Direct Amide Coupling of Non-activated Carboxylic Acids and Amines Catalysed by Zirconium(IV) Chloride

Helena Lundberg, Fredrik Tinnis, and Hans Adolfsson^{*[a]}

The amide bond is one of the most important functionalities found in nature. It constitutes the backbone of the biologically crucial peptides and is found in many natural products and the majority of pharmaceutically interesting compounds.^[1] It has been estimated that up to 25% of all synthetic pharmaceuticals contain at least one amide bond^[2] and a general protocol for the direct amidation of carboxylic acids is highly attractive for industry because it would lead to more cost-effective and greener processes with extraordinarily high atom economy.^[3] The quest for this type of general protocol remains one of the most important challenges in organic chemistry today.

The thermodynamically stable amide bond is, in principle, formed when a carboxylic acid reacts with an amine with the release of water. The energy threshold of the ammonium carboxylate salt formation must, however, be overcome, and a number of synthetic methods for amidation have been developed over the years. Direct amidation of carboxylic acids and amines occurs spontaneously at high temperatures $({>}160\,^{\circ}\mathrm{C}).^{[4{-}8]}$ However, this is not a feasible strategy for many substrates because sensitive functional groups do not survive under such harsh conditions. Milder methods have therefore been developed, most of which employ stoichiometric amounts of coupling reagents, such as carbodiimides, chloroformate and pyridinium compounds, or uronium, immonium, imidazolium and phosphonium salts.^[9,10] There has also been an example of an umpolung strategy in which the amine was made electrophilic with the use of N-iodo succinimide.[11]

Despite the efficiency of these protocols, they often suffer from complicated product isolations and poor atom economy, and the stoichiometric use of reagents generates high costs and a low product to waste ratio.^[3] To overcome some of these problems, different catalytic methods have also been developed. In the toolbox of the organic chemist, there are now a number of metal-catalysed protocols^[12] for amide bond formation, utilising starting materials such as nitriles, oximes, aldehydes and alcohols, as well as aminocarbonyla-

 [a] H. Lundberg, F. Tinnis, Prof. H. Adolfsson Department of Organic Chemistry, Stockholm University The Arrhenius Laboratory, SE-106 91, Stockholm (Sweden) Fax: (+46) 8-154908
E-mail: hansa@organ.su.se tion methods. Metal-catalysed aminolysis of esters has also been reported.^[13]

However, the ideal situation is to directly couple carboxylic acids with amines producing water as the only by-product. Since this process leads to an initial salt formation, during which the generation of the carbon-nitrogen bond in the amide and subsequent release of water has a high energy barrier, the use of a catalytic setup would be most desirable. Up to now, only a few catalytic systems for the direct amide coupling of carboxylic acids and amines have been developed. Organocatalytic methods employing enzymes^[14-16] have been used to some extent, although they have a limited substrate scope. Other protocols that use arylboronic acids and esters^[17-26] as catalysts have been reported, although, to the best of our knowledge, without examples in which the enantiopurity of chiral starting materials is fully conserved. In some cases the ee even drops significantly, as in the report by Yamamoto et al. in which the amidation of enantiopure N-tert-butoxycarbonyl (N-Boc) valine resulted in a product with only 81 % ee.[24]

In addition to arylboronic acids, other non-metallic and metallic Lewis acids, including heterogeneous Lewis acidic materials, have been employed as mediators or catalysts for the amidation reaction.^[27-38] Moreover, early transitionmetal complexes, like titanium(IV) species, have been found to act as mediators. In 1970, Wilson and Weingarten^[39] reported that stoichiometric amounts of TiCl₄ in THF mediated the formation of carboxamides in modest to good yields over several days of reaction time. Shteinberg and co-workers have reported that a catalytic amount of Ti(OBu)₄ (20 mol%) could be used in the acylation of anilines with benzoic acids in toluene, ortho-xylene and decane at reflux.^[40,41] In 1988, Nordahl and Carlson^[42] used a catalytic amount of TiCl₄ (30 mol%) for the amidation of benzoic acid with different amines in toluene at reflux. In the same year, Mader and Helquist^[43] reported Ti(OiPr)₄-mediated lactamisations of amino acids in 1,2-dichloroethane at reflux. Good yields of lactams were achieved with 50 mol % of $Ti(OiPr)_4$, although lower yields were obtained with truly catalytic amounts of the titanium source. Furthermore, they reported that only ammonium carboxylate salts were formed with Ti(OiPr)4 as the catalyst for intermolecular amide couplings in a variety of solvents.^[44]

Due to the importance of the amide bond in a vast array of applications, and the clear lack of a general catalytic protocol for the formation of this functional group, we were in-

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trigued by the challenge and started to investigate the possibility of generating a direct catalytic amidation method starting from carboxylic acids. The aim of the study was to develop a method that, in contrast to the aforementioned reports, was applicable for a wide range of substrates and could be performed with low catalyst loadings at the lowest possible temperature. The temperature was an issue for us mainly due to mildness of the reaction conditions, but also to make sure that the system would be truly catalytic. Since quantitative conversions can be obtained at 160 °C with simple substrates,^[4-8] a considerable amount of the amide formed in catalytic reactions run in toluene or *ortho*-xylene heated at reflux can be assumed to be the result of a background reaction.

To our delight we found that all examined zirconium complexes were efficient as catalysts for the amidation reaction (Scheme 1), and isolated yields of up to >99% of the



Scheme 1. Zirconium-catalysed amide formation.

formed amide **3a** were obtained with a 10 mol% catalyst loading. Since zirconium tetrachloride (Table 1, entry 3) was found to be the most efficient, as well as the most attractively priced (\$300 for 1 kg of $ZrCl_4$ as compared to \$7680 for the same amount of $Zr(OtBu)_4$ or $Zr(OEt)_4$ from Strem Chemicals Inc., November 2011), we decided to continue our investigation by using this compound as the catalyst of choice. We found that the catalyst loading could be reduced

Table 1. The zirconium(IV)-catalysed direct amidation of phenyl acetic acid with benzylamine.

Entry	Catalyst	Solvent	Catalyst Loading [mol%]	Isolated yield [%]
1 ^[a]	$Zr(OtBu)_4$	THF	10	93
2 ^[a]	$Zr(OEt)_4$	THF	10	93
3 ^[a]	$ZrCl_4$	THF	10	>99
4 ^[a,b]	$ZrCl_4$	THF	2	>99
5 ^[a]	_	THF	-	10
6 ^[b]	-	THF	-	13
7 ^[b,c]	$ZrCl_4$	1,4-dioxane	2	98 (8)
8 ^[b,c]	$ZrCl_4$	CH_2Cl_2	2	92 (11)
9 ^[b,c]	$ZrCl_4$	CH ₃ CN	2	86 (10)
10 ^[b,c]	$ZrCl_4$	toluene	2	94 (5)

[a] Reaction conditions: phenylacetic acid (1.2 mmol), benzyl amine (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 a N₂ atmosphere. Reaction time: 24 h. [b] Reaction conditions: phenylacetic acid (1 mmol), benzyl amine (1.2 mmol), and otherwise identical conditions to those given above. [c] The values presented within parentheses refer to the yield (as determined by using NMR spectroscopy) obtained in the background reaction performed with molecular sieves (0.5 g) but without the zirconium catalyst.

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to as little as 2 mol% while maintaining the activity for the model substrate (Table 1 entry 4). Furthermore, we found that the reaction was rather insensitive to the stoichiometry of these particular reactants because equally good results were obtained by using either a slight excess of the acid or of the amine. For the formation of most other amides and for reactions in other solvents, the use of an excess of the amine component was highly beneficial (see below).

To verify that the amidation reactions are indeed catalysed by the Lewis acids, experiments were performed with only molecular sieves present (Table 1, entries 5 and 6). These reactions resulted in 10–13 % yields of the amide depending on the stoichiometry between the amine and acid components. The poor outcome of the uncatalyzed reactions clearly shows that the high yields in Table 1, entries 1–4 are truly the result of zirconium catalysis. In addition, performing the zirconium-catalysed amidation without any water scavengers present resulted in notably reduced yields.

Further optimisation of the reaction conditions was performed by taking different solvents into consideration. The results show that ethereal solvents are the most effective, although the amidation also works well in other common organic solvents (Table 1, entry 4 and 7–10). In contrast to the use of THF, for which the reagent stoichiometry was less sensitive, better yields were obtained if an excess of the amine was used. Furthermore, it should be stressed that the successful results with these types of substrates were obtained at markedly lower reaction temperatures than previously reported by using other Lewis acidic metal catalysts.

The simplicity of this catalytic amidation protocol, for which the amine is simply added to an inert mixture of carboxylic acid, catalyst and molecular sieves in dry THF at 70 °C, is further emphasised by the exceptionally straightforward workup needed for the isolation of the products. Analytically pure samples of amide **3a** were obtained by simple filtration of the reaction mixture through a pad of silica by using EtOAc/Et₃N (200:1) as the eluent. Moreover, extractive workup of the reaction mixture is equally efficient. Amide **3a** was prepared as stated above, but, instead of filtration through silica, the reaction mixture was filtered through Celite to remove the molecular sieves. The filtrate was diluted with dichloromethane, extracted with aqueous HCl (1 M) and, after drying and evaporation of the solvent, the analytically pure product was obtained in 96 % yield.

As demonstrated by the results presented in Table 1, several solvents were compatible with the zirconium catalyst for the amidation reaction. This feature is extremely valuable, and opens up the reaction to the use of different solvents for individual substrates, matching their solubility properties. In this study, we decided to continue with the fairly non-toxic and low boiling THF as the solvent of choice, and a number of different carboxylic acids and amines were screened, employing the amidation protocol presented above.

As shown in Table 2, individual amides were isolated in good to excellent yields. The reaction conditions tolerate a significant number of structurally different acid substrates,

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Table 2. Scope of the zirconium chloride-catalysed direct amidation of carboxylic acids.[a] ZrCl₄ (2–10 mol%) R² N. R³ 4Å MS 3 R³ 2 THF, 70 °C, 0.4 M, 24 h 0 II Ph **3c**, 99%^[b] 3a, 99%^[b,e] **3b**, >99%^[b] MeO O_2N **3d**. 85%^[c,f] **3e**, 76%^[c,f] 3f. 88%^[c,f] **3g**, 95%^[d] 3h, >99%^[d] **3i**, 99%^[d] ŃН Boc Cbz **3j**, >99%^[b,e] **3k**, >99%^[b,e] 3I, 63%^[C] Boc 3m, 62%^[c] **3n**, 73%^[c] 30, 65%^[c] **3q**, 93%^[d] **3r**, 93%^[b] **3p**, 95%^[b,e] (CH₂)₁₀CH₃ (CH₂)₁₀CH₃ 3t, 89%^[d] **3s**, 94%^[d] Ċ **3u**, 83%^[c,g] **3v**, 70%^[c,g] 3w, 82%^[c,g]

[a] Reaction conditions: carboxylic acid (1 mmol), amine (1.2 mmol), ZrCl₄ (2–10 mol%), and activated 4 Å molecular sieves (0.5 g), in dry THF (amine concentration: 0.4 M) at 70 °C in a sealed tube under a N₂ atmosphere. Reaction time: 24 h. All compounds (**3a–3w**) were isolated as analytically pure samples after simple filtration of the reaction mixture through a plug of silica by using EtOAc/Et₃N (200:1) as the eluent. [b] 2 mol% ZrCl₄ [c] 10 mol% ZrCl₄ [d] 5 mol% ZrCl₄ [e] Carboxylic acid (1.2 mmol), amine (1 mmol). [f] Reaction temperature: 100 °C. [g] Carboxylic acid (1 mmol), amine (1.5 mmol). Reaction temperature: 100 °C.

including heteroaromatic, aliphatic, α -halogenated and α -substituted carboxylic acids, as well as N-protected amino acids.^[45]

To verify that the products are formed through zirconium catalysis, we performed amidations of all of the substrates presented in Table 2 without adding the zirconium catalyst. In the majority of cases examined, the uncatalyzed reaction resulted in <10% yield of the amides and in none of the examples given in Table 2 was the yield higher than 18% (see the Supporting Information).

Ethers and thioethers (3b and 3c) are unaffected by the amidation reaction, and common acid sensitive organic protecting groups, such as acetals (3r and 3w) and carbamates (3k-n), remain untouched after the reaction. Chiral enantiomerically pure N-protected amino acids are converted into their corresponding amides without racemisation,^[45] emphasising the mildness of this procedure. The amide formation by using enantiopure 1-phenylethylamine also occurs with complete retention of configuration.^[46] The zirconium-catalysed amidation reaction is somewhat sensitive towards sterically hindered substrates, and does not work as well with aromatic acids,^[47] such as benzoic acid and its derivatives. To increase the yield of these more difficult substrates (3d-f) the amount of catalyst was adjusted to 10 mol% and the reaction temperature was set at 100 °C. Despite the increase in the reaction temperature, the yields of the uncatalyzed background reactions are, in these cases, not higher than those observed for the other substrates at 70°C.

The reaction conditions tolerate the use of a variety of amine reactants for which the use of benzylic or aliphatic primary amines gives secondary amides in good to excellent yields. Tertiary amides $3\mathbf{u}-\mathbf{w}$ were formed in good yields by using 10 mol% ZrCl₄ at 100 °C. In addition to the amides presented in Table 2, we performed a direct zirconium-catalysed amidation on the structurally more complex nonsteroidal anti-inflammatory drug indomethacin (Scheme 2). The reaction between indomethacin and benzyl amine smoothly produced the corresponding amide in 97% isolated yield.



Scheme 2. Preparation of N-benzyl indomethacin amide.

The mild and selective zirconium-catalysed amidation protocol proved easy to scale up, as demonstrated by a gram scale experiment in which 20 mmol of (phenylthio)acetic acid (1c) and 24 mmol of benzylamine (2a) were reacted in THF at a concentration of 1.6 M. The reaction resulted in 5.11 g (19.9 mmol, 99% yield) of analytically pure amide 3c



Scheme 3. Gram-scale preparation of amide 3c.

after filtration of the reaction mixture through a silica pad (Scheme 3). Moreover, the use of a reaction setup in which phenyl acetic acid (1a) and benzyl amine (2a) were heated at reflux in THF (70°C) in a dry round-bottomed flask equipped with a condenser, under otherwise identical conditions to those presented in Table 2, resulted in an 89% isolated yield of amide 3a. The latter example, which was performed on a 40 mmol scale, demonstrates that the catalytic amidation reaction can productively be performed by using conventional laboratory equipment. In comparison to other published gram-scale methods, this zirconium-catalysed amidation protocol has the advantage of being milder, less toxic, and more compatible with different common solvents. For instance, the boric acid catalysed system requires a higher reaction temperature, and results in racemisation of the chiral starting material when such compounds are employed.^[48] Furthermore, the toxicity of boric acid is significantly higher than that of ZrCl₄.^[49]

There are several possible mechanisms by which the zirconium-catalysed amidation reaction could proceed. Earlier studies on Lewis acid catalysed amidations^[31,41] suggest that the mechanism might proceed through a route similar to that of the catalytic amidation of esters, as proposed by, for example, Bonora et al.^[50] With this view in mind, the activation of the carboxylic acid can be envisioned as carbonyl coordination to zirconium in a classic Lewis acidic fashion (Scheme 4a). In light of the recent study by Whiting et al., the possibility of hydrogen-bonded dimeric carboxylic acid species cannot be ruled out.^[8] Another possibility is simultaneous activation of both the carbonyl and the leaving group, as depicted in Scheme 4b. In both cases, the acid becomes electropositive enough for subsequent attack by the amine.



Scheme 4. Possible zirconium-mediated activation modes of carboxylic acids in analogy with the proposed mechanism for the titanium-catalysed amidation reactions of esters (X = hydrogen-bond accepting ligand/ atom). a) Direct Lewis acid activation by carbonyl activation. b) Simultaneous Lewis acid activation of the carbonyl and leaving-group activation by intramolecular hydrogen bonding. c) Leaving-group activation by formation of zirconium carboxylates.

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The formation of zirconium carboxylates would lead to efficient leaving group activation (Scheme 4c). Early transition metals like zirconium have relatively labile ligands that can easily undergo ligand substitution in solution. The formation of metal-oxygen bonds is favoured for zirconium, but zirconium-amine complexes can also form. Wilson and Weingarten^[39] put forth the possibility that their titaniummediated amidation reaction proceeds through a ligand exchange of the original complex with carboxylic acids and amines. They argue that, if this is the case, more sterically demanding substrates would probably result in lower yields. That trend also exists for the zirconium-catalysed system described herein, but this tendency is well known for most catalytic systems and the argument is not conclusive. It is also possible that a mechanism in which two or more zirconium ions interact to form a catalytic complex is at work, in analogy to the amidation mechanism for titanium(IV) butoxide at 145°C suggested by Shteinberg et al.^[51] Future work will shed more light upon the mechanism of the ZrCl₄-catalysed amide coupling of carboxylic acids and amines, and mechanistic investigations are currently being pursued.

To conclude, despite the fact that the formation of amides is one of the most performed reactions in the production of fine chemicals and pharmaceuticals, very few efficient catalytic amidation processes of non-activated carboxylic acids have been reported up to now.^[52] Furthermore, none of the existing methods allow full conservation of the enantiomeric purity of the process going from a chiral starting materials to the products. Herein, we have presented a novel, mild, versatile, effective and environmentally benign protocol for direct amidation by using catalytic amounts of inexpensive zirconium(IV) chloride. This simple and high-yielding method tolerates a wide range of functionalities, including acid labile groups, and is suitable for the amidation of both simple and more complex starting materials, such as indomethacin. The method conserves the enantiomeric purity of the starting materials and is suitable for larger scale syntheses, which indicates its usability in research laboratories, as well as in industrial applications.

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