DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
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**EEROLD VELLEMÄE**

# Applications of mischmetal in organic synthesis

TARTU UNIVERSITY
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Faculty of Science and Technology, Institute of Chemistry, University of Tartu, Estonia

Dissertation in organic chemistry

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# LIST OF ORIGINAL PUBLICATIONS

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II. Vellemäe, E., Lebedev, O., Sillard R., Mäeorg, U. A Selective method for cleavage of N-Troc protected hydrazines and amines in mild conditions using mischmetal and TMSCl. *Journal of Chemical Research,* **2006**, 685–687.

III. Vellemäe, E., Lebedev, O., Mäeorg, U. A mild method for cleavage of N-Tos protected amines using mischmetal and $TiCl_4$. *Tetrahedron Letters,* **2008**, 49, 1373–1375.

IV. Vellemäe, E., Stepanov, V., Mäeorg, U. A Mild Approach to the De-protection of Troc from Protected Amines Using Mischmetal and TMSCl. Submitted in *Synthetic communications* **2009** (Submitted, paper number LSYC-2009-3626).

### Author's contribution

**Paper I** Performed all the experimental work and greatest part of the analysis. Prepared the manuscript.

**Paper II** Performed the experimental work and greatest part of analysis. Prepared the manuscript.

**Paper III** Performed all of the experimental work and greatest part of analysis. Prepared the manuscript

**Paper IV** Performed all the experimental work and greatest part of analysis. Prepared the manuscript

# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| ACN | acetonitrile |
| All | allyl |
| Boc | *t*-butoxycarbonyl |
| bp | boiling point |
| Bz | benzene |
| Bn | benzyl |
| Cbz | benzyloxycarbonyl |
| Cp | cyclopentadiene |
| CSA | camphor sulfonic acid |
| DMF | dimethylformamide |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| Ln | lanthanoides |
| MeOH | methanol |
| MM | Mischmetal |
| mp | melting point |
| MsOH | methanesulfonic acid |
| Nf | 1-naphtyl |
| NMR | nuclear magnetic resonance |
| Ph | phenyl |
| Pmp | 4-methoxyphenyl |
| r.t. | room temperature |
| rfx | reflux |
| Rf | retention factor |
| HMPA | Hexamethylphosphoramide |
| Hal | halogene |
| IR | infrared |
| Tos | *p*-toluenesulfonyl |
| Troc | 2,2,2-trichloroethoxycarbonyl |
| TsCl | tosylchloride |
| TEA | triethylamine |
| THF | tetrahydrofurane |
| TMSCl | trimethylchlorosilane |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| TsOH | p-toluenesulfonic acid |
| US | ultra sound |
| wt% | mass percent |

# 1. INTRODUCTION

Mischmetal (MM) is an alloy of rare-earth metals of the cerium group with cerium as the major constituent. This material is also called cerium mixed metal [1], mischmetal [2], cerium complex metal or rare earth MM and cerium MM [3]. A typical composition includes approximately (by mass) 45-55% cerium and 15-25% lanthanum, neodymium 10-20% and praseodymium 5-10% with small amounts of other metals also present in the alloy [4].

MM was first produced industrially in 1908 by Auer von Welsbach [4], who succeeded in finding an outlet for surplus rare earth material left from the production of lighter flints. From that point onward MM found several applications in industrial chemistry, especially in the metallurgical industry. Approximately 90% of the whole production of MM was used in the steel making [4].

The use of rare earth metals and their compounds in organic chemistry has grown considerably during the past 30 years [5] with samarium, cerium, lanthanum, ytterbium, neodymium, dysprosium metals/salts being the most studied ones [6]. These elements clearly differ in terms of reactivity from magnesium, zinc and copper – the metals, what has been applied in organic synthesis for more than 100 years [5]. However, the drawback of the use of lanthanoids in organic synthesis is the high price of pure metals or their compounds, causing significant efforts to be directed into finding cheaper alternatives. One way to reduce the cost of the process is the use of cheap MM instead of expensive pure lanthanoids (Sm, Nd) or their salts, such as $SmI_2$ [5,6]. This should profoundly reduce the cost of reactions without significant changes in the results. Despite the progress made in applying MM for the organic synthesis [6,7], its main use is a together with expensive Sm or $SmI_2$ to reduce the amounts of later. However, there are very few examples of the neat MM used as the main reagent or reductant that have been reported so far [6, 8–11].

Thus, main goal of this doctoral thesis was to investigate usability of the MM as a main reagent in various applications in the organic synthesis, where MM has been activated with easily available activators such as TMSCl or $TiCl_4$ with simple, reproducible and cheap procedure.

# 2. LITERATURE OVERVIEW

## 2.1. General information of mischmetal (mm)

MM is mainly an alloy consisting of first four lanthanoid metals in various naturally occurring proportions. This material is also called cerium mischmetal, cerium complex metal, rare earth mischmetal or mischmetal [1–4]. A typical composition includes approximately 45–55% cerium, 15–25% lanthanum, 10–20% neodymium and 5–10% praseodymium with small amounts of other metals by mass [4]. In the following table (Table 1) are shown the composition of MM, which have been produced in different countries [4].

**Table 1.** Composition of MM, produced in various countries

| Metal[a] | Austria | USA | Japan | Brazil | Russia | China |
|---|---|---|---|---|---|---|
| La | 23 | 18–28 | 23 | 18 | 25 | 20 |
| Ce | 50 | 50–55 | 52 | 55 | 53 | 55 |
| Pr | 5 | 4–6 | 5 | 7 | 5 | 6 |
| Nd | 19 | 12–18 | 16 | 17 | 14 | 17 |
| Sm | 0,2 | <0,1 | – | – | – | – |
| Other | 3 | <2 | 4 | 5 | 3 | 2 |

[a] – composition of lanthanoids are given in mass percents

Historically, MM was prepared from monazite $LnPO_4$, an anhydrous phosphate of the light lanthanoids and thorium. The ore was first "cracked" by a reaction at high temperatures with either concentrated sulfuric acid or sodium hydroxide [2]. The electrolysis of those molten anhydrous lanthanoide chlorides (mixed with other anhydrous halides to improve the melt behaviour) led to the formation of molten MM, which would be then cast into ingots. Any samarium content of the ore tended not to be reduced to the metal, but accumulated in the molten halide, from which it could be later profitably isolated. Currently, the high demand for neodymium has made it profitable to remove all of the heavier lanthanoids and neodymium (and sometimes all of the praseodymium as well) from the natural-abundance lanthanoide mixture for separate sale, and to include only La-Ce-Pr or La-Ce in the most economical forms of MM [2]. Thus, cheapest grade MM is typically priced at less than 10 dollars per kilogram [1].

In the beginning of 20th century scientists began searching for applications where rare-earth metals could be utilised in. Among the first discoveries/ inventions to bear practical fruits turned out to be lighter flint and the MM in steel production which remain in use even a century later [2,4].

While MM has found several applications in the industrial chemistry since the beginning of the 20th century [4], its first use in organic synthesis had to wait until 1999 when it was applied as a co-reductant in the catalytic Barbier type reactions [1]. The following sections describe the properties of MM and its applications in greater detail.

## 2.2. Properties of MM

MM is ductile metal alloy, easily machinable and workable, MM may be easily extruded at temperatures just below its melting point (mp 780 - 840 $^{o}$C). The freshly cut surface has a metallic grey/shiny appearance. In moist air, the surface oxidizes to form yellow to greenish-grey rare-earth hydroxide carbonates or oxide hydrates. Some oils can protect the surface against corrosion, but only for a limited period of time. Alloying with l-2 wt% of magnesium increases the corrosion resistance. Ingot metal burns above 150 $^{o}$C in pure oxygen, however chips, turnings and powder burn at this temperature even in air producing oxides and nitrides. MM reacts in dilute mineral acids, accompanied by the evolution of hydrogen. However, the pyrophoric character of MM may cause autoignition of the finely divided metal [4].

The physical and chemical properties of MM are being determined by the properties of its four main constituents: cerium, lanthanum, neodymium and praseodymium. In the following table (Table 2) are shown the main physical properties of Ce, La, Nd and Pr [2].

**Table 2.** Main physical properties of La, Ce, Pr and Nd

| | La | Ce | Pr | Nd |
|---|---|---|---|---|
| Density, g/cm$^3$ | 6,12 | 6,77 | 6,77 | 7,01 |
| Melting point, $^{o}$C | 920 | 804 | 935 | 1024 |
| Boiling point, $^{o}$C | 3470 | 3470 | 3017 | 3210 |
| Valence in aqueous solutions | 3 | 3 or 4 | 3 | 3 |
| Colour of $M^{3+}$ ion | colourless | colourless | yellow-green | pink |

Lanthanoids are very reactive metals and their activity could be compared to the alkaline earth metal such as Sc or Y [2]. All the rare earth metals readily react in dilute mineral acids with evolution of hydrogen. Reaction of the metal by concentrated sulfuric acid is some extent less active. The lanthanoids does not react with hydrofluoric acid because thin film of $LnF_3$ forms on the surface of the metal and protects it from further attack by the acid. A mixture of equal parts of concentrated nitric acid and concentrated hydrofluoric acid attacks most rare-earth metals only superficially, except tantalum, and thus may be used to purify corresponding alloys or separate tantalum from it. Lanthanoides also react with organic acids, but at considerably slower rates than with mineral acids at the same concentration [2].

The reaction rate of rare earth metals with water varies depending on the metal. Generally light rare earth metals react with water, slowly at room temperature and vigorously at higher temperature. The high standard reduction potential ($E^{o}$ is –2,4 up to –2,1 V) indicate that each of the rare earth elements is

a powerful reducing agent in aqueous acidic solution and forms the 3+ ion readily [2,12].

Reaction of halogens with lanthanoides gaves $LnX_3$ irrespective of the metal, but with the reaction of $F_2$ in case of Ce, Pr and Tb the corresponding tetrafluorides are formed. The general route to $LnX_3$ is the reaction of $Ln_2O_3$ with aqueous HX, resulting in the hydrated halides, $LnX_3(H_2O)_x$ (x = 6,7) [13]. The anhydrous chloride is usually made by dehydrating $LnCl_3(H_2O)_x$ using $SOCl_2$ or $NH_4Cl$ at low pressures and moderate temperatures [5]. Also it is possible to produce lanthanoide chlorides in the laboratory conditions and avoiding the high temperatures by sonication of metal powder with hexachloroethane in anhydrous THF or by reacting the lanthanoide with mercury(II)chloride in anhydrous THF. In reactions where lanthanoide halides are formed in THF, the corresponding salts also contain three molecules of solvent [5]. Lanthanoide(II) halides, especially iodides, are predominant synthetic precursors in preparations of corresponding organometallic reagents [5].

## 2.3. Applications of MM in industry

The most important uses of MM or cerium are metallurgical. The metallurgical importance of rare-earth metals is based on reactions to form complexes with oxygen, hydrogen, nitrogen, sulfur, arsenic, bismuth and antimony reducing the effects of these elements on the properties the metals [14]. To avoid the formation of harmful rare earth oxide inclusions by secondary reactions of the MM with residual slag and atmospheric oxygen, the MM plunged into the molten metal under an inert gas atmosphere. MM is added as lumps, rods, or wire [15].

### 2.3.1. Iron and steel

Rare-earth sulfides and oxide sulfides are formed in liquid steel and precipitate as globular particles uniformly dispersed. The globes are deformable during rolling and do not form stringers. This is called sulfide shape control and is used micro-alloyed or HSLA (high-strength low-alloy) steels to reduce anisotropy in toughness and bend formability. This is especially important for pipeline steels that are used at subzero temperature in the Arctic [16].

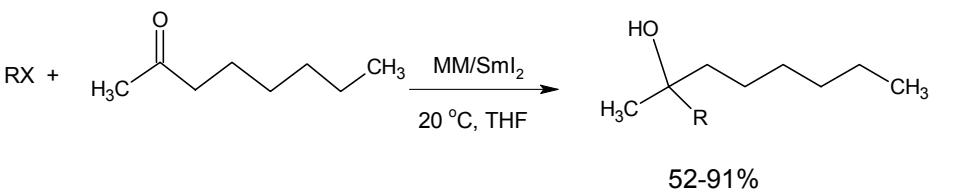
MM may also trap hydrogen and thus diminish hydrogen-induced cracking. Hot shortness in stainless steel can be reduced by removal of tramp elements (As, Br, Sb) together with sulfides. Heat and oxidation resistance can be increased by MM which forms protective surface layers of rare earth oxides together with oxides of the steel components, for example, $Cr_2O_3$ that are resistant to scaling and spalling. MM or cerium-containing master alloys are added to cast iron to improve ductility, toughness and microstructure. Cerium allows graphite to form nodules, causing nucleation in spheroid and vermicular cast iron and neutralizes the harmful effect of the tramp elements [17]. The

addition rate depends on the application and preparation of the steel or iron melt. For sulfide shape control and modularization of graphite up to 1 kg of MM per ton is added. Other effects require larger additions, up to 8 kg per ton [17]. Addition of MM to copper alloys improves tensile strength and deep-drawing properties [18,19]. The heat resistance and ductility of aluminum conductor cables are improved without any significant decrease in electrical conductivity. Titanium alloys show higher grade of grain refinement, better mechanical properties and improved corrosion resistance as result of MM additions. The need for improved galvanizing compositions without affecting formability, weldability and paintability led to the development of Galfan, which is the classical zinc-aluminum eutectic alloy (95 with Zn. 5 wt% Al) with 0.05 wt% MM in its composition [20]. In nickel and cobalt-based super-alloys for turbine engines, cerium increases oxidation and sulfidation resistance at high temperatures. Cerium and MM are also used as scrubbers to absorb traces of gas in evacuated devices. MM is said to increase the efficiency of fuel consumption and to decrease CO and NO contents in the exhaust of internal combustion engines if steam is passed through MM spirals before injection into the carburetor [4]. The pyrophoric character of mischmetal alloyed with iron and magnesium is used in flint production and pyrotechnics [20].

## 2.4 MM in organic synthesis

The applications of MM in organic synthesis are exclusively related to the use of $SmI_2$, where it has been used as a co-reductant for the purpose of reducing the amount of expensive $SmI_2$ used in the reaction. In the last few years some procedures where MM has been applied in the synthesis without $SmI_2$ have been published. Thus in the next section the overview of those reactions is presented.

Historically the first example where MM has been used in the organic chemistry was the catalytic Barbier type reaction [1] (Scheme 1).

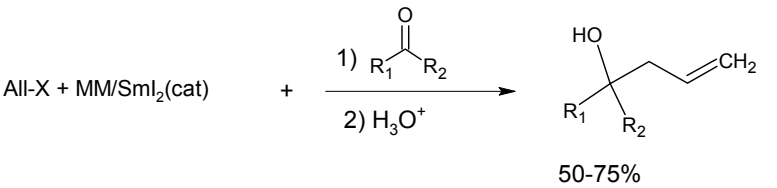



RX = $CH_2$=CH-$CH_2$-Br, $CH_2$=CH-$CH_2$-Cl, Ph$CH_2$-Br and Et-I

**Scheme 1**

A few years later the same workgroup has published their results concerning the usability of MM/$SmI_2$ in the Grignard-type allylation and benzylation of

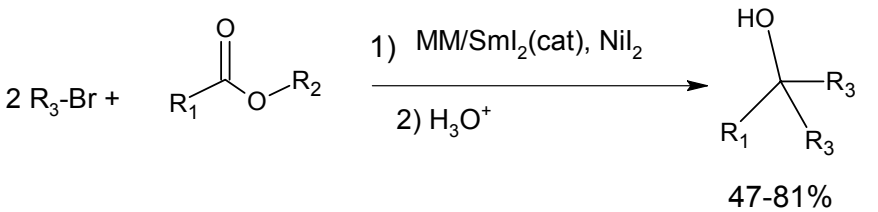
ketones and aldehydes. Catalytic reactions of allylic halides were tested with ketones and aldehydes in the Grignard-type reaction (Scheme 2) [7].




X = Br, I
$R_1$ = H, $CH_3$, Ph
$R_2$ = $CH_3$, Ph, *n*-$C_7H_{15}$

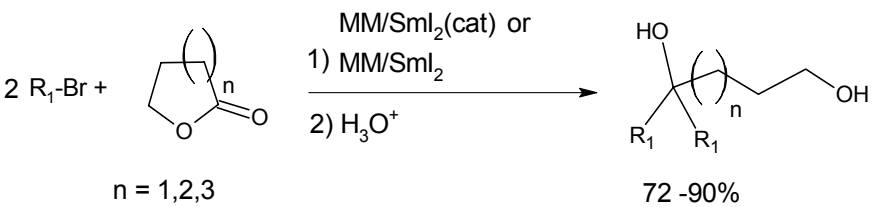
**Scheme 2**

Marie-Isabelle Lannou *et al.* [21] examined the reactivity of the system $MM/SmI_2$ in the reactions of less active electrophiles such as esters and lactones. In either case they applied catalytic Barbier-type and Grignard-type approach. They observed that reactions proceeded smoothly and produced corresponding products in good to excellent yields (Scheme 3 and Scheme 4).




$R_1$ = Ph or *i*-$C_3H_7$
$R_2$ = Et, *t*-Bu
$R_3$ = All, or $PhCH_2$

**Scheme 3**

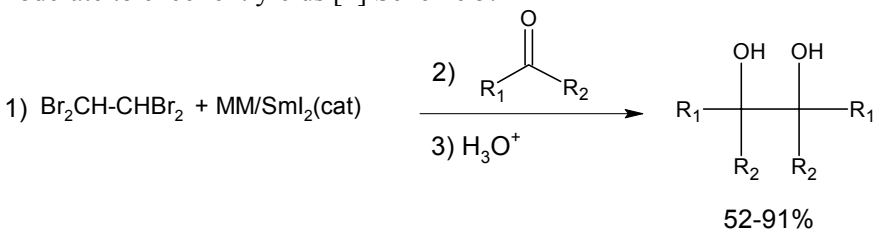



$R_1$ = All, Bn

**Scheme 4**

During the investigation they found that with an alkyl halide, a catalytic quantity of nickel diiodide must be added in some cases to achieve reactions. It was also found that nickel diiodide is not always necessary, showing that the mischmetall/$SmI_2$ (catalytic) system can be more reactive than samarium diiodide in stoichiometric amounts [21].

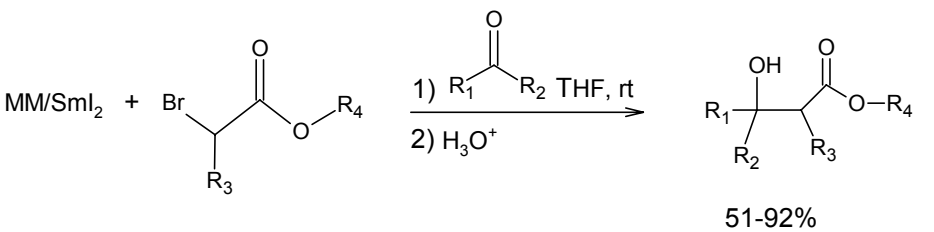
Another application of MM is its use for the pinacol coupling reactions of carbonyl compounds. The pinacol coupling of acetophenone can be readily performed with $SmI_2$ as a catalyst and MM (activated by treatment with tetrabromoethane) as a co-reductant, produces corresponding pinacols in moderate to excellent yields [1] Scheme 5.




$R_1$ = Ph, *t*-Bu
$R_2$ = H, $CH_3$

**Scheme 5**

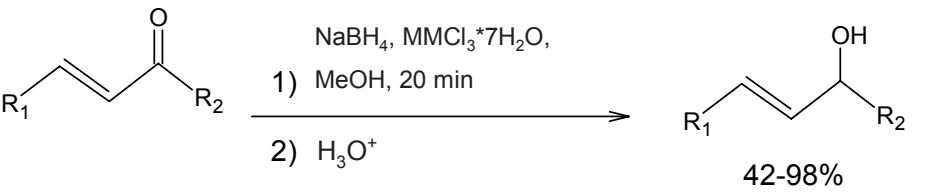
Kagan *et al.* have conducted pioneering work in the field of $SmI_2$ and $YtI_2$ mediated Reformatsky-type reactions [22], but no reaction using samarium diiodide in catalytic amounts with MM has been reported before Namy *et al.* [6]. They examined the reactivity of the MM/$SmI_2$ system in Reformatsky type reactions which gave moderate to excellent yields (Scheme 6).




$R_1$ = $PhCH_2CH_2$, Ph, *n*-$C_7H_{15}$
$R_2$ = H, $CH_3$
$R_3$ = $CH_3$, Et, *t*-Bu
$R_4$ = Et, $CH_3$

**Scheme 6**

Lannou *et al.* [8] described application of MM trihalide hydrates in Luche–type reductions of α,β-unsaturated ketones instead of classical Luche reagent ($NaBH_4/CeCl_3 \cdot 7H_2O$). In that particular reaction MM trihalide hydrates were synthesized in a one-step procedure from the inexpensive alloyed MM before the reaction, which gave moderate to excellent yields (Scheme 7).

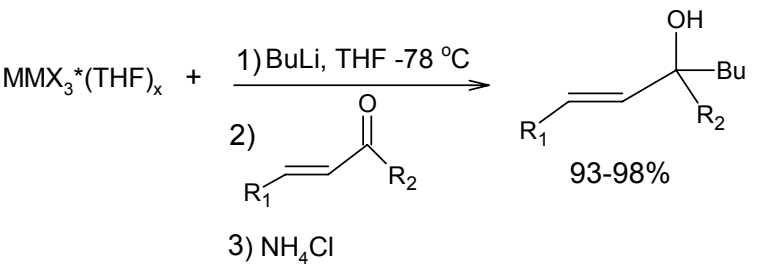



$R_1$ = PhCO, Ph,
$R_2$ = $CH_3$, Ph

**Scheme 7**

Thus $MMCl_3$ exhibited the same reactivity as cerium trichloride in the sodium borohydride reduction of highly conjugated ketones (Luche-type reduction).

Namy *et al.* [6] described the application of anhydrous MM trihalides (Cl, Br, I) in Imamoto-type reactions with a α,β-unsaturated aldehydes or ketones, which gave corresponding unsaturated alcohols in excellent yields (Scheme 8).



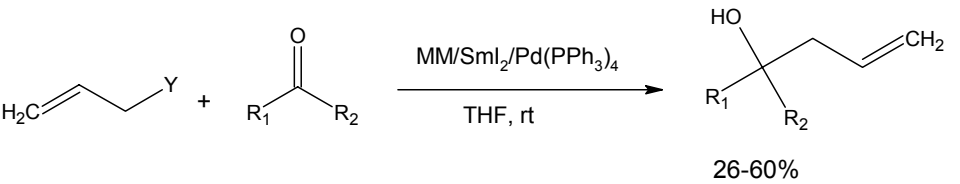

X = Cl, Br or I
$R_1$ = Ph, 2,6,6-trimethyl-1-cyclohexene-1-yl
$R_2$ = H, $CH_3$

**Scheme 8**

They also found that there is no need to use pure lanthanoide halides which have been prepared from pure metals since the use of the alloy leads to the formation of very active complexes and gave same results.

Another variation of these reaction have been developed by Médegan, S. *et al.* [23]. They succsessfully applied the MM/[$SmI_2$/Pd(0)] system to mediate the

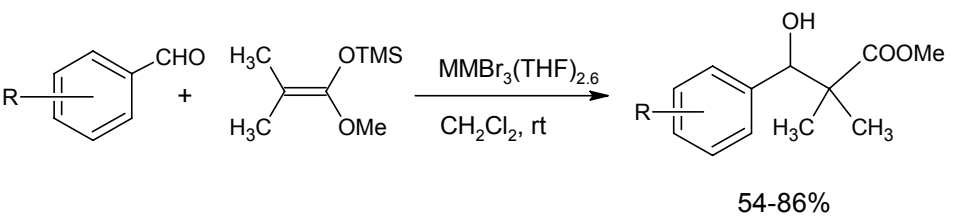
allylation of ketones using a variety of allylic esters (acetates, carbonates and phosphates) Thus, the catalytic reaction in question has been carried out using $SmI_2$ and $Pd(PPh_3)_4$ in catalytic amounts together with MM as the co-reductant. They tested those reaction conditions on the large variety of ketones and aldehydes (Scheme 9).




Y = $OCOCH_3$, $OPO(OCH_2CH_3)_2$, $OC(O)_2CH_3$
$R_1$,$R_2$ = -$(CH_2)_5$-, *n*-$C_4H_9$, $CH_3$, *n*-$C_6H_{13}$, H, Ph, $PhCH_2CH_2$

**Scheme 9**

Szymoniak *et al.* showed that using MM instead of La or Ce as the reductant gave usually higher yields compared to the use of pure metals. Other applications for MM tribromides and triiodides are in Mukaiyama aldol-type reaction [6], which is an useful tool for the formation of carbon–carbon bonds in organic chemistry and have been extensively developed (Scheme 10).



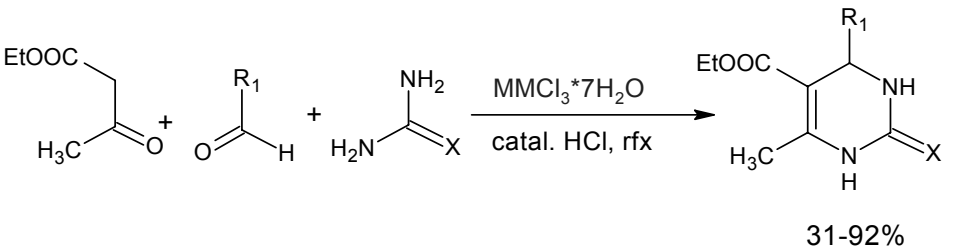

R = H, p-$OCH_3$, p-Cl, p-Br, p-$NO_2$

**Scheme 10**

The reactions proceed smoothly at room temperature, and reaction times generally depend only on the nature of the substituent in aromatic ring. For electron-withdrawing groups, the reaction can require up to 20 h to proceed to the completion, whereas for electron-donating groups the reaction was complete within an hour.

The growing interest in multicomponent reactions and the elucidation of the mechanism of the Biginelli reaction has led to the development of the various strategies to improve the results [9]. Many of these methods involve use of expensive reagents. Namy *et al.* [9] applied lanthanoide trichloride hydrates and MM in the Biginelli reaction the direct synthesis of 3,4-dihydropyrimidin-

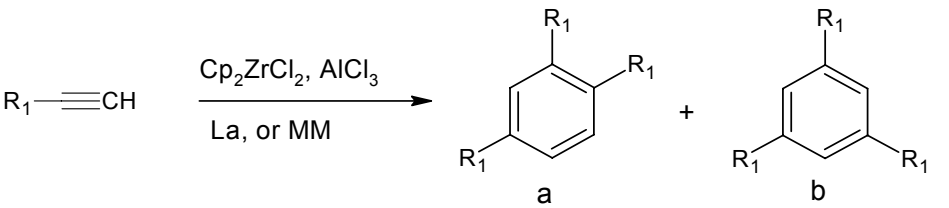
2(1H)-ones. The yields were moderate to excellent when using lanthanoide trichloride heptahydrates derived from MM (Scheme 11).




X = O, S
$R_1$ = Ph, p-$MeOC_6H_4$, m-$BrC_6H_4$, p-$HOC_6H_4$, p-$O_2NC_6H_4$

**Scheme 11**

Szymoniak *et al.* [10] described an interesting method for the trimerization and cyclotrimerization reactions of alkynes through MM and zirconocene based catalysis. Employing the lanthanoide-originated zirconocene reagent makes those reactions possible, which gives corresponding aryls in good to excellent yields (Scheme 12).



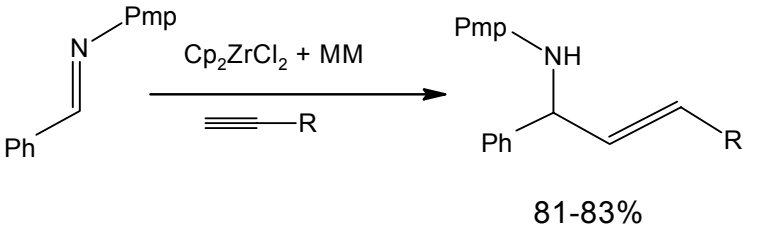

the ratio a/b is 1 or 1.5 and overal yield is 67-80%

$R_1$ = Ph, p-$MeC_6H_4$, p-$MeOC_6H_4$, 1-naphthyl

**Scheme 12**

Szymoniak *et al.* showed that using MM instead of neat La as reductant gave the same results.

Namy *et al*. [11] have also shown that MM is a useful reductant when used together with $Cp_2ZrCl_2$ in the coupling reactions of imines with alkynes (Scheme 13).




Pmp = p-$MeOC_6H_4$
R = Ph, *n*-$C_5H_{11}$

**Scheme 13**

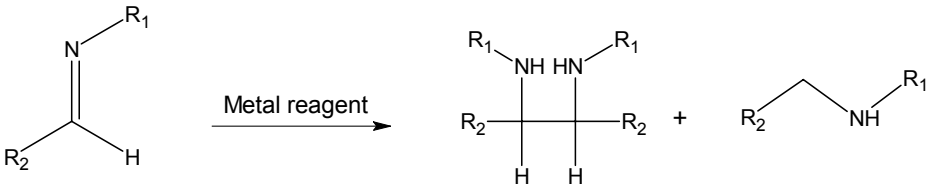
Thus, based on the short overview, where it has been demonstrated that MM can be used in different ways in the field of the organic synthesis some general features of the alloy can be pointed out:

1. MM has been used mainly as a co-reductant along with samarium diiodide in order to reduce amount of the later used in the reaction and it is the most widely applicable co-reductant for that purpose. Moreover, the system MM/$SmI_2$ can sometimes be more efficient than stoichiometric samarium diiodide or pure lanthanoides themselves [21,23].
2. In Luche and Imamoto-type reactions, complex halides prepared from MM show the same efficiency and selectivity or even better results as the pure lanthanoide halides [6,8].

As MM powder can be easily obtained and stored, and is usually more reactive and cheaper than commercially available lanthanoide metal powders, it has full potential to become a very useful reagent in organic synthesis.

## 2.5 Pinacol coupling of imines

1,2-diamines are valuable synthetic targets, which can be also employed as versatile auxiliaries for asymmetric synthesis [24]. Moreover, these substances are known to be biologically active and of therapeutic importance [25, 26]. Modern approach to the synthesis of these compounds is based on the pinacol-type coupling of imines. The synthesis of 1,2-diamines starts from imines and is mediated by a variety of metals and metal reagents conjunction with their salts such as: Zn/$Me_3SiCl$ [27], $TiCl_3$/Li [28], Sm/$Cp_2TiCl_2$ [29], $SmI_2$ [30], In/$NH_4Cl$ [31], Al/KOH and Bi/KOH [32], $AlBr_3$/Pb and TFA [33], $HgCl_2$/Mg and $TiCl_4$ [34], Zn [35], Zn/Mg [36], Zn [37], $TiCl_4$/Mg [38], Mn [39], $SmI_2$/$NiI_2$ [40], $TiCl_4$, Mg/Hg [41], Na, Li, Ba, Al(Hg) Mg($MgI_2$) [42], Sm/$I_2$ [43], $YtBr_2$ [44], $NbCl_4$ [45], Sm, Yb$(OTf)_3$, $SmI_2$/Yb$(OTf)_3$ [46]. The overall process for the corresponding reaction is described by the following Scheme 14.

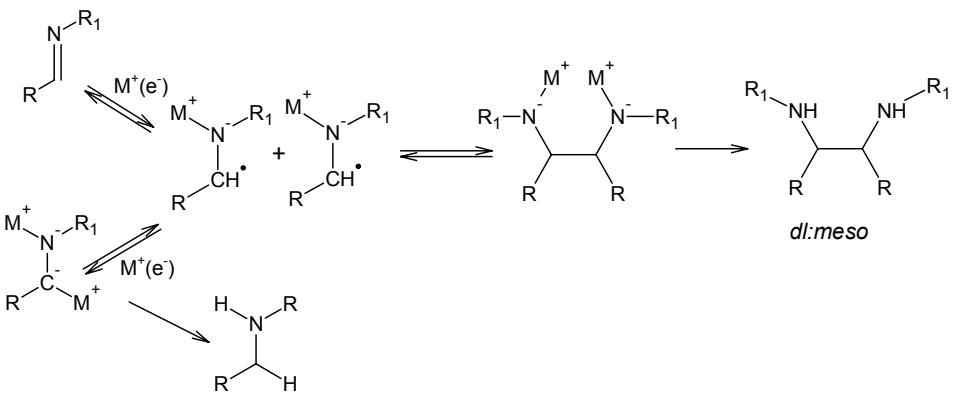



$R_1$, $R_2$ = Ar, or Alk

**Scheme 14**

However, Zn/Cu pair have been applied to conduce a numerous reactions in organic synthesis, such as: in the McMurry reaction [47], in the Reformatsky reaction [48], in the transformation of acid chlorides into aldehydes [49], in the synthesis of five- and six- member heterocycles [50], etc. Still, it is best of our knowledge, that there are only two publications considering Zn/Cu pair in the pinacol type couplind of imines [51, 52].

Pinacol-type coupling of imines to vicinal diamines is in many aspects very similar to the pinacol coupling of carbonyl compounds [53, 54] which has been extensively studied during the last thirty years or so [55]. However, imines are generally less reactive than corresponding carbonyl compounds because of the higher reduction potentials and sterical reasons (substituents at the nitrogen atom), and tend to give simple reduction products mono amines. Reactions with imines are also generally less stereoselective compared to couplings of carbonyl compounds under similar conditions. In addition, vicinal diamines formed are sensitive to oxidative cleavage, especially in the presence of acids or Lewis acids [56]. It has been also observed that diamine dianions are easily cleaved to radical anions [27, 57] and consequently the final yield of diamine depends on the equilibrium between the coupling and the cleavage reactions (Scheme 15).



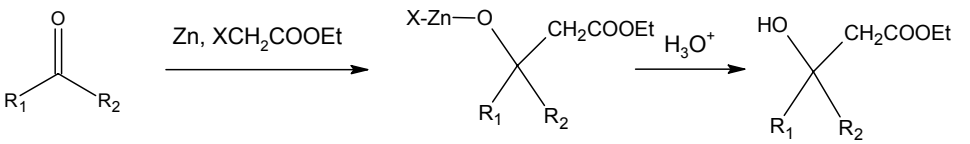

R, $R_1$ = Alk, or Ar

**Scheme 15**

Such reversibility of coupling also shifts the product isomeric ratio to the thermodynamically controlled value [57]. For example, the thermodynamically controlled isomerisation has been used for conversion of *meso*-diamine its *dl*-isomer [27]. Similarly to the pinacol couplings of carbonyl compounds, the imino-pinacol coupling is usually performed with aryl derivatives (in Scheme 20 R, $R_1$ are Ar). The most common substrates are arylimines derived from arylaldehydes. The amine partner has been varied more, but still simple aryl or alkyl groups are preferred as N-substituents. Highly diastereoselective coupling (towards useful *dl*-isomer) of imines is very rare. Still, there is one example of enantioselective imino-pinacol coupling [51], using an excess of enantiomerically pure camphor sulfonic acid

## 2.6 Reformatsky reaction

The classical form of the well-known Reformatsky reaction, introduced for the first time in 1887 consists of the zinc-induced formation of β-hydroxyalkanoates from ethyl α-haloacetates in a reaction with aldehydes or ketones [58] (Scheme 16).

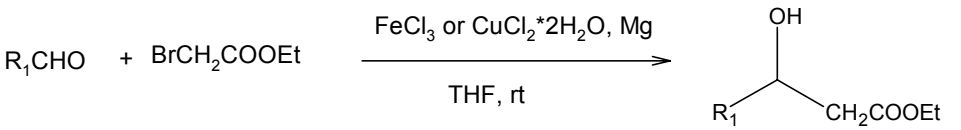



**Scheme 16**

In the Reformatsky-type reaction the organozinc compounds are prepared from α-halogenoesters in the same manner as Grignard reagents. This reaction is possible due to the stability of esters against organozinc reagents. The very low basicity of zinc enolates, does not initiate the proton transfer and the scope of carbonyl addition partners is quite broad. Thus, Reformatsky reactions have been recognized as one of the most useful methods for the formation of carbon–carbon bonds, because it proceeds under neutral conditions. Therefore this reaction became a valuable tool in modern organic synthesis with a broad applicability and great versatility in numerous inter- and intramolecular reactions involving a great variety of electrophiles. Also in recent years many articles have been published where Zn has been substituted with other metals [59]. The next section presents a short overview of those reactions.

Dubey A. K. *et al*. found that simple and very efficient procedure of performing Reformatsky reaction of aldehydes is to carry it out in the THF in the presence of low valent iron or copper that were prepared in situ, employing a

bimetal redox strategy through reduction of $FeCl_3$ or $CuCl_2*2H_2O$ with Mg [60] (Scheme 17).

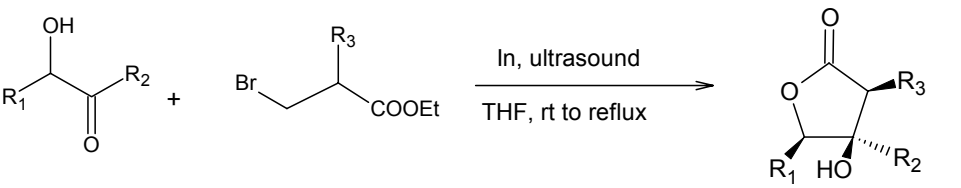



$R_1$ = $C_6H_{13}$, *n*-$C_9H_{19}$, Ph, p-(*i*-Pr)$C_6H_4$, p-$MeOC_6H_4$

**Scheme 17**

The reaction time is quite long, up to 8 hours, but the yields are 70 to 84 %.

Baba, A. *et. al.* applied indium in the Reformatsky reaction with α-hydroxyl ketones. The corresponding reaction conduced in the THF at room temperature and presence of ultrasound [61] (Scheme 18).

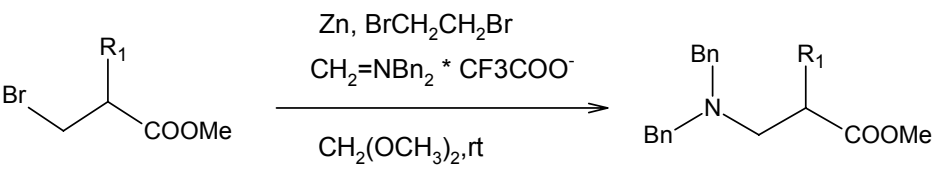



R1 = Ph, p-$MeC_6H_4$, COOMe
R2 = Ph, p-$MeC_6H_4$
R3 = Me, *i*-Pr, t-Bu, c-pentyl, *n*-$C_5H_{11}$

**Scheme 18**

The reaction time is up to 12 hours, yields are variable, from 10 to 87%.

Philippe Karoyan, P. *et al.* reported their findings on a new and highly efficient general strategy for the synthesis of α-amino acids by homologation of R-amino acids via Reformatsky reaction, with yields from 10 to 87% (Scheme 19) [62].




$R_1$ = $CH_3$, *i*-Bu, $PhCH_2$, $CH_2CO_2$, *t*-Bu

**Scheme 19**

## 2.7. Cleavage of Troc group from amines and hydrazines

The Troc group has been introduced into organic synthesis by Woodward in 1966 [63] for use in the peptide chemistry. It is a stable protecting group, which can be easily used for the masking of hydroxy and amino groups [64]. Therefore the Troc has been often used in the synthesis of biologically active compounds such as Apratoxin A [65], Isotaxel [66], aminoacridines [67], *etc*. Troc group also allows selective protection of hydrazines in the presence of other protecting groups and it is possible to proceed with an orthogonal stepwise cleavage of Troc followed by substitution by another reagent [68]. This is a very useful feature that can be utilized in the preparation of protected hydrazines [68], hydrazino acids and azapeptides [69]. According to the originally published Troc cleavage method [63] that is still being actively used today, the removal is carried out via reductive elimination process using Zn dust in 90 % aqueous AcOH. Thus, the classical deprotection conditions do not allow easily reducible or acid-sensitive groups to be retained in substrates [70]. In addition, we have sometimes observed small amounts of by-products formed during the cleavage of the Troc group from Boc(Cbz)N-N(Troc)Boc, when treated with Zn in AcOH [68]. In order to prevent side reactions and to find better reaction conditions several modifications of the original method have been proposed - the reduction using Zn-Cu in AcOH, Zn-Pb in AcOH, Cd-Pb couple in AcOH, Cd in AcOH-DMF [64]. However these methods still need acidic reaction media to cleave the Troc group.

As opposed to the methods mentioned above, several new methods have been published in recent years where Troc group has been cleaved under neutral conditions and in moderately polar solvents such as Zn in MeOH, Zn-Cu or Zn-Ag couples in MeOH, Zn in THF-$H_2O$, Na-Hg alloy in THF-MeOH [71]. Most of those new methods utilize zinc or its couples as the reducing reagent, but due to variable quality of commercially available zinc powder, the reproducibility of these procedures tend to be low.

In the recent years a few methods were published where Troc group was removed in the pH-neutral conditions, using for example In/$NH_4Cl$ in EtOH-$H_2O$ [70] mixture, or using Zn-*N*-methylimidazole in ethyl acetate or acetone [72]. Also, numerous papers have been published in the recent years where lanthanoides and corresponding salts were used for this purpose, including $SmI_2$ in THF has been applied to remove Troc group [71]. It has been also published a methods for removal of Troc group by $(Bu_3Sn)_2$ in benzene or DMF under microwave radiation [64]. Regardless of good yields of some methods mentioned and the reagents used for this purpose are notably expensive (In, $SmI_2$). Also another problem still remains, those procedures were applied exclusively in the absence of other well-known protecting groups such as Cbz, Boc, Tos and Ac.

## 2.8 Deprotection of Tos group from amines

Sulfonamides, including para-toluenesulfonyl, are one of the most stable protective group [71] for the reactive N-H moiety. The utility of the N-tosyl group as a removable protecting group for the amino function has been shown in organic synthesis for long time[71]. This group is stable under various experimental conditions like catalytic hydrogenation, treatment with acids, bases or reductants commonly used for the removal of other protective groups. This stability contributes to its usefulness, but makes N-tosyl group quite difficult to remove [73]. Most often the solution of metallic sodium or, alternatively, a solution of lithium in liquid ammonia is requied [74, 75]. Consequently with such drastic conditions being used, serious side reactions have been reported and the yields of regenerated free amine are poor [76]. The Tos group has also been cleaved by employing solution of $NaAlH_2(OCH_2CH_2OCH_3)$ or $LiAlH_4$ in toluene [77]. The other most widely used strategy for cleavage of Tos group is based on acid hydrolysis, however that requires high concentration of mineral acid at elevated temperatures for extended periods of time. Used approaches include HBr and P [78], $HClO_4$ in AcOH [79], HF-Py in anisole [80], 48% aq. HBr and phenol, 30% HBr in AcOH [81].

Thus, with classical deprotection methods requiring vigorous or even brutal reaction conditions, those methods cannot be considered as "convenient" for the cleavage of Tos group. In order to prevent side reactions and to find better reaction conditions several new methods have been published where the Tos group has been cleaved under milder condition using following approaches: Li-naphtalenide in THF [82], Li and p-di-*t*-butylbifenyl in THF [83], Na in 2-propanol [84], Mg in MeOH with sonication [85], Na(Hg) in MeOH [86], $TiCl_3$ and Li in THF [87]. Most of those new methods still utilize metallic alkali metals like Li or Na or highly reactive compounds such as $LiAlH_4$, and are not suitable methods for molecules that include easily reducible moieties/(functional groups). Moreover, in order to complete deprotection reaction without significant formation of the side products, the methods require deep cooling of the reaction mixture – Li-naphthalenide or Li with p-di-*t*-butylbifenyl in THF need to be cooled to –78$^{o}$C [82]; or alternatively, they need high temperatures and/or long reaction times to accomplish the deprotection reaction. For example, when using $NaAlH_2(OCH_2CH_2OCH_3)$ in order to remove Tos group, the reaction requires approximately 20 h reflux in toluene [77]. While some of the reported methods allow then the removal of Tos group at room temperature, those methods require long reaction times for the cleavage of Tos group in good yield. For example when using Li and $TiCl_3$ in THF, it takes approximately 18 h in THF at room temperature for reaction to proceed to completion [87]. Other methods that removing the Tos group very quickly at room temperature have also been reported [85], but the procedure was used exclusively in the presence of other well known protecting groups such as Boc-, Z- or Ac-, all of which activate amines. Unfortunately this method does not work with aromatic and aliphatic amines [85, 88] not containing activating groups mentioned

above. Numerous papers have been published recently where lanthanoides and their salts were adapted for the cleavage of the Tos group [89, 90]. Regardless of good yields of some methods mentioned, the reagents employed are either rather expensive ($SmI_2$) [90] or possess remarkable hazard to environment and human health (Na/Hg).

# 3. AIMS OF STUDY

1. To find good activator and cheap activation method for MM and test these conditions in the imino-pinacol type reaction and also compare the obtained results with other metal reagents such as Zn/Cu couple and Devarda alloy.

2. Investigate the usability of the mild activation conditions in the Reformatsky type reactions, especially the addition of the ethyl-bromoacetate into the azocompounds. Also explore the reduction properties of MM/TMSCl system.

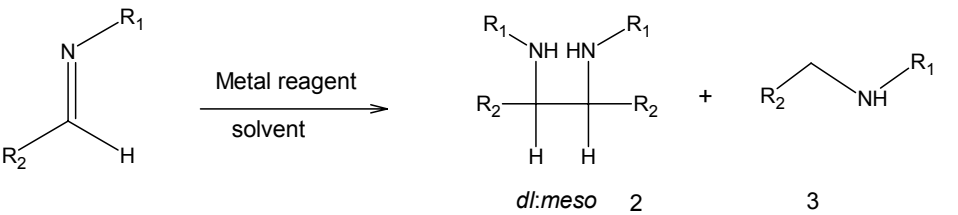
3. Investigate usability of MM/TMSCl system for selective cleavage of Troc protecting group from various Troc-protected substrates and study the influence of the other well-known protecting or functional groups (such as Boc,- Cbz-, Ac-, Tos-, MeO-, -COOEt, -COOH, and -CN) on the cleavage reaction.

4. Investigate usability of $TiCl_4$/MM system for selective cleavage of the Tos protecting group from the various Tos-protected substrates and to study the influence reaction presence of other well know protecting or functional groups such as Boc-, Cbz-, Ac-, Tos-, MeO- and -COOH to the cleavage.

# 4. RESULTS AND DISCUSSION

## 4.1 MM, Zn-Cu couple and Devarda alloy as Active reagents for the pinacol coupling of imines[I]

When this investigation was started, there was only one paper where MM has been used in the organic synthesis, particularly in pinacol-type condensation of carbonyl compounds [1]. In that publication MM was used, but it has been previously activated by $SmI_2$ that is quite expensive. The main purpose of this project was to find alternative activator and cheap method of activation for MM and to apply those conditions for pinacol-type reaction of imines. Under typical conditions, two diastereomeric 1,2–diamines and the reduction product of C=N bond are obtained as shown on Scheme 20.




**Scheme 20.**

For pinacol coupling of imines a lot of reagents (see the section 2.5 Coupling of imines p. 19), has been used, but most of those methods utilize expensive reagents such as $SmI_2$ [30], In [31], $SmI_2/NiI_2$ [40] *etc.* Also, the quality of cheap commercially available zinc powder are variable and the reproducibility of these procedures tends to be low. Thus, cheap and good method for pinacol coupling of imines are still absent.

Therefore, our goal was to investigate the usability of MM for the synthesis of 1,2-diamines and compare the results with other cheap reagents such as Devarda alloy and Zn/Cu couple was also studied. However, Devarda alloy (Al 45%, Cu 50% and Zn 5%) is widely used in the analytical chemistry [91, 92], but it surprisingly has not found any synthetic application yet.

In order to achieve the simplest reaction conditions and based on the known properties of light lanthanoides (see section 2.2, p. 11) at the beginning some experiments were carried out without activators at all. The MM and N-benzylideneaniline was refluxed in THF or EtOH (under inert gas atmosphere) for several hours, however no reaction was observed. For initiation of the coupling process a number of different activators were studied. The results of these experiments are summarized in Table 3.

**Table 3.** Pinacol coupling of N-benzylideneaniline by MM with different activators

| Entry | Starting imine, g | MM, g | Solvent and reaction temp. | Reaction time, h | Activator | Conver-sion, % |
|---|---|---|---|---|---|---|
| 1 | 0.25 | 0.5 | EtOH, rfx | 2.5 | – | 0 |
| 2 | 0.25 | 0.5 | THF,rfx | 2.5 | – | 0 |
| 3 | 0.25 | 0.5 | THF, rfx | 0.7 | US | 0 |
| 4 | 0.25 | 0.5 | THF, rt | 1 | US | 0 |
| 5 | 0.15 | 0.3 | EtOH, rt | 4 | US | 0 |
| 6 | 0.15 | 0.3 | EtOH, rfx | 2.5 | US | 0 |
| 7 | 0.25 | 0.5 | THF, rfx | 2 | 36% HCl, 0.1 ml | <30 |
| 8 | 0.25 | 0.5 | EtOH, rfx | 2 | $CuCl_2 \times 2H_2O$, 0.13g | Traces |
| 9 | 0.25 | 0.5 | THF, rfx | 2 | Dest. $H_2O$, 0.025 ml | 0 |
| 10 | 0.15 | 0.3 | EtOH, rfx | 2 | $I_2$, 0.03 g | 0 |
| 11 | 0.15 | 0.3 | THF, rfx | 3 | $I_2$, 0.03 g | 0 |
| 12[a] | 0.15 | 0.3 | THF, rfx | 3 | $MM_xI_y$, 0.03 g | 0 |
| 13 | 0.15 | 0.3 | THF, rfx | 3 | TMSCl, 0.18 ml | >99 |
| 14 | 0.15 | 0.3 | THF, rfx | 3 | $TiCl_4$, 0.1 ml | 50[b] |
| 15 | 0.15 | 0.3 | THF, rfx | 3 | $Ni(OAc)_2$ 0.03 g | 0 |
| 16 | 0.15 | 0.3 | THF, rfx | 3 | $ZnCl_2$, 0.03g | 0 |
| 17 | 0.15 | 0.3 | THF, rfx | 3 | $CoCl_2$, 0.03g | 0 |
| 18 | 0.25 | 0.5 | THF, rfx | 2 | $NiI_2$, 0.07g | <30 |
| 19 | 0.15 | 0.3 | THF, rfx | 2 | $Ce(OBu)_4$, 0.07g | 0 |

[a] – $MM_xI_y$ (prepared according to the procedure in [31]

[b] – approximately 50 % of reduction product was also observed

Thus, based on the results of those experiments, the trimethylsilyl chloride (TMSCl) was found to be the best activator. The reactivity of the majority of other "activator" compounds was either lower or entirely absent. The reaction was conducted in the THF and before the 1 eq. imine was added, the 2.6 eq. MM was activated with 1.6 eq. of TMSCl by refluxing the mixture 30 minutes under argon. However, THF has been widely used solvent in the organic synthesis, but still it is not very convenient one, because it is highly flammable and gives easily highly-explosive peroxides on storage in air. Therefore several alternative solvents were tested and the N-benzylideneaniline was used again as a starting imine. The results are outlined on the Table 4.

**Table 4.** The influence of solvents in pinacol coupling of N-benzylideneaniline[a]

| Entry | Starting imine, g (mmol) | MM, g (mmol) | Solvent[a] | Time of reaction, h | Conversion, % |
|---|---|---|---|---|---|
| 1 | 0.25 (1.4 ) | 0,5g (3.5) | $CH_3CN$ | 6 | 50 |
| 2 | 0.25 (1.4 ) | 0,5g (3.5) | dry THF | 6 | 0 |
| 3 | 0.25 (1.4 ) | 0,5g (3.5) | $CH_2Cl_2$ | 6 | 0 |
| 4 | 0.25 (1.4 ) | 0,5g (3.5) | $CHCl_3$ | 6 | 0 |
| 5 | 0.25 (1.4 ) | 0,5g (3.5) | n-$C_6H_{14}$ | 6 | 0 |
| 6 | 0.25 (1.4 ) | 0,5g (3.5) | Ph-$CH_3$ | 6 | 0 |
| 7 | 0.25 (1.4 ) | 0,5g (3.5) | $Et_2O$ | 6 | 0 |
| 8 | 0.25 (1.4 ) | 0,5g (3.5) | THF + 1eq. $H_2O$ | 1.5 | >99 |

[a] – all the reactions were performed under argon atmosphere at reflux conditions

Based on the results obtained (Table 4 p. 28), the solvents other than THF were not appropriate for pinacol coupling. The importance of water in pinacol coupling of N-benzylideneaniline with MM in THF was also discovered. Indeed, unexpectedly the pinacol coupling did not occur in dry THF. During the studies it was found that in order to start the coupling reaction it was necessary to add 1.0 eq of $H_2O$ for the initiation of the coupling process. Without water no reaction occurred even after refluxing the reaction mixture with activated MM for several hours. In order to understand the reaction pathway better, the coupling reaction was studied with $D_2O$ instead of $H_2O$. The product was isolated and characterized by $^1H$, $^{13}C$ NMR and FTIR spectroscopy. The spectral data were essentially the same as the product obtained in typical procedure. Evidently, $H_2O$ reacts with TMSCl and the formed HCl is responsible for MM activation. To confirm the assumption, an equivalent amount of HCl in dioxane was used instead of water and that resulted in full conversion.

The work-up technique was found to be crucial. Common liquid–liquid extraction caused remarkable decomposition of the 1,2-diamines back to imines probably due to their prolonged contact with MM chlorides left in the solution. The, cleavage of C-C bond in 1,2-diamines is known to be induced by the atmospheric oxygen in the presence of Lewis acids [56]. In order to hold back the decomposition and to retain the diastereomeric ratio of product, column chromatography was used. No inversion of the diastereomeric ratio was noticed during the work-up.

The results of the pinacol coupling of several aldimines mediated by MM, Zn-Cu couple and Devarda alloy under appropriate reaction conditions are outlined in the Table 5.

**Table 5.** Pinacol coupling of aldimines with different reagents

| Entry | Compound | Reaction time, min | | | Crude yield % (2+3) | | |
|---|---|---|---|---|---|---|---|
| | | MM | Zn/Cu | Dev[a] | MM | Zn/Cu | Dev |
| 1 | Ph-CH=N-Ph | 90 | 40 | 120 | >99 | 77 | 89 |
| 2 | p-MeO-Ph-CH=N-Ph | 60 | 10 | 180 | 87 | 63 | 37 |
| 3 | Ph-CH=N-$CH_2$-Ph | 40 | 60 | 50 | 40 | 90 | 39 |
| 4 | Ph-CH=N-Ph-m-OMe | 90 | 60 | – | 89 | <99 | – |
| 5 | Ph-CH=N-Ph-p-OMe | 90 | 25 | 100 | 87 | 47 | 6 |
| 6 | o-HO-Ph-CH=N-Ph | 60 | 30 | 45 | 14 | 71 | 13 |
| 7 | Ph-CH=N-Nf | 90 | 15 | 360 | 11 | 58 | 0 |

| Entry | Compound | *d,l: meso* ratio | | | Reduction product (3) | | |
|---|---|---|---|---|---|---|---|
| | | MM | Zn/Cu | Dev[a] | MM | Zn/Cu | Dev |
| 1 | Ph-CH=N-Ph | 1,1:1 | 1:3.4 | 1:2.4 | 0 | 0 | 0 |
| 2 | p-MeO-Ph-CH=N-Ph | 1,2:1 | 1:1.2 | 1:2.6 | 0 | 0 | 0 |
| 3 | Ph-CH=N-$CH_2$-Ph | 1:11 | 99>1 | 1<99 | 0 | 0 | 0 |
| 4 | Ph-CH=N-Ph-m-OMe | 1,1:1 | 1:2.7 | – | 0 | 0 | – |
| 5 | Ph-CH=N-Ph-p-OMe | 1:2 | 1<99 | 99>1 | 0 | 0 | 0 |
| 6 | o-HO-Ph-CH=N-Ph | 99:1 | 1.2:1 | 2.2:1 | 0 | 0 | 32 |
| 7 | Ph-CH=N-Nf | 1,1:1 | 1:1.2 | – | 48 | 6 | 4 |

[a] – Devarda alloy

Under the conditions employed, mixtures of *d,l*- and *meso*-isomers were obtained in comparable amounts, in ratios from 1.2 : 1 up to 1 : 1.1. Compounds 3, 5 and 6 afforded excellent diastereoselectivity, furnishing only *d,l*- or *meso*-isomer depending on the compound and metal reagent used. These experimental results support the assumption that the structure of substrate and the nature of reducing agent are the most important factors in the control of reaction diastereoselectivity.

The simple C=N reduction was not typical for the majority of studied aldimines, except compounds 6 and 7 where monoamines were detected by $^{13}C$ NMR spectroscopy (see Table 5 p. 29). This can be explained by the relative bulkiness of the intermediate radical anion, hindering the coupling and therefore increasing the extent of the ordinary C=N reduction. The pinacol coupling with MM and Zn/Cu couple occurred smoothly, furnishing the products in moderate to excellent yields (up to 99). However, the same reaction with Devarda alloy generally gave modest yields (<50%), except only N-benzylideneaniline gave 89 % yield. This is interesting, because Devarda alloy also includes active metals such as Al and Zn. The exact reasons why the pinacol coupling of imines with Devarda alloy result in only moderate yields remains unclear, but one explanation could be that TMSCl is not the best activator for the Devarda alloy.

Thus, during this research an extremely simple, cheap and reproducible protocol for the use of MM in the reaction of pinacol coupling of imines has been developed.

## 4.2. A MM mediated Reformatsky type reaction of azocompounds

The based previous results demonstrated that system MM/TMSCl, worked successfully in pinacol coupling of imines. Therefore, it was proceeded to test those mild conditions in the Reformatsky-type reaction with azocompounds in order to produce directly the corresponding substituted hydrazines. To the best of our knowledge, Reformatsky-type reaction has not been applied yet in such manner. Therefore, it was first needed to study whether the MM/TMSCl system is capable to perform the corresponding Reformatsky-type reaction and if these conditions could be applicable with azocpmpounds. Thus, the acetophenone and ethyl bromoacetate were first tested as a model system with the MM/TMSCl to find out if it is possible to produce corresponding classical Reformatsky-type reaction. It was already known, that the MM needs to be activated before it can be used in the reaction and in order to keep the conditions as simple as possible some very cheap activators were studied, such as $BrCH_2CH_2Br$, $I_2$, $I_2$+TMSCl and TMSCl. The results of these experiments are outlined in the following Table 6.

**Table 6.** Activation of MM in Reformatsky reaction

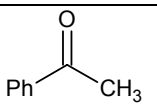
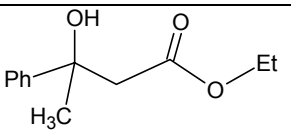
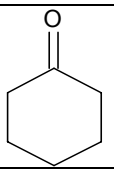
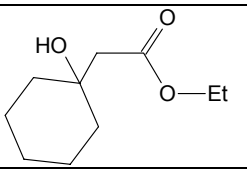
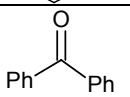
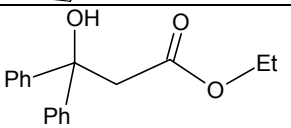
| Entry | $PhCOCH_3$, mmol/ $BrCH_2COOEt$, mmol | MM, mmol | Activator, mmol | Reaction[a] time (h) | Conversion, % |
|---|---|---|---|---|---|
| 1 | 0.5 / 1 | 0.7 | $BrCH_2CH_2Br$, 0.5 | 0.5 | 0 |
| 2 | 0.5 / 1 | 0.7 | $I_2$ (cat.) | 1 | 0 |
| 3 | 0.5 / 1 | 0.7 | $I_2$/TMSCl, cat./0.07 | 1.5 | >99[a] |
| 4 | 0.5 / 1 | 0.7 | TMSCl, 0.07 | 1 | >99[a] |
| 5 | 0.5 / 1 | 0.7 | $BrCH_2CH_2Br$, 0.5 | 0.5 | 0 |
| 6 | 0.5 / 1 | 0.7 | $I_2$ (cat.) | 1 | 0 |
| 7 | 0.5 / 1 | 0.7 | $I_2$/TMSCl, cat./0.07 | 1.5 | >99[a] |
| 8 | 0.5 / 1 | 0.7 | TMSCl, 0.07 | 1 | >99[a] |
| 9 | 0.35 / 0.7 | 1.4 | TMSCl, 0.07 | 1 | >99[a] |
| 10 | 0.35 / 0.7 | 1.4 | TMSCl, 1.4 | 0.3 | >99 |

a – In the reactions 3–5 instead of the Reformatsky type additon product a complex mixtures were formed

It was found that the reaction is very sensitive to water. Prior the reaction, the flask was flame-dried and cooled down in the argon atmosphere to the room temperature. When we used $BrCH_2CH_2Br$ and $I_2$ as an activators in order to activate MM, essentially applied the activation procedure published before [6]. However, those activation methods were not effective to activate MM in our case. However, TMSCl was found to be the best activator for activating the MM and the best results were obtained when the ratio of acetophenone, ethyl

bromoacetate, MM and TMSCl was 1:2:4:4. Thus, after optimizing the reaction conditions, other ketones were subjected to the reaction conditions described above (see entry 6, Table 6 p. 30). The results are outlined in Table 7**.**

**Table 7.** Reformatsky type reaction of MM with different ketones

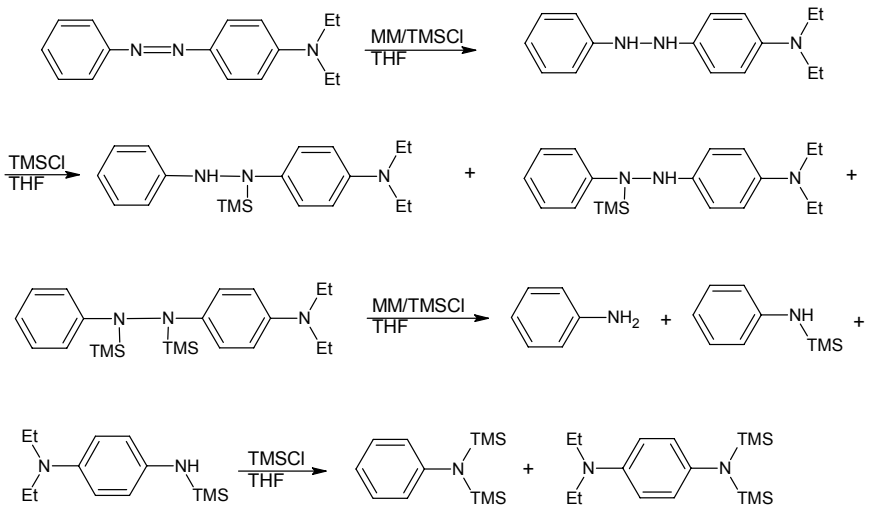
| Entry | Starting compound | Product | Reaction time, h | Crude yield, % |
|---|---|---|---|---|
| 1 |  |  | 0.3 | <99 |
| 2 |  |  | 1 | 24 |
| 3 |  |  | 3 | – |

The best results were obtained with acetophenone (99% yield of crude product). In case of cyclohexanone, the conversion was >99%, but the crude yield remained moderate. Also, it was surprise that benzophenone did not react at all supposedly due to large sterical hindrance around the reaction centre. Taking into account that the classical Reformatsky-type reactions with carbonyl compound were not our primary goal, we did not expand the scope of the reaction by using other ketones and did not optimize the separation procedure. Based on the some previously explored examples, it was confirmed that MM activated by TMSCl was able to perform Reformatsky-type reaction. A set of azocompounds what included electron withdrawing and electron donating substituents subjected to those reaction conditions described above. The results are outlined in the Table 8.

**Table 8.** Reformatsky type reaction of MM with azocompounds

| Entry | Starting compound | Reaction time, (h) | Products |
|---|---|---|---|
| 1 | Boc-N=N-Boc | 1.5 | Boc-NH-NH-Boc + Boc-NH-N(TMS)-Boc ratio (1:1) |
| 2 | Cbz-N=N-Ph | 0.5 | Cbz-NH-N(TMS)-Ph |
| 3 | Cbz-N=N-Boc | 2 | Cbz-NH-NH-Boc + Cbz-NH-N(TMS)-Boc ratio (1:1.5) |
| 4 | Boc-N=N-Ph | 0.5 | Boc-NH-N(TMS)-Ph |
| 5 | Ph-N=N-Ph | 1 | Ph-NH-NH-Ph + Ph-N(TMS)-N(TMS)-Ph ratio (1.5:1) |
| 6 | Tos-N=N-Ph | 0.5 | Mixture |
| 7 | Troc-N=N-Ph | 0.5 | Mixture |
| 8 | Cbz-N=N-Troc | 2 | Mixture |
| 9 | Boc-N=N-$C_6H_4$p-$NO_2$ | 0.5 | Mixture |
| 10 | Ph-NH-N=N-Ph | 1.5 | Mixture |
| 11 | Ph-N=N-$C_6H_4$p-$NH_2$ | 1 | Mixture |
| 12 | Ph-N=N-$C_6H_4$p-$N(Et)_2$ | 4 | Mixture |

In the course of these studies it has been confirmed that the reaction in itself proceeds smoothly, the reaction times in most cases were less than two hours and the starting materials were completely consumed. However, it was an absolute surprise that among so many azocompounds what was tested, no one of them gave the corresponding Reformatsky-type addition product. Instead of the Reformatsky-type addition product complex mixtures (reactions entry 6–12) and simple hyrdazines or their silylated forms (reactions entry 1–5) were produced. In order to achieve our goal, some modifcations to the reaction conditions were made such as: acetonitrile was used instead of THF, reactions were performed at the room temperature instead of the reflux conditions and also the ratio of MM/TMSCl/$BrCH_2COOEt$ was varied. The modifications affected only the time of the reaction, but not the final outcome. Thus, the attempts to perform the Reformatsky-type reaction with azocompounds were completely unsuccessful. In the course of these studies it was discovered that system MM/TMSCl has a remarkable reduction potential in the very dry aprotic media. Considering this and the used excess of the TMSCl can provide a tangible explanation why complex mixtures were formed. We proposed a following scheme for explanation how that complex mixture could be obtained (Scheme 21).



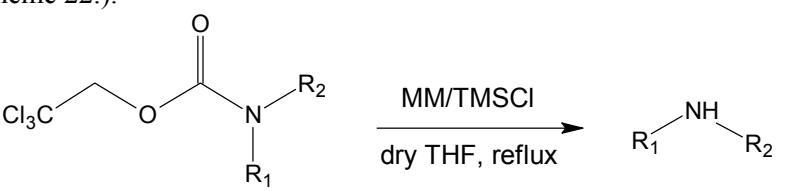

**Scheme 21**

In the example nine different products are possible. As was mentioned before the complex mixtures were not analyzed by the NMR, but only by the TLC. In that particular example we detected eight different spots on the TLC plate. Thus, it somewhat gives a distant confirmation of the scheme presented. The presented example was not the exception - the other azocompounds gave similar results.

## 4.3 Selective method for cleavage of Troc protecting group from hydrazines, amines and amino acids[II,IV]

Based on the previous results of the thesis, where it was discovered that the MM/TMSCl system has powerful reductive properties in the dry aprotic media (in dry THF), the cleavage of Troc group from various protected substrates was investigated subsequently.

The aim of our study was to investigate if it is possible to selectively cleave Troc protecting group in the presence of other well-known protecting groups such as Boc-, Tos-, Ac- and Cbz- groups, in the pH neutral conditions with MM/TMSCl from corresponding protected amines, amino acids and hydrazines (Scheme 22.).




**Scheme 22**

It was first tried to achieve the cleavage of Troc group under the simplest reaction conditions. The conditions tested were: MM in MeOH with ultrasonic treatment, MM in EtOH in the presence of catalytic amount of HCl, MM in THF in the presence of 1 equivalent of $H_2O$. All these reactions were performed at room temperature as well as under reflux with relevant solvent. Despite of known reaction of MM with water and alcohols none of these attempts resulted in the cleavage of Troc group. In order to facilitate the deprotection reaction different activators were studied: TMSCl, $NH_4Cl$ and 1,2-dibromoethane. The most efficient cleavage of Troc group was observed when 6.1 equivalents of MM and 9.3 equivalents of TMSCl were used (Table 9 entry 12).

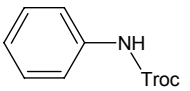
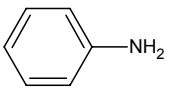
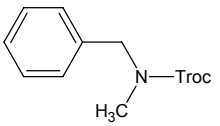
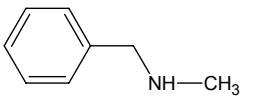
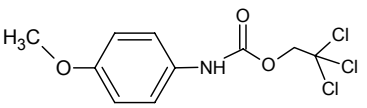
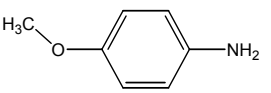
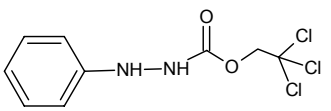
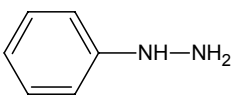
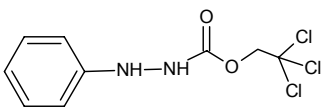
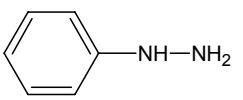
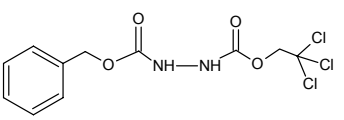
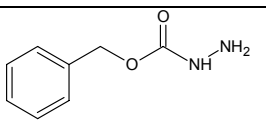
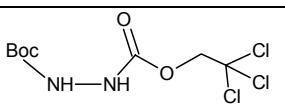
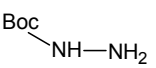
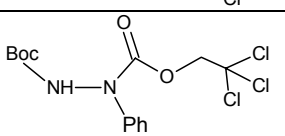
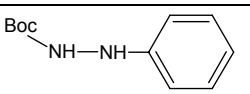
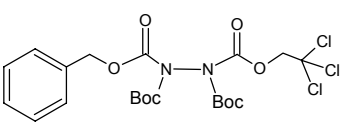
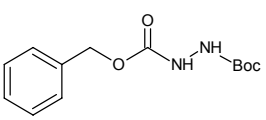
**Table 9.** Optimization of reaction conditions

| Entry[a] | Compound | MM (equiv) | Activators (equiv) | Conversion % |
|---|---|---|---|---|
| 1 | Z-NH-NH-Troc | 3.9 | TMSCl (3.8) | <10 |
| 2 | Ph-NH-NH-Troc | 3.8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1) | 50 |
| 3 | Z-NH-NH-Troc | 3.8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1) | 50 |
| 4 | Z-NH-NH-Troc | 3.8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1.6) | >90 |
| 5 | Ph-NH-Troc | 3.8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1,6) | >90 |
| 6 | p-$CH_3O$-Ph-NH-Troc | 3,8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1.6) | 50 |
| 7[b] | p-$CH_3O$-Ph-NH-Troc | 2.0 | $NH_4Cl$, (3) | <30 |
| 8 | Ph-NH-NH-Troc | 3.8 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 1.6) | >90 |
| 9 | p-$CH_3O$-Ph-NH-Troc | 3.8 | Br-$CH_2$-$CH_2$-Br (1.6) | 0 |
| 10 | p-$CH_3O$-Ph-NH-Troc | 4.5 | TMSCl , Br-$CH_2$-$CH_2$-Br (4: 2.3) | >80 |
| 11 | p-$CH_3O$-Ph-NH-Troc | 6.1 | TMSCl , Br-$CH_2$-$CH_2$-Br (4:1.6) | >90 |
| 12 | p-$CH_3O$-Ph-NH-Troc | 6.1 | TMSCl (9.3) | >99 |
| 13 | p-$CH_3O$-Ph-NH-Troc | 6.1[c] | TMSCl (9.3) | <10 |

a. All the reactions performed under reflux in dry THF
b. Reaction entry 7 was performed with MM in EtOH:$H_2O$ (3:2), but the reaction conditions were used as described in reference 70 and experiment was finished after 12 h
c. In the reaction entry 13 only Zn was used and reaction was finished after 4 h

Having first optimized the deprotection conditions, various Troc protected hydrazines as well as some aromatic and aliphatic Troc-protected amines were prepared according to methods previously published [93] and subjected to the deprotection conditions described above (entry 12, Table 9). The results are outlined in Table 10.

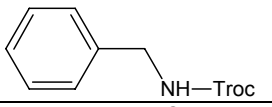
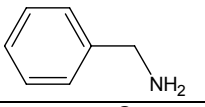
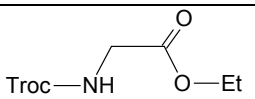
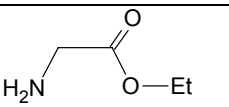
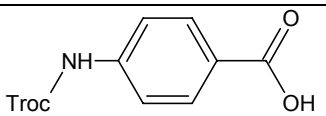
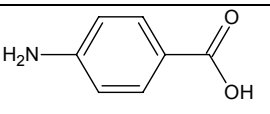
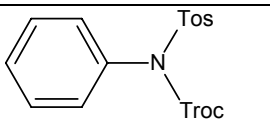
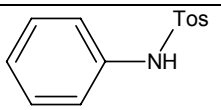
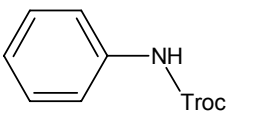
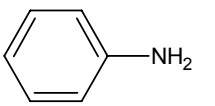
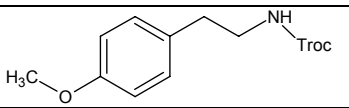
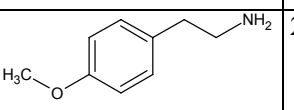
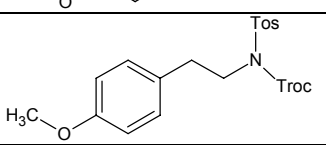
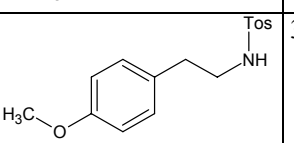
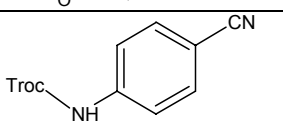
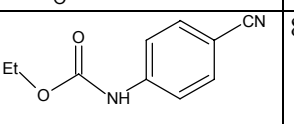
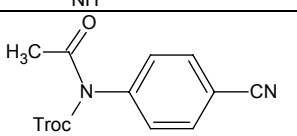
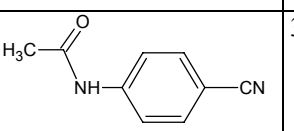
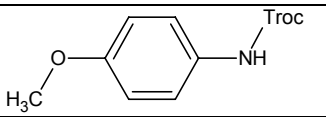
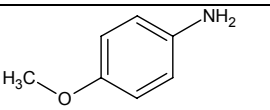
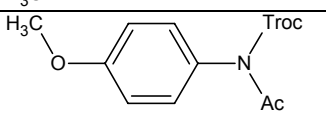
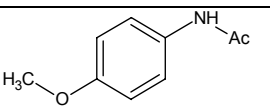
**Table 10.** Deprotection of Troc group from Troc-N compounds

| Entry | Compound | Product | Reaction time, h | Yield, % |
|---|---|---|---|---|
| 1 |  |  | 2 | 95[b] |
| 2 |  |  | 2 | 85[b] |
| 3 |  |  | 3 | 82 |
| 4 |  |  | 3 | 60 |
| 5[d] |  |  | 3 | 83 |
| 6 |  |  | 3 | >99 |
| 7 |  |  | 2 | >99 |
| 8 |  |  | 4 | 56 |
| 9 |  |  | 2,5 | 80 |

It can be seen that the reaction proceeds smoothly to furnish the corresponding deprotected products. In the course of these studies it was confirmed that the activated MM in THF is capable to remove Troc protecting group in the presence of other common protecting groups such as Boc and Cbz. The cleavage of Troc group was very selective except for compound entry 9 (Table 10, p. 35) where one Boc group was also removed. This result was expected because of the known destabilizing influence of Cbz group towards the Boc group, connected both at the same nitrogen. This phenomenon was demonstrated recently by the cleavage of Boc group from the Boc(Cbz)N-N($CH_3$)Boc in MeCN with $Mg(ClO_4)_2$ as a Lewis acid [68]. Other authors [94, 95] have also reported that Boc group undergoes reduction in stability if other protecting groups (Cbz, Boc, Ac) shared the same nitrogen atom and consequently they could be easily cleaved with Lewis acids. During the activation of MM the corresponding lanthanoide chlorides were formed and they act as Lewis acids in cleavage of Boc group. Taking into account this phenomenon, it should be possible to cleave with MM/TMSCl reagent selectively one Boc group from bis-Boc protected amines or hydrazines which include two Boc groups at the same nitrogen atom, but this lies beyond our present goal. Indeed the behaviour of MM under these conditions is interesting, as it allows selective cleavage of Troc group from Troc(Boc)N in substituted hydrazines while Boc group remains unattached. This is a very good example of orthogonality by the cleavage of Troc group. Taking into account that Troc group is generally removed via reductive elimination process, we suppose that lanthanoide chlorides formed during activation of MM, which act as mediators for deprotection of Troc group and MM itself behave as an electron donors. In the presence of water these salts can be hydrolysed effectively quenching the reaction. This could be the explanation why reaction must be conducted in water-free environments. These results were confirmed that MM/TMSCl system is able to cleave Troc group under neutral conditions from hyrdazines. Based on the previous results, where it was succsessfully demonstrated the ability of MM/TMSCl system in the selective cleavage of Troc group, initiated to study the limits of this method.

The aim of the following study was to explore this mild method when other well-known protecting and functional groups such as Tos, Ac, CN and COOEt are presented in substrate. Various Troc-protected aromatic and aliphatic amines were prepared, according to methods previously published [93] and subjected to the deprotection conditions described above (see entry 12, Table 9 p. 34). The results are outlined in the Table 11.

**Table 11.** Deprotection of Troc group from substituted amines

| Entry | Compound | Product | Reaction time, h | Yield, % |
|---|---|---|---|---|
| 1 |  |  | 3 | 62[c] |
| 2 |  |  | 4 | 88 |
| 3[a] |  |  | 24 | No reaction |
| 4 |  |  | 3 | 54[c] |
| 5 |  |  | 2 | 92 |
| 6 |  |  | 2 | 87 |
| 7 |  |  | 3 | 80 |
| 8 |  |  | 8 | 60[c] |
| 9 |  |  | 3 | 65[b] |
| 10 |  |  | 3 | 81 |
| 11 |  |  | 1,5 | 52[b,c] |

a. In the reaction number 3, 4 mmol of MM and 6,2 mmol of TMSCl was used instead of optimized conditions.

b. The yields of the products 9 and 11 were determined after purification of crude product by column chromatography.

c. brine was used for washing the extract instead of distilled $H_2O$

It shows that reactions proceeds smoothly, yielding the corresponding deprotected products. In the course of these studies was confirmed that activated MM in THF is capable selectively remove the Troc protecting group from aliphatic and aromatic amines in the presence of other well-known protecting groups such as Ac and Tos or presence of other potentially reactive functional groups such as CN and COOEt. The cleavage of Troc group was very selective under mild conditions and ester group, as well as other protecting groups remained unaffected. Behavior of the MM under these conditions is interesting, because it allows for the selective cleavage of Troc group from Troc(Tos)N fragments in substituted amines. The selective cleavage of Troc from Troc(Tos)N moiety is a very good example of the orthogonality of this method.

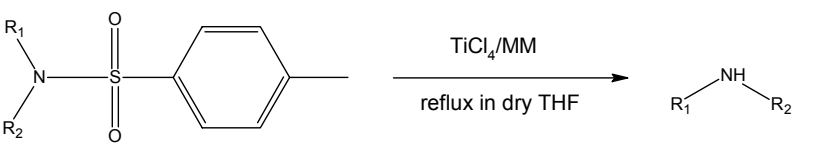
During this investigation it was found that TMSCl/MM system in THF cleaves Troc group from p-MeO-$C_6H_4$-NH-Troc considerably faster than in the published method [70], where Troc group was cleaved with In/$NH_4Cl$ in EtOH:$H_2O$. The reaction times were 3h and 4h respectively. Also, when was compared the reaction speed of p-MeO-$C_6H_4$-$(CH_2)_2$-NH-Troc with the compound of p-Br-$C_6H_4$-$(CH_2)_2$-NH-Troc from the same work [70], it was found out that TMSCl/MM system cleaves Troc group considerably faster than In/$NH_4Cl$ system. The reaction times for cleavage of Troc group from those compounds were 2h and 3h respectively.

It was also discovered that the rate of cleavage of Troc group from aliphatic or aromatic amines can be influenced by the adjacent protective group. A remarkable acceleration of the cleavage reaction was observed (see Table 11 entries 8, 9 and 10, 11 p. 37) if the Ac group was residing at the same nitrogen as the Troc group. It was expected that Tos group would also bring acceleration effect, similar to one observed in case of the Ac group. However, instead of acceleration, the deceleration effect was observed. (see Table 11 entry 4, 5 and 6, 7 p. 37). Supposedly this discrepancy can be explained by sterical hindrance, as the bulkiness of the Tos group does not allow the easy interaction between MM/TMSCl and the reaction centre. As it was mentioned before, the other authors [94, 95] have demonstrated similar phenomena in case of Boc group, in present work the impact of other protecting groups, like Ac or Boc on the Troc group reactivity was not observed. Usually the cleavage of Troc group with MM/TMSCl system from aromatic or aliphatic amines took about 2 to 3 hours of refluxing in THF, with some exceptions. For example, the cleavage of Troc group from Troc-protected p-aminobenzoic acid was not successful. There is a possibility that substituted benzoic acid could react with MM and form corresponding poorly soluble or even insoluble salts that were adsorbed on the surface of MM and thus interfering the corresponding cleavage reaction. Taking into account that benzoic acid and p-aminobenzoic acid can be converted to corresponding silyl esters [96, 97] by reaction with TMSCl, the amount of MM and TMSCl was increased 1.5 times compared to the optimized deprotection conditions in order to convert p-aminobenzoic acid *in situ* to corresponding silyl ester and then proceed the cleavage reaction. However, even after this modification the desired reaction did not occur even after refluxing the reaction

mixture for 24 hours. Another phenomenon was observed by the cleavage of the Troc group from starting compound entry 8 (see Table 11 p. 37). The reaction for the starting compound entry 9 (see Table 11 p. 37) was complete within 3 hours, but the cleavage of the Troc group from starting compound entry 8, (that is in fact very similar to the starting compound 9,) the reaction proceeded in a very different way. During this particular reaction the MM/TMSCl system did not cleave the Troc group, but instead of this transformed $CCl_3CH_2O$ group into the $CH_3CH_2O$ fragment. This unusual result could be explained by the fact that compound 8a includes cyano group in the conjugated p-position of the aromatic ring, where it could reduce the reactivity of the nitrogen centre and also the reaction time was increased considerably. Thus, low activity of nitrogen centre, presence of active metals and long reaction time at elevated temperatures, could be the reasons why this kind of transformation has taken place. As it was mentioned before, the role of adjacent protecting group could be very important not only for the speed of the cleavage reaction, but can also significantly change the path of reaction.
In summary, it was described that a new mild and cheap deprotection method for cleavage of the Troc group from various substrates using MM/TMSCl system in dry THF was successful. The reactions under these conditions are relatively fast and generally provide high yields. It was also demonstrated that this deprotection method could be successfully utilized for hydrazines and amines in the presence of Boc, Cbz, Tos, Ac, and CN and COOEt groups.

## 3.4. A mild method for cleavage of N-Tos protected amines using $TiCl_4$ and MM [III]

Based on the previous successful results of the thesis, where it was demonstrated that the MM/TMSCl system has very selectively cleaved Troc group without cleaving other protecting groups was initiated to study the limits of this method. Thus, those conditions were applied for cleavage of Tos group, which is known as a very stable protecting group and is therefore very difficult to remove in mild conditions. The aim of the new study was to find a fast, cheap and easily reproducible method for the removal of the Tos group from corresponding protected amines, hydrazines and amino acids under mild conditions. Here we report the results of our work where we utilize the MM for this purpose Scheme 23.




**Scheme 23**

As the first step for the optimization of this process, we applied the same reaction conditions reported in previous chapter. However it did not provide satisfactory results because the reaction with TMSCl proceeded to a sufficient extent only after refluxing the mixture for at least 48 hours. In order to increase the reaction temperature and to accelerate the deprotection reaction 1,4-dioxane was used as a solvent instead of THF. This attempt was unexpectedly unsuccessful – the cleavage reaction did not occur even after refluxing the mixture for 24 hours. In order to accelerate the reaction the influence of different activators was studied: $TiCl_4$, $SnCl_4$ and 1,2-dibromoethane. The results of the cleavage of Tos group with differently activated MM are outlined in Table 12.

**Table 12.** Optimization of reaction conditions of the Tos cleavage

| Entry[a] | Compound | Time, h | MM, equiv | Activators, equiv | Conversion[b], % |
|---|---|---|---|---|---|
| 1 | p-$CH_3O$-Ph-NH-Tos | 48 | 6.1 | TMSCl, 9.3 | <10 |
| 2 | p-$CH_3O$-Ph-NH-Tos | 48 | 6.1 | TMSCl, 18.2 | >90 |
| 3[b] | p-$CH_3O$-Ph-NH-Tos | 24 | 6.1 | TMSCl, 18.2 | 0 |
| 4 | p-$CH_3O$-Ph-NH-Tos | 24 | 6.1 | Br-$CH_2$-$CH_2$-Br, 5.2 | 0 |
| 5 | p-$CH_3O$-Ph-NH-Tos | 5 | 6.1 | Br-$CH_2$-$CH_2$-Br, TMSCl, 5.2:6.1 | traces |
| 6 | p-$CH_3O$-Ph-NH-Tos | 4 | 6.1 | Br-$CH_2$-$CH_2$-Br, $TiCl_4$, 5.2: 4.1 | 0 |
| 7 | p-$CH_3O$-Ph-NH-Tos | 4 | 6.1 | $SnCl_4$, 3.9 | 0 |
| 8 | p-$CH_3O$-Ph-NH-Tos | 4 | 6.1 | $TiCl_4$, 2.1 | 50 |
| 9 | p-$CH_3O$-Ph-NH-Tos | 4 | 6.1 | $TiCl_4$, 4.1 | >90 |
| 10 | p-$CH_3O$-Ph-NH-Tos | 2.5 | 6.1 | $TiCl_4$ (4.9) | >99 |
| 11 | Boc-NH-NH-Tos | 3 | 6.1 | $TiCl_4$, 4.9 | decompose |
| 12 | Cbz-NH-NH-Troc | 3 | 6.1 | $TiCl_4$, 4.9 | decompose |
| 13 | *n*-Bu-NH-Tos | 1.5 | 6.1 | $TiCl_4$, 4.9 | <99 |
| 14 | Ph-NH-Ac | 1.5 | 6.1 | $TiCl_4$, (4,9) | <99 |
| 15 | Ph-NH-Ac | 24 | 6.1 | $TiCl_4$: $H_2O$, 4.9:1 | 0 |

[a] All the reactions were performed under reflux in dry THF and under argon.
[b] in the reaction of 3 1,4-dioxane was used instead of THF.

The most efficient cleavage of Tos group was observed when approximately 6 equivalents of MM and 5 equivalents of $TiCl_4$ were used (Table 12 entry 10) and when the reaction speed of TMSCl with the $TiCl_4$ was compared it was noticeable that $TiCl_4$/MM system cleaves Troc group much faster than TMSCl/MM system. Having optimized the deprotection conditions, we have prepared various Tos protected aromatic amines, some aliphatic amines, hydrazines and amino acids were synthesised according to methods previously published [93] and subjected to the deprotection reaction under conditions described above (entry 10, Table 12). The results of the removal of Tos group are outlined in Table 13.

**Table 13.** Deprotection of Tos group with TiCl4/MM in dry THF

| Entry | Starting compound[a] | Reaction time, h | Product[b] | Yield isolated, % |
|---|---|---|---|---|
| 1 | Ph-NH-NH-Tos | 3 | Ph-NH-$NH_2$ | 23 |
| 2 | Ph-NH-Tos | 8 | Ph-$NH_2$ | 99 |
| 3 | Ph-N(Boc)-Tos | 5 | Ph-$NH_2$ | 50[c] |
| 4 | Ph-N(Troc)-Tos | 4 | Ph-$NH_2$ | 97 |
| 5 | p-MeO-Ph-NH-Tos | 2.5 | pMeO-Ph-$NH_2$ | 80 |
| 6 | Ph-$CH_2$-NH-Tos | 3 | Ph-$CH_2$-$NH_2$ | 40[b] |
| 7 | Ph-$CH_2$-N-(Me)-Tos | 6 | Ph-$CH_2$-NH-Me | 45 |
| 8 | p-MeO-Ph-$(CH_2)_2$-NH-Tos | 2.5 | p-MeO-Ph-$(CH_2)_2$-$NH_2$ | 40 |
| 9 | $(n\text{-}Bu)_2$-N-Tos | 3 | $(n\text{-}Bu)_2$-NH | 78 |
| 10 | N-Tos-(L)Proline | 3 | HN-(L)Proline | 80 |

[a] - yield after purification of crude product by column chromatography.

It can be seen that the reaction proceeds smoothly to furnish the corresponding amino and hydrazino compounds in good to excellent yields. The cleavage of the Tos group when employing the $TiCl_4$/MM system was relatively fast (usually 3 to 4 hours), and much faster than most of other methods [77,87] and reaction does not require high [77,87] or low [83] temperatures. Another important advantage of this method is that $TiCl_4$/MM allows the cleavage of the Tos group from non-activated primary and secondary aliphatic amines and also from aromatic amines under neutral reaction conditions. In the course of the studies it was confirmed that the activated MM in THF is capable to remove Tos protecting group in the presence of some other common functional groups such as MeO and Ph. However, the cleavage of Tos group was not very selective. When other well-known and widely used protective groups were present in the starting material, such as Boc, Troc, Cbz, Ac (Table 12 p. 40 and Table 13 p. 41), those groups were also completely removed under reaction conditions described. Two ways of acceleration of the cleavage of Tos group from aromatic amines were also discovered. Such acceleration was observed if in aromatic ring electron donating groups, such as MeO are included or if the same nitrogen atom includes some strong electron-withdrawing groups, such as Boc or Troc (see entry 3,4 and 5, Table 13). Taking this phenomenon into account, it should be possible to increase the speed of the cleavage reaction even further if more potent electron-withdrawing groups are to be used. To summarize, here we have described a new mild and cheap deprotection method for the cleavage of Tos group by using TiCl4/MM system in dry THF. The reactions under these conditions are relatively rapid and, as a rule, provide high yields.

# 5. EXPERIMENTAL

**Equipment and materials**

All reactions were conducted under reflux conditions and structures of all the starting compounds were confirmed by $^{1}H$ NMR and $^{13}C$ NMR spectroscopy. The progress of the reaction was monitored by TLC, HPLC or GC. Column chromatography was performed using MN Kieselgel 60 (70–230 mesh).

**$^{1}H$ and $^{13}C$ NMR spectra** were determined on a Bruker Avance$^{II}$ 200 instrument operating at 200 and 50 MHz respectively and TMS was used as reference.

**GC analyses** were performed on HP 5890A instrument with FID detector, using helium as carrier gas and fused silica capillary column Elite PE-5; 30 m × 0.25 mm.

**HR mass spectra** were measured with Thermo Electron LTQ Orbitrap ESI mass spectrometer.

**IR spectra** were measured on Spectrum BXII (Perkin Elmer) FTIR spectrometer with ATR device (Zn-Se), using KBr pellet technique.

**HPLC** analyses were performed with Watters M6000 isocratic eluent system (MeOH-$H_2O$ 75:25 or 85:15) on colmun Separon SX C18, 250 mm × 5,6mm.

**MM** was purchased from Redel-de Haen (50% Ce, 25% La, 16% Nd, 6% Pr).

**Pinacol coupling of imines with MM**

The freshly filed MM powder 100 mg (0.85 mmol) was added to the 5 ml of dry THF and activated with 180 μl (1.4 mmol) of TMSCl by refluxing 30 minutes under argon atmosphere. Then, 0.8 mmol $H_2O$ was added, followed by 0.8 mol of imine. When the conversion was complete (monitored by TLC (toluene–EtOAc 12:1 or toluene–EtOAc 10:1) or HPLC ), solvent and excess of the TMSCl were removed under reduced pressure. Crude product was purified on the short silica column using dichloromethane as eluent.

**Pinacol coupling of imines with Zn-Cu couple**

To the freshly prepared suspension of Zn-Cu couple (0.25 g $CuCl_2 \cdot 2H_2O$ was dissolved in hot water, then 1 g Zn powder was added to the solution. The solid was washed twice, with cold ethanol and the obtained material was used freshly) in 5 ml of EtOH imine (0.8 mmol) was added and stirred at ~80 °C. After all the imine was consumed (monitored by TLC (toluene–EtOAc 12:1 or toluene–EtOAc 10:1) or HPLC ), the reaction mixture was filtered through a thin layer of silica and evaporated to dryness.

**Pinacol coupling of imines with Devarda alloy**

To the stirred suspension of 0.25 g (5.3 mmol) Devarda alloy in 5 ml THF 0.18 ml (1,4 mmol) of TMSCl and (0.8 mmol) $H_2O$ was added dropwise, followed by 0.8 mmol of imine. After the reaction was complete (monitored by TLC (toluene–EtOAc 12:1 or toluene–EtOAc 10:1) or HPLC ), hot reaction mixture was filtered through the layer of celite directly into the ice-cold NaOH (10%)

solution in order to minimize the contact with possibly acidic inorganic salts. Aqueous layer was extracted 3 times with dichloromethane; organic extracts were washed until the pH was neutral, dried over $Na_2SO_4$, and evaporated to dryness.

**General procedure for synthesis of imines**

In a 100-$cm^3$ round-bottomed flask with a magnetic stirrer, freshly purified aldehyde (0.13 mmol) and aniline (or other amine) were dissolved in the toluene (or EtOH) and resulting mixture was stirred rapidly at room temperature. After few minutes a reaction occurs with evolution of heat and separation of water drops. The mixture was stirred until the starting material was completely consumed. Then the solvent was removed under vacuum and the crude product was purified by crystallization or vacuum distillation

**General procedure of Reformatsky type reaction of MM with different ketones or azocompounds**

Before the reaction the reaction flask was flame-dried and cooled to room temperature in the argon atmosphere. Then the freshly filed MM powder (1.4 mmol) was added to the 10 ml of dry THF and activated with 0.177 ml of TMSCl (1.4 mmol) by refluxing for 30 minutes under argon. After the activation the heating was turned off and obtained mixture was cooled to 40°C. Then, 0.35 mmol ketone or azocompound followed by 0.7 mmol of ethyl bromoacetate were added dropwise and the reaction mixture was heated again. The process of reaction was monitored by TLC (EtOAc:hexane, usually 4:1 or 2:1). When the starting material was consumed the MM powder was filtered off, the resulting filtrate was diluted with 30 ml $Et_2O$ and extracted with 5% aq. $NaHCO_3$ (3×15 ml). The combined organic layers were dried with $Na_2SO_4$. The products of all carbonyl compounds and some silylated hydrazines were confirmed with NMR spectroscopy.

**General procedure for cleavage of Troc group from substituted amines**

380 mg (2.7 mmol) of freshly, manually filed mischmetal powder (grain size 0.1–0.3 mm) was added to 10 ml of dry THF and activated with 0.52 ml (4.1 mmol) of TMSCl by refluxing for 30 minutes under an argon atmosphere. Then 0.44 mmol of Troc-protected starting compound was added and the obtained mixture was refluxed again. The progress of the deprotection reaction was monitored using TLC (EtOAc:hexane, usually 4:1 or 2:1). Before TLC analyse the sample was quenched with saturated $Na_2CO_3$. When the reaction was complete the MM powder was filtered off, the resulting filtrate was neutralized with 30 ml of saturated aqueous solution of $Na_2CO_3$ (or ~ 10% NaOH), stirred for 5 minutes and then extracted with dichloromethane (5×15 ml) and EtOAc (3×15 ml). The combined organic extracts were washed once with 0.2 M aq. citric acid, twice with distilled water (or brine) and then dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated to dryness;

if purification was needed, the crude product was purified by column chromatography.

**Preparation of the new compounds 7 and 8 in the Table 10**
Those compounds were prepared according to methods previously published [93].

**Spectral data of compound 7 in the table 10.**
$^{1}$H NMR ($CDCl_3$): δ = 1.48 (s, 9H Me Boc), 4.78 (s, 2 H, Troc), 6.6 (s, 1H, NH, Boc), 7.1 (s, 1H, NH, Troc).
$^{13}$C NMR ($CDCl_3$): δ = 28.2 (Me, Boc), 75.1 ($CH_2$, Troc), 82.2 ($C_q$, Boc), 94.9 ($CCl_3$,), 155.1 and 155.4 (C=O).
HRMS m/z calc. for Na-adduct =328.9839, found =328.9856.

**Spectral data of the compound 8 in the table 10.**
$^{1}$H NMR ($CDCl_3$): δ = 1.45 (s, 9H, Me, Boc), 4.86 (s, 2H, Troc), 6.60 (s, 1H, NH, Boc), 6.8–6.9/7.1–7.2 (m, 5H Ar).
$^{13}$C NMR ($CDCl_3$): δ = 28.3 (Me, Boc), 76.3 ($CH_2$, Troc), 85.3 ($C_q$, Boc), 93.9 ($CCl_3$,), 113.0 , 120.8, 129.2, 148.4 (Ar), 152.9 (C=O, Boc), 156.3 (C=O, Troc).
HRMS m/z calc. for Cl-adduct = 416.9942, found = 416.9962.

**Preparation of new compound 9 in the Table 11**
520 mg (1.77 mmol) of compound 8 (in the table 11 p. 38) and 1.3 ml (7.4 mmol) of DIPEA (N,N-diisopropylethylamine) was added to the 30 ml of acetonitrile. Then 0.5 ml (6.6 mmol) of AcCl was added and the obtained mixture was refluxed overnight under Ar atmosphere. The progress of the reaction was monitored using TLC (EtOAc:hexane, 2:1). When the reaction was complete the solvent was removed and the crude product was purified twice by column chromatography (EtOAc:hexane 1:2 and EtOAc:hexane 2:1). The collected fractions were combined and concentrated to provide 250 mg of desired compound 9. (mp = 58–60 $^{o}$C). The structure of new compound was confirmed by $^{1}$H NMR and $^{13}$C NMR, IR spectroscopy and HR mass spectrometry.
$^{1}$H NMR ($CDCl_3$): δ = 2.71 (s, 3H, $CH_3$, Ac), 4.74 (s, 2H, $CH_2$, Troc), 7.28/7.32 (d, 2H Ar), 7.72/7.76 (d, 2H Ar).
$^{13}$C NMR ($CDCl_3$): 26.3 ($CH_3$, Ac), 75.6 ($CH_2$, Troc), 94.1 ($CCl_3$, Troc), 112.0 (CN), 117.9, 129.7, 133.0, 141.2 (Ar), 151.1 (C=O, Troc), 172.0 (C=O, Ac).
FTIR ν ($cm^{-1}$): 2234 (CN), 1752, (C=O, Troc), 1716 (C=O), 1238 (C-O), 714 (C-Cl)
$C_{12}H_9Cl_3N_2O_3$ $M^{+}$+H calc. 334.97515, $M^{+}$+H found 334.97495.

**Preparation of the new compound 11 in the Table 11**
The compound of 11 was prepared essentially the same way as 9, except that instead of DIPEA, DMAP (4-dimethylaminopyridine) was used. The yield after purification was 25%, provided compound 11a (mp = 51–52$^{o}$C). The structure

of new compound was confirmed by $^{1}H$ NMR and $^{13}C$ NMR, IR spectroscopy and HR mass spectrometry.
$^{1}H$ NMR ($CDCl_3$): δ = 2.63 (s, 3H, $CH_3$, Ac), 3.82 (s, 3H, $CH_3O$) 4.74 (s, 2H, $CH_2$, Troc), 6.91/6.95 (d, 2H Ar), 7.05/7.09 (d, 2H Ar).
$^{13}C$ NMR ($CDCl_3$): 26.4 ($CH_3$, Ac), 55.5 ($CH_3O$), 75.4 ($CH_2$, Troc), 94.5 ($CCl_3$, Troc), 114.5, 129.4, 129.9, 152.8 (Ar), 159.4 (C=O, Troc), 172.6 (C=O, Ac).
FTIR ν ($cm^{-1}$): 1742 (Troc), 1719 (C=O, Ac), 1246 (C-O-C), 721 (C-Cl).
$C_{12}H_{12}Cl_3NO_4$ $M^+$+H calc. 339.99047, $M^+$+H found 339.99033.

**General procedure for deprotection of Tos group with $TiCl_4$/MM in dry THF**

456 mg (3.2 mmol) of the freshly filed MM powder were added to 10 ml of dry THF and activated with 0,24 ml (2,18 mmol) $TiCl_4$ by refluxing 20–30 minutes under argon atmosphere. Then, Tos-protected starting material (0.53 mmol) was added and the resulting mixture was refluxed for indicated period of time (Table 13). The progress of the deprotection reaction was monitored by TLC (EtOAc: hexane, usually 2:1). Before TLC analyse the sample was neutralized with 2M NaOH. When reaction was complete, the MM powder was filtered off and the resulting filtrate was neutralized with 30 ml of 2M NaOH aqueous solution, stirred for 5 minutes and then extracted with dichloromethane (5× 15 ml). The combined organic layers were washed twice with distilled water (or 5% NaCl solution) and dried over anhydrous $Na_2SO_4$. The mixture was then filtered and concentrated to dryness.

# 6. CONCLUSIONS

The results of the work leading to this thesis can be summarized as follows.

**The activation of the MM.**
During this research it was found that despite the known reactions of lanthanoides with water or alcohols, MM remains inert even when the reaction mixtures was refluxed for several hours in THF. No reaction was observed. For initiation of the corresponding reactions sets different activators were studied (36% HCl, $CuCl_2$ ×$2H_2O$, dest. $H_2O$, $I_2$, $MM_xI_y$ TMSCl, TiCl4, $Ni(OAc)_2$, $ZnCl_2$, $CoCl_2$, $NiI_2$, Ce(OBu)4). Based on the results of those experiments, the trimethylsilyl chloride (TMSCl) and $TiCl_4$ were found to be the best activators, judging by the corresponding reaction yields. The other compounds that have been tested have shown lower activating property (or none at all).

**Pinacol coupling of imines.**
In the pinacol coupling reaction of imines the TMSCl was found to be the best activator. During the study several important facts concerning the reaction were discovered and studied. First of all, when using MM as the main reagent in the pinacol coupling of imines, the corresponding reaction occurred only in THF. In other solvents (acetonitrile, toluene, n-hexane, diethyl ether, $CHCl_3$ and $CH_2Cl_2$) the reaction did not occur at all. The transformation using the MM and Zn/Cu couple occurred smoothly, furnishing the products in moderate to excellent yields (up to 99%), but the same reaction with Devarda alloy resulted in only modest yields. The simple C=N reduction was not typical for the majority of studied imines. It was found that in case of MM and Devarda alloy in order to the start coupling reaction it was necessary to add small amount of water. Without water no reaction occurred even after refluxing the reaction mixture with activated MM or Devarda alloy for several hours. This is an interesting fact, because in other studies where only MM has been investigated, the water interfered the reaction. Also the separation technique was found to be crucial in case of MM. Prolonged contact of the product with $MMCl_x$ (that act as a Lewis acid) caused decomposition of the product back onto the starting material. In order to decrease the decomposition reaction column chromatography has to be run immediately after the reaction has been completed.

**Reformatsky reaction with azocompounds.**
First, to the best of our knowledge, the Reformatsky-type reaction has not been applied to the azocompounds yet. Therefore, it was first needed to study whether the MM/TMSCl system is capable to perform the corresponding Reformatsky-type reaction and if these conditions could be applicable with azocompounds. Thus, the acetophenone and ethyl bromoacetate were first tested as a model system with the MM/TMSCl to find out if it is possible to produce corresponding classical Reformatsky-type reaction.

During the course of this study, it was also found that the reaction is very sensitive to water. Thus, prior to attempting to perform Reformatsky-type reaction the reaction flask was flame-dried and cooled to room temperature in argon atmosphere. However, during the research it was found that system MM/TMSCl was able to perform the classical Reformatsky reaction and the best results were obtained if the ratio of acetophenone, ethyl bromoacetate, MM and TMSCl was 1:2:4:4. In addition some other activation methods were also tested such as: Br-$CH_2$-$CH_2$-Br, $I_2$, but those methods were not activated MM and no reaction occurred.

After finding optimized reaction conditions, it was turned back to primary goal – to perform Reformatsky reaction with azocompounds. Despite the fact that the Reformatsky reaction proceeds smoothly with ketones, it completely refused to work with azocompounds. Instead of the Reformatsky-type addition products mainly complex mixtures and simple hyrdazines or their silylated derivates were formed. It was a surprise, as the reactions were performed in dry THF, where no proton source is present, which is usually necessary for this kind of transformation. Regardless of the problems encountered during the course of the work it was discovered that MM/TMSCl system possesses significant reductive properties.

**Selective cleavage of Troc and Tos groups from various N-protected compounds.**

During the course of this study the selective cleavage of Troc and Tos protecting groups from corresponding Troc- or Tos-protected hyrdazines, Troc-NH-$CH_2$-COOEt, amines, and amino acids, presence of other well known protecting groups (Cbz, Boc, Ac) in the THF and at pH neutral conditions through the use of the MM/TMSCl system was investigated. The most efficient cleavage of Troc group was observed when approximately 6 equivalents of MM and 9 equivalents of TMSCl were used. The removal of the Troc group under those conditions was fast and as a rule very selective. Behavior of MM under the reaction conditions is interesting, as it allows for the selective cleavage of Troc group from Troc(Tos)N or Troc(Ac)N in substituted amines while Ac and Tos group remain unaffected, this being a good example of the orthogonality of this method.

It was also discovered that the cleavage rate of the Troc group can be influenced by the adjacent protective group. The acceleration was observed if another deactivating protecting group was residing at the same nitrogen as the Troc group. When we began investigating the possibilities for the cleavage of the Tos group and applied the MM/TMSCl system for that purpose, it did not provide satisfactory results, as reaction times were too long. In order to accelerate the deprotection reaction the change of solvent from THF to dioxane was used, in order to increase the reflux temperature. Those attempts to facilitate the cleavage reaction with the increase of reaction temperature were unsuccessful. In order to cleave Tos protecting group TMSCl had to be substituted with $TiCl_4$. Taking into account that $TiCl_4$ is much more reactive than TMSCl, it was

generally expected that the selectivity of the reaction will be lover. Indeed, the $TiCl_4$/MM system, did not cleave only the Tos group, but other protecting groups as well. The cleavage of Tos group when employing the TiCl4/MM system was fast (usually in order of 3 to 4 hours) which is much faster than some other methods and reaction does not require too high or low temperatures. Another important advantage of this method is that $TiCl_4$/MM allows the cleavage of the Tos group from non-activated or slightly activated primary and secondary aliphatic amines and aromatic amines under neutral reaction conditions. Also, in the course of our work we have confirmed that it is possible to accelerate the cleavage of Tos group from aromatic amines in two ways. Such acceleration is observed if the aromatic ring includes electron donating groups, such as MeO or if some strong electron-withdrawing group, such as Boc or Troc were residing at the same nitrogen atom.

In summary, we have described several new applications of MM in several different reactions. During our work we proved that MM could be successfully applied in the organic synthesis as a main reagent without using expensive reagents such as Sm or $SmI_2$ and developed corresponding protocols.

# 7. SUMMARY IN ESTONIAN

## Mischmetalli rakendamine orgaanilises sünteesis

Mischmetal (MM) ehk Eesti keeles ka segametallina tuntud sulam on lantanoidide segu, mis on leidnud laialdast kasutamist metallurgias, kuid orgaanilises sünteesis on seda sulamit veel üsna vähe kasutatud. Siiani on MM kasutatud peamiselt kaasredutseerijana, eesmärgiga vähendada kalliste ($SmI_2$ ja Sm) hulka reaktsioonides. Siiski on juba avaldatud mõni töö, kus MM on kasutatud põhireagendina, kuid neid töid on veel väga vähe.

Seetõttu oli käesoleva doktoritöö eesmärk uurida MM-i kasutusvõimalusi orgaanilises sünteesis põhilise reagendina, ning leida selleks vajalik ning lihtsati reprodutseeritav ja töökindel metoodika, vältides seejuures kalliste regentide kasutamist.

Uurimustöö käigus leiti, et MM on eelnvevalt aktiveerimata inertne ning sulam ei ole sobilik imiinide pinakoolkondensatiooni, Reformatski reaktsiooni läbiviimiseks ega ka kaitserühmade (Troc ja Tos) selektiivseks eemaldamiseks amiinidelt, hüdrasiinidelt, Troc-NH-$CH_2$-COOEt ja amino hapetelt, teiste tuntud kaitserühmade juures olekul. Mitmete järgi proovitud aktivaatorite hulgast leiti ainult kaks aktivaatorit, mis võimaldasid MM edukalt aktiveerida. Nendeks olid TMSCl ja $TiCl_4$. Teised aktivaatorid ei suutnud MM kas piisavalt aktiveerida või puudus aktiveeriv toime üldse.

Imiinide pinakoolkondensatsioonil saadi pariamid tulemuisi, kui MM aktiveerimiseks kasutati TMSCl. Uurimistöö käigus ilmnes, et MM abil saab vastavat reaktsiooni läbi viia ainult THF-i keskonnas, ning väikese koguse vee manusel. Ilma veeta seda reaktsiooni ei toimu, isegi kui reaktsioonisegu keeta eelnevalt aktiveeritud MM mitme tunni vältel. Antud tulemus on eriti huvitav, sest teiste reaktsioonide käigus toimis vee lisamine reaktsiooni pidurdavana. Samuti leiti, et produkti eraldamise metoodika on olulise tähtsusega. Selleks, et vältida produkti lagunemist $MMCl_x$ toimel, on vaja peale reaktsiooni lõppu koheselt rakendada kolonnkromatograafiat.

MM rakendati Reformatsky reaktsioonil asoühendite korral, eesmärgiga oluliselt lihtsustada vastavate asendatud hürdeasiinide sünteesi. teadaolevalt pole asoühendite korral Reformatsky reaktsiooni veel rakendatud, mistõttu kasutati optimaalsete reaktsiooni tingimuste välja töötamiseks atsetofenooni ja bromoetaanhappe etüülestrit. Uurimuse käigus leiti, et klassikaline Reformatski reaktsioon toimub süsteemi MM/abil hõlpsasti. Eelnevalt leitud optimaalseid tingimusi rakendati asoühendite korral. Uurimistöö käigus selgus, et asoühendi korral Reformatsky reaktsiooni ei toimu. Oodatud reaktsiooni produktide asemel saadi keerulised ühendite segud, millest mõnel juhul tuvastati vastavaid hürdasiine või nende mono- ja di-silüülitud produkte.

Järgmiseks võeti vaatluse alla Troc ja Tos kaitserühmade selektiivne eemaldamine vastavatelt kaitstud amiinidelt ja hüdrasiinidelt.. Selle eesmärgi täitmiseks kasutati kas MM/TMSCl või $TiCl_4$/MM süsteemi kuivas THF. Troc

rühma eemaldamine toimus väga selektiivselt. Samuti ilmnes, et selle reaktsiooni kiirus sõltub olulisel määral sama lämmastiku juures oleva kaitserühma iseloomust. Samalaadseid efekte täheldati ka Tos kaitserühma korral. Tos rühma edukaks eemaldamiseks oli TMSCl asemel aktivaatorina vaja kasutada $TiCl_4$. Märgatavalt aktiivsema aktivaatori kasutuselevõtt kiirendas küll soovitud reaktsiooni, kuid langetas olulislet reaktsiooni selektiivsust, st Tos rühmaga koos eemaldati ka kõik ülejäänud kaitserühmad (v.a. – OMe).

Lõpetuseks võib öelda, et selle tööga on näidatud, et MM saab edukalt rakendada orgaanilises süsneesis ning selleks on loodud odav, töökindel ja kergesti reprodutseeritav metoodika**.**

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# PUBLICATIONS

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| 2004–2004 | HTI institute of chemistry in Burgdorf, in the workgroup of Prof. Franz Baumberger |

## Scientific publications


Vellemäe, E., Stepanov, V., Mäeorg, U. A Mild Approach to the Deprotection of Troc from Protected Amines Using Mischmetal and TMSCl. Submitted in *Synthetic communications* **2009** (Paper number LSYC-2009-3321).

Vellemäe, E., Lebedev, O., Mäeorg, U. A mild method for cleavage of N-Tos protected amines using mischmetal and $TiCl_4$. *Tetrahedron Letters,* **2008**, 49, 1373–1375

Vellemäe, E., Lebedev, O., Sillard R., Mäeorg, U. A Selective method for cleavage of N-Troc protected hydrazines and amines in mild conditions using mischmetal and TMSCl. *Journal of Chemical Research,* **2006**, 685–687.

Vellemäe, E., Tšubrik, O., Loog, O., Mäeorg, S., Mäeorg, U. Mischmetal and zinc-copper couple as efficient reagent for the pinacol coupling of aldimines. Journal of Chemical Research, 2006,149–150.

Vellemäe, E., Tšubrik, O., Loog, O., Mäeorg, S., Mäeorg, U. Mischmetal, zinc-copper couple, and devarda alloy in the pinacol coupling of aldimines. Proceedings of the Estonian Academy of Sciences. Chemistry 2003, 52(2), 91–95.

# CURRICULUM VITAE

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Vellemäe, E., Stepanov, V., Mäeorg, U. A Mild Approach to the Deprotection of Troc from Protected Amines Using Mischmetal and TMSCl. Submitted in *Synthetic communications* **2009** (Paper number LSYC-2009–3321).

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