Stockholms universitet

Group (IV) Metal-Catalyzed Direct Amidation

Synthesis and Mechanistic Considerations

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Till min familj

Abstract

The amide unit constitutes the backbone of proteins, and is present in a large number of pharmaceutically active molecules, polymeric materials such as nylon and Kevlar, as well as in food additives like aspartame. Amides are produced in enormous amounts every year, thus, environmentally friendly and selective methods for their formation are of great importance. This thesis deals with the direct formation of amides from non-activated carboxylic acids and amines with the aid of group (IV) metal complexes. Water is the only by-product of this environmentally benign process. This fact stands in contrast to the most common methods for amide formation to date, which involve the use of waste-intensive, expensive and often toxic coupling reagents. The catalytic protocols presented herein use titanium, zirconium and hafnium complexes under mild reaction conditions to produce amides in good to excellent yields. Furthermore, carbamates are demonstrated to be suitable sources of gaseous amines for the formation of primary and tertiary amides under catalytic conditions. In addition, preliminary results from ongoing mechanistic investigations of the zirconium- and hafnium-catalyzed processes are presented.

Sammanfattning

Amidfunktionaliteten är en kemisk enhet som utgör ryggraden i proteiner, och som även återfinns i en stor mängd läkemedelsmolekyler, polymera material som nylon och Kevlar, samt i tillsatser i livsmedelsindustrin, exempelvis aspartam. Amider produceras i enorma mängder varje år, och det är av stor vikt att utveckla miljövänliga och selektiva metoder för deras framställning. Denna avhandling behandlar direkt amidering av icke-aktiverade karboxylsyror och aminer med hjälp av katalytiska mängder metallkomplex, baserade på titan, zirkonium och hafnium. Den enda biprodukten från denna amideringsreaktion är vatten. Jämfört med de metoder som generellt används idag för amidsyntes, så är de presenterade metoderna avsevärt mer miljövänliga med avseende på toxicitet hos reagensen såväl som på mängden avfall som genereras. Dessutom redovisas här en katalytisk metod för syntes av primära och tertiära amider genom att använda olika karbamat som källa till gasformiga aminer, vilka annars kan vara praktiskt svåra att arbeta med. Preliminära resultat från en pågående mekanistisk studie av de zirkonium- och hafnium-katalyserade processerna är också inkluderade.

List of Publications

This thesis is based on the following papers, which will be referred to by Roman numerals I-V. Reprints were made with the kind permission from the publishers and the contribution by the author to each publication is clarified in Appendix A.

I. **Direct amide coupling of non-activated carboxylic acids and amines catalyzed by zirconium (IV) chloride**
Helena Lundberg, Fredrik Tinnis, Hans Adolfsson
Chem. Eur. J. **2012**, *18*, 3822.

II. **Zirconium (IV) chloride catalyzed amide formation from carboxylic acids and amines: *N*-Benzyl-2-(phenylthio)acetamide and (*S*)-*tert*-butyl 2-(benzylcarbamoyl)pyrrolidine-1-carboxylate**
Fredrik Tinnis, Helena Lundberg, Tove Kivijärvi, Hans Adolfsson
Accepted for publication in Organic Syntheses

III. **Titanium (IV) isopropoxide as an efficient catalyst for direct amidation of non-activated carboxylic acids**
Helena Lundberg, Fredrik Tinnis and Hans Adolfsson
Synlett **2012**, *23*, 2201.

IV. **Hafnium-catalyzed direct amidation at room temperature**
Helena Lundberg, Hans Adolfsson
ACS Catal. **2015**, *5*, 3271.

V. **Direct catalytic formation of primary and tertiary amides from non-activated carboxylic acids, employing carbamates as amine source**
Fredrik Tinnis, Helena Lundberg, Hans Adolfsson
Adv. Synth. Catal. **2012**, *13*, 2531.

The following papers prepared during the time of this Ph.D. work were not included in this thesis.

Metal-Free N-Arylation of Secondary Amides at Room Temperature
Fredrik Tinnis, Elin Stridfeldt, Helena Lundberg, Hans Adolfsson, Berit Olofsson (*Accepted for publication in Organic Letters*)

Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Propargylic Ketones
Andrey Shatskiy, Tovi Kivijärvi, Helena Lundberg, Fredrik Tinnis and Hans Adolfsson (*Submitted*)

Tandem α-Alkylation/Asymmetric Transfer Hydrogenation of Acetophenones with Primary Alcohols
Oleksandr Kovalenko, Helena Lundberg, Dennis Hübner, Hans Adolfsson *Eur. J. Org. Chem.* **2014**, *30*, 6639.

Ruthenium-Catalyzed Tandem-Isomerization/Asymmetric Transfer Hydrogenation of Allylic Alcohols
Tove Slagbrand, Helena Lundberg, Hans Adolfsson, *Chem. Eur. J.* **2014**, *49*, 16102.

Catalytic amide formation from non-activated carboxylic acids and amines
Helena Lundberg, Fredrik Tinnis, Nicklas Selander, Hans Adolfsson, *Chem. Soc. Rev.* **2014**, *43*, 2714.

High throughput screening of a catalyst library for asymmetric transfer hydrogenation of heteroaromatic ketones. Formal synthesis of (R)-Fluoxetine and (S)-Duloxetine
Elina Buitrago, Helena Lundberg, Hans Andersson, Per Ryberg, Hans Adolfsson, *ChemCatChem* **2012**, *4*, 2082.

Ruthenium-catalyzed asymmetric transfer hydrogenation of ketones in ethanol
Helena Lundberg, Hans Adolfsson, *Tetrahedron Lett.* **2011**, *52*, 2754.

Contents

Abbreviations

Abbreviations and acronyms are used in agreement with standards of the subject.[1] Only nonstandard and unconventional ones that appear in the thesis are listed here.

CDI	*N,N'*-carbonyldiimidazole
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HSAB	principle of hard and soft acids and bases
ee	enantiomeric excess
LA	Lewis acid
MTBE	methyl *tert*-butyl ether
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
THP	tetrahydropyran

1. Introduction

1.1 The amide functionality

The amide functionality is one of the most fundamental and abundant structural elements found in nature. It constitutes the backbone of proteins, and it is found in a vast number of synthetic structures, some of which are found in Figure 1. Approximately 25% of the pharmaceuticals present on the market contain at least one amide unit,[2] and the functional group was present in 2/3 of the drug candidates surveyed by three leading pharmaceutical companies in 2006.[3] Furthermore, it has been estimated that 16% of all reactions involved in the synthesis of modern pharmaceuticals are amine acylations, which make them the most commonly performed reaction in this field.[4] Apart from pharmaceuticals, polymers based on the amide linkage are important for a wide range of applications, from materials such as nylons and Kevlar, to more advanced uses for biomedical purposes, such as drug delivery.[5,6] In addition, the amide unit is commonly found as a key structural element in agrochemicals as well as in food additives, *e.g.* the artificial sweeteners aspartame and neotame.

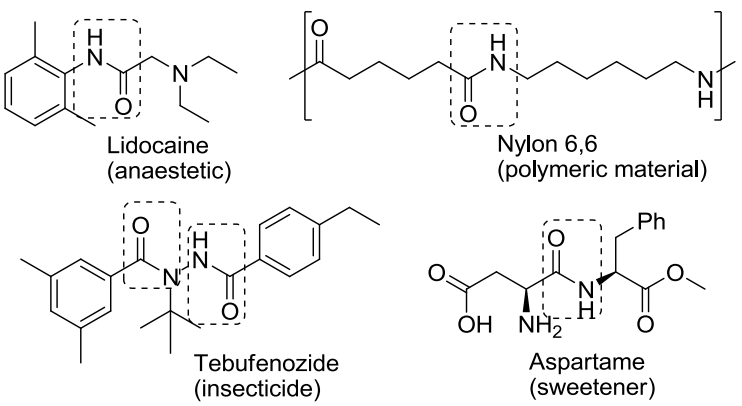


Figure 1. Commercial products containing the amide unit.

1.2 Lewis acids

A Lewis acid (LA) can be defined as an electron acceptor,[7] and both organic and inorganic compounds can act as such. Lewis acid-mediated and -catalyzed reactions constitute an enormous field in organic synthesis.[8,9] The group (IV) metals titanium, zirconium and hafnium alone have been reported to mediate a multitude of reactions as their corresponding tetra-valent complexes, ranging from polymerizations,[10,11] amide hydrolysis,[12,13,14] esterifications,[15,16] and Diels-Alder,[17,18] to Knoevenagel and aldol condensations.[19]

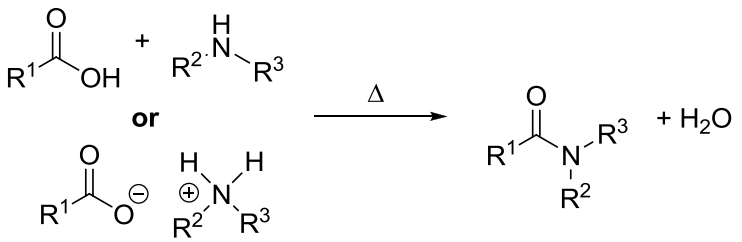
The classification of Lewis acids to describe their reactivity and selectivity has proved rather complicated. One of these classifications is acid strength, which is correlated to the ability of the Lewis acid to accept electrons from a Lewis base. Scales for Lewis acidity have for example been constructed using IR spectroscopy,[20, 21] as well as with the aid of NMR spectroscopy.[22] In organic reactions, the notion of acid strength does not fully explain the observed reactivitites and selectivities of Lewis acids. Other definitions such as the hardness and softness of Lewis acids (and bases) have been put forth as an attempt to explain their synthetic behavior (HSAB theory).[23] This theory states that a Lewis acid and base must be matched for an efficient reaction/bonding interaction to occur, such that "hard" acids with low polarizability of the outer electrons have energetically more favorable interaction with "hard" bases rather than "soft". The hard-hard interactions have been considered to have an ionic character, whereas soft-soft interactions can be described as more covalent in nature.[24] However useful, the HSAB theory has also received criticism for neglecting conflicting results for ambident nucleophiles, as well as for not taking into account the thermodynamic *versus* kinetic control of a reaction.[25] In addition to the above classifications of Lewis acids, Kobayashi and co-workers investigated the reactivities of a number of chloride complexes of Lewis acids in terms of oxophilicity and azaphilicity, determined by their ability to mediate the formation of either the aldol or the Mannich product from a mixture of an aldehyde, aldimine and a silyl enol ether.[26]

1.3 Synthetic strategies for amide formation

The amide functionality can be formed using a range of methods, and some synthetically useful strategies will be highlighted in this section.

1.3.1 Thermal amidation

Amides can be formed in high yields simply by heating a carboxylic acid and an amine at high temperatures, generally around 160-180 °C (Scheme 1). The direct thermal amidation has several advantages, such as simplicity and high atom economy. However, highly elevated reaction temperatures are not suitable for substrates which are thermally unstable, have low boiling points or have labile stereocenters which are easily racemized. In addition, the preparative value of thermal amidation can be limited by dehydration of the amide to the corresponding nitrile or tar formation at high reaction temperatures. [27,28]



Scheme 1. Thermal amidation uses heat as the only means for the formation of amide product from carboxylic acids and amines or their corresponding ammonium carboxylate salt.

The first general protocol for thermal amidation was published in 1931 by Mitchell and Reid, who reported on the formation of primary amides from aliphatic carboxylic acids and ammonia at temperatures up to 190 °C.[28] The same methodology was also applied for the formation of dimethylamides, and served as the basis for commercial synthesis of dimethylacetamide.[29] In 1989, Cossy and Pale-Grosdemange reported that the addition of 4 Å molecular sieves could improve the yields of the amide product under thermal conditions.[30] At temperatures between 140-180 °C, secondary amides of aliphatic, benzylic and conjugated carboxylic acids, and different amines were formed in high yields. Aromatic and secondary amines required higher reaction temperatures compared to aliphatic amines in order to form amide products in good yields. Similar results were also reported by Gooßen *et al.*[31] Recently, Grosjean *et al.* demonstrated that the use of azeotropic distillation allowed for efficient synthesis of amides under thermal conditions on production scale at 110 °C in refluxing toluene, even though the efficiency of the reaction was found to be substrate dependent.[32] Even

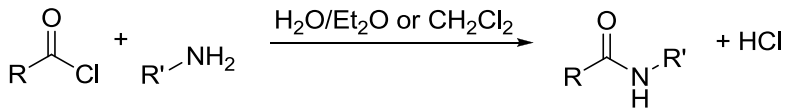
lower reaction temperatures (80 °C) were reported to be sufficient for efficient *N*-formylation of amines with formic acid.[33] In addition, peptides have been formed thermally at 120 °C without racemization of stereocenters.[34]

In recent years, several studies that employ microwave irradiation as heat source have been published. The general advantage of this type of heating compared to conventional heating is shorter reaction times. Loupy and co-workers showed that a reaction temperature of 150 °C during 30-120 min under microwave irradiation gave rise to good yields of amide products under solvent-free conditions.[35] Similarly, Orru and co-workers reported on the synthesis of a range of amides at 150-250 °C and 10 minutes reaction time under microwave irradiation and solvent-free conditions.[36] In addition to heating by microwave irradiation, radiowave frequency heating has also been used in the thermal amidation of carboxylic acids and amines by Rebrov and co-workers.[37] The authors reported that good to excellent yields of secondary and tertiary amides were obtained under solvent-free conditions within 10-20 minutes reaction time at 200 °C.

1.3.2 Stoichiometric strategies

Although amides can be formed thermally from their corresponding ammonium carboxylate salts, this reaction has generally been considered to be of limited preparative value due to the forcing reaction conditions needed.[38] To circumvent this problem, amide synthesis is most often carried out with the use of an activating agent to form carboxylic acid derivatives with a good leaving group, which is turned into the amide product upon subsequent aminolysis. In an analysis of the synthesis of drug candidates presented by three pharmaceutical companies in 2006, it was found that 65% of 128 surveyed compounds contained at least one amide unit.[3] Out of these, 44% were synthesized *via* an acid chloride and 36% were carried out using a coupling reagent.

The formation of amides from acid chlorides and amines is known as the Schotten-Baumann reaction (Scheme 2), and is often carried out in a two-phase system.[39,40] The synthesis of the acid chloride is commonly carried out by reacting a carboxylic acid with a chlorinating agent, such as thionyl chloride, cyanuric chloride or phosphorous trichloride.



Scheme 2. The Schotten-Baumann reaction: formation of an amide *via* an acid chloride.

The Schotten-Baumann reaction can be considered as a relatively environmentally benign synthesis when the acid chloride is synthesized from thionyl chloride, since the by-products from the synthesis and subsequent aminolysis, SO_2 and HCl, have low molecular weight, are non-carcinogenic and can easily be removed by bubbling the resulting gases through a basic solution.[41] However, this approach is generally not suitable for substrates with stereocenters close to the carbonyl or other acid-labile functional groups. The coupling of amino acids to form peptides, for example, is rather facilitated by the use of coupling reagents.[42,43,44] *N*,*N'*-Carbonyldiimidazole (CDI) is a commonly used reagent, both in small scale reactions as well as in industrial processes (Figure 2). An example of a commercial process for amide formation using CDI as the coupling reagent is the synthesis of sildenafil (Viagra).[45] Dicyclohexylcarbodiimide (DCC) is another well-established coupling reagent, sometimes used with hydroxy-benzotriazoles such as HOBt or HOAt as additives in order to prevent racemization of stereocenters (Figure 2). The hydroxy-benzotriazole unit is also found embedded as a structural element in other well-known coupling reagents such as the phosphonium salt PyBOP and the aminium salt HATU (Figure 2).

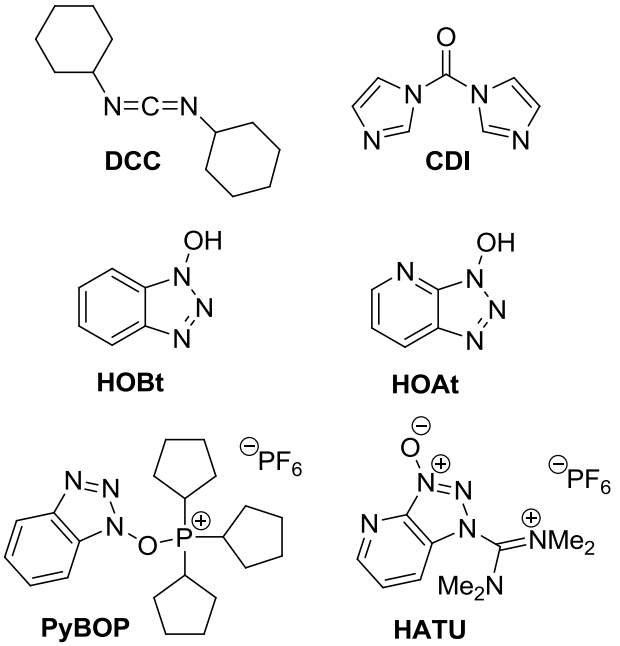


Figure 2. Common coupling reagents and additives.

The use of coupling reagents usually enables mild reaction conditions and good yields, but requires stoichiometric amounts of the reagent. Hence, at least one equivalent of waste is generated per product molecule formed, which leads to an overall low atom economy. The removal of this waste from the reaction mixture is a time-consuming and expensive process, in addition to the cost and toxicity of the coupling reagent itself. Due to these issues, as well as the importance of the amide functionality in the pharmaceutical industry, a catalytic and waste-free production of amides was voted to be a highlighted area of research by the American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Round-table (PR) in 2007.[41]

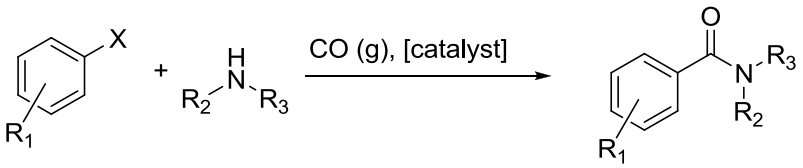
1.3.3 Catalytic strategies

To circumvent the problems of harsh reaction conditions and low atom economy, catalysis is a promising strategy for amide synthesis. In nature, enzymes readily catalyze this transformation, for example in the formation of peptides from amino acids. The selectivity of enzymes and their preference for particular substrates is however limiting from a general synthetic point of view. For this reason, the following section will focus on catalytic strategies with wider synthetic utility. Information on bio-catalysts for amide formation is covered elsewhere.[46] In addition to the references included in

this chapter, several reviews on the topic of catalytic amide formation are available.[27,47,48,49,50,51]

1.3.3.1 Aminocarbonylation

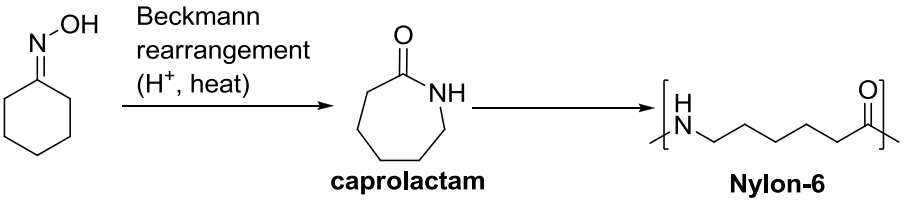
Transition metal-catalyzed aminocarbonylation of aryl halides (Scheme 3) has been known since the 1970's, when Heck and Schoenberg published the first protocol for this transformation.[52] Since then, methods for the formation of amides from carbon monoxide and amines using a variety of starting materials have been reported.[53,54,55,56] Aminocarbonylations are often catalyzed by palladium, and both homogeneous[57,58,59] as well as heterogeneous[60,61] systems are known for the amidation of aryl halides. In addition to this class of substrates, protocols for the aminocarbonylation of alkenes,[62,63] alkynes[64,65,66] and epoxides[67] have been reported. Aminocarbonylation of amides offers a convenient route to a wide range of arylamides, as well as to certain alkyl-, alkenyl- and alkynylamides. However, the use of hazardous gaseous carbon monoxide can be a practical obstacle, and the common need for an excess of reagents increases the environmental impact of this amidation methodology.



Scheme 3. Aminocarbonylation of arylhalides to form benzamides.

1.3.3.2 Rearrangement of oximes

Amides can be formed from oximes by the Beckmann rearrangement.[68] This process can be catalyzed by protic acid at high reaction temperature and is an important route to caprolactam, the starting material for Nylon-6 (Scheme 4).[69]



Scheme 4. Formation of caprolactam, a Nylon-6 precursor, *via* Beckmann rearrangement.

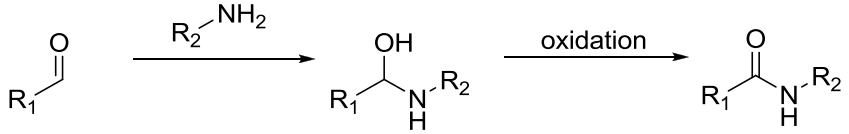
Metal-catalyzed protocols for the rearrangements of aldoximes and ketoximes to their corresponding primary and secondary amines have also

been developed.[70] For example, Crabtree and Gnanamgari reported on a one-pot procedure for the ruthenium-catalyzed rearrangement of *in situ*-formed aldoximes from aldehydes and hydroxylamines into primary amides.[71] Williams and co-workers developed an iridium-catalyzed oxidative version of the same reaction, allowing for the use of alcohols instead of aldehydes.[72] Mercury-catalyzed rearrangement of ketoximes to their corresponding secondary amides has also been reported,[73] as well as rearrangements catalyzed by iron complexes.[74,75]

Generally, the metal-catalyzed protocols for oxime rearrangement need elevated reaction temperatures. In addition, oximes are generally not readily available and need to be synthesized, which introduces extra syntheses and purification steps into the amide synthesis. These factors limit the general applicability of this approach to amide formation.

1.3.3.3 Oxidative strategies

Oxidative amidation of aldehydes into amides are known since the 1960's.[76] The formal steps of the transformation are the formation of a hemi-aminal intermediate by reaction of the amine and the aldehyde, followed by oxidation of the hemi-aminal to the amide (Scheme 5).[77]



Scheme 5. Reaction steps in the oxidative amide formation from aldehydes and amines.

Early work by Tamaru *et al.* utilized a palladium complex and stoichiometric amounts of an aryl halide as oxidant to form amides in good yields.[78] Copper iodide has also been used in catalytic amounts in combination with *tert*-butyl hydroperoxide (TBHP) for the oxidative amidation of aldehydes.[79] It should also be mentioned that TBHP alone has been used under metal-free conditions for the same transformation.[80] In addition, lanthanide-catalyzed Cannizzaro-type protocols have been reported, where one equivalent of aldehyde is used for the formation of the amide and another equivalent as oxidant.[81,82] Furthermore, organocatalytic protocols employing *N*-heterocyclic carbenes for oxidative amidation of aldehydes have been developed.[83,84]

Amides can also be formed from alcohols under oxidative conditions. The mechanism for this transformation is generally the same as in Scheme 5, with the addition of an extra oxidation step of the alcohol into the corresponding aldehyde. The seminal work in this field was performed by Milstein and co-workers, who developed a ruthenium pincer complex (Figure 3)

that produces hydrogen gas as by-product and hence avoids the use of external oxidants.[85] Other protocols have also been reported for the oxidative amide formation from alcohols.[48] For example, Grützmacher and co-workers used a rhodium complex with hydrogen peroxide as stoichiometric oxidant for the formation of primary and secondary amides.[86]

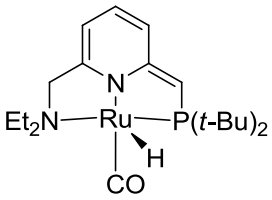
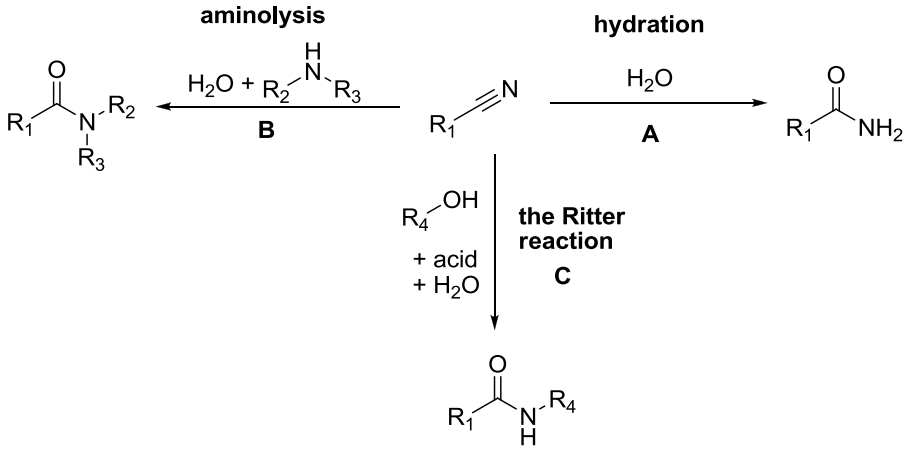


Figure 3. Milstein's dehydrogenative ruthenium catalyst.[85]

The oxidative formation of amides from aldehydes or alcohols and amines can be considered as an environmentally benign process if stoichiometric chemical oxidants can be avoided. For example Milstein's dehydrogenative ruthenium-catalyzed amidation is an excellent example of a green catalytic process.

1.3.3.4 Amides from nitriles and esters

Nitriles can rather easily be turned into amides. Several metal-based catalysts are known for the hydration of the nitrile functionality to form primary amides in good yields, generally at elevated reaction temperatures (Scheme 6, reaction A). Homogeneous catalysts based on ruthenium,[87] iridium,[87] rhodium[88] and gold[89] are known, as well as heterogeneous nanoparticle-sized catalysts based silver,[90] palladium, rhodium and molybdenum.[91] Nitriles can be subjected to aminolysis in the presence of water to generate secondary and tertiary amines with ammonia as by-product (Scheme 6, reaction B).[87,92,93] In addition, amides can be formed from nitriles *via* the Ritter reaction (Scheme 6, reaction C). Classically, the Ritter reaction takes place under harsh conditions using sulfuric acid and high reaction temperatures.[94,95] Metal-catalyzed versions exist that avoids the use of strong protic acid and allows for milder reaction conditions, even though an elevated reaction temperature is still generally required.[96,97,98,99] In addition, biocatalysis can be used for the transformation of nitriles into amides.[100]



Scheme 6. Different routes to amides from nitriles.

Esters are another versatile group of substrates that can be turned into amides upon aminolysis. The transformation has been known for several decades,[101] and protocols have been reported using sodium cyanide[102] and sodium methoxide[103] in catalytic amounts, as well as metal complexes based on *e.g.* cobalt,[104] antimony,[105] aluminum and zirconium.[106] Zirconium was also used by Porco and co-workers at room temperature, in combination with HOAt, to afford high yields of amide products.[107] In addition, complexes based on magnesium and calcium,[108] as well as lanthanum[109] and gold nanoparticles[110] have been reported to be efficient catalysts for the formation of amides from esters.

The transformation of nitriles and esters into amide products are useful and generally rather environmentally benign processes. The general need for high reaction temperatures in the transformation of nitriles is however limiting the substrate scope to thermally stable compounds.

1.3.3.5 Direct amidation

Direct amidation is the condensation reaction between a carboxylic acid and an amine, generating the amide product and water as the only by-product. As mentioned in the discussion on thermal direct amidation, this is a process with low environmental impact. Catalytic versions of direct amidation are often possible to perform at lower temperatures compared to thermal conditions, which ideally increases the substrate scope to include thermally labile and low-boiling carboxylic acids and amines. Even though several other useful and environmentally benign processes for the formation of amides exist (*vide infra*), catalytic direct amidation is especially interesting due to its potential for peptide formation without the need for prior chemical transformations of naturally abundant amino acids. There are a few examples of

Brønstedt acid-catalyzed direct amidation,[111,112,113,114,] and it has been suggested that the catalytic activity of some mesoporous silica materials[115,116,117] is due to the weak acidity of silanol groups.[118] The literature in the field of Brønstedt acid-catalyzed direct amidation is however very limited and Lewis acids are usually the catalysts of choice.

1.3.3.5.1 Boron-based catalysts

The use of boron-based compounds as catalysts has gained considerable interest in the last two decades. The Lewis acidity of the boron-based catalysts can efficiently be fine-tuned by substituents with different electronic and steric characters for the activation of different carboxylic acids. In general, boronic acids and their derivatives have high functional group tolerance and are more stable in the presence of water compared to other Lewis acids. This is an advantage in direct amidation, since water is generated as a by-product in the reaction.

Stoichiometric use of boron reagents to promote the condensation of carboxylic acids and amines has been known since the 1960's.[119] The first catalytic protocol was developed by Yamamoto and co-workers, who used an electron-deficient boronic acid for the formation of a range of amides in good yields in refluxing toluene (Figure 4).[120,121] The same group also developed polyfluorinated analogues, as well as a polystyrene-bound boronic acid, for facile separation and recyclability of the catalyst.[122,123] A similar polystyrene-bound boronic acid catalyst was also developed by Latta *et al.*[124] In addition, boronic acid catalysts supported onto mesocellular foam have been reported.[125]

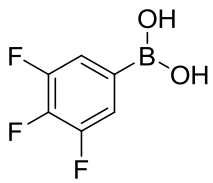
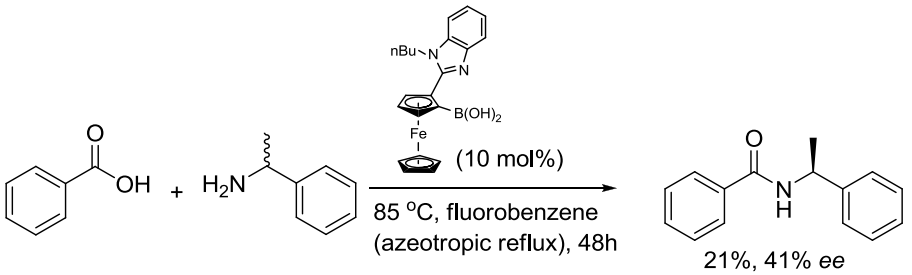


Figure 4. The first boronic acid catalyst for direct amidation.[120]

Bifunctional boronic acid catalysts have been developed by Whiting,[126] including an asymmetric boronic acid with a ferrocene backbone.[127] The latter enabled the so far only example of chiral resolution in direct amidation without enzymes, and the most successful example resulted in moderate yield and enantiomeric excess (21% yield, 41% *ee*) of the amide product after 48 hours in refluxing fluorobenzene (Scheme 7). Whiting also reported on the formation of dipeptides in moderate yields using electron-deficient boronic acid catalysts in stoichiometric amounts at 65 °C in fluorobenzene.[128] The formation of two dipeptides was also reported by

Sheppard and co-workers, using two equivalents of tris-(2,2,2-trifluoroethyl) borate as mediator at 80 °C in acetonitrile.[129] In addition, Huang and Sha reported on the formation of dipeptides from *N*-arylglycine esters, catalyzed by phenylboronic acid in refluxing xylene.[130] Furthermore, Yamashita *et al.* reported that alkylboronic acids are more active as catalysts for α-hydroxycarboxylic acids compared to arylboronic acids.[131]



Scheme 7. The first example of non-enzymatic chiral resolution of racemic amines in direct amidation.[127]

Boric acid is catalytically active in the formation of secondary and tertiary amides in refluxing toluene or xylene, displaying full chemoselectivity for *N*- over *O*-acylation.[132,133] Boric acid-catalyzed direct amidation has been used for the synthesis of several biologically active compounds.[134,135,136] The same catalyst in combination with PEG-400 also constitutes the only reported boron-based catalytic system for the formation of primary amides, using gaseous ammonia for the formation of 4-nitrobenzamide in high-boiling aromatic solvents.[137] Interestingly, boric acid did not display catalytic activity in the absence of polyethylene glycol.

All examples above required elevated temperatures of 65-170 °C for an efficient reaction to take place. However, in 2008, Hall and co-workers reported that 2-iodophenylboronic acid was an efficient catalyst already at 25 °C.[138] The reactions were carried out in dichloromethane and no racemization of stereocenters in the substrates was detected. A couple of years later, it was shown that an increased electron density of the iodide was beneficial for the reaction, and 2-iodo-5-methoxyphenylboronic acid was demonstrated to be a more active catalyst compared to the parent compound (Figure 5).[139] A heterogeneous polystyrene-bound variant was also developed.[140] In addition, Tam *et al.* recently reported that 2-furanylboronic acid is an active amidation catalyst at room temperature for a range of substrates (Figure 5).[141]

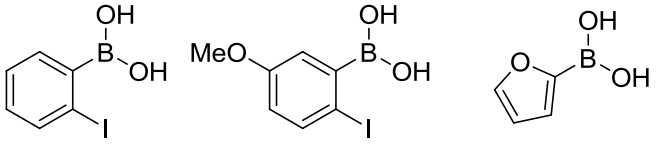


Figure 5. Boronic acid catalysts active at room temperature.

Boric and boronic acid catalysis for direct amidation at elevated temperature has proved successful even for scale-up synthesis, and several active catalysts have been developed. The emerge of catalytic methods for amide synthesis at room temperature has expanded the applicability of the methodology, and the use of boronic acid catalysis for peptide formation is interesting, even though stoichiometric amounts of catalyst were needed. A general drawback for the boric and boronic acid-catalyzed protocols is the need for water removal by Dean-Stark setups or molecular sieves. This is particularly pressing for the room temperature protocols, which need rather large amounts of molecular sieves for an efficient reaction. This requirement limits the possibilities for scale-up purposes somewhat.

1.3.3.5.2 Metal-based catalysts

Group (IV) metal complexes are the most common homogeneous metal catalysts for direct amidation. Their use as mediators for the formation of secondary and tertiary amides was first reported in 1970, when Wilson and Weingarten used stoichiometric amounts of $TiCl_4$ to form carboxamides from non-activated carboxylic acids and amines at room temperature.[142] Soon after, a patent was filed for a catalytic process describing the production of amides from different long chain fatty acids and amines, using 0.6–1 mol% of metal complexes based on Ti^{IV}, $Zr^{IV}$and Ta^{V} as catalysts at temperatures between 120-200 °C.[143] In the late 1980's, Nordahl and Carlson reported on the use of different Lewis acids including $TiCl_4$ and $AlCl_3$ in stoichiometric amounts in refluxing toluene for the formation of carboxamides from benzoic acid and a handful of primary and secondary amines.[144] During the same time, Mader and Helquist reported that good yields of lactams of different ring size could be formed using substoichiometric amounts of $Ti(O\textit{i}Pr)_4$ in refluxing 1,2-dichloroethane,[145] a strategy later employed in the synthesis of biologically active macrolactams.[146] Interestingly, the authors found that intermolecular amide products failed to form under their reaction conditions. Shteinberg and co-workers reported on the formation of benzamides in refluxing *o*-xylene (bp 144 °C) using $Ti(OBu)_4$ in catalytic amounts.[147,148,149] The same group also found that the same complex, in combination with PEG-400, could catalyze the formation of the primary amide 4-nitrobenzamide in trichlorobenzene at highly elevated reaction temperatures (160-185 °C).[150] In addition, Williams and co-workers developed a protocol for zirconium-catalyzed direct amidation in refluxing toluene, separate and in parallel to the work described in Paper I and II in this thesis.[151]

Other metal complexes have also found their use in homogeneous direct amidation catalysis (Scheme 8). The formation of five- to seven-membered lactams in near quantitative yield (95%) was reported by Steliou *et al.* using

10 mol% Bu_2SnO in refluxing xylene and a Dean–Stark trap for the removal of water.[152,153] $SnCl_2$ as well as CdO has also been reported to be active as catalysts in direct amidation between fatty acids and pyrrolidine in ionic liquids at 135 °C.[154] Moreover, Terada *et al.* reported that several polyvalent metal salts, especially $FeCl_3 \cdot 6H_2O$, were active as catalysts for the amidation of fatty acids and long-chain aliphatic amines in refluxing mesitylene.[155] In addition, $Zn(OAc)_2$ as well as the acetate complexes of sodium, calcium, magnesium, manganese and copper were shown to function as catalysts for the acetylation of amines in refluxing acetic acid.[156,157]

Scheme 8. Several metal complexes work well as homogeneous direct amidation catalysts.

A number of metal-containing heterogeneous and/or immobilized catalysts for direct amidation of synthetic relevance are also reported in the literature.[46] The most common metals in this field are zinc and iron. For example, *N*-formylation of amines with formic acid is mediated by ZnO in substoichiometric amounts under solvent-free conditions,[158] as well as by different porous metal oxides,[159,160] and even elemental zinc.[161] Nanosized zinc oxide particles dispersed in glycerol have also been reported to catalyze the formation of different amides.[162] Montmorillonite clays containing Fe^{3+} ions have been demonstrated to function as direct amidation catalysts.[163,164,165] Similarly, a chamosite clay containing iron (III) displayed catalytic activity for the acylation of amines with acetic acid,[166] as well as $FeCl_3$ supported by polyaniline nanofibers.[167] Iron-doped zeolite was also found to be an active and recyclable catalyst for the same reaction,[168] as well as scandium triflate anchored onto mesoporous silica (MCM-41) for acetylation of aliphatic amines.[169] Recently, metallic magnesium was also found to display catalytic activity in direct amidation.[170]

Group (IV) metal-containing heterogeneous and immobilized catalysts have also been reported for direct amidation. Kumar *et al.* reported on a zirconium/yttrium catalyst for the acetylation of a few amines including aniline,[171] and Xiao *et al.* developed a hafnium-catalyst supported onto fluorous silica for the *N*-formylation of amines.[172] $ZrOCl_2 \cdot 8H_2O$ was used as catalyst by Reddy *et al.* for the formation of primary amides under microwave irradiation, utilizing urea as the source of nitrogen.[173] The authors also reported that cerium ammonium nitrate can act as an efficient catalyst for the same reaction.[174] In addition, Martra and co-workers reported on the use of TiO_2 as catalyst under microwave irradiation at 100 °C.[175] The binding modes of carboxylic acids to the catalyst was also studied and surface bound TiO_2-

carboxylates were reported to be the electrophilic species in the reaction.[176,177] Furthermore, titanium (IV) species immobilized in ionic liquids were successfully used and recycled for lactamizations of long-chain amino acids at 100 °C.[178] In addition to the heterogeneous and immobilized catalysts references here, several variants of sulfated titania catalysts have been reported, along with aluminosilicate zeolites, sulfated tungstate and Al_2O_3 catalysts. However, the mechanism of these heterogeneous catalysts is not fully understood and it is not clear whether their metal content is of catalytic importance. This material is therefore beyond the scope of this thesis, and references to these catalysts, as well as a handful of other types, can be found elsewhere.[46,179]

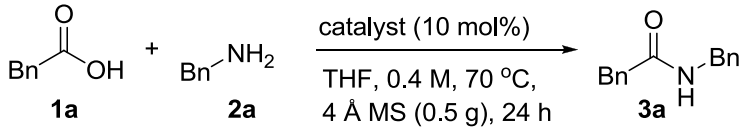
To summarize, several Lewis acidic metal complexes and materials are known to be catalytically active for direct amidation. Group (IV) metal complexes are the most well-documented class of homogeneous catalysts, whereas zinc and iron are the most common metals in heterogeneous catalysis. A general feature for metal-based catalysts is the need for elevated reaction temperature. This requirement is a limitation for the substrate scope, and also raises the question on to what extent the yield of the thermal amidation is contributing to the total yield of the reaction (see section 1.3.1). The need for water removal is another drawback for the homogeneous protocols, whereas the heterogeneous catalysts often suffer from a more limited substrate scope.

2. Catalytic direct amidation of non-activated carboxylic acids

2.1 In search of active catalysts

The ability of Lewis acids to activate carbonyl compounds for nucleophilic attack is well-documented in the literature. Early transition metals are known to be oxophilic in nature, and the work on *O*- versus *N*-selectivity performed by Kobayashi and co-workers indicated that the *O*-selective nature of early transition metal-based Lewis acids is enhanced by the use of electron-rich anionic ligands such as acetate and phenolate.[26] Encouraged by the work performed in the field of direct amidation using stoichiometric amounts of group (IV) metal complexes,[142,144,145] as well as their use in catalysis at high reaction temperatures,[147] we envisioned their potential for catalytic applications under milder conditions. We set out to test this hypothesis, and evaluated a series of different complexes for their catalytic activity in the condensation of phenylacetic acid and benzylamine. We wanted to develop a protocol that would be as mild as possible, and chose 70 °C as the starting point for testing the catalytic properties of the metal complexes with THF as the solvent. It was quickly found that molecular sieves were important for an efficient reaction, and 0.5 g activated sieves (4 Å, pellets) were used as a standard amount for a reaction on a 1 mmol scale of carboxylic acid. Gratifyingly, a number of the tested group (IV) complexes proved to be active catalysts under the chosen conditions (Table 1). In addition, the thermal reaction was found to be minimal under the reaction conditions (Table 1, entry 11).

Table 1. Evaluation of early transition metal complexes as catalysts in direct amidation.[a]



1.2:1 molar ratio
1 mmol scale

Entry	Catalyst	Isolated yield **3a** (%)
1	$TiCl_4$[b]	68
2	$Ti(OiPr)_4$	91
3	$Ti(OBu)_4$	89
4	$ZrCl_4$	99
5	$Zr(OtBu)_4$	93
6	$Zr(OEt)_4$	93
7	$Hf(OtBu)_4$	89
8	$Nb(OEt)_5$	88
9	$Y(OiPr)_3$	18[c]
10	$VO(OEt)_3$	21[c,d]
11	-	10

[a] 4 Å molecular sieves (0.5 g pellets) in dry THF (amine concentration 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere. [b] 1 M in toluene. [c] NMR-yield. [d] mixture of products.

2.1.1 Zirconium (IV) catalyzed amidation (Paper I-II)

With the promising results from the catalyst screening (Table 1) at hand, we decided to evaluate $ZrCl_4$ further for its catalytic ability in direct amidation. It was found that the catalyst loading could be reduced to 2 mol% without affecting the yield of the model amide **3a** after 24 hours (Table 2, entry 1-2). Interestingly, it was observed that the stoichiometry between the carboxylic acid and amine was not important when running the reaction in THF for 24 hours (Table 2, entries 2-3). The thermal amidation was observed to be slow under the reaction conditions and only low yields of amide **3a** were detected when the reaction was performed without the zirconium catalyst (Table 2, values in parenthesis). It is possible to envision the *in situ* formation of HCl under the reaction conditions. Since some reports on protic acid-catalyzed direct amidation are available, we were interested to see whether our results originated from such mediation. However, it was found that under these conditions, HCl is not the active catalyst (Table 2, entry 5). The amidation reactions were generally performed on a 1 mmol scale under nitrogen atmosphere in sealed tubes in the presence of 0.5 g activated molecular sieves (4 Å pellets). Considerably lower yields of product **3a** were obtained if the reaction was performed without sieves (Table 2, entry 4), as well as when the reaction temperature was lower than 70 °C.

Table 2. Evaluation of conditions for $ZrCl_4$-catalysis.

Entry	Catalyst	Solvent	Catalyst (mol%)	Isolated yield **3a** (%)[c]
1[a]	$ZrCl_4$	THF	10	>99
2[a]	$ZrCl_4$	THF	2	>99(10)[a]
3[b]	$ZrCl_4$	THF	2	>99(13)[b]
4[d]	$ZrCl_4$	THF	2	38
5[e]	HCl[f]	THF	20	8
6[b]	$ZrCl_4$	1,4-dioxane	2	99 (8)
7[b]	$ZrCl_4$	CH_2Cl_2	2	92 (11)
8[b]	$ZrCl_4$	CH_3CN	2	86 (10)
9[b]	$ZrCl_4$	toluene	2	94 (5)

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), catalyst (2 or 10 mol%) and activated 4 Å molecular sieves (0.5 g) in dry solvent (amine concentration 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h. [b] **1a** (1 mmol), **2a** (1.2 mmol), carboxylic acid concentration 0.4 M, otherwise identical conditions to those above. [c] The values presented within parentheses refer to the yield (as determined using ^{1}H-NMR) obtained in the background reaction performed with molecular sieves (0.5 g) but without zirconium catalyst. [d] no molecular sieves, otherwise identical conditions to those described in note b. [e] **1a** (0.5 mmol), **2a** (0.6 mmol), acid concentration 0.4 M, 0.25 g 4 Å MS (powder), otherwise identical conditions to those above. [f] 2 M in diethyl ether.

THF was chosen as the standard solvent, and a selection of amide products formed with the optimized zirconium-catalyzed conditions is illustrated in Figure 6 (see Paper I for a complete list). Both aliphatic and aromatic carboxylic acids were successfully used as substrates, even though the latter required reaction temperatures of 100 °C in order to result in good yields after 24 hours reaction time. Moreover, halogen-containing acids and amino acids with carbamate protecting groups were all converted into their corresponding benzyl amides in high yields (**3d**-**3h**). Importantly, no racemization was detected in the amino acid amide products (**3f** and **3g**) as determined by chiral HPLC. In addition, the anti-inflammatory drug indomethacin was converted into the corresponding amide **3i** in high yield. Primary and cyclic secondary amines were successfully used as coupling partners, whereas secondary acyclic amines unfortunately were found to react very slowly under the applied conditions. In addition, substrates with free hydroxyl groups, as well as aliphatic primary diamines failed to form amide products under the reaction conditions.

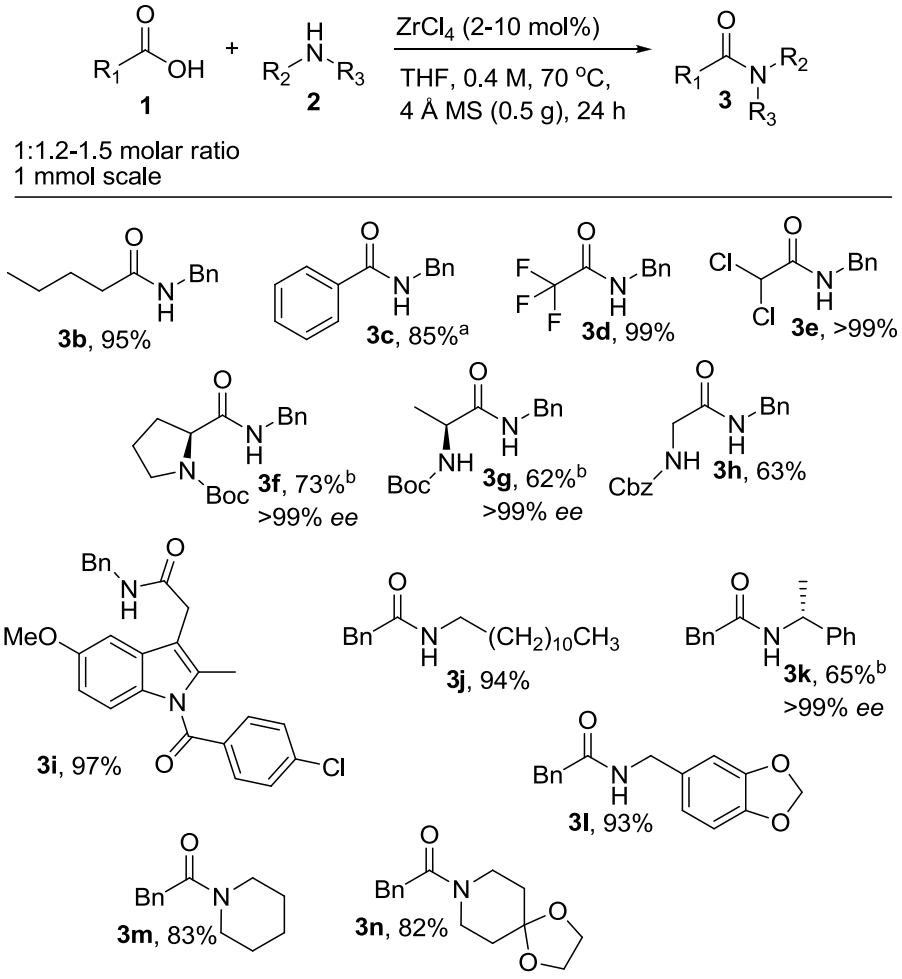
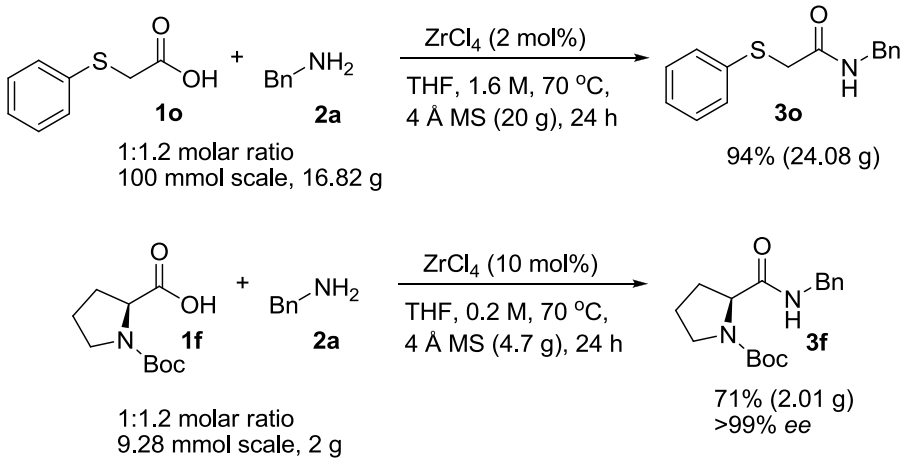


Figure 6. Selection of amide products formed by $ZrCl_4$-catalysis.

[a] Reaction temperature 100 °C. [b] No racemization was detected with chiral HPLC (Chiralcel AD column).

Furthermore, it was found that the catalytic protocol was suitable for scale-up using a round-bottomed flask equipped with reflux condenser. Hence, 100 mmol (16.82 g) of (thiophenyl)acetic acid and 2 g (9.28 mmol) Boc-protected proline were successfully converted into their corresponding *N*-benzyl amides in 94% (**3o**) and 71% (**3f**) isolated yield, respectively (Scheme 9, see paper II for experimental details). The isolation of products using the zirconium-catalyzed protocol is straight-forward, and filtration of the reaction mixture through a pad of silica with a slightly basic eluent (200:1 EtOAc:Et_3N) followed by concentration under reduced pressure was in most cases sufficient for the isolation of analytically pure amide products

(Paper I). In addition, extractive workup was also successfully applied (Paper II).



Scheme 9. Multigram-scale synthesis of amide products (Paper II).

2.1.2 Titanium (IV) catalyzed direct amidation (Paper III)

Several of the early transition metal complexes presented in Table 1 were found to be active catalysts for the direct amidation in THF. Apart from $ZrCl_4$, titanium (IV) isopropoxide caught our attention (Table 1, entry 2). Since this compound is an inexpensive and widely used chemical found in most research laboratories, we were interested to evaluate its performance in order to develop a simple and general amidation protocol. In addition, our preliminary result using this titanium complex was contradicting the findings by Mader *et al.* who reported that no intermolecular amides could be formed using this catalyst in 1,2-dichloroethane.[145] Interestingly, and analogous to the results obtained for $ZrCl_4$, we found that titanium-catalyzed amidation of phenylacetic acid (**1a**) and benzylamine (**2a**) to form amide **3a** worked well in several different solvents (Table 3). Performing the reaction in a sealed vial (10 mL) equipped with septum worked equally well as using a round-bottomed flask equipped with a condenser, as long as the atmosphere was kept inert (Table 3, entries 1-2). The isolated yield dropped significantly when the reaction was taking place in air (Table 3, entry 3), likely due to hydrolytic decomposition of the catalyst (see section 3.3). Solvents such as DMSO, DMF and acetonitrile resulted in lower yields of amide **3a** (Table 3, entries 6, 8 and 9).

Table 3. Solvent evaluation for Ti(O*i*Pr)$_4$-catalyzed direct amidation of phenylacetic acid **1a** and benzylamine **2a**.[a]

Entry	Solvent	Isolated yield **3a** (%)
1	THF	91
2[b]	THF	90
3[b,c]	THF	67
4	1,4-dioxane	86
5	Toluene	89
6	DMSO	68
7	CH_2Cl_2	93
8	DMF	63
9	CH_3CN	75

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), Ti(O*i*Pr)$_4$ (10 mol%), and 4Å molecular sieves (0.5 g), in dry THF (amine concentration 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere for 24 h.[b] Reflux conditions in round-bottomed flask with condenser under N_2 atmosphere. [c] Regular atmosphere.

A range of amide products were readily synthesized using titanium (IV) isopropoxide as catalyst in 10-20 mol% loading in THF, and selected examples can be found in Figure 7 (see Paper III for a complete list). Electronically and sterically demanding substrates such as cinnamic acid, cyclohexanecarboxylic acid and adamantanecarboxylic acid were isolated in moderate to good yields as their corresponding amides **3p**, **3r** and **3s**, using a reaction temperature of 100 °C. In analogy to the results obtained for the zirconium-catalyzed amidation, no racemization was detected when Boc-protected amino acids were transformed into their corresponding amide products (**3f** and **3g**). Unfortunately, the more labile stereocenter in (*S*)-ibuprofen underwent partial racemization under the reaction conditions and was isolated as the *N*-benzyl amide **3t** with an enantiomeric excess of 83%.

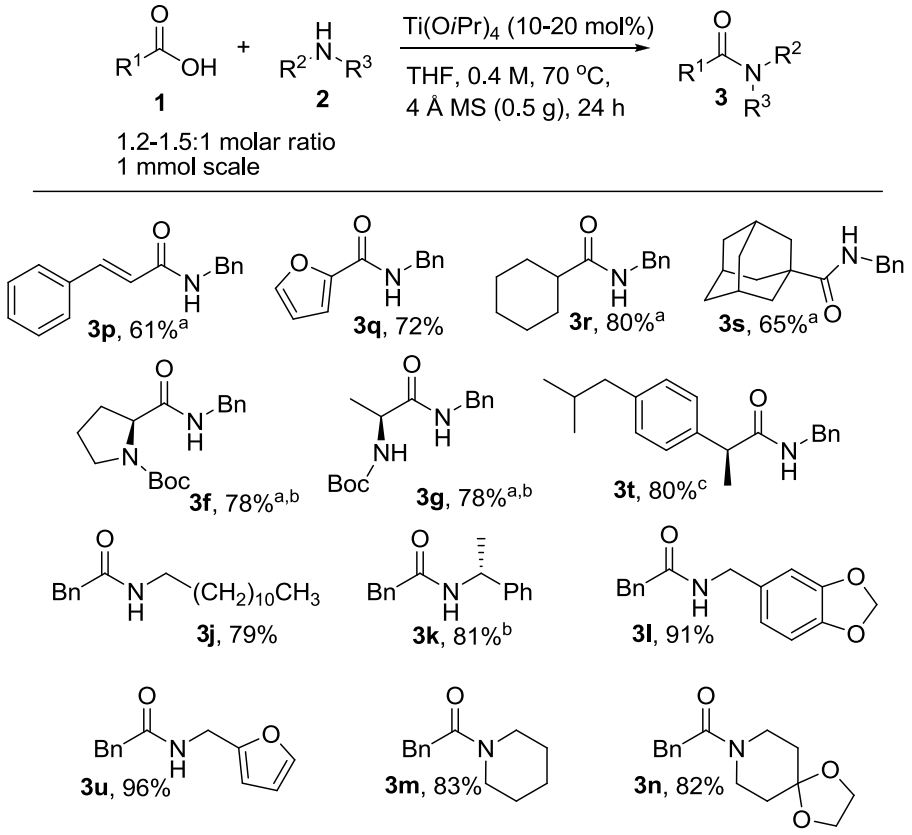


Figure 7. Selected amide products synthesized by titanium (IV) isopropoxide catalysis.

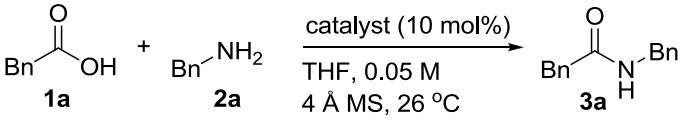
[a] Reaction temperature 100 °C. [b] No racemization was detected using chiral HPLC (Chiralcel AD column). [c] 83% *ee* was determined by chiral HPLC (Chiralcel IA column).

2.1.3 Hafnium (IV) catalyzed direct amidation (Paper IV)

The protocols for direct amidation using $ZrCl_4$ and $Ti(OiPr)_4$ in catalytic amounts were performed at a lower reaction temperature compared to other reported metal-catalyzed systems using similar catalysts.[147,148,151] However, we were interested to see whether we could find an even milder protocol, and once more, we set out to evaluate different transition metal complexes for their catalytic activity in direct amidation, this time at room temperature. As indicated in Table 4, group (IV) metal complexes were again found to show the highest activity in the formation of model amide **3a**, which is fortunate since they have a low toxicity and environmental impact. The best yield was obtained using the sandwich complex $Hf(Cp)_2Cl_2$ (hafnocene di-

chloride) as catalyst with a 10 mol% loading, resulting in 65% isolated yield of the amide after 48 hours (Table 4, entry 6). As expected, the thermal background reaction was found to be virtually non-existent even after 4 days of reaction time (Table 4, entry 1). In addition, it was found that HCl does not catalyze the formation of amides at this temperature (Table 4, entry 14).

Table 4. Catalyst evaluation for direct amidation at 26 °C.



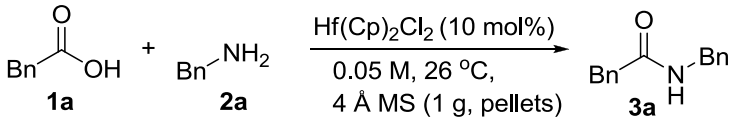
1:1 molar ratio, 0.5 mmol scale

Entry	Catalyst	MS (g)[a]	Reaction Time (days)	NMR yield **3a** (%)
1	-	0.5	4	1
2	$ZrCl_4$	0.25	2	25
3	$Zr(Cp)_2Cl_2$	0.25	2	33
4	$Zr(OH)_x(OAc)_y$	1	6	5
5	$HfCl_4$	0.25	2	33
6	$Hf(Cp)_2Cl_2$	0.25	2	65[b]
7	$Ti(O\mathit{i}Pr)_4$	0.25	2	1
8	$Ti(OBu)_4$	1	6	40
9	$Sb(OAc)_3$	0.25	2	20
10	$Sb(Ph)_3$	0.25	2	0
11	SbF_3	0.5	4	55
12	$AlF_3 \cdot H_2O$	0.25	2	0
13	Bi(III)oxide	0.25	2	0
14	HCl[d]	0.75[c]	2	0

[a] MS = 4 Å pellets [b] Isolated yield [c] MS = 4 Å powder, solvent = Et_2O [d] 2 M in Et_2O

An evaluation of solvents revealed that ethers were the most suitable solvent class for the transformation (Table 5), with diethyl ether giving rise to 88% isolated yield of amide **3a** after 72 hours (Table 5, entry 1). The use of THF resulted in 76% yield of **3a** after the same amount of time (Table 5, entry 6).

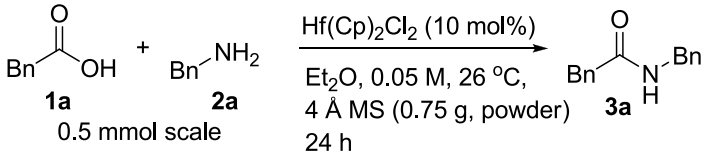
Table 5. Solvent evaluation for $Hf(Cp)_2Cl_2$-catalyzed direct amidation.



Entry	Solvent	Reaction time	Isolated yield **3a** (%)
1	Et_2O	3 days	88
2	*i*Pr_2O	3 days	4
3	MTBE	3 days	47
4	1,4-dioxane	3 days	64
5	THP	3 days	70
6	THF	3 days	76
7	*iso*-amyl alcohol	6 days	0
8	*tert*-amyl alcohol	6 days	6
9	dichloromethane	3 days	7
10	toluene	3 days	17

Furthermore, it was found that it was important to tune the amount of molecular sieves (see discussion in section 3.3), and it was determined that 0.75 g of activated powdered 4 Å molecular sieves was needed for an optimal reaction outcome on a 0.5 mmol reaction scale. The amine concentration was also found to significantly affect the reaction outcome. By increasing the equivalents of amine, a clear increase in the formation of amide **3a** is seen after 24 hours of reaction time (Table 6, entries 1-3). The standard conditions were therefore set to a 2:1 molar ratio of amine to carboxylic acid.

Table 6. The influence of amine concentration in hafnium-catalyzed direct amidation.

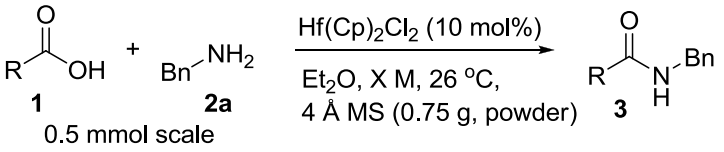


Entry	Equiv. **1a**	Equiv. **2a**	Isolated yield **3a** (%)
1	1	1	38
2	1	1.5	56
3	1	2	81

For certain substrates, the catalyst loading could be reduced to 5 mol% without loss in yield of the amide product. In addition, it was found that the solvent volume, and hence reaction concentration, played an important role for

some substrates (Table 7). The substrate scope for the hafnium-catalyzed protocol was therefore evaluated using optimized conditions for each substrate, with respect to catalyst loading and reaction concentration (solvent volume). A reaction time of 48 hours was chosen as standard to allow even slow reacting substrates to reach high conversions. It should however be noted that several substrates are fully converted long before this time. For example, amide **3ad** (Figure 8) was isolated in 92% already after 90 minutes. Vigorous stirring and freshly activated molecular sieves were in all cases crucial for an efficient reaction outcome.

Table 7. Concentration effects on reaction outcome for hafnium-catalyzed direct amidation.



Entry	Carboxylic acid	[M] carboxylic acid	Reaction time (h)	Amide	Isolated yield (%)
1	Valeric acid	0.05	48	**3b**	17
2	Valeric acid	0.1	48	**3b**	76
3	Phenylacetic acid	0.05	24	**3a**	81
4	Phenylacetic acid	0.1	24	**3a**	86
5	Phenylacetic acid	0.2	24	**3a**	81
6	Phenylacetic acid	0.4	24	**3a**	84

Reaction conditions: carboxylic acid (0.5 mmol), **2a** (1 mmol), $Hf(Cp)_2Cl_2$ (0.05 mmol), 4 Å MS (0.75 g), Et_2O, 26 °C

A selection of amide products are presented in Figure 8 (see Paper IV for a complete list). Analogous to the zirconium- and titanium-catalyzed protocols, no racemization was detected in the amino acid-derived amide products **3f-g** and **3v-x**. Gratifyingly, benzoic acid and cinnamic acid were converted into their corresponding benzylamides **3c** and **3p** in moderate to good yields. This is of particular interest, since conjugated acids generally react poorly in catalytic direct amidation[126,139] unless elevated reaction temperatures are used (100 °C in the zirconium- and titanium-catalyzed protocols, see section 2.1.1 and 2.1.2).[180,181] Good yields of the *N*-substituted phenylacetamides **3z-3ab** were obtained using both electron-rich and electron-poor benzylamines, and high yields were also obtained for the corresponding *N*-benzylamides **3ac-ae**, formed from chloride-substituted acetic acids. Of the latter, amide **3ac** is of special interest since the α-chloro substituent can easily serve as a handle for further synthetic manipulations. In addition, the synthesis of amide **3g** was scaled up 10 times to a 5 mmol reaction, resulting in good yield

after reaction in a round-bottomed flask, followed by extractive workup and purification by column chromatography.

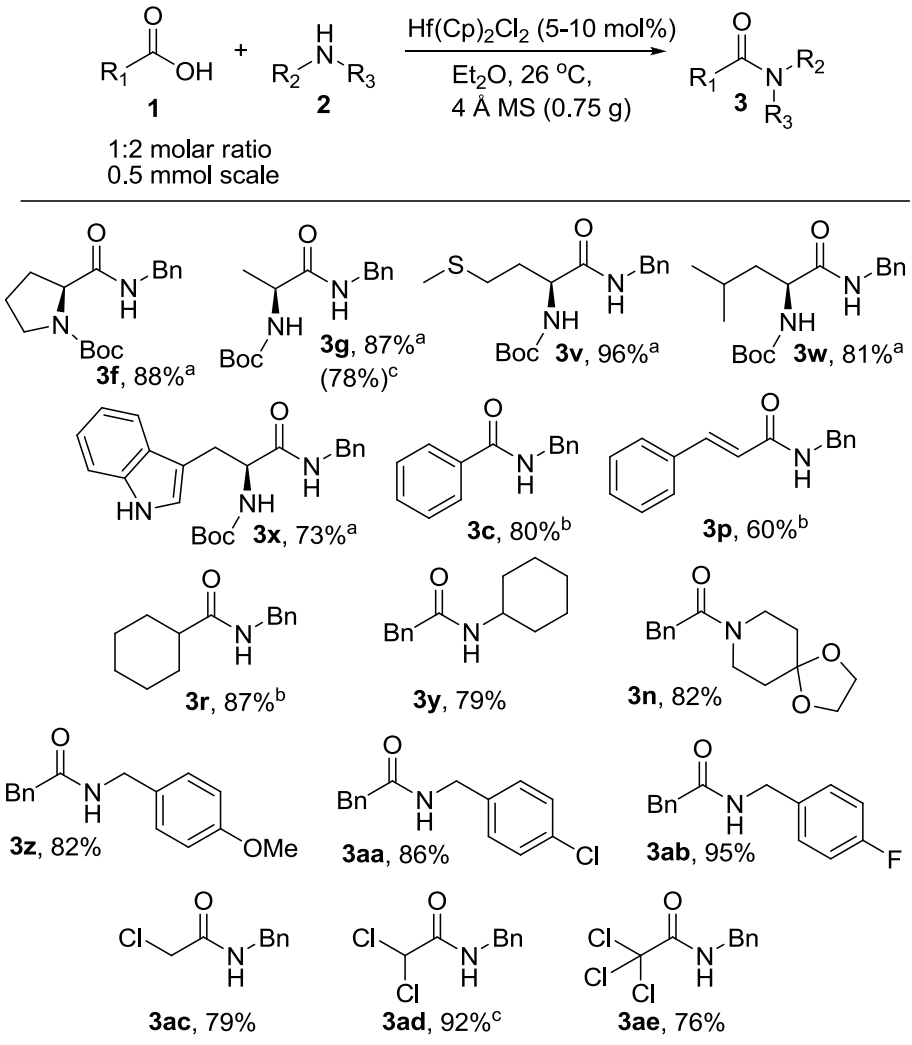
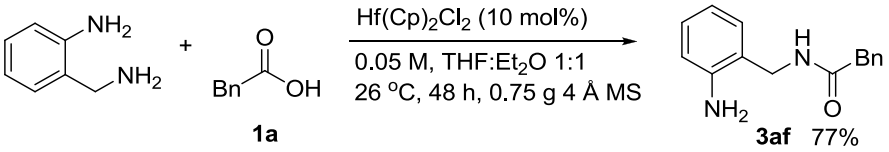


Figure 8. Selected amide products from hafnium-catalyzed direct amidation at room temperature.

[a] >99% *ee* determined by chiral HPLC (Chiralcel AD column). [b] 4 equivalents benzylamine. [c] 90 minutes reaction time. [c] 5 mmol scale reaction in round-bottomed flask, extractive workup and purification by column chromatography.

Anilines are poor nucleophiles in comparison to aliphatic amines, and generally need high reaction temperatures in order to work successfully in direct amidations.[126,147,148] All attempts to use the electron-rich *p*-anisidine in the amidation of phenylacetic acid **1a** failed using hafnium-catalysis. However,

the poor reactivity of anilines enabled the selective acylation of the aliphatic amine of 2-aminobenzylamine with phenylacetic acid to form the aminoamide **3af** (Scheme 10).



Scheme 10. Selective monoacylation of a diamine – the aromatic amine remains unchanged.

Analogous to the results presented in Paper I and III, secondary acyclic amines failed as coupling partners. This result was also obtained by Hall and co-workers for boronic acid-catalysis at room temperature.[138,139] The reason behind this observation is not clear, but it has previously been reported that these kind of amines display a higher degree of salt formation in thermal amidations in comparison to primary amines.[30] In addition, sterics might be expected to play a role. The chart in Figure 9 illustrates the dramatic drop in product yield which is seen when more sterically hindered amines were used. Whereas optimizations of the reaction conditions could circumvent this steric effect and enable a reasonable yield for amide **3k** (see Paper IV), other amines such as the secondary *N*-methylbenzylamine remained unreactive and failed to form the desired amide **3ai** even after several attempts to optimization. Interestingly, the same trend is not observed for a series of Boc-protected amino acids, with the exception of double substitution in the β-position (Figure 10). This observation might be due to unfavorable steric interactions of the substrate and the catalyst, which hinder the acid from adopting a binding mode that enables catalytic transformation. Unfortunately, all attempts to optimize the conditions for the formation of amide **3al** from Boc-valine failed (Figure 10).

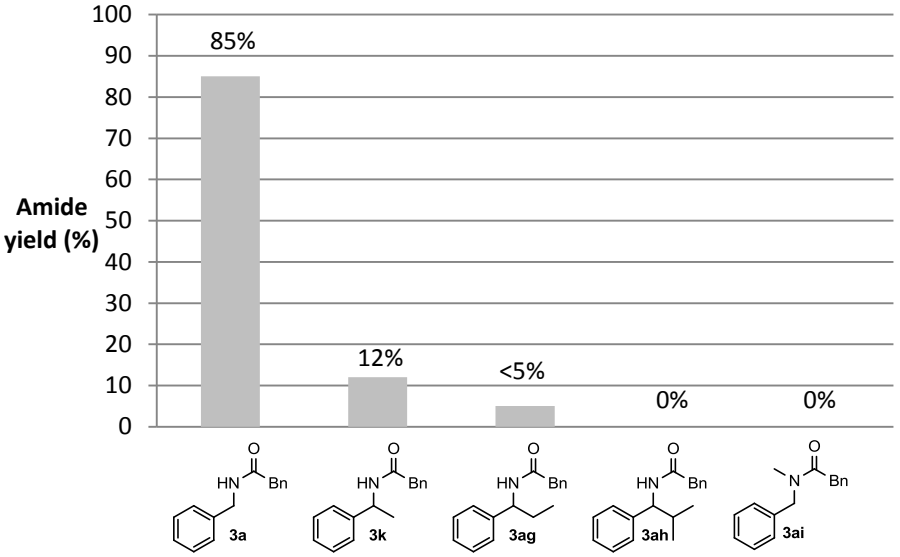


Figure 9. Steric hindrance in the amine affects the reaction outcome negatively.

Reaction conditions: **1a** (0.5 mmol), amine (1.0 mmol), $Hf(Cp)_2Cl_2$ (10 mol%), Et_2O (10 mL), 4 Å MS (powder, 0.75 g), 26 °C, 48 h.

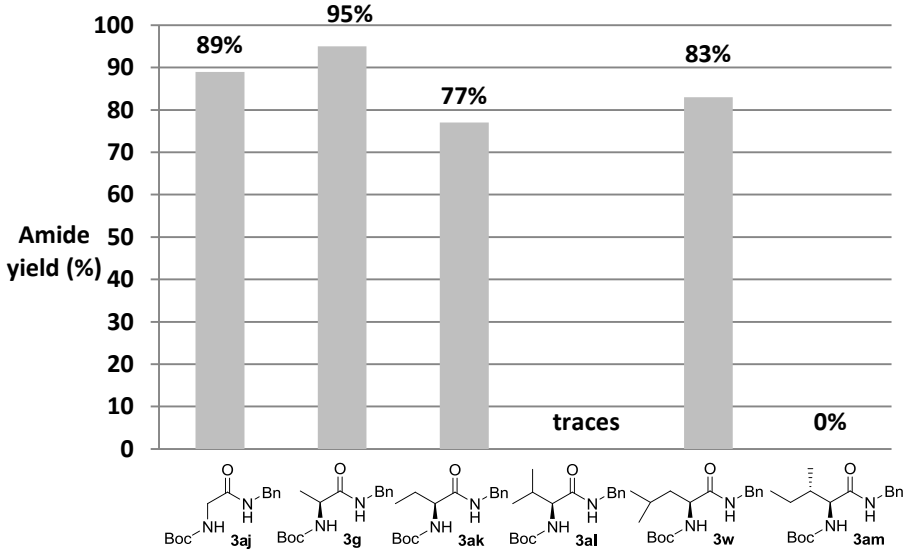
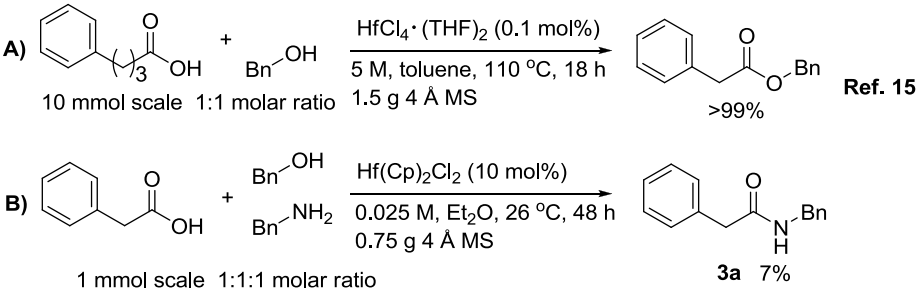


Figure 10. Steric hindrance in the β-position in the carboxylic side chain of the amino acid is clearly affecting the reaction outcome negatively.

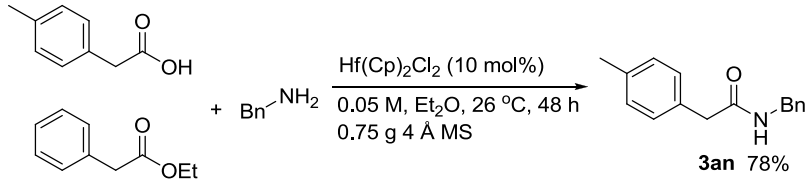
Reaction conditions: carboxylic acid (0.5 mmol), benzylamine (1.0 mmol), $Hf(Cp)_2Cl_2$ (10 mol%), Et_2O (10 mL), 4 Å MS (powder, 0.75 g), 26 °C, 48 h.

In addition to direct amidation of carboxylic acids, group (IV) metal complexes are known to catalyze other transformations of carboxylic acid derivatives. For example, $HfCl_4 \cdot (THF)_2$ and $Hf(OtBu)_4$ can catalyze the esterification of carboxylic acids with alcohols in refluxing toluene in excellent yields (Scheme 11, A).[15] In addition, intra- and intermolecular esterifications can be performed using $Hf(OTf)_4$ as catalyst in refluxing toluene.[16] However, when we used the hafnocene complex under the reaction conditions optimized for amidation, no esterification between phenylacetic acid and ethanol was observed. Instead, the catalyst was inhibited by the presence of alcohol, which was further demonstrated in a competition experiment between benzylamine and benzylalcohol, which resulted in only 7% conversion with full selectivity for the formation of amide **3a** (Scheme 11, B). Interestingly, the observed reactivity was opposite to that described for $Hf(OTf)_4$, which was found to be fully selective for esterification over amidation.[16]



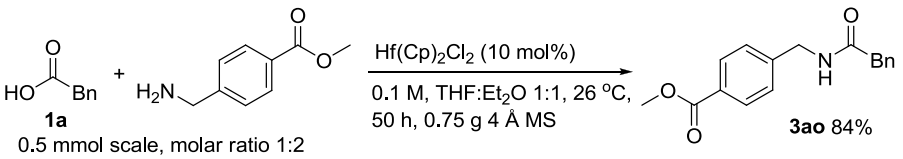
Scheme 11. Hf (IV) complexes catalyze ester formation at high temperatures (A) but not at room temperature (B).

Group (IV) metal complexes have also been reported to catalyze the aminolysis of esters to form amides. Up to 95% yield of amide products were observed at room temperature in THF, using 10 mol% $Zr(OtBu)_4$ and 10 mol% 1-hydroxy-1-azabenzotriazole (HOAt) as catalysts as reported by Porco and co-workers.[107] However, under our hafnium-catalyzed conditions, the ester functionality was found to be inert and only starting material was recovered when ethyl phenylacetate was mixed with two equivalents of benzylamines. The observed chemoselectivity was further confirmed in a competition experiment between ethyl phenylacetate, p-tolylacetic acid and benzylamine. This experiment resulted in full selectivity for the amidation of the carboxylic acid and amide **3an** was isolated in 78% yield (Scheme 12).



Scheme 12. The hafnium catalyst is fully selective for amidation of carboxylic acids over esters.

The observed inertness of esters under hafnium-catalyzed amidation conditions indicated that this functionality can act as a protecting group for additional carboxylic acid moieties present in a substrate. This concept proved successful and amide **3ao** was isolated in 84% yield with the ester functionality untouched (Scheme 13).



Scheme 13. Amidation of phenylacetic acid with the aminoester methyl-(4-methylamino)-benzoate.

Unfortunately, all attempts to form dipeptides from Boc- and Cbz-protected amino acids and amino acid esters (methyl- ethyl- and benzylesters) failed under the reaction conditions, despite several attempts for optimization. In addition, aliphatic primary diamines as well as substrates containing free hydroxyl-groups failed to form amide products.

2.2 Carbamates as the source of amine (Paper V)

Direct thermal formation of primary amides from carboxylic acids can be achieved with gaseous ammonia under harsh reaction conditions (200 °C and 7 bar anhydrous gaseous ammonia).[182] In addition, very few catalysts are known for the direct formation of primary amides from carboxylic acids, despite the importance of the functionality in *e.g.* pharmaceutically active molecules (Figure 11). Only three examples of metal-catalyzed protocols for this transformation were known before 2012,[150,173,174] and the lack of a general method inspired us to investigate the activity of group (IV) metal complexes for this transformation.

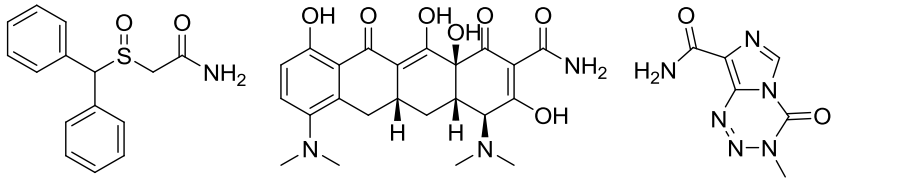


Figure 11. Top-selling drugs (2010, US retail) containing a primary amide moiety.

Using group (IV) metal complexes in catalytic amounts, different ammonia sources were evaluated in the transformation of phenylacetic acid to the corresponding primary amide **4a**. As illustrated in Table 8, several sources of ammonia could be used in combination with different metal complexes to produce phenylacetamide **4a**. Due to the operational inconvenience of gaseous ammonia, it was evaluated as a THF solution (Table 8, entry 1), however, only trace amounts of product were obtained. The best result was achieved with three equivalents of ammonium carbamate **7** (≤ 6 molar equivalents of ammonia to carboxylic acid), which in combination with 20 mol% titanium (IV) chloride enabled a quantitative yield of the target amide **4a** after 24 hours at 100 °C (Table 8, entry 6). The use of zirconium (IV) chloride and hafnium (IV) chloride in catalytic amount also gave rise to efficient reactions, providing the amide product **4a** in yields of 75% and 70%, respectively (Table 8, entries 10 and 13). The use of group (IV) alkoxides resulted in lower yields of amide **4a**, compared to the corresponding chloride complexes (Table 8, entries 8, 9, 11 and 13). For comparative reasons, the previously reported amidation catalysts phenylboronic acid and 2-iodophenylboronic acid[138] were evaluated in the formation of primary amides. The use of these two catalysts resulted in poor yields of amide **4a** (Table 8, entries 14 and 15), indicating that group (IV) metal complexes are superior catalysts in this reaction. Since ammonium carbamate decomposes into two equivalents of ammonia and one equivalent of carbon dioxide upon heating, pressure is built up inside the reaction vessel. For this reason, the amidation reactions were successfully performed in either Ace pressure tubes, suitable for pressures up to 150 psig (10.34 bar), or in vials equipped with caps and septa.

The thermal reaction using ammonium carbamate **7** without catalyst present, resulted in essentially no conversion of the acid into the amide (Table 8, entry 16). Other ammonia sources such as formamide, sulfamic acid, ammonium chloride and urea were also evaluated, however resulting in no or poor yields of the target amide, as well as in the formation of byproducts.

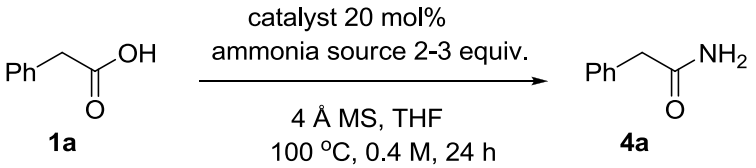
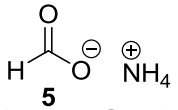
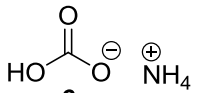
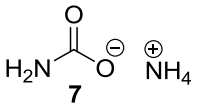


Table 8. Evaluation of catalysts and ammonia sources for the formation of amide **4a**.

Entry	NH_3-source	Catalyst	Isolated yield (%)
1[c,d]	NH_3	$TiCl_4$	trace[e]
2	 **5** (2 equivalents)	$Ti(OiPr)_4$	13
3	 **6** (2 equivalents)	$TiCl_4$	28
4		$Ti(OiPr)_4$	23
5		$ZrCl_4$	10
6	 **7** (3 equivalents)	$TiCl_4$	99
7[d]		$TiCl_4$	99
8		$Ti(OiPr)_4$	27
9		$Ti(OBu)_4$	28
10		$ZrCl_4$	75
11[b]		$Zr(OtBu)_4$	53
12		$HfCl_4$	70
13[b]		$Hf(OtBu)_4$	53
14		$PhB(OH)_2$	10
15		2-I-$PhB(OH)_2$	17
16		-	2

[a] Reaction conditions: **1a** (1.0 mmol), ammonia equivalent (2 - 3 mmol), catalyst (20 mol%), and activated 4 Å molecular sieves (0.5 g, pellets) in dry THF (acid concentration 0.4 M at 100 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h. [b] Yield determined by ^{1}H-NMR. [c] Ammonia (0.4 M in THF, 6 equivalents). [d] Carboxylic acid concentration 0.067 M. [e] Yield determined by ^{1}H-NMR.

A substrate evaluation was performed, using $TiCl_4$ and $ZrCl_4$ as catalysts in combination with three equivalents of ammonium carbamate at 100 °C (THF) or 120 °C (toluene) in the presence of 0.5 g molecular sieves to 1 mmol carboxylic acid. The primary amides were formed in good to excellent yields and selected results can be found in Figure 12 (see Paper V for a complete list). Unfortunately, the stereocenter in the Boc-protected proline amide **4f** was found to be partially racemized, a result which stands in contrast to the catalyzed formation of the corresponding *N*-benzyl amide of Boc-proline (Paper I - IV). The thermal formation of primary amides under the reaction conditions resulted in 2-14% yield.

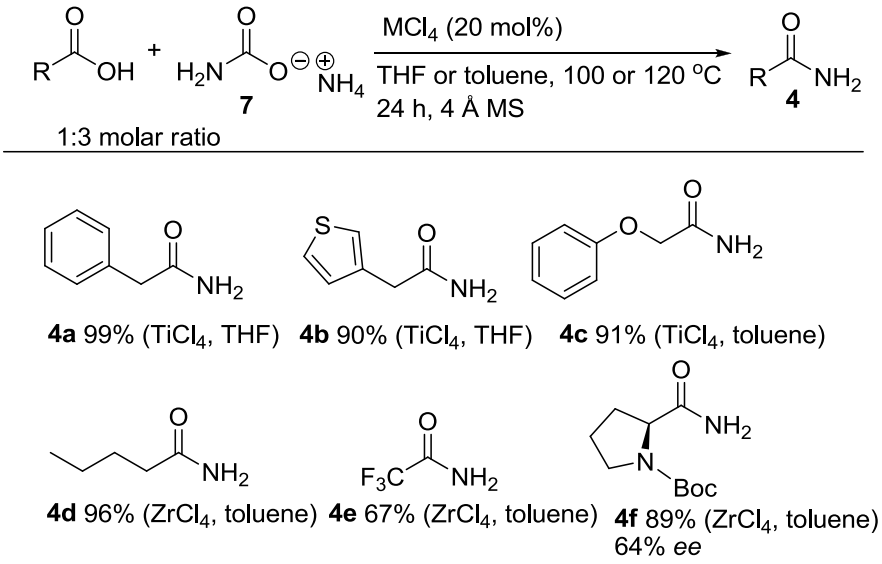


Figure 12. Selected examples of primary amides formed by group (IV) metal catalysis.

To compare our catalytic method to known literature procedures, we tried to reproduce the zirconyl chloride and cerium ammonium nitrate catalyzed amidations under microwave irradiation, reported by Reddy and co-workers.[173,174] However, in our hands, the reported protocols did not result in the formation of any primary amide product.

The successful use of ammonium carbamate as ammonia source encouraged us to expand the investigations to the formation of other amides, where a suitable carbamate could serve as a convenient equivalent to gaseous amines. For this purpose, we decided to evaluate the commercially available dimethylammonium dimethylcarbamate **8** (Figure 14), as an equivalent to dimethylamine. The resulting *N*,*N*-dimethyl amide moiety can for example be found in the top-selling drug Ambien CR, which is used in the treatment of insomnia (Figure 13).[183]

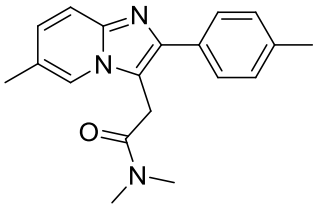


Figure 13. The *N*,*N*-dimethylamide motif is present in the pharmaceutical zolpidem, used in the treatment of insomnia.

A series of *N*,*N*-dimethyl amides were synthesized in good to excellent yields when different carboxylic acids were reacted with two equivalents of **8**, using 20 mol% titanium (IV) or zirconium (IV) chloride as catalysts (Figure 14, see Paper V for a complete list). For comparative reasons, dimethylamine in THF (2M) was used in a stoichiometry of 4:1 amine:acid, together with 20 mol% $ZrCl_4$ for the amidation of phenylacetic acid under otherwise identical reaction conditions to those described in Figure 14. The resulting isolated yield of amide **9a** was found to be somewhat lower compared to when the carbamate was used (74% *vs*. 85%). The non-catalyzed thermal background reaction using dimethylcarbamate **8** resulted in 5–14% yield of the corresponding *N*,*N*-dimethylamides, indicating that the major amount of amides formed in the catalytic reaction is mediated by the metal complex. For comparative reasons, phenylboronic acid and 2-iodophenylboronic acid were also evaluated as catalysts for the formation of *N*,*N*-dimethyl-2-phenylacetamide **9a**, resulting in significantly lower yields of the target amide (42% and 31%, respectively).

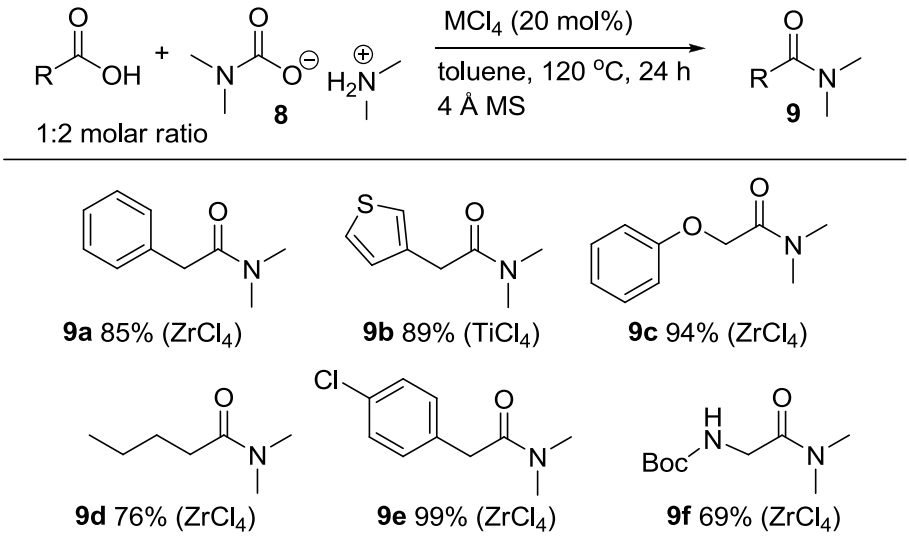


Figure 14. Selected examples of *N*,*N*-dimethylamides formed by group (IV) metal catalysis.

3. Reaction characteristics and mechanistic considerations (Paper IV and Appendix B)

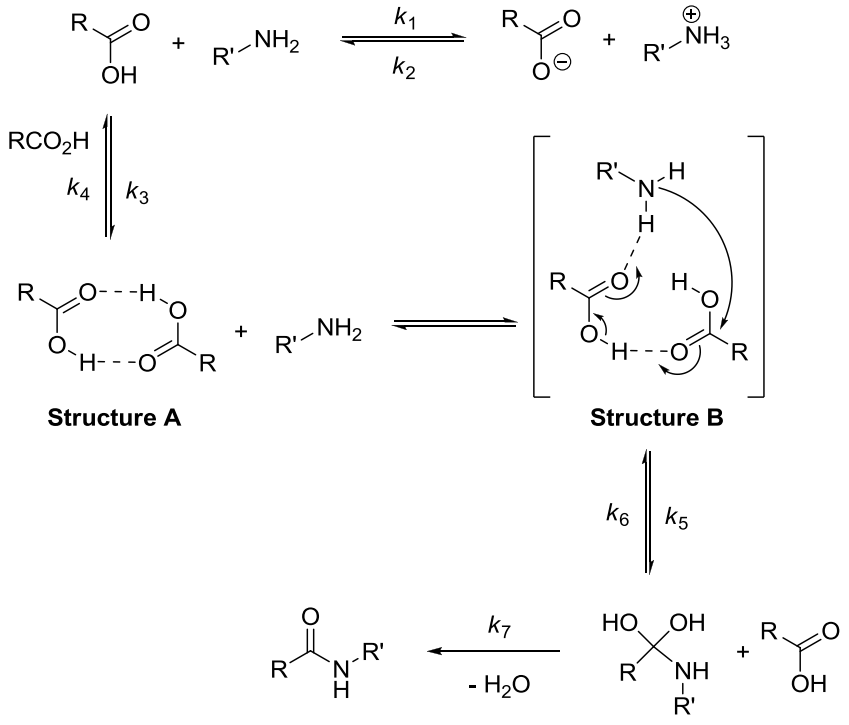
This chapter focuses on the mechanistic aspects of group (IV) metal-catalyzed direct amidation. In addition to the experimental results on hafnium-catalysis (Paper IV) and the on-going mechanistic study on zirconium-catalysis (Appendix B), relevant literature on other Lewis acid-catalyzed protocols, as well as on thermal amidation, is included for comparative purposes.

3.1 Rate dependencies

3.1.1 Rate behaviors in thermal amidation

Whiting and co-workers studied the rate of thermal amidation for two carboxylic acids in refluxing toluene and found that the reaction rate displayed a first order dependence on 4-phenylbutyric acid, when reacted with two different amines.[184] The first order rate dependence on carboxylic acid is consistent with the formation of an acyl intermediate, which the authors suggested to be an *in situ* formed carboxylic anhydride. The anhydride was also demonstrated to undergo fast aminolysis to form the amide product in a separate experiment. The dependence of the reaction rate on amine concentration under thermal conditions was not discussed by the authors.

A couple of years later, Whiting and co-workers continued their mechanistic studies of the thermal amidation using spectroscopic and kinetic techniques.[185] The authors demonstrated that a 20% excess of either amine or carboxylic acid enhanced the reaction rate, however only to a small extent compared to the equimolar reaction. The small rate enhancement was considered to be insignificant, and the authors concluded that direct thermal amidation is neither general acid- nor general base-catalyzed. In addition, DFT-calculations refuted the previous idea of an anhydride intermediate in the mechanism. Instead, a bridging dimer of two neutral carboxylic acids was proposed to be the likely intermediate in thermal amidation (Structure A, Scheme 14). The proximity of the second carboxylic acid was proposed to facilitate proton transfer in the nucleophilic attack of the amine (Structure B, Scheme 14).



Scheme 14. Proposed mechanism for thermal amidation, suggested by Whiting and co-workers.[185]

3.1.2 Rate behaviors in bor(on)ic acid-catalyzed amidations

The rate dependencies on the different reaction components for the boric and boronic acid-catalyzed direct amidation reaction were studied by Whiting and co-workers.[184] In analogy to the results for thermal amidation, the catalyzed reactions followed first order kinetics for the concentration of carboxylic acid under the employed reaction conditions. The authors point out that the first order rate behavior is consistent with the formation of an acyl- or possibly a diacyl-boronate species as an intermediate in the catalytic cycle when arylboronic acids are used as catalysts (Figure 15). The stoichiometric reaction between acyl-boronate species and amines to form amides has been known for a long time,[27] and it is generally assumed that species of this type are intermediate structures in boronic acid-catalyzed amidations.[120,138,139,186,187] The rate dependencies on amine and catalyst were not mentioned by the authors.

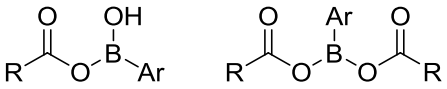
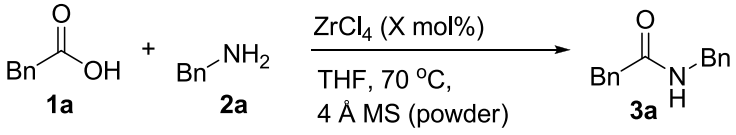


Figure 15. Proposed acyl- and diacylboronate intermediates in boronic acid-catalyzed direct amidation.

In addition to the mechanistic work carried out by the group of Whiting, Hall and co-workers performed kinetic investigations using 5-methoxy-2-iodophenyl boronic acid as catalyst at room temperature.[139] It was found that the reaction displayed first order rate dependence on catalyst, and that excess of amine retarded the reaction. It was also observed that the concentration of carboxylic acid was optimal at 0.1 M for 10 mol% catalyst loading, and that changes to this concentration was detrimental to the reaction outcome. Due to these complications, the rate orders in carboxylic acid and amine were not established.

3.1.3 Rate behaviors in zirconium-catalyzed amidations (Appendix B)

To further understand the zirconium-catalyzed system we developed (Paper I and II), the rate behaviors of the system were studied by varying the concentrations of $ZrCl_4$, phenylacetic acid (**1a**) and benzylamine (**2a**) while keeping the reaction volume and loading of activated 4 Å powdered molecular sieves constant (Scheme 15). Samples of approximately 50 µL were removed with a syringe at certain time intervals and the sample was injected into deuterated methanol and subjected to ^{1}H-NMR analysis. The results presented in this chapter are part of an on-going mechanistic work, and the data is meant to serve as the basis for qualitative discussion.



Scheme 15. Zirconium-catalyzed direct formation of **3a**.

3.1.3.1 Rate dependence on zirconium (IV) chloride

Figure 16 illustrates the influence of the zirconium concentration on the reaction rate. As expected, a higher loading of $ZrCl_4$ leads to a higher reaction rate, and the reaction is clearly positive order in catalyst. Interestingly, the reaction using a catalyst concentration of 0.02 M (5 mol%) reached 42% NMR-yield at 70 °C after 90 minutes, whereas the reaction using 0.03 M (7.5 mol%) catalyst reached an NMR-yield of approximately 90% after the same amount of time. If a reaction order of 1 in zirconium were at hand, an

increase in catalyst loading with 50% should lead to an increase in rate with the same order of magnitude. This does not seem to fit the results obtained for zirconium-catalyzed amidation, and the observed relationship between rate and catalyst loading suggests a reaction order >1 in $ZrCl_4$.

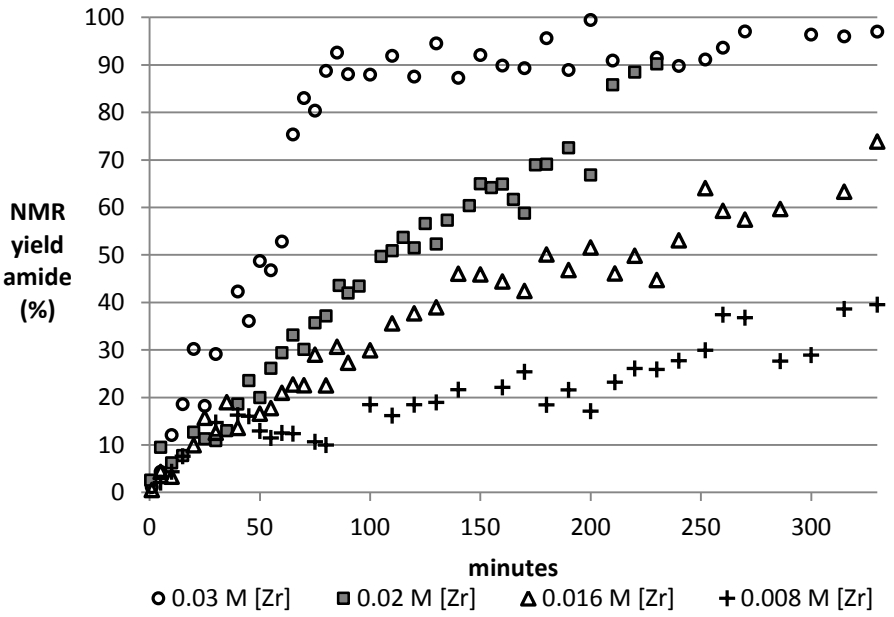


Figure 16. Reaction profiles for the formation of amide **3a** at different concentrations of $ZrCl_4$.

Reaction conditions: **1a** (0.4 M, 2 mmol), **2a** (0.4 M, 2 mmol), $ZrCl_4$ (X M), 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

3.1.3.2 Rate dependence on benzylamine

The zirconium-catalyzed direct amidation reaction was found to display positive order rate dependence on benzylamine. The chart in Figure 17 shows the reaction profiles at different amine concentrations. Similar to what was seen for $ZrCl_4$, the reaction rate was clearly increased upon addition of more than one equivalent of amine in a way that indicates a rate dependence order >1 in amine. This observation suggests that the amine is not only acting as a nucleophile in the amidation reaction, but rather is involved in several processes. The nature of these different roles will be subject to further investigations during the course of the on-going mechanistic study. It is interesting to note that the positive rate dependence on benzylamine for $ZrCl_4$-catalyzed amidation stands in direct contrast to the results Hall and coworkers obtained for the 5-methoxy-2-iodophenylboronic acid catalyst.[139]

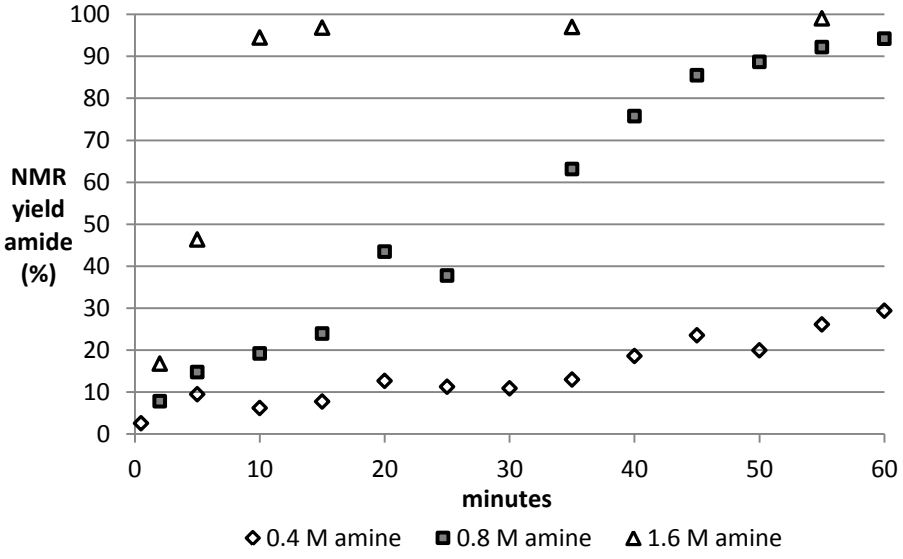


Figure 17. Reaction profiles for the formation of amide **3a** at different concentrations of benzylamine.

Reaction conditions: **1a** (0.4 M, 2 mmol), **2a** (X M), $ZrCl_4$ (0.02 M, 0.1 mmol), 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

3.1.3.3 Rate dependence on phenylacetic acid

The chart in Figure 18 shows the rate behavior for different concentrations of phenylacetic acid (**1a**). Notably, this reaction component was found to have a negative effect on the reaction rate and the reaction appears to negative order in carboxylic acid, which is opposed to what has previously been described for boric and boronic acid catalysis (see section 3.1.2). The differences in rate orders in substrates between the zirconium- and bor(on)ic acid-catalyzed direct amidation reactions, indicate that the operating mechanisms for these systems are not analogous.

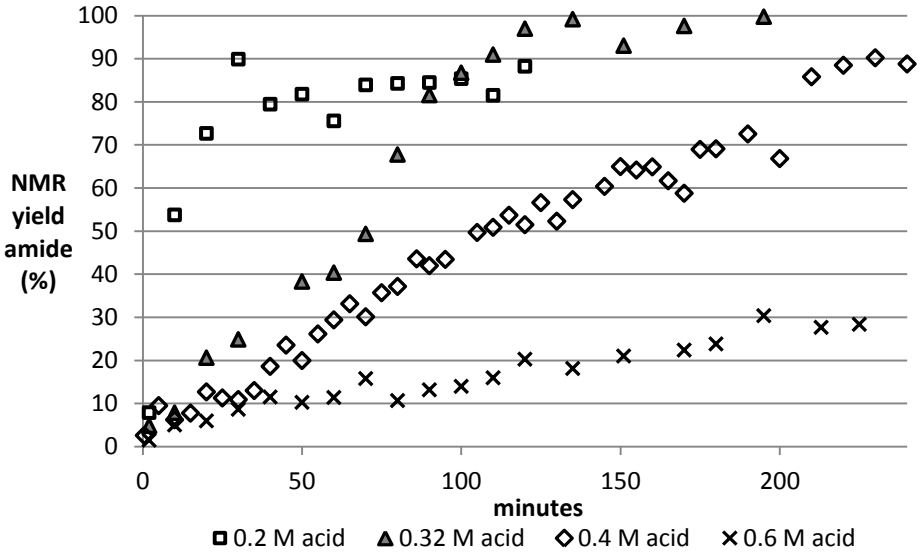
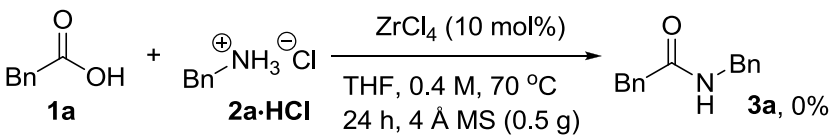


Figure 18. Reaction profiles for the formation of amide **3a** at different concentrations of phenylacetic acid.

Reaction conditions: **1a** (X M), **2a** (0.4 M, 2 mmol), $ZrCl_4$ (0.02 M, 0.1 mmol), 4Å MS (1 g, powder), THF (5 mL), 70 °C.

One explanation to the inhibitory effect of the carboxylic acid on the reation rate might be that the excess of acidic protons from the carboxylic acid effectively decreases the concentration of free amine, which was seen to be important for the reaction rate in $ZrCl_4$-catalyzed amidation (section 3.1.3.2). This hypothesis is strengthened by a control experiment between phenylacetic acid **1a** and the hydrochloride salt of benzylamine (Scheme 16), which failed to form amide product after 24 hours at 70 °C. The same behavior was also observed for thermal lactamization at different pH's, as described by Camilleri *et al*.[188] At this point, however, it cannot be ruled out that an excess of carboxylic acid might also affect other steps in the mechanism which are of importance for the reaction rate, and further investigations are needed to elucidate the mechanistic role of this reaction component.



Scheme 16. Control experiment using protonated benzylamine.

3.2 Electronic influences of substrates

The electronic properties of carboxylic acids and amines are closely related to their corresponding pK_a /pK_b values, where a low pK_a is expected from an acid with electron withdrawing substituents. The pK_a value of a carboxylic acid in aqueous solution is not the same as the pK_a value in organic solvents, since the energies correlated to charge separation are different in different media. For this reason, one should be careful when comparing the ability of different species to donate a proton in organic solvents solely based on their respective pK_a values in water. However, a trend in pK_a values in aqueous medium will often be the same in an organic solvent, when comparing a series of similar compounds. For example, the pK_a values for acetic acid are higher in both water (4.8) and DMSO (12.3) compared to those for dichloroacetic acid (1.30 in water and 6.36 in DMSO), which in turn are higher than the pK_a values for trichloroacetic acid (0.66 in water and 2.5 in DMSO).[189] Apart from pK_a, the electronic properties of a series of structurally similar substrates can also be described by Hammett parameters. Relating the reaction rate constant to such parameters for a series of similar substrates can reveal important information about the rate-limiting or turnover-limiting step of a reaction.

3.2.1 The electronic effects of carboxylic acids

3.2.1.1 Thermal and bor(on)ic acid-catalyzed direct amidation

It has been demonstrated that the pK_a of a carboxylic acid influences the reaction outcome in thermal direct amidations. Whiting and co-workers reported that a low pK_a of the carboxylic acid affected the reaction outcome negatively under thermal conditions, whereas an acid with a higher pK_a formed amide products more readily.[185] The authors observed that bromoacetic acid (pK_a 2.69 in water) did not form amide products under thermal conditions even after 48 hours of reaction time in toluene (50 or 120 °C), whereas phenylbutyric acid (pK_a 4.76 in water) reacted with a series of amines to form the corresponding amides. Benzoic acid (pK_a 4.19 in water) has a pK_a value in-between the other two, and was observed to form amide products in yields intermediate to those obtained for phenylbutyric acid and bromoacetic acid. By calorimetric measurements of the total heat output, as well as by NMR-analysis and/or elemental analysis, the authors found that the poor ability of electron-poor carboxylic acids to form amides was correlated to a high degree of ammonium salt formation upon mixing with an amine. Interestingly, Whiting's results for the thermal amidation were in contrast to those reported by Loupy and co-workers, who did not find any strong correlations between the pK_a of the carboxylic acid and its reactivity

in thermal amide formation and at 150 °C under microwave irradiation and solvent-free conditions.[35]

In addition to the results for thermal amidation, Whiting and co-workers demonstrated that a low pK_a of the carboxylic acid negatively affects the outcome of boric acid- and 2-iodophenylboronic acid-catalyzed amidation. All conclusions were based on analysis of the reaction yields, and no kinetic data was presented.[185]

3.2.1.2 Hafnium-catalyzed direct amidation (Paper IV)

The electronic properties of the carboxylic acid are of importance for the reaction rate in the hafnium-catalyzed system. As illustrated in Figure 19, the three chlorinated acetic acids form the corresponding *N*-benzyl amide products at a higher rate compared to phenylacetic acid during the first 90 minutes of the hafnium-catalyzed amidation. Interestingly, dichloroacetic acid is the fastest to react and forms the corresponding *N*-benzyl amide in around 90% yield after only 90 minutes of reaction time (Table 9, entry 3). This observation might suggest that there are counteracting effects involved, which need to be balanced. On the one hand, high electron-withdrawing capacity of the substituents on the carboxylic acid makes the carbonyl carbon more electrophilic. If the anionic charge of the carboxylate is stabilized by the cationic metal center of the catalyst, the electrophilic carbonyl would be more susceptible for attack by the amine. On the other hand, stronger acids protonate the amine to a larger extent, thereby effectively decreasing the concentration of the nucleophile. Such a scenario would mimic the effect of performing the reaction with a higher concentration of carboxylic acid, which was observed to decrease the reaction rate in the zirconium-catalyzed system (see section 3.1.3).

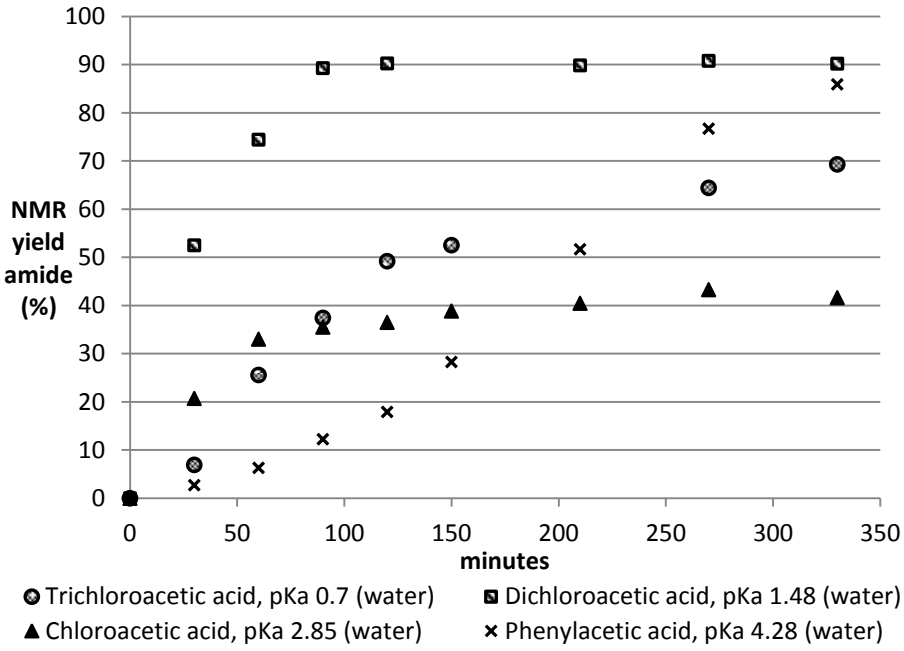
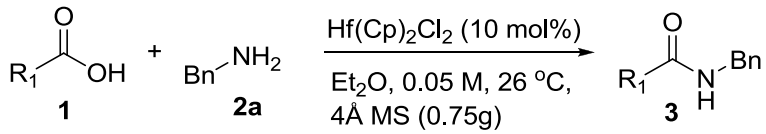


Figure 19. Reaction profiles for the hafnium-catalyzed direct amidation using carboxylic acids with different pK_a values.

Reaction conditions: carboxylic acid (0.05 M, 0.5 mmol), **2a** (0.1 M, 1 mmol), $Hf(Cp)_2Cl_2$ (0.005 M, 0.05 mmol), 4 Å MS (0.75 g, powder), Et_2O (10 mL), 26 °C.

When the reactions were stirred for the times indicated in Table 9, all corresponding *N*-benzyl amides were isolated in good yields, revealing that the pK_a of the carboxylic acid does not have a significant effect on the thermodynamics of the reaction.

Table 9. Hafnium-catalyzed amidation of benzylamine with carboxylic acids with different pK_a values.



1:2 molar ratio
0.5 mmol scale

Entry	Carboxylic acid	pK_a (H_2O)	Reaction time (h)	Amide	Isolated Yield (%)
1	Phenylacetic acid	4.28	24	**3a**	81
2	Trichloroacetic acid	0.7	48	**3ae**	76
3	Dichloroacetic acid	1.48	1.5	**3ad**	92
4	Chloroacetic acid	2.85	48	**3ac**	79

3.2.1.3 Zirconium-catalyzed direct amidation (Appendix B)

The effect of the electronic properties of the carboxylic acid on the reaction rate was studied in the zirconium-catalyzed system at 70 °C (Figure 20) using three differently substituted benzoic acids and an excess of benzylamine. The difference in reaction profiles between 4-nitrobenzoic acid (pK_a 3.41 in water), 4-chlorobenzoic acid (pK_a 4.03 in water) benzoic acid (pK_a 4.19 in water), 4-toluic acid (pK_a 4.37 in water) and 4-methoxybenzoic acid (pK_a 4.47 in water) is apparent: the electron-poor acids react considerably faster than benzoic acid, which in turn is faster than the more electron-rich acids with a higher pK_a. The higher reaction rate for electron-poor carboxylic acids under zirconium-catalyzed conditions suggests that the activation energy for the turnover-limiting step is affected by the electron density of the carboxylic acid. There are several possibilities which could explain this observation. For example, the carboxylic acid might bind to the metal catalyst as the corresponding carboxylate. If the coordination of the carboxylic acid species to the metal is turnover-limiting, the high abundance of carboxylate species in the reaction mixture could explain the faster rates for electron-poor carboxylic acids. However, the negative rate order in carboxylic acid (see section 3.1.3.3) suggests that the formation of a metal-carboxylate complex is not turnover-limiting. Rather, the attack of the amine on the carbonyl, or the collapse of the resulting tetrahedral intermediate, might be the turnover-limiting step for the transformation (see section 3.5 for further discussion). The different shapes of the curves in Figure 20 might indicate that the acid is involved in other processes as well. The sigmoidal shape of the reaction profiles for the majority of the substrates is a sign of an induction time for the formation of the active catalyst. This is unfortunate since it complicates the construction of Hammett plots.

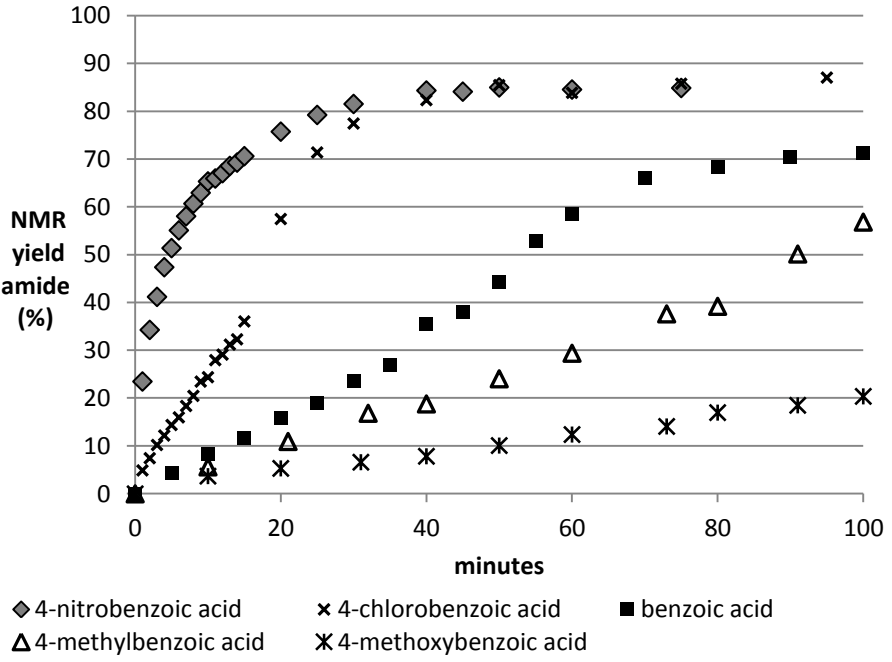


Figure 20. Reaction profiles for the $ZrCl_4$-catalyzed direct amidation of differently substituted benzoic acids with benzylamine (**2a**).

Reaction conditions: carboxylic acid (0.4 M, 1 mmol), **2a** (1.6 M, 4 mmol), $ZrCl_4$ (0.1 mmol), 4 Å MS (0.5 g, powder), THF (2.5 mL), 70 °C.

3.2.2 The electronic effects of amines

3.2.2.1 Thermal and bor(on)ic acid-catalyzed direct amidation

Amines with different electronic properties were studied by Loupy and co-workers for thermal amidation under microwave irradiation and solvent-free conditions.[35] It was observed that the reactivities of a series of amines, determined as the yield of the reaction after a certain time, were in the order: benzylamine (pK_b 4.67) > n-octylamine (pK_b 3.35) > *p*-anisidine (pK_b 8.36) > aniline (pK_b 9.37). The order of reactivity does not mirror the pK_b values in water for these amines, and no relationship between these two parameters was possible to establish. Similarly, Whiting and co-workers did not find any simple relationships between basicity/salt-forming ability of amines and their reactivity in thermal amide formation, again determined as the amide yield after a certain time.[185] The exception was aniline, which was the least reactive amine for both salt formation and amidation. The lack of a trend

between amine basicity and its ability to form amides was also apparent for amidations catalyzed by boric acid and *o*-iodophenylboronic acid. Whiting and co-workers concluded that both steric and electronic effects must be contributing to the ability of an amine to form amides under thermal, boric and boronic acid-catalyzed conditions. The authors pointed out that these two factors seem to be well-balanced for benzylamine, which they found to be the most reactive amine in the amidation reaction, despite being neither most basic nor least sterically hindered. Kinetic data was presented by neither Loupy nor Whiting.

3.2.2.2 Hafnium-catalyzed direct amidation (Paper IV)

Aware about the above-mentioned "benzylic effect" and the complicated matter of comparing structurally different amines, we were interested to see whether different electronic properties in a series of benzylamines would reveal any correlation between rate and pK_b. Hence, four different benzylamines were reacted with phenylacetic acid under hafnium-catalyzed conditions. As can be seen in Figure 21, the reaction rates of the halogen-substituted amines (4-fluorobenzylamine and 4-chlorobenzylamine) are somewhat lower during the first 150 minutes compared to the two more electron-rich amines (benzylamine and 4-methoxybenzylamine). However, the rate in the linear region seems to be approximately the same for all amines. These observations might indicate that the electron density of the amine is of importance for the formation of the active hafnium-based catalyst, *i.e.* the induction time, whereas it is not important for the turnover-limiting step of the hafnium-catalyzed amidation.

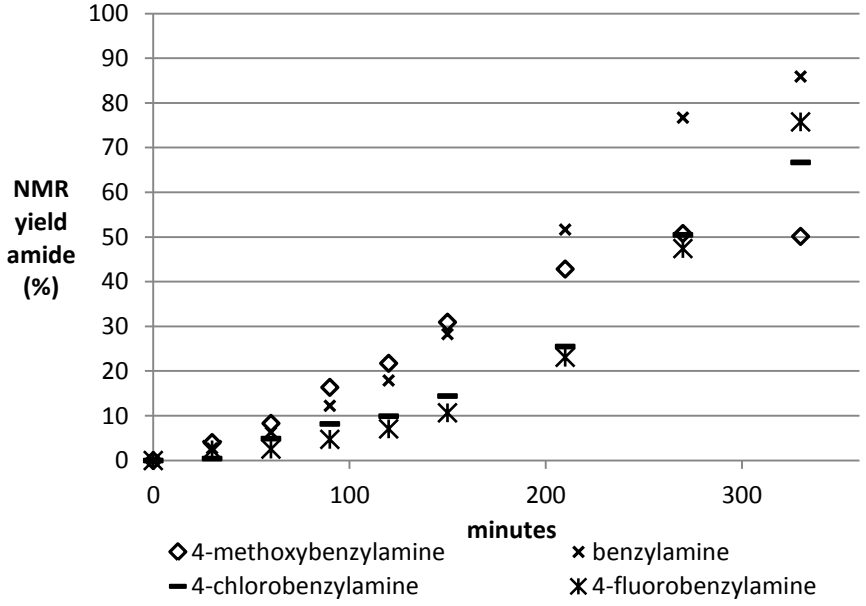
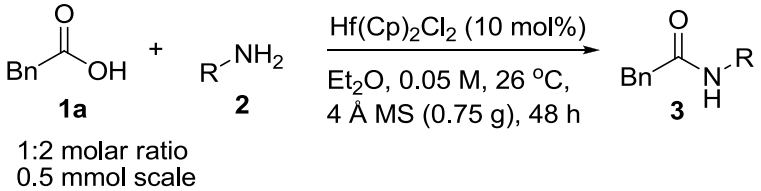


Figure 21. Reaction profiles for the hafnium-catalyzed amidation of **1a** and differently substituted benzylamines.

Reaction conditions: **1a** (0.05 M, 0.5 mmol), amine (0.1 M, 1 mmol), $Hf(Cp)_2Cl_2$ (0.005 M, 0.05 mmol), 4 Å MS (0.75 g, powder), Et_2O (10 mL), 26 °C.

The differently substituted benzylamines resulted in high yields of their corresponding amides after 48 h reaction time, indicating that the thermodynamics of the reaction is not affected by electronic properties of the benzylamine (Table 10).

Table 10. Hafnium-catalyzed amidation of phenylacetic acid with differently substituted benzylamines.



1:2 molar ratio
0.5 mmol scale

Entry	Amine	Amide	Isolated yield (%)
1	Benzylamine	**3a**	81
2	4-Methoxybenzylamine	**3z**	82
3	4-Chlorobenzylamine	**3aa**	86
4	4-Fluorobenzylamine	**3ab**	95

3.2.2.3 Zirconium-catalyzed direct amidation (Appendix B)

In contrast to the results for the hafnium-catalyzed direct amidation (Figure 21), no significant difference in rate of product formation was seen using differently substituted benzylamines under zirconium-catalyzed conditions at 70 °C (Figure 22). This lack of trend might suggest that the substituent on the aromatic ring is too remote to significantly affect the electronic density of the amine. In addition, and in contrast to the hafnium-catalyzed system, no difference in induction time is seen when differently substituted amines are used. This observation is likely due to faster formation of the active catalyst, possibly as a function of a faster ligand coordination/exchange for $ZrCl_4$ compared to $Hf(Cp)_2Cl_2$, or simply as a function of reaction temperature (70 °C for Zr-catalysis *versus* 26 °C for Hf-catalysis).

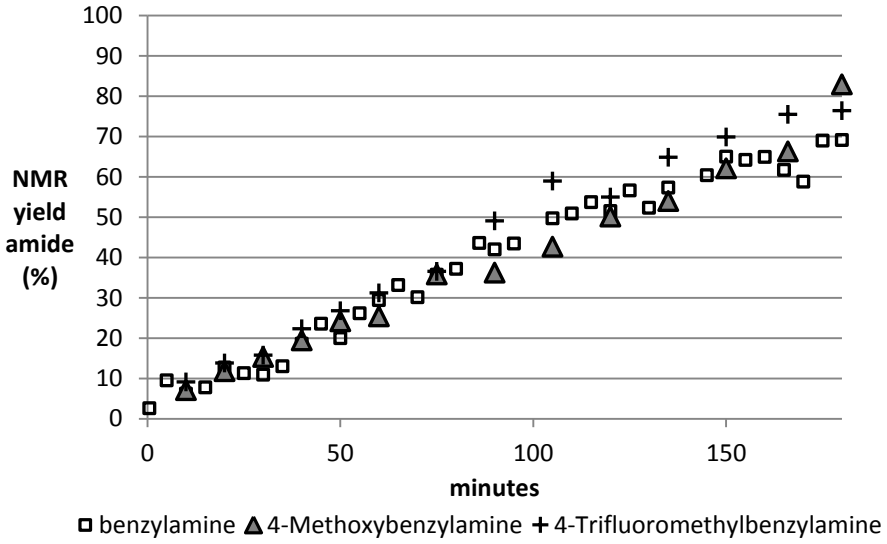


Figure 22. Reaction profiles for the zirconium-catalyzed amidation of **1a** and differently substituted benzylamines.

Reaction conditions: **1a** (0.4 M), amine (0.4 M), $ZrCl_4$ (0.02 M), 4 Å MS (powder, 0.5 g/mmol **1a**), THF, 70 °C.

3.3 The role of water

The formation of water during the course of the reaction is generally a challenge in direct amidation, and a system for efficient removal of water is described for the majority of the protocols with homogeneous catalysts. For thermal amidations, the high reaction temperatures alone can be sufficient to remove water by evaporation and drive the equilibrium towards product formation.[28,190] For homogeneous catalytic protocols using boronic acids or metal complexes in refluxing aromatic hydrocarbons, azeotropic distillation of water or the use of molecular sieves in a Soxhlet thimble are commonly

used techniques.[120,126,147] Catalytic protocols at reaction temperatures of 70 °C or less have been reported using molecular sieves directly in the reaction mixture to scavenge water.[138,139,141,180,181] The importance of water removal is a drawback from a scale-up point of view, and ways to get around it while still keeping mild reaction conditions would be most valuable. Notably, the reported heterogeneous metal catalysts do not require water scavengers (see references in section 1.3.3.5.2). It is not clear whether this is due to a high stability of the catalysts, or the fact that many of the systems employ high catalyst loadings,[158,159] and/or reaction temperatures at which the thermal amidation is efficient and contributes to a large fraction of the yield.[161,162,172,175]

3.3.1 Boronic acid-catalyzed systems

The explanation to why water needs to be scavenged in homogeneous, catalytic amide formation is likely different for different systems. In contrast to earlier findings where boronic acid-catalyzed amidation was found to follow first order kinetics in catalyst concentration (see section 3.1.2), Whiting and co-workers found that the boronic acid catalyst displayed zero order kinetics in catalyst as well as slower reaction rates when water was not azeotropically removed from the reaction mixture.[27] The authors concluded that the acylation step of the amine is fast compared to the rate of water removal, and that the overall rate for the amidation reaction is limited by the mass transfer rate of water. In addition, Wang *et al.* reported that the formation of the intermediate acylboronate species is thermodynamically unfavored and requires water removal in order to drive the equilibrium.[187]

Hall and co-workers studied the role of water closely using the 5-methoxy-2-iodophenyl boronic acid catalyst at 25 °C in dichloromethane.[139] The authors evaluated different dehydrating agents and identified 4 Å molecular sieves as the most efficient water scavenger. In addition, it was found that the amount of molecular sieves was important, which in their case meant ≥1 g of activated 4 Å molecular sieves per 0.5 mmol carboxylic acid. The role of the molecular sieves was further studied, and it was concluded that the molecular sieves are likely to have a dual role in the reaction. On the one hand, the sieves trap the formed water and thereby prevent the hydrolysis of the acyl-boronate intermediate (see section 3.1.2). On the other hand, the molecular sieves act as a water reservoir which can reversibly release enough water to prevent the dehydration of the boronic acids into boroxines, which were reported to be unreactive as catalysts.

3.3.2 Group (IV) metal-catalyzed systems (Paper IV and Appendix B)

Similar to what was described for boronic acid catalysts, Shteinberg *et al.* reported on the importance of efficient water removal in the titanium tetrabutoxide-catalyzed condensation of benzoic acid and aniline in refluxing *o*-xylene.[191] We were interested to see whether this was equally important for the zirconium- and hafnium-catalyzed systems, and decided to study the effect of molecular sieves on group (IV)-catalyzed direct amidation reaction. The THF used in the reactions was pre-dried and contained less than 20 ppm of water at the start of the reaction. As expected, it was found that the presence of molecular sieves was crucial for an efficient reaction for both the zirconium-catalyzed and hafnium-catalyzed system. Interestingly, it was also found that the amount of molecular sieves needed to be tuned to achieve the highest reaction rate for the zirconium-catalyzed protocol. As can be seen in Figure 23, the reaction proceeded slowly in the absence of molecular sieves. The rate increased dramatically upon the addition of activated molecular sieves, displaying the highest initial rate between 0.25 - 0.5 g of molecular sieves per mmol phenylacetic acid (Figure 23). A clear decrease in reaction rate was seen when ≥ 1 g of molecular sieves were used.

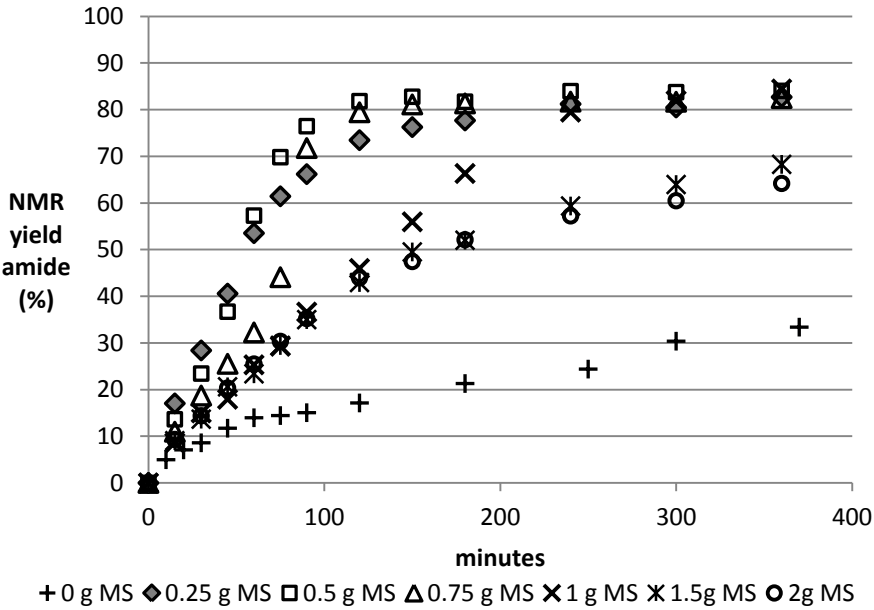


Figure 23. Reaction profiles for the zirconium-catalyzed direct amidation of phenylacetic **1a** and **2a** in the presence of different amounts of molecular sieves.

Reaction conditions: **1a** (0.4 M, 1 mmol), **2a** (0.48 M, 1 mmol), $ZrCl_4$ (0.02 M, 0.05 mmol), 4 Å MS (powder), THF (2.5 mL), 70 °C.

The effect on the reaction by the loading of molecular sieves, which was seen for the zirconium-catalyzed system, was also visible in the hafnium-catalyzed reaction (Figure 24). As can be seen, 1.5 g of activated molecular sieves per mmol phenylacetic acid **1a** gave rise to the highest amide yield at the end of the reaction, whereas both smaller and larger amounts resulted in lower product yield.

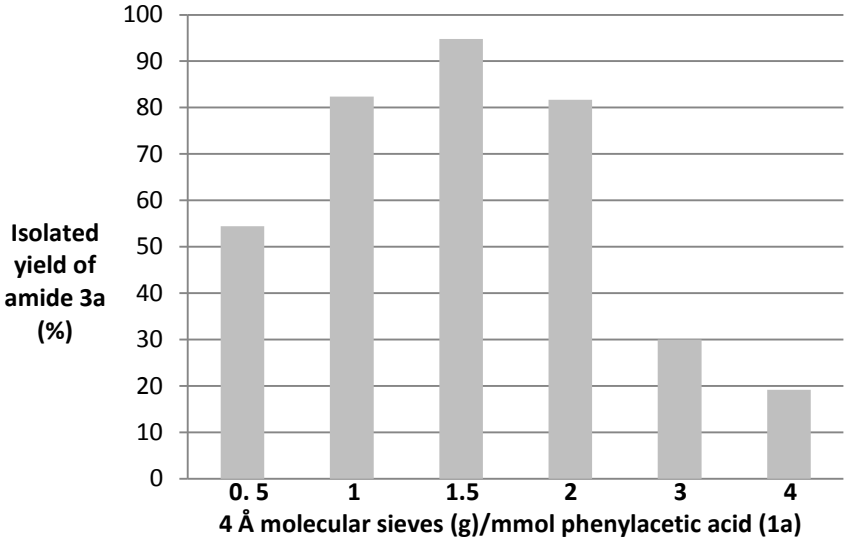


Figure 24. Reaction outcome of hafnium-catalyzed amidation between **1a** and **2a** using different amounts of molecular sieves.

Reaction conditions: **1a** (0.05 M, 0.5 mmol), **2a** (0.1 M, 1 mmol), $Hf(Cp)_2Cl_2$ (0.005 M, 0.05 mmol), 4 Å MS (powder), Et_2O (10 mL), 26 °C, 48 h.

The need for a balanced amount of desiccant in group (IV) metal-catalyzed direct amidation is interesting, and points towards multiple functions for the molecular sieves in the reaction, analogous to their role in the arylboronic acid catalysis at room temperature (see section 3.3.1). On the one hand, group (IV) metal complexes are known to be hydrolytically unstable,[192] and molecular sieves are likely required in the reaction vessel to prevent the water formed in the condensation to decompose the catalyst and/or reactive intermediates in the catalytic cycle. On the other hand, the presence of some water seems to be needed for an efficient reaction. The reason for this is unclear, but might be due to the need for partial hydrolysis of the metal complex to form the active catalyst in a similar fashion to what was proposed by Shteinberg and co-workers for a titanium-based amidation catalyst (see further discussion in section 3.4).[193,194] It is also possible that one or several water molecules are assisting in one or several steps in the catalytic cycle.

3.4 The structure of group (IV) metal complexes

Chloride complexes of group (IV) metals are generally hydrolytically unstable, and form metal-oxygen bonds upon contact with water.[195] These metal oxides are prone to aggregate, and several different aggregates can form as a result of partial or full hydrolysis of group (IV) metal chloride complexes.[195] It is known that group (IV) metals can form stable complexes with ethers such as THF,[196] and the THF complexes of titanium (IV), zirconium (IV) and hafnium (IV) chloride are commercially available. The metals can also react with amines and form amido complexes, some of which are also commercially available. In addition, it is known that group (IV) metals can form complexes with carboxylic acids. For example, the structure of hafnocene dichloride in the presence of long-chain carboxylic acids and triethylamine in anhydrous THF has been studied by Pandey *et al*.[197] The authors found that the fatty acid can displace either one chloride or one chloride and one cyclopentadienyl ring to form complexes of the type $Cp_2Hf(CO_2R)Cl$ or $CpHf(CO_2R)_2Cl$, where the former is monomeric and the latter exhibits a higher molecular complexity. The ratio of hafnocene dichloride to fatty acid was found to be the determining factor for which of the two complexes were formed, and the carboxylic acid binds as a bidentate anionic carboxylate ligand to the metal center (Figure 25).

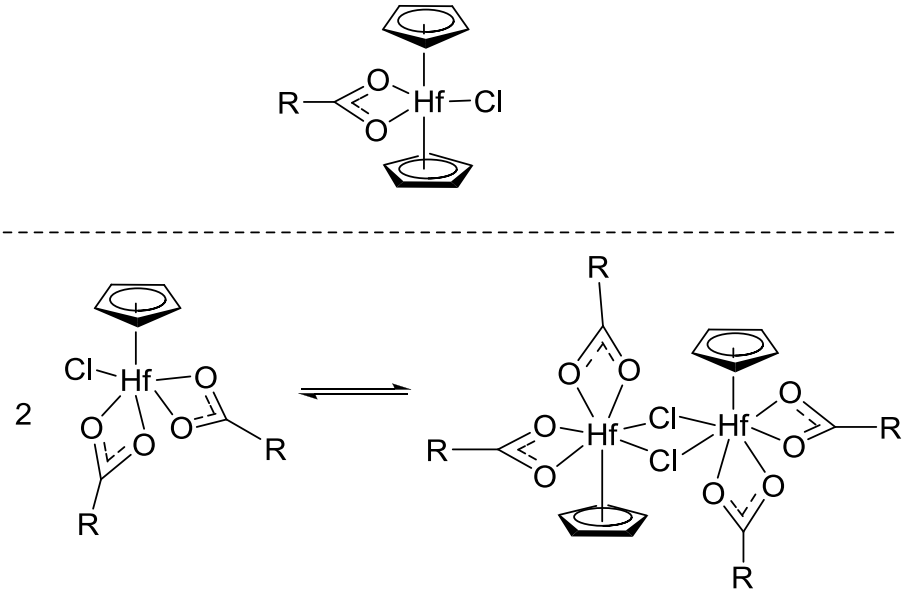


Figure 25. Hafnium carboxylate complexes studied by Pandey *et al*.[197]

In addition, Alcock *et al*. have shown that titanium tetrachloride reacts with carboxylic acids to form complexes of the type $TiCl_3(O_2CR)$.[198] These complexes can react further and undergo partial hydrolysis to form dimers with a bridging oxygen atom between the metal centers and two coordinated THF molecules *trans* to the oxygen bridge. Instead of THF molecules, the dimer

can also accommodate neutral carboxylic acids in the same positions (Figure 26).[199,200]

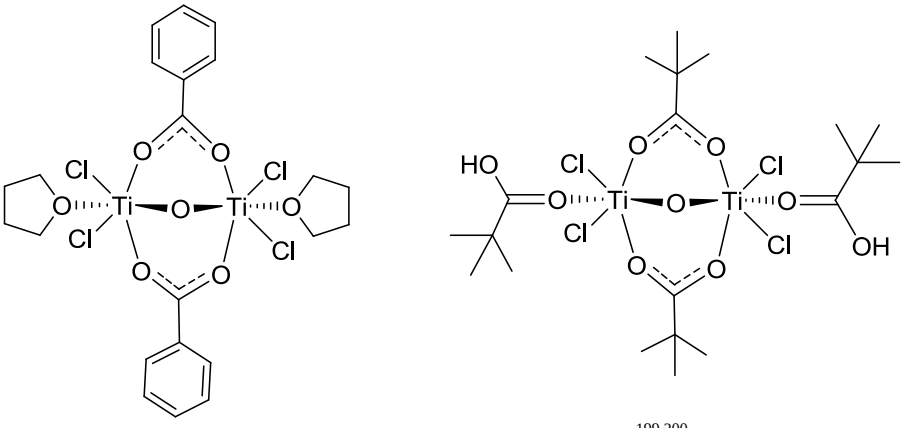


Figure 26. Dimeric titanium complexes isolated by Alcock *et al*.[199,200]

Oxygen-bridged dimeric structures (μ-oxo compounds) are also reported for zirconocene and hafnocene chloride complexes, as well as structures where one or both of these chlorides are replaced by other ligands.[201] Interestingly, a general property of the μ-oxo compounds of the type $[Cp_2MCl]_2O$ is their reactivity towards protic reagents HX to reform monomers of the type Cp_2MClX.[201] For example, the monoacylate complex $Cp_2Zr(CO_2R)Cl$ forms upon treatment of the corresponding μ-oxo compound $[Cp_2ZrCl]_2O$ with a carboxylic acid at 20 °C.[201,202]

Shteinberg and co-workers investigated the catalytic activity of titanium tetrabutoxide in direct amidation between benzoic acid and aniline as a function of water content.[191,193,194,203] In the first study, the authors found that the yield of benzanilide in refluxing *o*-xylene after 1 hour reached a maximum when the titanium catalyst had been exposed to air for 4 hours prior to the reaction.[193] Prolonged exposure of the catalyst resulted in an insoluble precipitate, which displayed no catalytic activity. Further studies, using an desiccator equipped with a hygrometer, allowed for quantification of absorbed water into the catalyst, and it was concluded that the highest catalytic activity was achieved with a water content of 1.35 mol/mol catalyst.[194] In addition, the authors performed ^{1}H-NMR experiments and proposed that the most active catalyst is a linear polymeric titanium-oxo species, which enable multicentered coordination of the substrates (Figure 27).

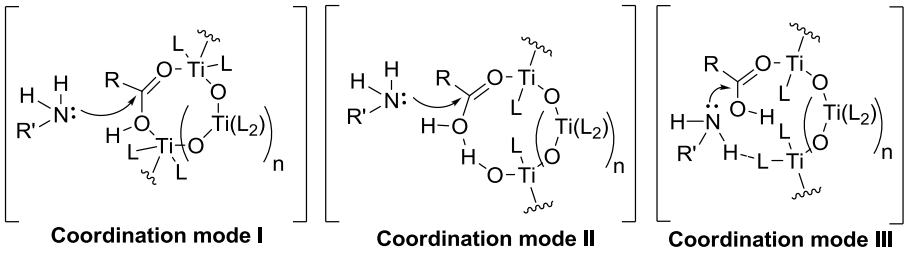


Figure 27. Multicentered coordination modes to a linear polymeric titanium catalyst, suggested by Shteinberg and co-workers.[194]

In addition, the authors reported that the kinetic behavior of the titanium-catalyzed system is more sensitive to water in the very early stages of the reaction.[191] It was observed that the slow rate of a reaction without water removal takes off rapidly when azeotropic distillation is started, indicating that the titanium catalyst is not decomposing in the presence of water (~3 equivalents to catalyst), even though the amidation itself needs efficient water removal to proceed. This somewhat surprising stability of the generally hydrolytically unstable titanium (IV) catalyst was proposed to be due to a stabilizing effect of carboxylate ligands, which would make water coordination to the catalyst reversible. The authors also showed that the presence of benzoic acid indeed increased the hydrolytic stability of the catalyst, which was measured as the formation of an insoluble titanium oxide precipitate as a function of water added to the catalyst in *o*-xylene.[203] Interestingly, benzanilide imposed even more stability towards irreversible hydrolysis of the catalyst. The authors concluded that it is likely that several different titanium complexes can form under the reaction conditions and proposed several possibles structures, some of which are illustrated in Figure 28. The authors also state the possibility that several of the potentially formed complexes display catalytic abilities to some extent.

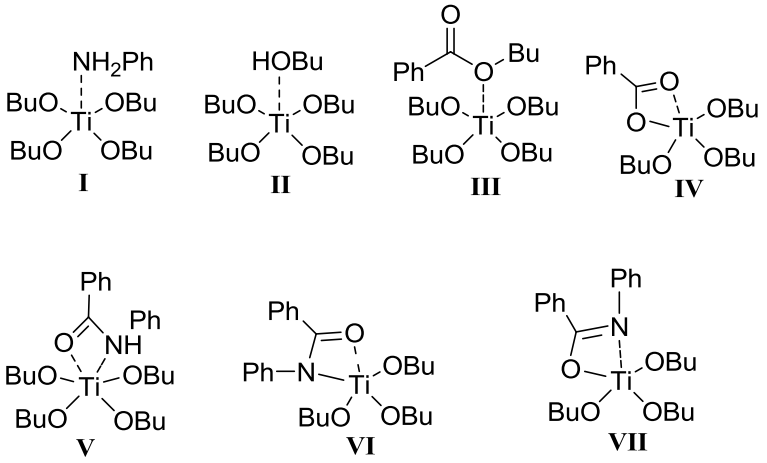


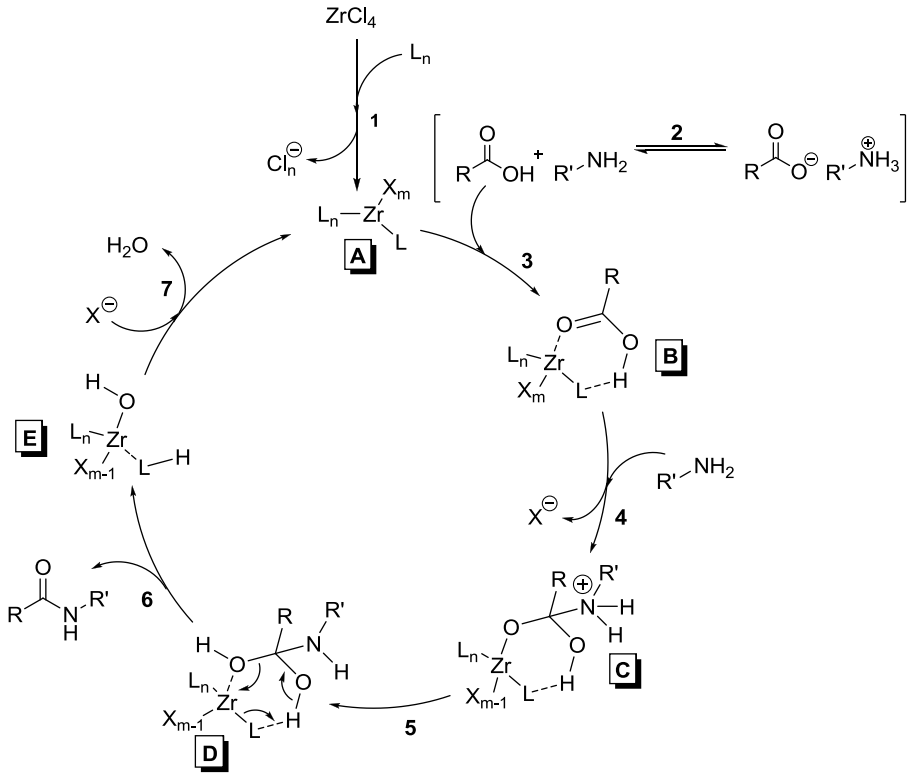
Figure 28. Coordination complexes of titanium (IV) butoxide in the direct amidation of benzoic acid and aniline, as suggested by Shteinberg *et al.*[203]

The many coordination possibilities of the reaction components, solvent included, to the catalyst in the amidation reaction catalyzed by group (IV) metals make the structural prediction of the active catalytic species complicated. As pointed out by Shteinberg *et al.*, it is also possible that several different complexes might be catalytically active. It is however very likely that water is actively involved in the mechanism in some way, since the need for a balanced amount of molecular sieves is necessary for optimal reaction outcome (see section 3.3). The documented behavior of different group (IV) metal complexes to partially hydrolyze and form oligomers with bridging oxygens, which can coordinate carboxylic acids and amides, is likely giving rise to catalytically important species. In addition, it cannot be ruled out that the corresponding metal oxides of titanium, zirconium and hafnium are the true catalysts in the amidation reaction. For example, Arkhipova *et al.* proposed that titanium dioxide formed *in situ* from $Ti(OiPr)_4$, along with the intermediate species, are the real catalysts for intra- and intermolecular direct amidation in ionic liquids.[178] It should however be noted that the authors did not use any water scavenging technique for their amidation reactions. Investigations by Arena *et al.* showed that their most active titanium oxide catalyst for direct amidation displayed 0^{th} order rate dependence on the substrates, indicating that the adsorption and desorption of the substrates/product is the turnover-limiting step for the acylation of aniline at 110 °C.[177] This rate behavior is clearly not seen in the case of the $ZrCl_4$-catalyzed protocol (see section 3.1.2 and 3.1.3), suggesting that zirconium dioxide is not the true catalyst for this reaction, assuming that the adsorption/desorption rates are similar for TiO_2 and ZrO_2 at elevated temperatures. In addition, Arena *et al.* reported that ZrO_2 was not a particularly active catalyst in the acylation of aniline with propanoic acid (9% amide yield after 24 h at 110

°C, compared to 47% for the most active TiO_2 catalyst).[177] At this point, however, the structure(s) of the active catalyst(s) are unclear, and more experimental work in combination with on-going DFT-calculations on the $ZrCl_4$-catalyzed will hopefully shed more light upon the matter in due time.

3.5 Proposed schematic mechanism

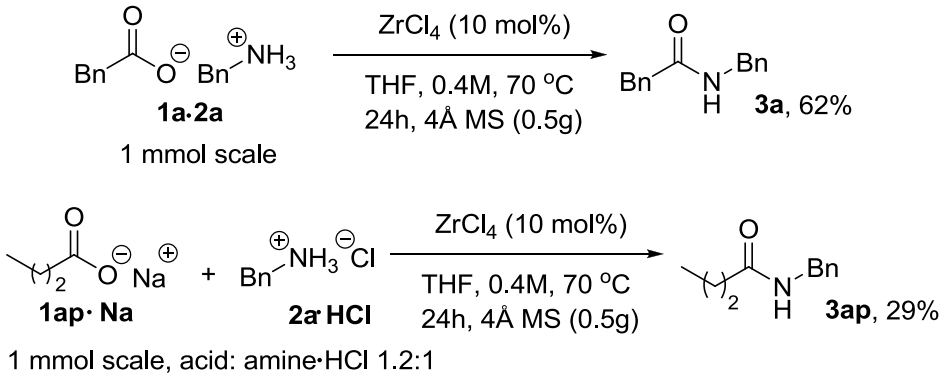
Despite the complicated situation regarding the structure of the active catalyst(s), a schematic catalytic cycle can be formulated that fits the preliminary qualitative kinetic results obtained from the zirconium-catalyzed amidation (Scheme 17). The structures A-E represent a mechanistic suggestion and are not confirmed experimentally. Since the thermal background reaction for this process was shown to be very slow (13% after 24 hours), that process is not taken into account here.



1. ligand coordination/exchange
2. salt equilibrium
3. substrate coordination
4. nucleophilic attack
5. proton transfer
6. product dissociation
7. dehydration and catalyst regeneration

Scheme 17. Schematic mechanistic proposal for the zirconium-catalyzed direct amidation.

The amidation reaction is competing with the formation of ammonium carboxylate salt (step 2 in Scheme 17). The salt is in equilibrium with the free acid and amine in organic solvents as shown by Whiting and co-workers,[185] and amide product can be formed in high yield even if the reaction is started with the ammonium carboxylate as substrate (Scheme 18). The equilibrium between free carboxylic acid and amine and the ammonium carboxylate is highly substrate dependent for thermal amidations,[185] and is likely the explanation for the concentration dependence on the reaction outcome that was observed in the hafnium-catalyzed system (Table 7, section 2.1.3).



Scheme 18. Amide product can be formed from the corresponding ions of carboxylic acid and benzylamine under $ZrCl_4$-catalysis.

Amidation is however not taking place if both the amine and the carboxylic acid are fully protonated (Scheme 16, section 3.1.3) and the negative rate behavior in carboxylic acid (see section 3.1.3) is likely an effect of the effective decrease in amine concentration by pushing the salt equilibrium towards ammonium carboxylate, in accordance with Le Chatelier's principle. In addition, the negative rate behavior in carboxylic acid suggests that the formation of an intermediate structure by coordination of the acid to the catalyst is a fast process and not turnover-limiting.

Electron-withdrawing substituents on the carboxylic acid were found to be beneficial for the reaction rate (Figures 19 and 20, section 3.2.1.2 and 3.2.1.3). This observation is compatible with assigning the nucleophilic attack on the carbonyl carbon by the amine to be the turnover-limiting step (step **4** in Scheme 17). It is also possible to envision that electron-withdrawing substituents destabilize the electron-poor carbon of the tetrahedral intermediate **D** (step **6** in Scheme 17), which could favor its collapse into the amide product. The positive rate dependence on both zirconium and amine indicates that these two species are involved in the turnover-limiting step of the reaction (see section 3.1.1 and 3.1.2). The reaction profile plots visually indicates that the rate order in these two species is likely >1, which might suggest that the turnover-limiting step involves more than one of these species, even though more experimental work and analysis is needed to con-

firm this. If the rate order of these two components are confirmed to be >1, this might suggest that the ligand-assisted hydrogen bonding in structures **B-D** in Scheme 17 is rather an intermolecular assistance by additional amine and/or zirconium species. The postulated proton transfers in steps 5 and 7, as well as the dehydration in step 7, are also instances where internal or external species with hydrogen bonding capacity might play an important role. More experimental work and DFT-calculations will hopefully shed light upon the mechanistic features of group (IV) metal-catalyzed direct amidations.

4. Conclusions and outlook

In this thesis, catalytic protocols for the direct formation of amides from carboxylic acids and amines with the aid of titanium, zirconium and hafnium complexes are reported (Paper I-IV). These protocols are milder than previously reported metal-catalyzed systems, and allow for amidation of various amines and carboxylic acids in good yields. The ease with which these protocols can be scaled up to gram scale reactions is attractive, as well as the conservation of enantiomeric purity in amino acids (Paper I-IV). In addition, the hafnium-catalyzed system (Paper IV) is the first example of a metal-catalyzed amidation at room temperature. The high chemoselectivity towards the carboxylic acid in the presence of esters is a particularly attractive feature of this protocol, as well as the possibility of selectively acylating aliphatic amines over aromatic. The use of carbamates as the source of gaseous ammonia and dimethylamine in direct amidation is another substantial contribution to the field (Paper V), since very few catalytic procedures are known for the formation of primary amides. In addition, preliminary kinetic results suggest that group (IV) metal-catalyzed amidations proceed *via* a different mechanism than boronic acid-catalyzed amidation.

Despite the development in the field, challenges remain for group (IV) metal-catalyzed amidation. The need for continuous water removal, and molecular sieves in particular, is a drawback and the development of a water tolerant catalytic protocol would be highly useful. Furthermore, the herein reported catalysts are incompatible with substrates containing free hydroxyl-groups, which limit the substrate scope of the amidation reaction. In addition, the catalysts are incompatible with aliphatic diamines, which make their application in condensation polymerization to form polyamides impossible. The development of catalysts that are less sensitive towards coordination of the substrates would therefore be valuable from a synthetic point of view. It would also be valuable with the development of catalytic protocols for the formation of primary amides under milder reaction conditions, to allow for the use of thermally unstable substrates and substrates with labile stereocenters. Moreover, all attempts to form dipeptides using the presented protocols have failed. This is unfortunate, since catalytic formation of peptides from amino acids is one of the ultimate goals for method development in the field of direct amidation. Future work in this field should focus on addressing this challenge, preferably without the use of molecular sieves in order to enable easy access to peptides *via* solid-phase synthesis.

In contrast to most other areas that utilize metal-based catalysts, direct amidation protocols are mediated by metal salts with simple counter ions such as halides, alkoxides or acetates. One might therefore expect a future development of metal-based catalysts with more complex ligands to fine-tune the reactivity of the metal center. In-depth studies on the mechanism will provide insight into the action of the catalyst and aid in the design of such ligands, which might provide the means to solve (at least some of) the remaining challenges within the field of direct amidation.

5. Appendix A

The following contributions to the papers included in the publication list were made by the author of this thesis:

Paper I

Formulated the research idea and found the initial conditions for the study, performed 50% of the synthetic work and the analyses, wrote 50% of the article and took part in writing the supporting information.

Paper II

Performed parts of the synthetic work, took part in writing the article.

Paper III

Took part in the design of the study, performed 50% of the synthetic work and the analyses, wrote 50% of the article and took part in writing the supporting information.

Paper IV

Designed the study, performed all synthetic work and analyses, wrote 90% of the article and wrote the supporting information.

Paper V

Took part in the design of the study, performed 50% of the synthetic work and the analyses, wrote 50% of the article and took part in writing the supporting information.

6. Appendix B

The rate behaviors of the zirconium-catalyzed amidation were studied by varying the concentrations of $ZrCl_4$, phenylacetic acid (**1a**) and benzylamine (**2a**) while keeping the loading of activated 4 Å powdered molecular sieves constant. Samples of approximately 50 μL were removed with a syringe at certain time intervals and the sample was injected into deuterated methanol and subjected to ^{1}H-NMR analysis (Bruker, 400 MHz). Conversions and NMR-yields were calculated as the relative intensity of the benzylic protons of the amino side of the amide compared to the aromatic protons, which take into account the aromatic signals for starting materials, products, ammonium salt and potential by-products. All reactions were carried out under nitrogen gas in oven-dried 20 mL vials from Biotage, equipped with a teflon-coated magnetic stirring bar and a crimp-on cap with septum. The powdered 4 Å molecular sieves (Sigma-Aldrich) were activated by flame-drying under vacuum for 10 minutes (5 g MS in a 100 ml round-bottomed flask), and were thereafter allowed to cool under vacuum and subjected to an atmosphere of nitrogen gas. BHT-stabilized THF (Sigma-Aldrich) was pre-dried and dispensed from a VAC-system and contained less than 20 ppm of water at the start of the reaction.

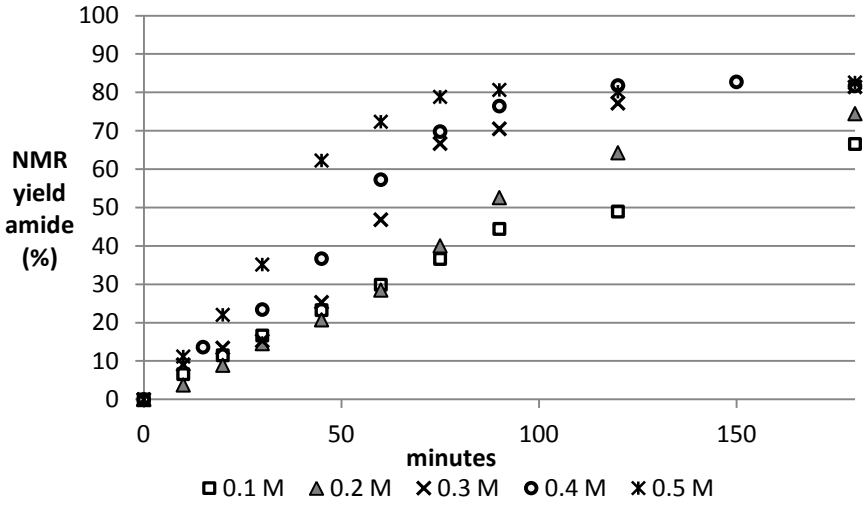


Figure B1. Reaction profiles for the $ZrCl_4$-catalyzed amidation of phenylacetic acid (**1a**) and benzylamine (**2a**) at different reaction mixture concentrations as a function of solvent volume.

Reaction conditions: phenylacetic acid (1 mmol), benzylamine (1.2 mmol), $ZrCl_4$ (0.05 mmol), 4 Å MS (0.5 g, powder), THF, 70 °C.

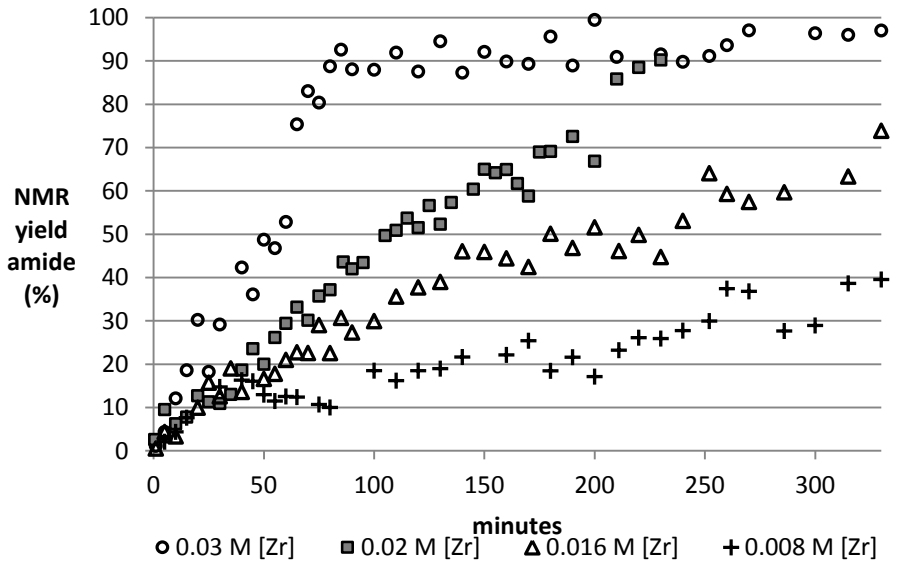


Figure B2. Reaction profiles for the formation of amide **3a** at different concentrations of $ZrCl_4$.

Reaction conditions: phenylacetic acid (0.4 M, 2 mmol), benzylamine (0.4 M, 2 mmol), $ZrCl_4$, 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

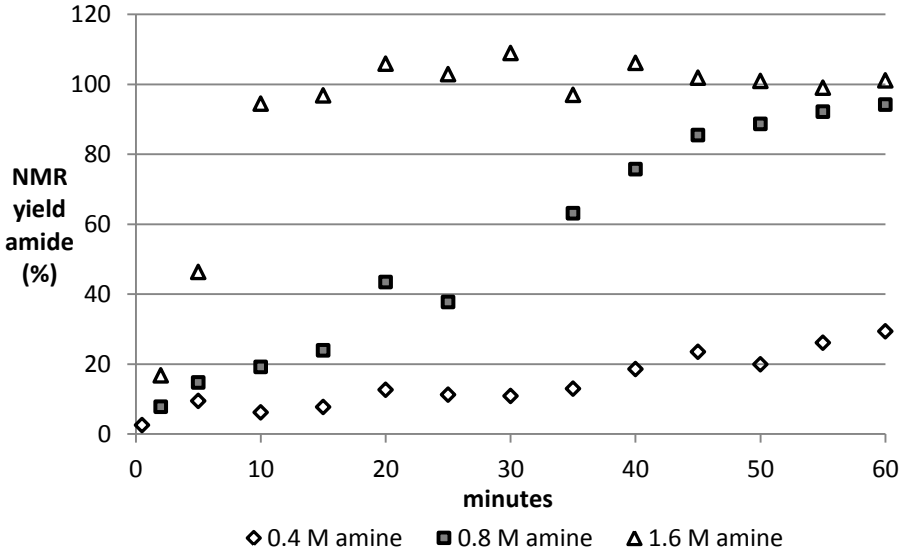


Figure B3. Reaction profiles for the formation of amide **3a** at different concentrations of benzylamine.

Reaction conditions: phenylacetic acid (0.4 M, 2 mmol), benzylamine, $ZrCl_4$ (0.02 M, 0.1 mmol), 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

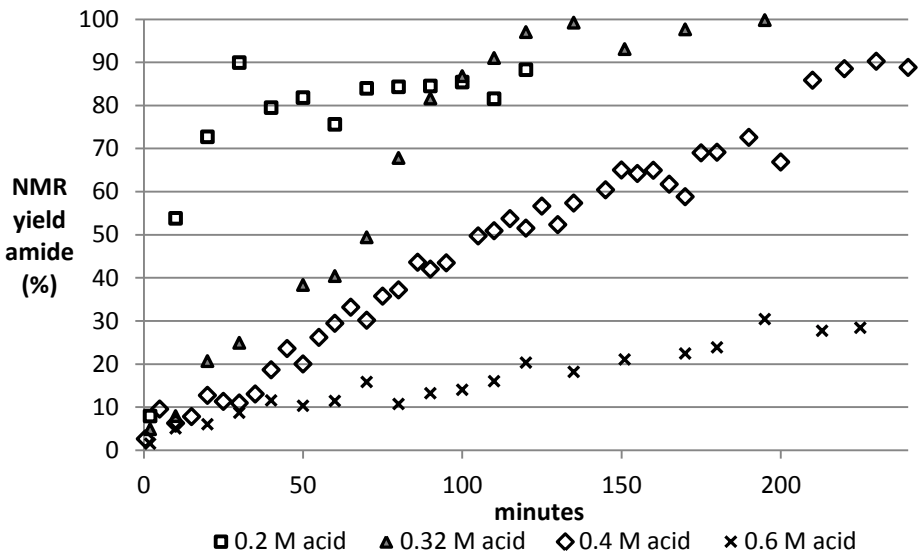


Figure B4. Reaction profiles for the formation of amide **3a** at different concentrations of carboxylic acid.

Reaction conditions: phenylacetic acid, benzylamine (0.4 M, 2 mmol), $ZrCl_4$ (0.02 M, 0.1 mmol), 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

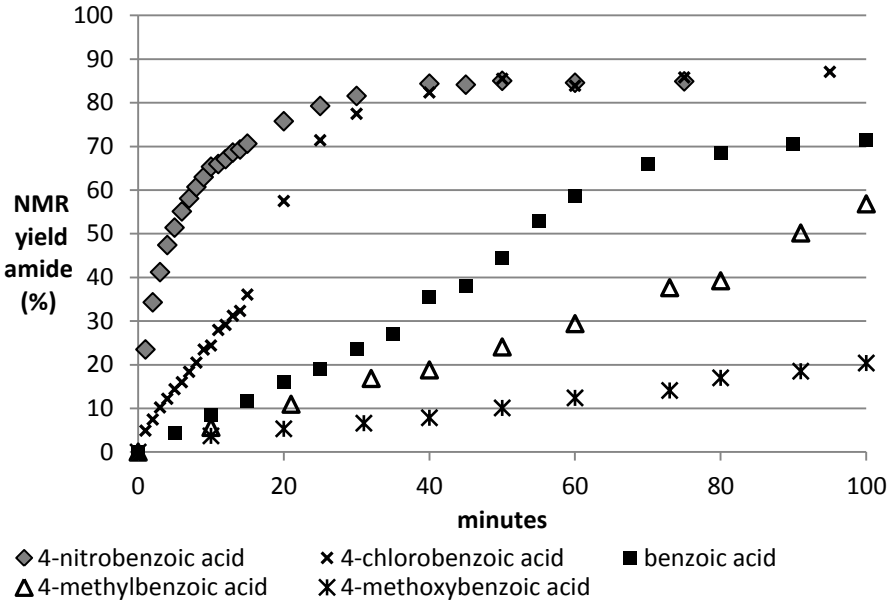


Figure B5. Reaction profiles for the $ZrCl_4$-catalyzed direct amidation of differently substituted benzoic acids with benzylamine.

Reaction conditions: carboxylic acid (0.4 M, 1 mmol), benzylamine (1.6 M, 4 mmol), $ZrCl_4$ (0.1 mmol), 4 Å MS (0.5 g, powder), THF (2.5 mL), 70 °C.

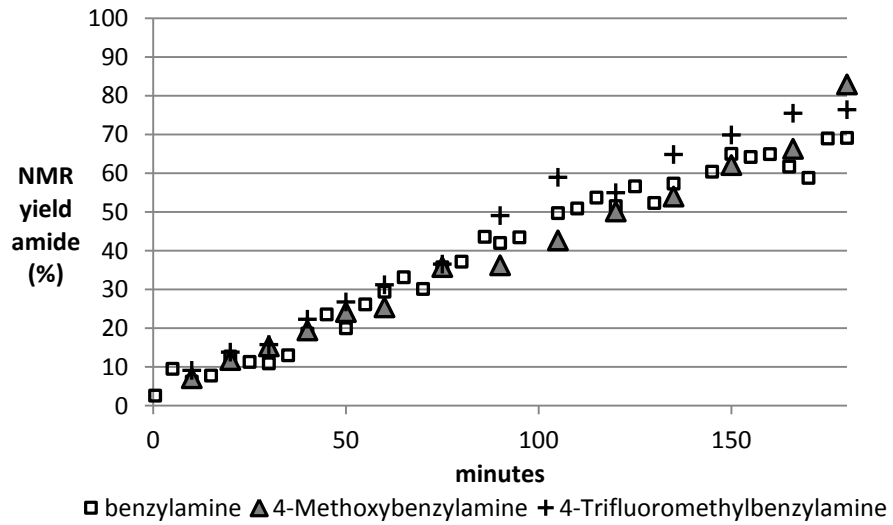


Figure B6. Reaction profiles for the zirconium-catalyzed amidation of phenylacetic acid and differently substituted benzylamines.

Reaction conditions: phenylacetic acid (0.4 M), benzylamine (0.4 M), $ZrCl_4$ (0.1 mmol), 4 Å MS (powder), THF, 70 °C.

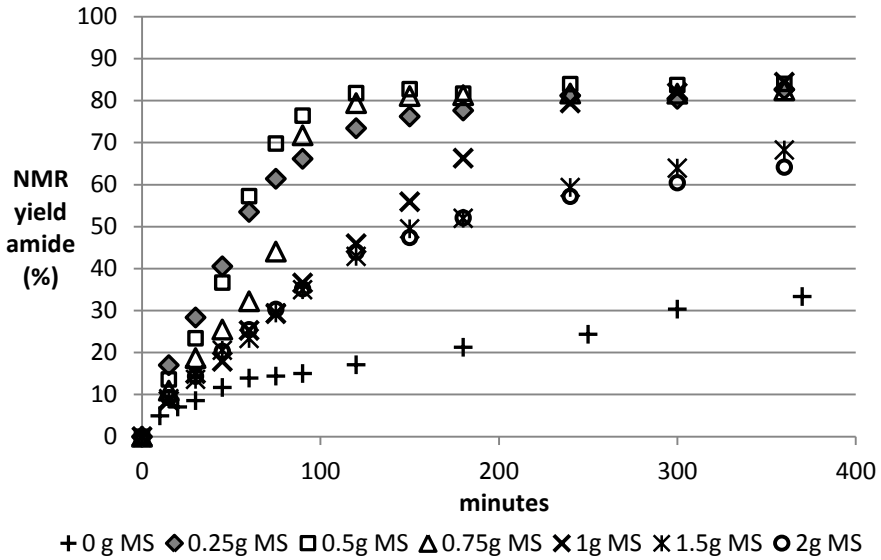


Figure B7. Reaction profiles for the zirconium-catalyzed direct amidation of phenylacetic acid and benzylamine in the presence of different amounts of molecular sieves.

Reaction conditions: phenylacetic acid (0.4 M, 1 mmol), benzylamine (0.48 M), $ZrCl_4$ (0.02 M), 4 Å MS (powder), THF (2.5 mL), 70 °C.

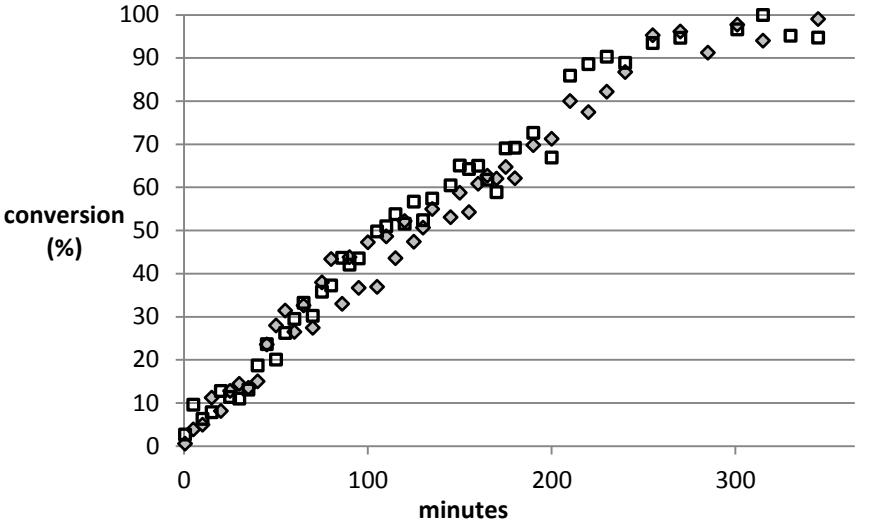


Figure B8. Reaction profiles for two identical zirconium-catalyzed direct amidation of phenylacetic acid and benzylamine.

Reaction conditions: phenylacetic acid (0.4 M, 2 mmol), benzylamine (0.4 M), $ZrCl_4$ (0.04 M), 4 Å MS (1 g, powder), THF (5 mL), 70 °C.

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