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„MILD AND CHEMOSELECTIVE REDUCTION OF ISOCYANATES TO FORMAMIDES BY THE SCHWARTZ REAGENT“

verfasst von / submitted by

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Patricia Alina Kalkus

ABSTRACT

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Addition of the *in situ* generated Schwartz reagent to widely available isocyanates constitutes a chemoselective, high-yielding, and versatile approach to the synthesis of variously functionalized formamides. The method, as a three-component-type reaction, involves *in situ* generation of the Schwartz reagent ($Cp_2Zr(H)Cl$) from Cp_2ZrCl_2 and the reductant, $LiAlH(O\text{-}t\text{-}Bu)_3$, and immediate reaction with a substrate. Substrates include aliphatic and aromatic isocyanates, which are reduced to the corresponding formamides. Steric and electronic factors or the presence of sensitive functionalities (esters, nitro groups, nitriles, alkenes) do not compromise the potential of the method. Full preservation of the stereochemical information contained in the starting materials is observed. Compared to prior methods, this method has advantage in that reagents are inexpensive and stable, reaction times are short, and reaction temperatures are conveniently at room temperature (rt).

ZUSAMMENFASSUNG

Die Reaktion von in situ-generierter Schwartz-Reagens mit weitverbreiteten Isocyanaten stellt einen chemoselektiven, hochflexiblen und vielseitigen Ansatz zur Synthese von Formamiden mit verschiedensten funktionellen Gruppen dar. Das Verfahren als Dreikomponenten-Reaktion beinhaltet die in situ-Erzeugung des Schwartz-Reagens ($Cp_2Zr(H)Cl$) aus Cp_2ZrCl_2 und dem Reduktionsmittel $LiAlH(O\text{-}t\text{-}Bu)_3$ und der sofortigen Reaktion mit einem Substrat. Als Substrate können hierbei aliphatische und aromatische Isocyanate verwendet werden welche dann im Rahmen der Reaktion zu den entsprechenden Formamiden reduziert werden. Sterische und elektronische Faktoren oder das Vorhandensein empfindlicher funktioneller Gruppen (Ester, Nitrogruppen, Nitrile, Alkene) beeinträchtigen das Potenzial der Methode dabei nicht. Dabei kann also der vollständige Erhalt, der in den Ausgangsmaterialien enthaltenen stereochemischen

Informationen beobachtet werden. Im Vergleich zu früheren Verfahren hat diese neue Methode den Vorteil, dass die Reagenzien kostengünstig und chemisch stabil sind und man vergleichsweise geringe Reaktionszeiten hat, außerdem ist es möglich die Reaktion bei Raumtemperatur durchzuführen.

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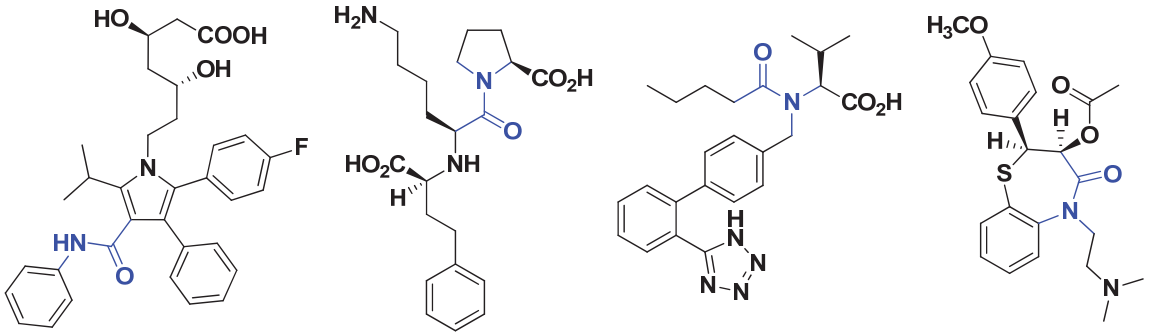
CHAPTER 1. INTRODUCTION

1. INTRODUCTION

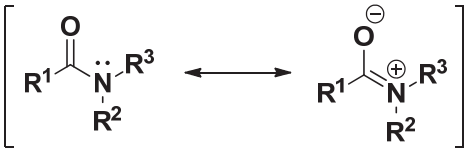
1.1 Amide bond: a privileged scaffold in organic synthesis

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs. For example, Atorvastatin, the top selling drug worldwide since 2003, blocks the production of cholesterol and contains an amide bond (Scheme 1.1),[1] as do Lisinopril (inhibitor of angiotensin converting enzyme),[2] Valsartan (blockade of angiotensin-II receptors),[3] and Diltiazem (calcium channel blocker used in the treatment of angina and hypertension).[4]



Scheme 1.1. Examples of top drugs containing an amide bond.

The amide group is planar, which includes the first carbon atoms of the R groups attached to the carbonyl group and to the nitrogen atom. The lone pair electrons on nitrogen are delocalized into the carbonyl group. Hence, the C–N bond is strengthened by this interaction, taking on partial double bond character (Scheme 1.2). This also means that we no longer have free rotation about the C–N bond which we would expect if it were only a single bond. Therefore, two rotamers should be possible, an s-*cis* and s-*trans*. The amide group as a whole is made more stable as a result of the delocalization.



Scheme 1.2. Delocalization of the lone pair electrons on nitrogen into the carbonyl group.

Amide formation is clearly one of the most numerous reactions explored in organic synthesis. Likely explanations for this include the wide range of robust methodologies available for the synthesis of amide bonds, as a result of the efforts made in the area of peptide synthesis,[5,6] the ready availability of starting materials by a range of synthetic methods, and the relative ease of purification of the reaction products, factors that contribute to the amenability of the reaction to high throughput parallel synthesis.[7] However, in comparison with the secondary and tertiary amide analogues, the strategies for the synthesis of formamides are rather limited.

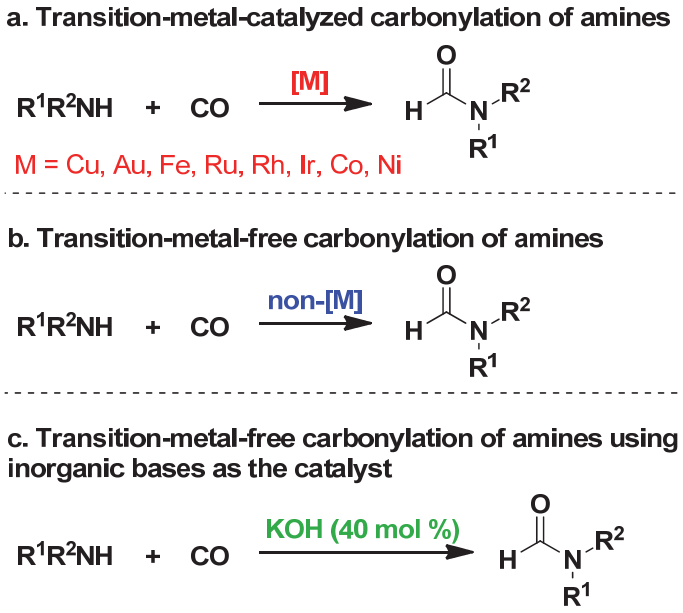
1.2 Diverse approaches to the synthesis of formamides

Formamides are important intermediates in the synthesis of many biologically active molecules or related backbones.[8-10] In addition, they also provide starting materials for the introduction of versatile functional groups[11-13] and undergo elegant transformations catalyzed by transition metals.[14-17] Owing to their many applications, numerous approaches have been developed for their synthesis.[18,19]

Of the known procedures, the *N*-formylation of amines using various C_1 building blocks is one of the most economic and straightforward methods.[19] The C_1 building blocks that have been used for the *N*-formylation of amines include chloroform,[20] formic acid and its derivatives,[21-23] paraformaldehyde,[24] methanol,[25] CO_2,[26] and CO.[27] From the viewpoints of atom economy and practicality, CO is the most attractive and ideal carbonyl source because it is cheap, readily available, and produces no additional waste.

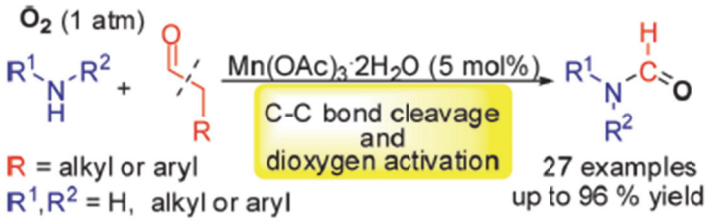
For the CO-based carbonylative transformation of amines, various procedures have been developed and the oxidative carbonylation of amines to ureas using various transition-metal catalysts is well established.[28,29] However, the direct carbonylation of amines to N-formamides by using transition metal catalysts (e.g. Cu,[30] Fe,[31] Zn,[32] Ru,[33] Rh,[34] Ni[35]) is much less explored (Scheme 1.3a). Additionally, some metal-free procedures have been developed. In the literature, NaOMe has been reported as a catalyst for the carbonylation of dimethylamine and this procedure has been applied in industry for the production of dimethylformamide (DMF) (Scheme 1.3b).[36]

In 2015, Li and Wu developed a new, simple, practical, and efficient procedure for the *N*-formylation of amines by using CO as the carbonyl source.[37] This procedure features the following advantages. 1) There is no need for transition metals or any additives. 2) Cheap and stable catalysts are employed enabling large-scale applications. 3) Purification of the final products is easy because a gaseous formylation reagent is used (Scheme 1.3c). However, the obtention of aromatic formamides is rather limited by employing this methodology, where different substituted anilines were unreactive even under harsher conditions.



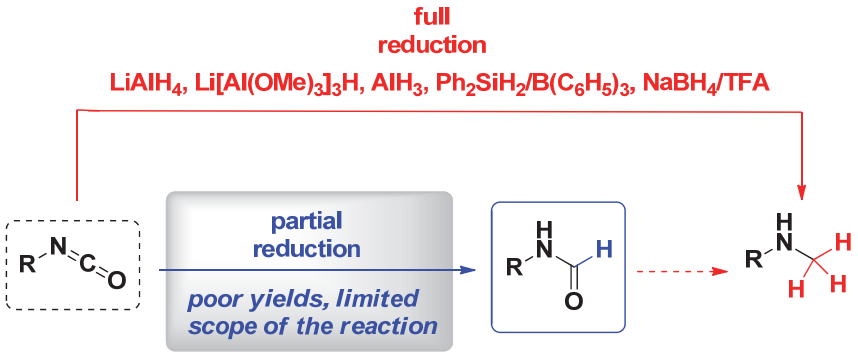
Scheme 1.3. *N*-Formylation reactions of amines with CO.

An additional approach to the synthesis of formamides has been reported by Jiao and co-workers,[38] where they demonstrated a novel Mn-promoted aerobic oxidative C-C bond cleavage of aldehydes with dioxygen activation (Scheme 1.4). This chemistry realized the aerobic oxidative cleavage of a carbon-carbon σ-bond with an inert alkyl chain fragment as the leaving group. The use of molecular oxygen (1 atm) as the oxidant, reactant, and initiator to trigger this radical process under mild conditions makes this transformation green and practical.



Scheme 1.4. Mn-promoted aerobic oxidative C-C bond cleavage of aldehydes with dioxygen activation to afford formamides.

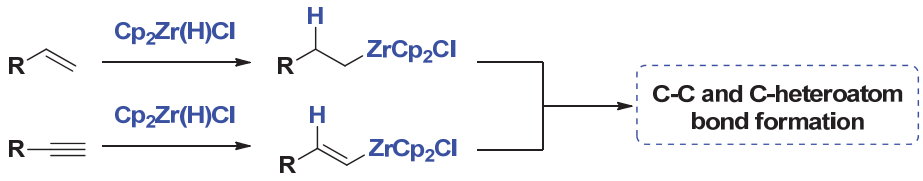
Undoubtedly, the reduction of isocyanates has been envisaged as an interesting way to synthesize formamides. However, not all the attempts have allowed the partial reduction until the formamide moiety (Scheme 1.5). The reduction of isocyanates with $LiAlH_4$ has been known since the 1950´s when Wessely and Swoboda[39] reported their first full reduction to *N*-methylamines, confirmed shortly after by Finholt.[40] The same outcome was also observed with other powerful reducing agents such as $Ph_2SiH_2/B(C_6F_5)_3$[41] or $NaBH_4$/TFA.[42] On the other hand, partial reduction of isocyanates to formamides was achieved by Lorenz and Becker with two examples of *N*-arylformamides obtained via the reduction of isocyanates with Ph_3SnH with poor yields (40-50%),[43] while Noltes observed that trialkyltin hydrides reacted better with arylisocyanates than alkyl counterparts.[44] Moreover, scattered examples of this chemistry come from work by Ojima (Pd-catalyzed hydrosilylation)[44] and Howell (amine-catalyzed hydrogenation).[45]



Scheme 1.5. Diverse approaches for the reduction of isocyanates.

1.3 A versatile reducing agent: the Schwartz reagent

Since the first preparation of $Cp_2Zr(H)Cl$ (bis(cyclopentadienyl)zirconium(IV) chloride hydride) by Wailes and Weigold in 1970,[46] organozirconium chemistry has been widely studied and applied in organic synthesis.[47-49] This reagent was developed by Jeffrey Schwartz in the mid-1970s and hence bears his name.[50-53] The hydrozirconation reaction, in which the addition of Schwartz reagent to alkenes and alkynes leads to organozirconocenes, can be considered as the first synthetically useful application of the zirconocene complexes in organic chemistry (Scheme 1.6).[47-49]



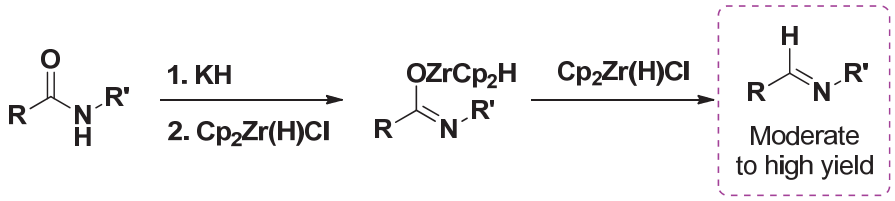
Scheme 1.6. Hydrozirconation reaction of alkenes and alkynes by the Schwartz reagent.

Systematic investigations in the late 1970s and 1980s by Negishi further expanded the synthetic scope of these complexes.[54] Since then, the interest in organozirconium chemistry has been significantly increased due to the unique ability of the Schwartz reagent and related organozirconocenes to promote uncommon transformations.

Meanwhile, many new reactions of the Schwartz reagent such as reductions have been uncovered and developed gradually.

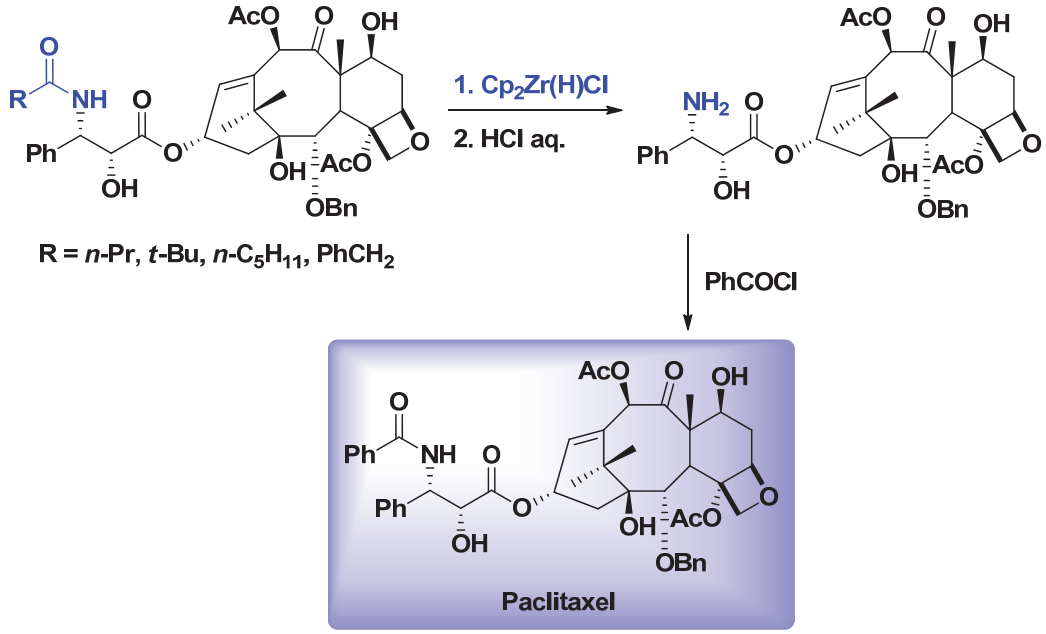
Other than hydrozirconation applications leading to C-C and C-heteroatom bond formation, the Schwartz reagent has been found to be a powerful and selective reducing agent for carbonyl group and other functional groups, especially amides. In the late 1980s, Wang and co-workers reported a series of results on reductions of aldehydes, ketones, epoxides and esters to alcohols as well as hydrozirconations of imines and nitriles using the Schwartz reagent in benzene in the 30-60 °C temperature range.[55,56] In 1997, Zablocka and co-workers found that Schwartz reagent effects reduction of a variety of phosphine oxides and sulfides to phosphines under mild conditions.[57] Reduction of phosphine oxides or sulfides can be achieved using several reagents, but most of the reducing reagents used, such as $LiAlH_4$, are not very selective.[57]

In 1990s, the Ganem group found[58] and developed[59] a new methodology for the reduction of secondary amides to *N*-substituted imines using the Schwartz reagent (Scheme 1.7). This is an important functional group interconversion because imines are usually reduced more rapidly than amides by most metal hydride reagents and thus the reduction of amides to imines is difficult to control. The Ganem method achieves this transformation.



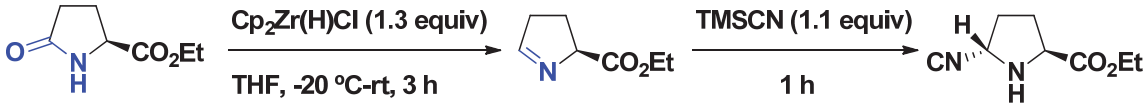
Scheme 1.7. Reduction of secondary amides to *N*-substituted imines using the Schwartz reagent.

The value of the Ganem protocol has been dramatically demonstrated in the large-scale synthesis of a taxol derivative in which the Schwartz reagent is used to reductively cleave the secondary amide in the side chain from a mixture of derivatives extracted from the yew tree, followed by benzoylation to synthesize paclitaxel, an anticancer drug (at least US$ 1 billion in sales per year) (Scheme 1.8).[60]



Scheme 1.8. Application of the Schwartz reagent in the total synthesis of paclitaxel.

Another recent application which shows the potential of the Schwartz reagent is the selective reduction of a lactam to an imine and its subsequent transformation (Scheme 1.9).[61]



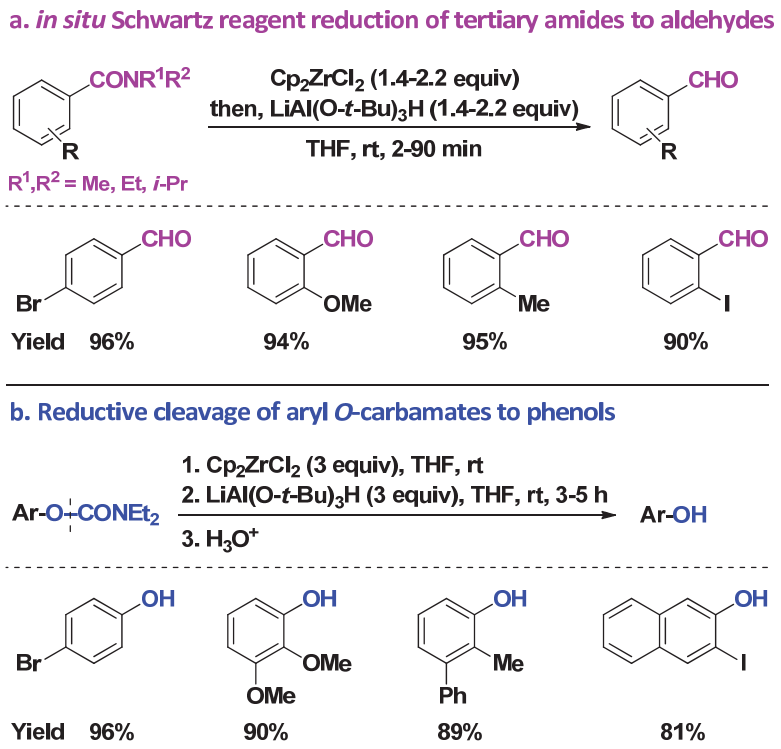
Scheme 1.9. Selective reduction of a lactam to an imine by the Schwartz reagent.

In addition, tertiary amides are generally difficult to reduce selectively. A convenient procedure for the reduction of tertiary amides to aldehydes by $Cp_2Zr(H)Cl$ under very mild conditions was discovered by the Georg group in 2000.[62] Combined with later studies,[62-64] these results demonstrate the use of the Schwartz reagent as an effective method to reduce a variety of tertiary amides, including dialkyl, methoxymethyl (Weinreb amides) and even Evans *N*-acyloxazolidinone, directly to the corresponding aldehydes in high yields in very short reaction times (<30 min) at room temperature. Significantly, this

method has excellent functional group tolerance and high selectivity with no or little over-reduction. It is noteworthy that ester, NHBoc, nitrile, halo and nitro groups survive the reduction conditions. However, ketone and aldehyde groups are reduced to the corresponding alcohols under the conditions which effect amide reduction at room temperature. Most recently, this methodology has been successfully applied to the reduction of chiral amides with little or no erosion of diastereomeric excess.[65]

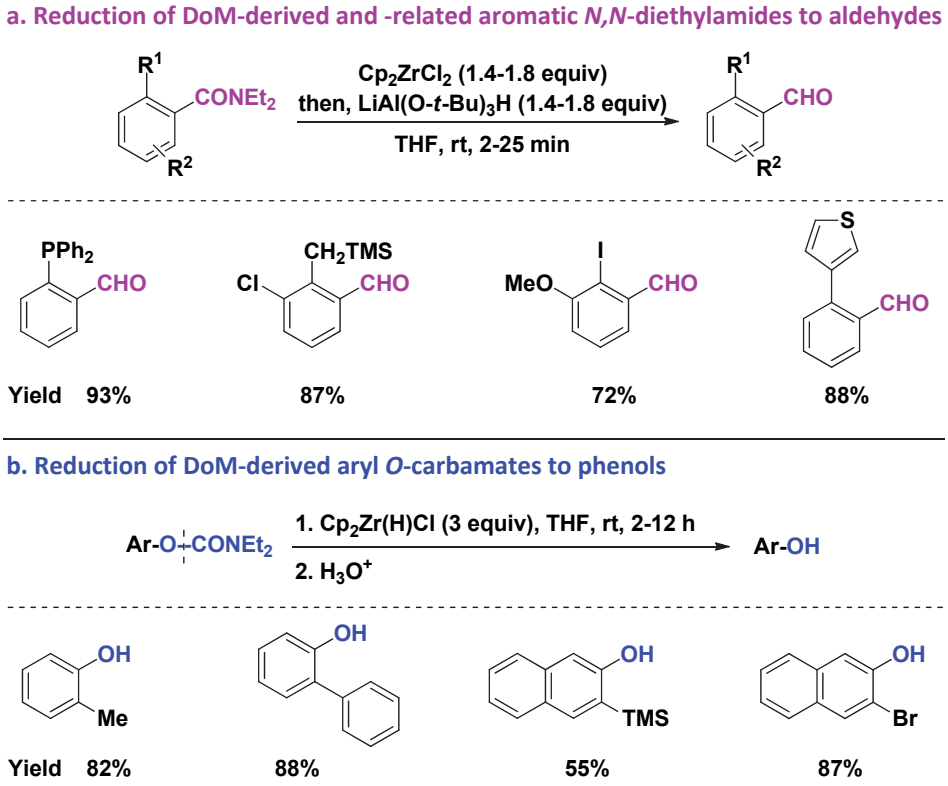
However, although Schwartz reagent is commercially available, it is expensive and problematic for long-term storage due to its sensitivity to air, light and moisture.[47,49] Moreover, this reagent is feebly soluble in common inert solvents. These drawbacks lower the effective use of the Schwartz reagent and limit it's application. That is why in the last years, several *in situ* procedures for independent generation of the Schwartz reagent have been reported, using diverse hydride sources such as $LiAlH_4$,[66] $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al),[66] *t*-BuMgCl,[66,67] $LiEt_3BH$,[68] and DIBAL-H[69] which led to the formation of a heterogeneous reagent. To overcome these deficits, Snieckus and co-workers developed a useful protocol for the *in situ* generation of the Schwartz reagent[70] which has the following features: i) avoidance of the step for the separate preparation of the Schwartz reagent and its over-reduction to Cp_2ZrH_2 which existed in the previous direct use of the reagent;[47,71] ii) generation of a Schwartz reagent which provides a more reactive reagent compared to that prepared in direct fashion; iii) lower cost: above 50% cost reduction compared to direct use of the Schwartz reagent ($LiAl(O\text{-}t\text{-}Bu)_3H$ 1M solution in THF–US$ 580/mol and Cp_2ZrCl_2–US$ 700/mol, in comparison with $Cp_2Zr(H)Cl$–US$ 3,020/mol)[72]; iv) less sensitivity in handling, and advantage of long-time storage of both reagents, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1M solution in THF) and Cp_2ZrCl_2 compared to the Schwartz reagent.[47]

Precisely, Snieckus and co-workers have demonstrated the *in situ* Schwartz reagent utility in the efficient reduction of amides to aldehydes[70] (Scheme 1.10a) and aryl *O*-carbamates to phenols[73] (Scheme 1.10b) with great tolerance of diverse functional groups.



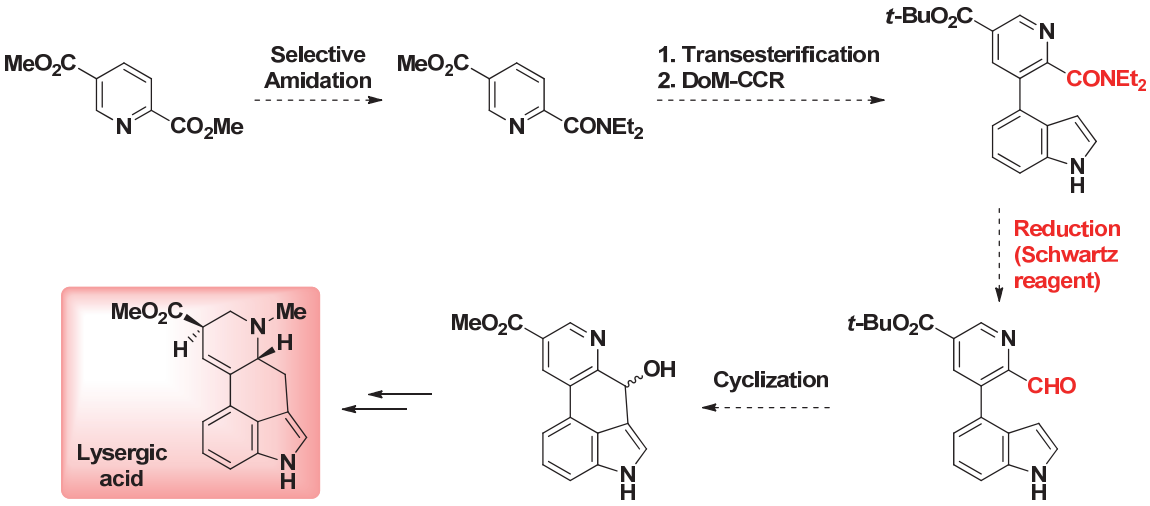
Scheme 1.10. Reduction of amides to aldehydes (a), and aryl *O*-carbamates to phenols (b) by the Schwartz reagent.

Notably, the *in situ* Schwartz reduction, when connected to the Directed *Ortho* Metalation strategy (DoM chemistry) of benzamides and aryl *O*-carbamates provides new routes to polysubstituted aromatic and heteroaromatic aldehydes[70] (Scheme 1.11a) and phenols[73] (Scheme 1.11b) which are not available or difficult to prepare by conventional aromatic chemistry. Thus, the *in situ* method may provide access to new commodity molecules that, aside from having intrinsic value, may be useful for conversion to substances that can benefit human health and material resources.



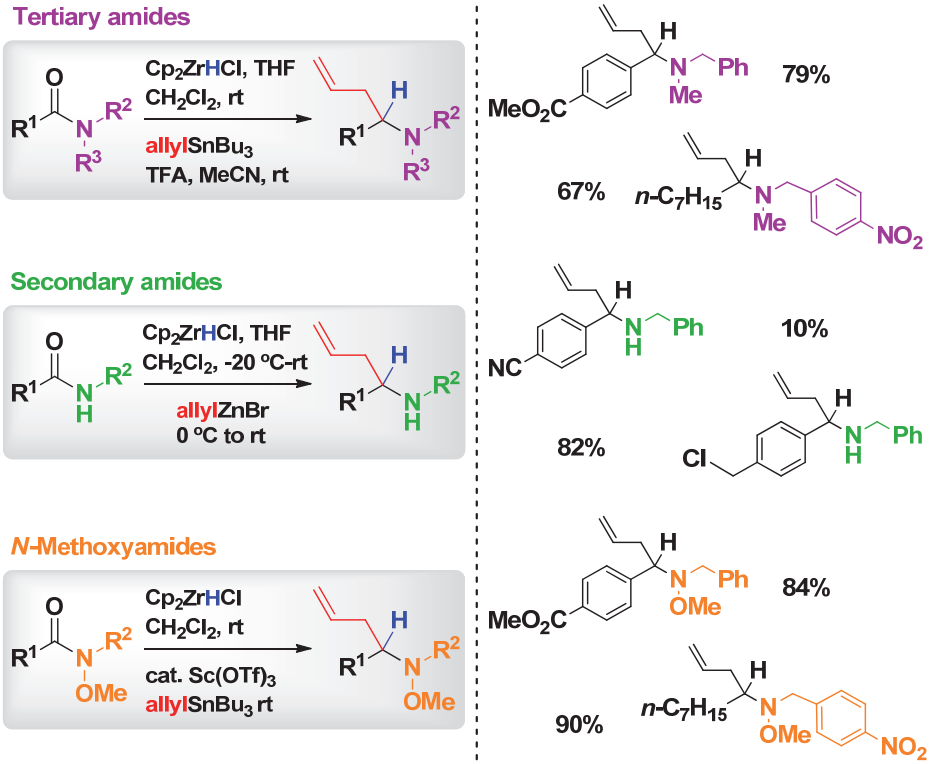
Scheme 1.11. Reduction of DoM derived benzamides (a), and aryl *O*-carbamates (b) by the Schwartz reagent.

The efficiency and chemoselectivity of such reactions prompted the use of the Schwartz reagent in an approach to the synthesis of lysergic acid. Lysergic acid is a representative of the Ergot alkaloids which possess the widest biological activity found in any family of natural products.[74,75] Since the first total synthesis of racemic lysergic acid by Woodward and co-workers in 1956,[76] this unique structure, exhibiting the tetracyclic ergoline skeleton which contains a tetrahydropyridine and a C3-C4 fused indole, has attracted the interest of synthetic chemists. To date, eleven syntheses of lysergic acid have been reported. A new route towards the synthesis of lysergic acid have been recently developed by Snieckus and co-workers, where the key steps are selective amidation, DoM-Suzuki cross coupling reaction (CCR) and chemoselective amide to aldehyde reduction using the *in situ* Schwartz reagent method (Scheme 1.12).



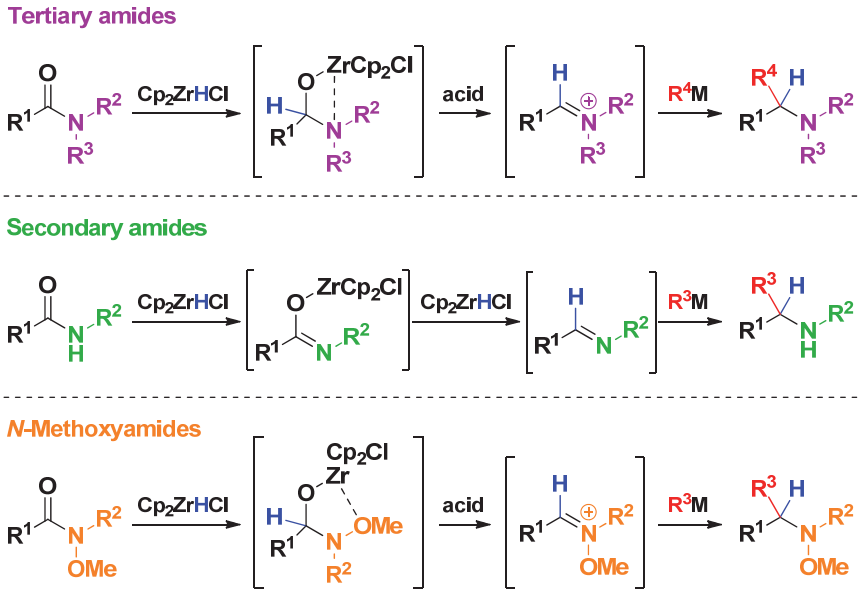
Scheme 1.12. Application of the Schwartz reagent in the total synthesis of lysergic acid.

Contemporaneously, Chida-Sato group extended the synthetic utility of the Schwartz reagent by its nucleophilic addition to inert amide carbonyls.[77-79] This transformation is undoubtedly a powerful tool for the synthesis of multi-substituted amines found in complex natural products and pharmaceuticals.[80] They developed a chemoselective nucleophilic addition to tertiary amides, secondary amides, and *N*-methoxyamides in the presence of a variety of functional groups, such as methyl esters, which conventionally require protection prior to nucleophilic addition[79] (Scheme 1.13).



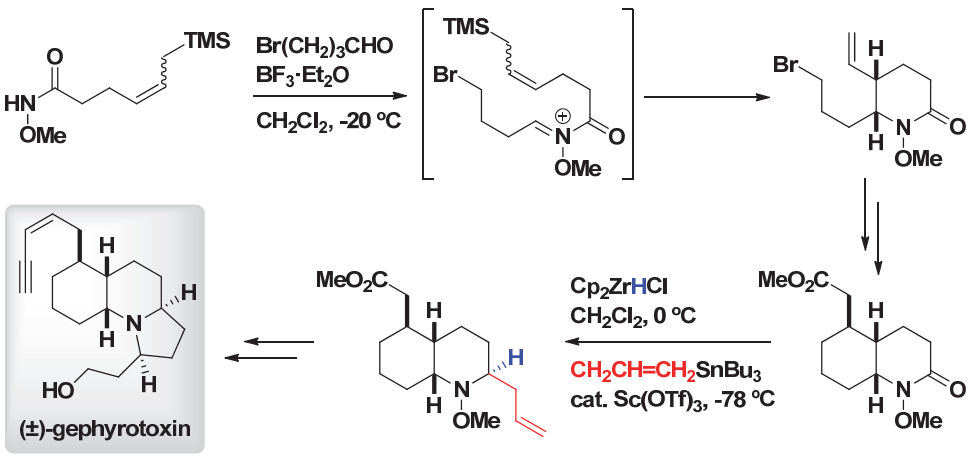
Scheme 1.13. Chemoselective reductive allylation of tertiaty amides, secondary amides, and *N*-methoxyamides.

The reaction consisted of three steps: 1) reduction of the amide carbonyl, 2) formation of an iminium ion with an acid, and 3) carbon-carbon bond formation. The key to success was the high oxophilicity of the Schwartz reagent, which enabled direct reduction of the amide carbonyl group.[79] In addition, the high electrophilicity of the iminium ions generated allowed use of mild nucleophiles in the carbon-carbon bond-forming process (Scheme 1.14). The combination of these properties resulted in reductive nucleophilic addition in the presence of other sensitive functional groups.



Scheme 1.14. Representative chemoselective nucleophilic additions to amide carbonyl groups through carbon-carbon bond formation.

The methodology developed minimizes extra steps, for example, protecting group manipulations and redox reactions, and facilitate the synthesis of complex alkaloids from readily available amide groups. Thus, Chida-Sato group accomplished the total synthesis of (±)-gephyrotoxin, which presents the most concise and efficient synthesis of this natural product to date[78] (Scheme 1.15).



Scheme 1.15. Total synthesis of (±)-gephyrotoxin by chemoselective nucleophilic addition.

CHAPTER 2. OBJECTIVES

2. OBJECTIVES

Formamides are important intermediates in the synthesis of many biologically active molecules or related backbones.[8-10] Several approaches have been developed for their synthesis,[18,19] highlighting the diverse attempts involving the reduction of isocyanates. Isocyanates represent a versatile class of organic molecules[81,82] which, due to the excellent electrophilicity of the heterocumulene carbon enable the smooth addition of a plethora of nucleophiles ranging from alcohols (synthesis of carbamates),[83] amines (synthesis of ureas)[84-86] to carbanions (synthesis of amides, *vide infra*). If the procedure could be extended to the addition of a hydride nucleophile, a straightforward and direct route to inaccessible formamides could be envisaged.

During the last decade, the Schwartz reagent has increased its synthetic appeal. The broad utility and application of the *in situ* Schwartz reagent methodology has allowed the expansion of the use of this reagent as a reducing agent.

Taking into account the lack of studies on the reduction of isocyanates to formamides in the last > 30 years, we look at redesigning the transformation, considering that crucial for its success is identifying a reliable reducing agent with high chemoselectivity.

CHAPTER 3. RESULTS AND DISCUSSION

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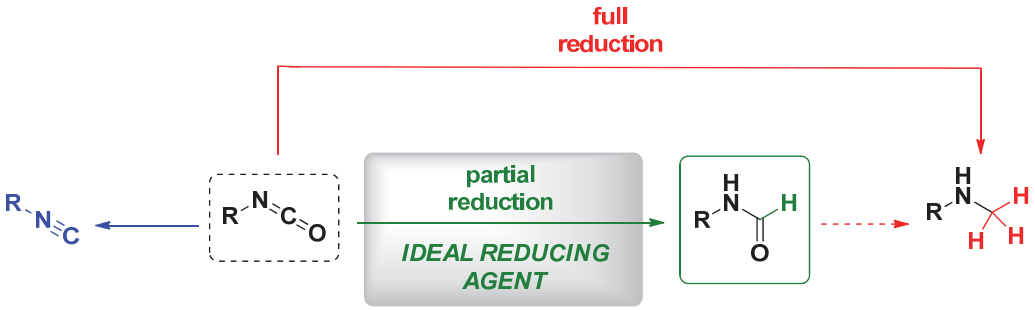
3.1. Optimization of the reaction conditions for the reduction of isocyanates to formamides

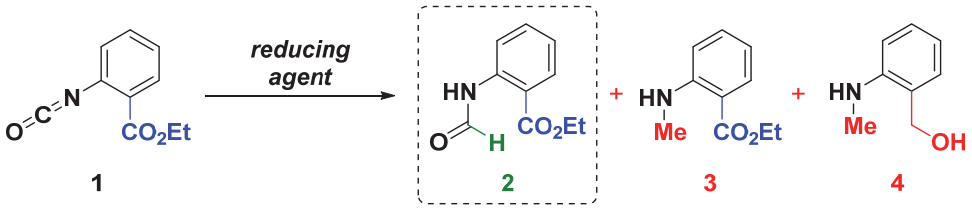
As we discussed in Chapter 1, the reduction of isocyanates to formamides has been previously reported. However, such transformation has been plagued with difficulties, namely, the full reduction of isocyanates to the corresponding amines that can be further complicated by the reduction of isocyanates to isocyanides (in the presence of Ph_2(*t*-Bu)SiLi or Cl_3SiH/amine), and the lack of chemoselectivity of the reducing agent employed. As depicted in Scheme 3.1, the ideal reducing agent for the desired transformation should present two main features: 1) it should chemoselectively halt the reduction at the formamide level (*i.e.* partial reduction) and, 2) it should not react with additional functionalities under the reductive conditions employed.



Scheme 3.1. Addition of hydrides to isocyanates.

We began our investigations with the model isocyanate **1**, which presents an ester as an additional electrophilic moiety susceptible to reduction. As summarized in Table 1, treatment with various reducing agents could in principle provide a mixture of three different products, namely the targeted 2-ethoxycarbonyl formamide **2**, 2-methylaminobenzoate **3** (in which the starting isocyanate was fully reduced at the corresponding amine) and the completely reduced 2-methylaminobenzylic alcohol **4**.

Table 1. Model reaction: Optimization.



Entry	Reducing agent (equiv)	Solvent	Temp (°C) / time (h)	Ratio **2**:**3**:**4**	Yield of **2** (%)[a]
1	DIBAL-H (1.0)	THF	0 / 0.5	2:1:1	12
2	$LiAlH_4$ (0.3)	THF	0 / 0.5	0:0:1	-[b]
3	$NaBH_4$ (0.3)	THF	0 / 0.5	1:0:0	30
4	$NaBH_4$ (1.0)	THF	0 / 0.5	1:0:0	34
5	$NaBH_4$ (1.0)	THF	40 / 2	1:0:0	37
6	Et_3SiH (1.5)	THF	0 / 1	1:1:1	6[c]
7	Hantzsch ester (1.2)	THF	0 / 1	1.5:1.5:1	36
8	Cp_2ZrHCl[d] (1.2)	THF	rt / 1	1:0:0	78
9	Cp_2ZrHCl[e] (1.2)	THF	rt / 1	1:0.2:0	65
10	Cp_2ZrHCl[e,f] (1.2)	THF	rt / 1	1:0:0	87
11	Cp_2ZrHCl[e,f] (1.2)	2-MeTHF	rt / 1	1:0:0	92

[a] Isolated yield. [b] Compound **4** was obtained in 46% isolated yield. [c] An overall conversion of 22% was observed by ^{1}H-NMR. [d] Cp_2ZrHCl supplied from commercial source. [e] Cp_2ZrHCl prepared according Snieckus protocol (ref 70). [f] $LiAl(O\text{-}t\text{-}Bu)_3H$ (1 M in THF) was added to Cp_2ZrCl_2 at 0 °C.

The use of DIBAL-H afforded a mixture of the three possible products with a limited conversion (entry 1). Increasing the reducing power of the reagent ($LiAlH_4$), the fully reduced compound **4** was formed as the unique product (entry 2), in agreement with the seminal studies discussed before. A milder reagent such as $NaBH_4$, improved dramatically the selectivity. However, the yield was far from optimal (entry 3), even in the presence of increased loading, or after higher temperatures / longer reaction times (entries 4-5). Other common reagents such as triethylsilane (entry 6) or the Hantzsch ester[87,88] (entry 7)

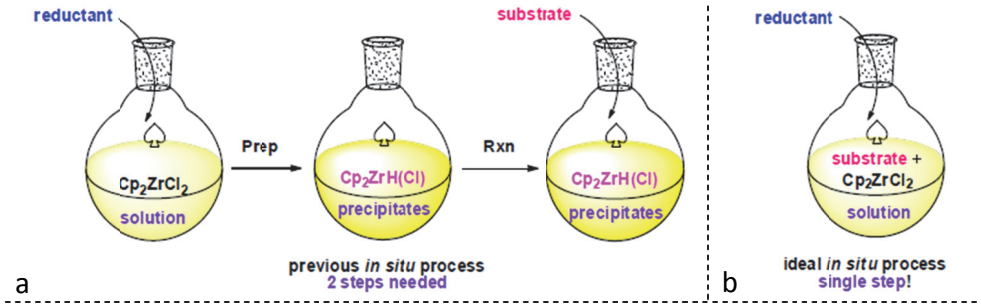
provided mixtures of the three possible products in limited yields. Pleasingly, a satisfactory 78% yield of the desired compound **2** – under full chemocontrol - was achieved by employing the commercially available Schwartz reagent[46,52,53,89-91] (Cp_2ZrClH, entry 8). Indeed, this reagent features excellent chemoselectivities as showcased in illuminating works by Georg,[62-64] Ganem,[58-60] Snieckus[70,73] and Furman[92] among others,[65,93,94] during independent investigations on amide-type reduction chemistry. Because of the well-known issues associated the use of commercially available reagent,[47,49,69] we found it highly beneficial to generate it according to the recently described Snieckus protocol from Cp_2ZrCl_2 and $LiAl(O\text{-}t\text{-}Bu)_3H$ (more information in section 3.2).[70] Interestingly, when the addition of the latter reagent was performed at rt, chemoselectivity was affected as a consequence of the reducing capability of the same $LiAl(O\text{-}t\text{-}Bu)_3H$ (entry 9). However, performing such addition at 0 °C and then, removing the cooling bath enabled us to access **2** in 87% isolated yield with full chemocontrol (entry 10). Further improvement could be observed by running the reaction in 2-methyltetrahydrofuran (2-MeTHF, entry 11), nowadays considered a versatile alternative to THF in terms of eco-compatibility for organometallic reactions.[95]

3.2. General protocol for the synthesis of formamides *via* the *in situ* generated Schwartz reagent

The Schwartz reagent is widely used in synthetic organic chemistry in hydrozirconation and a number of reactions emanating therefrom.[47-49] Although the Schwartz reagent is commercially available, it is expensive (US$ 28/g) and is problematic for long-term storage due to its sensitivity to air, light and moisture.[47] To date, *in situ* generation procedures using different hydride sources such as *t*-BuMgCl,[67] $LiEt_3BH$,[68] and DIBAL-H[69] for the hydrozirconation reaction have been reported, but all of these are based on the initial preparation of the Schwartz reagent for use in subsequent reactions (Scheme 3.2a). In the first reduction step, the Schwartz reagent formed is typically contaminated with Cp_2ZrH_2 and other salts.[47] In such a one-pot two-step process, if the reductant used to generate the Schwartz reagent were to remain, byproducts would contaminate the end product

since the reductant would react with the substrate and intermediates. Thus, the main disadvantages of these methods include over-reduction, poor solubility, and contaminants that may affect efficient reduction. That is why we decided to employ the Snieckus protocol for the *in situ* generation of the Schwartz reagent. This methodology presents the following main feature: its preparation and reaction is feasible in a real one-pot procedure in order that the *in situ* prepared reagent is in a pure and really fresh state for immediate reaction with a substrate (Scheme 3.2b). The advantage of this procedure would be the avoidance of the step for separate preparation of the Schwartz reagent and its over-reduction to Cp_2ZrH_2 which constitute deficiencies in the previous preparations of the reagent.[47,71]

Therefore, as a general protocol for the synthesis of formamides *via* the *in situ* generated Schwartz reagent we dissolved in anhydrous 2-MeTHF the corresponding isocyanate and Cp_2ZrCl_2. Then the mixture was cooled at 0 °C due to we observed during the optimization of the reaction conditions that the chemoselectivity was affected as a consequence of the reducing capability of the $LiAl(O\text{-}t\text{-}Bu)_3H$. Afterward, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1 M in THF) was added dropwise at 0 °C for the *in situ* formation of the Schwartz reagent and then, the cooling bath was removed, allowing the mixture to reach rt (Scheme 3.2c).



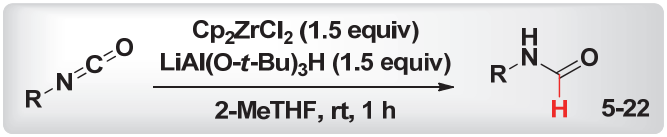
c

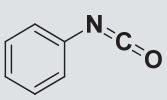
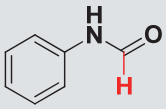
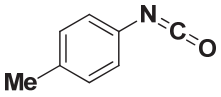
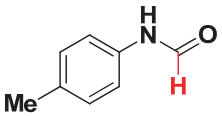
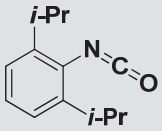
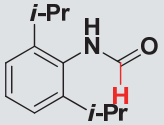
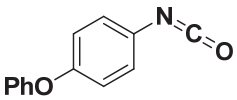
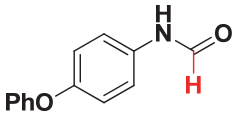
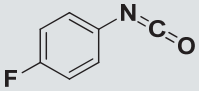
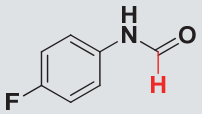
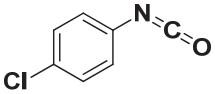
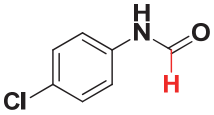
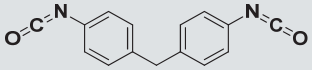
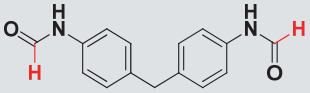
Scheme 3.2. *In situ* processes for the generation of the Schwartz reagent. *a* and *b*[70], *c* (this work).

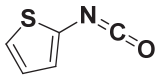
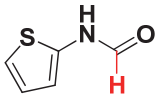
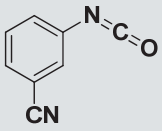
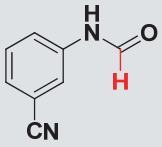
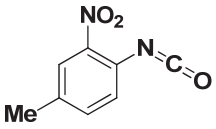
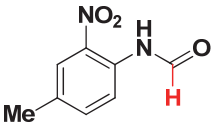
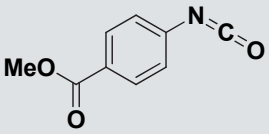
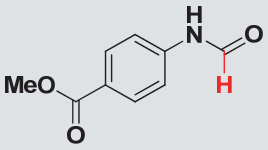
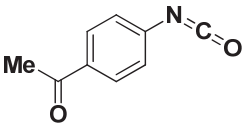
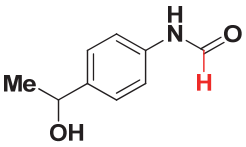
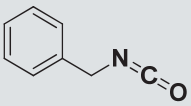
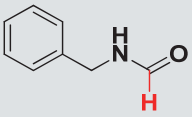
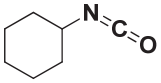
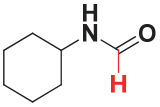
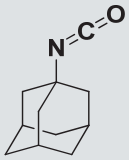
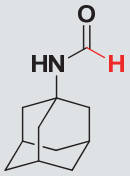
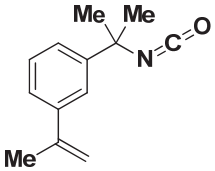
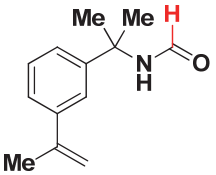
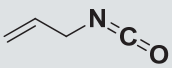
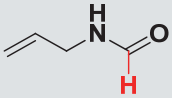
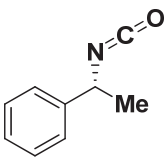
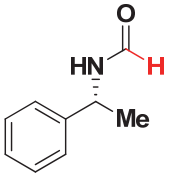
3.3. Scope and chemoselectivity of the reaction

With these optimized conditions in hand, we explored the scope of the reaction. Both aromatic and aliphatic isocyanates react smoothly, providing the corresponding formamides (**5**-**16**) and (**17**-**22**) respectively, in high yields (Table 2).

Table 2. Scope of the reaction.



Entry	Isocyanate	*In situ* Schwartz Reagent (equiv)	Product	Yield
5		1.5		93%
6		1.5		89%
7		1.5		95%
8		1.5		94%
9		1.5		90%
10		1.5		84%
11		3.0		86%

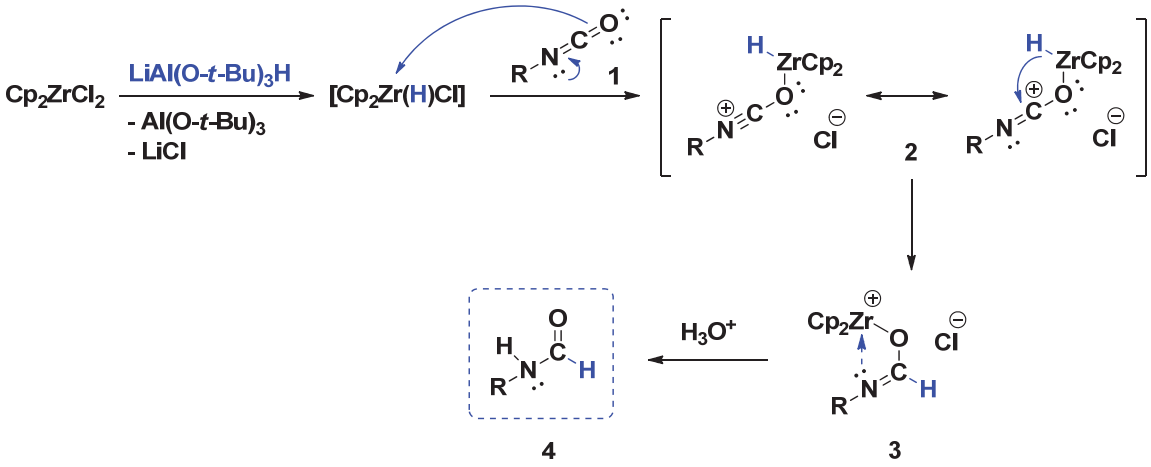
12		1.5		92%
13		1.5		83%
14		1.5		83%
15		1.5		80%
16		2.0		87%
17		1.5		88%
18		1.5		84%
19		1.5		92%
20		1.5		87%
21		1.5		91%
22		1.5		93% (*er* > 99:1)

Pleasingly, substitution on the aromatic ring does not adversely influence the reaction outcome: both electron-releasing (alkyl, alkoxy, *e.g.* **6**-**8**) and electron-withdrawing [halogens (**9**-**10**), nitrile (**13**), nitro (**14**), ester (**15**)] functionalities are tolerated. Interestingly, sterically hindered isocyanates provide the expected products in high yield not only in the case of aromatic substituents (**7**), but also for aliphatic analogues (**19**, **20**) thus, overcoming the well-known issues concerning the low reactivity of the corresponding amines towards acylating agents.[96] The following additional points on the chemoselectivity of the protocol are worth of mention: *a*) hydride delivery takes place exclusively on the isocyanate without affecting sensitive functionalities such as nitrile (**13**) or nitro (**14**); *b*) Additionally, the presence of esters decorating aromatic nuclei does not alter at all the chemoselectivity (**15**): the concomitant reduction of this functional group was not observed at all; *c*) Olefinic fragments (known to be susceptible to the Schwartz reagent under different conditions)[48,53,70,90] were not affected under the reaction conditions (**20**-**21**); *d*) the use of optically-active isocyanate allowed us to prepare the corresponding formamide in excellent enantiopurity without minimal erosion of the stereochemical information (**22**); *e*) Heteroaromatic ring in the case of aromatic isocyanate (**12**) did not compromise the efficiency of the methodology; *f*) The multiple reduction of a bis-isocyanate was possible as indicated in the case of di-formamide **11**. In line with previous studies by Georg,[63] a highly reactive aromatic ketone was concomitantly reduced to the secondary alcohol under the reaction conditions (**16**). Thus, the isocyanate reduction is a fast reaction which suppresses other functional group reductions under the conditions employed. Of particular applicative significance is the one step, straightforward access to formamide **8** known to manifest mutagenic properties.[97]

3.4. Proposed mechanism of reaction

Finally, we propose a possible mechanism for the reduction of isocyanates to formamides (Scheme 3.3), in an analogous way to the mechanism proposed by Georg and co-workers for the reduction of amides to aldehydes.[62] This mechanism begins with the addition of the Schwartz reagent to an isocyanate **1**, followed by an intramolecular hydride transfer of

2 to form a zirconated tetrahedral intermediate **3** which leads, after quench with water, to the formamide product **4**. In this process, as a key feature, a coordination between Zr and N in the tetrahedral intermediate **3** is suggested which strongly stabilizes the intermediate delaying to collapse until hydrolysis.



Scheme 3.3. Proposed reaction mechanism of the reduction of isocyanates to formamides mediated by the Schwartz reagent.

CHAPTER 4. CONCLUSIONS

4. CONCLUSIONS

In conclusion, we have developed an expeditious route to *N*-formamides through the high chemoselective nucleophilic addition of the *in situ* generated Schwartz reagent to widely available isocyanates. Key characteristics of the transformation are: 1) uniformly high yields and full retention of the steric information contained in the starting materials; 2) excellent chemoselectivity in the presence of functionalities sensitive to reductive conditions such as nitro, cyano, ester, alkene groups. The synthetic potential of the formamide moiety in medicinal chemistry allows envisaging further applications of this reaction.

CHAPTER 5. EXPERIMENTAL PART

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5.1 General methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected.

Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). The analyses were performed by Mag. Dr. Martin Zehl.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) and with a Bruker DRX spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C) at 297 K using a "directly" detecting broadband observe (BBFO) probe. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 77.0 ppm (^{13}C in $CDCl_3$). Spin-spin coupling constants (J) are given in Hz. In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments.

The HPLC equipment consisted of an Agilent High Performance Liquid Chromatograph 1100 with variable wavelength detector and fluorescence detector. Analyses were performed in a Chiralpak® IA column, at λ = 220 nm with a mobile phase of *n*-hexane/*i*-propanol (97:3, v/v) at a flow rate of 0.75 mL/min. The analyses were performed by Karen de la Vega Hernández.

THF and 2-MeTHF were distilled over Na / benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar and TCI Europe, otherwise specified. Solutions were evaporated under reduced pressure with a rotary evaporator. TLC was carried out on aluminium sheets precoated with silica gel $60F_{254}$ (Macherey-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm) and/or KMnO4 (aq.) was used as revealing system.

5.2 General procedures for experiments represented in Table 1 (entries 1-8)

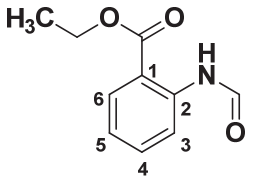
To a solution of 2-(ethoxycarbonyl)phenyl isocyanate **1** (0.191 g, 1.0 mmol, 1.0 equiv) in dry THF (5 mL) at the proper temperature, the corresponding reducing agents were added dropwise (*see conditions indicated in Table 1 of Chapter 3)*. After the appropriate time, the reactions were quenched with the following reagents: NH_4Cl (entries 1, 6, 7) / H_2O and 2.5 M NaOH (entry 2) / H_2O (entries 3-5) / H_2O and 1 M HCl (entry 8), respectively. The aqueous layers were extracted with Et_2O (3x) and the organic phases were combined. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crudes were purified by flash SiO_2 column chromatography to yield the products indicated in Table 1.

5.3 General procedure for the reduction of isocyanates to formamides with the *in situ* generated Schwartz reagent

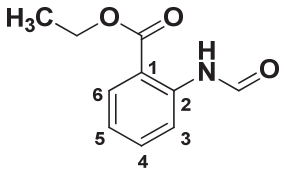
To an oven-dried and argon-flushed flask was added the isocyanate and Cp_2ZrCl_2. The reagents were dissolved in anhydrous 2-MeTHF at rt and then the mixture was cooled at 0 °C. $LiAl(O\text{-}t\text{-}Bu)_3H$ (1 M in THF) was added dropwise at 0 °C and then, the cooling bath was removed, allowing the mixture to reach rt. After the appropriate time, the reaction was quenched with H_2O (5 mL) and stirred for 1-2 min. Then, a solution of 1 M HCl (4 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the organic layers were combined. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crudes were purified by flash SiO_2 column chromatography to yield the product.

5.4 Characterization of compounds

2-Ethoxycarbonyl formamide (2)



s-*cis* rotamer



s-*trans* rotamer

2

By following the *General Procedure*, to a solution of 2-(ethoxycarbonyl)phenyl isocyanate (**1**) (0.191 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **2** was obtained in 92% yield (0.177 g) as a brown oil, after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 83:17

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.03 (s, 1H, NH), 8.68 (d, *J* = 8.5 Hz, 1H, Ph H-3), 8.49 (s, 1H, HC=O), 8.03 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ph H-6), 7.51 (t, *J* = 7.9 Hz, 1H, Ph H-4), 7.09 (t, *J* = 7.7 Hz, 1H, Ph H-5), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.93 (OC=O), 159.46 (HC=O), 140.29 (Ph C-2), 134.43 (Ph C-4), 130.73 (Ph C-6), 122.94 (Ph C-5), 120.96 (Ph C-3), 115.26 (Ph C-1), 61.39 (OCH_2), 14.03 (CH_3).

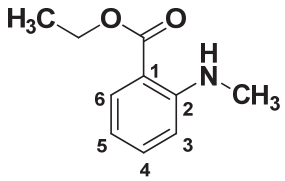
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.50 (br s, 1H, NH), 8.93 (d, *J* = 11.0 Hz, 1H, HC=O), 8.02 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ph H-6), 7.49 (m, 1H, Ph H-4), 7.35 (d, *J* = 8.2 Hz, 1H, Ph H-3), 7.12 (m, 1H, Ph H-5), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.87 (OC=O), 161.21 (HC=O), 139.86 (Ph C-2), 134.18 (Ph C-4), 131.71 (Ph C-6), 123.20 (Ph C-5), 116.11 (Ph C-1), 115.51 (Ph C-3), 61.39 (OCH_2), 14.03 (CH_3).

HRMS (ESI), *m/z* calcd. for $C_{10}H_{12}NO_3$ $[M+H]^+$ 194.0817; found 194.0820.

2-(Methylamino)benzoate (3)



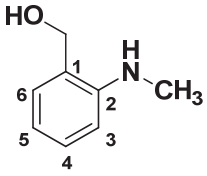
3

Obtained as a pale yellow oil, as reported in Table 1 (entries 1, 6, 7, and 9) (Chapter 3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.94 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, Ph H-6), 7.69 (br s, 1H, NH), 7.39 (ddd, ^3J = 8.6 Hz, ^3J = 7.1 Hz, ^4J = 1.7 Hz, 1H, Ph H-4), 6.74-6.54 (m, 2H, Ph H-3,5), 4.33 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 2.92 (s, 3H, $HNC\underline{H_3}$), 1.39 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$).
^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.76 (OC=O), 152.09 (Ph C-2), 134.59 (Ph C-4), 131.61 (Ph C-6), 114.38 (Ph C-5), 110.76 (Ph C-3), 110.26 (Ph C-1), 60.23 ($O\underline{C}H_2CH_3$), 29.61 ($HN\underline{C}H_3$), 14.43 ($OCH_2\underline{C}H_3$).

HRMS (ESI), *m/z* calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025; found 180.1028.

2-Methylaminobenzylic alcohol (4)



4

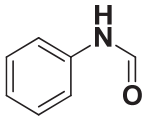
Obtained as a pale yellow oil, as reported in Table 1 (entries 1, 2, 6, and 7) (Chapter 3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (ddd, ^3J = 7.8 Hz, ^3J = 6.4 Hz, ^4J = 1.5 Hz, 1H, Ph H-4), 7.04 (d, J = 6.6 Hz, 1H, Ph H-6), 6.70 (t, J = 7.3 Hz, 2H, Ph H-3,5), 4.58 (s, 2H, HOC$\underline{H_2}$), 3.48 (br s, 2H, NH, OH), 2.86 (s, 3H, HNC$\underline{H_3}$).

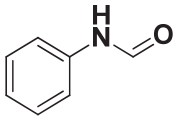
^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.54 (Ph C-2), 129.68 (Ph C-4), 128.98 (Ph C-6), 124.50 (Ph C-1), 116.50 (Ph C-5), 110.22 (Ph C-3), 64.52 (HO$\underline{C}H_2$), 30.37 (HN$\underline{C}H_3$).

HRMS (ESI), *m/z* calcd. for $C_8H_{12}NO$ $[M+H]^+$ 138.0919; found 138.0921.

***N*-Phenylformamide (5)**



s-*cis* rotamer



s-*trans* rotamer

5

By following the *General Procedure*, to a solution of phenyl isocyanate (0.119 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **5** was obtained in 93% yield (0.112 g) as a pale brown solid; mp 46 °C (lit.[98] 46-48 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

s-*cis* : s-*trans* = 76:24

s-*cis* rotamer:

^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.25 (s, 1H, HC=O), 7.56 (d, J = 7.4 Hz, 2H, Ph H-2,6), 7.31 (m, 2H, Ph H-3,5), 7.11 (m, 1H, Ph H-4).

^{13}C NMR (125 MHz, MeOH-d_4): δ = 161.61 (C=O), 139.95 (Ph C-1), 129.94 (Ph C-3,5), 125.56 (Ph C-4), 121.03 (Ph C-2,6).

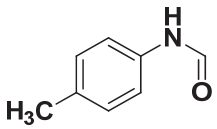
s-*trans* rotamer:

^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.70 (s, 1H, HC=O), 7.34 (m, 2H, Ph H-3,5), 7.17 (m, 2H, Ph H-2,6), 7.14 (m, 1H, Ph H-4).

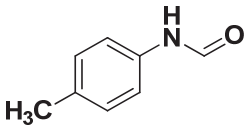
^{13}C NMR (125 MHz, MeOH-d_4): δ = 164.82 (C=O), 139.01 (Ph C-1), 130.65 (Ph C-3,5), 125.87 (Ph C-4), 119.57 (Ph C-2,6).

HRMS (ESI), *m/z* calcd. for C_7H_8NO $[M+H]^+$ 122.0606; found 122.0609.

***N*-*p*-Tolylformamide (6)**



s-*cis* rotamer



s-*trans* rotamer

6

By following the *General Procedure*, to a solution of *p*-tolyl isocyanate (0.133 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **6** was obtained in 89% yield (0.120 g) as a white solid; mp 53 °C (lit.[98] 50-54 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

s-*cis* : s-*trans* = 76:24

s-*cis* rotamer:

^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.21 (s, 1H, HC=O), 7.43 (d, *J* = 8.4 Hz, 2H, Ph H-2,6), 7.12 (d, *J* = 8.2 Hz, 2H, Ph H-3,5), 2.29 (s, 3H, CH_3).

^{13}C NMR (125 MHz, MeOH-d_4): δ = 161.45 (C=O), 136.34 (Ph C-1), 135.29 (Ph C-4), 130.35 (Ph C-3,5), 121.06 (Ph C-2,6), 20.91 (CH_3).

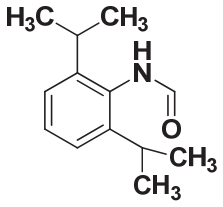
s-*trans* rotamer:

^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.62 (s, 1H, HC=O), 7.15 (d, *J* = 8.2 Hz, 2H, Ph H-3,5), 7.04 (d, *J* = 8.4 Hz, 2H, Ph H-2,6), 2.30 (s, 3H, CH_3).

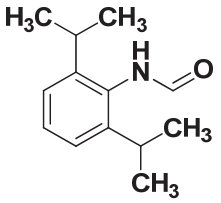
^{13}C NMR (125 MHz, MeOH-d_4): δ = 164.85 (C=O), 136.34 (Ph C-1), 135.77 (Ph C-4), 131.07 (Ph C-3,5), 119.82 (Ph C-2,6), 20.79 (CH_3).

HRMS (ESI), *m/z* calcd. for $C_8H_{10}NO$ $[M+H]^+$ 136.0762; found 136.0759.

***N*-(2,6-Diisopropylphenyl)formamide (7)**



s-*cis* rotamer



s-*trans* rotamer

7

By following the *General Procedure*, to a solution of 2,6-diisopropylphenyl isocyanate (0.203 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **7** was obtained in 95% yield (0.195 g) as a yellow solid; mp 161 °C (lit.[99] 160 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

s-*cis* : s-*trans* = 38:62

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (s, 1H, HC=O), 7.33 (d, *J* = 7.3 Hz, 1H, Ph H-4), 7.20 (d, *J* = 7.8 Hz, 2H, Ph H-3,5), 6.79 (br s, 1H, NH), 3.11 (quint, *J* = 6.9 Hz, 2H, C*H*$(CH_3)_2$), 1.21 (d, *J* = 6.9 Hz, 12H, CH(C*H*$_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.61 (C=O), 146.08 (Ph C-2,6), 129.28 (Ph C-1), 128.86 (Ph C-4), 123.58 (Ph C-3,5), 28.78 (*C*H$(CH_3)_2$), 23.62 (CH(*C*H$_3)_2$).

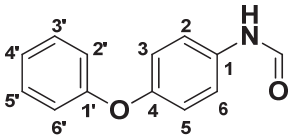
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 12.0 Hz, 1H, HC=O), 7.34 (d, *J* = 7.7 Hz, 1H, Ph H-4), 7.21 (d, *J* = 7.9 Hz, 2H, Ph H-3,5), 6.96 (br d, *J* = 12.0 Hz, 1H, NH), 3.21 (quint, *J* = 6.9 Hz, 2H, C*H*$(CH_3)_2$), 1.21 (d, *J* = 6.9 Hz, 12H, CH(C*H*$_3)_2$).

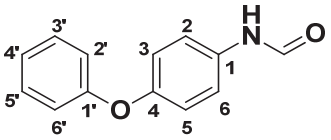
^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.04 (C=O), 146.74 (Ph C-2,6), 129.72 (Ph C-1), 128.99 (Ph C-4), 123.82 (Ph C-3,5), 28.37 (*C*H$(CH_3)_2$), 23.62 (CH(*C*H$_3)_2$).

HRMS (ESI), *m/z* calcd. for $C_{13}H_{20}NO$ $[M+H]^+$ 206.1545; found 206.1549.

***N*-(4-Phenoxyphenyl)formamide (8)**



s-*cis* rotamer



s-*trans* rotamer

8

By following the *General Procedure*, to a solution of 4-phenoxyphenyl isocyanate (0.211 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **8** was obtained in 94% yield (0.200 g) as a brown solid; mp 51 °C, after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

s-*cis* : s-*trans* = 53:47

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H, HC=O), 7.79 (br s, 1H, NH), 7.51 (d, *J* = 8.8 Hz, 2H, Ph H-2,6), 7.35 (m, 2H, Ph H-3',5'), 7.09 (m, 1H, Ph H-4'), 6.98 (m, 4H, Ph 3,5,2',6').

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.16 (C=O), 157.23 (Ph C-1'), 153.79 (Ph C-4), 132.21 (Ph C-1), 129.72 (Ph C-3',5'), 123.16 (Ph C-4'), 121.70 (Ph C-2,6), 119.51 (Ph 3,5), 118.60 (Ph C-2',6').

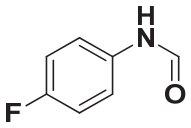
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (br d, *J* = 9.1 Hz, 1H, NH), 8.59 (d, *J* = 11.4 Hz, 1H, HC=O), 7.32 (m, 2H, Ph H-3',5'), 7.12 (m, 1H, Ph H-4'), 7.08 (m, 2H, Ph H-2,6), 7.01 (m, 2H, Ph 3,5), 7.00 (m, 2H, Ph 2',6').

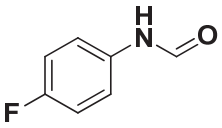
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.07 (C=O), 157.00 (Ph C-1'), 154.80 (Ph C-4), 131.89 (Ph C-1), 129.80 (Ph C-3',5'), 123.43 (Ph C-4'), 120.97 (Ph C-2,6), 120.03 (Ph 3,5), 118.45 (Ph C-2',6').

HRMS (ESI), *m/z* calcd. for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0868; found 214.0869.

***N*-(4-Fluorophenyl)formamide (9)**



s-*cis* rotamer



s-*trans* rotamer

9

By following the *General Procedure*, to a solution of 4-fluorophenyl isocyanate (0.137 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **9** was obtained in 90% yield (0.125 g) as a brown solid; mp 65 °C (lit.[100] 66 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 7:3).

s-*cis* : s-*trans* = 60:40

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1H, HC=O), 7.30 (br s, 1H, NH), 7.51 (m, 2H, Ph H-2,6), 7.08 (m, 2H, Ph H-3,5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.91 (Ph C-1), 159.73 (C=O), 132.61 (Ph C-4), 121.89 (Ph C-2,6), 115.96 (Ph C-3,5).

$^1J(^{13}C,^{19}F)$ = 243,6 Hz, $^2J(^{13}C,^{19}F)$ = 21,8 Hz, $^3J(^{13}C,^{19}F)$ = 8,1 Hz, $^4J(^{13}C,^{19}F)$ = 2,3 Hz.

s-*trans* rotamer:

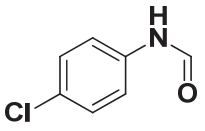
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 11.4 Hz, 1H, HC=O), 7.92 (br s, 1H, NH), 7.05 (m, 2H, Ph H-2,6), 7.02 (m, 2H, Ph H-3,5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.61 (C=O), 160.91 (Ph C-1), 132.82 (Ph C-4), 121.47 (Ph C-2,6), 116.76 (Ph C-3,5).

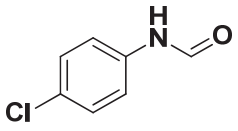
$^1J(^{13}C,^{19}F)$ = 242,4 Hz, $^2J(^{13}C,^{19}F)$ = 23,0 Hz, $^3J(^{13}C,^{19}F)$ = 8,1 Hz, $^4J(^{13}C,^{19}F)$ = 3,5 Hz.

HRMS (ESI), *m/z* calcd. for C_7H_7FNO $[M+H]^+$ 140.0512; found 140.0510.

***N*-(4-Chlorophenyl)formamide (10)**



s-*cis* rotamer



s-*trans* rotamer

10

By following the *General Procedure*, to a solution of 4-chlorophenyl isocyanate (0.153 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **10** was obtained in 84% yield (0.130 g) as a pale brown solid; mp 101 °C (lit.[101] 100-102 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 7:3).

s-*cis* : s-*trans* = 61:39

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (s, 1H, HC=O), 7.50 (d, *J* = 8.7 Hz, 2H, Ph H-2,6), 7.30 (d, *J* = 8.7 Hz, 2H, Ph H-3,5), 7.19 (br s, 1H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.92 (C=O), 135.20 (Ph C-1), 129.32 (Ph C-2,6), 121.24 (Ph C-3,5).

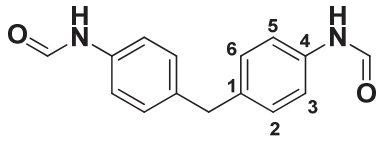
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 11.4 Hz, 1H, HC=O), 7.69 (br s, 1H, NH), 7.34 (d, *J* = 8.6 Hz, 2H, Ph H-3,5), 7.03 (d, *J* = 8.6 Hz, 2H, Ph H-2,6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.16 (C=O), 135.42 (Ph C-1), 130.04 (Ph C-2,6), 120.32 (Ph C-3,5).

HRMS (ESI), *m/z* calcd. for C_7H_7ClNO $[M+H]^+$ 156.0216; found 156.0217.

***N,N'*-(Methylenebis(4,1-phenylene))diformamide (11)**



11

By following the *General Procedure*, to a solution of 4,4'-methylenebis(phenyl isocyanate) (0.250 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.876 g, 3.0 mmol, 3.0 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (3.0 mL, 3.0 mmol, 3.0 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **11** was obtained in 86% yield (0.218 g) as a brown solid; mp 140-142 °C, after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 74:26

s-*cis* rotamer:

^{1}H NMR (500 MHz, Acetone-d_6): δ = 9.25 (s, 2H, NH), 8.33 (s, 2H, HC=O), 7.58 (m, 4H, Ph H-3,5), 7.17 (m, 4H, Ph H-2,6), 3.90 (s, 2H, CH_2).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 160.46 (C=O), 138.55 (Ph C-1), 138.09 (Ph C-4), 130.62 (Ph C-2,6), 120.97 (Ph C-3,5), 41.85 (CH_2).

s-*trans* rotamer:

^{1}H NMR (500 MHz, Acetone-d_6): δ = 9.13 (s, 2H, NH), 8.74 (d, *J* = 11.1 Hz, 2H, HC=O), 7.21 (m, 4H, Ph H-2,6), 7.17 (m, 4H, Ph H-3,5), 3.92 (s, 2H, CH_2).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 163.25 (C=O), 138.55 (Ph C-1), 138.46 (Ph C-4), 131.31 (Ph C-2,6), 119.75 (Ph C-3,5), 41.72 (CH_2).

HRMS (ESI), *m/z* calcd. for $C_{15}H_{15}N_2O_2$ $[M+H]^+$ 255.1134; found 255.1137.

***N*-(Thiophen-2-yl)formamide (12)**

s-*cis* rotamer s-*trans* rotamer

12

By following the *General Procedure*, to a solution of 3-thienyl isocyanate (0.125 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **12** was obtained in 92% yield (0.117 g) as a brown solid; mp 57 °C (lit.[102] 57 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 74:26

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H, HC=O), 7.60 (d, *J* = 3.2 Hz, 1H, Th H-3), 7.55 (br s, 1H, NH), 7.25 (m, 1H, Th H-4), 7.02 (d, *J* = 5.2 Hz, 1H, Th H-5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.01 (C=O), 134.09 (Th C-2), 124.89 (Th C-4), 120.81 (Th C-5), 111.38 (Th C-3).

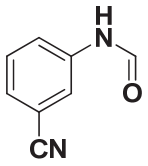
s-*trans* rotamer:

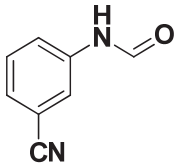
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 11.6 Hz, 1H, HC=O), 7.67 (br s, 1H, NH), 7.34 (m, 1H, Th H-4), 6.92 (d, *J* = 3.9 Hz, 1H, Th H-5), 6.87 (d, *J* = 1.7 Hz, 1H, Th H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.58 (C=O), 135.04 (Th C-2), 126.87 (Th C-4), 121.05 (Th C-5), 110.33 (Th C-3).

HRMS (ESI), *m/z* calcd. for C_5H_6NOS $[M+H]^+$ 128.0170; found 128.0173.

***N*-(3-Cyanophenyl)formamide (13)**





s-*cis* rotamer s-*trans* rotamer

13

By following the *General Procedure*, to a solution of 3-cyanophenyl isocyanate (0.144 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **13** was obtained in 83% yield (0.121 g) as a white solid; mp 147 °C, after purification with silica gel chromatography (eluent hexane:EtOAc 7:3).

s-*cis* : s-*trans* = 85:15

s-*cis* rotamer:

^{1}H NMR (500 MHz, Acetone-d_6): δ = 9.67 (br s, 1H, NH), 8.43 (s, 1H, HC=O), 8.17 (m, 1H, Ph H-2), 7.89 (d, *J* = 8.2 Hz, 1H, Ph H-6), 7.56 (m, 1H, Ph H-5), 7.50 (d, *J* = 7.7 Hz, 1H, Ph H-4).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 161.12 (C=O), 140.77 (Ph C-1), 131.75 (Ph C-5), 128.69 (Ph C-4), 125.02 (Ph C-6), 123.63 (Ph C-2), 119.77 (CN), 114.13 (Ph C-3).

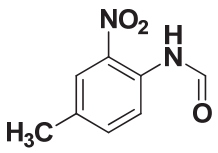
s-*trans* rotamer:

^{1}H NMR (500 MHz, Acetone-d_6): δ = 9.47 (br d, *J* = 10.6 Hz, 1H, NH), 8.95 (s, 1H, HC=O), 7.70 (m, 1H, Ph H-2), 7.60 (m, 1H, Ph H-6), 7.56 (m, 1H, Ph H-5), 7.50 (d, *J* = 7.7 Hz, 1H, Ph H-4).

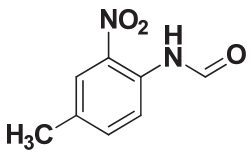
^{13}C NMR (125 MHz, Acetone-d_6): δ = 163.16 (C=O), 141.14 (Ph C-1), 132.30 (Ph C-5), 128.69 (Ph C-4), 124.93 (Ph C-6), 123.55 (Ph C-2), 119.59 (CN), 114.73 (Ph C-3).

HRMS (ESI), *m/z* calcd. for $C_8H_7N_2O$ $[M+H]^+$ 147.0558; found 147.0555.

***N*-(4-Methyl-2-nitrophenyl)formamide (14)**



s-*cis* rotamer



s-*trans* rotamer

14

By following the *General Procedure*, to a solution of 4-methyl-2-nitrophenyl isocyanate (0.178 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **14** as obtained in 83% yield (0.149 g) as a yellow solid; mp 125 °C (lit.[103] 124-125 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 7:3).

s-*cis* : s-*trans* = 77:23

s-*cis* rotamer:

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.91 (s, 1H, HC=O), 7.85 (d, *J* = 2.0 Hz, 1H, Ph H-3), 7.83 (d, *J* = 8.4 Hz, 1H, Ph H-6), 7.52 (dd, ^3J = 8.9 Hz, ^4J =2.0 Hz, 1H, Ph H-5), 2.35 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.05 (C=O), 139.76 (Ph C-2), 135.20 (Ph C-5), 133.42 (Ph C-4), 130.66 (Ph C-1), 124.90 (Ph C-3), 123.96 (Ph C-6), 19.87 (CH_3).

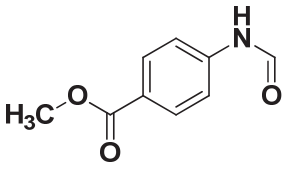
s-*trans* rotamer:

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.85 (d, *J* = 2.0 Hz, 1H, Ph H-3), 7.70 (d, *J* = 8.3 Hz, 1H, Ph H-6), 7.36 (d, *J* = 7.9 Hz, 1H, Ph H-5), 2.37 (s, 3H, CH_3).

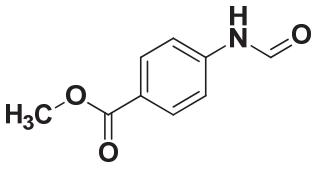
^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.49 (C=O), 139.76 (Ph C-2), 133.42 (Ph C-4), 130.66 (Ph C-1), 129.31 (Ph C-5), 125.61 (Ph C-6), 124.90 (Ph C-3), 20.92 (CH_3).

HRMS (ESI), *m/z* calcd. for $C_8H_9N_2O_3$ $[M+H]^+$ 181.0613; found 181.0611.

4-Methoxycarbonyl formamide (15)



s-*cis* rotamer



s-*trans* rotamer

15

By following the *General Procedure*, to a solution of 4-(methoxycarbonyl)phenyl isocyanate (0.177 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in

dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **15** was obtained in 80% yield (0.143 g) as a white solid; mp 123 °C (lit.[104] 123-125 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

s-*cis* : s-*trans* = 55:45

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (s, 1H, HC=O), 8.02 (m, 2H, Ph H-3,5), 7.63 (d, *J* = 8.6 Hz, 2H, Ph H-2,6), 7.58 (br s, 1H, NH), 3.90 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.48 (OC=O), 159.01 (HC=O), 140.88 (Ph C-1), 130.90 (Ph C-3,5), 126.12 (Ph C-4), 119.04 (Ph C-2,6), 52.14 (CH_3).

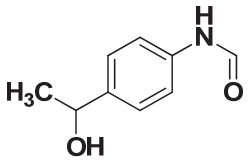
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.85 (d, *J* = 11.2 Hz, 1H, HC=O), 8.04 (m, 2H, Ph H-3,5), 7.13 (d, *J* = 8.5 Hz, 2H, Ph H-2,6), 3.91 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.27 (OC=O), 161.93 (HC=O), 140.77 (Ph C-1), 131.55 (Ph C-3,5), 126.60 (Ph C-4), 117.15 (Ph C-2,6), 52.23 (CH_3).

HRMS (ESI), *m/z* calcd. for $C_9H_{10}NO_3$ $[M+H]^+$ 180.0661; found 180.0659.

N-[4-(1-Hydroxyethyl)phenyl]formamide (16)



16

By following the *General Procedure*, to a solution of 4-acetylphenyl isocyanate (0.161 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.584 g, 2.0 mmol, 2.0 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (2.0 mL, 2.0 mmol, 2.0 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **16** was obtained in 87% yield (0.144 g) as

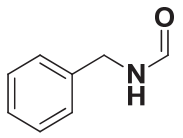
a brown solid; mp 134-136 °C, after purification with silica gel chromatography (eluent hexane:EtOAc 8:2).

^{1}H NMR (500 MHz, Acetone-d_6): δ = 8.21 (s, 1H, HC=O), 7.47 (d, *J* = 8.5 Hz, 2H, Ph H-2,6), 7.28 (d, *J* = 8.5 Hz, 2H, Ph H-3,5), 4.79 (q, *J* = 6.2 Hz, 1H, C*H*(OH)CH_3), 4.13 (s, 1H, OH), 1.38 (d, *J* = 6.4 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 142.53 (Ph C-4), 140.22 (Ph C-1), 127.23 (Ph C-3,5), 119.78 (Ph C-2,6), 70.26 (*C*H(OH)CH_3), 26.83 (CH_3).

HRMS (ESI), *m/z* calcd. for $C_9H_{12}NO_2$ $[M+H]^+$ 166.0868; found 166.0865.

***N*-Benzylformamide (17)**



17

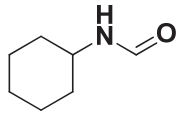
By following the *General Procedure*, to a solution of benzyl isocyanate (0.133 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **17** was obtained in 88% yield (0.119 g) as a white solid; mp 60 °C (lit.[98] 60-62 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.31 (t, *J* = 7.5 Hz, 2H, Ph H-3,5), 7.25 (d, *J* = 8.2 Hz, 2H, Ph H-2,6), 7.22 (d, *J* = 7.3 Hz, 1H, Ph H-4), 6.47 (s, 1H, NH), 4.23 (s, 2H, CH_2).

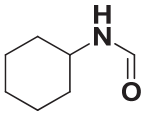
^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.12 (C=O), 140.96 (Ph C-1), 128.27 (Ph C-3,5), 127.03 (Ph C-2,6), 126.60 (Ph C-4), 42.97 (CH_2).

HRMS (ESI), *m/z* calcd. for $C_8H_{10}NO$ $[M+H]^+$ 136.0762; found 136.0766.

***N*-Cyclohexylformamide (18)**



s-*trans* rotamer



s-*cis* rotamer

18

By following the *General Procedure*, to a solution of cyclohexyl isocyanate (0.125 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **18** was obtained in 84% yield (0.107 g) as a brown solid; mp 40 °C (lit.[105] 38-40 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*trans* : s-*cis* = 80:20

s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (s, 1H, HC=O), 5.82 (br s, 1H, NH), 3.82 (m, 1H, Cy H-1), 1.88/1.33 (m, 4H, Cy H-2,6), 1.69/1.15 (m, 4H, Cy H-3,5), 1.62 (m, 2H, Cy H-4).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.39 (C=O), 47.04 (Cy C-1), 32.90 (Cy C-2,6), 25.30 (Cy C-3,5), 24.65 (Cy C-4).

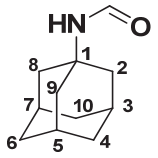
s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1H, HC=O), 5.99 (br s, 1H, NH), 3.28 (s, 1H, Cy H-1), 1.85/1.27 (m, 4H, Cy H-2,6), 1.69/1.15 (m, 4H, Cy H-3,5), 1.62 (m, 2H, Cy H-4).

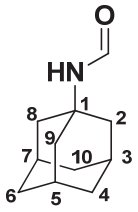
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.60 (C=O), 50.99 (Cy C-1), 34.56 (Cy C-2,6), 24.90 (Cy C-3,5), 24.65 (Cy C-4).

HRMS (ESI), *m/z* calcd. for $C_7H_{14}NO$ $[M+H]^+$ 128.1075; found 128.1074.

***N*-(Adamantan-1-yl)formamide (19)**



s-*cis* rotamer



s-*trans* rotamer

19

By following the *General Procedure*, to a solution of 1-adamantyl isocyanate (0.177 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **19** was obtained in 92% yield (0.165 g) as a pale yellow solid; mp 134 °C (lit.[106] 134 °C), after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 65:35

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 12.4 Hz, 1H, HC=O), 5.75 (br s, 1H, NH), 2.13 (m, 3H, Adam H-3,5,7), 1.83 (d, *J* = 2.6 Hz, 6H, Adam H-2,8,9), 1.71/1.65 (m, 6H, Adam H-4,6,10).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.03 (C=O), 50.68 (Adam C-1), 44.19 (Adam C-2,8,9), 35.84 (Adam C-4,6,10), 29.24 (Adam C-3,5,7).

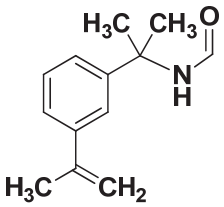
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 1.9 Hz, 1H, HC=O), 5.12 (br s, 1H, NH), 2.08 (m, 3H, Adam H-3,5,7), 2.02 (d, *J* = 2.9 Hz, 6H, Adam H-2,8,9), 1.68 (m, 6H, Adam H-4,6,10).

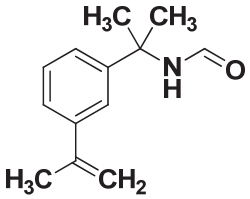
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.21 (C=O), 52.14 (Adam C-1), 41.81 (Adam C-2,8,9), 36.20 (Adam C-4,6,10), 29.35 (Adam C-3,5,7).

HRMS (ESI), *m/z* calcd. for $C_{11}H_{18}NO$ $[M+H]^+$ 180.1388; found 180.1386.

***N*-(2-(3-(Prop-1-en-2-yl)phenyl)propan-2-yl)formamide (20)**



s-*cis* rotamer



s-*trans* rotamer

20

By following the *General Procedure*, to a solution of 3-isopropenyl-α,α-dimethylbenzyl isocyanate (0.201 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **20** was obtained in 87% yield (0.177 g) as a brown oil, after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 70:30

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (s, 1H, HC=O), 7.48 (s, 1H, Ph H-2), 7.40-7.29 (m, 3H, Ph H-4,5,6), 6.56 (br d, *J* = 11.7 Hz, 1H, NH), 5.35-5.12 (d, 2H, $C\underline{H_2}$=C(CH_3)Ph), 2.15 (s, 3H, CH_2=C($C\underline{H_3}$)Ph), 1.69 (s, 6H, HNC($C\underline{H_3}$)$_2$Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.37 (C=O), 146.27 (Ph C-1), 143.04 (Ph C-3), 141.77 (CH_2=$\underline{C}$(CH_3)Ph), 128.60 (Ph C-5), 124.59 (Ph C-4), 124.27 (Ph C-6), 122.30 (Ph C-2), 113.12 ($\underline{C}H_2$=C(CH_3)Ph), 56.39 (HN$\underline{C}$(CH_3)$_2$Ph), 31.20 (HNC($\underline{C}H_3$)$_2$Ph), 21.88 (CH_2=C($\underline{C}H_3$)Ph).

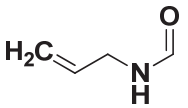
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (s, 1H, HC=O), 7.48 (s, 1H, Ph H-2), 7.40-7.29 (m, 3H, Ph H-4,5,6), 6.06 (br s, 1H, NH), 5.35-5.09 (d, 2H, $C\underline{H_2}$=C(CH_3)Ph), 2.15 (s, 3H, CH_2=C($C\underline{H_3}$)Ph), 1.75 (s, 6H, HNC($C\underline{H_3}$)$_2$Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.32 (C=O), 145.98 (Ph C-1), 143.33 (Ph C-3), 141.43 (CH_2=$\underline{C}$(CH_3)Ph), 128.35 (Ph C-5), 124.19 (Ph C-6), 123.81 (Ph C-4), 121.88 (Ph C-2), 112.67 ($\underline{C}H_2$=C(CH_3)Ph), 56.21 (HN$\underline{C}$(CH_3)$_2$Ph), 29.10 (HNC($\underline{C}H_3$)$_2$Ph), 21.88 (CH_2=C($\underline{C}H_3$)Ph).

HRMS (ESI), *m/z* calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1388; found 204.1390.

***N*-Allylformamide (21)**



s-*cis* rotamer

s-*trans* rotamer

21

By following the *General Procedure*, to a solution of allyl isocyanate (0.083 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **21** was obtained in 91% yield (0.077 g) as a colorless liquid, after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 84:16

s-*cis* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (s, 1H, HC=O), 6.18 (br s, 1H, NH), 5.80 (m, 1H, CH_2=C*H*CH_2), 5.18/5.13 (m, 2H, C*H*$_2$=CHCH_2), 3.89 (t, *J* = 5.8 Hz, 2H, CH_2=CHC*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.18 (C=O), 133.39 (CH_2=*C*HCH_2), 116.54 (*C*H_2=CHCH_2), 40.34 (CH_2=CH*C*H_2).

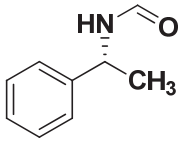
s-*trans* rotamer:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 12.0 Hz, 1H, HC=O), 6.10 (br s, 1H, NH), 5.83 (m, 1H, CH_2=C*H*CH_2), 5.22/5.17 (m, 2H, C*H*$_2$=CHCH_2), 3.82 (m, 2H, CH_2=CHC*H*$_2$).

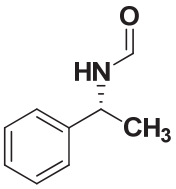
^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.89 (C=O), 134.23 (CH_2=*C*HCH_2), 116.78 (*C*H_2=CHCH_2), 43.88 (CH_2=CH*C*H_2).

HRMS (ESI), *m/z* calcd. for C_4H_8NO $[M+H]^+$ 86.0606; found 86.0603.

(*R*)-*N*-(1-Phenylethyl)formamide (22)



s-*cis* rotamer



s-*trans* rotamer

22

By following the *General Procedure*, to a solution of (R)-1-phenylethyl isocyanate (0.147 g, 1.0 mmol, 1.0 equiv) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)$_3$H (1.5 mL, 1.5 mmol, 1.5 equiv) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **22** was obtained in 93% yield (0.139 g) as a brown oil; $[\alpha]_D^{20}$ +158 ° (*c* 0.5, $CHCl_3$; lit.[107] +161.4 °, *c* 0.5, $CHCl_3$), after purification with silica gel chromatography (eluent hexane:EtOAc 9:1).

s-*cis* : s-*trans* = 91:9

s-*cis* rotamer:

^{1}H NMR (500 MHz, Acetone-d_6): δ = 8.13 (s, 1H, HC=O), 7.70 (br s, 1H, NH), 7.37 (m, 2H, Ph H-2,6), 7.32 (t, *J* = 7.6 Hz, 2H, Ph H-3,5), 7.23 (m, 1H, Ph H-4), 5.13 (quint, *J* = 7.2 Hz, 1H, HNC*H*CH$_3$), 1.44 (d, *J* = 7.0 Hz, 3H, HNCHC*H*$_3$).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 161.38 (C=O), 145.70 (Ph C-1), 129.87 (Ph C-3,5), 128.36 (Ph C-4), 127.58 (Ph C-2,6), 48.54 (HN*C*HCH$_3$), 23.34 (HNCH*C*H$_3$).

s-*trans* rotamer:

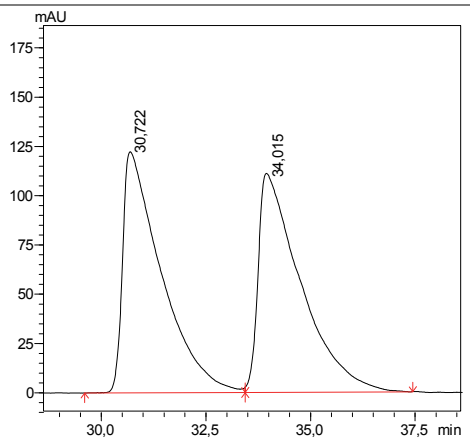
^{1}H NMR (500 MHz, Acetone-d_6): δ = 8.17 (d, *J* = 11.6 Hz, 1H, HC=O), 7.70 (br s, 1H, NH), 7.37 (m, 2H, Ph H-2,6), 7.32 (t, *J* = 7.6 Hz, 2H, Ph H-3,5), 7.23 (m, 1H, Ph H-4), 4.80 (m, 1H, HNC*H*CH$_3$), 1.52 (d, *J* = 6.9 Hz, 3H, HNCHC*H*$_3$).

^{13}C NMR (125 MHz, Acetone-d_6): δ = 165.14 (C=O), 146.24 (Ph C-1), 130.06 (Ph C-3,5), 128.58 (Ph C-4), 127.41 (Ph C-2,6), 52.77 (HN*C*HCH$_3$), 24.47 (HNCH*C*H$_3$).

HRMS (ESI), *m/z* calcd. for $C_9H_{12}NO$ $[M+H]^+$ 150.0919; found 150.0922.

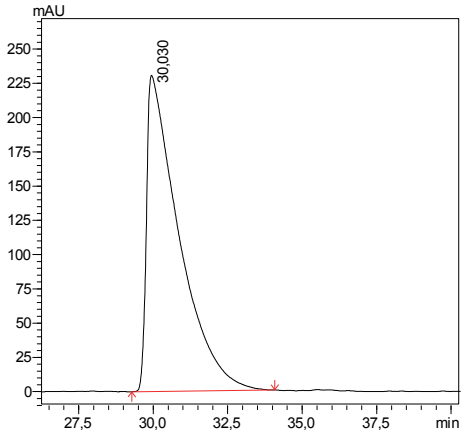
HPLC Chiralpak® IA; λ = 220 nm; *n*-hexane/*i*-propanol 97/3; flow rate = 0.75 mL/min.

Racemate



Peaks	Retention time (min)	Area	Area (%)
1	30.722	7870950	50.110
2	34.015	7836320	49.890
Total		15707270	100.000

Enantioenriched



Peaks	Retention time (min)	Area	Area (%)
1	30.030	17445937	100.000

CHAPTER 6. REFERENCES

6. REFERENCES

(1) Graul, A.; Castaner, J. *Drugs Future* **1997**, *22*, 956.

(2) Patchett, A. A. *J. Med. Chem.* **1993**, *36*, 2051.

(3) de Gasparo, M.; Whitebread, S. *Regul. Pept.* **1995**, *59*, 303.

(4) Ananthanarayanan, V. S.; Tetreault, S.; Saint-Jean, A. *J. Med. Chem.* **1993**, *36*, 1324.

(5) Han, S. Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.

(6) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.

(7) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2.

(8) Pettit, G.; Kalnins, M.; Liu, T.; Thomas, E.; Parent, K. *J. Org. Chem.* **1961**, *26*, 2563.

(9) Shinohara, T.; Takeda, A.; Toda, J.; Kohno, M.; Sano, T. *Heterocycles* **1999**, *51*, 119.

(10) Czifrák, K.; Gyollai, V.; Koever, K. E.; Somsak, L. *Carbohydr. Res.* **2011**, *346*, 2104.

(11) Ding, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9226.

(12) Yang, Y.; Huang, H.; Wu, L.; Liang, Y. *Org. Biomol. Chem.* **2014**, *12*, 5351.

(13) Wang, X.; Wang, Q.-G.; Luo, Q.-L. *Synthesis* **2015**, 49.

(14) Nandra, G. S.; Pang, P. S.; Porter, M. J.; Elliott, J. M. *Org. Lett.* **2005**, *7*, 3453.

(15) Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2094.

(16) Kumar, G. S.; Maheswari, C. U.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11748.

(17) Armanino, N.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 6814.

(18) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.

(19) Wang, Z.-G.; Lu, M. *RSC Adv.* **2014**, *4*.

(20) Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synthesis* **2003**, 2317.

(21) Ganapati-Reddy, P.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.

(22) Deutsch, J.; Eckelt, R.; Koeckritz, A.; Martin, A. *Tetrahedron* **2009**, *65*, 10365.

(23) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2010**, *51*, 4186.

(24) Saidi, O.; Bamford, M. J.; Blacker, A. J.; Lynch, J.; Marsden, S. P.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 5804.

(25) Ortega, N.; Richter, C.; Glorius, F. *Org. Lett.* **2013**, *15*, 1776.

(26) Motokura, K.; Takahashi, N.; Kashiwame, D.; Yamaguchi, S.; Miyaji, A.; Baba, T. *Catal. Sci. Technol.* **2013**, *3*, 2392.

(27) Choi, Y.-S.; Shim, Y. N.; Lee, J.; Yoon, J. H.; Hong, C. S.; Cheong, M.; Kim, H. S.; Jang, H. G.; Lee, J. S. *Appl. Catal. A* **2011**, *404*, 87.

(28) Díaz, D. J.; Darko, A. K.; McElwee-White, L. *Eur. J. Org. Chem.* **2007**, 4453.

(29) B. Gabriele, G.; Salerno, R.; Mancuso, M.; Costa, J. *Org. Chem.* **2004**, *69*, 4741.

(30) Saegusa, T.; Kobayashi, S.; Hirota, K.; Ito, Y. *Tetrahedron Lett.* **1966**, *7*, 6125.

(31) Dombek, B. D.; Angelici, R. J. *J. Catal.* **1977**, *48*, 433.

(32) Yoshida, Y.; Asano, S.; Inoue, S. *Chem. Lett.* **1984**, 1073.

(33) Bitsi, G.; Jenner, G. *J. Organomet. Chem.* **1987**, *330*, 429.

(34) Durand, D.; Lassau, C. *Tetrahedron Lett.* **1969**, *10*, 2329.

(35) Martin, W. E.; Farona, M. F. *J. Organomet. Chem.* **1981**, *206*, 393.

(36) Hamada, E.; Yokoyama, T.; Usui, Y. *(Mitsubishi Rayon Co., Ltd., Japan), JP 2002128747 A* **2002**.

(37) Li, W.; Wu, X.-F. *Chem. Eur. J.* **2015**, *21*, 1.

(38) Zhang, C.; Xu, Z.; Shen, T.; Wu, G.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 2362.

(39) Wessely, F.; Swoboda, W. *Monatsh. Chem.* **1951**, *82*, 621.

(40) Finholt, A. E.; Anderson, C. D.; Agre, C. L. *J. Org. Chem.* **1953**, *18*, 1338.

(41) Tan, M.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 4912.

(42) Turnbull, K.; Krein, D. M. *Synthesis* **1999**, 391.

(43) Lorenz, D. H.; Becker, E. I. *J. Org. Chem.* **1963**, *28*, 1707.

(44) Noltes, J. G.; Janssen, M. J. *J. Organomet. Chem.* **1964**, *1*, 346.

(45) Howell, H. G. *Synth. Commun.* **1983**, *13*, 635.

(46) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405.

(47) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2005**, *8*, 1.

(48) Marek, I. *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Weinheim, 2002.

(49) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.

(50) Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Ed.* **1976**, *15*, 333.

(51) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1976**, *98*, 262.

(52) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(53) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(54) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.

(55) Wang, J.; Zhang, Y.; Xu, Y.; Lin, Z. *Gaodeng Xuexiao Huaxue Xuebao* **1989**, *10*, 263.

(56) Wang, J.; Zhang, Y.; Xu, Y.; Bai, G. *Youji Huaxue* **1989**, *9*, 41.

(57) Zablocka, M.; Delest, B.; Igau, A.; Skowronska, A.; Majoral, J. P. *Tetrahedron Lett.* **1997**, *38*, 5997.

(58) Schedler, D. J. A.; Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 5035.

(59) Schedler, D. J. A.; Li, J.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 4115.

(60) Ganem, B.; Franke, R. R. *J. Org. Chem.* **2007**, *72*, 3981.

(61) Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597.

(62) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

(63) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408.

(64) Spletstoser, J. T.; White, J. M.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 2787.

(65) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130.

(66) Negishi, E.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett.* **1984**, *25*, 3407.

(67) Makabe, H.; Negishi, E. *Eur. J. Org. Chem.* **1999**, 969.

(68) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257.

(69) Huang, Z.; Negishi, E.-i. *Org. Lett.* **2006**, *8*, 3675.

(70) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390.

(71) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

(72) *Sigma-Aldrich catalog* **2010**.

(73) Morin, J.; Zhao, Y.; Snieckus, V. *Org. Lett.* **2013**, *15*, 4102.

(74) Groger, D.; Floss, H. G. *Alkaloids* **1998**, *50*, 171.

(75) Hofmann, A. *Pharmacology* **1978**, *16 Suppl 1*, 1.

(76) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

(77) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950.

(78) Sato, T.; Chida, N. *Org. Biomol. Chem.* **2014**, *12*, 3147.

(79) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. *Chem. Eur. J.* **2014**, *20*, 17565.

(80) Xiao, K.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 8314.

(81) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457.

(82) Ulrich, H. *Chemistry and Technology of Isocyanates*; Wiley: New York, 1996.

(83) Spino, C.; Joly, M.-A.; Godbout, C.; Arbour, M. *J. Org. Chem.* **2005**, *70*, 6118.

(84) Spyropoulos, C.; Kokotos, C. G. *J. Org. Chem.* **2014**, *79*, 4477.

(85) Dubé, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

(86) Le, H. V.; Ganem, B. *Org. Lett.* **2011**, *13*, 2584.

(87) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637.

(88) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.

(89) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373.

(90) Marek, I.; Chinkov, N.; Levin, A. *Synlett* **2006**, 0501.

(91) Negishi, E.-i.; Takahashi, T. *Synthesis* **1988**, 1.

(92) Ulikowski, A.; Furman, B. *Org. Lett.* **2016**, *18*, 149.

(93) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 904.

(94) Piperno, A.; Carnovale, C.; Giofrè, S. V.; Iannazzo, D. *Tetrahedron Lett.* **2011**, *52*, 6880.

(95) Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez de María, P.; Alcántara, A. R. *ChemSusChem.* **2012**, *5*, 1369.

(96) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

(97) Miyauchi, M.; Endoh, Y.; Uematsu, T. *Bull. Environ. Contam. Toxicol.* **1995**, *55*, 446.

(98) Ma'mani, L.; Sheykhan, M.; Heydari, A.; Faraji, M.; Yamini, Y. *Applied Catalysis A: General* **2010**, *377*, 64.

(99) Kamer, P. C. J.; Nolte, R. J. M.; Drenth, W. *J. Am. Chem. Soc.* **1988** *110*, 6818

(100) Rheinboldt, H.; Levy, A. *Univ. Sao Paulo, Faculdade filosof., cienc. e letras, Bol. No. 129, Quimica* **1951**, *3*, 69.

(101) Wang, Y. X.; Jia, L.; Shi, Z. *Chinese Chemical Letters* **2003**, *14*, 561.

(102) Outurquin, F. *Bull. Soc. Chem. Fr.* **1976**, 883.

(103) Harvey, I. W.; McFarlane, M.; Moody, D. J.; Smith, D. M. *J Chem Soc, Perkin Trans 1* **1988**, 681.

(104) Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 1983.

(105) Azuaje, J.; Coelho, A.; Maatougui, A. E.; Blanco, J. M.; Sotelo, E. *ACS Comb. Sci.* **2011**, *13*, 89.

(106) Wanka, L.; Cabrele, C.; Vanejews, M.; Schreiner, P. R. *Eur. J. Org. Chem.* **2007**, *2007*, 1474.

(107) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870.

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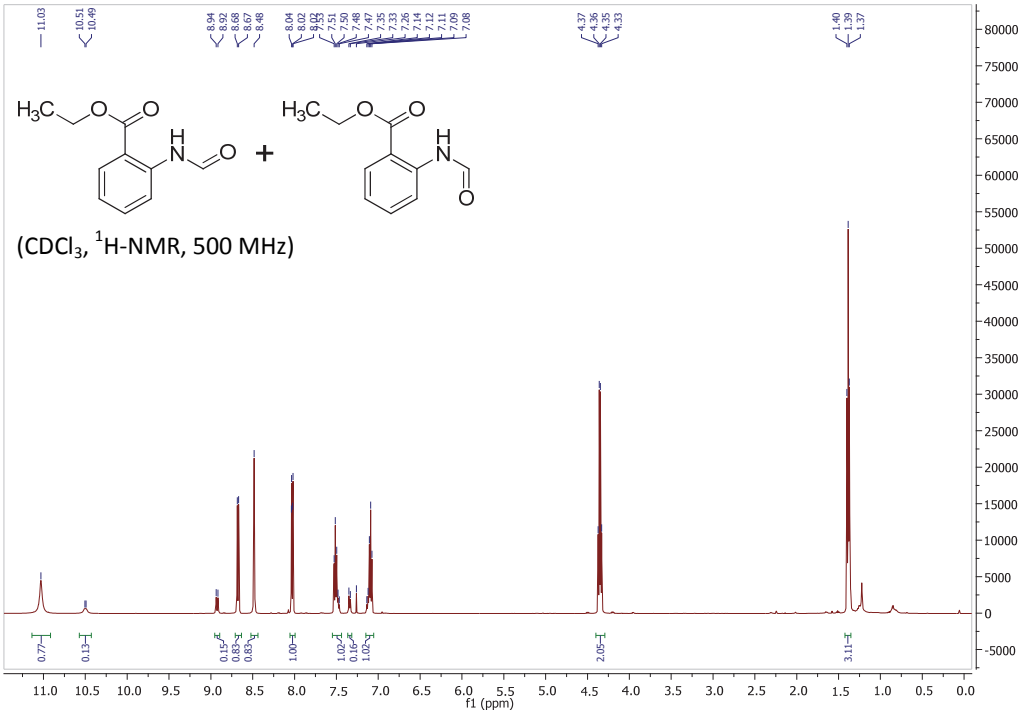
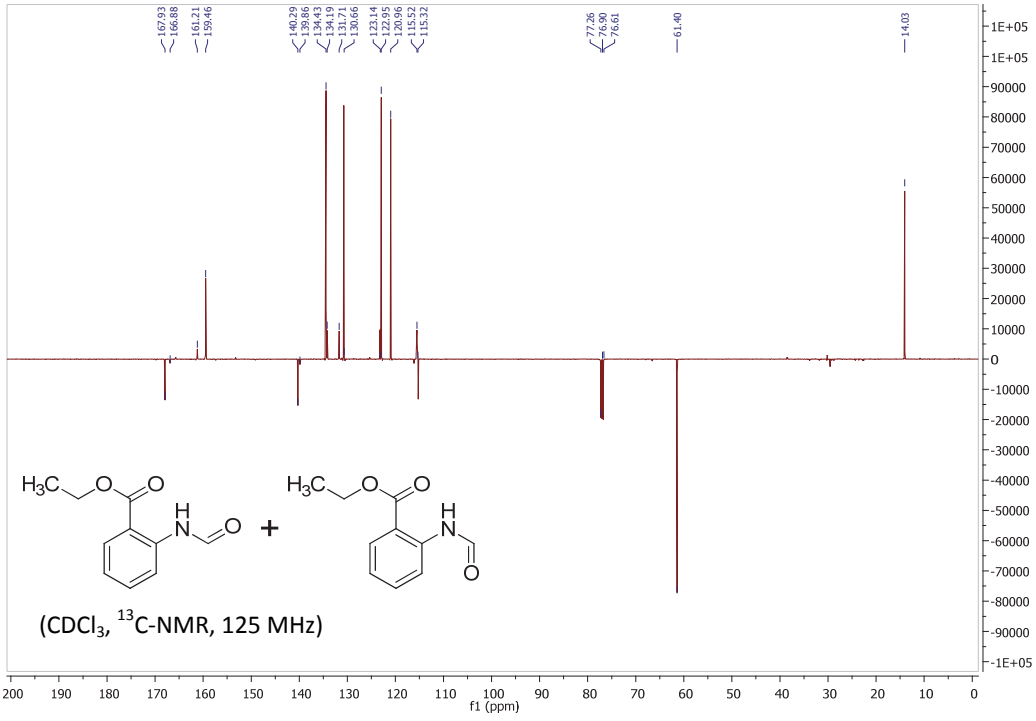
APPENDIX

APPENDIX

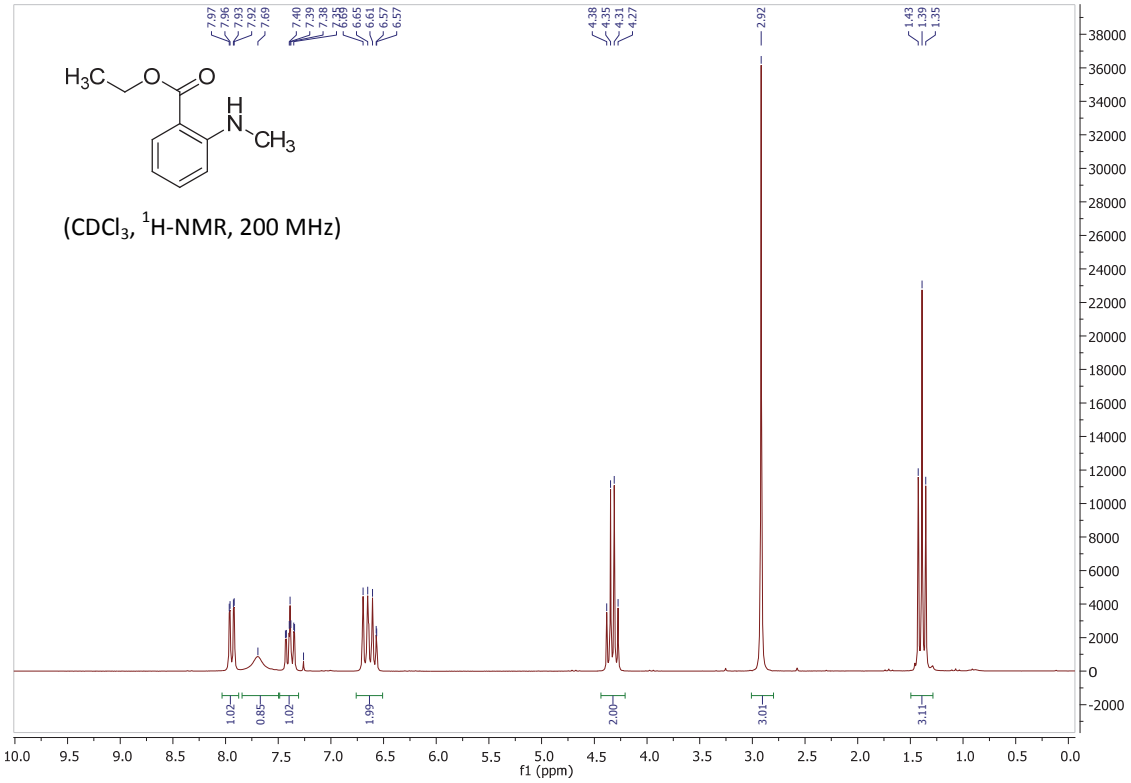
NMR spectra of the synthesized compounds

2-Ethoxycarbonyl formamide (2)

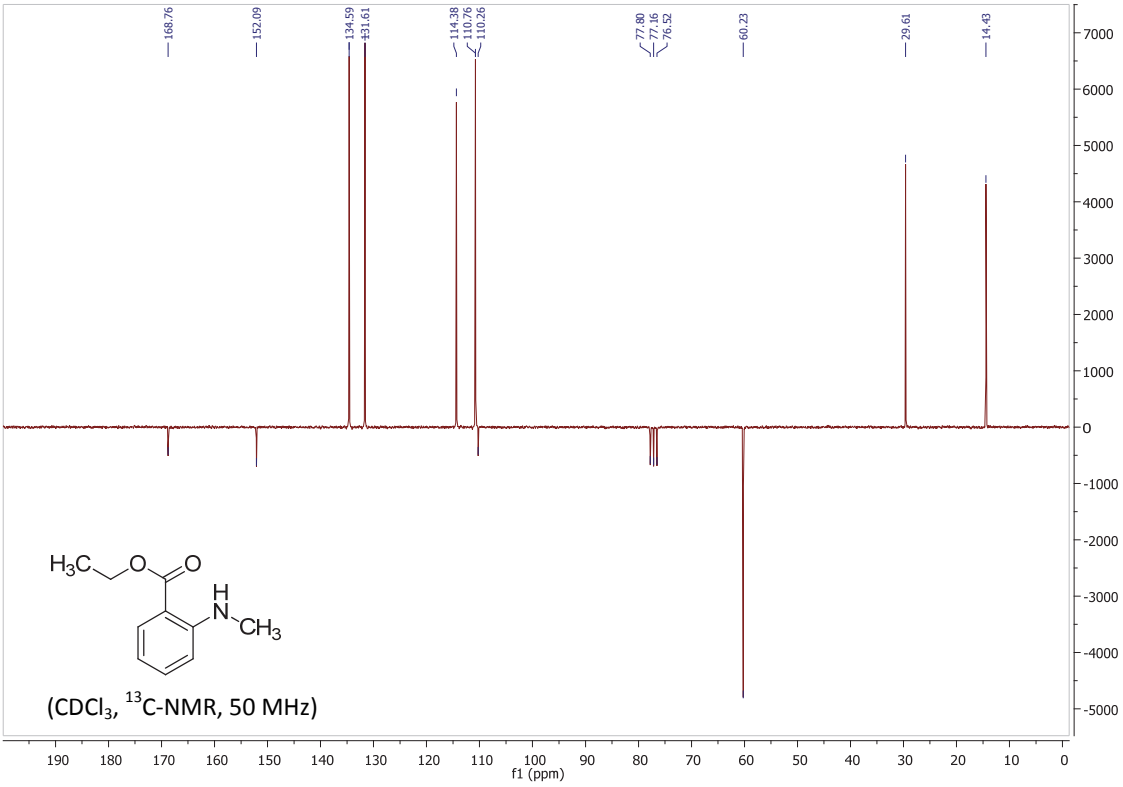




2-(Methylamino)benzoate (3)

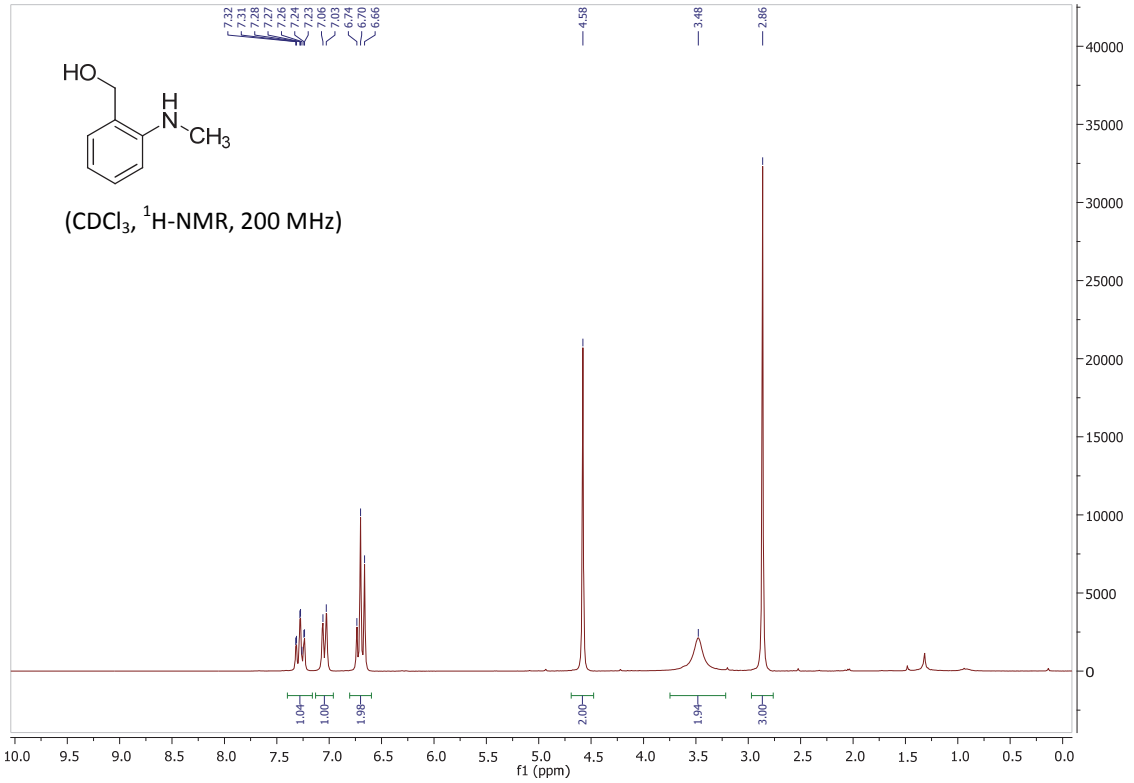


(CDCl$_3$, ^{1}H-NMR, 200 MHz)

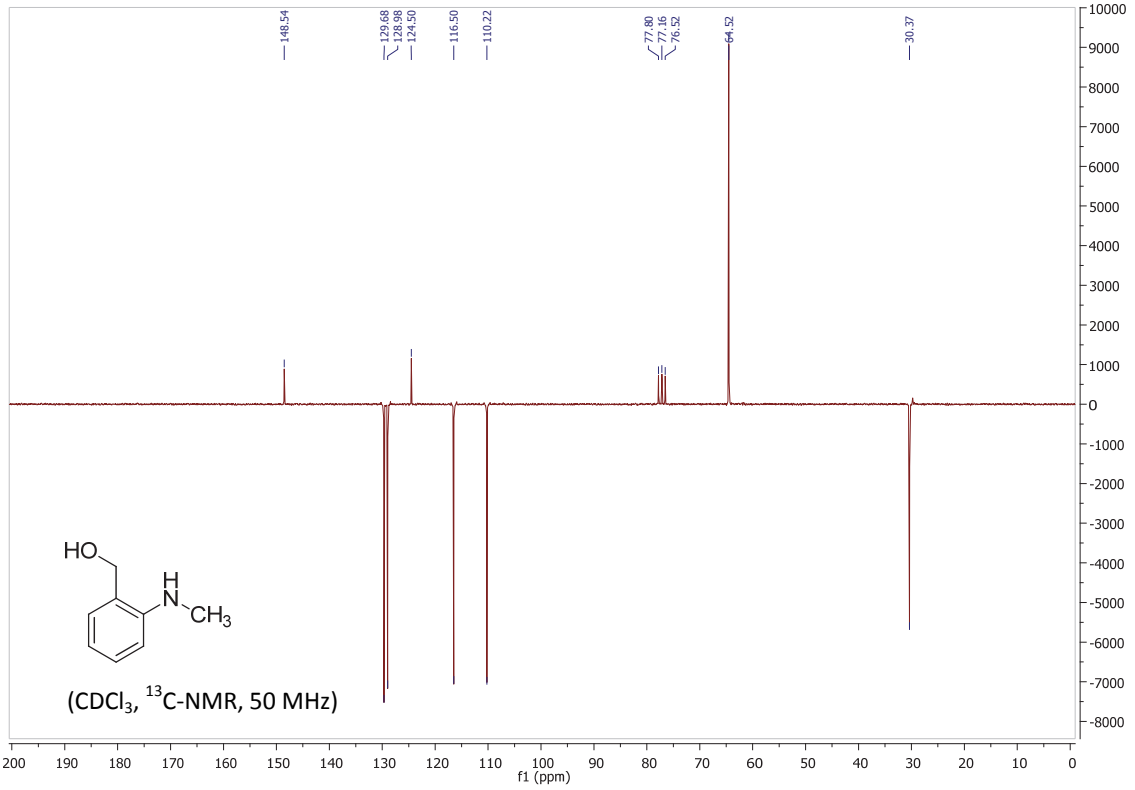


(CDCl$_3$, ^{13}C-NMR, 50 MHz)

2-Methylaminobenzylic alcohol (4)

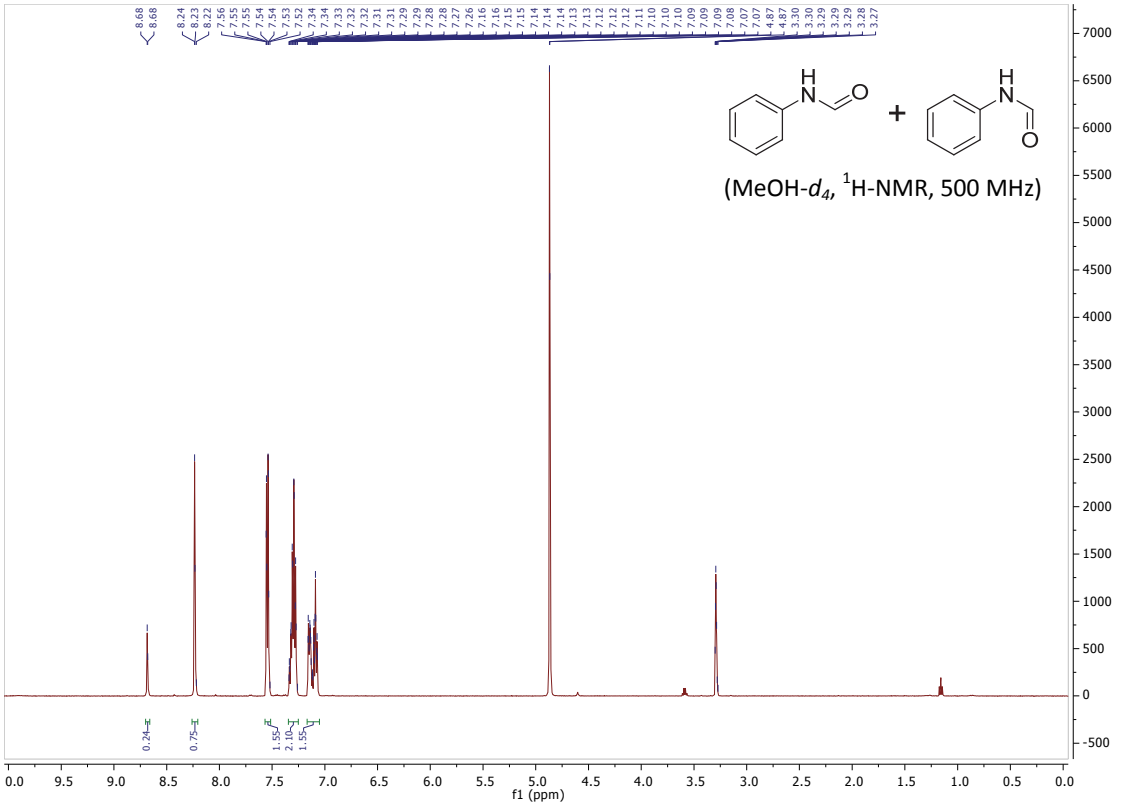


($CDCl_3$, ^{1}H-NMR, 200 MHz)

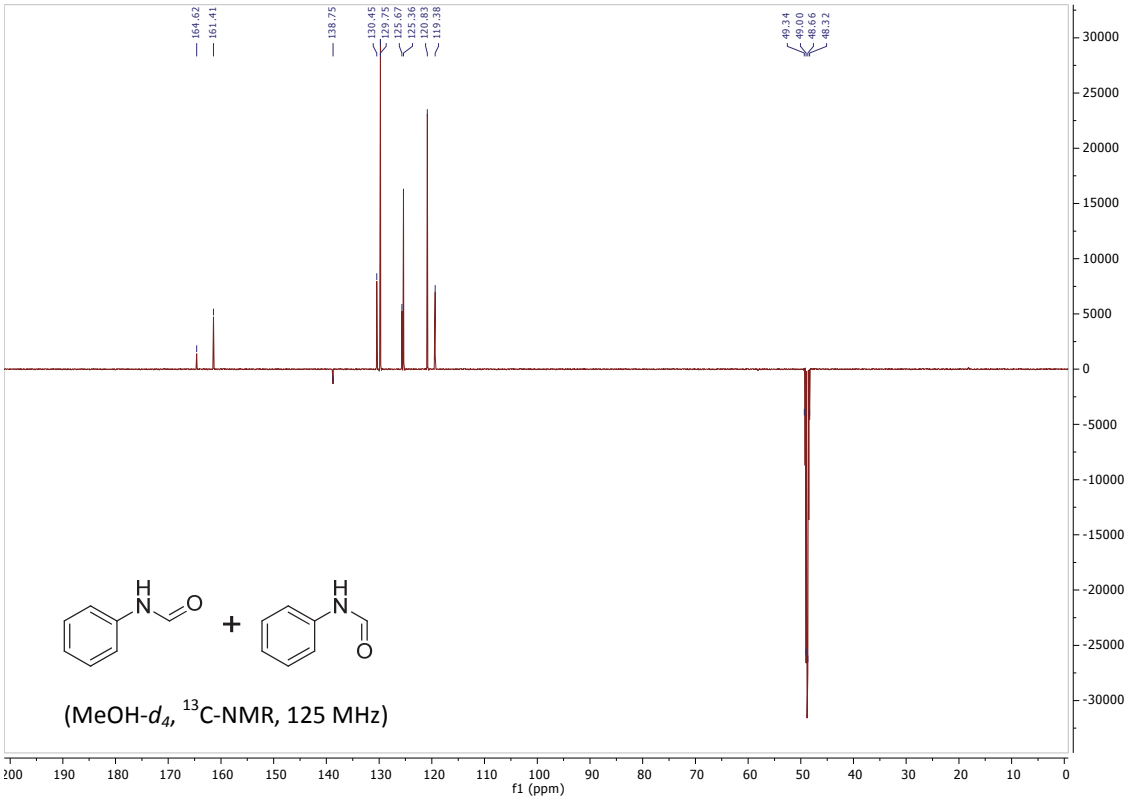


($CDCl_3$, ^{13}C-NMR, 50 MHz)

N-Phenylformamide (5)

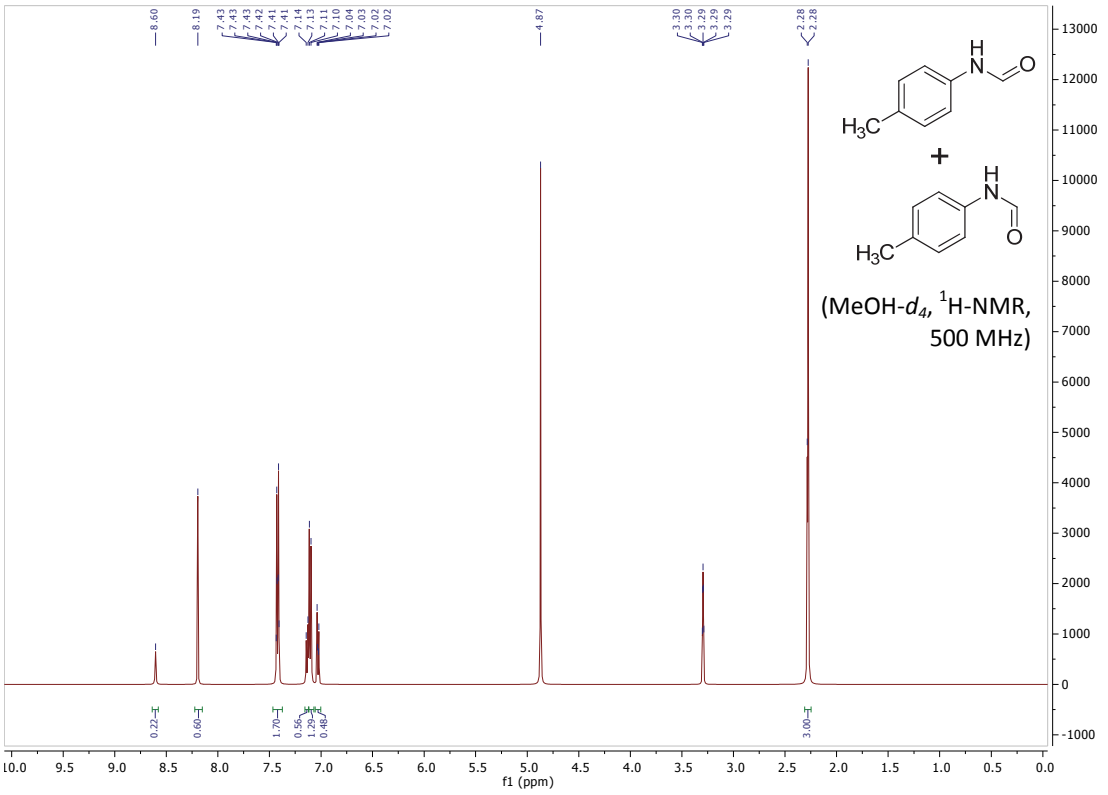


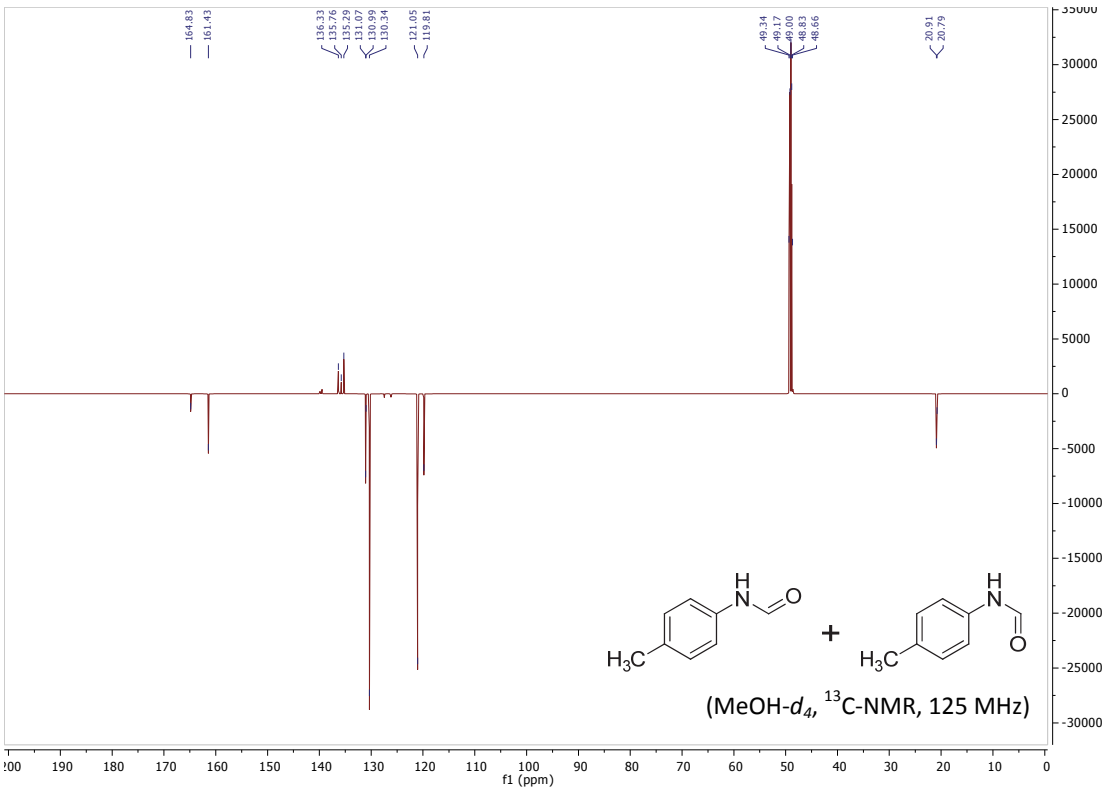
(MeOH-d_4, ^{1}H-NMR, 500 MHz)



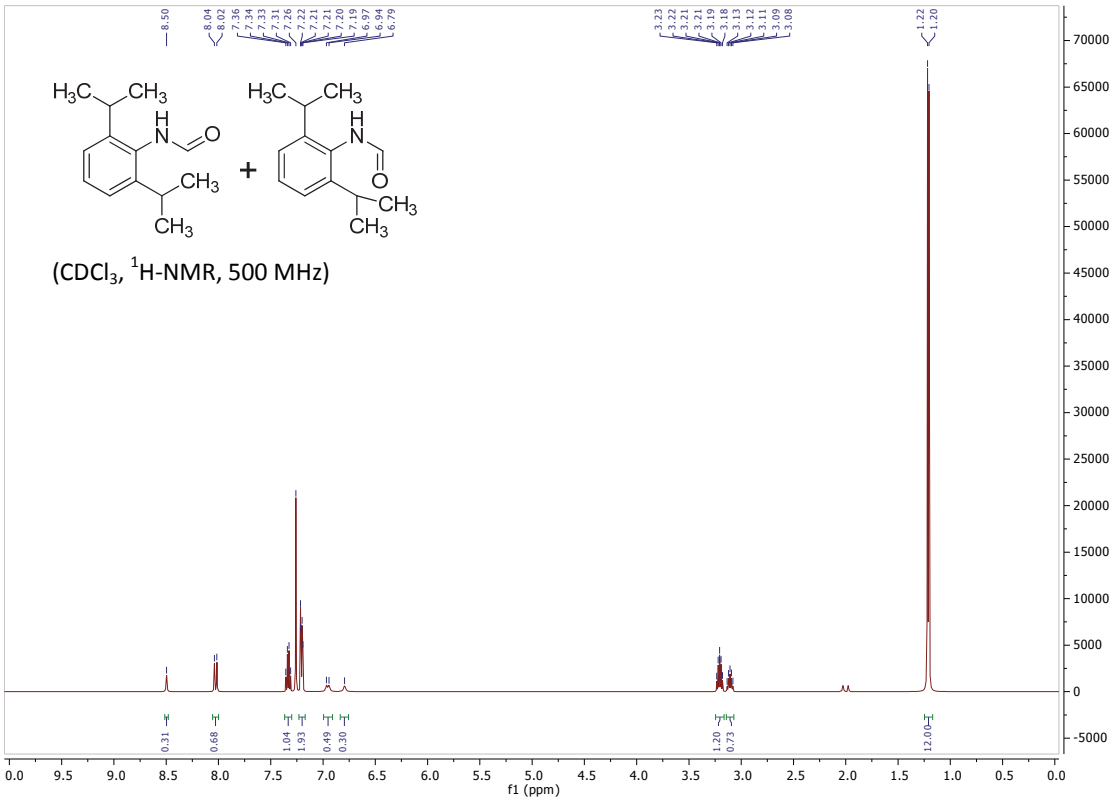
(MeOH-d_4, ^{13}C-NMR, 125 MHz)

N-*p*-Tolylformamide (6)

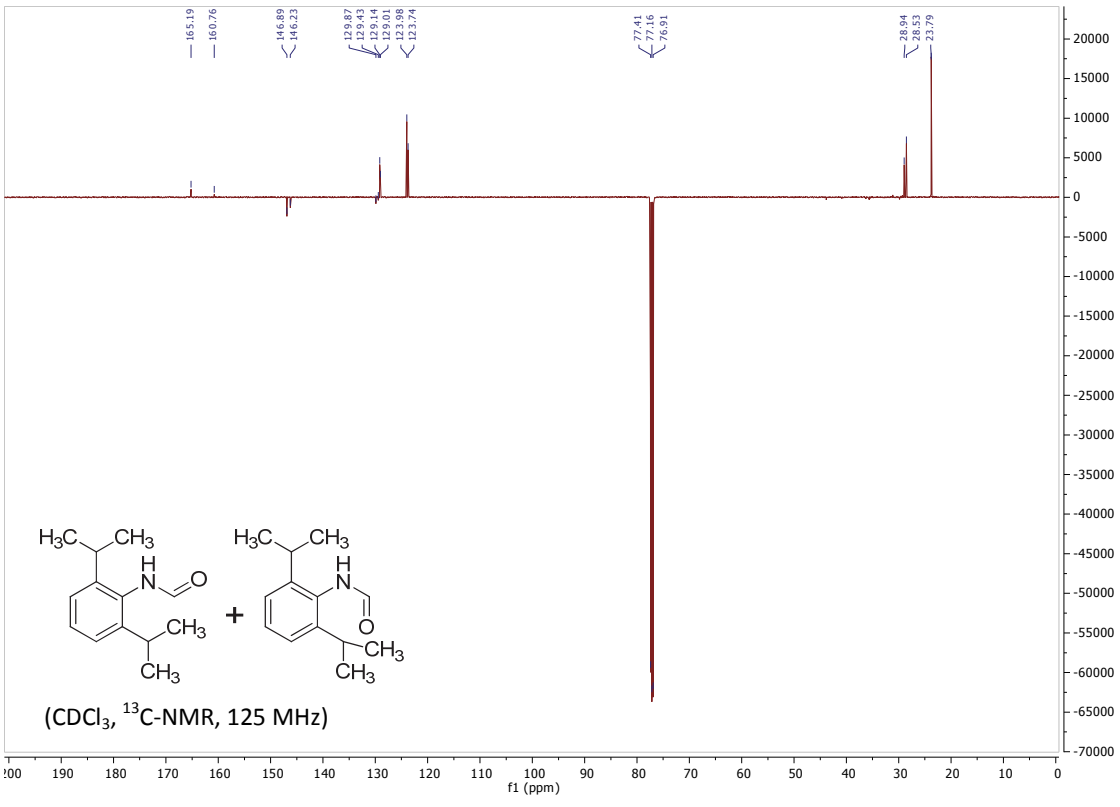




N-(2,6-Diisopropylphenyl)formamide (7)

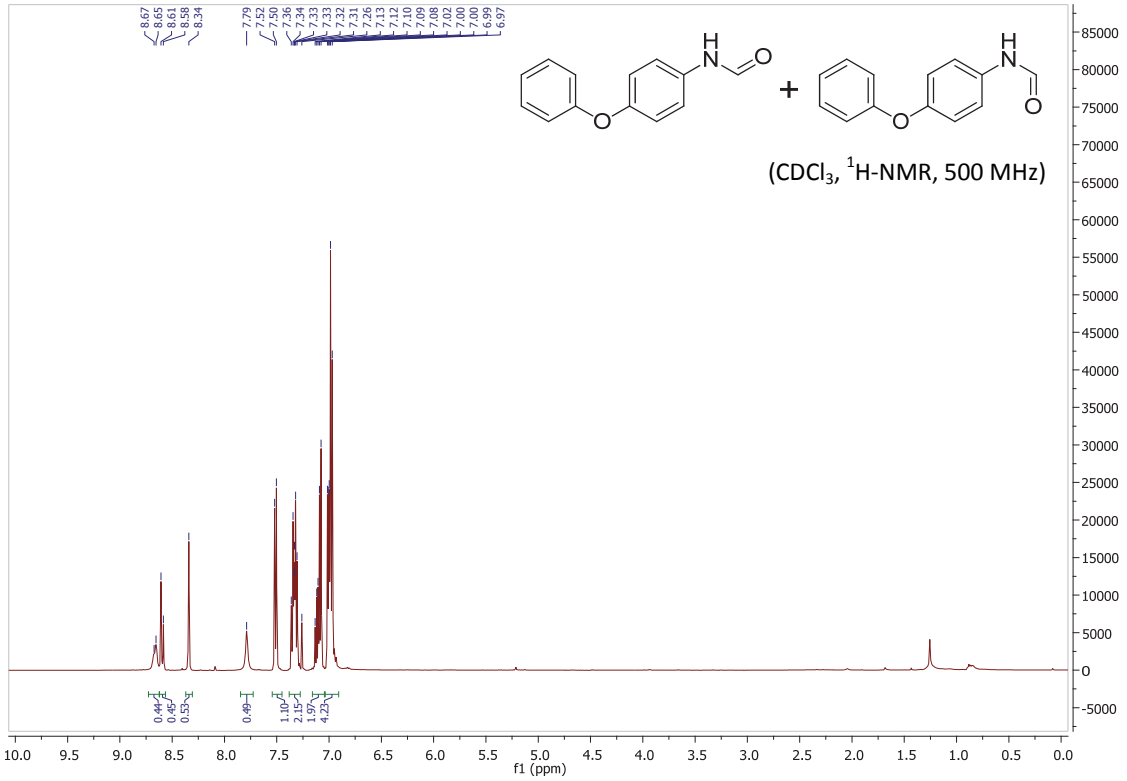


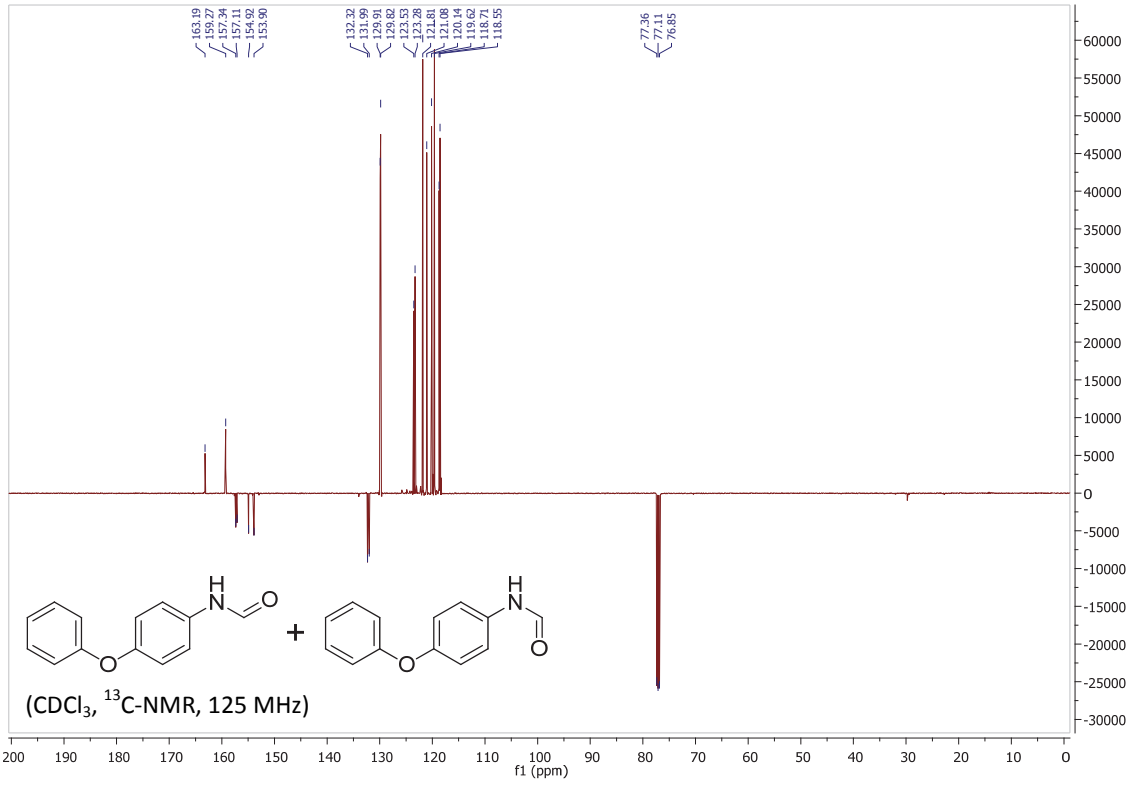
(CDCl$_3$, ^{1}H-NMR, 500 MHz)



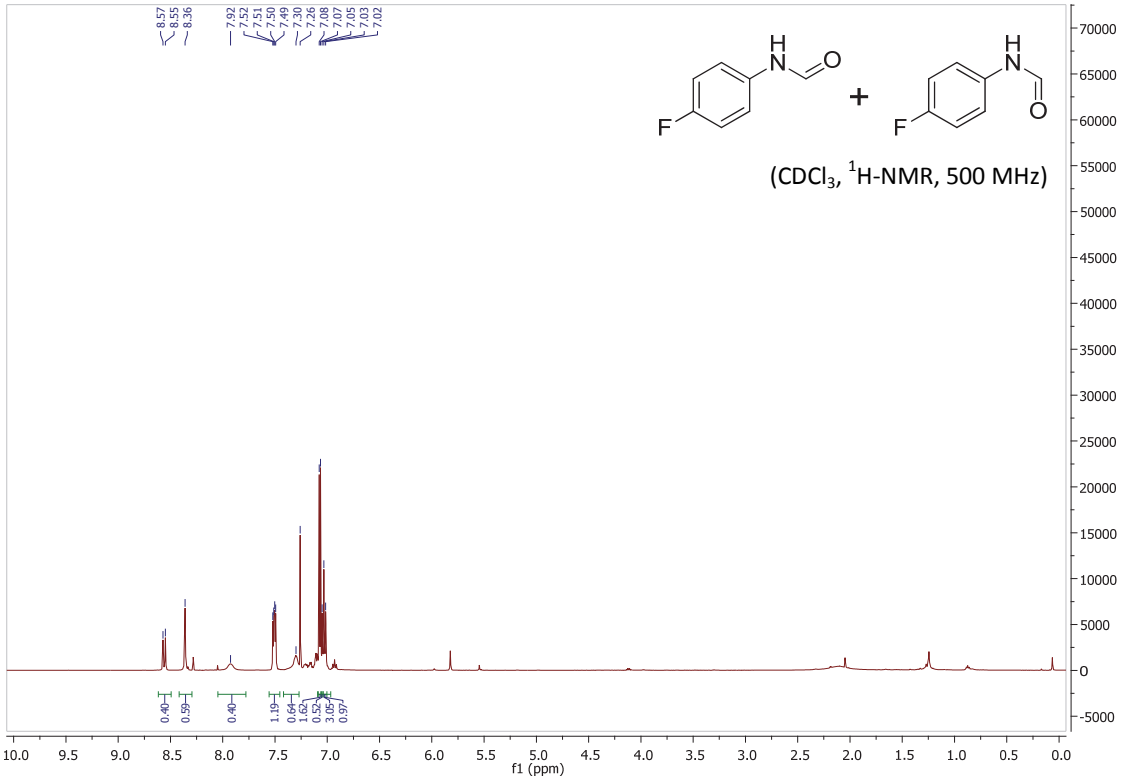
(CDCl$_3$, ^{13}C-NMR, 125 MHz)

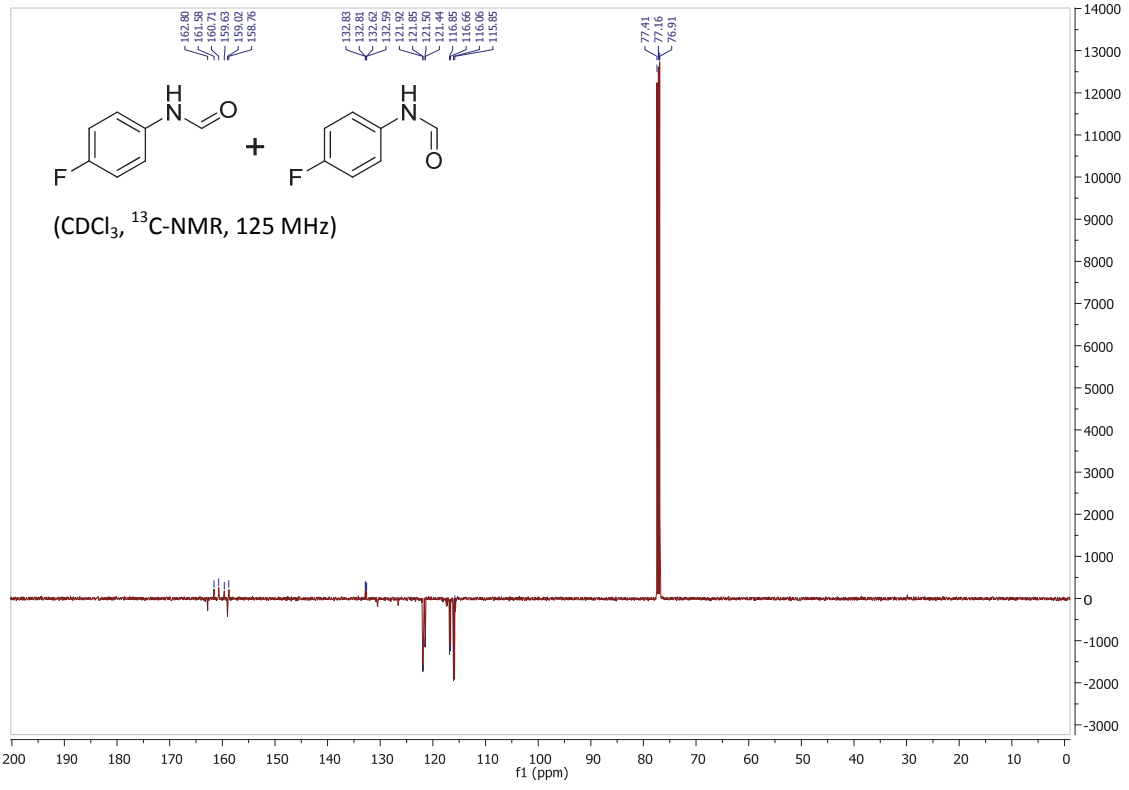
N-(4-Phenoxyphenyl)formamide (8)



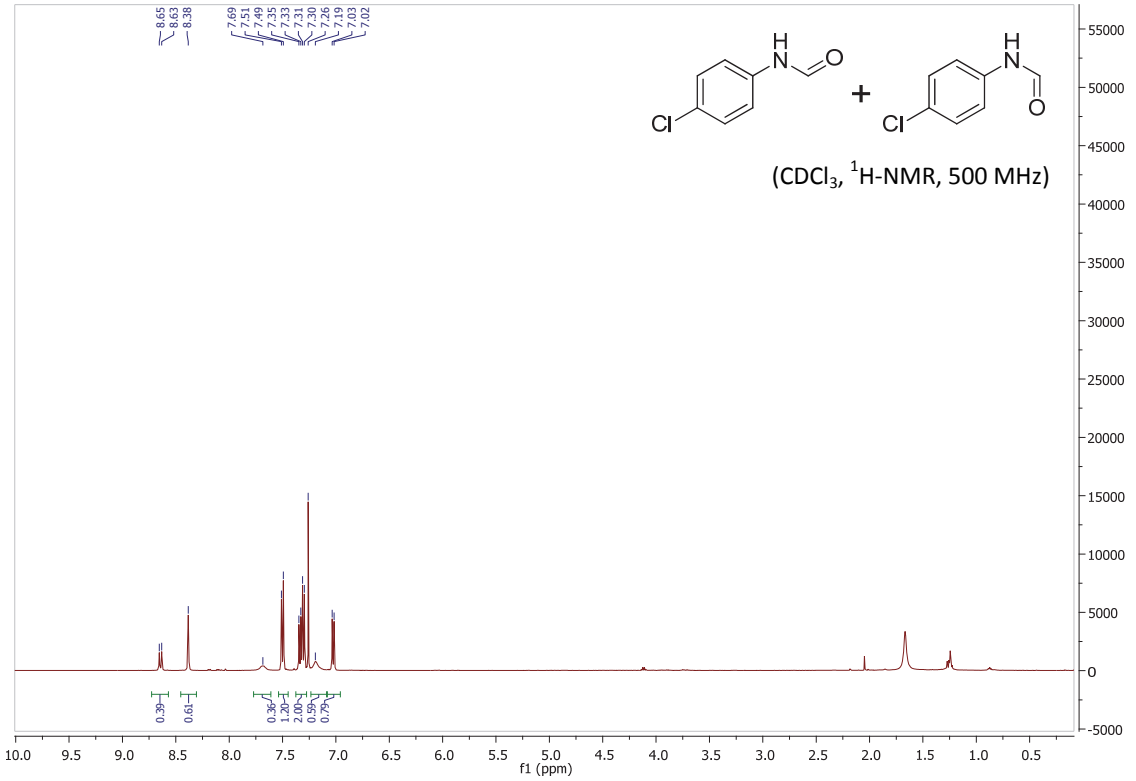


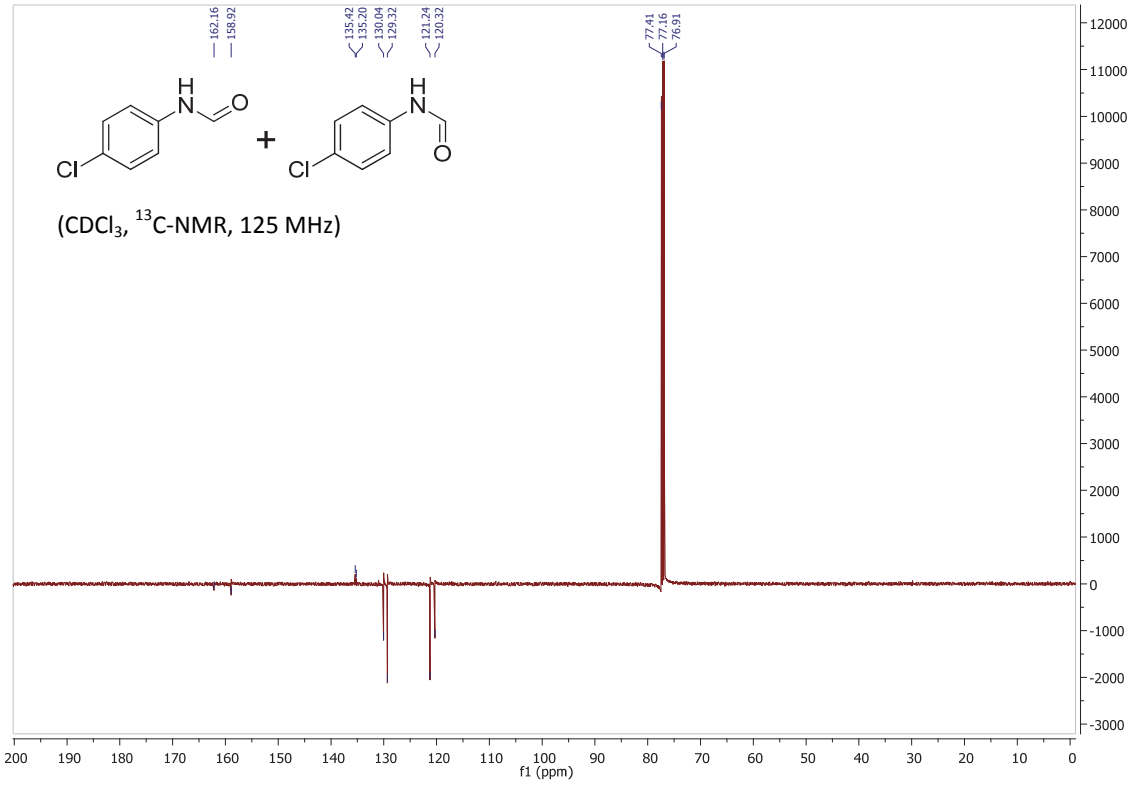
N-(4-Fluorophenyl)formamide (9)



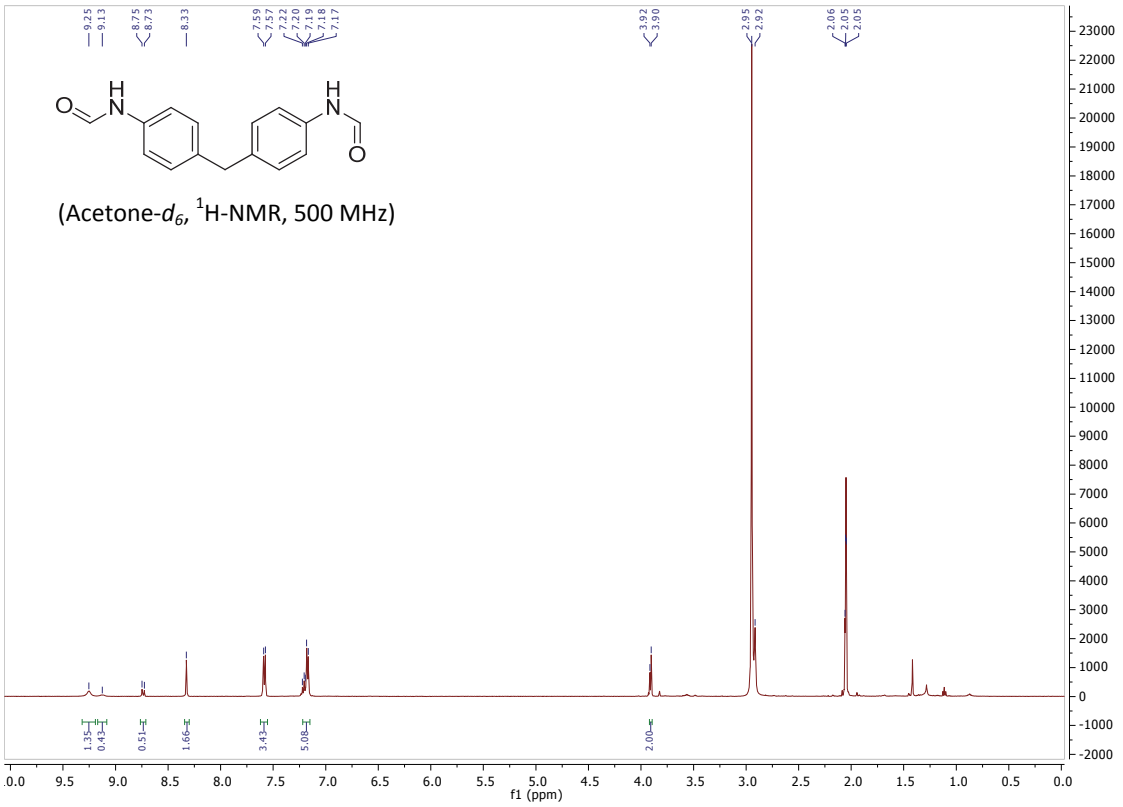


N-(4-Chlorophenyl)formamide (10)

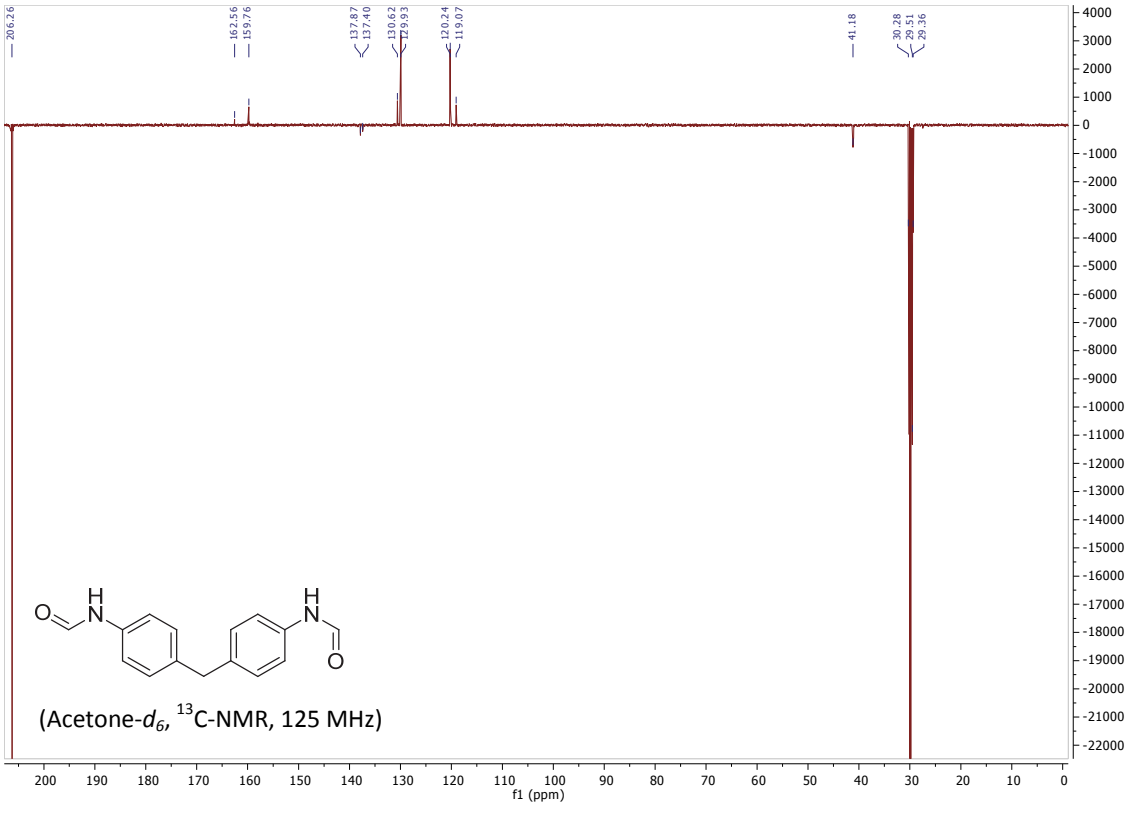




N,N'-(Methylenebis(4,1-phenylene))diformamide (11)

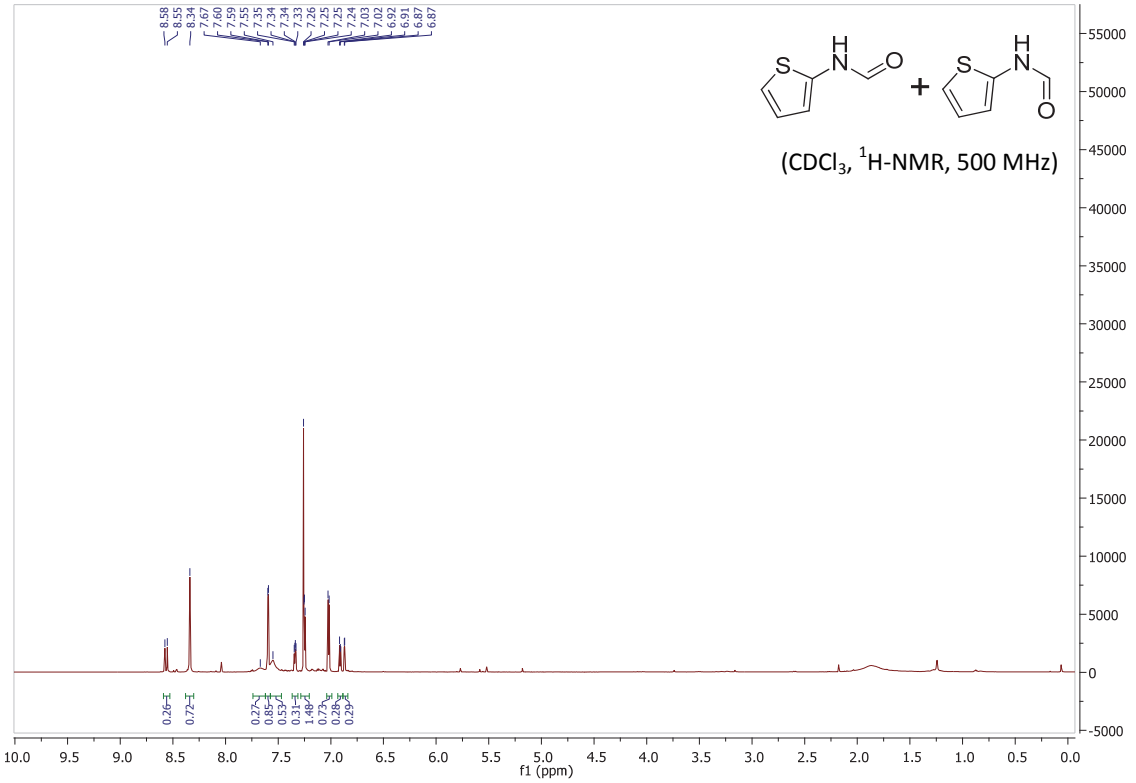


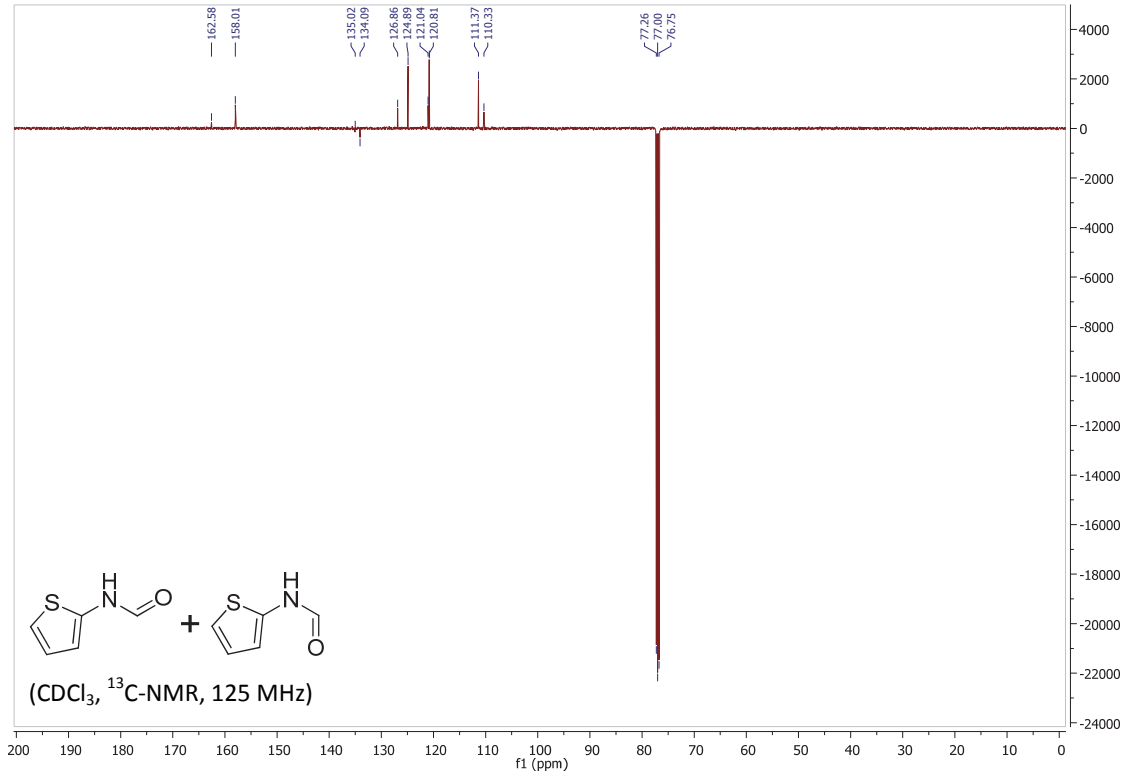
(Acetone-d_6, ^{1}H-NMR, 500 MHz)



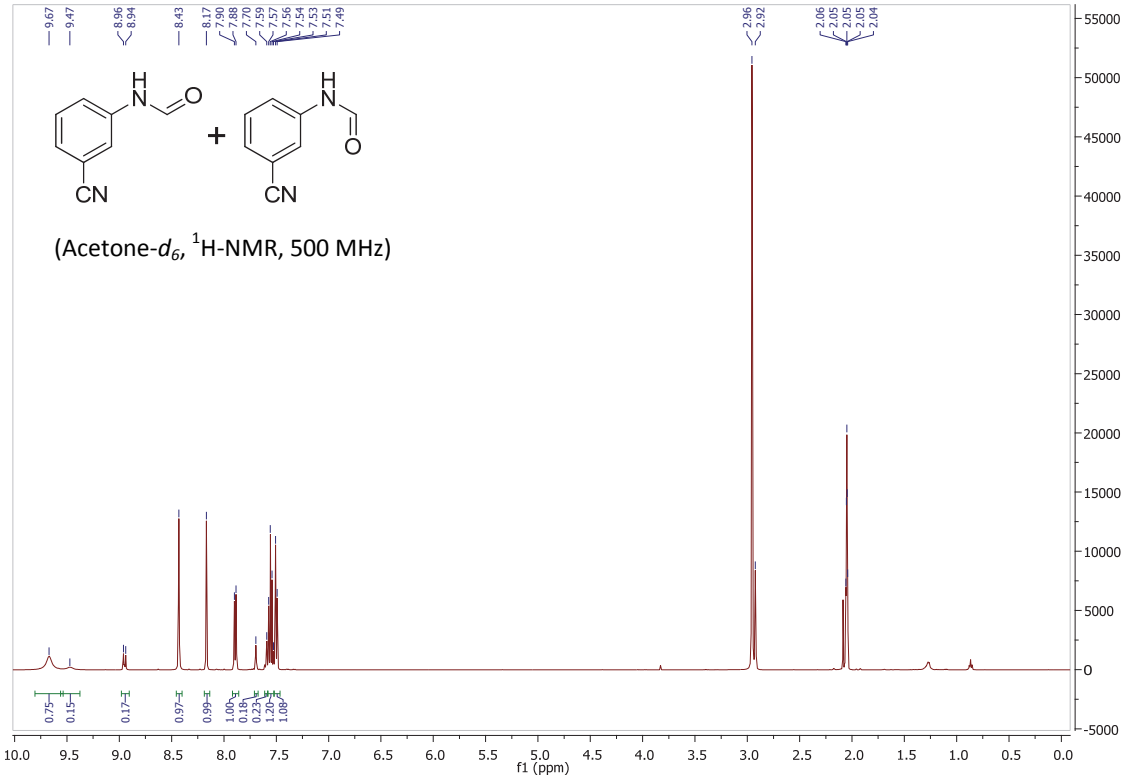
(Acetone-d_6, ^{13}C-NMR, 125 MHz)

N-(Thiophen-2-yl)formamide (12)

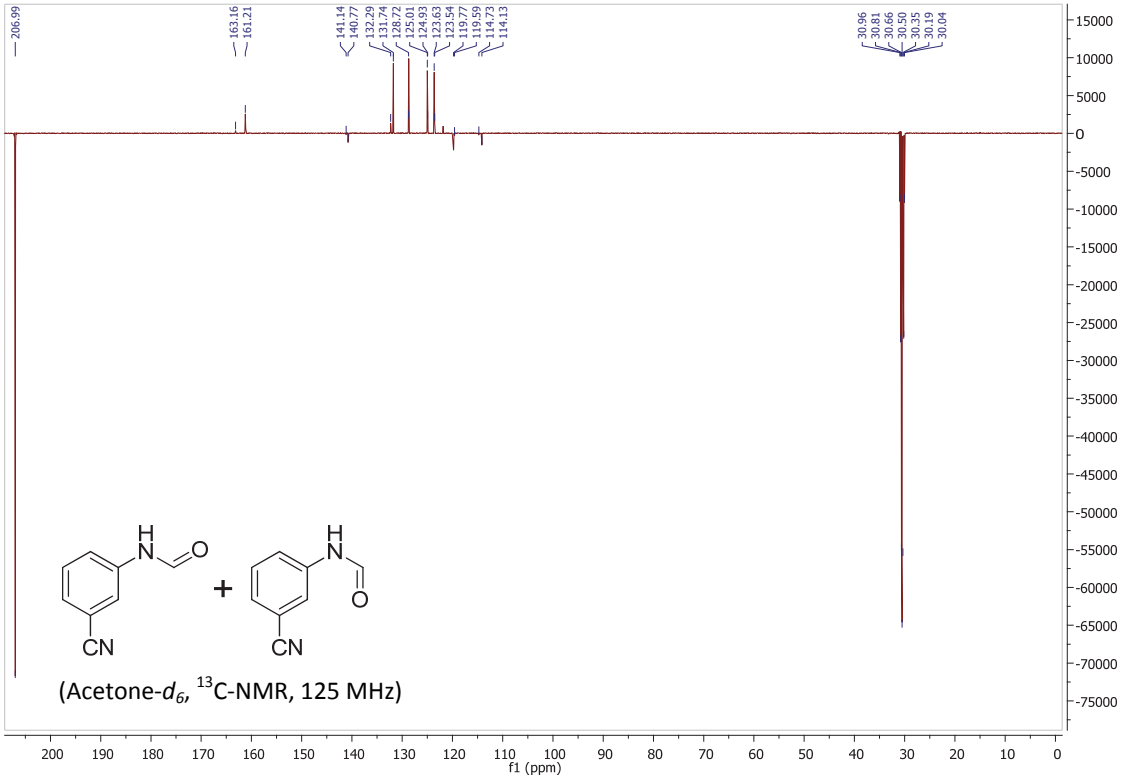




N-(3-Cyanophenyl)formamide (13)

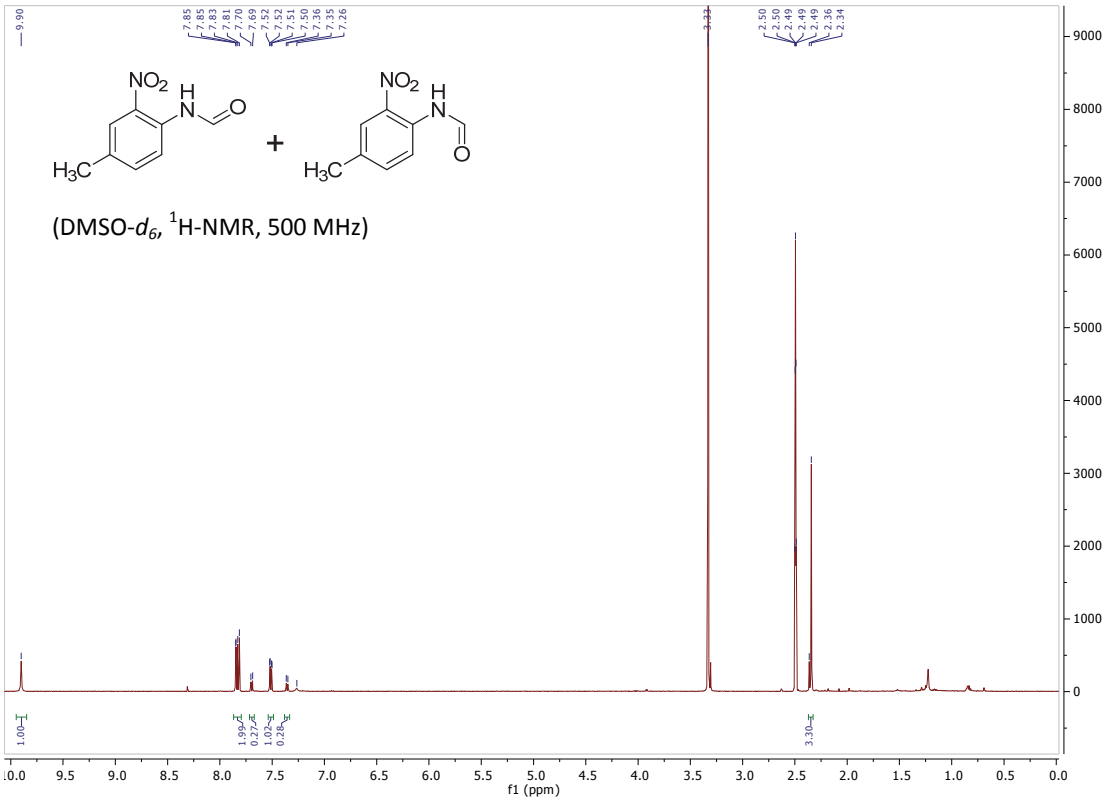


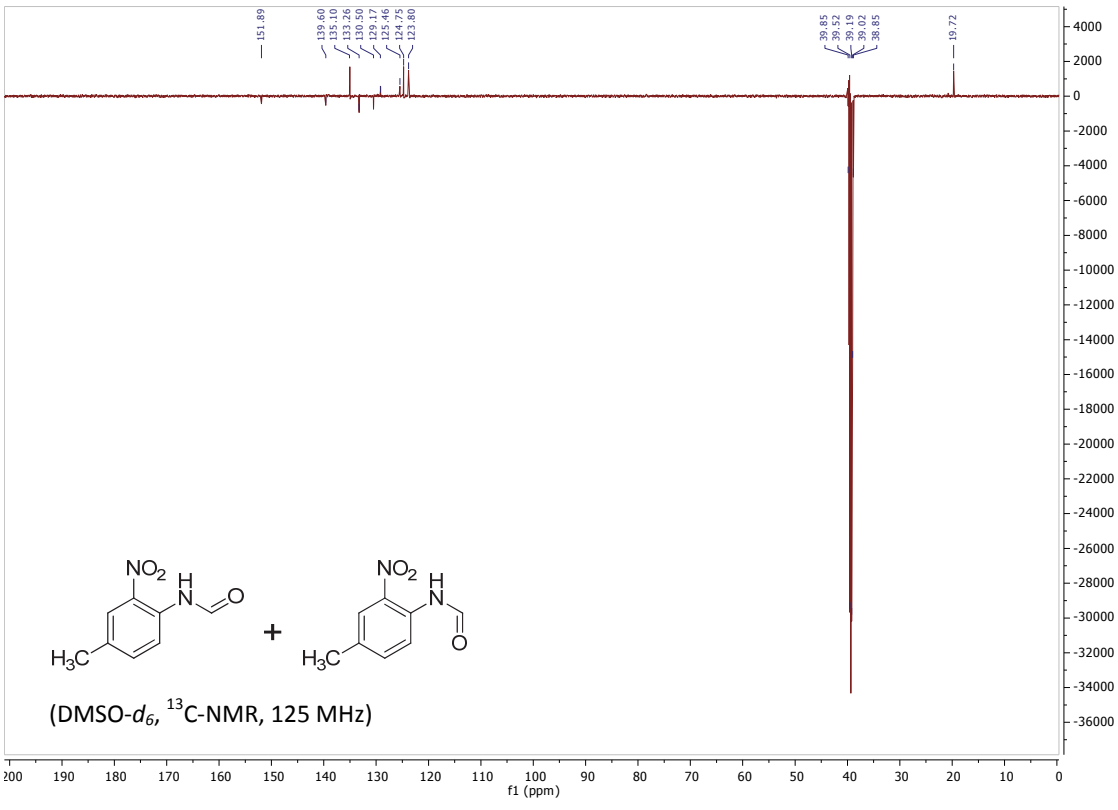
(Acetone-d_6, ^{1}H-NMR, 500 MHz)



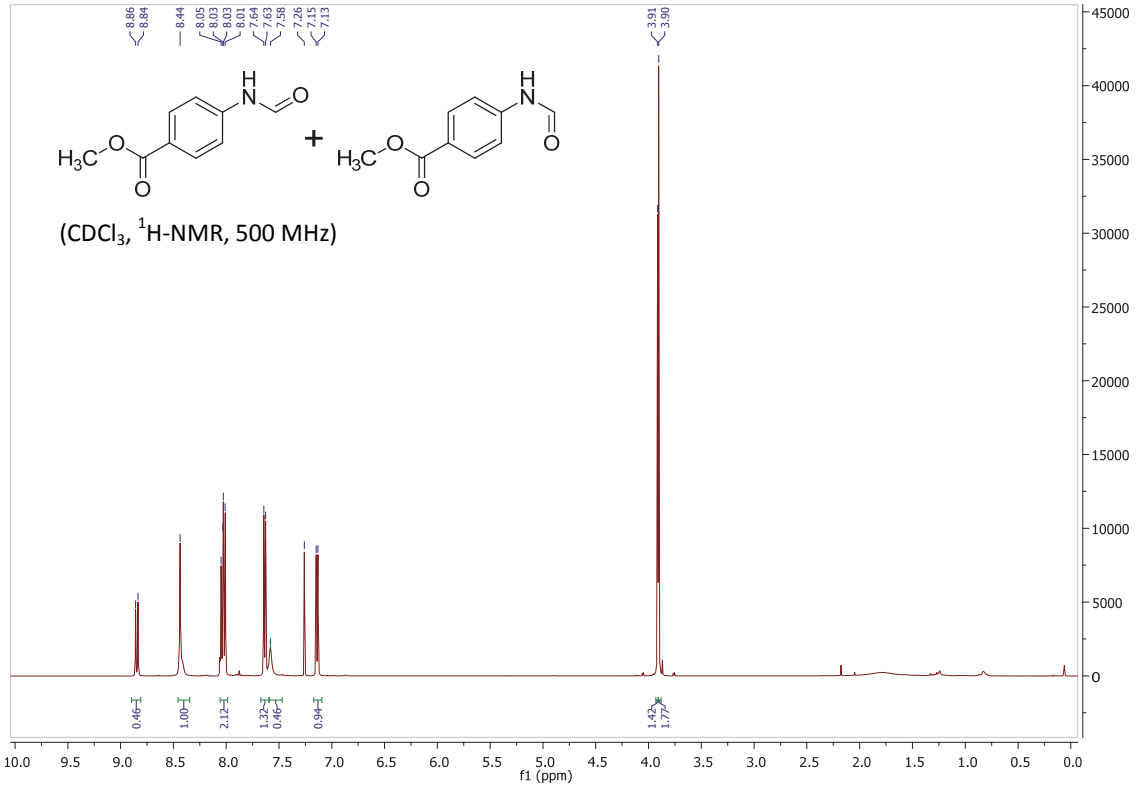
(Acetone-d_6, ^{13}C-NMR, 125 MHz)

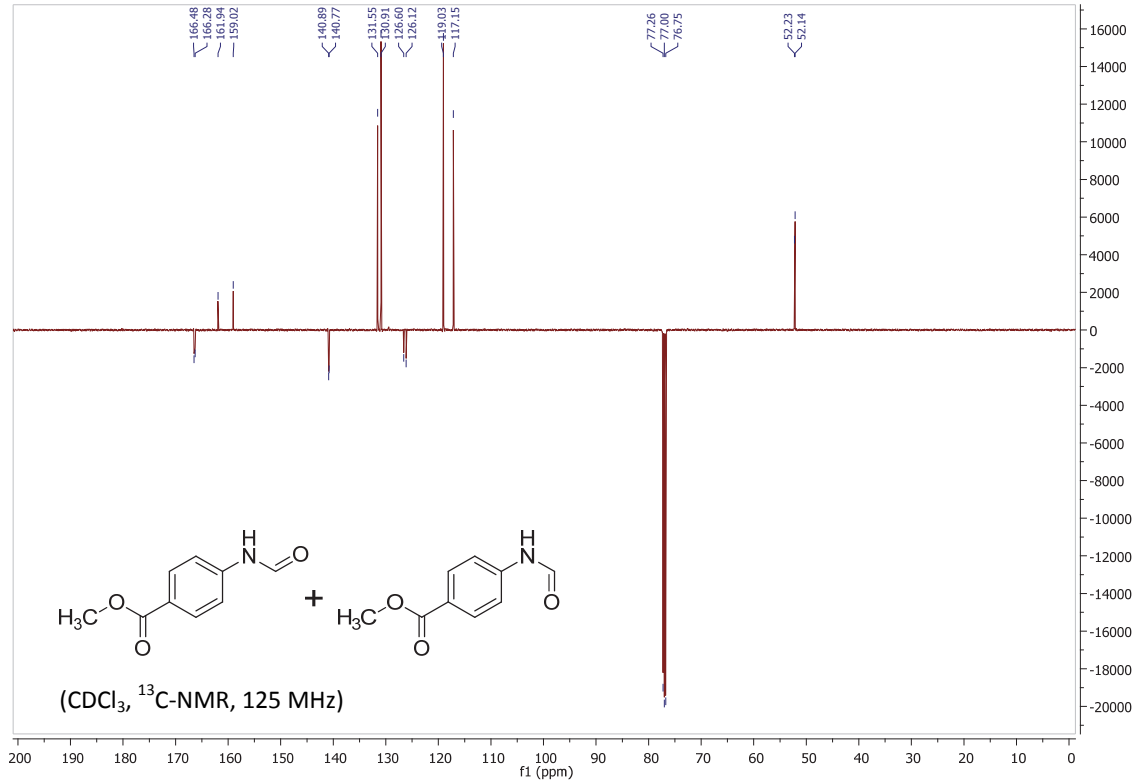
N-(4-Methyl-2-nitrophenyl)formamide (14)



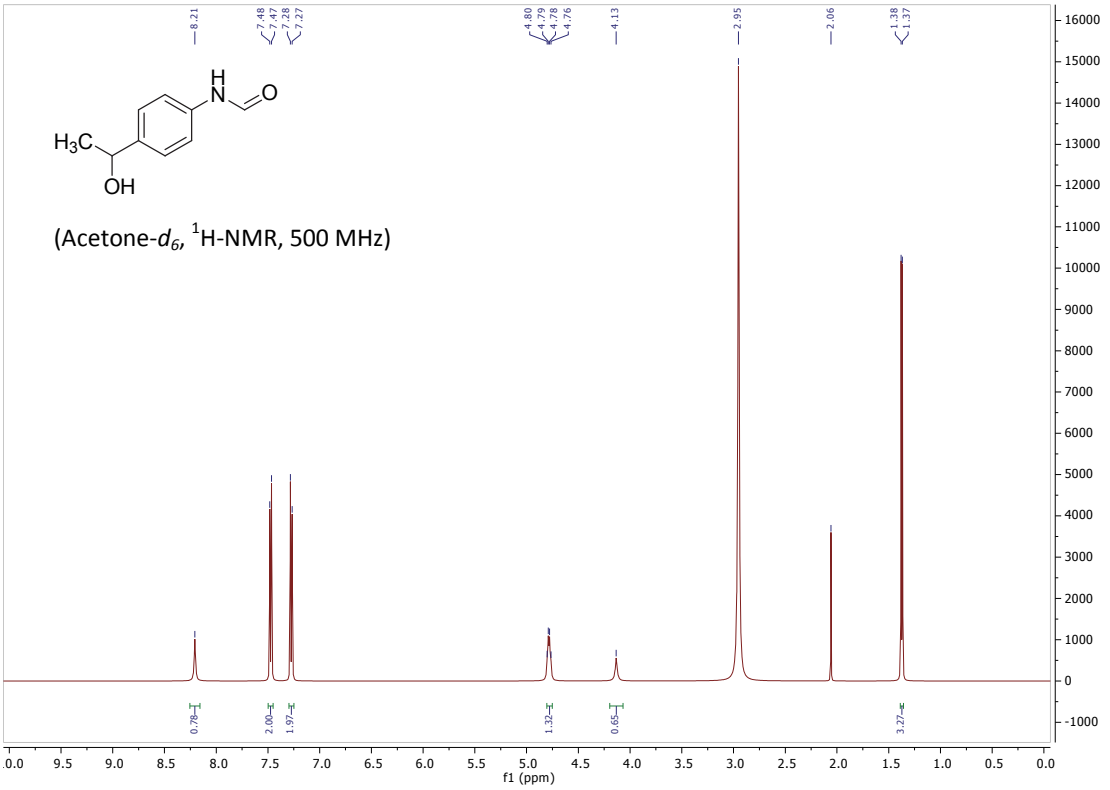


4-Methoxycarbonyl formamide (15)

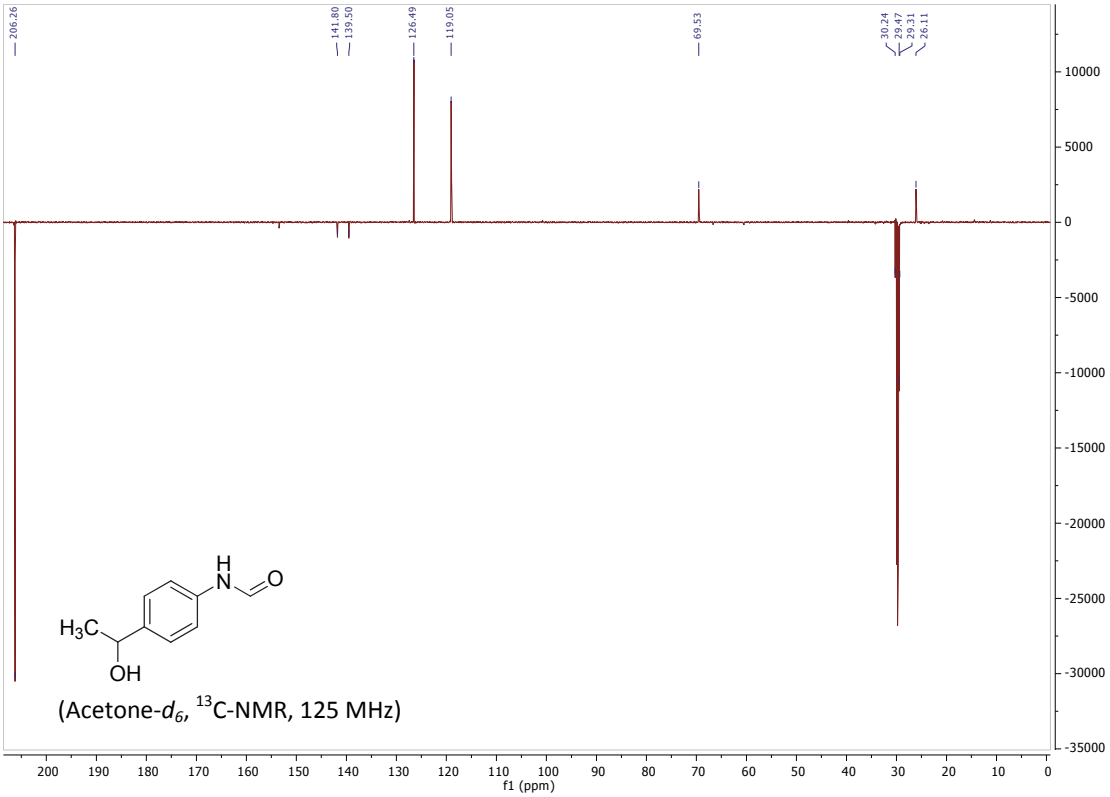




N-[4-(1-Hydroxyethyl)phenyl]formamide (16)

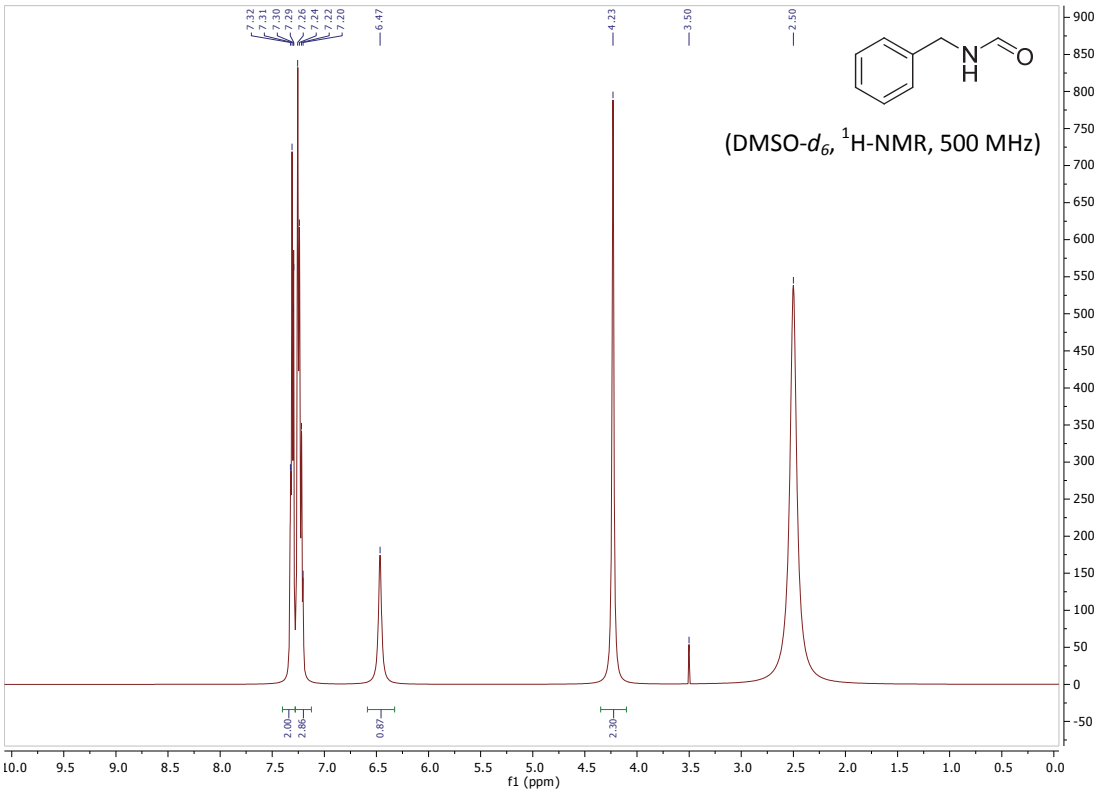


(Acetone-d_6, ^{1}H-NMR, 500 MHz)

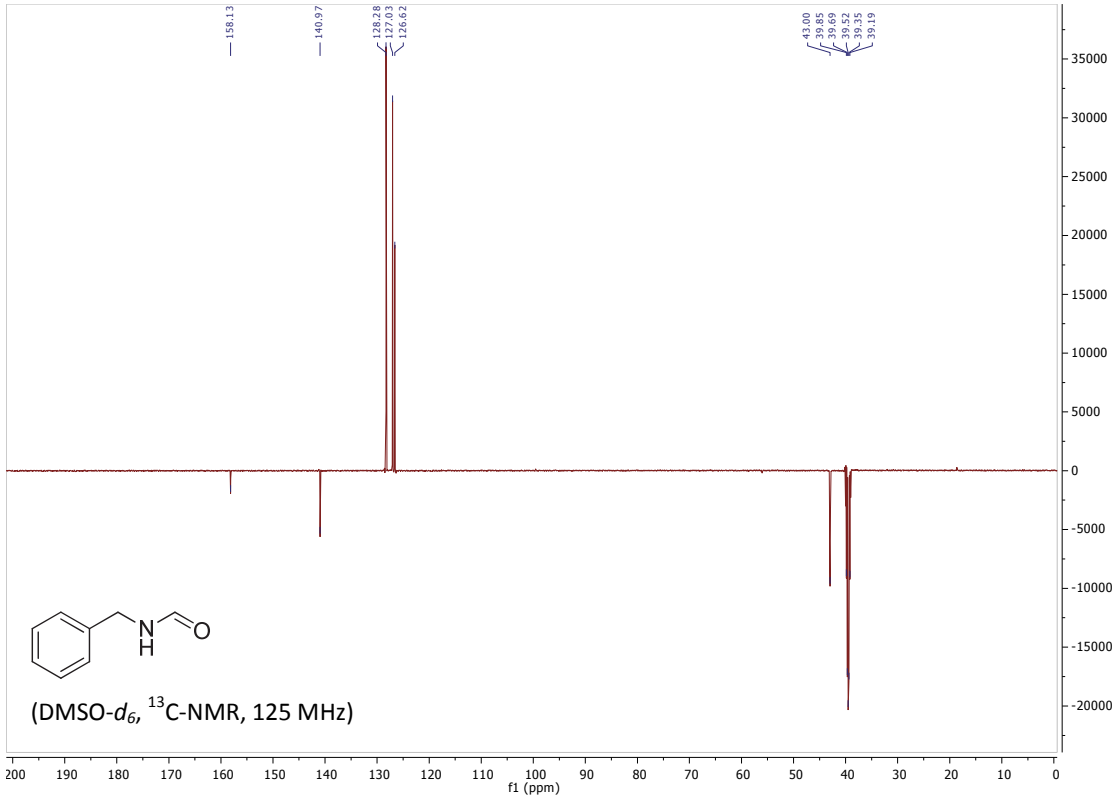


(Acetone-d_6, ^{13}C-NMR, 125 MHz)

N-Benzylformamide (17)

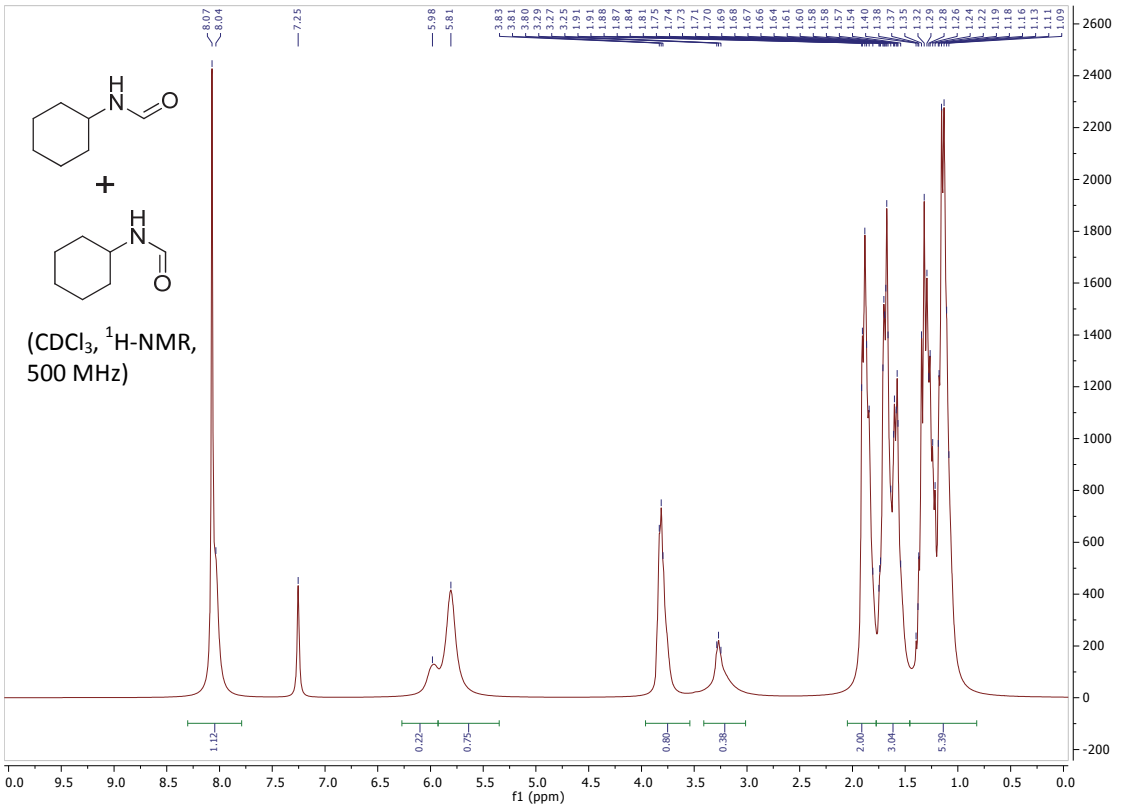


(DMSO-d_6, ^{1}H-NMR, 500 MHz)

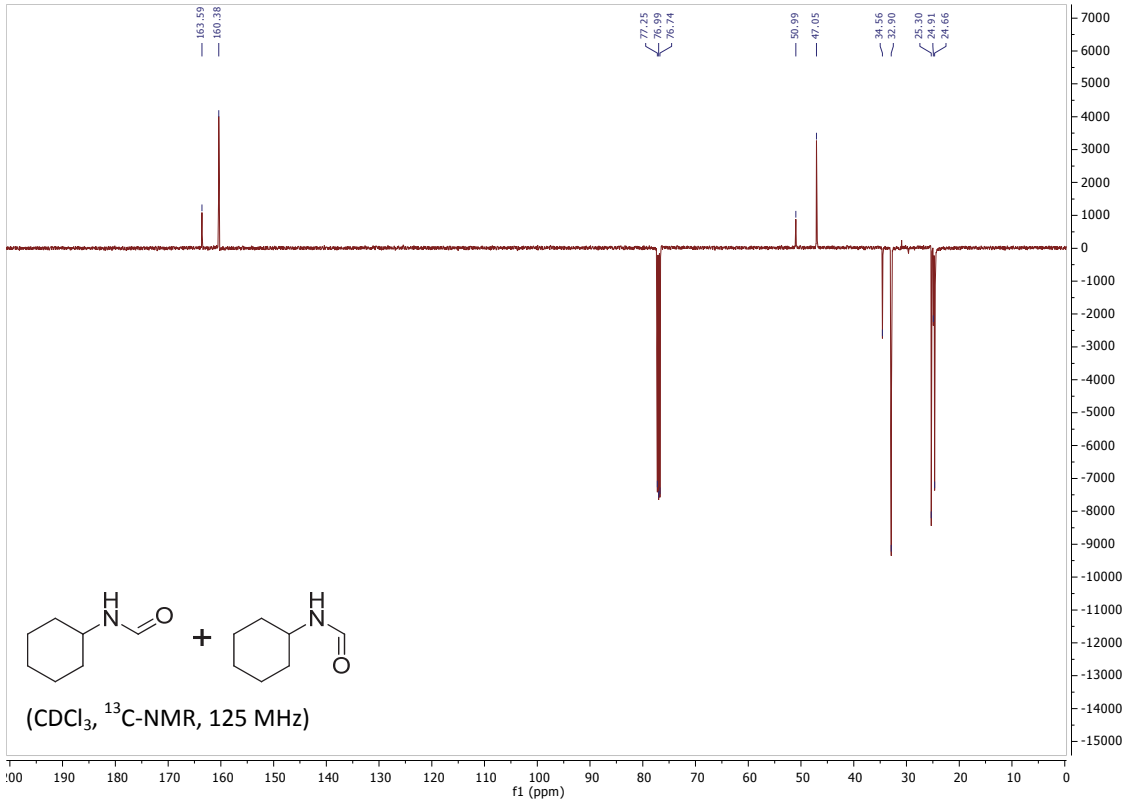


(DMSO-d_6, ^{13}C-NMR, 125 MHz)

N-Cyclohexylformamide (18)

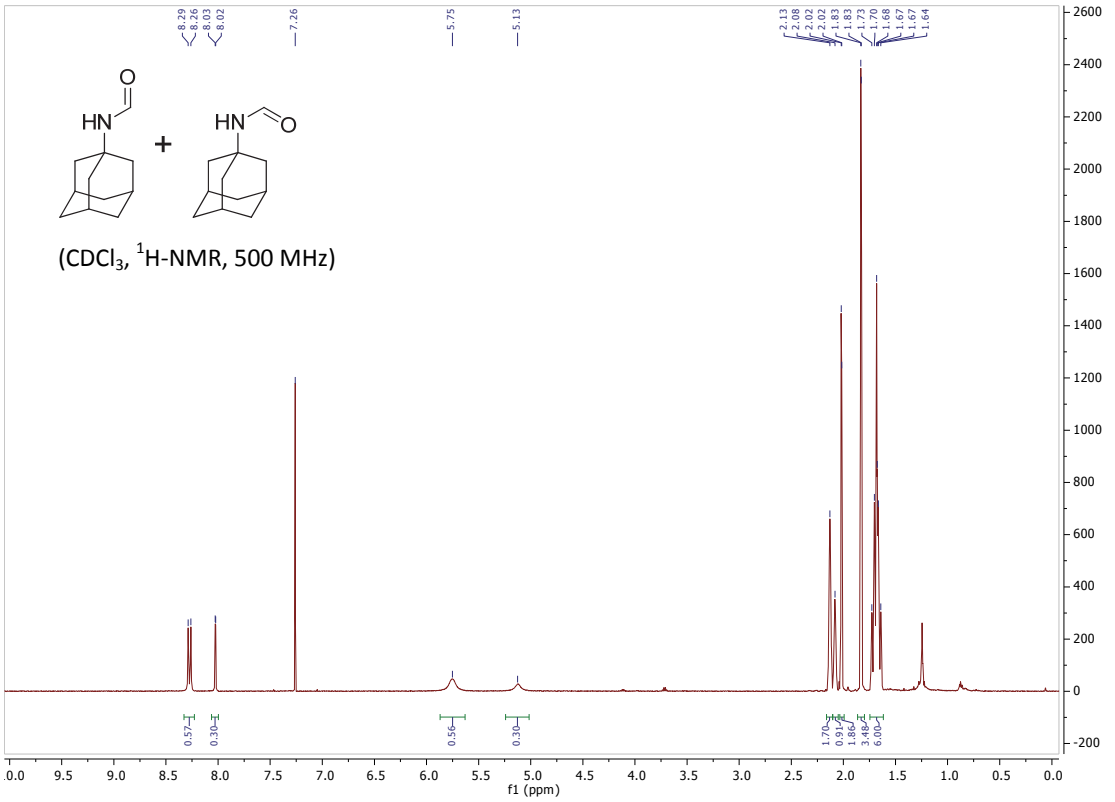


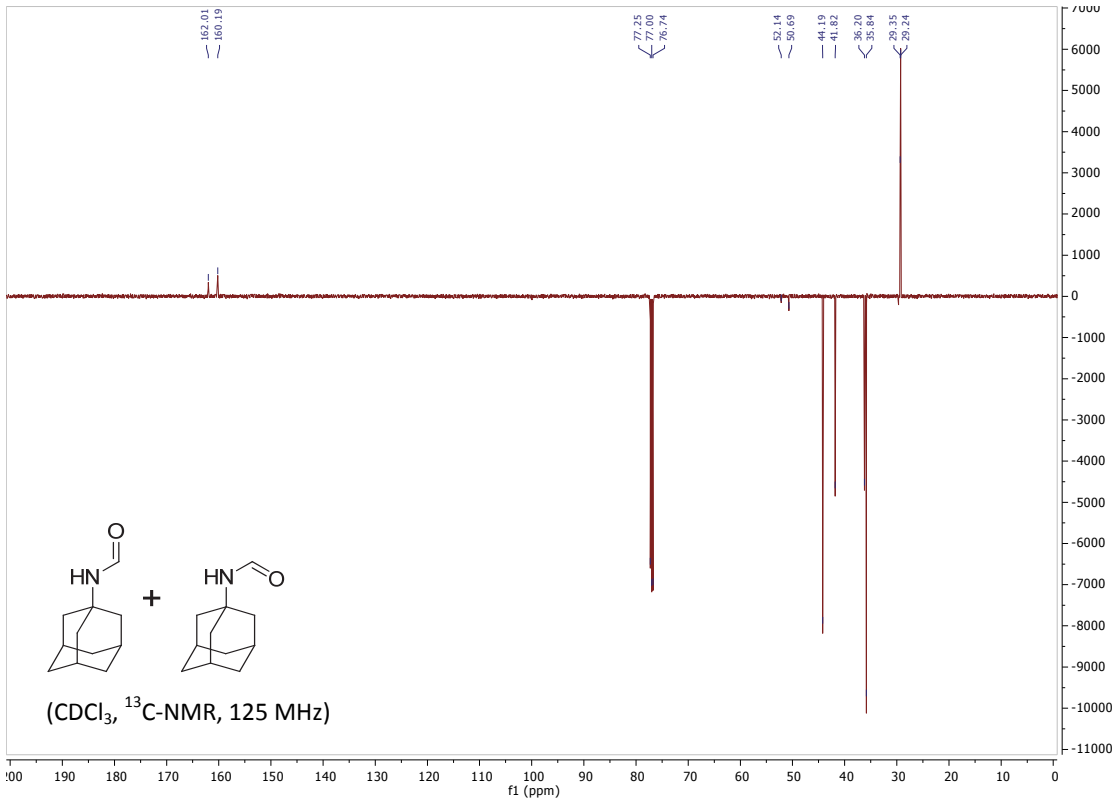
($CDCl_3$, ^{1}H-NMR, 500 MHz)



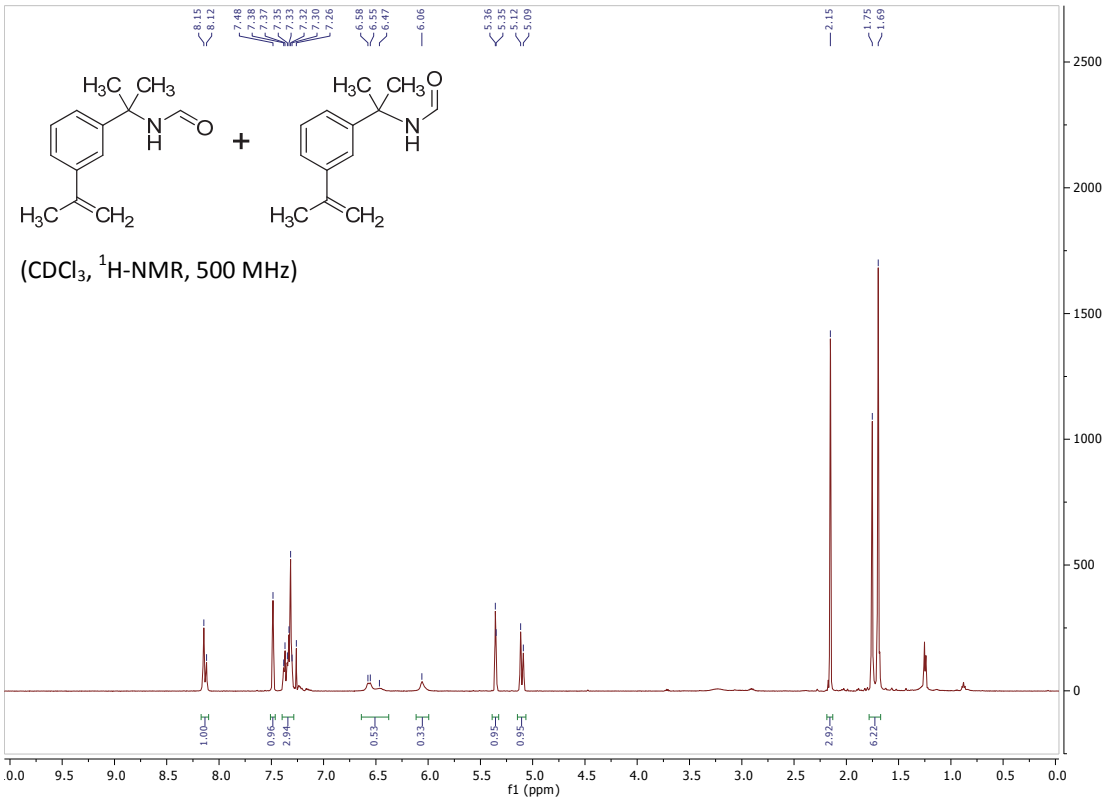
($CDCl_3$, ^{13}C-NMR, 125 MHz)

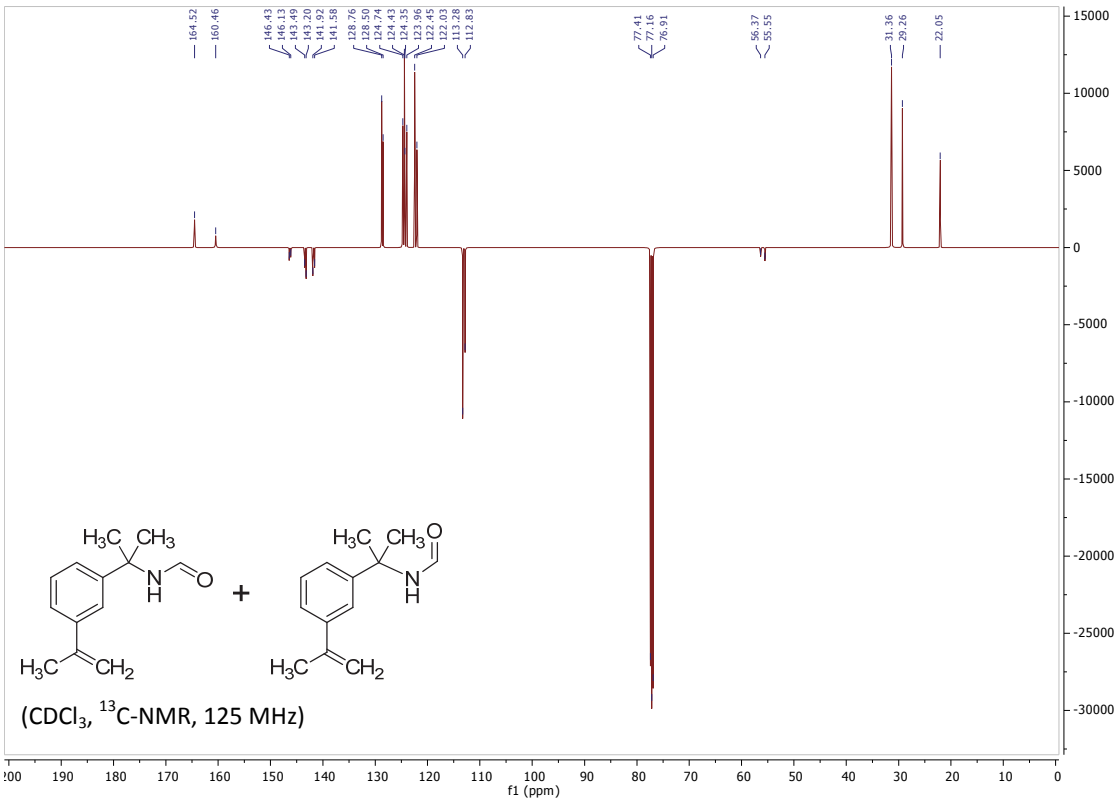
N-(Adamantan-1-yl)formamide (19)



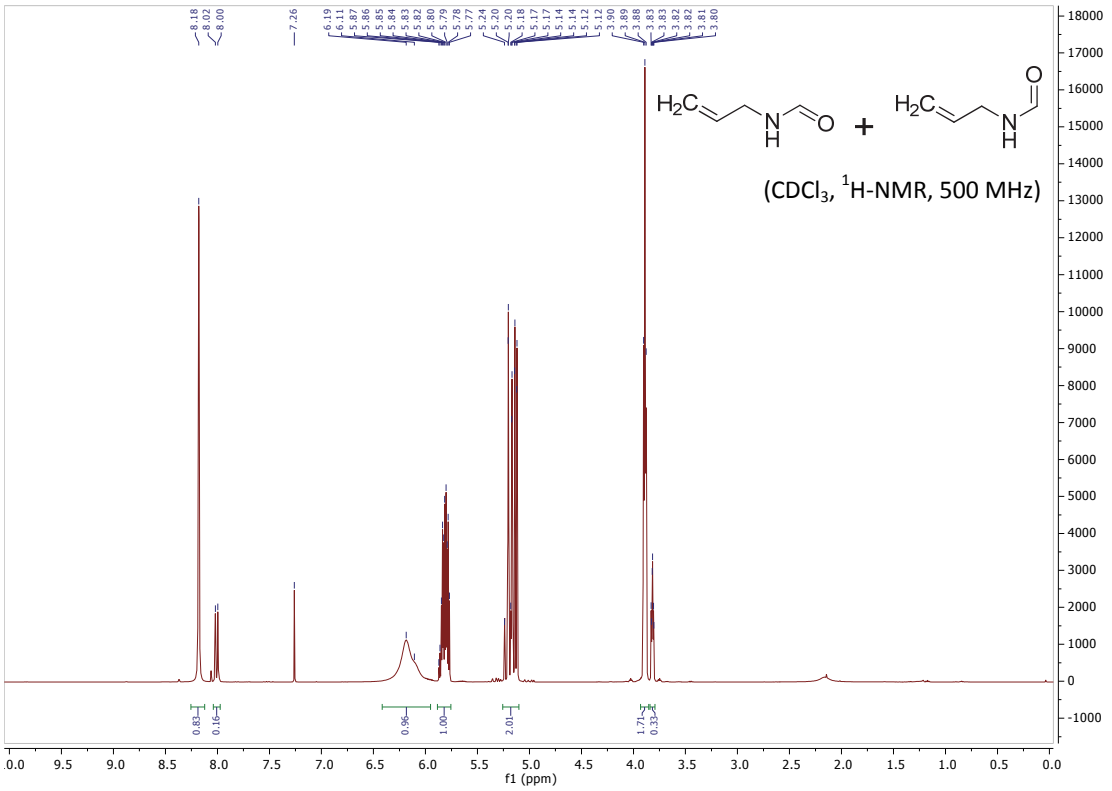


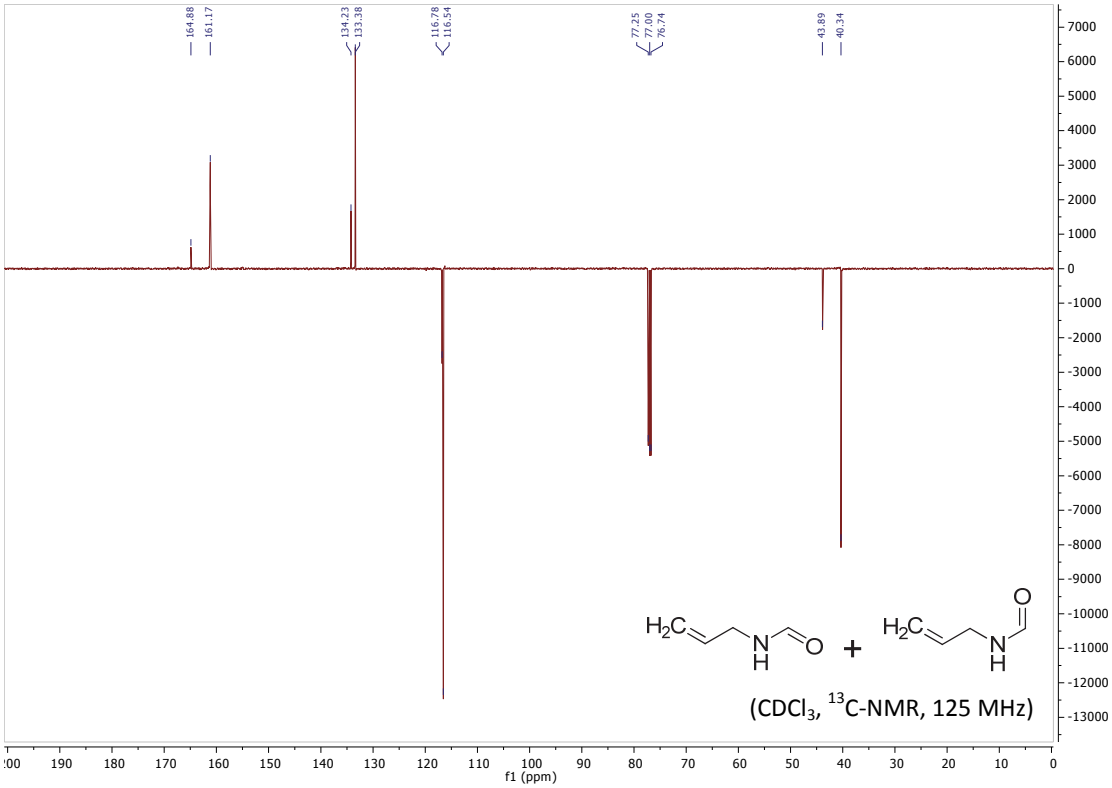
N-(2-(3-(Prop-1-en-2-yl)phenyl)propan-2-yl)formamide (20)





N-Allylformamide (21)





(*R*)-*N*-(1-Phenylethyl)formamide (22)