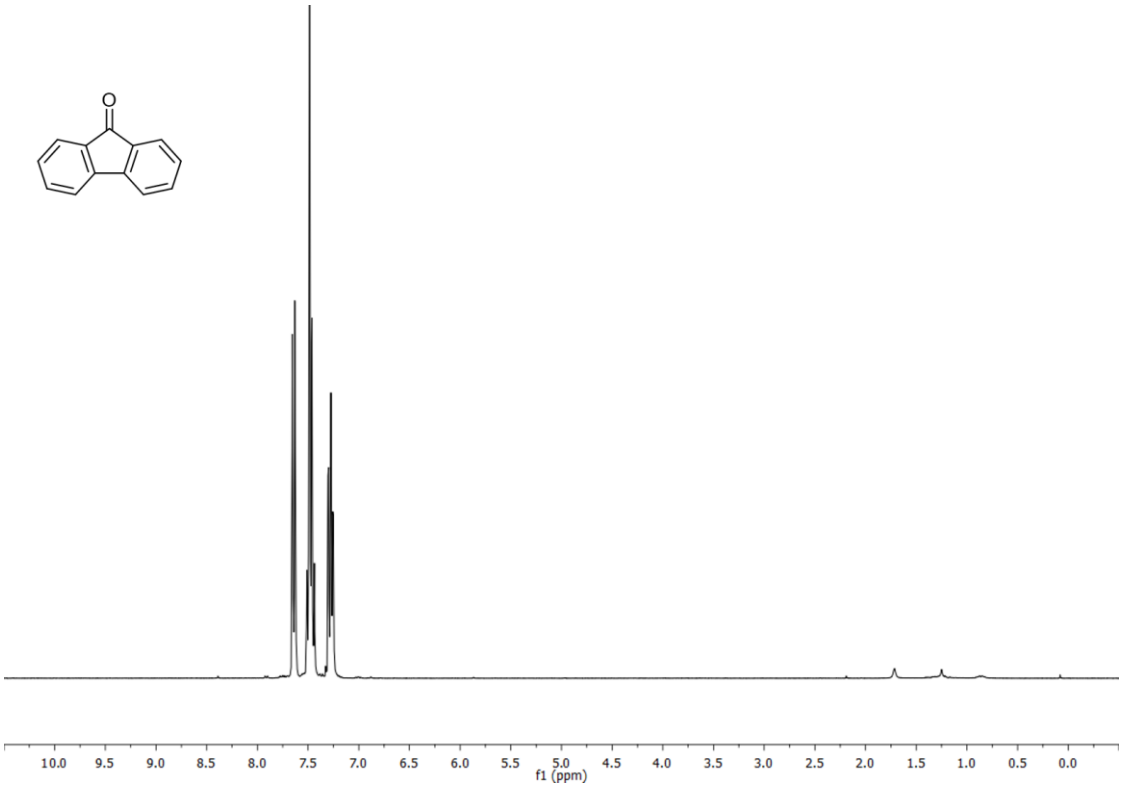
2.6 NMR Spectra

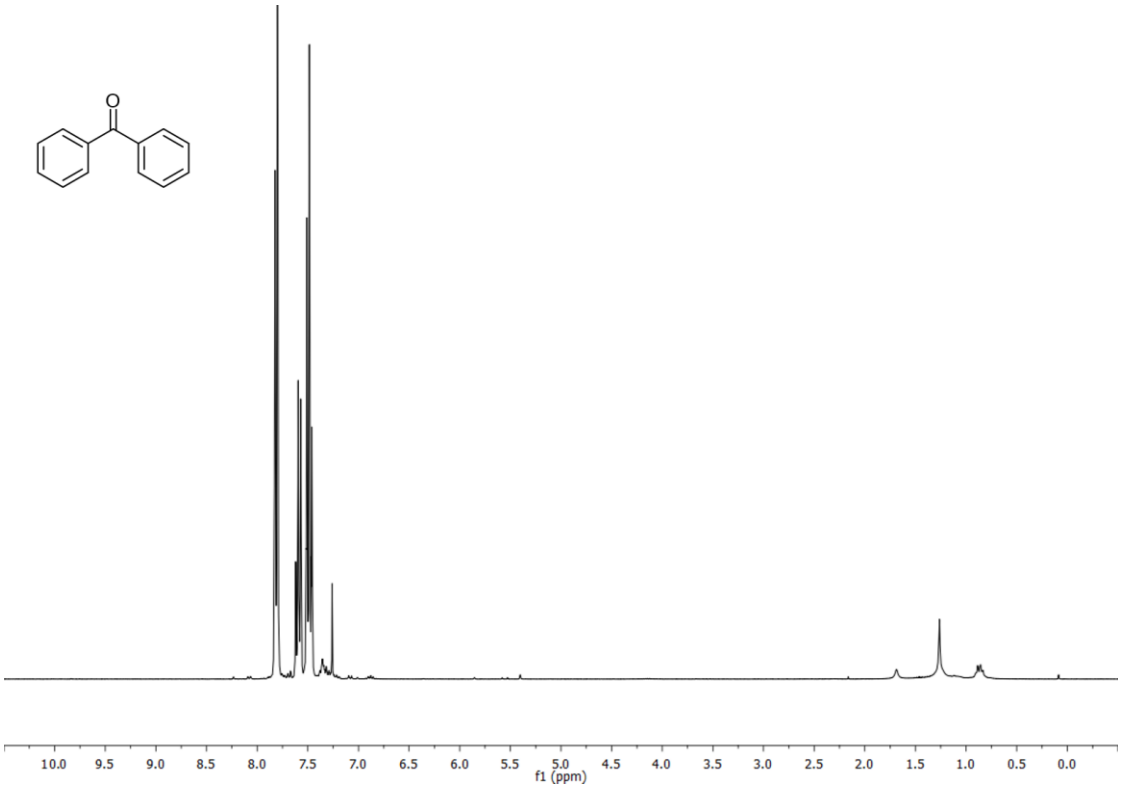
4,4'-Dimethoxybenzophenone (1b): ^{1}H NMR (300 MHz, $CDCl_3$)



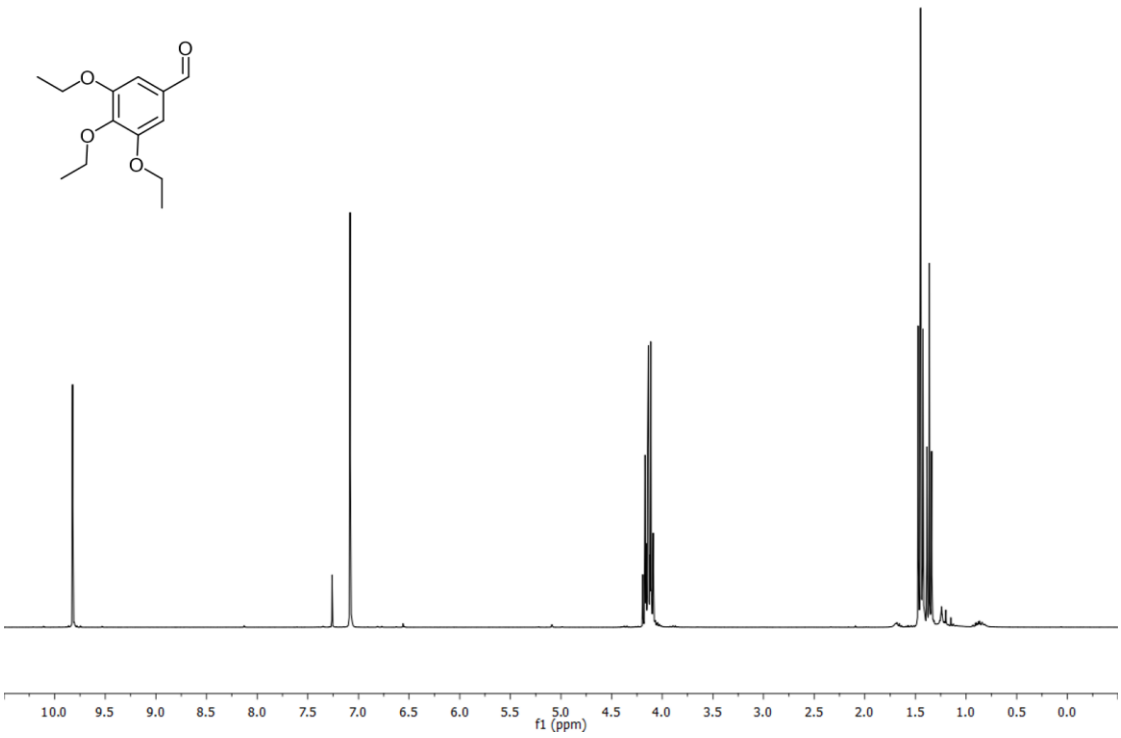
9-Fluorenone (2b): ^{1}H NMR (300 MHz, $CDCl_3$)



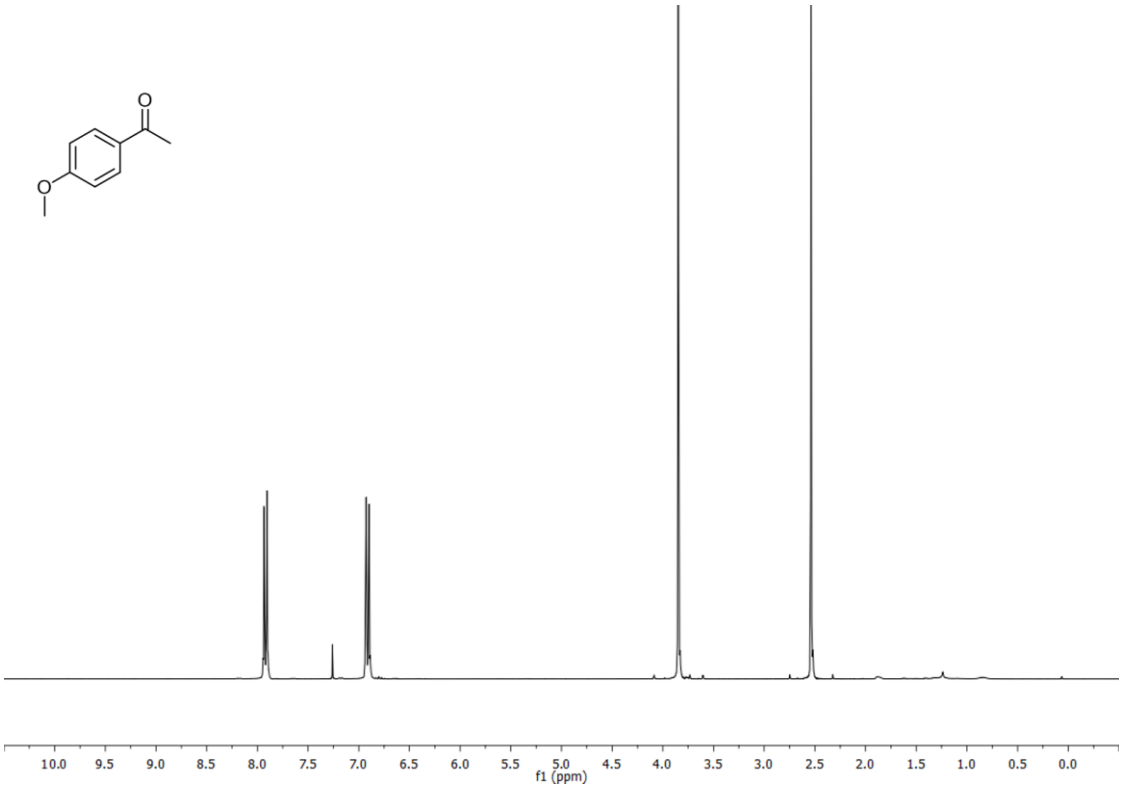
Benzophenone (3b): ^{1}H NMR (300 MHz, $CDCl_3$)



3,4,5-Triethoxybenzaldehyde (5b): ^{1}H NMR (300 MHz, $CDCl_3$)



4-Methoxyacetophenone (6b): ^{1}H NMR (300 MHz, $CDCl_3$)



3 Solvent-free coupling of aryl halides with pyrroles applying visible-light photocatalysis

A novel reactor for solvent-free, visible-light-driven photocatalytic transformations was developed. By rotation of the reaction vessel, the reaction mixture forms a thin film, which allows efficient excitation of the photocatalyst. The reactor was used for the coupling of aryl halides with pyrrole derivatives and phosphites, applying rhodamine 6G as the photocatalyst and *N,N*-diisopropylethylamine as the sacrificial electron donor. The necessary amounts of photocatalyst, trapping reagent, and sacrificial electron donor were reduced significantly compared to those for literature known reactions in solution, while isolating the products in moderate to good yields. In general terms, this solvent-free methodology is an interesting alternative to solution photocatalysis due to the presence of high mole fractions of trapping reagent, the exclusion of by-products formed with the solvent, and the reduction of toxic solvent waste.

This chapter was published: M. Obst, R. S. Shaikh, B. König, *React. Chem. Eng.* **2017**, *2*, 472. Reproduced by permission of the Royal Society of Chemistry. *Author contributions:* M.O. developed the reactor, performed the photocatalytic reactions and wrote the manuscript. M.O. and R.S.S. developed the concept of the project. B.K. supervised the project and is corresponding author.

3.1 Introduction

Visible-light photocatalysis applying an organic photoredox catalyst is a valuable approach for mild and efficient transformations.[1,2] Harsh reaction conditions and expensive reagents are avoided and the use of light energy often enables reactions, which are kinetically hindered or endothermic. The conversion of light energy into chemical redox power is achieved by the excitation of a visible-light-absorbing photocatalyst and subsequent electron transfer, leading to an organic transformation.[2,3] Typically, photocatalytic reactions are performed in solution. However, in many cases, it is helpful to perform reactions under solvent-free conditions as undesired side reactions with the solvent, such as hydrogen atom transfer, can be avoided and the formation of byproducts is minimized. Furthermore, the absence of a solvent leads to high reactant and catalyst concentrations, which can be advantageous as the trapping of a reactive intermediate should be favored by the presence of high amounts of trapping reagent. In the case of quantitative product formation, work-up is significantly facilitated.[4] Reports on solvent-free visible-light photocatalysis are quite limited, including the oxidation of benzyl alcohol with an organic photocatalyst,[5] the oxidation of benzenes to phenols,[6] the use of fullerenes linked to silica gel for the oxidation of various organic substrates,[7] and the application of semiconducting photocatalysts, such as titanium dioxide and other metal oxides.[8–10] Recently, we reported the solvent-free oxidation of benzylic alcohols applying riboflavin tetraacetate as a photocatalyst under blue light irradiation. The reactions were run in a novel milling apparatus, suitable for the conversion of solid substrates.[11]

Herein, we developed a methodology for solvent-free photocatalytic conversions applying an organic photocatalyst in order to combine the advantages of photocatalysis and solvent-free operation. For this purpose, we constructed a novel reactor, which is suitable for efficient photocatalytic transformations of viscous reaction mixtures, realized by the formation of thin films. When searching for an adequate model reaction to establish our methodology, our attention was drawn to C-C coupling reactions. Palladium-catalyzed cross-coupling reactions are widely applied in organic synthesis, including important and valuable standard methods such as the Heck, Suzuki, Stille, Negishi, and Sonogashira coupling reaction.[12–15] Due to the sensitivity of palladium-based catalysts to oxygen and water, dry solvents

must be used and the reaction must be performed in an inert atmosphere. Therefore, many attempts have been made to perform cross-coupling reactions under solvent-free conditions.[16] In this context, mechanochemistry proved to be very useful: Heck, Suzuki, and Sonogashira coupling reactions were performed in a ball mill in an aerobic environment.[17–19] Recently, C-C coupling reactions were realized by applying visible-light photocatalysis: aryl radicals (generated from the corresponding halides) were coupled with pyrroles, using rhodamine 6G as the photocatalyst under blue light irradiation and *N,N*-diisopropylethylamine (DIPEA) as the sacrificial electron donor. This system was established by our group and is a very promising approach due to its mild reaction conditions and high functional group tolerance.[20] However, high amounts of trapping reagent, DIPEA, and rhodamine 6G are necessary. Thus, through its transfer to solvent-free conditions, we aspired to both the improvement of the catalytic system from an atom-economic point of view and the development of a new photocatalytic methodology.

3.2 Results and Discussion

Our target reaction was the coupling of aryl halides and pyrroles with rhodamine 6G as the photocatalyst. Aryl halides possessing an electron-withdrawing moiety, such as nitrile or ester, can be applied as substrates to generate an aryl radical. Upon blue light absorption, rhodamine 6G is excited and reduced by a sacrificial electron donor yielding the rhodamine 6G radical anion. This can be excited again by blue light (450 nm) transferring an electron to the substrate and regenerating rhodamine 6G in the ground state, the reduction being the rate-determining step as the rate depends on the substituents present in the aryl halide. The aryl halide radical anion cleaves into a halogen anion and an aryl radical, which attacks the pyrrole. The resulting radical is oxidized and deprotonated restoring the heteroaromatic π-system to give the sp2-sp2 coupling product. In general, the crucial point in the catalytic mechanism is the fast trapping of the reactive aryl radical by the pyrrole derivative in order to prevent side reactions such as the formation of the reduced by-product by hydrogen atom abstraction from the solvent. Recently, this was realized by applying high amounts of the trapping reagent, typically 13 to 26 equivalents relative to the substrate.[20] However, for effective trapping, not only the amount but also the mole fraction of the trapping reagent, χ(tr), must be considered.

It is defined as the molar amount of the trapping reagent, n(tr), divided by the total amount of all substances present in the reaction mixture (sub = substrate; solv = solvent; Rh = rhodamine 6G):

$$\chi(\mathrm{tr}) = \frac{\mathrm{n(tr)}}{\mathrm{n(tr)} + \mathrm{n(sub)} + \mathrm{n(solv)} + \mathrm{n(Rh)} + \mathrm{n(DIPEA)}}$$

Keeping the amount of substrate, rhodamine 6G, and DIPEA constant, a high χ(tr) is equal to a high trapping reagent/substrate ratio, which favors the trapping, which is why we envisaged to maximize the χ(tr) value. In this context, the amounts of both the trapping reagent and the solvent can be varied. The coupling of *ortho*-bromobenzonitrile to *N*-methylpyrrole was recently performed applying 10% rhodamine 6G and 1.4 equivalents of DIPEA in DMSO.[20] For this system, Figure 1 shows the mole fraction of the trapping reagent and its dependence on the amounts of the trapping reagent and solvent, with fixed amounts of substrate, rhodamine 6G, and DIPEA. In the literature, the reaction of 0.1 mmol of substrate in 1.5 mL (21.1 mmol) of DMSO is reported.[20] As illustrated in Figure 1, an increase of n(tr) at that amount of solvent raises the χ(tr) value only slightly, and high n(tr) values are necessary. A more elegant and simple way to increase χ(tr) is to decrease the amount of solvent. By doing so, χ(tr) reaches its maximum when no solvent is used at all, given a certain n(tr) value. In the solvent-free system, a slight increase of n(tr) causes a strong increase of χ(tr) (dashed graph), whereas it is practically impossible to reach a comparable χ(tr) value when 21.1 mmol of solvent is present. In other words, solvent-free operation achieves much higher χ(tr) values at lower amounts of trapping reagent, compared to reactions in solution. While 1.8 mmol (18 eq.) of trapping reagent corresponds to a χ(tr) of ca. 0.08 in solution, a more than tenfold value (0.88) is achieved in the solvent-free system. Consequently, by transferring the catalytic system to solvent-free conditions, it should be possible to significantly reduce the necessary amount of trapping reagent and, by that, to improve the atom economy. Another issue is the oxidation of the sacrificial electron donor (DIPEA) by the excited rhodamine 6G. In solvent-free operation, the resulting high concentration of DIPEA should favor the effective reduction of rhodamine 6G and hinder the undesired deactivation by fluorescence.

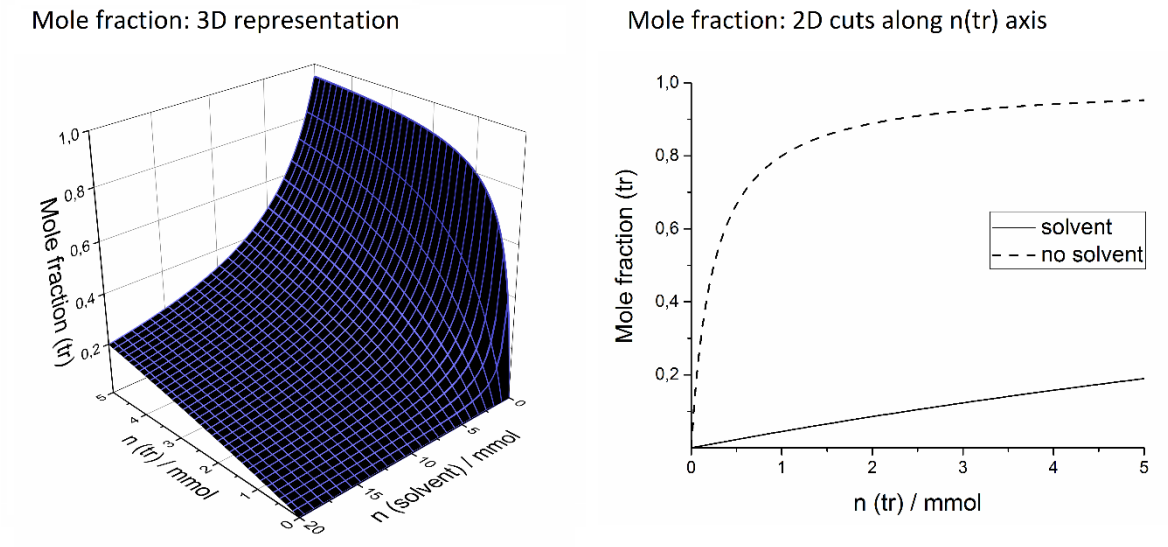


Figure 1. Left: Dependence of the mole fraction of the trapping reagent (*N*-methylpyrrole) on the amount of the trapping reagent and solvent. Right: Dependence on the amount of the trapping reagent with (21.1 mmol, 1.5 mL) and without the solvent.

We began the development of the solvent-free photocatalytic methodology by designing a suitable reactor. Solvent-free photocatalysis bears several challenges, excluding the application of conventional laboratory reaction setups. First, the penetration depth of light in heterogeneous systems is low, because of scattering by solid particles and absorption of light by catalyst molecules in the outer part of the reaction mixture, which leads to shielding of the catalyst molecules and impedes their excitation. The latter can be critical even in homogeneous solution, especially at high catalyst concentrations.[21] Considering the much higher catalyst concentrations in solvent-free systems, it becomes obvious that this is the main issue, which must be addressed when constructing a reactor. Another problem is the limited diffusion in solvent-free systems: depending on the reactants, more or less viscous pastes are formed and the realization of catalytic cycles is difficult. It is often crucial that charge and energy transfer can occur quickly, which requires mobility of both catalyst and reactant molecules within the reaction mixture. Furthermore, homogenization is a demanding task due to the high viscosity, excluding the use of a magnetic stirrer.

From all these considerations, we draw the conclusion that it is necessary to realize thin films of the reaction mixture in order to achieve a high relative surface area, which is crucial for efficient excitation of the photocatalyst. Based on this, we

recently constructed a rod mill apparatus, which is suitable for the conversion of solid substrates. Therein, a film of the reaction mixture is realized, which enables efficient excitation of the photocatalyst. Using the reactor, we could oxidize several benzylic alcohols to their corresponding carbonyl compounds with riboflavin tetraacetate under blue light irradiation with oxygen as the terminal oxidant.[11] The novel “rotating film reactor”, suitable for the conversion of paste-like mixtures, is shown in Figure 2. It consists of a crimp glass vial similar to the ones used for homogeneous photocatalysis. It is fixed to a glass stick, which is linked to a KPG stirrer, and can be closed with a septum to achieve inert conditions, or left open, which is necessary for reactions with oxygen as the terminal oxidant. The glass vial is surrounded by four LEDs installed on an aluminum frame. A reaction is performed by filling the reaction mixture into the vial, followed by transfer to inert conditions, if necessary, and sonication in an ultrasonic bath. The vial is then fixed on the KPG stirrer and the rotation is switched on (1200 rpm). The resulting centrifugal force presses the reaction mixture against the inner wall of the vial, forming a film. Eventually, the LEDs are switched on and the reaction can proceed.

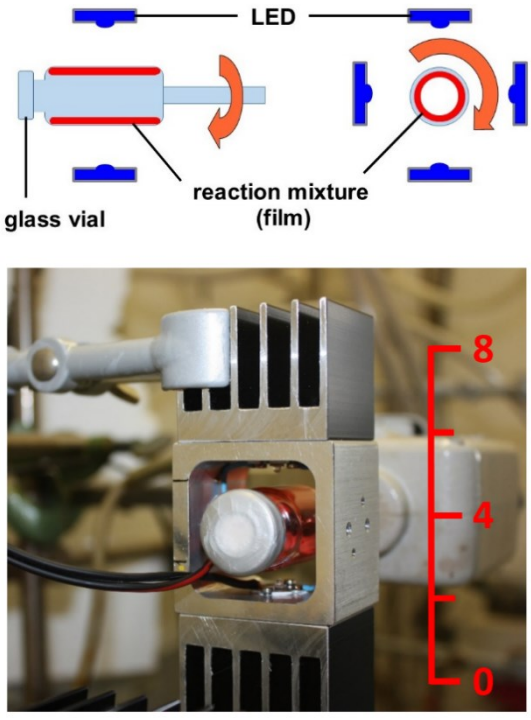
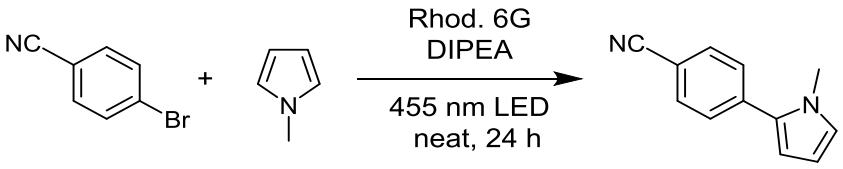


Figure 2. Rotating film reactor, schematic (side and front view) and photograph (numbers on the ruler indicate cm).

In order to evaluate the rotating film reactor and to optimize the reaction conditions, we applied *para*-bromobenzonitrile as the substrate and *N*-methylpyrrole as the trapping reagent, leading to the C-C coupling product **1** (Table 1).

Table 1. Optimization of reaction conditions for the coupling of *para*-bromobenzonitrile with *N*-methylpyrrole to produce **1** with isolated yields.



Entry	Rhodamine 6G (%)	*N*-Methylpyrrole (eq.)	DIPEA (eq.)	Yield (%)
1	10	3	1.0	38
2	5	3	1.0	50
3	2	5	1.0	60
4	2	5	1.5	49
5	10	5	1.2	60
6	10	5	1.4	58
7	0	5	1.0	5[a]
8	5	5	0	21[a]
9[b]	5	5	1.0	0[a]

[a] conversion, determined by GC; [b] in the dark

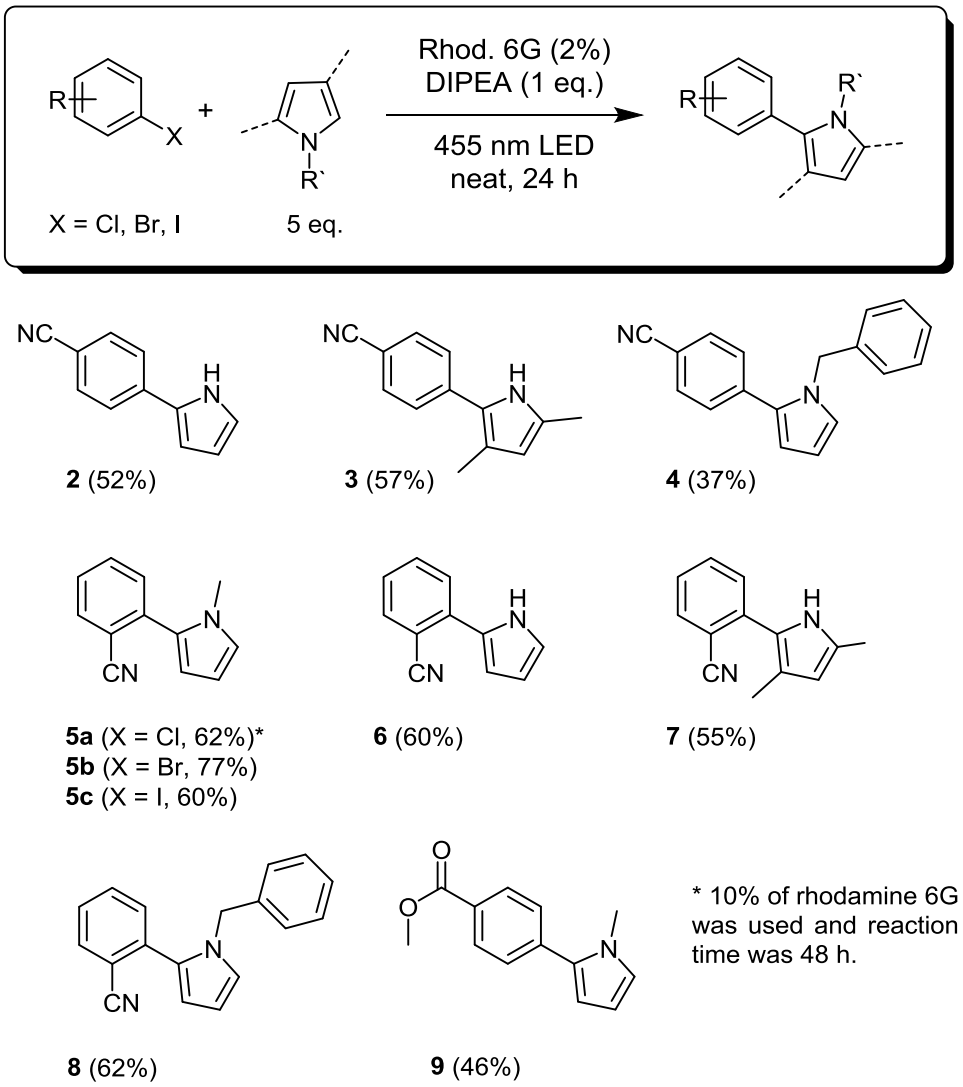
In an initial trial applying 10% rhodamine 6G, 3 equivalents of *N*-methylpyrrole, and 1 equivalent of DIPEA, we could isolate the product in 38% yield, showing that the reaction proceeds under solvent-free conditions in the rotating film reactor (entry 1). As mentioned above, high catalyst concentrations impede the efficient excitation of the catalyst molecules within the reaction mixture, especially in heterogeneous systems. Therefore, we decreased the catalyst loading to 5%, which increased the yield to 50% (entry 2). However, in both reactions, solid particles and partial phase separation occurred. To overcome this problem, we performed the reaction with 5 equivalents of *N*-methylpyrrole. Being the only liquid component, *N*-methylpyrrole acts as an excipient, enabling the formation of a film and the mobility of the catalyst and substrate molecules. Moreover, we decreased the catalyst loading to 2% to further enhance the excitation efficiency (entry 3). To our delight, this increased the

yield to 60%. We then varied the amount of the sacrificial electron donor, DIPEA. Raising the DIPEA amount to 1.5 equivalents decreased the yield to 49% (entry 4).

In this reaction, bleaching of rhodamine 6G was observed. Thus, we applied 10% rhodamine 6G and 1.2 as well as 1.4 equivalents of DIPEA (entries 5 and 6). By doing so, we obtained the products in 60% and 58% yield, which is similar to entry 3. Thus, more than one equivalent of DIPEA seems to bleach parts of the catalyst, which is why more rhodamine 6G is necessary to compensate for this effect. To summarize, we obtained the optimized reaction conditions as 2% rhodamine 6G, 5 equivalents of *N*-methylpyrrole, and 1 equivalent of DIPEA. For entry 3, the thickness of the film formed from the reaction mixture is 0.26 mm (calculated using the volume of the reaction mixture and the reactor geometry). The control reactions showed that only traces of the product were formed without rhodamine 6G (entry 7), whereas 21% conversion was observed in the absence of DIPEA (entry 8). In the dark, no product was formed (entry 9). For the optimized conditions (entry 3), the mole fraction, χ(tr), of *N*-methylpyrrole is 0.71, applying 5 equivalents. In the literature, by applying 18 equivalents of *N*-methylpyrrole, χ(tr) was only 0.08 for the same reaction.[20] Thus, by solvent-free operation, we achieved a ninefold χ(tr) value with less than one third of the equivalents of the trapping reagent compared to the reaction in solution.

Having optimized the reaction conditions using *N*-methylpyrrole, we applied other radical trapping reagents, including pyrrole, 2,4-dimethylpyrrole, and *N*-benzylpyrrole (Scheme 1). With *para*-bromobenzonitrile as the substrate, we obtained the products **2**, **3**, and **4** in moderate yields. The application of *ortho*-bromobenzonitrile with *N*-methylpyrrole as the trapping reagent led to a significantly higher yield (77%, product **5b**), which is possibly due to the better stabilization of the radical anion when the nitrile group is located in the *ortho*-position. This reaction was recently performed in solution, resulting in 78% yield.[20] Using *ortho*-iodobenzonitrile as the substrate resulted in a good yield (product **5c**). However, for *ortho*-chlorobenzonitrile, bleaching of the photocatalyst and little conversion of the substrate in GC occurred. Therefore, we increased the catalyst loading to 10% and the reaction time to 48 h and isolated the product **5a** in good yield. The best-performing substrate *ortho*-bromobenzonitrile was then coupled with pyrrole, 2,4-dimethylpyrrole, and *N*-benzylpyrrole. The products **6**, **7**, and **8** were isolated in moderate to good yields (60%, 55%, and 62%); in solution, product **6** had been

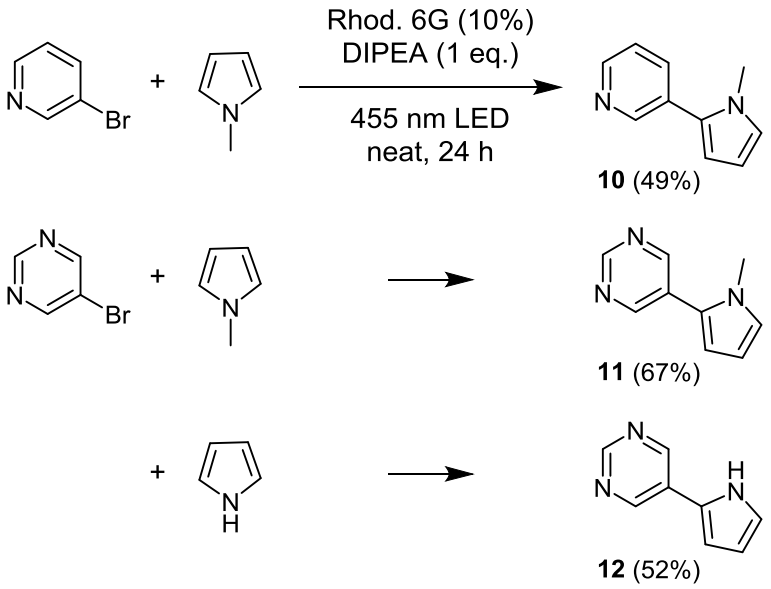
isolated in 64% yield.[20] Hence, for the products **5b** and **6**, we were able to achieve similar yields to those in solution, but with lower amounts of the trapping reagent, photocatalyst, and DIPEA. Similar to *para*-bromobenzonitrile, *N*-methylpyrrole as the trapping reagent resulted in the highest yields when comparing all pyrrole derivatives used. The reaction of methyl 4-bromobenzoate with *N*-methylpyrrole led to the formation of product **9** in moderate yield.



Scheme 1. Coupling of aryl halides with pyrrole derivatives.

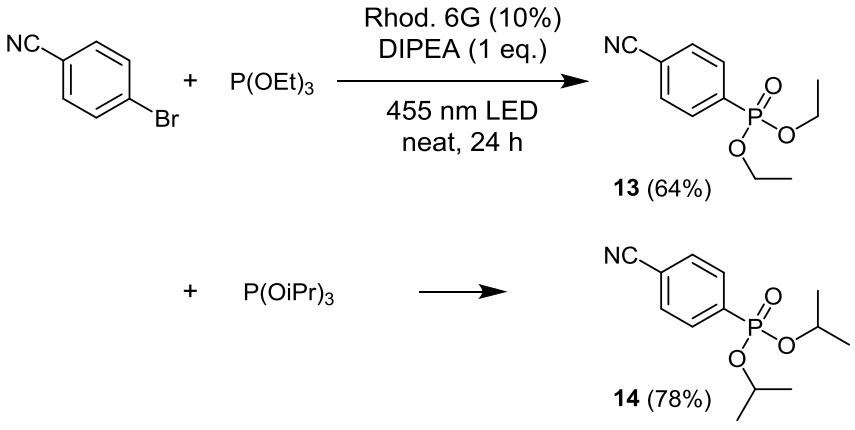
We then moved to nitrogen heteroaryl bromides as substrates; in the literature, their coupling with pyrrole derivatives using the rhodamine 6G system has already been reported.[20] First, we applied 3-bromopyridine as the substrate (Scheme 2). However, with 2% rhodamine 6G, we observed bleaching and low conversion, so we increased the catalyst loading to 10%, which resulted in moderate yield (product **10**, 49%); in the literature, the reported yield for this product is 59%.[20] The same

conditions were then used for the coupling of 5-bromopyrimidine with *N*-methylpyrrole and pyrrole, resulting in good and moderate yields (products **11** and **12**, 67% and 52%).



Scheme 2. Coupling of nitrogen heteroaryl bromides with pyrroles.

Recently, the rhodamine 6G system was also applied in solution (DMSO) for the coupling of aryl bromides with phosphites, yielding aryl phosphonates.[22] We performed the solvent-free coupling of *para*-bromobenzonitrile with triethylphosphite and triisopropylphosphite, applying 10% rhodamine 6G, resulting in the products **13** and **14** in good yields (Scheme 3); the yields reported in the literature are 76% for product **13** and 80% for product **14**.[22]



Scheme 3. Coupling of *para*-bromobenzonitrile with phosphites.

3.3 Conclusion

We have developed a novel rotating film reactor for solvent-free, visible-light-driven photocatalytic transformations. In this reactor, rotation of the reaction vial generates a thin film, which enables efficient excitation of the photocatalyst due to the high relative surface area. The applicability of the reactor was shown for the solvent-free coupling of aryl halides with pyrroles and phosphites, applying rhodamine 6G as the photocatalyst and DIPEA as the sacrificial electron donor; the products were isolated in moderate to good yields. Compared to reactions recently performed in solution, we could significantly decrease the amount of trapping reagent, rhodamine 6G, and DIPEA. The solvent-free operating conditions lead to much higher mole fraction values of the trapping reagent than those in solution, allowing lower amounts of the trapping reagent to be used and thus improving the overall atom economy. To summarize, this solvent-free methodology is a promising alternative to conventional photocatalysis performed in solution. It may be beneficial for reactions where undesired side reactions with the solvent lead to by-product formation. Moreover, reactions may profit from high substrate and catalyst concentrations, facilitating the trapping of radical intermediates. Furthermore, solubility problems, which are caused by the different polarity of reactants and catalyst, are overcome.

3.4 Experimental

3.4.1 Materials and methods

The solid starting materials (except rhodamine 6G) were ground in a pestle and mortar before use. NMR spectra were recorded on a Bruker Avance 300.

3.4.2 Technical data of the rotating film reactor

Four LEDs (455 nm, 700 mA) on a square aluminum frame (inner diameter = 35 mm) were used. The outer diameter of the glass vial was 22 mm, the inner diameter was 19 mm and the LED-vial distance was 3 mm. The inner height of the vial was 28 mm. The power of LED irradiation was 28.1 mW cm^{-2}.

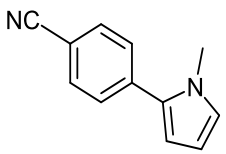
3.4.3 Synthesis

General procedure: The ground substrate and rhodamine 6G were weighed into the reaction vial, which was capped with a septum and transferred to inert conditions (three vacuum-nitrogen cycles). Subsequently, DIPEA and the trapping reagent were added with a microsyringe and the reaction mixture was sonicated for 1 min. The vial was then fixed on the stirrer and rotated for 1 min. The reaction was performed by rotation (1200 rpm) and irradiation with four blue LEDs (455 nm) for 24 h. The thickness of the films formed from the reaction mixtures was calculated to be in the range of 0.22 mm to 0.40 mm (depending on the reaction). Purification was performed by flash column chromatography (Biotage). For dry load preparation, the crude mixture was dissolved in dichloromethane, 0.95 g of dry silica gel were added and the dichloromethane was removed under reduced pressure. The dry load was transferred to the column and the product was isolated using a gradient of ethyl acetate in petroleum ether (if not indicated otherwise), increasing the amount of ethyl acetate from 0% to 10%. Fractions containing the product were identified by thin layer chromatography and combined. The solvent was evaporated and the product was dried *in vacuo*.

Compounds 1, 2, 5, 6, 10, 13, and 14 are reported in the literature:

Compound	Literature
1, 5, 6, 10	20
2	23
13, 14	22

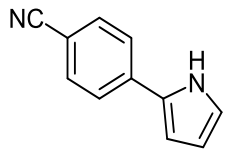
4-(1-Methyl-1H-pyrrol-2-yl)benzonitrile (1)



Procedure for entry 3 (Table 1): 4-bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 76.9 mg (60%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72–7.63 (m, 2H), 7.56–7.47 (m, 2H), 6.84–6.77 (m,

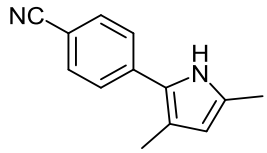
1H), 6.37 (dd, J = 3.7, 1.8 Hz, 1H), 6.25 (dd, J = 3.7, 2.7 Hz, 1H), 3.73 (s, 3H). EI-MS m/z calculated for $C_{12}H_{10}N_2$ $[M]^+$: 182.0844, found: 182.0838.

4-(1H-Pyrrol-2-yl)benzonitrile (2)



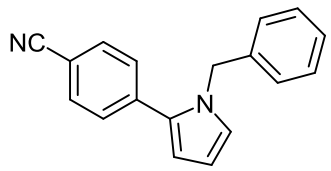
4-Bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with pyrrole (245 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 60.9 mg (52%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.91 (bs, 1H), 7.66–7.50 (m, 4H), 7.00–6.92 (m, 1H), 6.72–6.65 (m, 1H), 6.39–6.32 (m, 1H). ESI-MS m/z calculated for $C_{11}H_8N_2$ $[MH]^+$: 169.0765, found: 169.0772.

4-(3,5-Dimethyl-1H-pyrrol-2-yl)benzonitrile (3)



4-Bromobenzonitrile (109.2 mg, 0.6 mmol) was reacted with 2,4-dimethylpyrrole (309 µL, 3.0 mmol, 5 eq.) applying rhodamine 6G (5.7 mg, 0.012 mmol, 2%) and DIPEA (105 µL, 0.6 mmol, 1 eq.). Yield: 67.5 mg (57%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.26 (bs, 1H), 7.64–7.57 (m, 2H), 7.51–7.43 (m, 2H), 5.92–5.86 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.0, 132.5, 130.0, 125.1, 124.8, 120.0, 119.5, 111.6, 107.5, 13.2, 13.1. ESI-MS m/z calculated for $C_{13}H_{12}N_2$ $[MH]^+$: 197.1078, found: 197.1077.

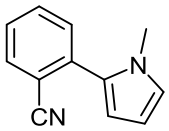
4-(1-Benzyl-1H-pyrrol-2-yl)benzonitrile (4)



4-Bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with 1-benzylpyrrole (540 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 68.2 mg (37%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.63–7.55 (m, 2H), 7.46–7.38 (m, 2H), 7.37–7.25 (m, 3H), 7.06–6.98 (m, 2H), 6.90–6.83

(m, 1H), 6.43 (dd, J = 3.6, 1.7 Hz, 1H), 6.37–6.31 (m, 1H), 5.21 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.1, 137.7, 132.9, 132.3, 128.9, 128.5, 127.7, 126.2, 125.3, 119.0, 111.0, 110.0, 109.3, 51.0. ESI-MS m/z calculated for $C_{18}H_{14}N_2$ $[MH]^+$: 259.1235, found: 259.1228.

2-(1-Methyl-1H-pyrrol-2-yl)benzonitrile (5)



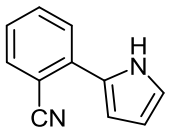
Characterization: ^{1}H NMR (300 MHz, $CDCl_3$): 7.78–7.71 (m, 1H), 7.66–7.58 (m, 1H), 7.48–7.36 (m, 2H), 6.81 (dd, J = 2.6, 1.8 Hz, 1H), 6.43 (dd, J = 3.7, 1.8 Hz, 1H), 6.26 (dd, J = 3.7, 2.7 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 136.9, 133.6, 132.5, 130.9, 129.9, 127.5, 124.9, 118.7, 112.7, 111.5, 108.3, 34.9. EI-MS m/z calculated for $C_{12}H_{10}N_2$ $[M]^+$: 182.0844, found: 182.1188.

5a. 2-Chlorobenzonitrile (96.3 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (33.5 mg, 0.07 mmol, 10%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). The reaction time was 48 h. Yield: 83.2 mg (64%).

5b. 2-Bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 98.8 mg (77%).

5c. 2-Iodobenzonitrile (160.3 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 77.9 mg (60%).

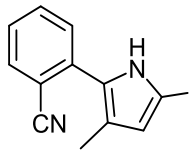
2-(1H-Pyrrol-2-yl)benzonitrile (6)



2-Bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with pyrrole (245 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 71.1 mg (60%). ^{1}H NMR (300 MHz, $CDCl_3$): 9.23 (bs, 1H), 7.68–7.50 (m, 3H), 7.30–7.18 (m, 1H), 7.01–6.92 (m, 1H), 6.88–6.81 (m, 1H), 6.39–6.31 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 135.7, 134.1, 133.2, 128.2, 126.7, 125.9,

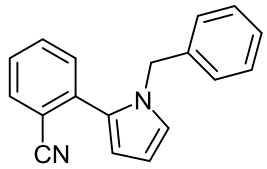
120.9, 120.2, 110.4, 106.0. EI-MS m/z calculated for $C_{11}H_8N_2$ $[M]^+$: 168.0687, found: 168.1010.

2-(3,5-Dimethyl-1H-pyrrol-2-yl)benzonitrile (7)



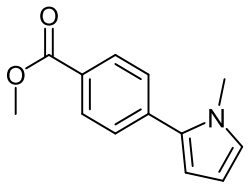
2-Bromobenzonitrile (109.2 mg, 0.6 mmol) was reacted with 2,4-dimethylpyrrole (309 µL, 3.0 mmol, 5 eq.) applying rhodamine 6G (5.7 mg, 0.012 mmol, 2%) and DIPEA (105 µL, 0.6 mmol, 1 eq.). Yield: 65.2 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.29 (s, 1H), 7.71–7.63 (m, 1H), 7.61–7.52 (m, 1H), 7.51–7.43 (m, 1H), 7.33–7.23 (m, 1H), 5.92–5.85 (m, 1H), 2.30 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.1, 133.9, 132.6, 129.6, 129.4, 125.9, 123.1, 120.1, 119.6, 110.5, 109.3, 13.1, 12.8. EI-MS m/z calculated for $C_{13}H_{12}N_2$ $[M]^+$: 196.1000, found: 196.1366.

2-(1-Benzyl-1H-pyrrol-2-yl)benzonitrile (8)



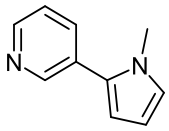
2-Bromobenzonitrile (127.4 mg, 0.7 mmol) was reacted with 1-benzylpyrrole (539 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 114.6 mg (62%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.73–7.66 (m, 1H), 7.58–7.48 (m, 1H), 7.43–7.33 (m, 2H), 7.32–7.19 (m, 3H), 6.99–6.90 (m, 2H), 6.98–6.83 (m, 1H), 6.50 (dd, J = 3.6, 1.7 Hz, 1H), 6.39–6.31 (m, 1H), 5.12 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.2, 136.9, 133.5, 132.4, 130.9, 130.0, 128.7, 127.7, 127.6, 126.5, 124.4, 118.5, 113.2, 112.0, 109.0, 51.12. EI-MS m/z calculated for $C_{18}H_{14}N_2$ $[M]^+$: 258.1157, found: 258.1617.

Methyl 4-(1-methyl-1H-pyrrol-2-yl)benzoate (9)



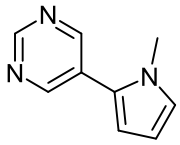
Methyl 4-bromobenzoate (150.5 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (6.7 mg, 0.014 mmol, 2%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 69.3 mg (46%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.11–8.03 (m, 2H), 7.53–7.45 (m, 2H), 6.80–6.74 (m, 1H), 6.36 (dd, J = 3.7, 1.8 Hz, 1H), 6.24 (dd, J = 3.6, 2.7 Hz, 1H), 3.94 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.0, 137.8, 133.5, 129.8, 127.9, 125.2, 110.1, 108.3, 52.1, 35.4. EI-MS m/z calculated for $C_{13}H_{13}NO_2$ $[M]^+$: 215.0946, found: 215.1332.

3-(1-Methyl-1H-pyrrol-2-yl)pyridine (10)



Rhodamine 6G (33.5 mg, 0.07 mmol, 10%) was weighed into the reaction vial, which was transferred to inert conditions, followed by the addition of 3-bromopyridine (67 µL, 0.7 mmol), DIPEA (122 µL, 0.7 mmol, 1 eq.), and 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.). Yield: 54.7 mg (49%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.74–8.63 (m, 1H), 8.58–8.46 (m, 1H), 7.73–7.65 (m, 1H), 7.32 (dd, J = 7.8, 4.8 Hz, 1H), 6.80–6.72 (m, 1H), 6.30 (dd, J = 3.6, 1.8 Hz, 1H), 6.23 (dd, J = 3.6, 2.7 Hz, 1H), 3.67 (s, 3H). EI-MS m/z calculated for $C_{10}H_{10}N_2$ $[M]^+$: 158.0844, found: 158.0842.

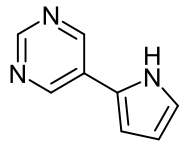
5-(1-Methyl-1H-pyrrol-2-yl)pyrimidine (11)



5-Bromopyrimidine (111.3 mg, 0.7 mmol) was reacted with 1-methylpyrrole (311 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (33.5 mg, 0.07 mmol, 10%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 75.0 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$): 9.12 (s, 1H), 8.77 (s, 2H), 6.83–6.75 (m, 1H), 6.35 (dd, J = 3.7, 1.8 Hz, 1H), 6.26–6.19 (m, 1H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 156.5, 155.4, 127.5, 127.0, 126.0,

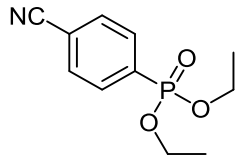
110.9, 108.8, 35.3. EI-MS m/z calculated for $C_9H_9N_3$ $[M]^+$: 159.0796, found: 159.1125.

5-(1H-Pyrrol-2-yl)pyrimidine (12)



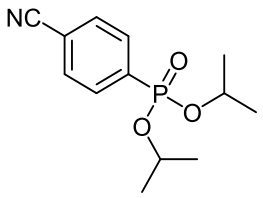
5-Bromopyrimidine (111.3 mg, 0.7 mmol) was reacted with pyrrole (245 µL, 3.5 mmol, 5 eq.) applying rhodamine 6G (33.5 mg, 0.07 mmol, 10%) and DIPEA (122 µL, 0.7 mmol, 1 eq.). Yield: 52.7 mg (52%). ^{1}H NMR (300 MHz, DMSO-d_6): 11.63 (s, 1H), 9.05 (s, 2H), 8.93 (s, 1H), 7.05–6.97 (m, 1H), 6.82–6.73 (m, 1H), 6.24–6.15 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 154.9, 151.0, 126.8, 124.4, 121.3, 109.7, 107.8. ESI-MS m/z calculated for $C_{12}H_{10}N_2$ $[MH]^+$: 146.0718, found: 146.0718.

Diethyl (4-cyanophenyl)phosphonate (13)



4-Bromobenzonitrile (72.8 mg, 0.4 mmol) was reacted with triethylphosphite (346 µL, 2.0 mmol, 5 eq.) applying rhodamine 6G (19.2 mg, 0.04 mmol, 10%) and DIPEA (68 µL, 0.4 mmol, 1 eq.). Flash column chromatography was performed using a gradient of ethyl acetate in dichloromethane. Yield: 60.9 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.92–7.80 (m, 2H), 7.75–7.65 (m, 2H), 4.20–3.95 (m, 4H), 1.27 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 133.9 (d, J = 187.7 Hz), 132.2 (d, J = 9.9 Hz), 132.0 (d, 14.9 Hz), 117.8, 115.9 (d, J = 3.6 Hz), 62.7 (d, J = 6.7 Hz), 16.3 (d, J = 6.3 Hz). EI-MS m/z calculated for $C_{11}H_{14}NO_3P$ $[M]^+$: 239.0711, found: 239.0696.

Diisopropyl (4-cyanophenyl)phosphonate (14)



4-Bromobenzonitrile (54.6 mg, 0.3 mmol) was reacted with triisopropylphosphite (370 µL, 1.5 mmol, 5 eq.) applying rhodamine 6G (14.4 mg, 0.03 mmol, 10%) and DIPEA (51 µL, 0.3 mmol, 1 eq.). Yield: 62.5 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.92–7.79 (m, 2H), 7.72–7.63 (m, 2H), 4.75–4.58 (m, 4H), 1.31 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 135.4 (d, J = 188.3 Hz), 132.2 (d, J = 9.8 Hz), 131.9 (d, J = 14.9 Hz), 117.9, 115.6 (d, J = 3.6 Hz), 71.6 (d, J = 5.8 Hz), 24.0 (d, J = 4.1 Hz), 23.8 (d, J = 4.8 Hz). EI-MS m/z calculated for $C_{13}H_{18}NO_3P$ $[M]^+$-CH_3: 252.0789, found: 252.0780.

3.5 References

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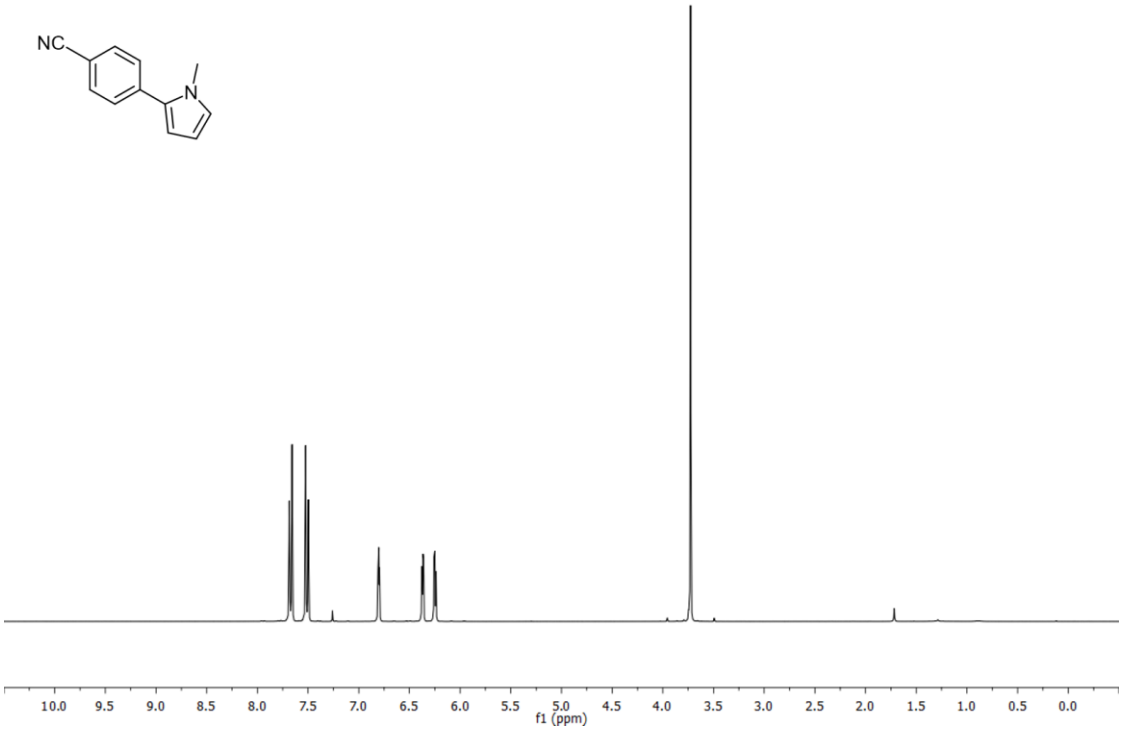
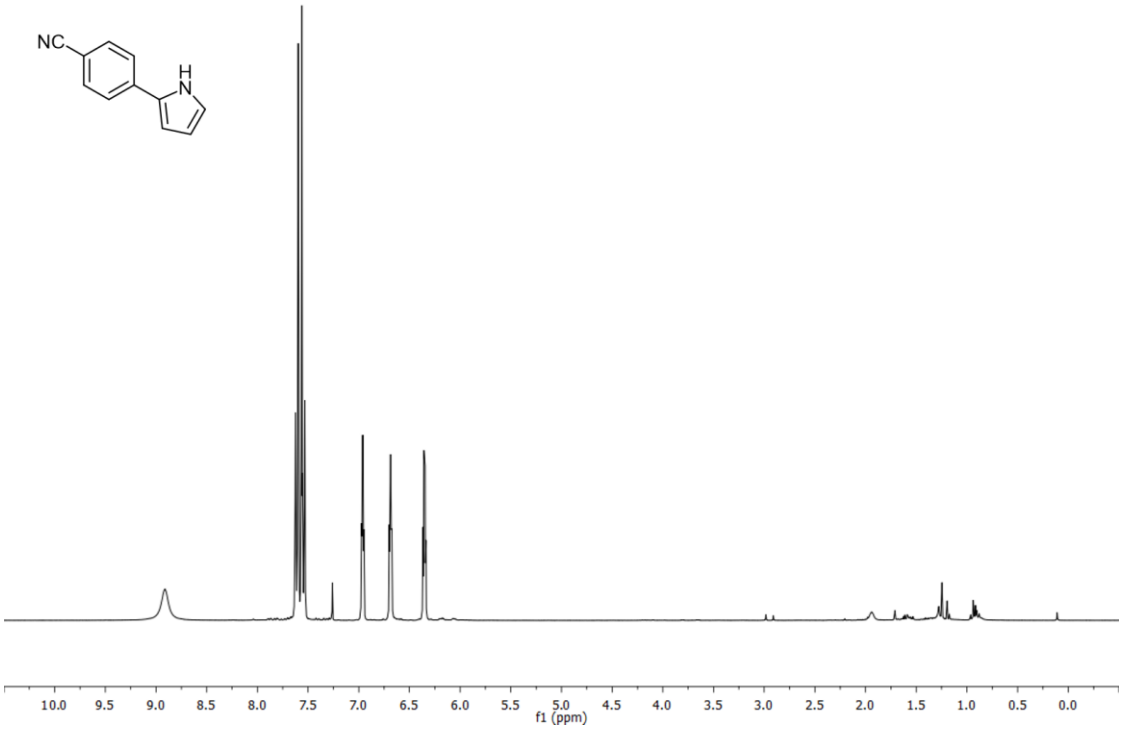
3.6 NMR Spectra

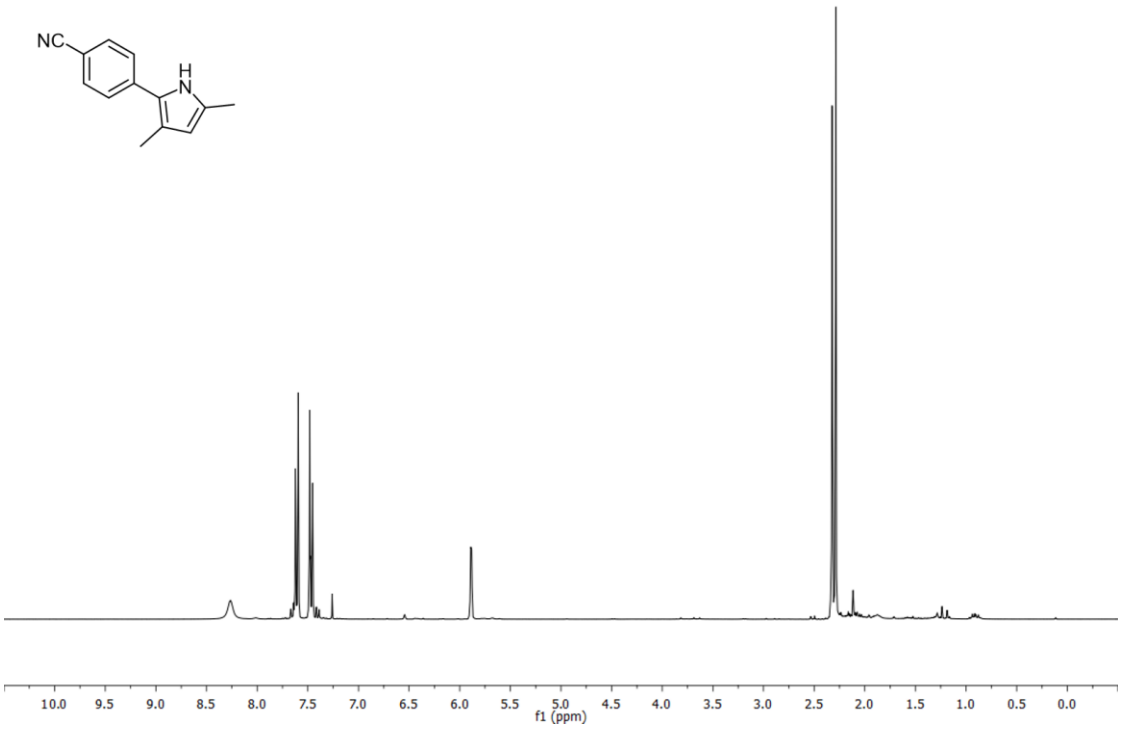
4-(1-Methyl-1H-pyrrol-2-yl)benzonitrile (1): ^{1}H NMR (300 MHz, $CDCl_3$)



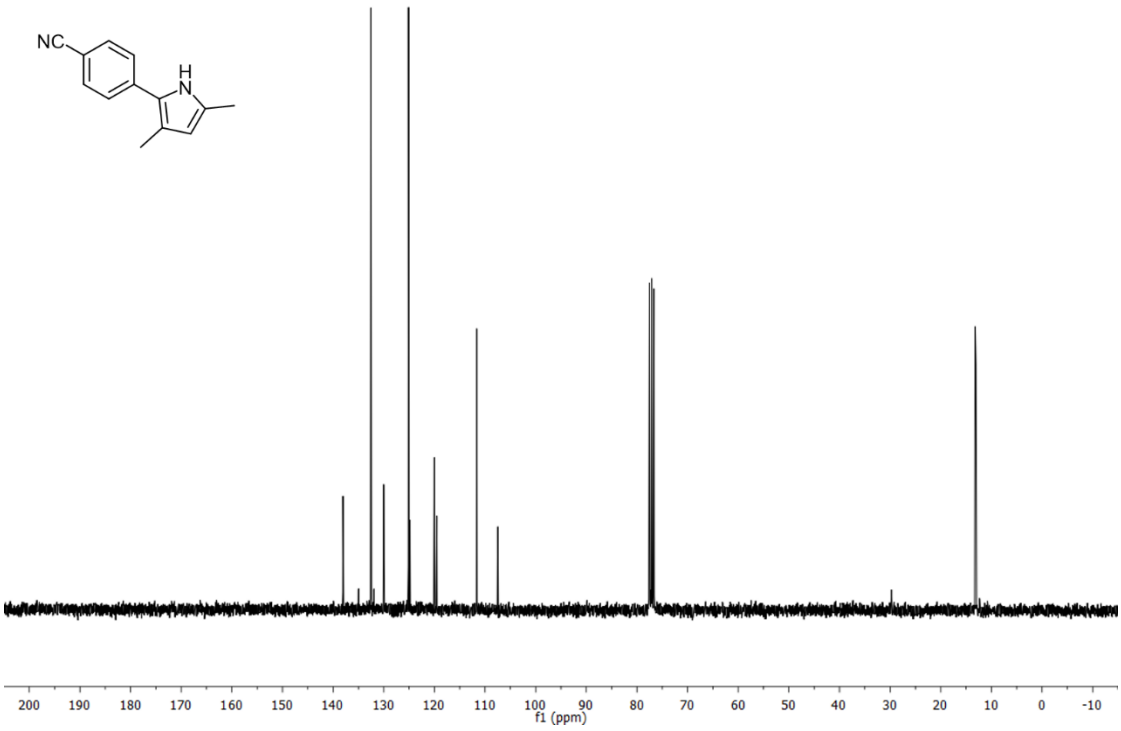
4-(1H-Pyrrol-2-yl)benzonitrile (2): ^{1}H NMR (300 MHz, $CDCl_3$)



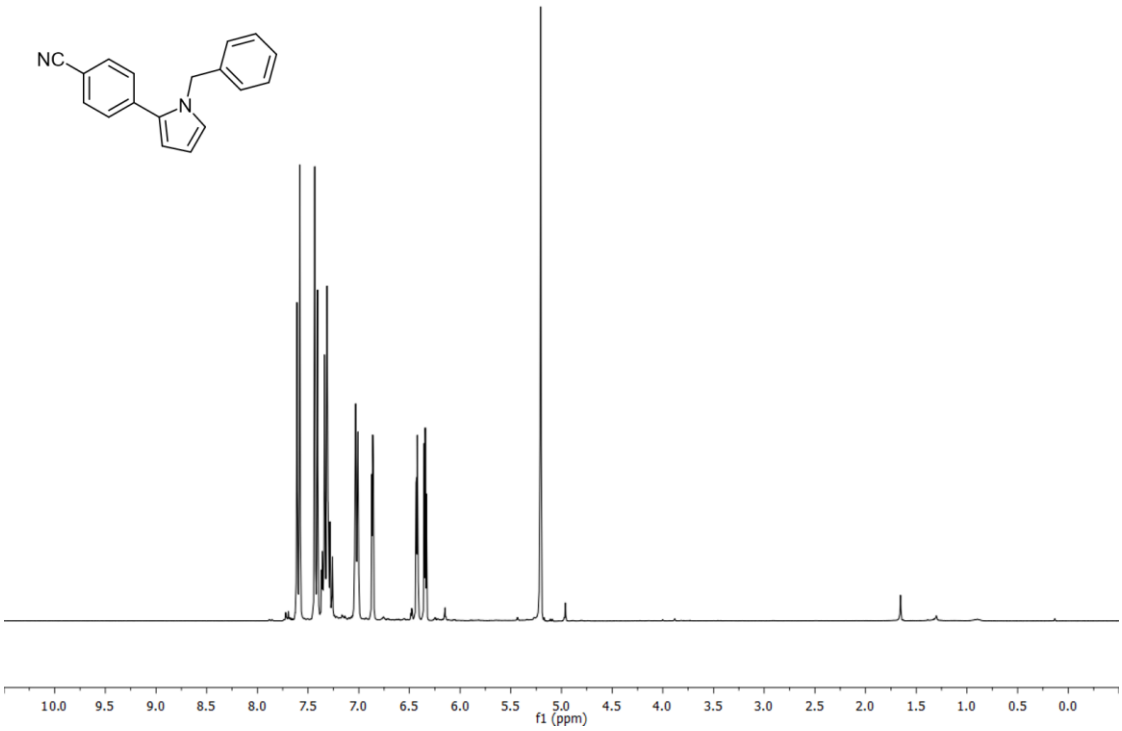
4-(3,5-Dimethyl-1H-pyrrol-2-yl)benzonitrile (3): ^{1}H NMR (300 MHz, $CDCl_3$)



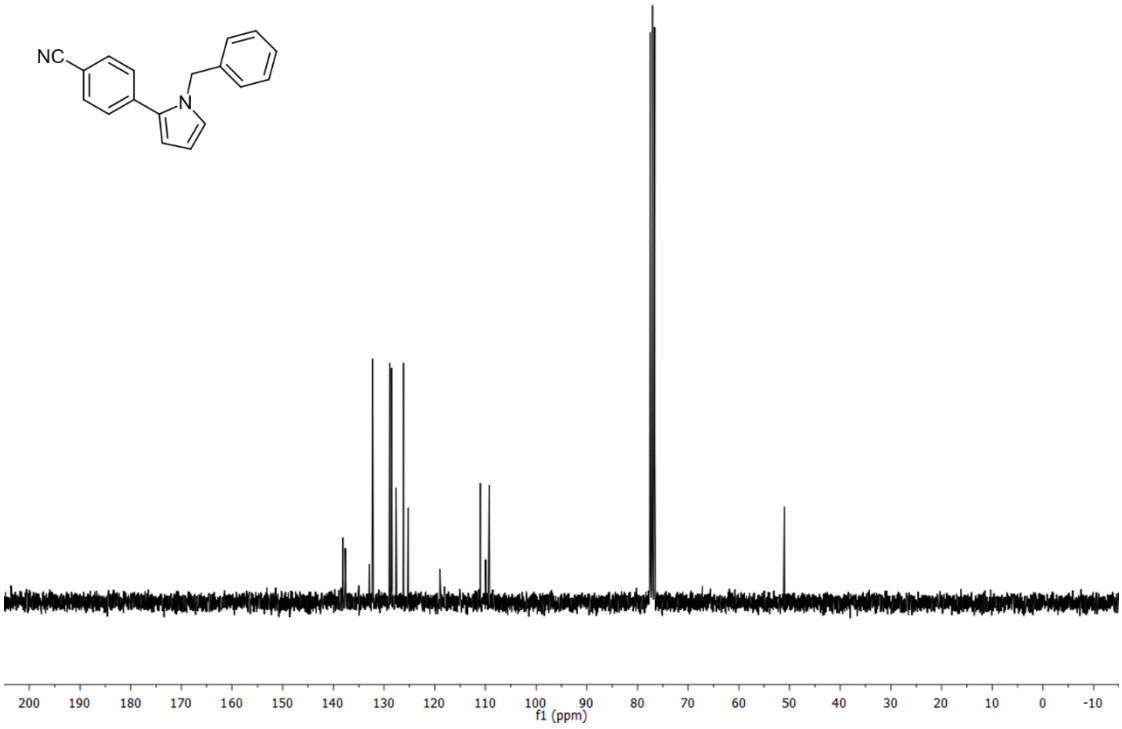
^{13}C NMR (75 MHz, $CDCl_3$)



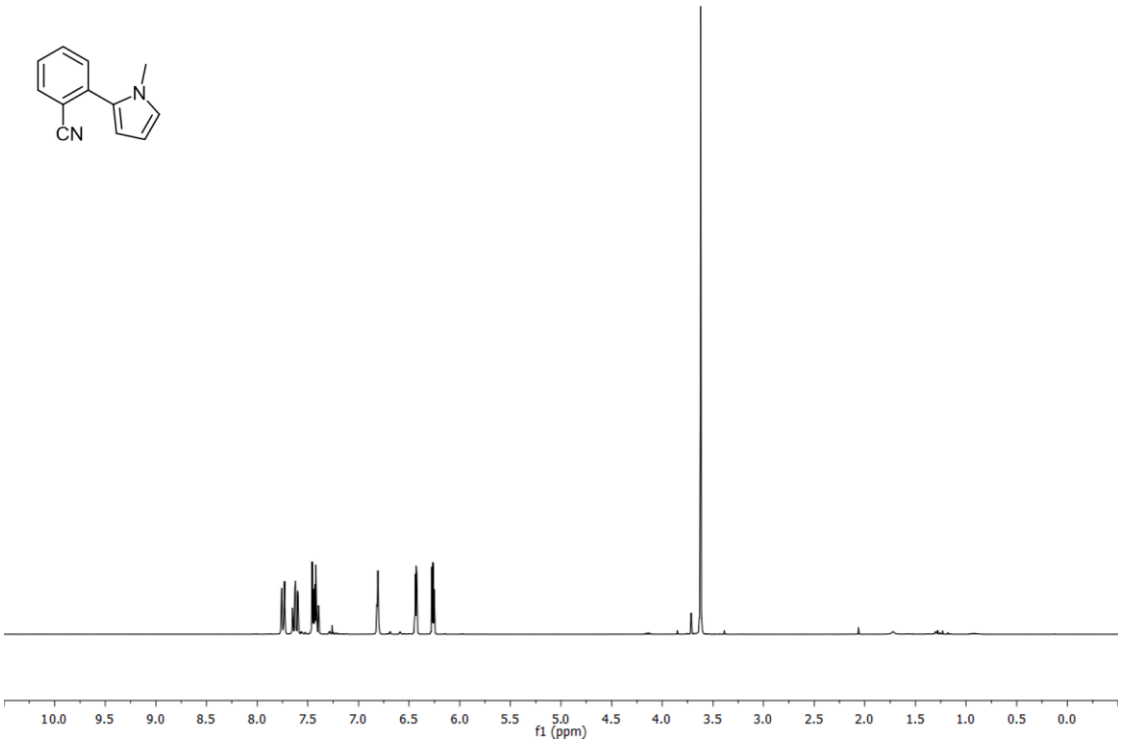
4-(1-Benzyl-1H-pyrrol-2-yl)benzonitrile (4): ^{1}H NMR (300 MHz, $CDCl_3$)



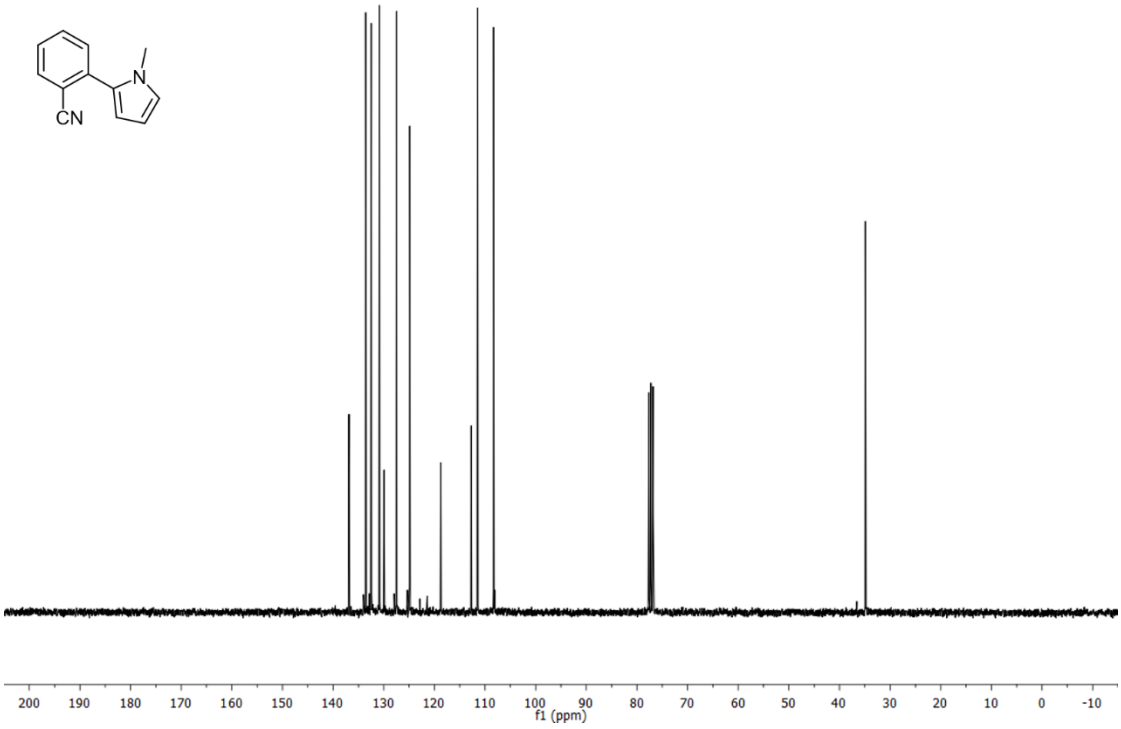
^{13}C NMR (75 MHz, $CDCl_3$)



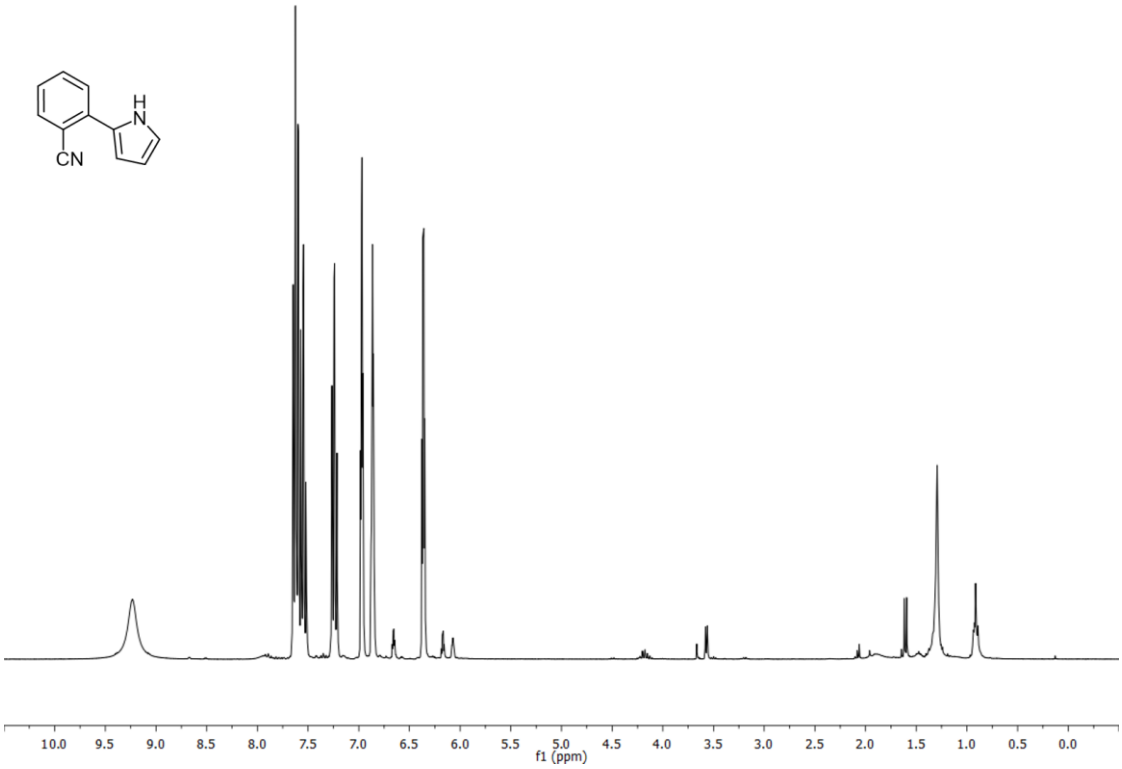
2-(1-Methyl-1H-pyrrol-2-yl)benzonitrile (5): ^{1}H NMR (300 MHz, $CDCl_3$)



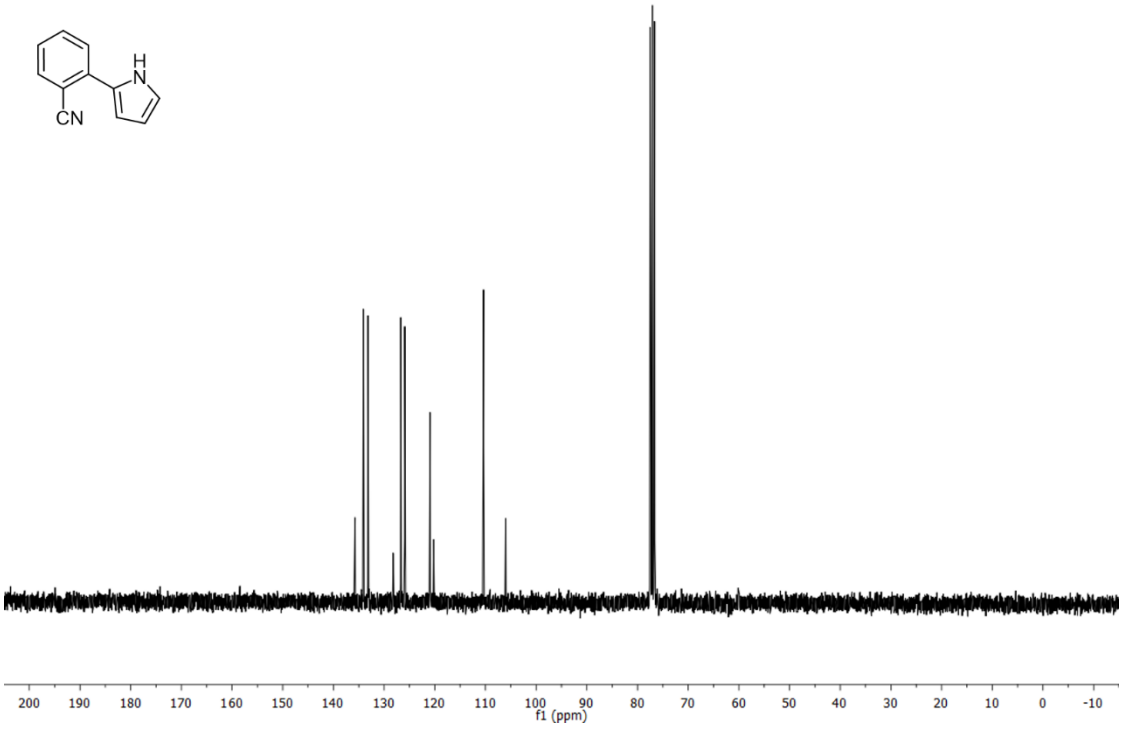
^{13}C NMR (75 MHz, $CDCl_3$)



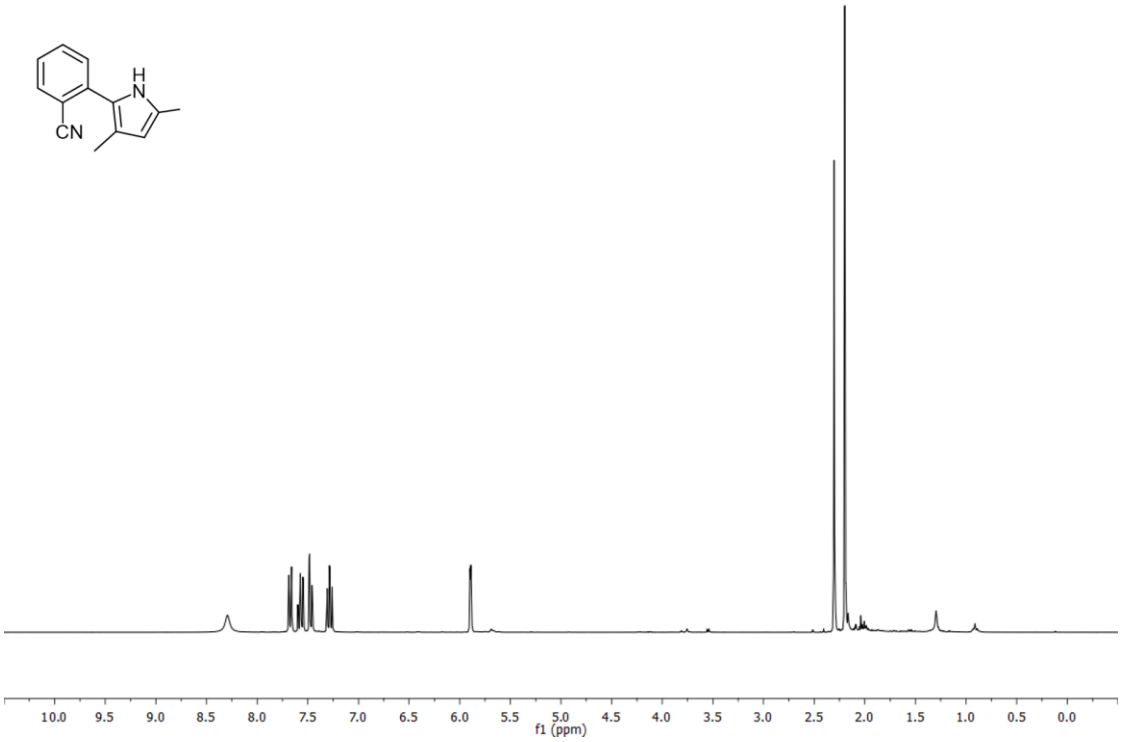
2-(1H-Pyrrol-2-yl)benzonitrile (6): ^{1}H NMR (300 MHz, $CDCl_3$)



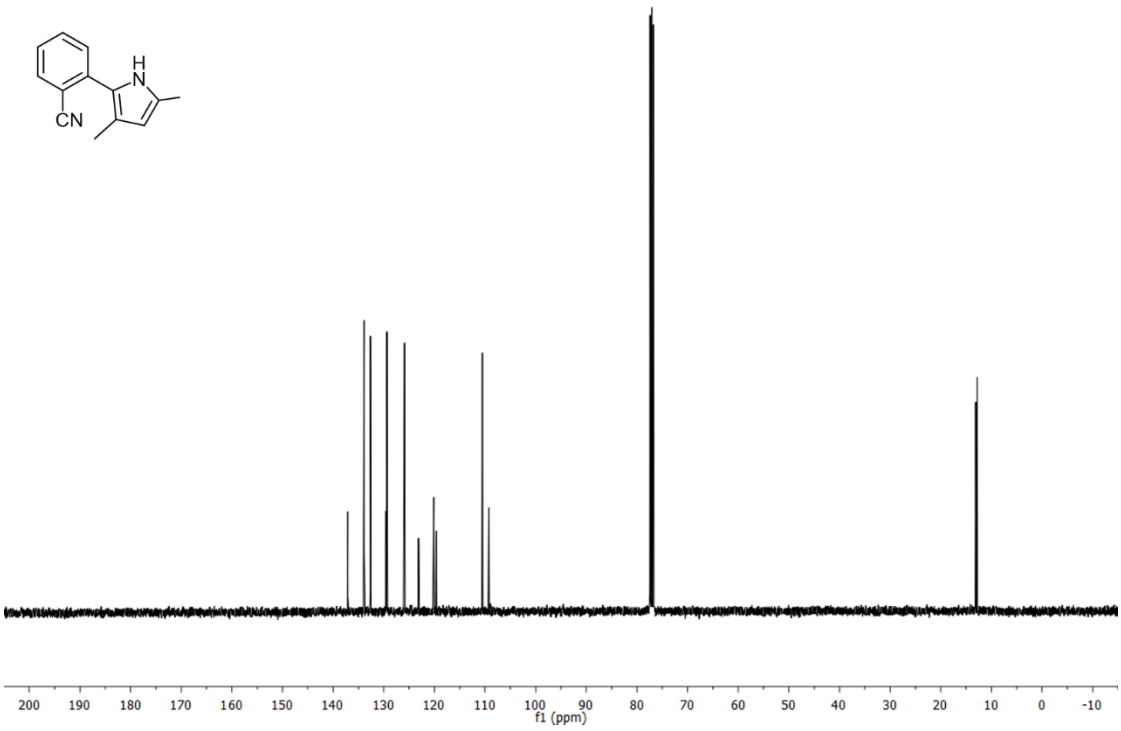
^{13}C NMR (75 MHz, $CDCl_3$)



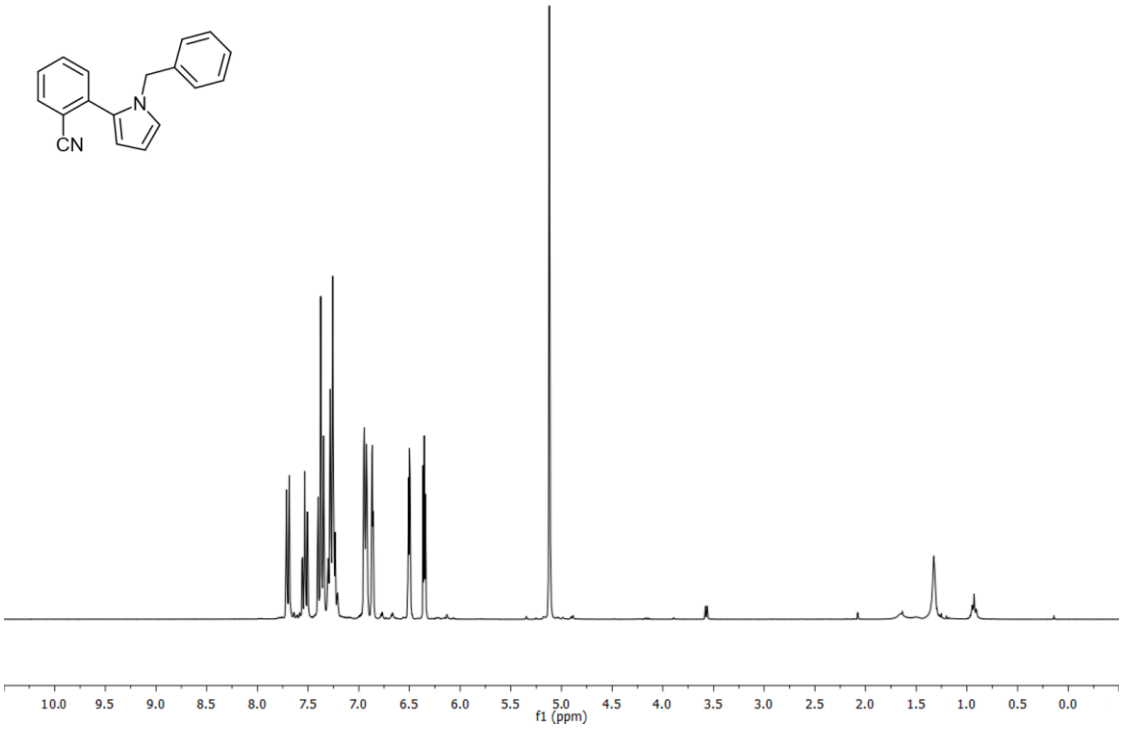
2-(3,5-Dimethyl-1H-pyrrol-2-yl)benzonitrile (7): ^{1}H NMR (300 MHz, $CDCl_3$)



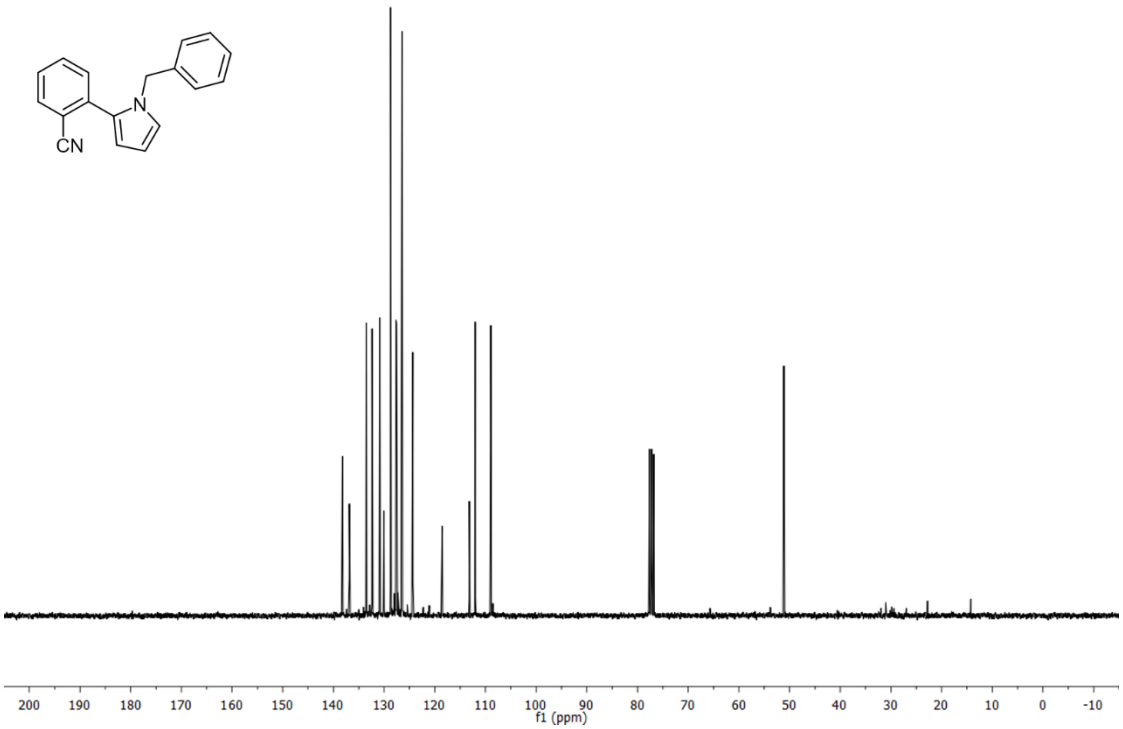
^{13}C NMR (75 MHz, $CDCl_3$)



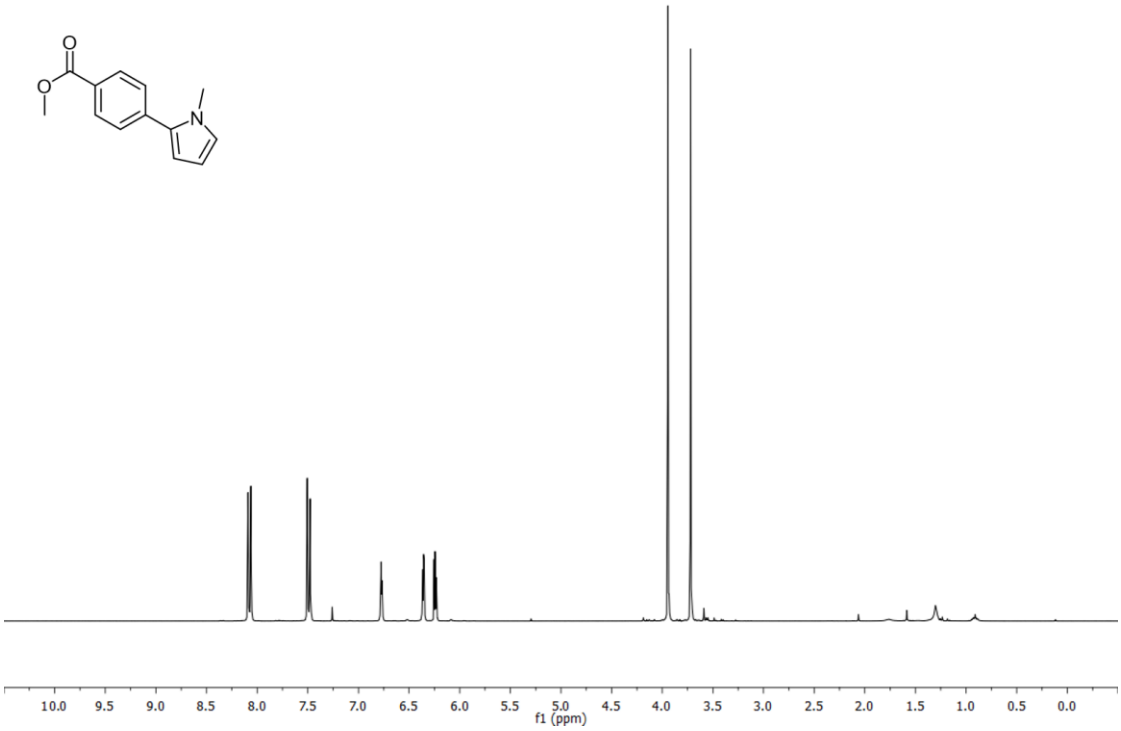
2-(1-Benzyl-1H-pyrrol-2-yl)benzonitrile (8): ^{1}H NMR (300 MHz, $CDCl_3$)



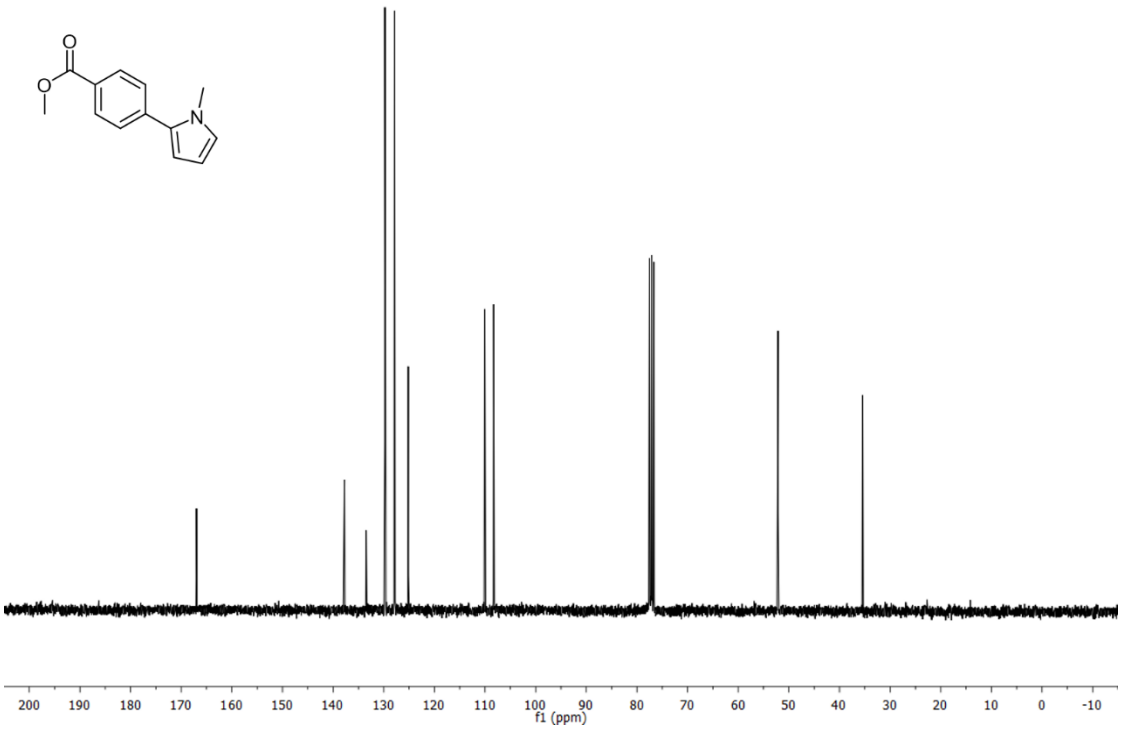
^{13}C NMR (75 MHz, $CDCl_3$)



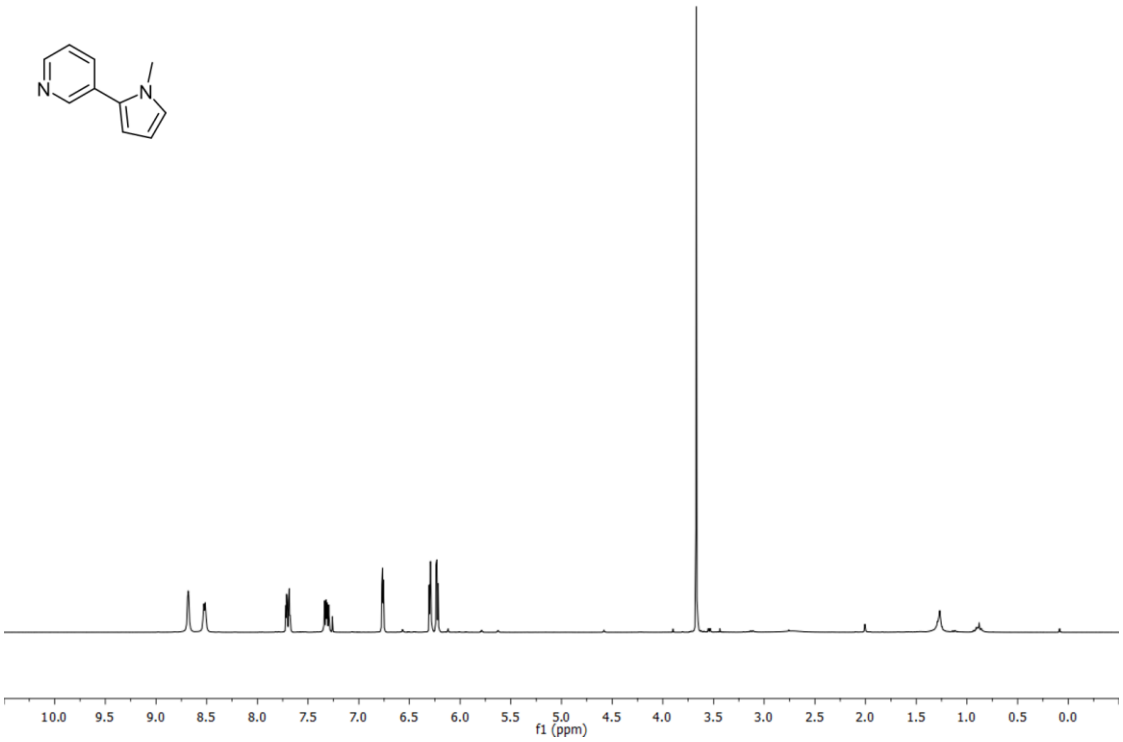
Methyl 4-(1-methyl-1H-pyrrol-2-yl)benzoate (9): ^{1}H NMR (300 MHz, $CDCl_3$)



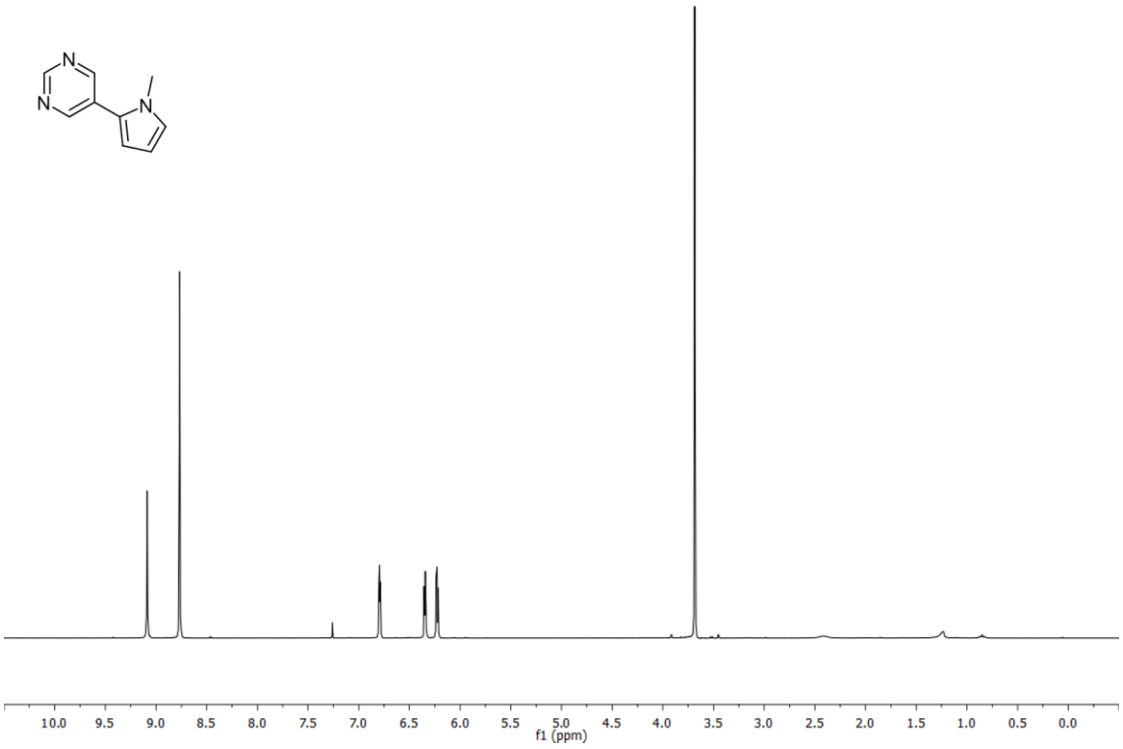
^{13}C NMR (75 MHz, $CDCl_3$)



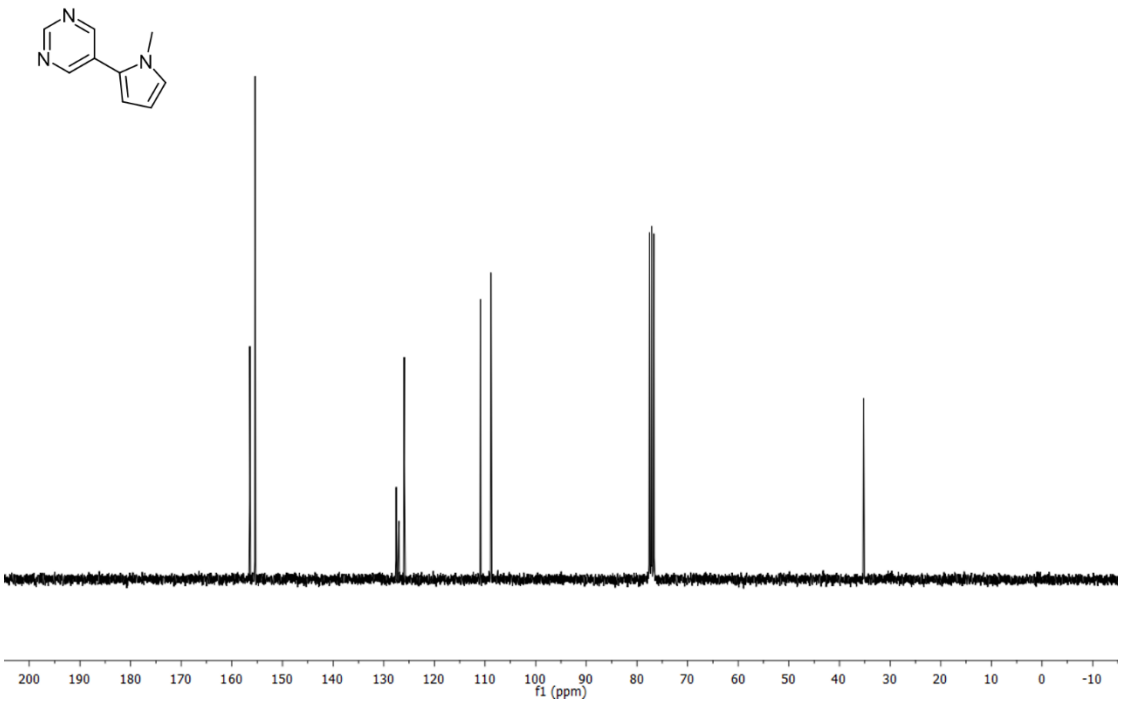
3-(1-Methyl-1H-pyrrol-2-yl)pyridine (10): ^{1}H NMR (300 MHz, $CDCl_3$)



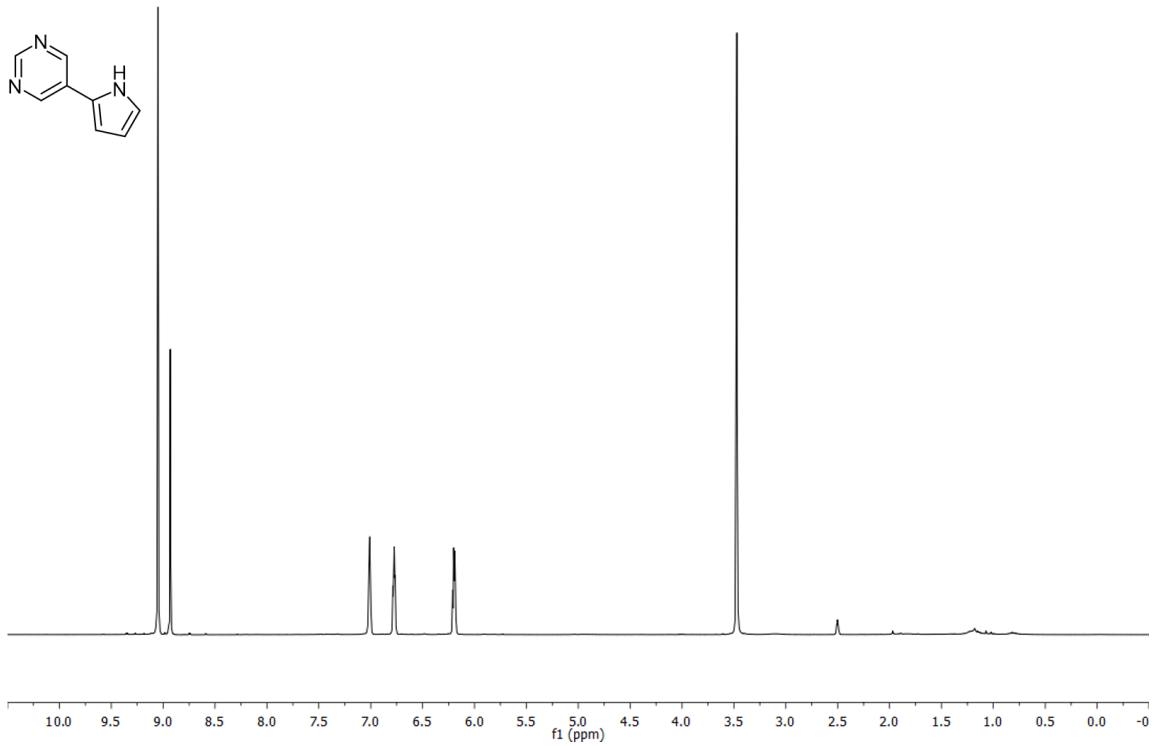
5-(1-Methyl-1H-pyrrol-2-yl)pyrimidine (11): ^{1}H NMR (300 MHz, $CDCl_3$)



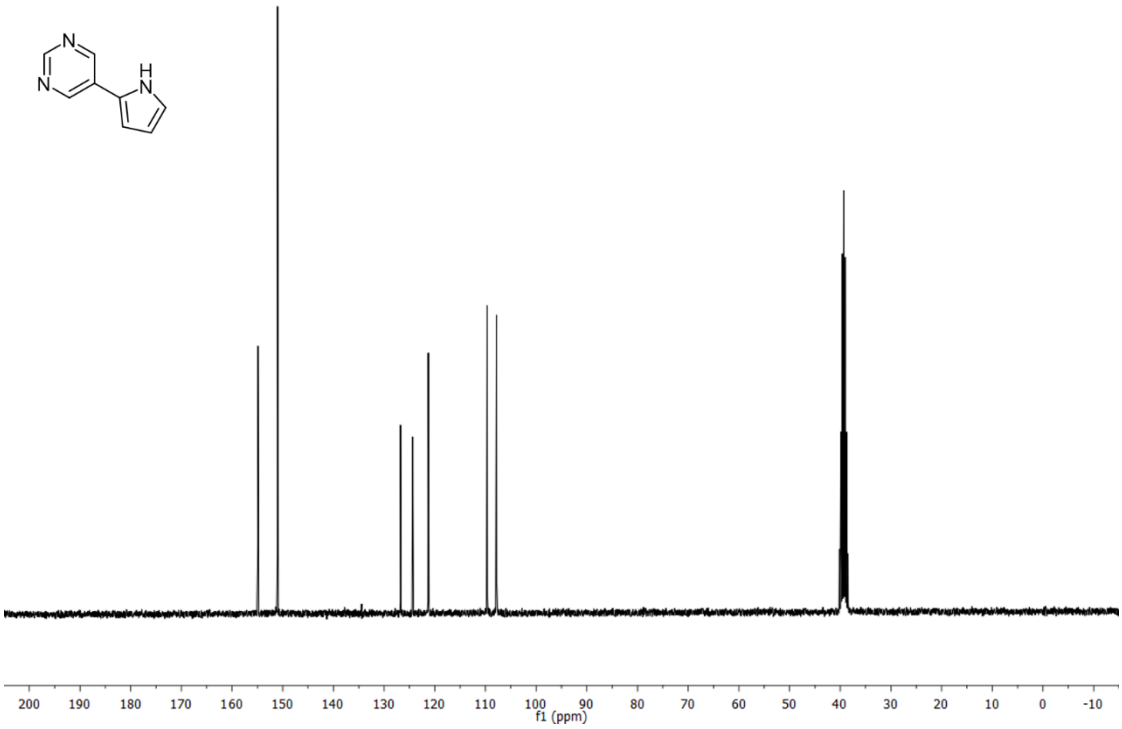
^{13}C NMR (75 MHz, $CDCl_3$)



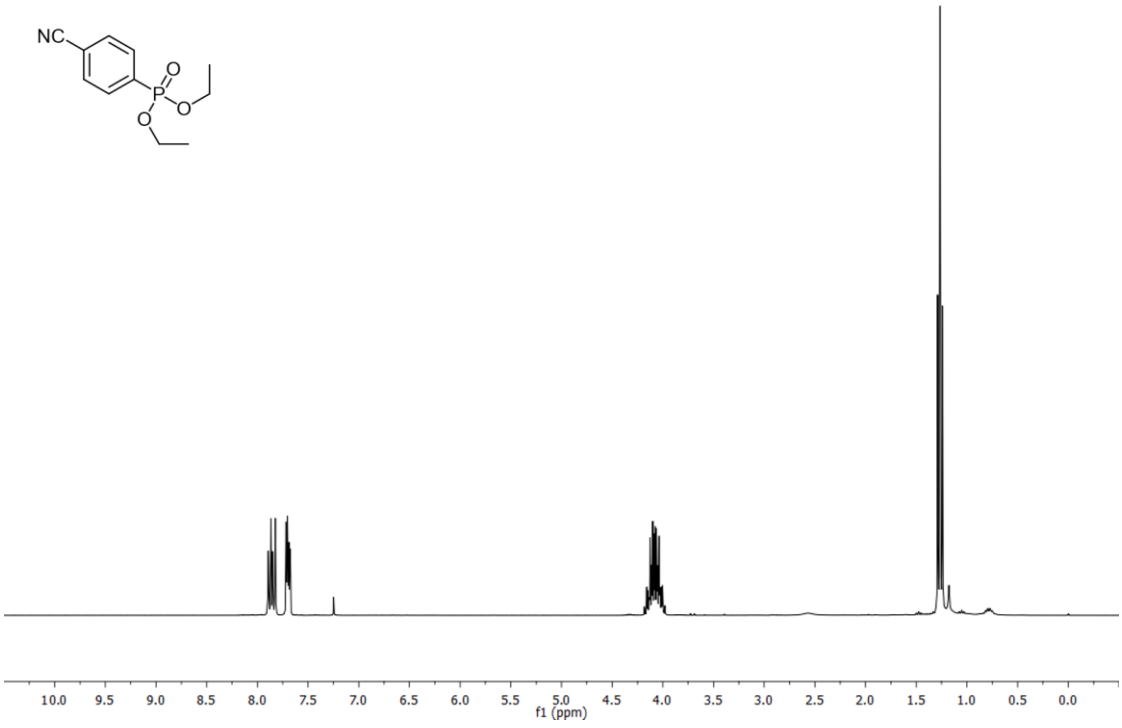
5-(1H-Pyrrol-2-yl)pyrimidine (12): ^1H NMR (300 MHz, $CDCl_3$)



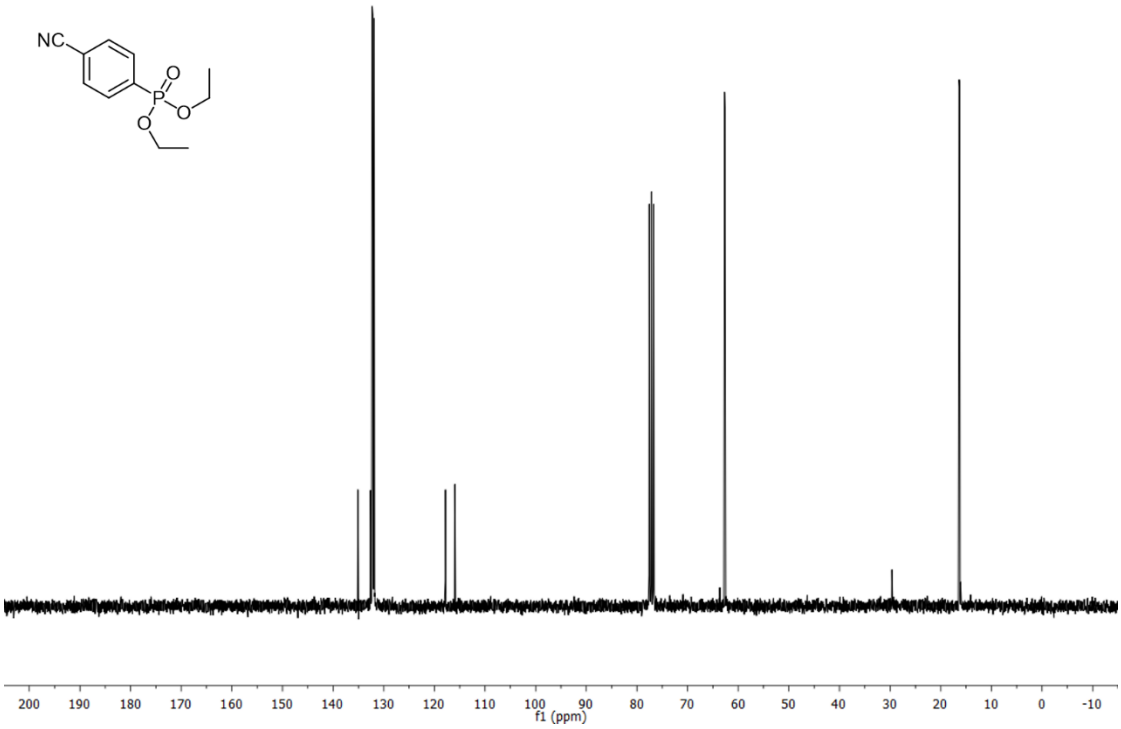
^{13}C NMR (75 MHz, $CDCl_3$)



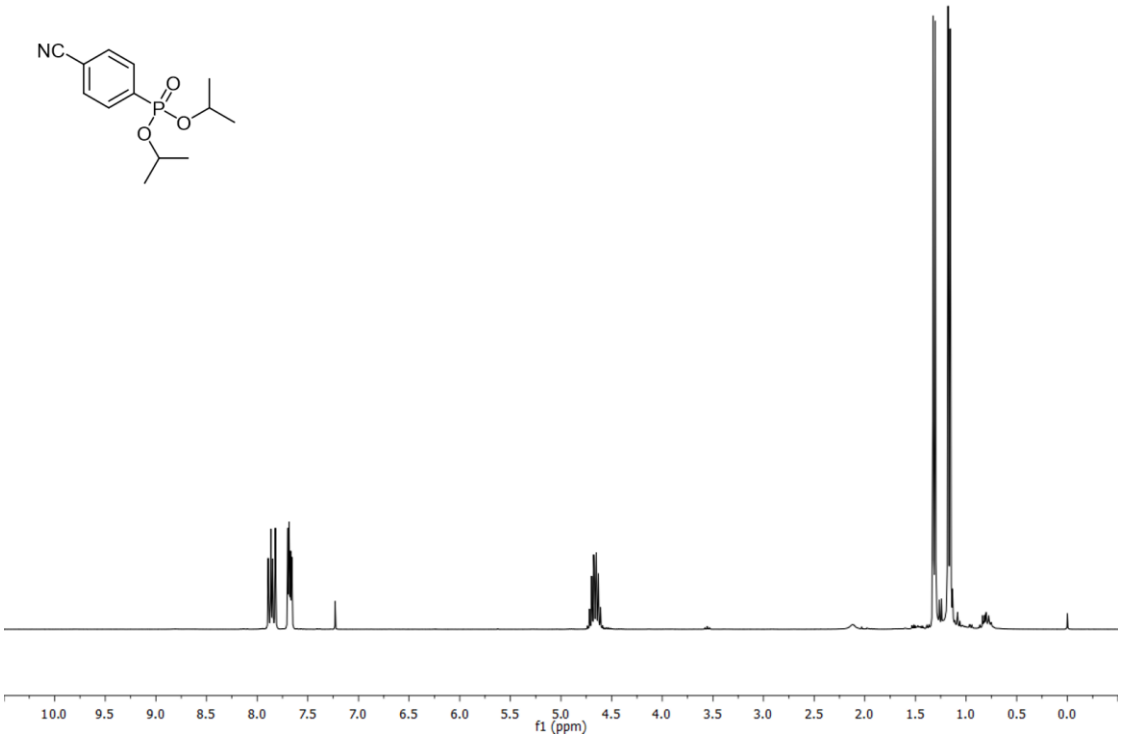
Diethyl (4-cyanophenyl)phosphonate (13): ^1H NMR (300 MHz, $CDCl_3$)



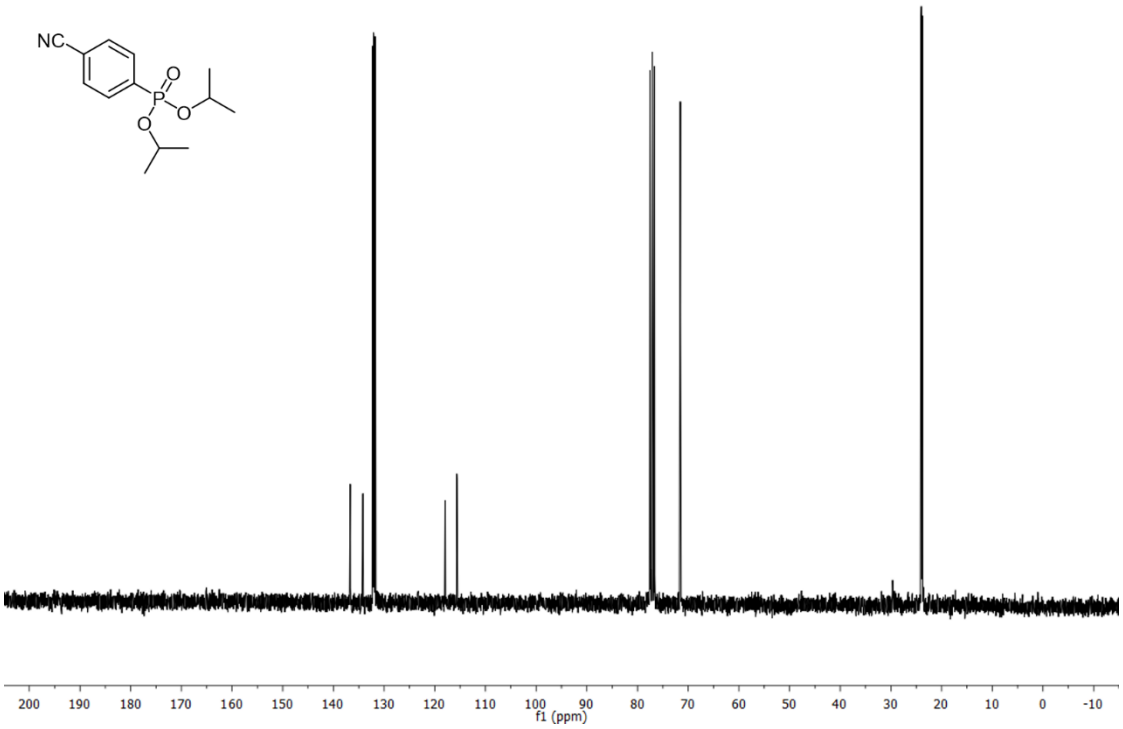
^{13}C NMR (75 MHz, $CDCl_3$)



Diisopropyl (4-cyanophenyl)phosphonate (14): ^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



4 Preparation of propargyl amines in a $ZnCl_2$–dimethylurea deep-eutectic solvent

The coupling of an aldehyde, an amine, and an alkyne to yield propargyl amines was performed in a deep-eutectic solvent composed of zinc chloride and dimethylurea. The deep-eutectic solvent acts simultaneously as catalyst and solvent giving access to a variety of propargyl amines, which were isolated in moderate to very good yields.

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Author contributions: M.O. and A.S. performed the syntheses. M.O. wrote the manuscript. B.K. and S.B. supervised the project and are corresponding authors.

4.1 Introduction

Deep-eutectic solvents (DES) have been continuously investigated in academic and applied research for more than a decade. DES are nontoxic, biodegradable, cheap, easy to prepare, possess a low vapor pressure and often good thermal stability.[1–3] A first report on DES dates back to 2003, when Abbott et al. described the formation of DES based on quaternary ammonium salts and urea.[4] In general, a DES is defined as a mixture of two or three components forming an eutectic with a lower melting point than each of the pure components. Due to the formation of hydrogen bonds and other noncovalent interactions, the melting point of a typical DES is below 100 °C; some DES are liquid even at room temperature.[1] Most DES consist of a hydrogen bond donor and a hydrogen bond acceptor. In this context, hydrogen bond donors can be alcohols, saccharides, carboxylic acids, and urea derivatives. Hydrogen bond acceptors can be organic halide salts, such as ammonium salts (choline chloride, for example). Metal salts, such as $ZnCl_2$, $FeCl_3$, and $SnCl_2$, can also form a DES with a hydrogen bond donor.[5] DES have received substantial interest as solvents for organic syntheses, for example in metal-catalyzed transformations like the azide-alkyne cycloaddition and palladium catalyzed C-C coupling reactions, which were performed in saccharide-based DES.[6,7] Furthermore, organolithium and Grignard reagents were reacted with ketones and imines in choline chloride–glycerol DES.[8,9] An elegant approach is the application of a DES acting as solvent and catalyst simultaneously. For example, DES based on tartaric acid and urea derivatives were used in the synthesis of indoles,[10] pyrimidopyrimidinediones,[11] dihydropyrimidinones,[12] and hydantoins.[13]

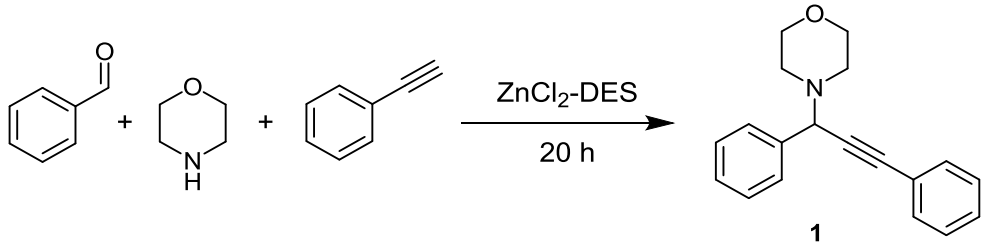
The A^3-coupling is a three-component reaction of an amine, an aldehyde, and an alkyne, leading to a propargyl amine. It is catalyzed by transition-metal ions, such as Cu(I), Cu(II), Zn(II), and Fe(III). The amine and the aldehyde react to form an iminium ion *in situ*, followed by attack of the metal-activated alkyne. Due to the facile availability of propargyl amines, the A^3-coupling is a valuable tool for the synthesis of N-heterocycles.[14] During the last decade, the A^3-coupling has been investigated extensively and various approaches were developed, exploring the scope of the starting materials, choice of metal catalysts and reaction medium. For example, the reaction was performed under solvent-free conditions,[15] in ionic liquids,[16] and catalyzed by magnetic nanoparticles in a DES.[17]

Several DES with a metal salt as one of the components are reported and some were already applied in synthesis. In particular, a DES formed by zinc chloride and choline chloride was used as solvent and catalyst, for example, in the synthesis of amides from aldehydes and nitriles,[18] alkylation[19] and acylation[20] of arenes, and acylation of alcohols.[21]

4.2 Results and Discussion

The fact that zinc salts are effective catalysts for the A^3-coupling[22,23] motivated us to perform the A^3-coupling in a DES based on a zinc salt. In this system, the zinc salt would act as one of the DES components and catalyst simultaneously, making the addition of an external metal catalyst unnecessary due to the dual role of the reaction medium.

As zinc chloride is reported to form DES with several hydrogen bond donors,[1,5] we chose this salt as one of the DES components. Choline chloride, acetamide, urea, and dimethylurea were tested as second DES component, and the coupling of benzaldehyde, morpholine, and phenylacetylene, leading to propargyl amine derivative **1**, was chosen to optimize the reaction conditions (Scheme 1, Table 1).



Scheme 1. Reaction of benzaldehyde, morpholine, and phenylacetylene, leading to propargyl amine derivative **1**.

The DES were simply prepared by mixing the two solid components and heating the mixture until a clear liquid occurred. First, $ZnCl_2$–choline chloride (2:1) was tested at 100 °C. Only traces of the product were formed (entry 1, Table 1). Drawbacks of this approach are the high viscosity of the DES, which necessitated a high reaction temperature due to its high melting point and its high hydrophilicity: The starting materials were not completely soluble in the DES, forming a turbid emulsion.

Table 1. Screening of hydrogen bond donors for the synthesis of propargyl amine derivative **1**.

Entry	H bond donor	Ratio $ZnCl_2$: H bond donor	T (°C)	Yield (%)
1	choline chloride	2:1	100	traces
2	acetamide	1:4	80	33
3	acetamide	1:4	100	traces
4	urea	2:7	80	phase separation
5	dimethylurea	2:7	80	67

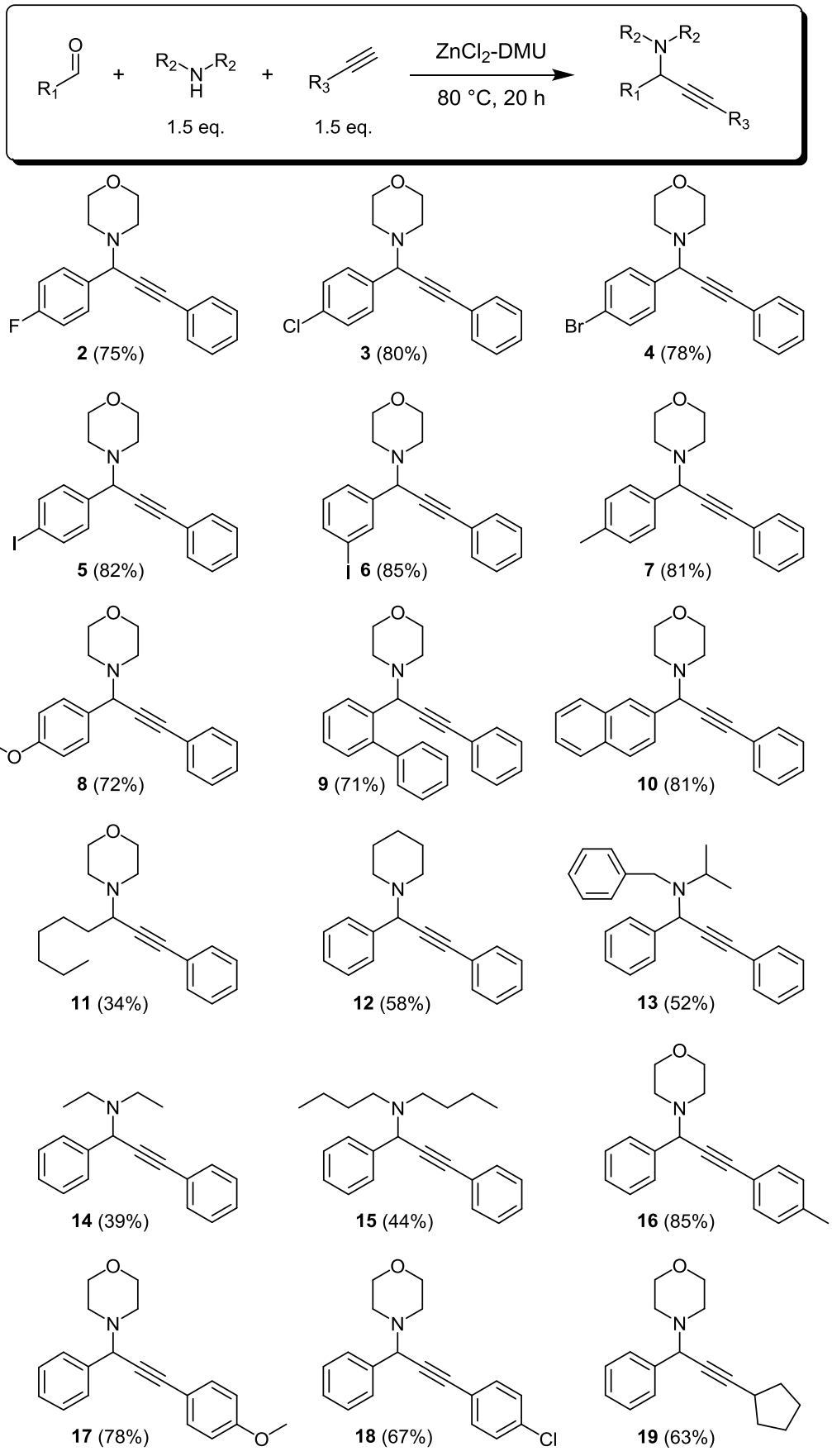
To overcome these problems, $ZnCl_2$–acetamide (1:4) was investigated, possessing lower viscosity and higher hydrophobicity. The starting materials were soluble in the DES, and the product was isolated in 33% yield (entry 2). At higher temperature (100 °C) only traces of product were isolated (entry 3). Therefore, the system was not investigated further. In $ZnCl_2$–urea (2:7), the starting materials did not dissolve, forming a separate layer (entry 4). Hence, the more hydrophobic $ZnCl_2$–dimethylurea (2:7) was tested. Fortunately, the starting materials dissolved readily in this DES, forming a homogeneous reaction mixture, and the product was isolated in 67% yield (entry 5). With this encouraging observation, the optimization was continued with $ZnCl_2$–dimethylurea (Table 2).

Table 2. Optimization of reaction conditions for the synthesis of propargyl amine derivative **1** in $ZnCl_2$–dimethylurea (2:7).

Entry	T (°C)	Morpholine (eq.)	Phenylacetylene (eq.)	Yield (%)
1	60	1	1	52
2	80	1	1	67
3	100	1	1	59
4	80	1.1	1.2	73
5	80	1.2	1.3	77
6	80	1.5	1.5	88

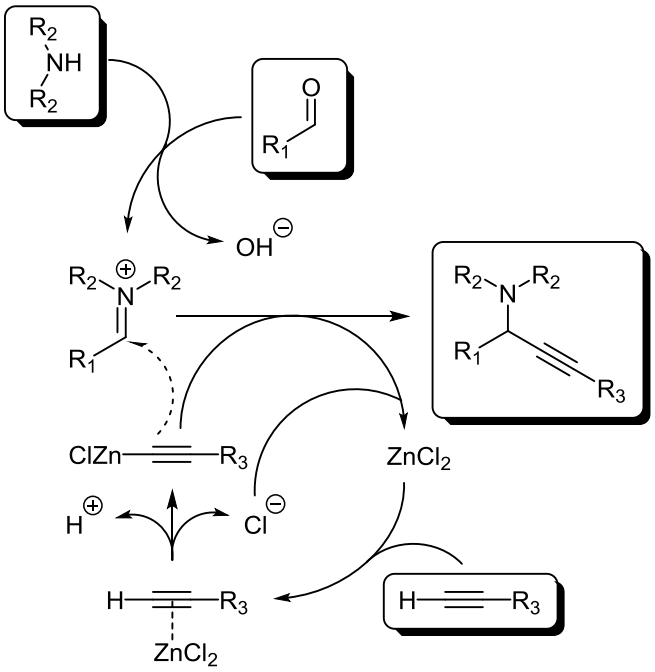
First, the reaction temperature was varied, applying one equivalent of morpholine and one equivalent of phenylacetylene for 20 hours. Decreased reaction temperature (60 °C) resulted in lower yield (52%, entry 1), similar to a higher reaction temperature of 100 °C, which decreased the yield to 59% (entry 3). Next, higher amounts of morpholine and phenylacetylene were applied. A slight excess of morpholine (1.1 eq.) and phenylacetylene (1.2 eq.) relative to benzaldehyde increased the yield to 73% (entry 4); similarly, a small increase in yield could be achieved by applying 1.2 equivalents of morpholine and 1.3 equivalents of phenylacetylene (77%, entry 5). When 1.5 equivalents of morpholine and 1.5 equivalents of phenylacetylene were applied, the product was isolated in very good yield (88%, entry 6). To summarize, the optimized reaction conditions in $ZnCl_2$–dimethylurea were obtained as 1.5 equivalents of amine and 1.5 equivalents of alkyne at 80 °C.

Having optimized the reaction conditions, the scope of the aldehyde, amine, and alkyne component was investigated, starting with variation of the aldehyde component and reaction with morpholine and phenylacetylene (Scheme 2). The application of benzaldehyde derivatives with halogen atoms in *para* position resulted in the products **2**–**5** in good to very good yields. Similarly, 3-iodobenzaldehyde furnished the corresponding propargyl amine derivative **6** in very good yield. The reaction of 4-methylbenzaldehyde resulted in 81% yield of product **7**, whereas the presence of a methoxy group in *para* position lowered the yield to 72% (product **8**), which is probably due to the decrease in electrophilic character of the carbonyl group. A similar yield was achieved with a phenyl group in *ortho* position (product **9**). 2-Naphthaldehyde as aldehyde component resulted in 81% of product **10**, while aliphatic heptanal gave product **11** in a low yield of 34%. Next, the amine component was varied. In all cases, the product yields were significantly lower than for morpholine. While the use of piperidine and isopropylbenzylamine resulted in moderate yields (58%, product **12**; 52%, product **13**), the linear aliphatic amines diethylamine and dibutylamine gave about 40% (products **14** and **15**). Finally, the effect of substitution on the alkyne component was studied, by varying the *para* substitution on phenylacetylene. 4-Methylphenylacetylene resulted in 85% of product **16**. 4-Methoxy- and 4-chloro substitution decreases the yield slightly (products **17** and **18**). Aliphatic cyclopentylacetylene resulted in good yield of product **19** (63%).



Scheme 2. Synthesis of propargyl amine derivatives in $ZnCl_2$–dimethylurea (2:7).

A plausible reaction mechanism for the synthesis of propargyl amine derivatives is shown in Scheme 3. $ZnCl_2$ coordinates to the alkyne and forms an acetylide, which attacks the iminium ion generated from the aldehyde and the amine. Upon formation of the propargyl amine, $ZnCl_2$ is released.



Scheme 3. Proposed reaction mechanism for the synthesis of propargyl amine derivatives in $ZnCl_2$–dimethylurea (2:7).

Finally, the recyclability of the $ZnCl_2$–dimethylurea DES was tested, and product **1** could be isolated in very good yield applying the same DES for three cycles (see Experimental).

4.3 Conclusion

In summary, a $ZnCl_2$–dimethylurea DES is an interesting alternative reaction medium for the synthesis of propargyl amine derivatives. The recyclable DES acts simultaneously as catalyst and solvent and is prepared from cheap chemicals.

4.4 Experimental

4.4.1 Materials and Methods

N,N-Dimethylurea (DMU) was dried by dissolving in isopropanol and stepwise removal of isopropanol *in vacuo*, interrupted by cooling the solution in an ice bath and subsequent drying *in vacuo* at 80 °C. Zinc chloride was dried *in vacuo* at 140 °C.

4.4.2 Synthesis

Preparation of the DES: The reactions were performed in 2 g of $ZnCl_2$ / DMU DES (molar ratio 2:7), if not indicated otherwise. DMU (1.39 g, 15.8 mmol) and $ZnCl_2$ (0.61 g, 4.5 mmol) were weighed into the reaction vessel and the mixture was heated to 80 °C until a clear liquid occurred, indicating the formation of the DES.

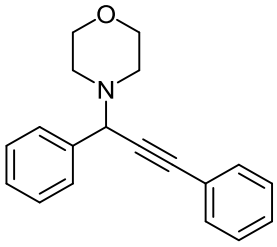
General procedure for synthesis of propargyl amines: The aldehyde was added to the DES, followed by the amine (1.5 eq.) and the alkyne (1.5 eq.) and the reaction was performed at 80 °C for 20 h. For work-up, the hot reaction mixture was diluted with 2 mL water and extracted four times with 5 mL ethyl acetate. The combined organic layers were dried over sodium sulfate and the product was isolated applying flash column chromatography (gradient of ethyl acetate in petroleum ether).

Recycling of the DES: After extraction with ethyl acetate, water was removed from the DES *in vacuo*. The residue was heated to 80 °C until the DES formed again, followed by the addition of the starting materials and repetition of the reaction. Isolated yields for the synthesis of 4-(1,3-diphenyl-2-propyn-1-yl)-morpholine (product **1**): Cycle 1: 78%; Cycle 2: 82%; Cycle 3: 83%.

All compounds except compounds **5**, **6**, **9**, **13**, and **19** are reported in literature:

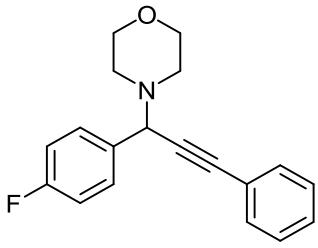
Compound	Literature
1–4, 7, 8, 10	22
11	24
12	25
14	26
15	27
16, 17	28
18	29

4-(1,3-Diphenyl-2-propyn-1-yl)-morpholine (1)



Procedure for entry 2 (Table 2): Benzaldehyde (202 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 486 mg (88%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72–7.69 (m, 2H), 7.60–7.56 (m, 2H), 7.45–7.35 (m, 6H), 4.85 (s, 1H), 3.84–3.73 (m, 4H), 2.75–2.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.8, 131.9, 128.7, 128.4, 128.3, 127.9, 123.0, 88.6, 85.1, 67.2, 62.1, 49.9. EI-MS m/z calculated for $C_{19}H_{19}NO$ $[M]^+$: 277.1467, found: 277.1445.

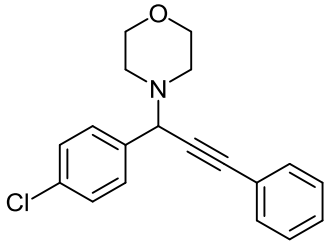
4-[1-(4-Fluorophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (2)



4-Fluorobenzaldehyde (215 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 449 mg (75%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.67–7.60 (m, 2H), 7.57–7.51 (m, 2H), 7.38–7.32 (m, 3H), 7.12–7.03 (m, 2H), 4.79 (s, 1H), 3.82–3.68 (m, 4H), 2.64 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75

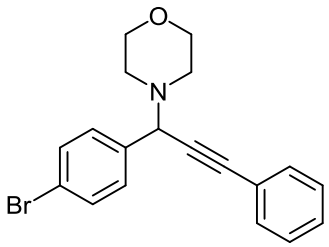
MHz, $CDCl_3$): 164.0, 160.8, 133.7, 131.8, 130.2, 128.4, 122.8, 115.2, 115.0, 88.8, 84.7, 67.1, 61.3, 49.8. ESI-MS m/z calculated for $C_{19}H_{18}FNO$ $[MH]^+$: 296.1451, found: 296.1461.

4-[1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (3)



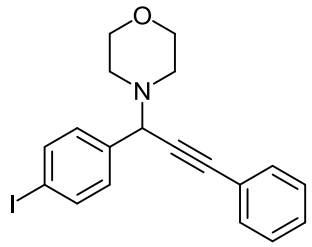
4-Chlorobenzaldehyde (281 mg, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 517 mg (80%). ^1H NMR (300 MHz, $CDCl_3$): 7.64–7.58 (m, 2H), 7.57–7.50 (m, 2H), 7.39–7.31 (m, 5H), 4.78 (s, 1H), 3.82-3.68 (m, 4H), 2.64 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 136.5, 133.6, 131.9, 129.9, 128.5, 128.4, 89.0, 84.4, 67.1, 61.4, 49.8. ESI-MS m/z calculated for $C_{19}H_{18}ClNO$ $[MH]^+$: 312.1156, found: 312.1157.

4-[1-(4-Bromophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (4)



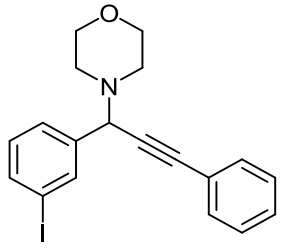
4-Bromobenzaldehyde (268 mg, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 570 mg (78%). ^1H NMR (300 MHz, $CDCl_3$): 7.58–7.48 (m, 6H), 7.38–7.32 (m, 3H), 4.76 (s, 1H), 3.81–3.68 (m, 4H), 2.63 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.0, 131.9, 131.4, 130.3, 128.5, 128.4, 122.7, 121.8, 89.0, 84.3, 67.1, 61.5, 49.8. ESI-MS m/z calculated for $C_{19}H_{18}BrNO$ $[MH]^+$: 356.0651, found: 356.0664.

4-[1-(4-Iodophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (5)



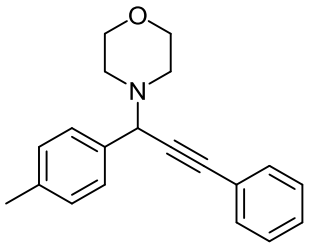
4-Iodobenzaldehyde (232 mg, 1.0 mmol) was reacted with morpholine (131 µL, 1.5 mmol) and phenylacetylene (165 µL, 1.5 mmol). The reaction was performed in 1 g of melt, prepared from 0.31 g $ZnCl_2$ and 0.69 g DMU. Yield: 336 mg (82%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.73–7.67 (m, 2H), 7.54–7.49 (m, 2H), 7.42–7.37 (m, 2H), 7.36–7.31 (m, 3H), 4.76 (s, 1H), 3.81–3.66 (m, 4H), 2.63 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.5, 137.4, 131.8, 130.6, 128.5, 128.4, 122.7, 93.6, 89.0, 84.1, 67.1, 61.5, 49.8. ESI-MS m/z calculated for $C_{19}H_{18}INO$ $[MH]^+$: 404.0512, found: 404.0533. EA (%, theoretical values in brackets): C 56.50 (56.59), H 4.36 (4.50), N 3.38 (3.47).

4-[1-(3-Iodophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (6)



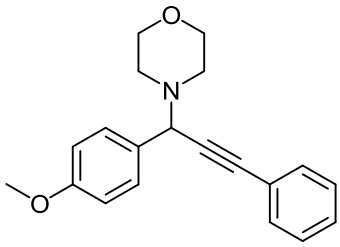
3-Iodobenzaldehyde (464 mg, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 688 mg (85%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.00 (s, 1H), 7.68–7.60 (m, 2H), 7.57–7.48 (m, 2H), 7.39–7.32 (m, 3H), 7.11 (t, J = 7.8 Hz, 1H), 4.75 (s, 1H), 3.82–3.68 (m, 4H), 2.63 (t, J = 4.4 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 140.3, 137.5, 136.9, 131.9, 130.0, 128.5, 128.4, 127.9, 122.7, 94.3, 89.1, 84.0, 67.1, 61.4, 49.8. ESI-MS m/z calculated for $C_{19}H_{18}INO$ $[MH]^+$: 404.0512, found: 404.0555. EA (%, theoretical values in brackets): C 55.78 (56.59), H 4.55 (4.50), N 3.23 (3.47).

4-[1-(4-Methylphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (7)



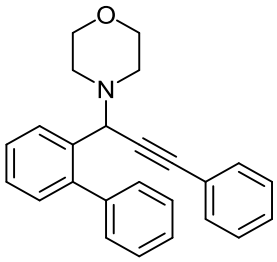
4-Methylbenzaldehyde (236 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 474 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.55–7.53 (m, 4H), 7.36–7.33 (m, 3H), 7.22–7.19 (m, 2H), 4.78 (s, 1H), 3.81–3.70 (m, 4H), 2.71–2.60 (m, 4H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.5, 134.8, 131.8, 129.0, 128.6, 128.3, 128.2, 123.1, 88.3, 85.4, 67.2, 61.8, 49.9. ESI-MS m/z calculated for $C_{20}H_{21}NO$ $[MH]^+$: 292.1702, found: 292.1707.

4-[1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (8)



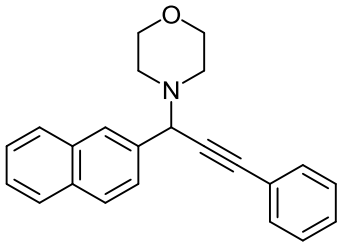
4-Methoxybenzaldehyde (243 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 446 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.59–7.52 (m, 4H), 7.37–7.32 (m, 3H), 7.96–7.91 (m, 2H), 4.76 (s, 1H), 3.81–3.70 (m, 7H), 2.71–2.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 159.3, 131.8, 129.9, 129.8, 128.4, 128.3, 123.1, 113.6, 88.3, 85.5, 67.2, 61.5, 55.3, 49.9. ESI-MS m/z calculated for $C_{20}H_{21}NO_2$ $[MH]^+$: 308.1651, found: 308.1644.

4-[1-(2-Phenylphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (9)



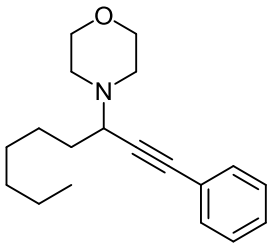
2-Phenylbenzaldehyde (323 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 508 mg (71%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.88–7.79 (m, 1H), 7.60–7.28 (m, 13H), 4.70 (s, 1H), 3.73–3.56 (m, 4H), 2.71–2.55 (m, 2H), 2.51–2.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.8, 141.1, 135.7, 131.8, 130.5, 129.6, 129.3, 128.3, 128.2, 127.8, 127.1, 127.0, 123.1, 88.1, 85.9, 67.2, 58.8, 49.9. ESI-MS m/z calculated for $C_{25}H_{23}NO$ $[MH]^+$: 354.1859, found: 354.1894. EA (%, theoretical values in brackets): C 84.24 (84.95), H 6.44 (6.56), N 3.78 (3.96).

4-[1-(2-Naphthalenyl)-3-phenyl-2-propyn-1-yl]-morpholine (10)



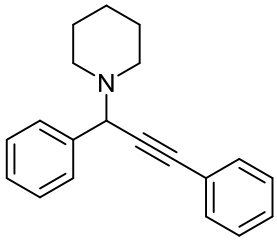
2-Naphthaldehyde (312 mg, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 536 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.13 (s, 1H), 7.95–7.74 (m, 4H), 7.65–7.56 (m, 2H), 7.56–7.46 (m, 2H), 7.42–7.34 (m, 3H), 4.97 (s, 1H), 3.86–3.68 (m, 4H), 2.79–2.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 135.4, 133.1, 131.9, 128.4, 128.2, 128.1, 127.7, 127.6, 126.6, 126.2, 126.1, 123.0, 88.9, 85.0, 67.2, 62.2, 50.0. ESI-MS m/z calculated for $C_{23}H_{21}NO$ $[MH]^+$: 328.1702, found: 328.1706.

4-[1-(2-Phenylethynyl)heptyl]-morpholine (11)



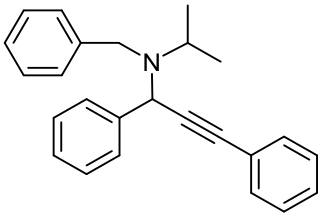
Heptaldehyde (282 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 196 mg (34%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.47–7.40 (m, 2H), 7.32–7.28 (m, 3H), 3.83–3.71 (m, 4H), 3.51 (t, J = 7.4 Hz, 1H), 2.80–2.73 (m, 2H), 2.62–2.55 (m, 2H), 1.78–1.67 (m, 2H), 1.60–1.25 (m, 8H), 0.91–0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 131.7, 128.3, 128.0, 67.1, 58.2, 49.7, 32.9, 31.8, 29.1, 26.6, 22.6, 14.1. ESI-MS m/z calculated for $C_{19}H_{27}NO$ $[MH]^+$: 286.2172, found: 286.2168.

1-(1,3-Diphenyl-2-propyn-1-yl)-piperidine (12)



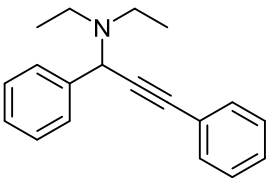
Benzaldehyde (202 µL, 2.0 mmol) was reacted with piperidine (297 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 322 mg (58%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.84–7.82 (m, 2H), 7.70–7.67 (m, 2H), 7.54–7.40 (m, 6H), 4.97 (s, 1H), 2.80–2.68 (m, 4H), 1.83–1.58 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.9, 132.0, 128.7, 128.5, 128.3, 128.2, 127.7, 88.2, 86.3, 62.6, 50.9, 26.4, 24.7. ESI-MS m/z calculated for $C_{20}H_{21}N$ $[MH]^+$: 276.1753, found: 276.1786.

Benzyl-isopropyl-(1,3-diphenyl-2-propyn-1-yl)-amine (13)



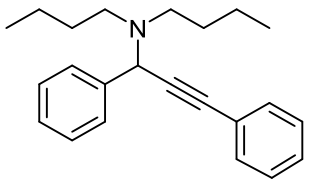
Benzaldehyde (202 µL, 2.0 mmol) was reacted with isopropylbenzylamine (494 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 327 mg (52%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.81–7.78 (m, 2H), 7.62–7.59 (m, 2H), 7.45–7.24 (m, 11H), 5.05 (s, 1H), 3.94–3.83 (m, 2H), 3.19–3.05 (m, 1H), 1.35–1.32 (m, 3H), 1.21–1.19 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 140.8, 140.4, 131.6, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.2, 126.7, 123.6, 88.4, 87.7, 53.5, 50.4, 48.5, 22.8, 17.7. ESI-MS m/z calculated for $C_{25}H_{25}N$ $[MH]^+$: 340.2066, found: 340.2108. EA (%, theoretical values in brackets): C 88.56 (88.45), H 7.26 (7.42), N 3.98 (4.13).

Diethyl-(1,3-diphenyl-2-propyn-1-yl)-amine (14)



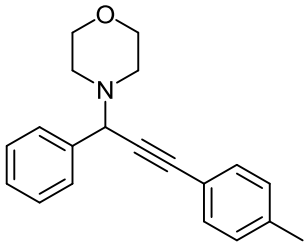
Benzaldehyde (202 µL, 2.0 mmol) was reacted with diethylamine (309 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 205 mg (39%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.88–7.85 (m, 2H), 7.68–7.65 (m, 2H), 7.53–7.39 (m, 6H), 5.22 (s, 1H), 2.87–2.66 (m, 4H), 1.24 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 140.0, 131.9, 128.5, 128.4, 128.2, 127.4, 123.6, 87.7, 86.3, 57.2, 44.8, 13.8. ESI-MS m/z calculated for $C_{19}H_{21}N$ $[MH]^+$: 264.1753, found: 264.1773.

Dibutyl-(1,3-diphenyl-2-propyn-1-yl)-amine (15)



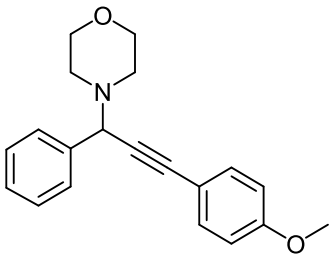
Benzaldehyde (202 µL, 2.0 mmol) was reacted with dibutylamine (510 µL, 3.0 mmol) and phenylacetylene (330 µL, 3.0 mmol). Yield: 278 mg (44%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.70–7.68 (m, 2H), 7.55–7.51 (m, 2H), 7.38–7.26 (m, 6H), 5.04 (s, 1H), 2.51 (t, J = 7.0 Hz, 4H), 1.51–1.16 (m, 8H), 0.86 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 140.1, 132.0, 128.5, 128.4, 128.1, 127.3, 123.6, 87.7, 86.2, 57.5, 50.7, 30.6, 20.6, 14.2. ESI-MS m/z calculated for $C_{23}H_{29}N$ $[MH]^+$: 320.2379, found: 320.2416.

4-[3-(4-Methylphenyl)-1-phenyl-2-propyn-1-yl]-morpholine (16)



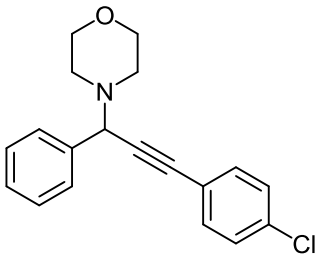
Benzaldehyde (202 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and 4methylphenylacetylene (380 µL, 3.0 mmol). Yield: 496 mg (85%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.75–7.73 (m, 2H), 7.53–7.34 (m, 5H), 7.21–7.18 (m, 2H), 4.85 (s, 1H), 3.86–3.74 (m, 4H), 2.77–2.65 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.4, 138.1, 131.8, 129.2, 128.7, 128.3, 127.9, 120.1, 88.8, 84.5, 67.2, 62.2, 50.0, 21.6. ESI-MS m/z calculated for $C_{20}H_{21}NO$ $[MH]^+$: 292.1702, found: 292.1699.

4-[3-(4-Methoxyphenyl)-1-phenyl-2-propyn-1-yl]-morpholine (17)



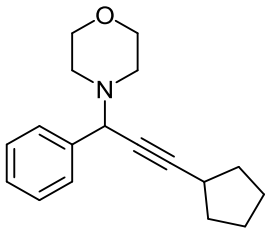
Benzaldehyde (202 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and 4methoxyphenylacetylene (389 µL, 3.0 mmol). Yield: 498 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.70–7.68 (m, 2H), 7.53–7.48 (m, 2H), 7.43–7.30 (m, 3H), 7.91–7.86 (m, 2H), 4.81 (s, 1H), 3.79–3.74 (m, 7H), 2.72–2.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 159.7, 138.1, 133.3, 128.7, 128.3, 127.8, 115.1, 114.0, 88.4, 83.6, 67.2, 62.1, 55.3, 50.0. ESI-MS m/z calculated for $C_{20}H_{21}NO_2$ $[MH]^+$: 308.1651, found: 308.1644.

4-[3-(4-Chlorophenyl)-1-phenyl-2-propyn-1-yl]-morpholine (18)



Benzaldehyde (101 µL, 1.0 mmol) was reacted with morpholine (131 µL, 1.5 mmol) and 4chlorophenylacetylene (205 mg, 1.5 mmol). The reaction was performed in 1 g of melt, prepared from 0.31 g $ZnCl_2$ and 0.69 g DMU. Yield: 238 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.67–7.64 (m, 2H), 7.48–7.30 (m, 7H), 4.81 (s, 1H), 3.82–3.70 (m, 4H), 2.71–2.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.6, 134.3, 133.1, 128.7, 128.6, 128.3, 127.9, 121.5, 87.5, 86.3, 67.2, 62.1. ESI-MS m/z calculated for $C_{19}H_{18}ClNO$ $[MH]^+$: 312.1156, found: 312.1154.

4-(3-Cyclopentyl-1-phenyl-2-propyn-1-yl)-morpholine (19)



Benzaldehyde (202 µL, 2.0 mmol) was reacted with morpholine (261 µL, 3.0 mmol) and cyclopentylacetylene (348 µL, 3.0 mmol). Yield: 341 mg (63%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.58–7.54 (m, 2H), 7.37–7.24 (m, 3H), 4.55 (s, 1H), 3.76–3.65 (m, 4H), 2.81–2.71 (m, 1H), 2.53 (t, J = 4.6 Hz, 4H), 2.02–1.90 (m, 2H), 1.83–1.55 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.5, 128.6, 128.1, 127.5, 93.3, 74.7, 67.2, 61.6, 49.7, 34.3, 30.4, 25.0. ESI-MS m/z calculated for $C_{18}H_{23}NO$ $[MH]^+$: 270.1859, found: 270.1869.

4.5 References

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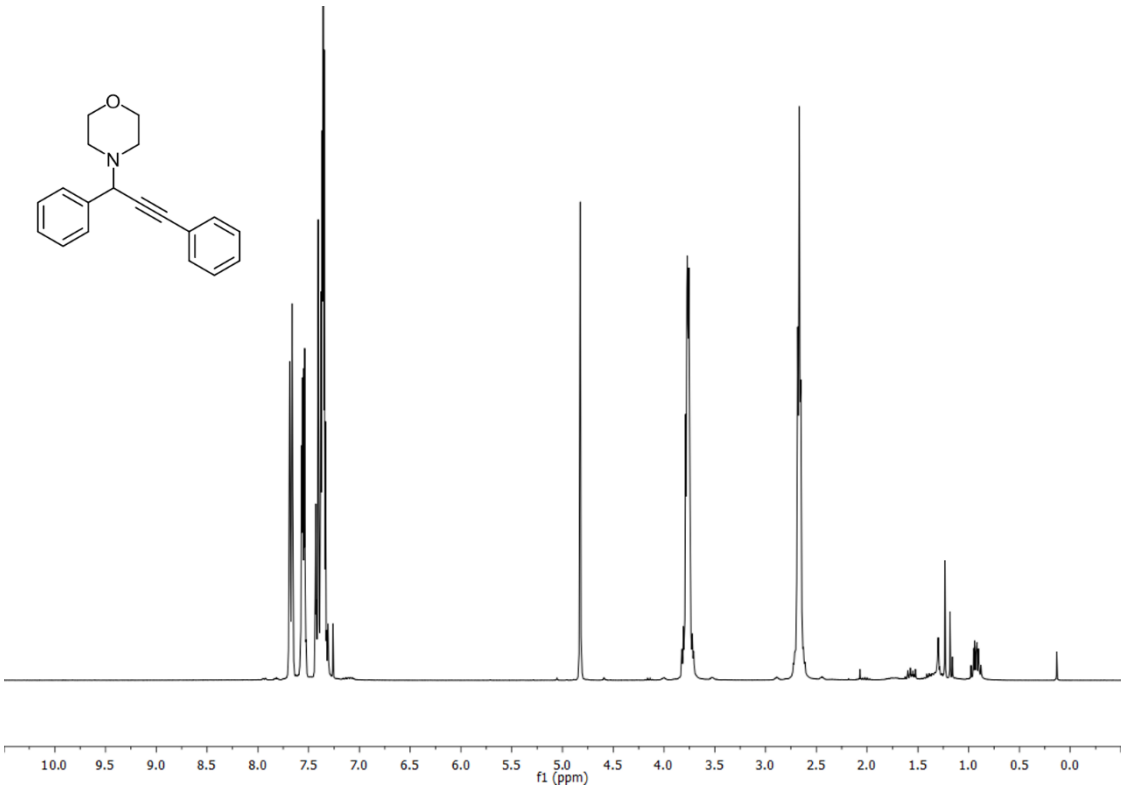
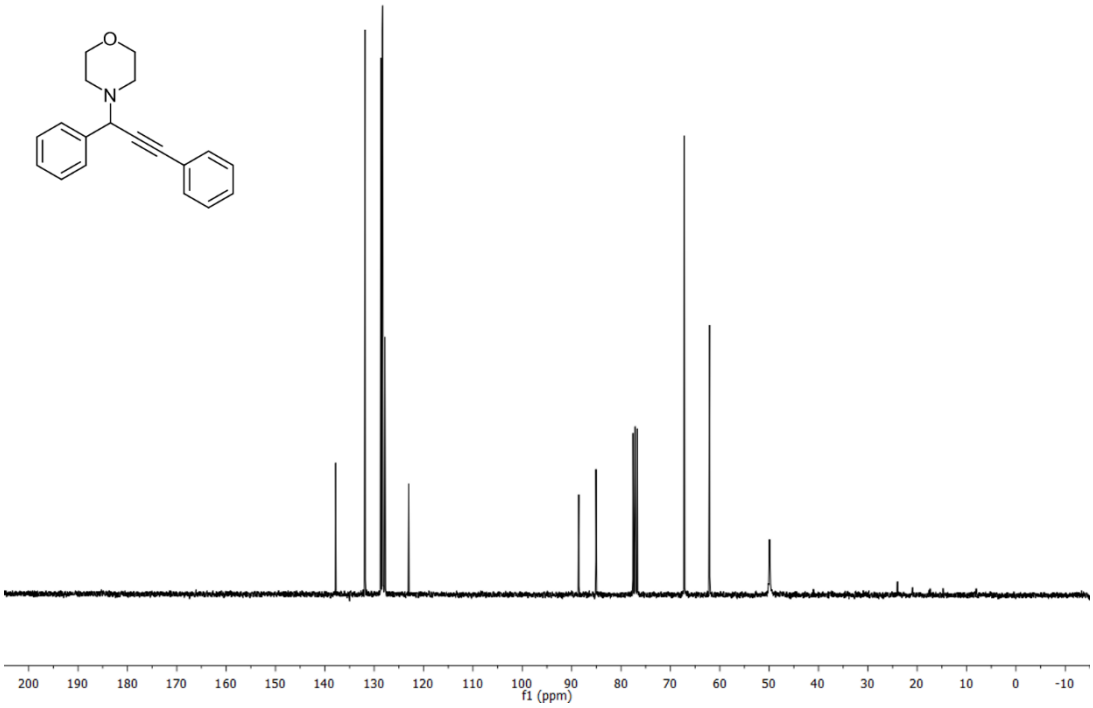
4.6 NMR Spectra

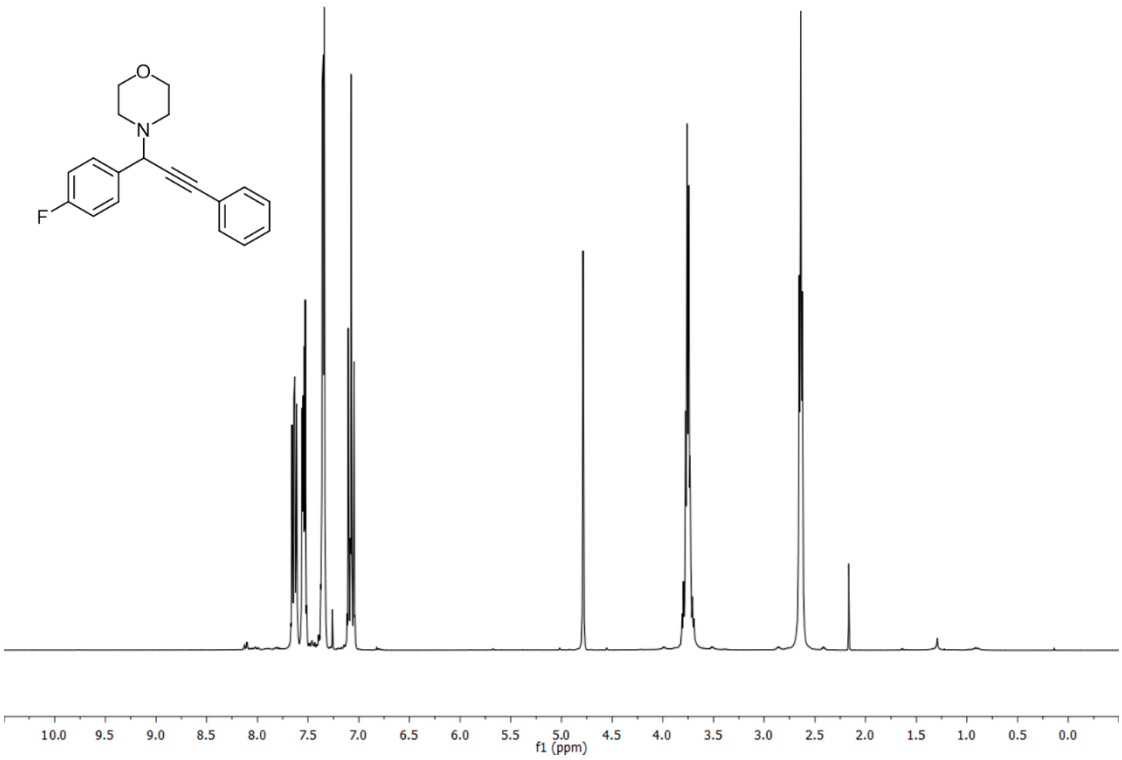
4-(1,3-Diphenyl-2-propyn-1-yl)-morpholine (1): ^{1}H NMR (300 MHz, $CDCl_3$)



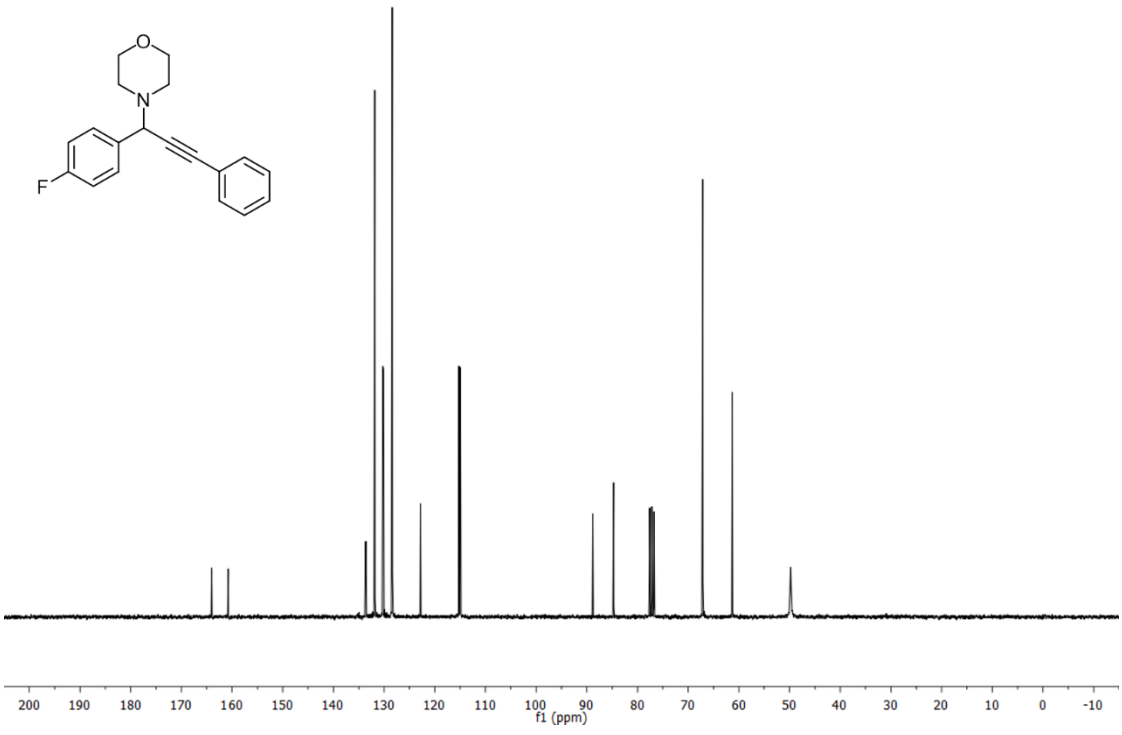
^{13}C NMR (75 MHz, $CDCl_3$)



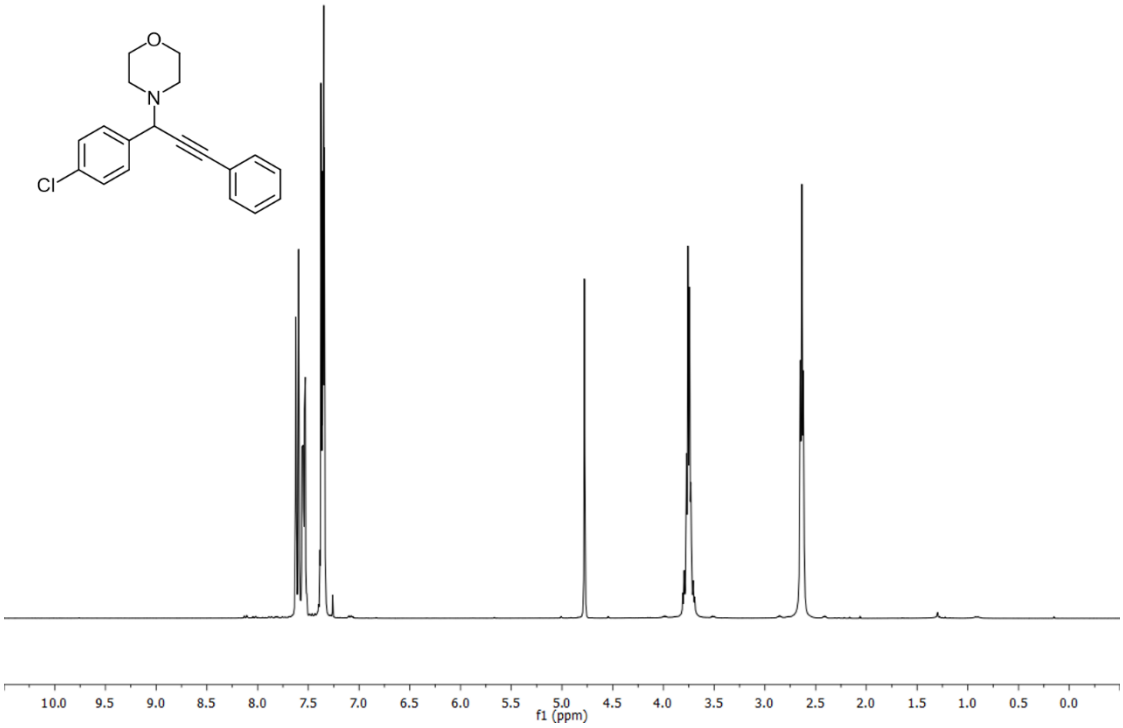
4-[1-(4-Fluorophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (2): ^{1}H NMR (300 MHz, $CDCl_3$)



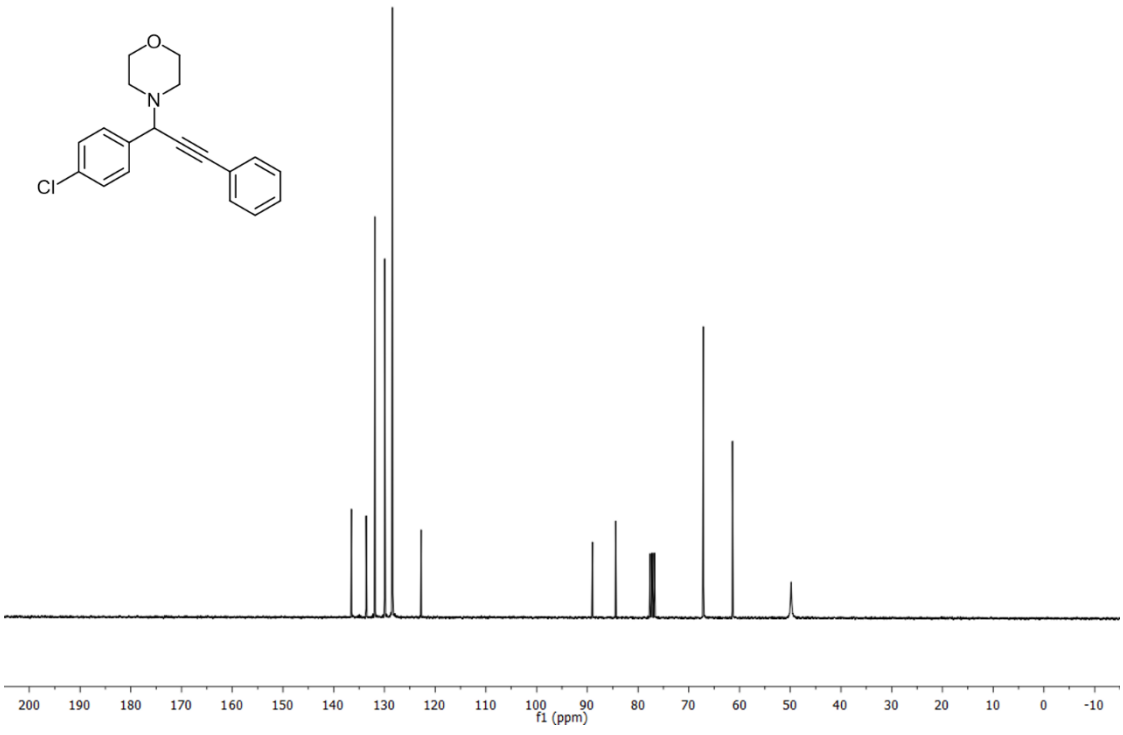
^{13}C NMR (75 MHz, $CDCl_3$)



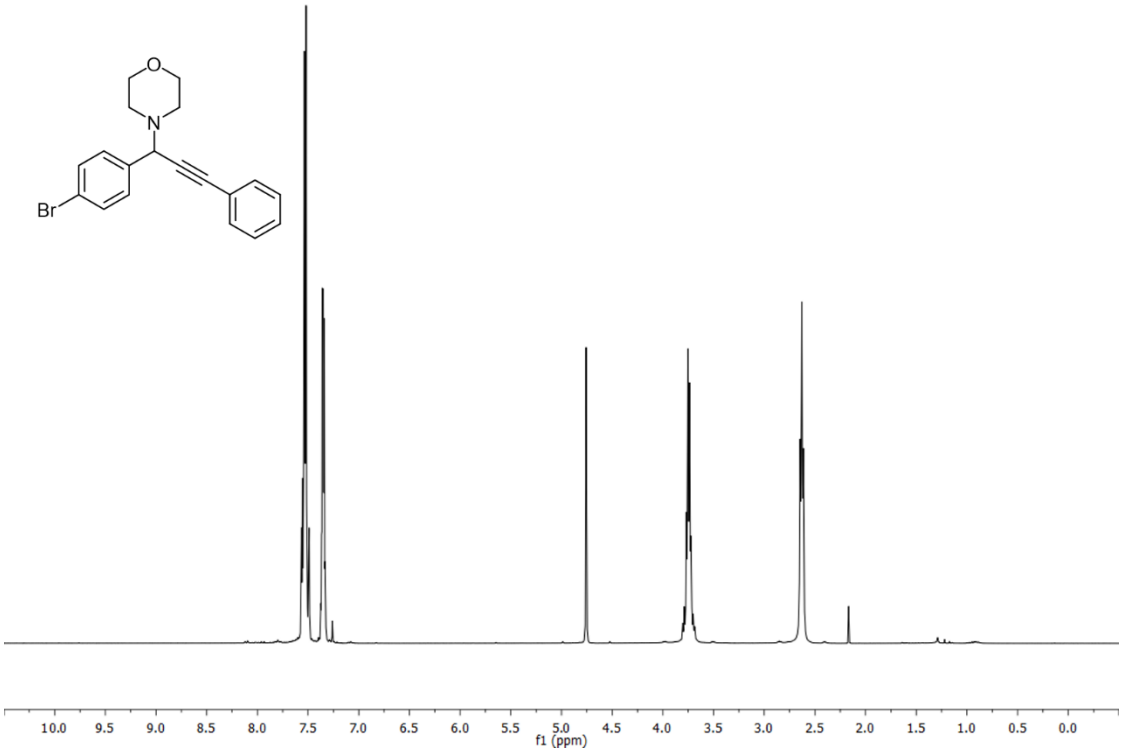
4-[1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (3): ^{1}H NMR (300 MHz, $CDCl_3$)



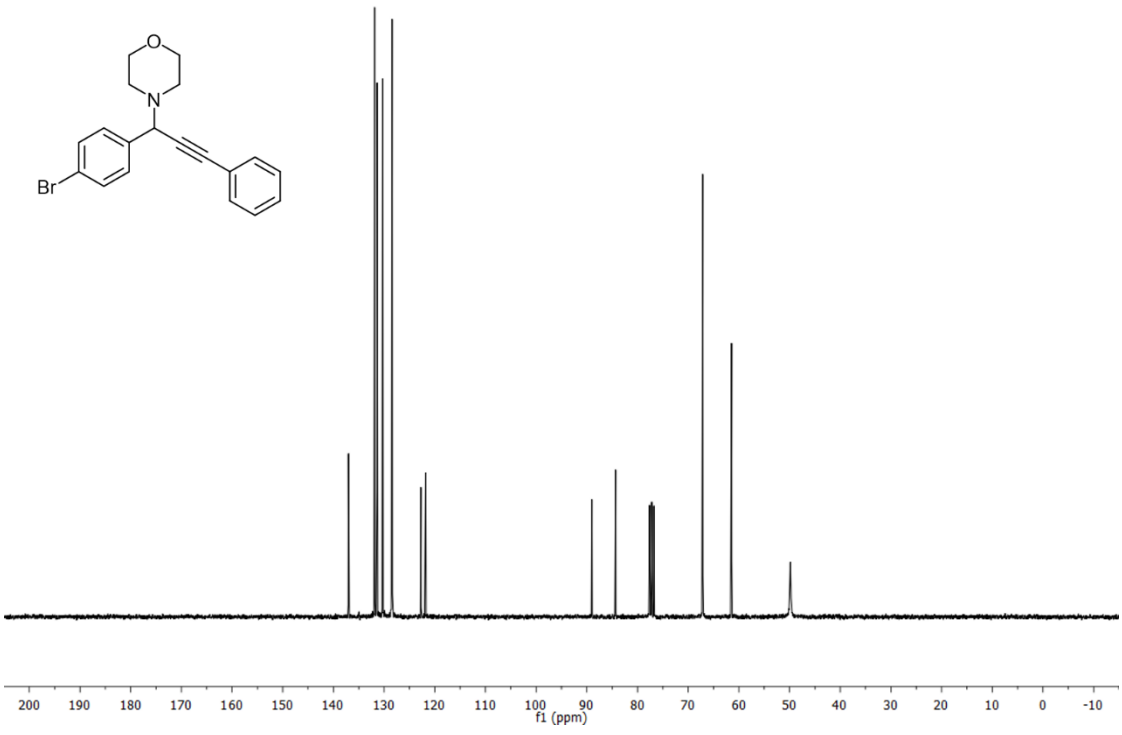
^{13}C NMR (75 MHz, $CDCl_3$)



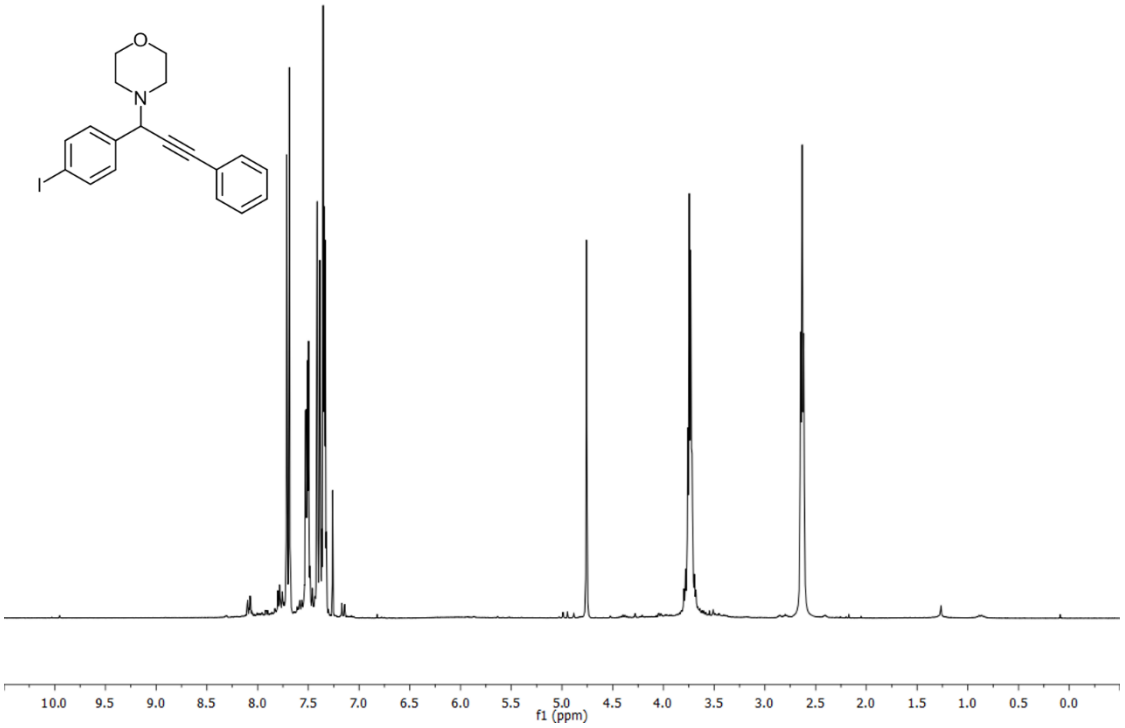
4-[1-(4-Bromophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (4): ^{1}H NMR (300 MHz, $CDCl_3$)



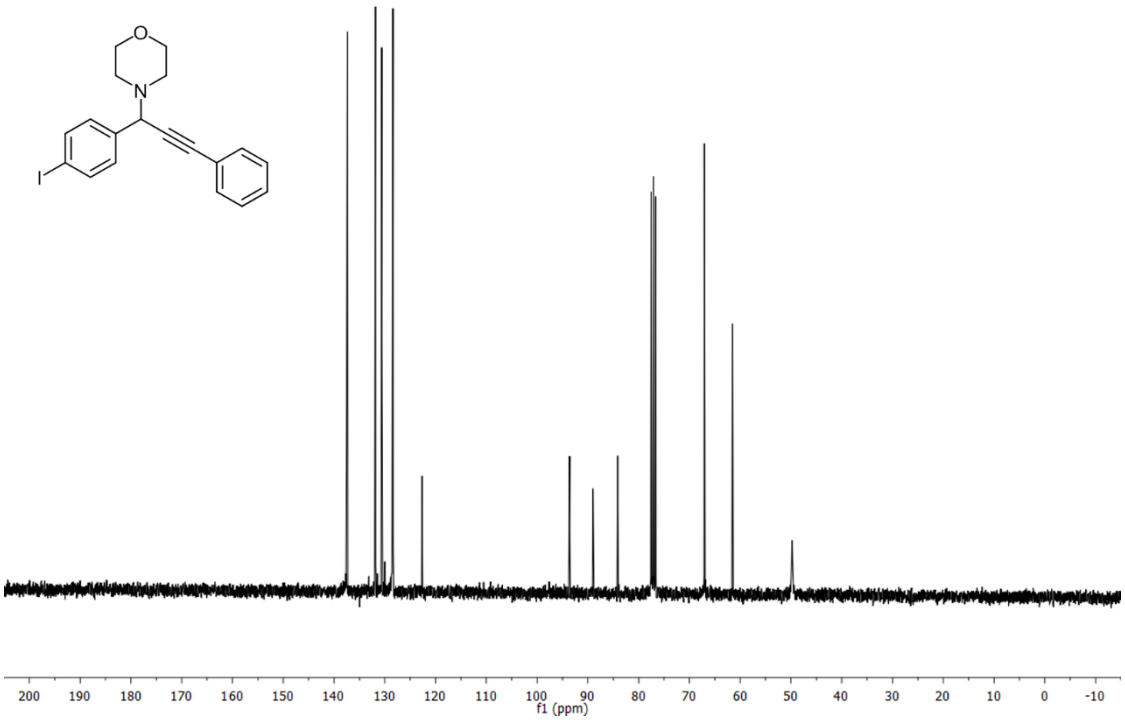
^{13}C NMR (75 MHz, $CDCl_3$)



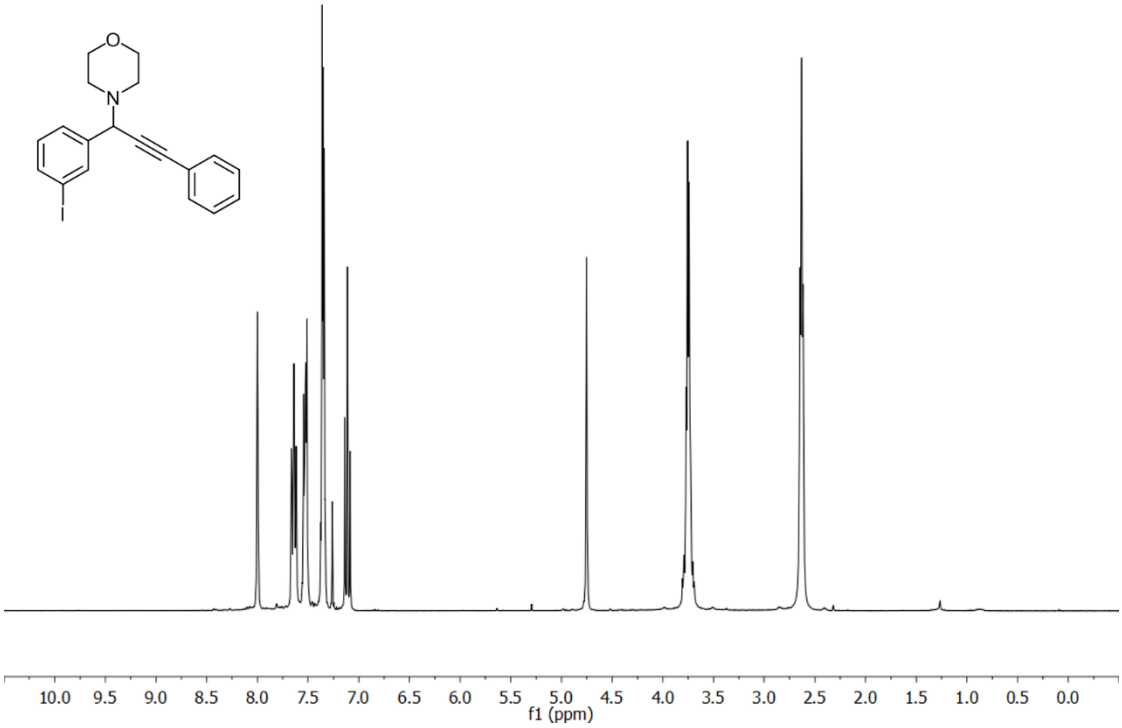
4-[1-(4-Iodophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (5): ^{1}H NMR (300 MHz, $CDCl_3$)



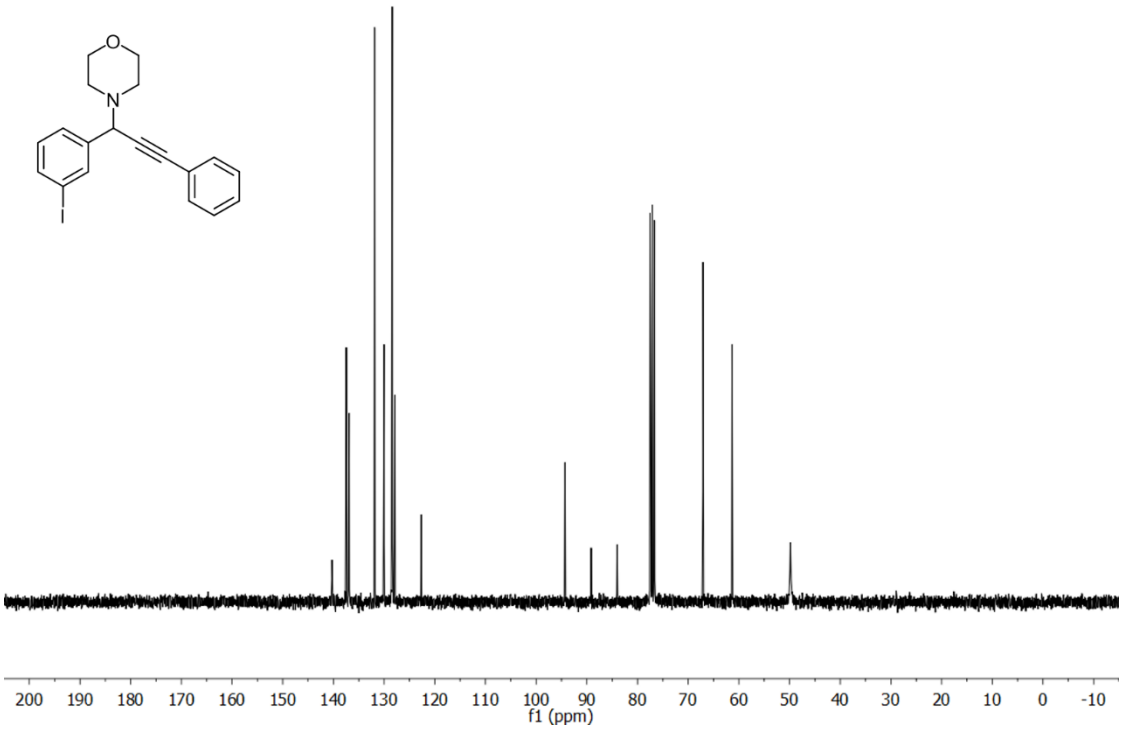
^{13}C NMR (75 MHz, $CDCl_3$)



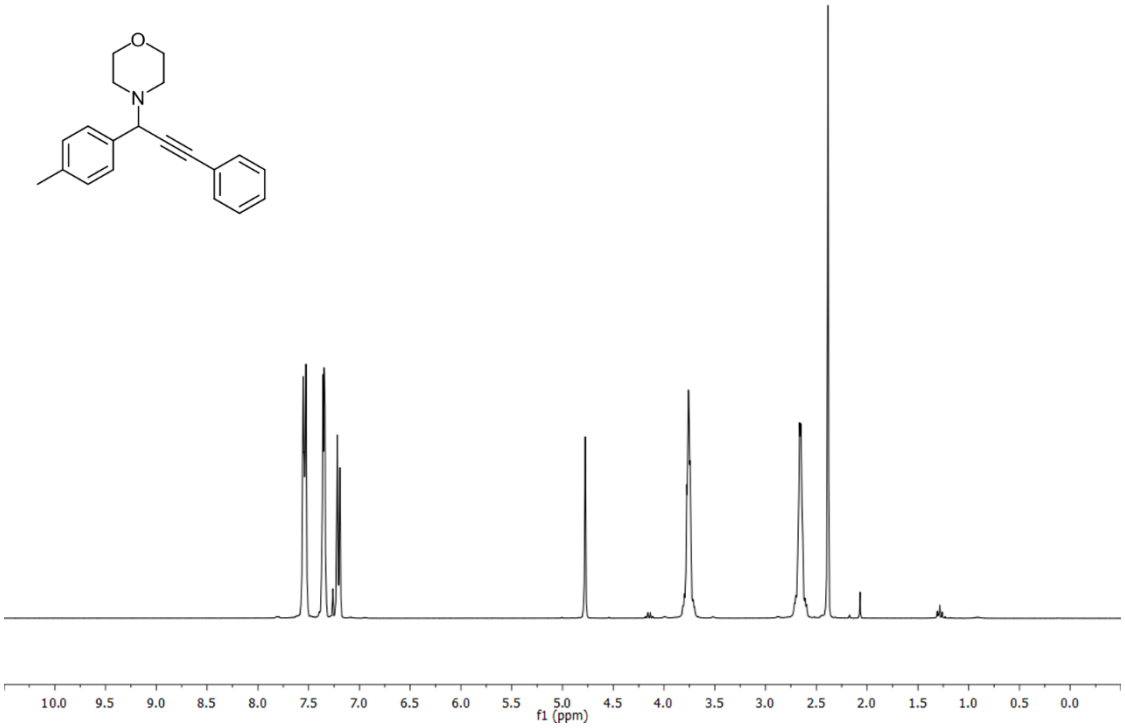
4-[1-(3-Iodophenyl)-3-phenyl-2-propyn-1-yl]-morpholine (6): ^{1}H NMR (300 MHz, $CDCl_3$)



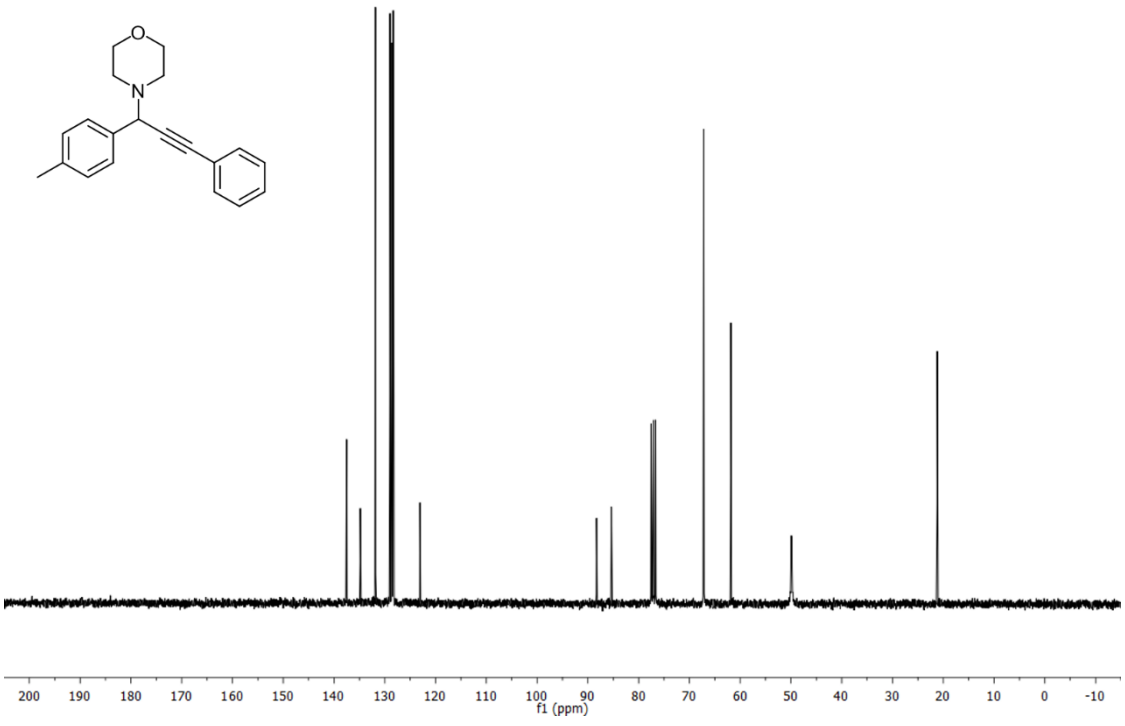
^{13}C NMR (75 MHz, $CDCl_3$)



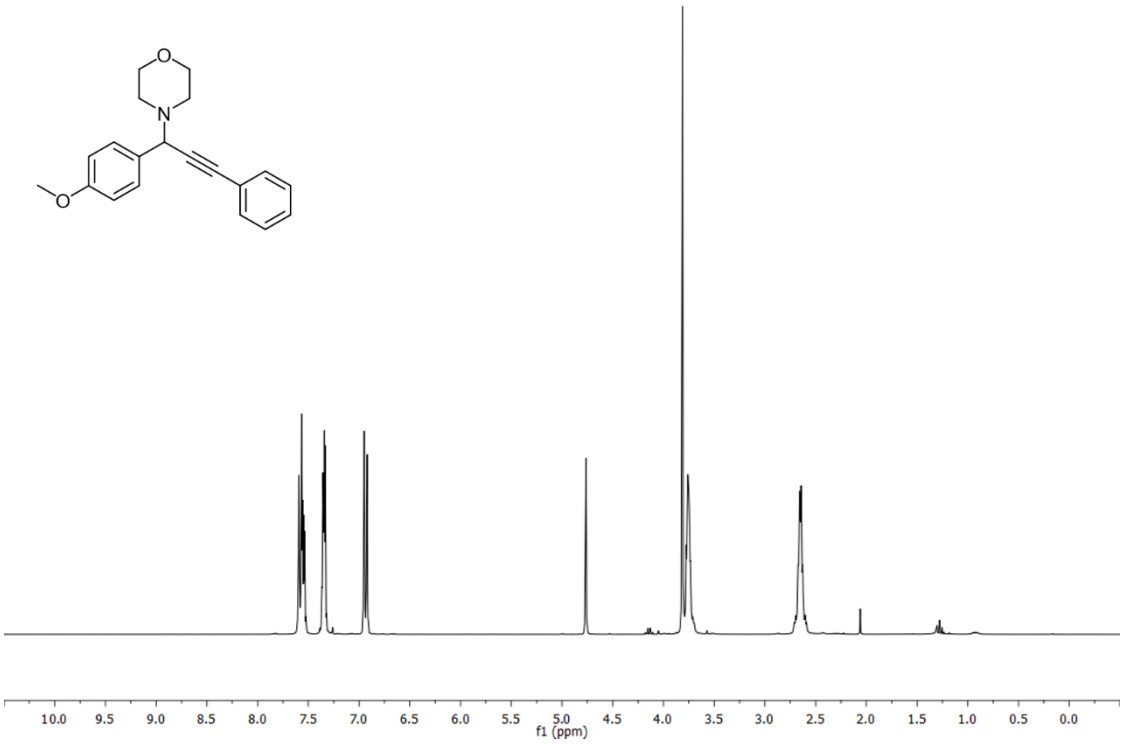
4-[1-(4-Methylphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (7): ^{1}H NMR (300 MHz, $CDCl_3$)



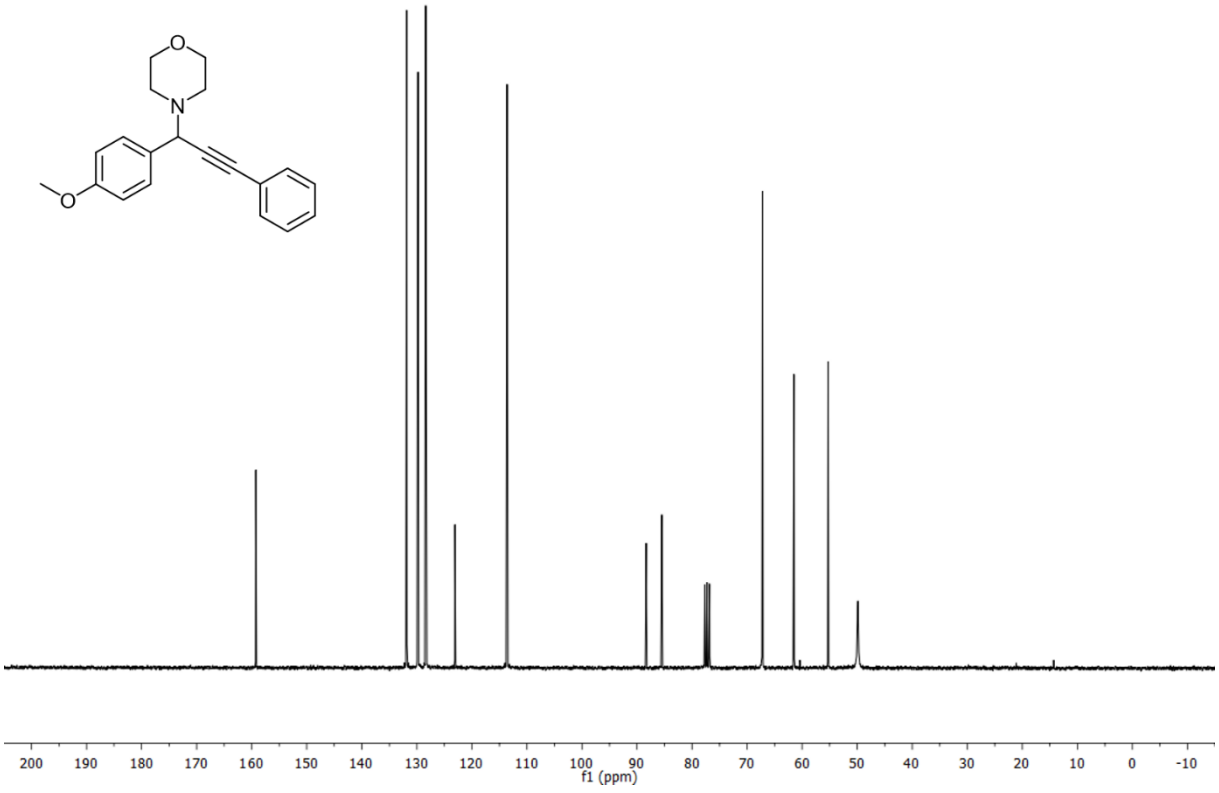
^{13}C NMR (75 MHz, $CDCl_3$)



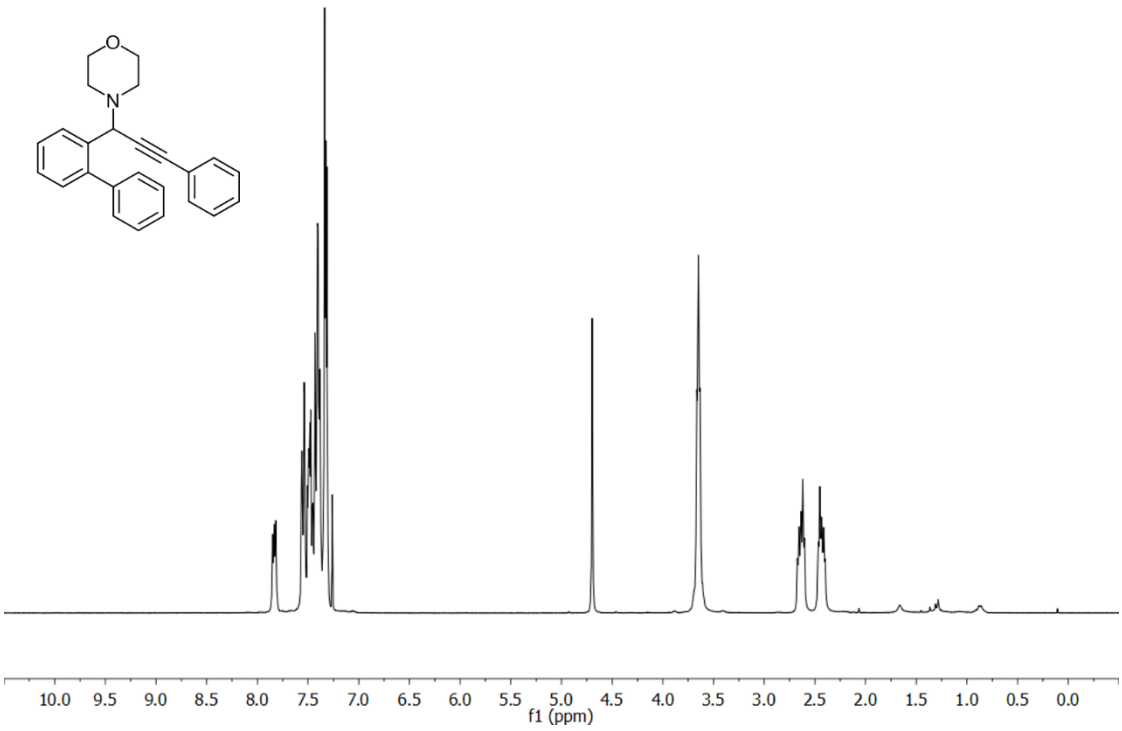
4-[1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (8): ^{1}H NMR (300 MHz, $CDCl_3$)



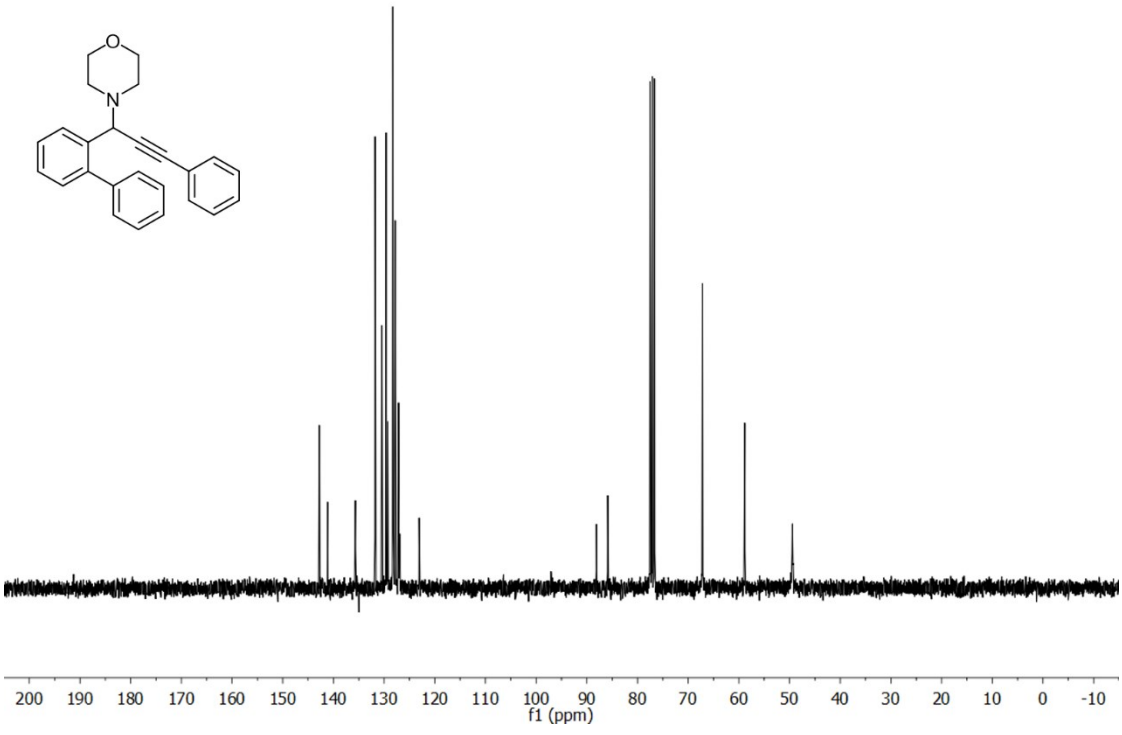
^{13}C NMR (75 MHz, $CDCl_3$)



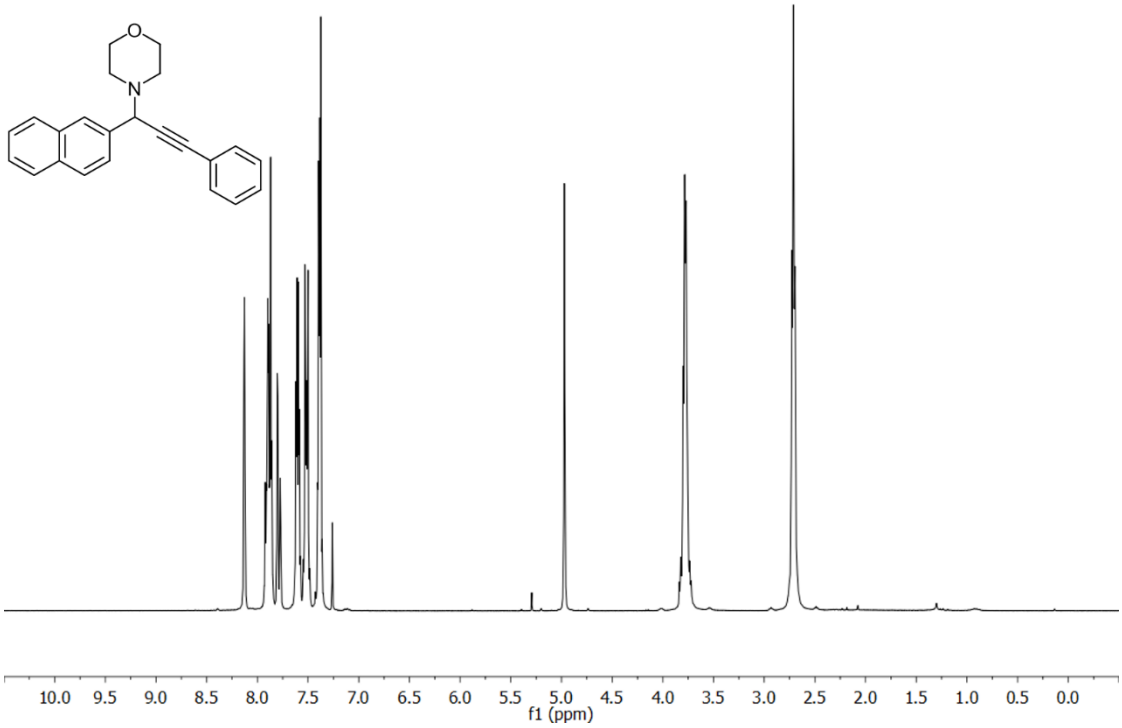
4-[1-(2-Phenylphenyl)-3-phenyl-2-propyn-1-yl]-morpholine (9): ^{1}H NMR (300 MHz, $CDCl_3$)



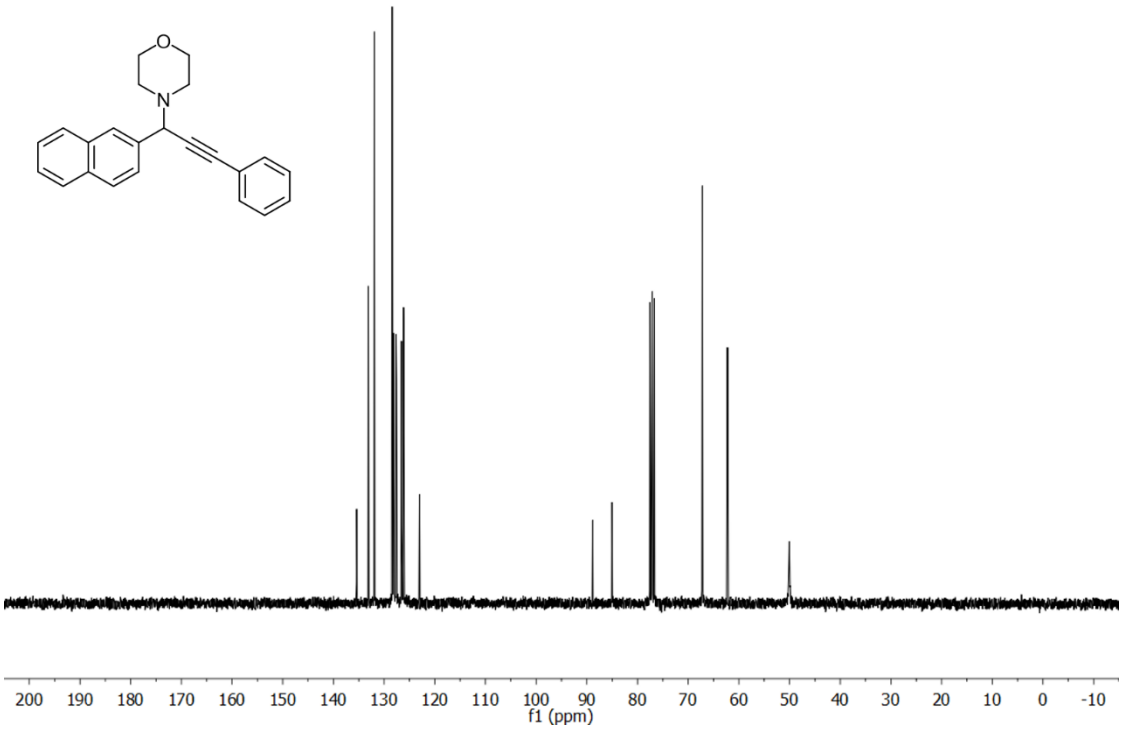
^{13}C NMR (75 MHz, $CDCl_3$)



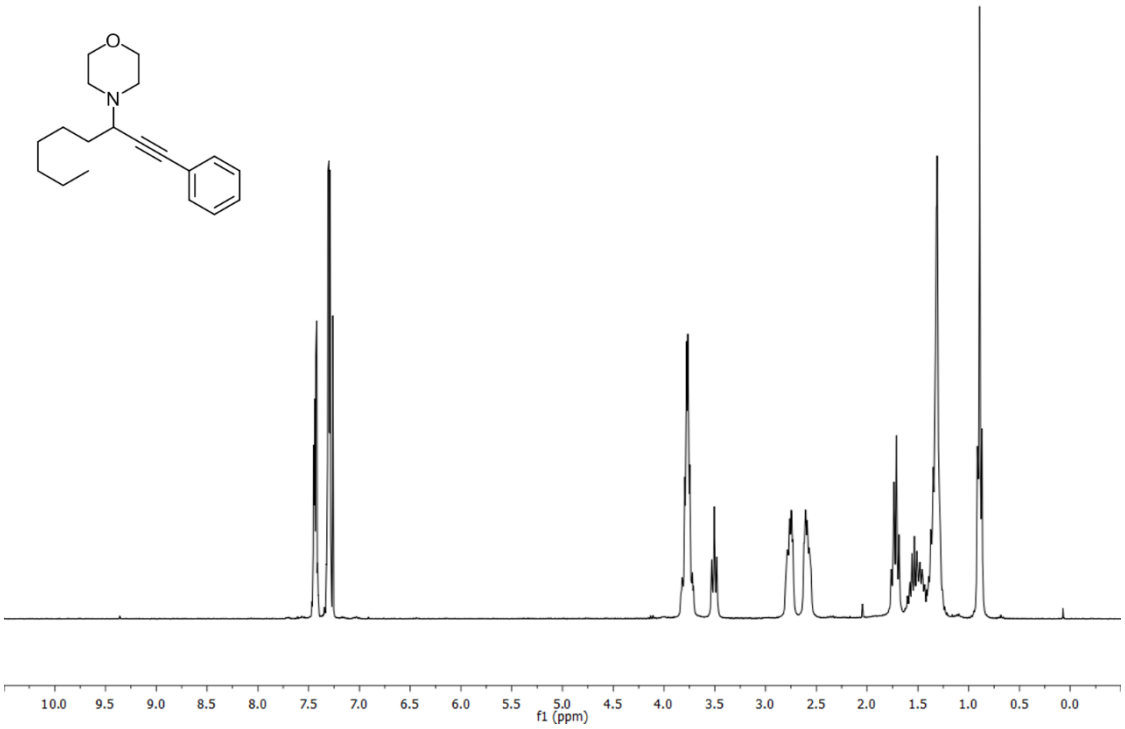
4-[1-(2-Naphthalenyl)-3-phenyl-2-propyn-1-yl]-morpholine (10): ^{1}H NMR (300 MHz, $CDCl_3$)



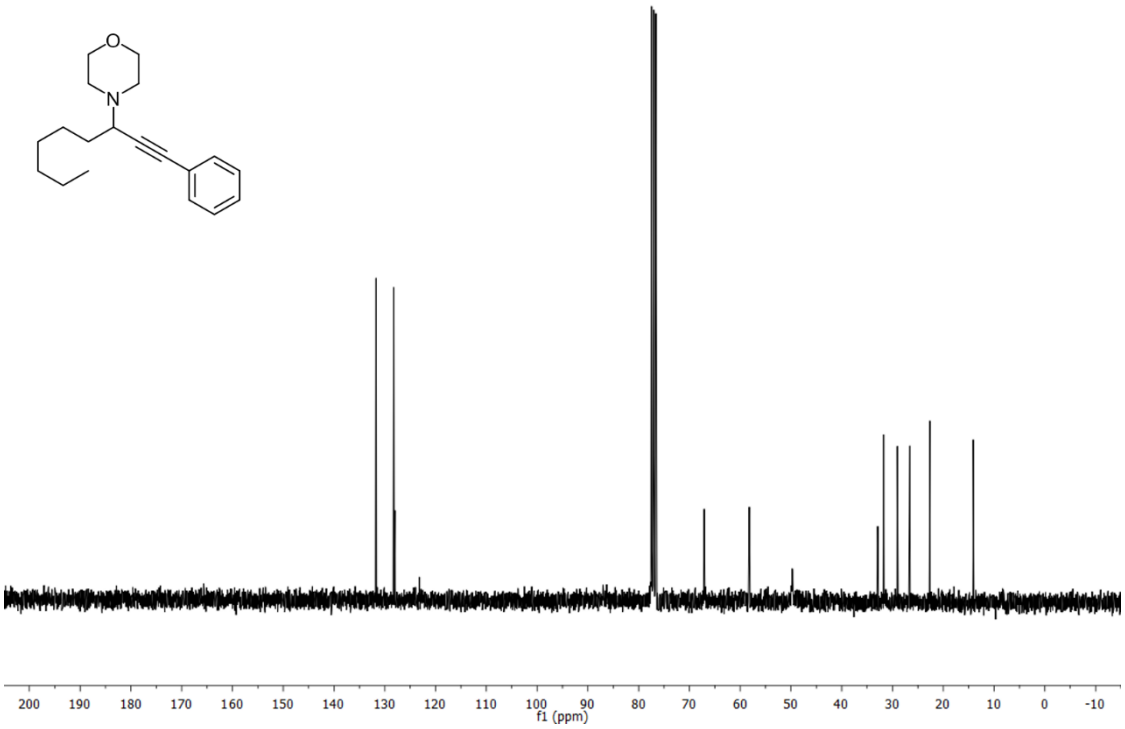
^{13}C NMR (75 MHz, $CDCl_3$)



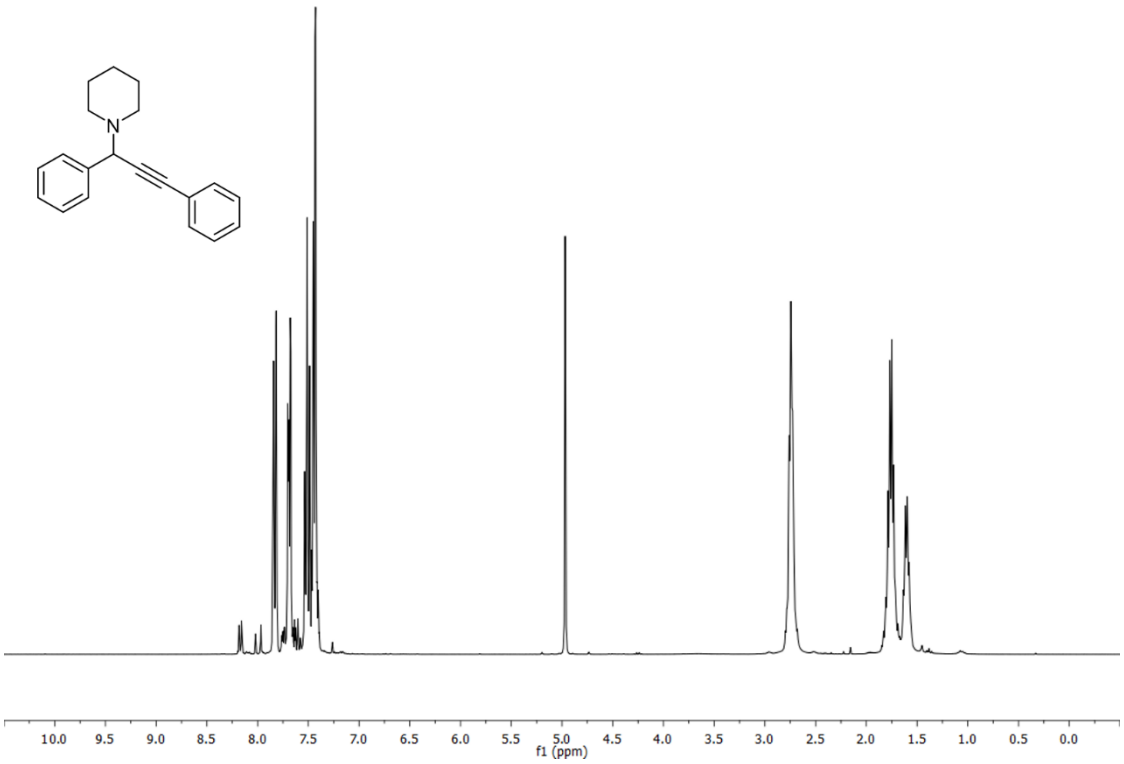
4-[1-(2-Phenylethynyl)heptyl]-morpholine (11): ^{1}H NMR (300 MHz, $CDCl_3$)



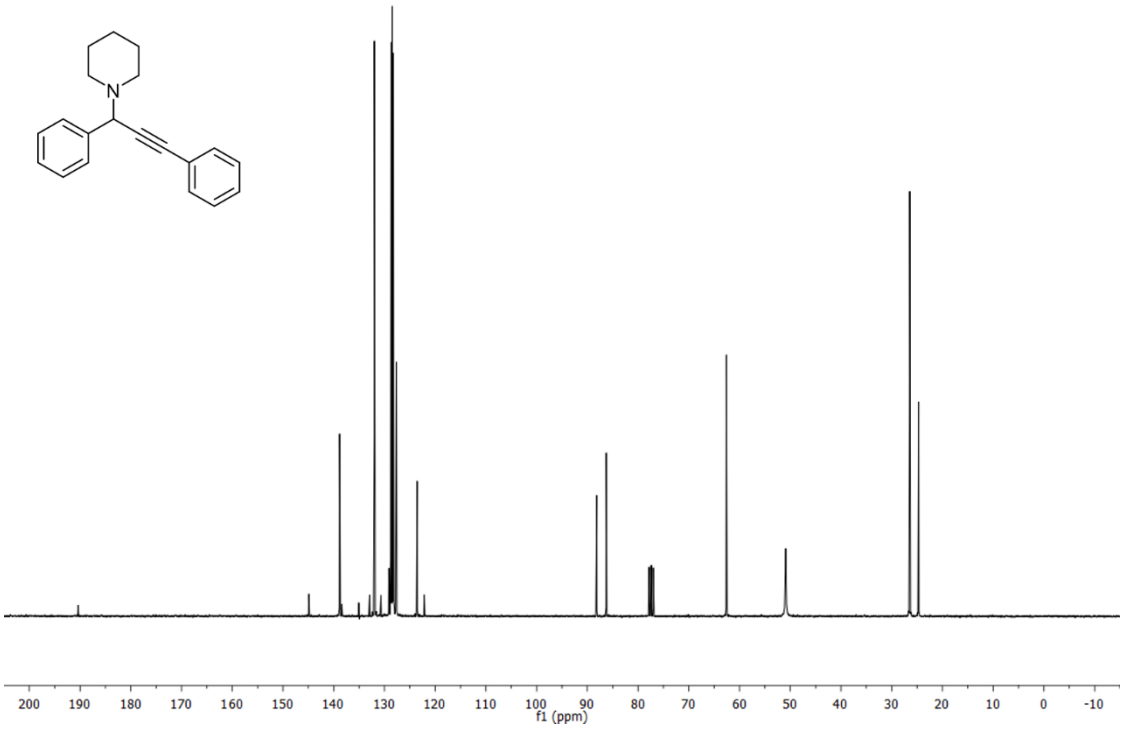
^{13}C NMR (75 MHz, $CDCl_3$)



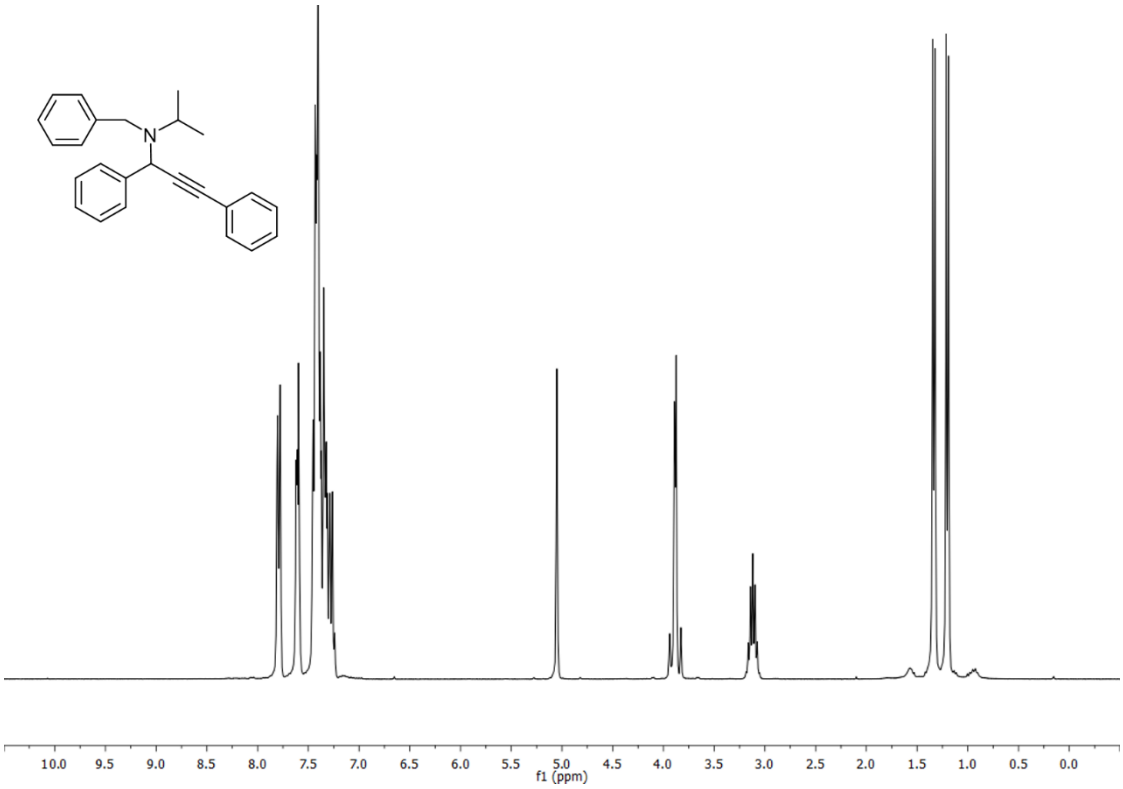
1-(1,3-Diphenyl-2-propyn-1-yl)-piperidine (12): ^{1}H NMR (300 MHz, $CDCl_3$)



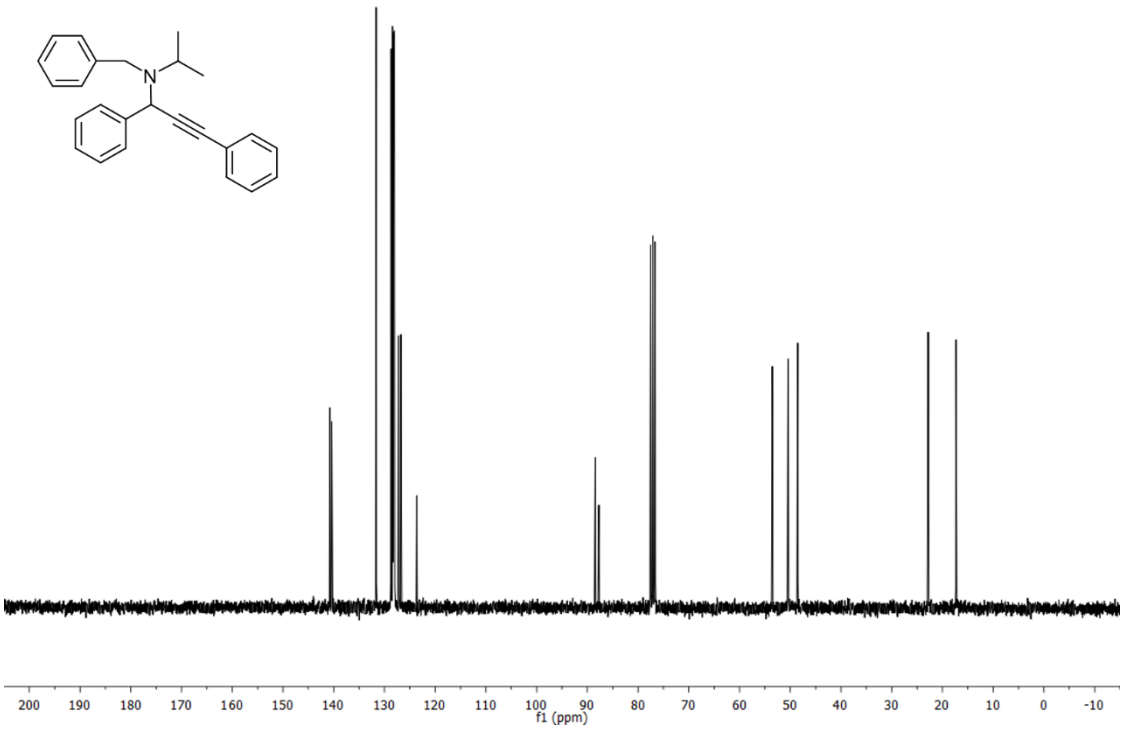
^{13}C NMR (75 MHz, $CDCl_3$)



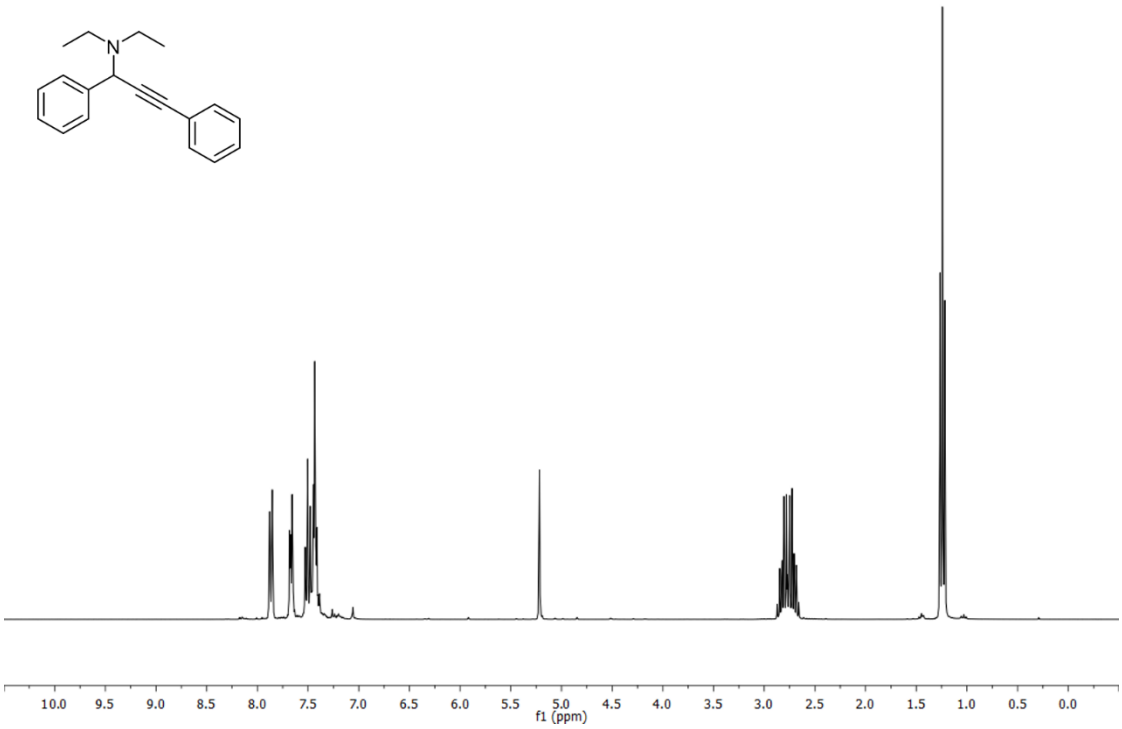
Benzyl-isopropyl-(1,3-diphenyl-2-propyn-1-yl)-amine (13): ^{1}H NMR (300 MHz, $CDCl_3$)



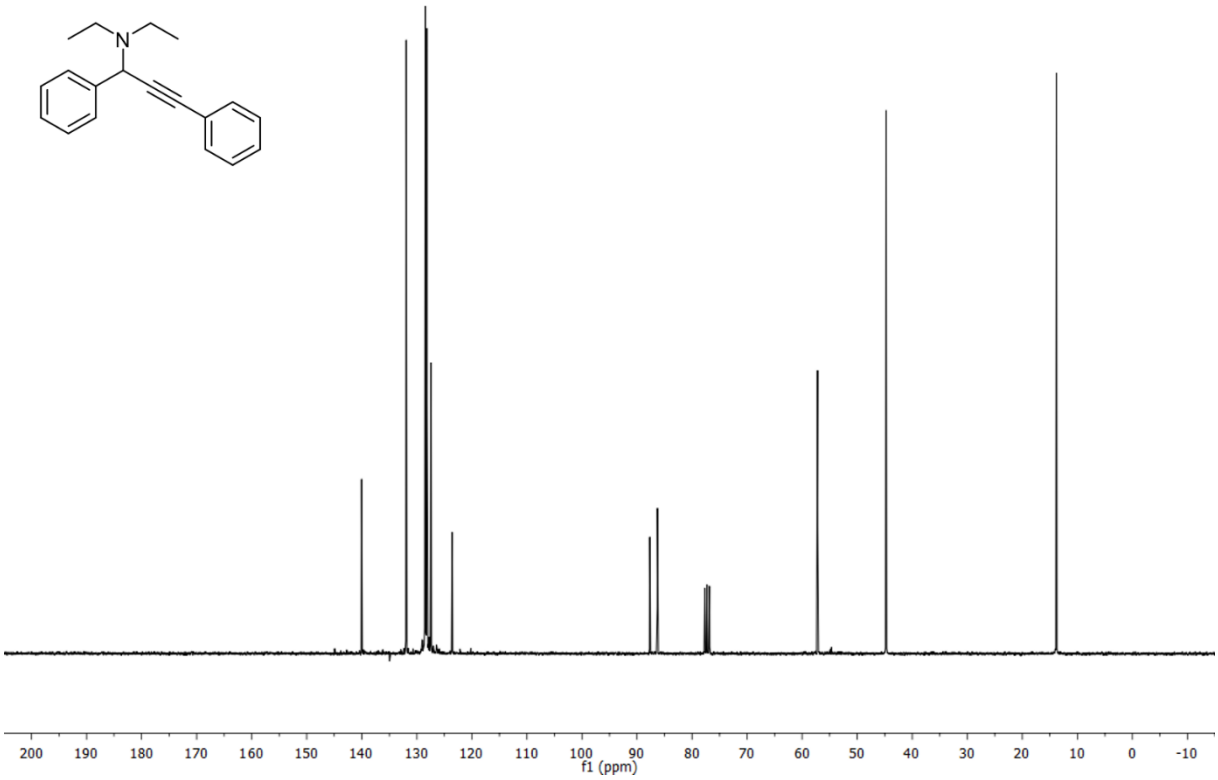
^{13}C NMR (75 MHz, $CDCl_3$)



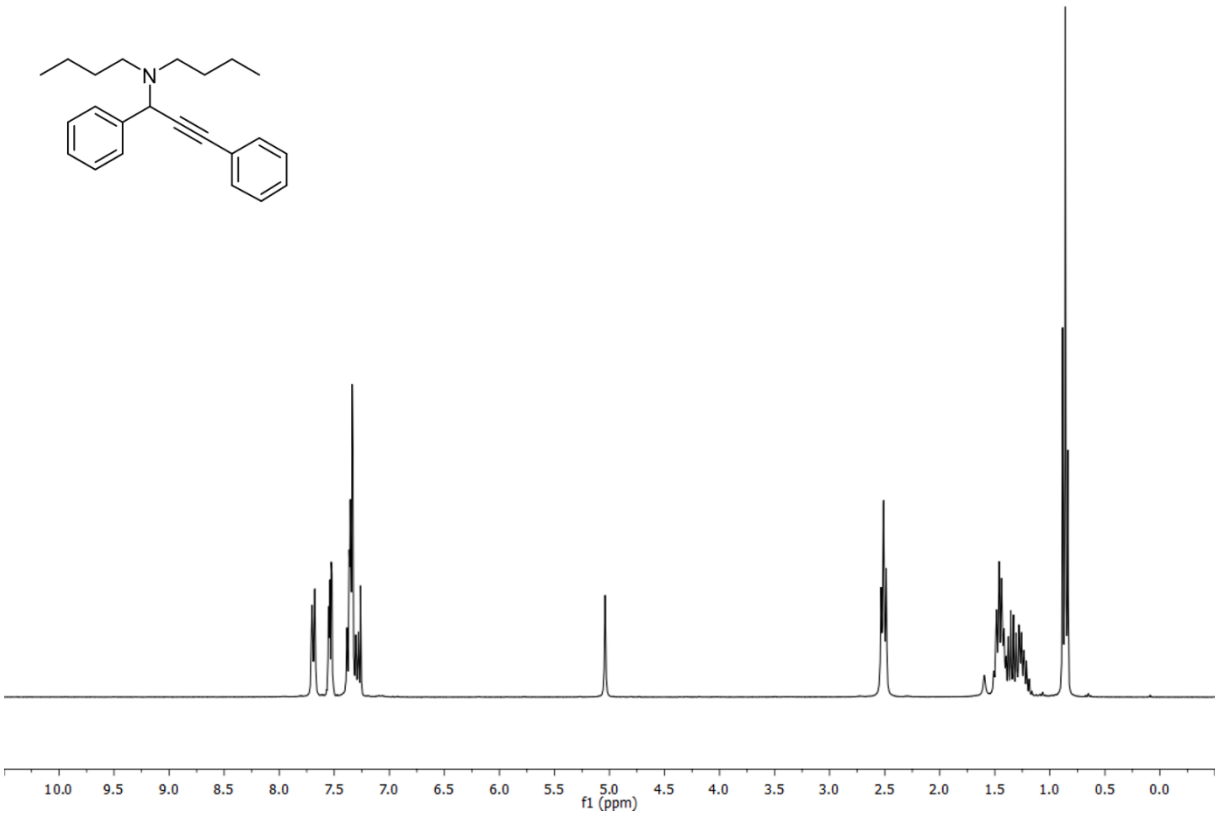
Diethyl-(1,3-diphenyl-2-propyn-1-yl)-amine (14): ^{1}H NMR (300 MHz, $CDCl_3$)



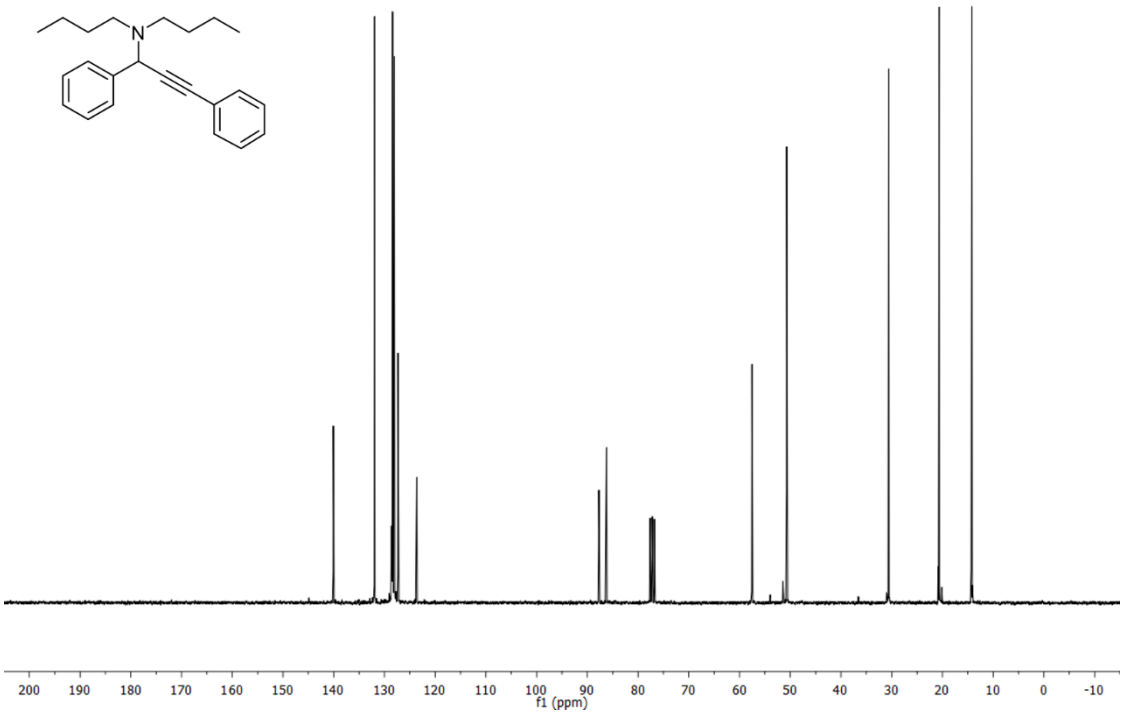
^{13}C NMR (75 MHz, $CDCl_3$)



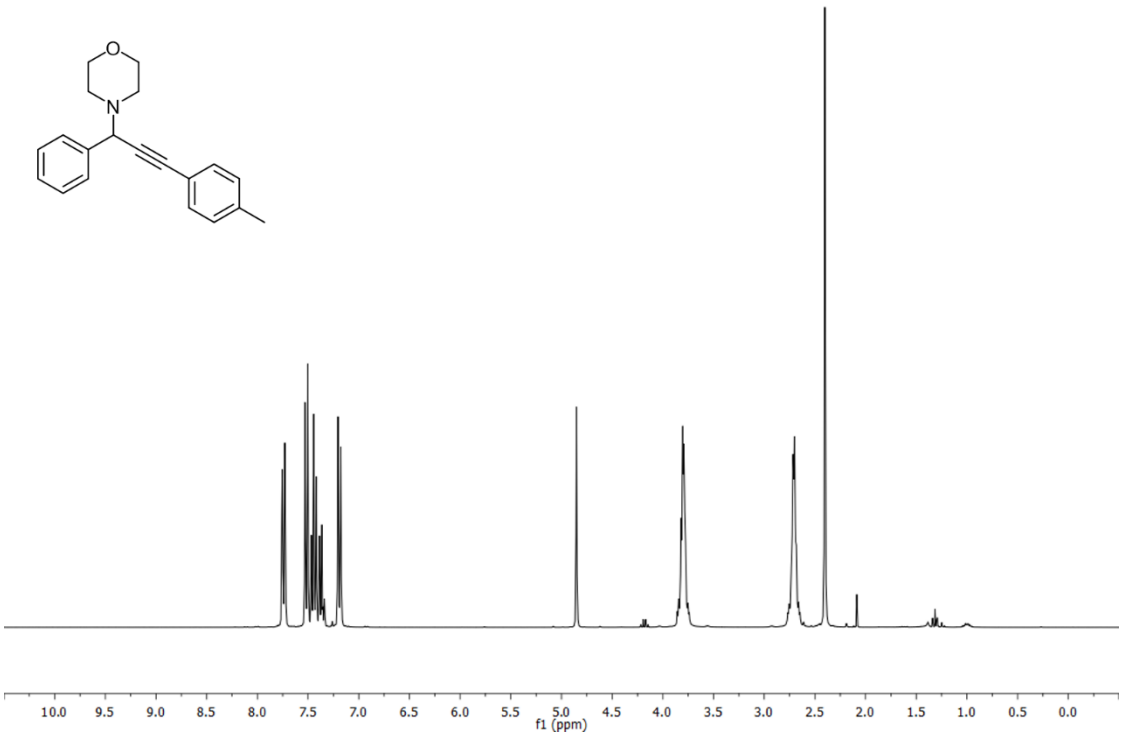
Dibutyl-(1,3-diphenyl-2-propyn-1-yl)-amine (15): ^{1}H NMR (300 MHz, $CDCl_3$)



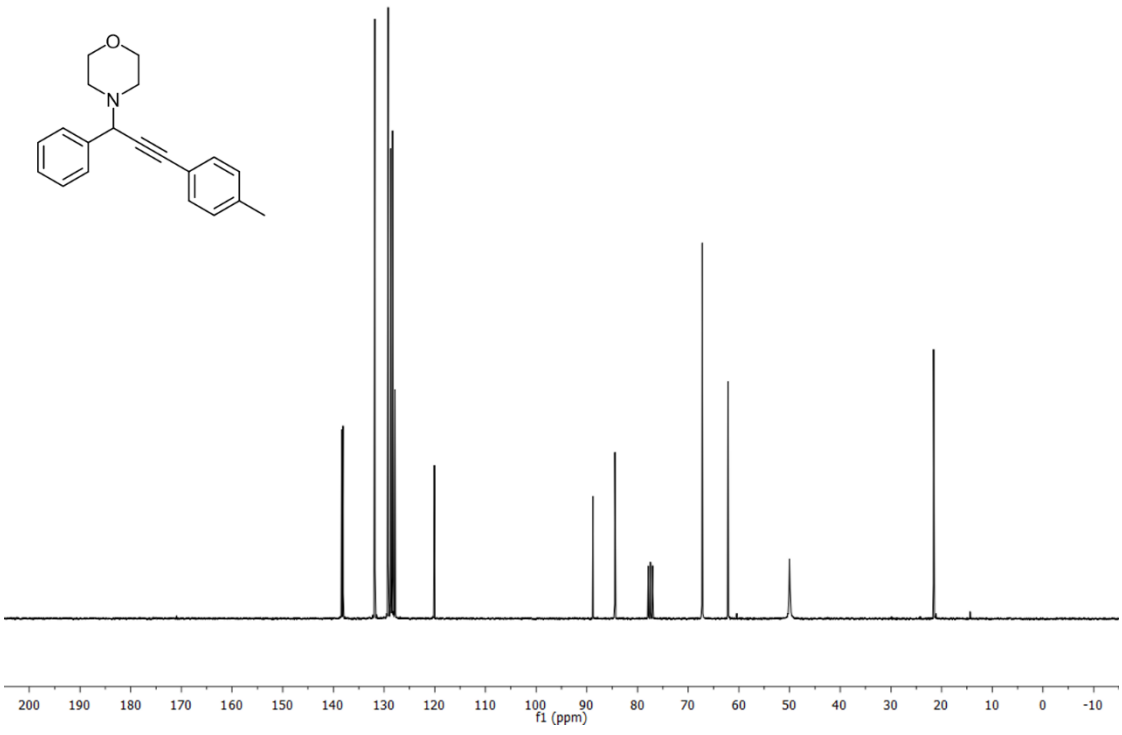
^{13}C NMR (75 MHz, $CDCl_3$)



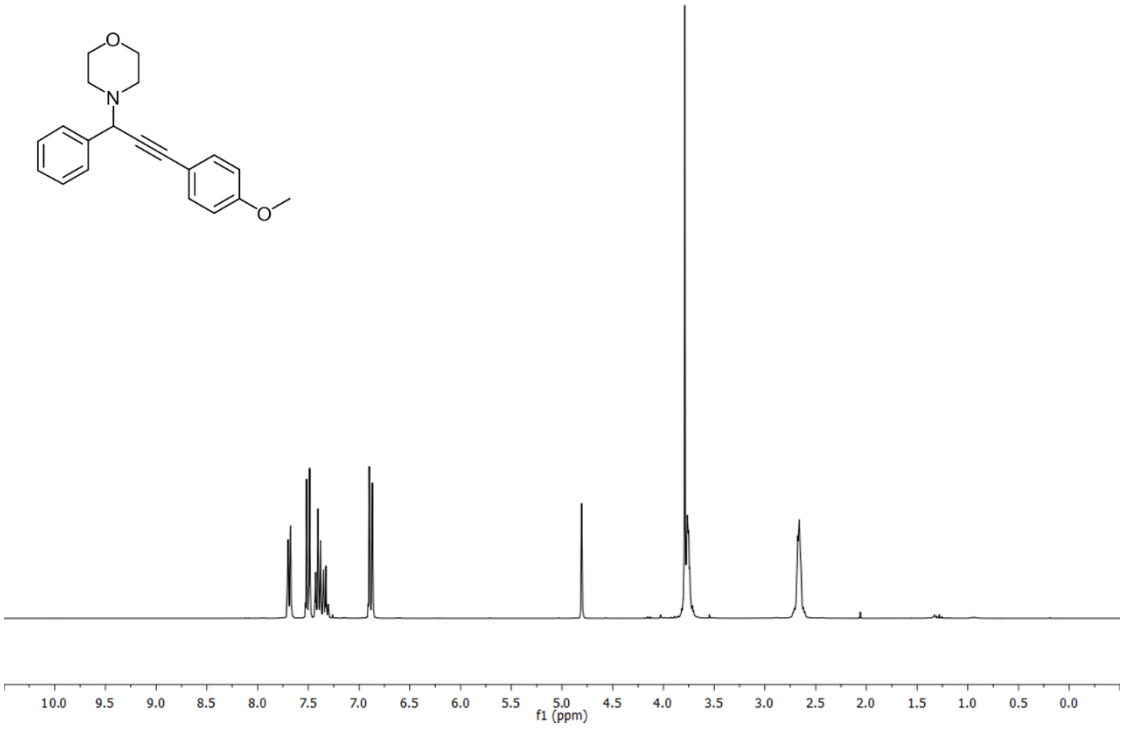
4-[3-(4-Methylphenyl)-1-phenyl-2-propyn-1-yl]-morpholine (16): ^{1}H NMR (300 MHz, $CDCl_3$)



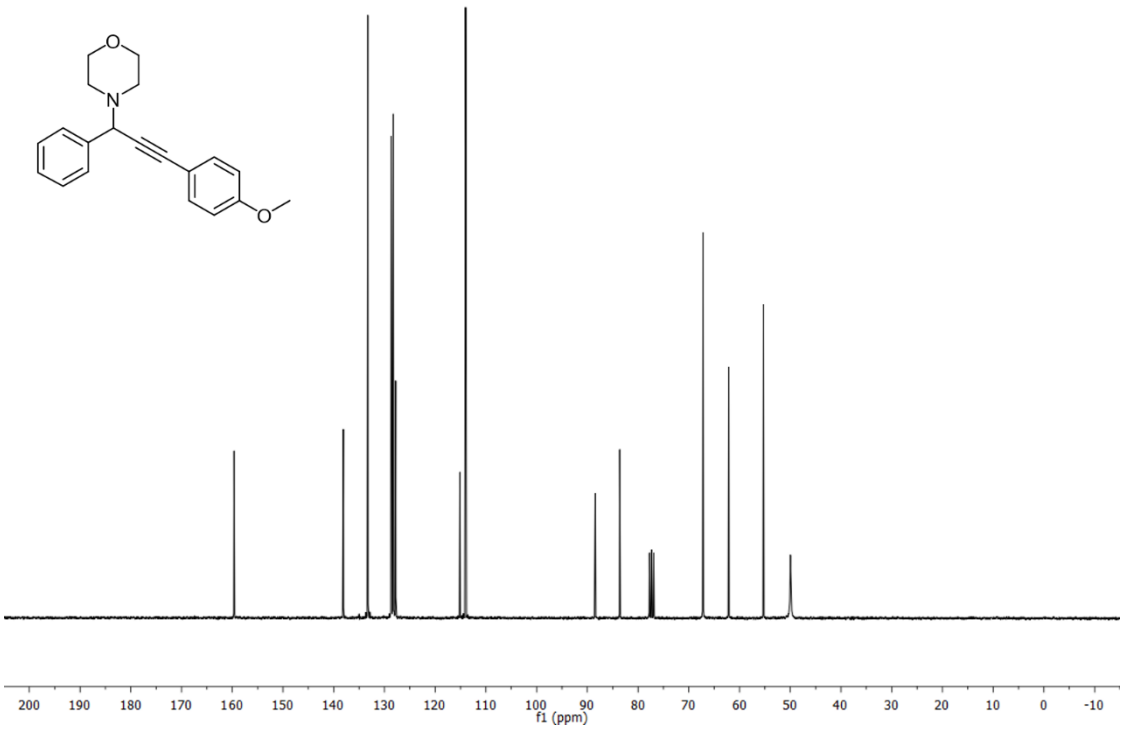
^{13}C NMR (75 MHz, $CDCl_3$)



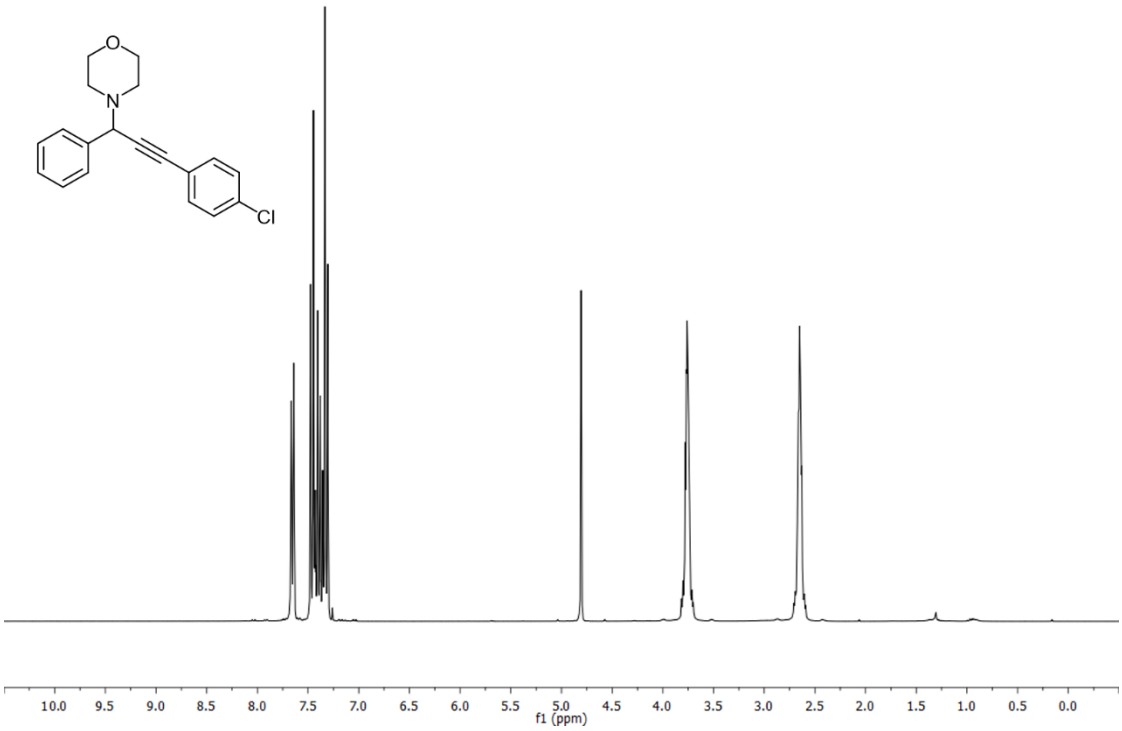
4-[3-(4-Methoxyphenyl)-1-phenyl-2-propyn-1-yl]-morpholine (17): ^{1}H NMR (300 MHz, $CDCl_3$)



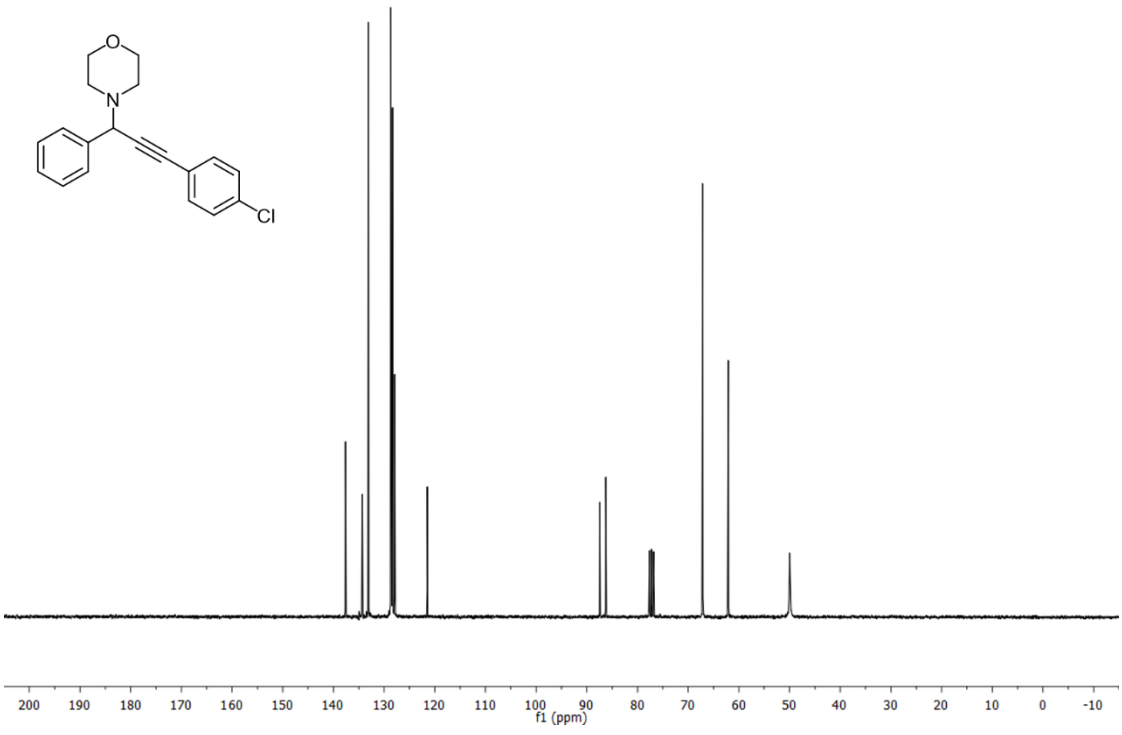
^{13}C NMR (75 MHz, $CDCl_3$)



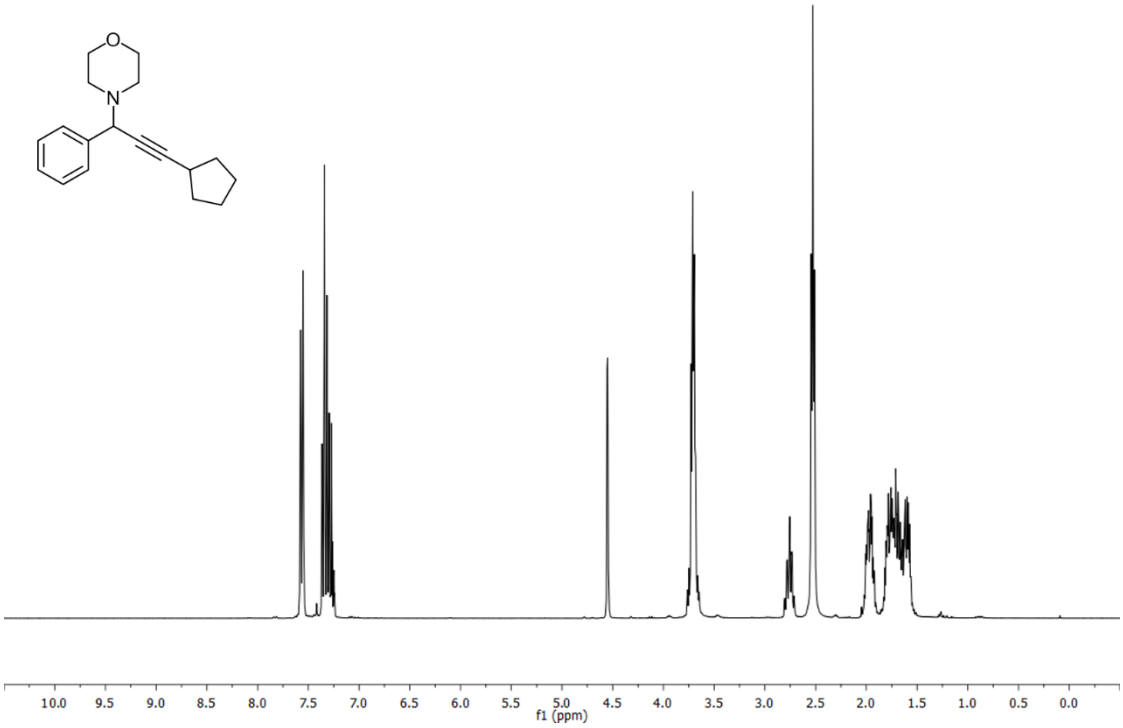
4-[3-(4-Chlorophenyl)-1-phenyl-2-propyn-1-yl]-morpholine (18): ^{1}H NMR (300 MHz, $CDCl_3$)



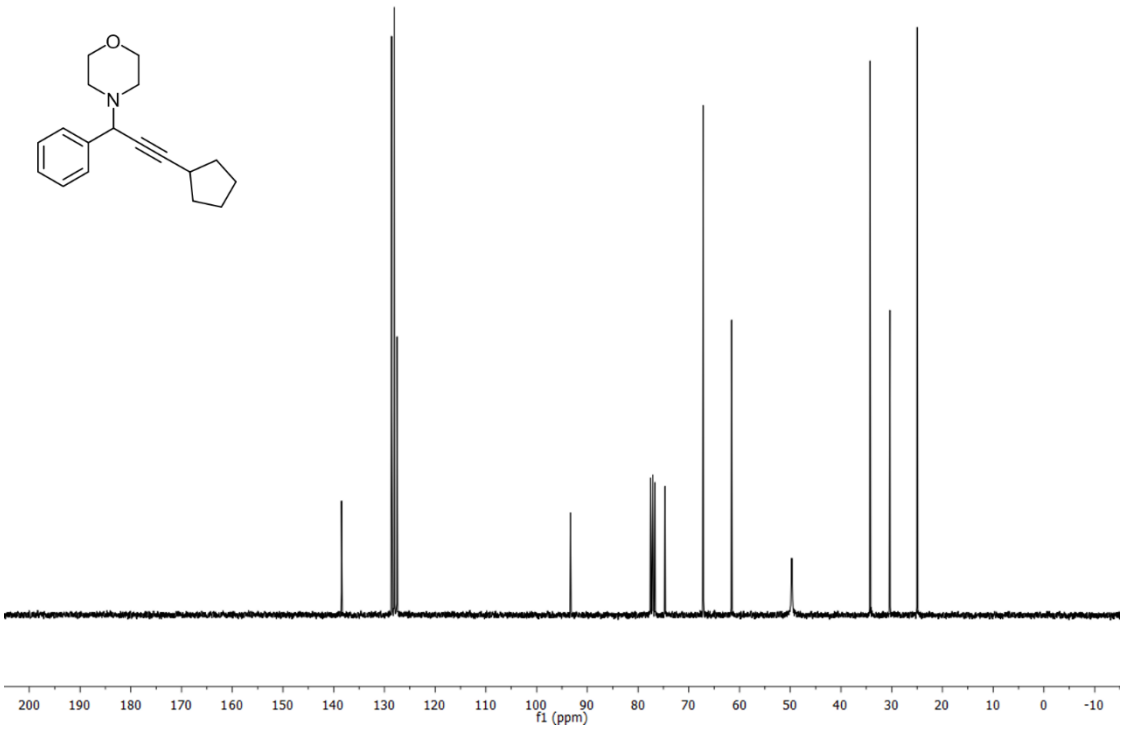
^{13}C NMR (75 MHz, $CDCl_3$)



4-(3-Cyclopentyl-1-phenyl-2-propyn-1-yl)-morpholine (19): ^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



5 Coupling reactions and reductions in deep-eutectic solvents applying zinc

Reductive coupling reactions and reductions with zinc were investigated in acidic deep-eutectic solvents based on choline chloride. The Barbier reaction of benzaldehyde and allyl bromide was performed in ChCl–lactic acid, while other halide substrates, such as benzyl bromide or methyl bromoacetate, showed no reaction or resulted in low conversion. Furthermore, acidic deep-eutectic solvents could be applied in the reduction of benzaldehyde by zinc; the application of further substrates, including ketones, alkynes, alkenes, and nitriles and N-heterocycles, was not successful.

5.1 Coupling reactions

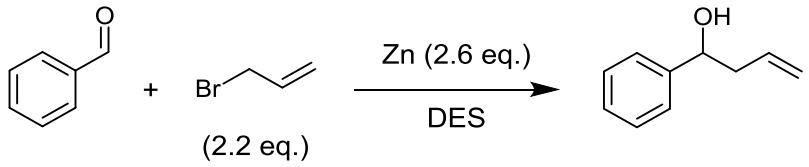
5.1.1 Introduction

The Barbier and Reformatsky reaction are standard methods for the reduction of a carbonyl group to an alcohol while simultaneously forming a C-C bond. A metal, mostly zinc, tin, and magnesium, inserts into a carbon-halogen bond, resulting in a carbon nucleophile, which then attacks the carbonyl, forming an alcohol. The Barbier reaction is usually performed with an allyl halide, but can also involve an alkyl or aryl residue, whereas an α-halo-ester, such as ethyl bromoacetate, is applied in the Reformatsky reaction. For the Barbier reaction, THF is a suitable solvent; for allyl halides, the reaction proceeds in THF-water mixtures as well.[1] In general, the passivation layer on zinc can decrease the reactivity and impede the reaction. Therefore, to generate active zinc, several methods were established, including washing with hydrochloric acid, the addition of dibromoethane or trimethylchlorosilane, and ultrasonic irradiation.[2] An elegant approach to generate reactive zinc is the reduction of a zinc salt by an alkali metal, which may also include the addition of a catalytic amount of an electron carrier, such as naphthalene. However, the preparation of this so-called “Rieke-zinc” can be laborious and must be performed in an inert atmosphere.[3,4]

It is known that DES dissolve a variety of metal salts, such as carbonates and oxides.[5,6] Hence, in a metal-DES suspension, the metal surface formed by the oxide (“passivation”), should dissolve in the DES, generating the metal in its elemental and thus active form *in situ*, facilitating the insertion of the metal into the carbon-halogen bond. Furthermore, the conditions in a DES and in the classical solvents for the Barbier reaction are very different, including polarity, coordination of the substrate, water content, and participation in the hydrogen bond network. This should considerably influence the reactivity and open the way to new and interesting synthetic pathways. Therefore, by performing coupling reactions with zinc in a DES, we envisaged both the facilitation of the experimental procedure and the exploration of the reactivity of organozinc compounds.

5.1.2 Results and Discussion

As a test reaction, the synthesis of 1-phenylbut-3-en-1-ol from benzaldehyde and allyl bromide was chosen (Scheme 1).



Scheme 1. Synthesis of 1-phenylbut-3-en-1-ol in DES.

First, the solubility of allyl bromide in various DES, based on dimethylurea, choline chloride (ChCl), and menthol, was tested (Table 1). DES formed by a saccharide and a urea derivative, such as dimethylurea–fructose and dimethylurea–mannose, possess melting points near or higher as the melting point of allyl bromide (70 °C), which is why they are no suitable solvents. The high viscosity of ChCl–citric acid and ChCl–tartaric acid excluded their application as well.

In all tested DES based on DMU, allyl bromide is not soluble, either forming an emulsion consisting of small droplets or a separate layer on top of the DES. Regarding choline chloride-based DES, allyl bromide is soluble only in ChCl–lactic acid. In ChCl–levulinic acid, an emulsion is formed. In all the other ChCl-based DES, allyl bromide forms a separate layer. Allyl bromide dissolves readily in menthol-based DES, which is probably due to the low polarity of menthol.

Table 1. Solubility of allyl bromide in DES.

Comp. 1	Comp. 2	Ratio	mp (°C)	Solubility
dimethylurea	$ZnCl_2$	7:2	50	emulsion
	citric acid	7:2	65	n. s.
	tartaric acid	7:3	?	n. s.
choline chloride	urea	1:2	12	n. s.
	glucose	1:2	14	n. s.
	sorbitol	1:1	RT	n. s.
	lactic acid	1:2	RT	soluble
	phenylacetic acid	1:1	25	n. s.
	levulinic acid	1:2	RT	emulsion
	vanillin	1:2	17	n. s.
	NMU	1:2	?	n. s.
menthol	lactic acid	1:2	RT	soluble
	pyruvic acid	1:2	RT	soluble

"emulsion": small droplets are formed (hardly visible), so that the mixture appears turbid; upon standing, the phases partly separated

For the synthesis of 1-phenylbut-3-en-1-ol, allyl bromide and zinc were used in 2.2 and 2.6 equivalents according to the literature.[7] In general, for an efficient transformation, at least 2 equivalents of these reactants are necessary. Though, when tin is used, 1 equivalent of tin is sufficient to achieve high yields, e.g. for reactions in ionic liquids.[8,9]

First, the reaction was performed in DMU–$ZnCl_2$ (7:2). After formation of the DES, allyl bromide was added at 55 °C, followed by the slow (spatula-wise) addition of zinc. After 1 hour stirring at 55 °C, benzaldehyde was added dropwise and the reaction mixture was stirred for 1 more hour. For work-up, saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate. GC analysis showed that the product forms in conversion of about 40%; considerable amounts of benzoic acid were formed as well. However, this result showed that the reaction can proceed in an emulsion and that complete dissolving of the substrates in the DES is not necessary.

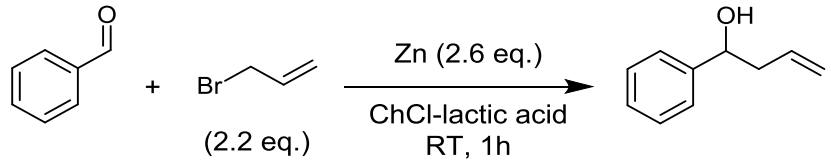
Next, the reaction was performed in menthol–lactic acid and menthol–pyruvic acid at room temperature. In both DES, the product was formed. However, benzoic acid was also formed in comparable amounts. Furthermore, isolation of the product was difficult: being quite hydrophobic, menthol dissolved in ethyl acetate during extraction and the product obtained after column chromatography contained about 25% of menthol. Due to the large excess of menthol as a DES component, optimization of the column separation was not successful. The corrected yield of the product was only 25% and this system was not optimized further.

Then, ChCl–lactic acid (1:2) was tested as solvent at room temperature. Regarding the sequence of addition of the reactants, the experimental procedure was changed: zinc was slowly added to the DES (within half an hour) and the suspension was stirred to dissolve the oxide and carbonate layer in the DES, thereby generating active zinc. Subsequently, allyl bromide was added dropwise, and the mixture was stirred at room temperature, followed by benzaldehyde addition and further stirring for 1 hour. In a first trial, the reaction mixture was stirred for 100 min after addition of allyl bromide and 10 mmol benzaldehyde in 5 g DES (c_{BA} = 2 mmol/g) were applied. As confirmed by GC, the product was formed; however, benzaldehyde was reduced to benzyl alcohol to a large extent (Table 2, entry 1). In fact, zinc acts as reducing agent in acidic environment. Interestingly, raising the concentration of the reaction mixture leads to higher relative amount of the product and strongly decreases the competing reduction. The overall conversion of benzaldehyde remained constant (entries 2 and 3). Addition of the allyl bromide directly after zinc results in the formation of more benzyl alcohol (entry 4). When a solution of allyl bromide in the DES was prepared first and zinc was added afterwards, the same result was obtained (entry 5). Even a longer stirring of a zinc and allyl bromide containing mixture does not decrease the side product formation (entry 6).

Therefore, to suppress the competing reduction of benzaldehyde, it is necessary to

1) apply high concentrations of the reactants in the DES and
2) activate zinc by stirring it in the DES before addition of allyl bromide.

Table 2. Synthesis of 1-phenylbut-3-en-1-ol in ChCl–lactic acid (1:2); reaction time after benzaldehyde addition always 1 h.



entry	c_{BA} (mmol/g)	t1 (min)	t2 (min)	Benzaldehyde (%)	Benzyl Alc. (%)	Product (%)
1	2	100	60	7	36	57
2	3	100	60	5	12	83
3	4	100	60	7	4	89
4	4	0	60	6	12	82
5[a]	4	0	60	9	12	79
6	4	0	180	13	15	72
7[b]	4	120	60	60	6	34
8[c]	4	135	60	3	2	95 (81*)

*Isolated yield

c_{BA} = concentration of benzaldehyde (starting material)

t1 = time of stirring suspension of zinc in DES

t2 = time of stirring suspension of zinc and allyl bromide in DES

[a] zinc was added to solution of allyl bromide in DES

[b] 1 eq. of zinc and 2 eq. of allyl bromide were used

[c] mechanical stirring

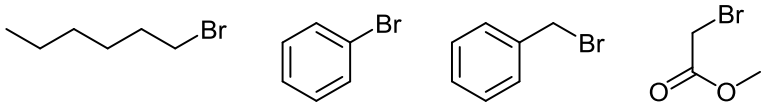
In all reactions applying 20 mmol of benzaldehyde, the high viscosity of the reaction mixture, caused by large amounts of zinc, made stirring and homogenization difficult. After 1 hour of stirring, the zinc suspension became much more viscous, hindering an adequate mixing with the magnetic stirring plate. Adding the allyl bromide directly after the zinc provided a low-viscous reaction mixture; however, as mentioned above, it is crucial to activate the zinc in the DES in the absence of any other reactant for at least two hours. Therefore, zinc was used in one equivalent only, giving a non-viscous suspension and enabling sufficient homogenization. However, the product was formed in low conversion and benzyl alcohol was formed as byproduct (entry 7), indicating the necessity of a zinc excess with respect to

benzaldehyde. To overcome the problem of homogenization, a new setup was developed, based on mechanic stirring. Applying this setup, the product was formed in very good conversion and isolated in 81% yield (entry 8). Activation of the zinc in the DES was performed at low-frequency stirring (30 rpm) as it was observed that high-frequent stirring may induce high viscosity and the formation of solid clods.

When the reaction was performed in neat lactic acid (5g), the product was formed in less than 10% and many side-products were formed. Furthermore, handling and stirring of the reaction mixture was rather difficult due to the high viscosity of the lactic acid. This proves the necessity of DES formation with choline chloride.

When zinc was replaced by tin, the product was formed in 92% conversion and no benzyl alcohol was detected, indicating that tin does not reduce benzaldehyde (c_{BA} = 15 mmol/g). The application of magnesium resulted in low conversion of about 10%.

Following optimization of the reaction conditions, further substrates were tested in ChCl–lactic acid, including bromohexane, bromobenzene, benzyl bromide, and methyl bromoacetate (Scheme 2). However, in all cases, no product was formed.



Scheme 2. Substrates tested for reaction with benzaldehyde in ChCl–lactic acid (1:2); see Table 2, entry 8 for reaction conditions.

Next, the reaction of benzaldehyde with methyl bromoacetate was performed in different ChCl-based DES, including ChCl–levulinic acid (1:2), ChCl–malonic acid (1:1), ChCl–oxalic acid (1:1), and ChCl–phenylacetic acid (1:2). In ChCl–levulinic acid, the product was formed in low conversion of about 35%; in the other DES, only traces of the product were observed. For optimization, the reaction time (after benzaldehyde addition) was increased to 2 h and the time of stirring the suspension of zinc in DES was varied from 0 h to 2 h. However, the conversion did not increase significantly.

5.2 Reductions

5.2.1 Introduction

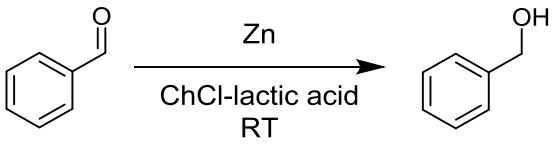
The selective reduction of functional groups plays a crucial role in organic synthesis and can be performed applying metals, among a variety of other methods. Zinc, magnesium, lithium, and sodium are typical metals used for reduction; herein, we focus on zinc due to its stability in air and moisture. Standard methodologies apply zinc together with a proton source, usually an acid; the reduction occurs via a single electron transfer (SET) to the substrate (e.g. a carbonyl or an alkyne), followed by protonation of the resulting anion. A second SET and subsequent protonation gives the product. For example, the reduction of alkynes with zinc powder was performed applying hydrochloric, phosphoric, benzoic, and acetic acid in THF under reflux.[10] Recently, the reduction of carbonyls with zinc powder was reported applying aqueous ammonium chloride as proton source in THF. Under mild conditions (RT or 60 °C), aliphatic and aromatic aldehydes and ketones were reduced to the corresponding alcohols, leaving other functional groups untouched, such as nitrile, ester, epoxy, and alkene. Remarkably, the selectivity of carbonyl reduction was temperature-dependent: in a molecule containing both an aldehyde and an alcohol functionality, the aldehyde was reduced exclusively at room temperature, whereas both the aldehyde and the ketone were reduced at 60 °C.[11] Next to zinc powder, Rieke zinc was shown to reduce functional groups selectively, including aromatic aldehydes, alkynes, and nitrobenzene. Ketones, aliphatic alkenes and nitriles were not reduced. The high reactivity of Rieke zinc allowed the application of weak proton sources, such as methanol or water, instead of a mineral acid.[12] Another possibility to generate active zinc is the sonoelectroreduction of zinc chloride, resulting in elemental zinc as a powder, which was used for the reduction of alkynes in water.[13]

The application of zinc powder in a DES for reductions is promising in a double sense. First, in an acidic DES, the acid serves as proton source. Second, the passivating layer on the zinc (consisting of oxides and carbonates) should be dissolved by the DES, generating active zinc *in situ*, facilitating the reduction.

5.2.2 Results and Discussion

The investigations of functional group reduction started with benzaldehyde as test substrate in ChCl–lactic acid (1:2) (Table 3). The reactions were performed at room temperature and mixing was achieved using a mechanic stirrer (see 5.1). In a first trial, one equivalent of zinc was added to the DES, followed by the direct addition of benzaldehyde and stirring the reaction mixture for 2 hours (entry 1). In this reaction, no product and small amounts of benzoic acid were formed. Increasing the amount of zinc to 2 equivalents resulted in 60% of the product, along with benzoic acid and several other by-products in small amounts (entry 2). When zinc was activated by stirring in the DES for 3 hours, 89% of product were observed (entry 3). Longer reaction time (3.5 h) raised the amount of product slightly and isolation furnished the product in 88% yield (entry 4). Applying three equivalents of zinc resulted in nearly quantitative conversion (entry 5). When the reaction was performed according to the procedure in entry 4, but applying iron (2 eq.) instead of zinc, no product was formed.

Table 3. Reduction of benzaldehyde in ChCl–lactic acid (1:2); c_{BA} = 2 mmol/g.



Entry	Zn (eq.)	t1 (h)	t2 (h)	Benzaldehyde (%)	Product (%)
1	1	0	2	95	0
2	2	0	2	26	60
3	2	3	2	9	89
4	2	3	3.5	6	94 (88*)
5	3	2	2	1	99

*Isolated yield

t1 = time of zinc activation in DES

t2 = reaction time

Having optimized the reaction conditions, further ChCl-based DES were tested as solvent for the reduction of benzaldehyde (Table 4). The application of levulinic acid, malonic acid, and phenylacetic acid resulted in good to quantitative product formation. In ChCl–oxalic acid, the product was formed in 35% conversion and a mixture of by-products, including toluene, benzoic acid, and 1,2-diphenyloxirane

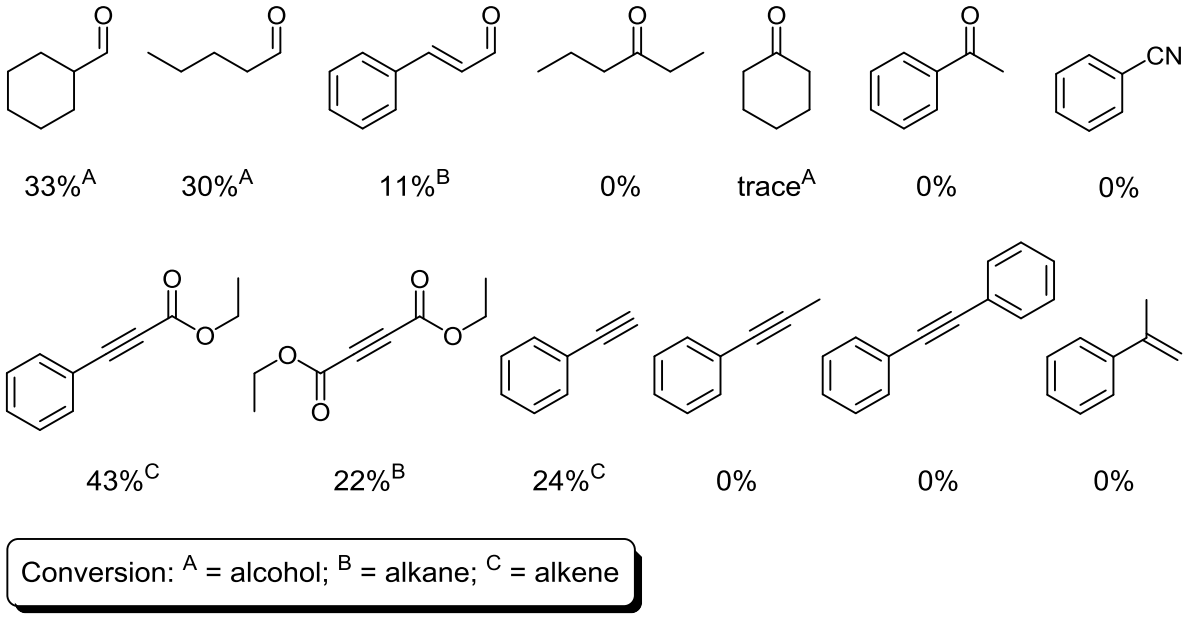
was formed as well in about 10% conversion. In ChCl–Xylitol and ChCl–Urea, no product was formed. This leads to the conclusion that the presence of an acid is crucial for the reduction.

Table 4. Reduction of benzaldehyde in ChCl-based DES; c_{BA} = 2 mmol/g; see Table 3, entry 4 for reaction conditions.

	Levulinic acid	Malonic acid	Oxalic acid	Phenylacetic acid	Xylitol	Urea
Ratio*	1:2	1:1	1:1	1:2	1:1	1:2
T (°C)	RT	RT	50	50	50	RT
Prod. (%)	100	92	35	83	0	0

***ChCl : H donor

Next, the reduction of further substrates was tested in ChCl–lactic acid, including carbonyls, alkenes, and alkynes, which are shown in Scheme 3 with the observed conversion.

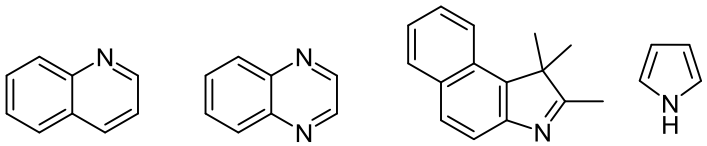


Scheme 3. Substrates tested for reduction in ChCl–lactic acid (1:2); $c_{Substrate}$ = 2 mmol/g; see Table 3, entry 4 for reaction conditions.

As shown in Scheme 3, aliphatic aldehydes were reduced to the corresponding alcohols in low conversion, whereas no reduction was observed for ketones. Interestingly, the double bond of cinnamon aldehyde was reduced in 11% conversion next to traces of the alcohol. Benzonitrile and α-methylstyrene were not reduced. Regarding the alkyne group, 1-phenyl-1-propyne and diphenylacetylene

were found to be stable, while phenylacetylene and ethyl phenylpropiolate were reduced to the corresponding alkenes in low and moderate conversion, respectively. Remarkably, the triple bond of bis(ethoxycarbonyl)acetylene was reduced to the single bond, however in low conversion. To increase the conversion of phenylacetylene and ethyl phenylpropiolate, three eq. of zinc were applied, giving the same result. Higher temperature (50 °C and 70 °C) increased the conversions of both substrates slightly; however, at 70 °C, a considerable part of the reaction mixture solidified during the reaction, impeding work-up.

Next, the reduction of N-heterocycles was investigated in acidic DES, including ChCl–lactic acid, ChCl–levulinic acid, ChCl–malonic acid, and ChCl–phenylacetic acid. Pyrrole was reacted in ChCl–lactic acid only. The reactions were performed applying the optimized conditions for benzaldehyde reduction shown in Table 3, entry 4. Only 1,1,2-trimethylbenz[e]indole showed reduction of the double bond adjacent to the nitrogen in trace, whereas all other N-heterocycles were not reduced.



Scheme 4. N-Heterocycles tested for reduction in DES; $c_{Substrate}$ = 2 mmol/g; see Table 3, entry 4 for reaction conditions.

5.3 Conclusion

The reductive coupling of allyl bromide to benzaldehyde, applying zinc, was investigated in DES. It was found that the number of applicable DES is quite limited, which is mainly due to the high polarity of the DES, resulting in low solubility of the allyl bromide. Furthermore, high melting points, requiring high reaction temperatures, and high viscosities excluded the application of many DES, especially DES based on saccharides. However, a DES composed of choline chloride and lactic acid fulfilled the requirements of a solvent for the allylation: it is liquid at room temperature, possesses a low viscosity, and readily dissolves the allyl bromide. The reaction of allyl bromide with benzaldehyde applying zinc was found to proceed, the product was isolated in very good yield, and the competing reduction of benzaldehyde could be suppressed by applying high concentrations of the reactants

and stirring the zinc-DES suspension prior to reactant addition. The application of bromohexane, bromobenzene, benzyl bromide, and methyl bromoacetate in ChCl–lactic acid under these conditions was not successful. However, in ChCl–levulinic acid, the reaction of methyl bromoacetate with benzaldehyde occurred in low conversion, but optimization (variation of temperature and reaction time) did not increase the conversion significantly.

Furthermore, DES were applied in the reduction of functional groups. While benzaldehyde could be reduced to benzyl alcohol in very good yield in ChCl–lactic acid and showed very good conversion in other acidic ChCl-based DES as well, the reduction of further functional groups, such as alkynes, ketones and aliphatic aldehydes was not successful, resulting in low or no conversion. Similarly, N-heterocycles showed no reduction in acidic ChCl-based DES. Carbonyls can be reduced under mild conditions (aq. NH_4Cl at RT or 60 °C) and activated alkynes are easily reduced by Rieke zinc, which is why the application of ChCl–DES does not possess an advantage over the reported methods.

To conclude, ChCl-based DES can act as solvent for the Barbier reaction and the reduction of aromatic aldehydes. However, the scope of this method is quite limited, and it is inferior to methods reported in the literature. While there are hints that the DES dissolves the passivation layer of zinc, this does not correspond to an improvement of the reaction. Nevertheless, DES are promising solvents for coupling reactions and reductions with a metal; future studies should focus on the improvement of known procedures, making use of the typical properties of DES. For example, the Grignard reaction is of interest, because it could be beneficial to generate active magnesium in a DES.

5.4 Experimental

5.4.1 Materials and Methods

ChCl was dried *in vacuo* at 120 °C before use. All other DES components were used without drying.

5.4.2 Synthesis

Synthesis of 1-phenylbut-3-en-1-ol in ChCl–lactic acid (1:2) - procedure for optimized conditions (Table 2, entry 8): The DES was prepared by heating a mixture of ChCl (2.18 g, 15.6 mmol) and lactic acid (2.82 g, 31.3 mmol) to 80 °C until a clear liquid was formed. The DES was allowed to cool to RT and zinc powder (3.33 g, 5.1 mmol) was added. The suspension was stirred for 135 min, followed by the addition of allyl bromide (3.75 ml, 43.4 mmol). After stirring at RT for 60 min, benzaldehyde (2.04 ml, 20.0 mmol) was added, followed by 60 min stirring of the reaction mixture at RT. For work-up, saturated aq. NH_4Cl (10 ml) was added and the solid was filtered off. The remaining liquid was extracted with ethyl acetate (4 x 5 ml) and the combined organic layers were dried over sodium sulfate. The product was isolated applying flash column chromatography (gradient of ethyl acetate in petrol ether). Yield: 2.41 g (81 %). ^{1}H NMR (300 MHz, $CDCl_3$): 7.43–7.24 (m, 5H), 5.90–5.72 (m, 1H), 5.21–5.09 (m, 2H), 4.70 (t, J = 6.5 Hz, 1H), 2.62–2.39 (m, 3H).

Synthesis of benzyl alcohol in ChCl–lactic acid (1:2) - procedure for optimized conditions (Table 3, entry 4): The DES was prepared as reported above, followed by the addition of zinc powder (1.31 g, 20.0 mmol). The suspension was stirred for 3 h, followed by the addition of benzaldehyde (1.01 ml, 10.0 mmol). After stirring at RT for 3.5 h, saturated aq. NH_4Cl (10 ml) was added and the solid was filtered off. The remaining liquid was extracted with ethyl acetate (4 x 5 ml) and the combined organic layers were dried over sodium sulfate. The product was isolated applying flash column chromatography (gradient of ethyl acetate in petrol ether). Yield: 0.95 g (88 %). ^{1}H NMR (300 MHz, $CDCl_3$): 7.39–7.27 (m, 5H), 4.59 (s, 2H), 3.48 (s, 1H).

Reduction of further substrates in ChCl–lactic acid (1:2) - general procedure: The procedure for the synthesis of benzyl alcohol was followed, applying 10 mmol of the substrate in each reaction. The crude extract was analyzed by GC.

Reduction in other DES: The procedure for the synthesis of benzyl alcohol was followed, applying 10 mmol of the substrate in each reaction. The crude extract was analyzed by GC. All reactions were performed applying a substrate concentration in the DES of 2 mmol/g, usually 10 mmol of substrate in 5 g DES. The amounts of the DES components and the reaction temperatures are given in Table 5.

Table 5. ChCl-based DES applied in reduction (masses of the DES components and reaction temperatures).

	Levulinic acid	**Malonic acid**	**Oxalic acid**	**Phenylacetic acid**	**Xylitol**	**Urea**
Ratio*	1:2	1:1	1:1	1:2	1:1	1:2
m_{ChCl} (g)	1.87	2.86	3.04	1.69	2.39	2.68
m_{HBD} (g)	3.13	2.14	1.96	3.31	2.61	2.32
T (°C)	RT	RT	50	50	50	RT

* ChCl : H donor

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6 Summary

Methods for solvent-free photocatalysis and the synthesis in deep-eutectic solvents were developed.

Chapter 1 gives an overview about reported approaches on synthesis without conventional solvents driven by thermal, mechanical, and light energy. This includes reactions in the solid state, namely mechanochemistry and solid-state photochemistry, and in liquid mixtures, focusing on photocatalysis and thermal reactions. Furthermore, the application of unconventional solvents, namely ionic liquids and deep-eutectic solvents, is discussed.

In **Chapter 2**, a method for the solvent-free oxidation of benzylic alcohols by visible-light photocatalysis is presented. A novel rod mill reactor was developed, based on the formation of thin films of the reaction mixture. Applying this reactor, several solid benzylic alcohols were oxidized to their corresponding carbonyl compounds under blue light irradiation with riboflavin tetraacetate as photocatalyst and oxygen as terminal oxidant.

Chapter 3 presents a method for the solvent-free photocatalytic conversion of paste-like reaction mixtures in a novel rotating film reactor. By rotation of the reaction vessel, a thin film is generated from the reaction mixture, enabling an efficient excitation of the photocatalyst by blue light irradiation. The reactor was used for the coupling of aryl halides with pyrrole derivatives and phosphites, applying rhodamine 6G as the photocatalyst and DIPEA as the sacrificial electron donor. The necessary amounts of photocatalyst, trapping reagent, and sacrificial electron donor were reduced significantly compared to those for literature known reactions in solution and high mole fractions of the trapping reagent are achieved.

In **Chapter 4**, the synthesis of propargyl amines from an aldehyde, an amine, and an alkyne ("A^3-coupling") in a deep-eutectic solvent is reported. The deep-eutectic solvent consists of zinc chloride and dimethylurea, acts simultaneously as catalyst and solvent and can be recycled. A variety of propargyl amines was isolated in moderate to very good yields.

Chapter 5 reports on reductive coupling reactions and reductions applying zinc in acidic deep-eutectic solvents based on choline chloride. The Barbier reaction of benzaldehyde and allyl bromide proceeds in ChCl–lactic acid; other halide substrates showed no reaction or resulted in low conversion. Furthermore, the reduction of benzaldehyde proceeds in very good conversion in several deep-eutectic solvents investigated. However, other substrates, including ketones, alkynes, alkenes, nitriles, and N-heterocycles, did not react.

7 Zusammenfassung

Gegenstand dieser Arbeit war die Entwicklung neuer Methoden für die lösungsmittelfreie Photokatalyse und die Synthese in tiefeutektischen Lösungsmitteln.

Kapitel 1 gibt einen Überblick zu lichtgetriebenen, thermischen und mechanochemischen Synthesen, die ohne konventionelle Lösungsmittel ablaufen. Dies beinhaltet lösungsmittelfreie Methoden im Festkörper (Mechanochemie und Photochemie) und in Flüssigkeiten (Photokatalyse und thermische Reaktionen). Weiterhin wird die Anwendung unkonventioneller Lösungsmittel (ionische Flüssigkeiten und tiefeutektische Lösungsmittel) diskutiert.

In **Kapitel 2** wird eine Methode zur lösungsmittelfreien Oxidation von benzylischen Alkoholen durch Photokatalyse mit sichtbarem Licht vorgestellt. Hierbei wurde ein Mühlenreaktor entwickelt, in dem dünne Schichten der Reaktionsmischung erzeugt werden. Mittels dieses Reaktors wurden mehrere benzylische Alkohole unter Bestrahlung mit blauem Licht und Anwendung von Riboflavintetraacetat als Photokatalysator und Sauerstoff als terminalem Oxidationsmittel zu ihren entsprechenden Carbonylverbindungen oxidiert.

Kapitel 3 stellt eine Methode zur lösungsmittelfreien photokatalytischen Umsetzung pastöser Reaktionsmischungen in einem Rotationsfilmreaktor vor. Durch Rotation des Reaktionsgefäßes wird aus der Reaktionsmischung ein dünner Film erzeugt, was eine effiziente Anregung des Photokatalysators durch Bestrahlung mit blauem Licht ermöglicht. Der Reaktor wurde für die Kupplung von Arylhaliden mit Pyrrolderivaten und Phosphiten mit Rhodamin 6G als Photokatalysator und DIPEA als Elektronendonor eingesetzt. Die notwendigen Mengen an Photokatalysator, Radikalabfangreagenz und Elektronendonor wurden im Vergleich zu literaturbekannten Reaktionen deutlich reduziert. Das Radikalabfangreagenz kann in hohen relativen Stoffmengenanteilen eingesetzt werden, was für den effizienten Abfang kurzlebiger Intermediate vorteilhaft ist.

In **Kapitel 4** wird die Synthese von Propargylaminen aus einem Aldehyd, einem Amin und einem Alkin („A^3-coupling“) in einem tiefeutektischen Lösungsmittel vorgestellt. Das tiefeutektische Lösungsmittel besteht aus Zinkchlorid und Dimethylharnstoff, wirkt gleichzeitig als Katalysator und Lösungsmittel und kann recycelt werden. Eine Vielzahl von Propargylaminen wurde in moderater bis sehr guter Ausbeute isoliert.

In **Kapitel 5** wird über die reduktive Kupplung und Reduktionen mit Zink in sauren tief-eutektischen Cholinchlorid-basierten Lösungsmitteln berichtet. Es wurde festgestellt, dass die Barbier-Reaktion in ChCl–Milchsäure stattfindet; andere Substrate zeigten keinen oder nur geringen Umsatz. Weiterhin konnte Benzaldehyd in mehreren tief-eutektischen Lösungsmitteln reduziert werden. Die Verwendung weiterer Substrate (Ketone, Alkine, Alkene, Nitrile und N-Heterocyclen) war aber nicht erfolgreich.

8 Abbreviations

Ar	aryl
BA	benzaldehyde
$CDCl_3$	deuterated chloroform
ChCl	choline chloride
DES	deep-eutectic solvent
DIPEA	*N,N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
DMU	dimethylurea
EA	elemental analysis
ee	enantiomeric excess
EI-MS	electron ionization mass spectrometry
ESI-MS	electrospray mass spectrometry
eq.	equivalents
GC	gas chromatography
IL	ionic liquid
IR	infrared
J	coupling constant (NMR)
LED	light-emitting diode
RFTA	riboflavin tetraacetate
RT	room temperature
NMR	nuclear magnetic resonance spectroscopy
PC	photocatalyst
Rhod. 6G	rhodamine 6G
SET	single electron transfer
TSE	twin screw extrusion

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe des Literaturzitats gekennzeichnet.

Regensburg, 04.04.2018 Martin Obst