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Direct Catalytic Formation of Primary and Tertiary Amides from Non-Activated Carboxylic Acids, Employing Carbamates as Amine Source

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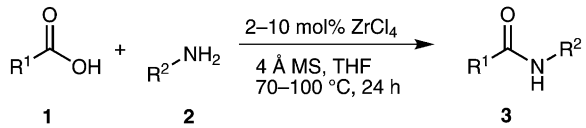
Abstract: The operationally simple titanium(IV)- or zirconium(IV)-catalyzed direct amidation of non-activated carboxylic acids with ammonium carbamates generates primary, and tertiary *N,N*-dimethyl-substituted amides in good to excellent yields.

Keywords: amides; carboxylic acids; catalysis; titanium; zirconium

Herein we present a novel, simple and efficient catalytic method for the direct formation of primary and *N,N*-dimethyl-substituted tertiary amides from non-activated carboxylic acids, using the non-gaseous precursors ammonium carbamate and dimethylammonium dimethylcarbamate, respectively. Carboxamides are common functional groups in a variety of natural and synthetic compounds. Since about 25% of all pharmaceuticals available on the global market contain at least one amide group,[1] the development of efficient and inexpensive methods for the formation of the amide bond has become an important issue. Direct amidation of carboxylic acids *via* heating of the corresponding ammonium salts is a procedure which only works for non-sensitive compounds.[2] Therefore a multitude of different coupling reagents utilizing milder reaction conditions have been developed for the formation of amides.[3] All those methods are based on the activation of the carboxylic acid using stoichiometric reagents, which leads to processes with an overall poor atom economy. In an analysis performed by three top pharmaceutical companies it was found that amide coupling reactions were involved in 84 out of the 126 of the drug candidates surveyed.[4] Carboxylic acid chloride derivatives, or coupling reagents were used in 80% of these cases and in 2007, the American Chemical Society Green Chemistry Institute ranked the formation of amides avoiding poor atom economy reagents as the most challenging task in organic chemistry.[5] Despite the difficulty of overcoming the salt formation when a carboxylic acid and an amine are brought together, a limited number of catalytic systems for the direct amidation has been reported, where the use of various boron-based catalysts has received most attention. In comparison with amide formation using thermal conditions (i.e., heating of ammonium salts), the use of catalysts based on boronic acids or borates allows for milder reaction conditions and, in general, most secondary and certain tertiary amides can be prepared in good to excellent yields with these methods.[6] There are also reports on enzymatic protocols with a small substrate scope,[7] and a few reported protocols on metal catalysis performed at high reaction temperatures,[8,9] where the thermal background reaction can be expected to be significant. Recently we demonstrated that zirconium(IV) chloride is a highly efficient catalyst for the direct amidation of non-activated carboxylic acids with primary and secondary amines, respectively.[10] The operationally simple amidation reactions were performed at 70 °C in THF in the presence of molecular sieves as water scavenger (Scheme 1). The formed amides were isolated in excellent yields, and we observed no racemization of chiral centers present in the products.[10]

The direct catalytic formation of primary amides from non-activated carboxylic acids is a reaction even less explored than the catalytic formation of secondary and tertiary amides. Primary amides are typically formed using stoichiometric reaction conditions with



Scheme 1. Zirconium-catalyzed direct amidation of carboxylic acids.

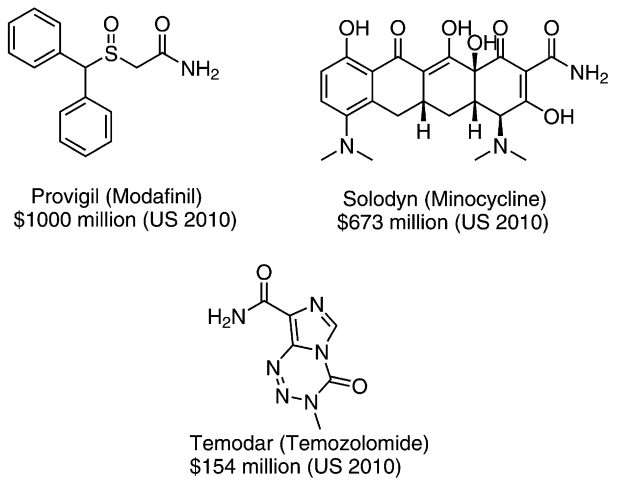
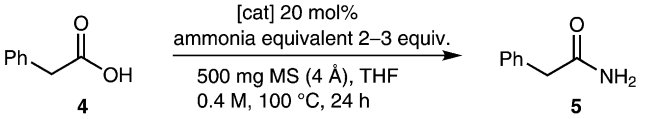


Figure 1. Blockbuster drugs containing the primary amide functionality.

activated carboxylic acid derivatives in combination with ammonia, or ammonium salts, or *via* partial hydrolysis of the corresponding nitriles.[11] Since Milstein and co-workers reported on the ruthenium-catalyzed oxidative transformation of alcohols to amides, the development of this methodology has been extended to the formation of primary amides.[12] It has also been shown that primary amides can be formed from palladium-catalyzed aminocarbonylation of aryl halides.[13] Carboxylic acids are attractive sources of starting material due to the high versatility and availability. Nevertheless, there are very few reports on catalytic transformation of non-activated carboxylic acids into primary amides. Two enzymatic protocols are reported, which work for a limited set of substrates, and require long reaction times (3–17 days).[14] Recently, two different metal-catalyzed protocols were presented by Reddy and co-workers, for the formation of primary amides from non-activated carboxylic acids and urea, under microwave heating.[15]

The fact that the primary amide functionality is part of several blockbuster drugs (Figure 1),[16] and the obvious lack of a green and general catalytic protocol for their formation inspired us to take a closer look at this reaction. The direct thermal formation of primary amides from carboxylic acids can be performed with ammonia under harsh reaction conditions (200 °C and 7 bar anhydrous gaseous ammonia).[17] In our previous study on the direct amidation of carboxylic acids with primary and secondary amines, we found that zirconium tetrachloride efficiently catalyzed this transformation. With the aim to find a milder and more user-friendly method, we set out to evaluate the above-mentioned catalytic amidation method for the formation of primary amides. We conducted a series of experiments using phenylacetic acid (**4**) and different sources of ammonia, in combination with various group IV catalysts (Table 1). Due to the operational inconvenience of gaseous ammonia, we decided to test it as a THF solution (Table 1, entry 1), however only resulting in traces of phenylacetamide (**5**). The use of ammonium formate, or ammonium bicarbonate, resulted in low yields of the primary amide (**5**) (Table 1, entries 2–5). When the amidation reaction was performed with ammonium carbamate (**6**), the desired primary amide was obtained in significantly higher yields, and with three equivalents of the amine source in the presence of 20 mol% $TiCl_4$, quantitative formation of phenylacetamide was achieved (Table 1, entry 6). Zirconium(IV) chloride and hafnium(IV) chloride also proved to be efficient as catalysts, providing the amide product **5** in yields of 75% and 70%, respectively (Table 1, entries 10 and 13). The use of group IV alkoxides as catalysts resulted in lower yields in comparison to the corresponding chloride complexes. Since ammonium carbamate decomposes into two molecules of ammonia and one molecule of carbon dioxide upon heating, pressure is

Table 1. Selected results using various sources of ammonia for the direct formation of phenylacetamide **5** from phenylacetic acid **4**.[a]



Entry	NH_3 equivalent	Catalyst	Yield[b] [%]
1[c,d,e]	NH_3 (0.4 M in THF)	$TiCl_4$	trace
2	$[NH_4][HCO_2]$	$Ti(O\text{-}i\text{-}Pr)_4$	13
3	$[NH_4][HCO_3]$	$TiCl_4$	28
4	$[NH_4][HCO_3]$	$Ti(O\text{-}i\text{-}Pr)_4$	23
5	$[NH_4][HCO_3]$	$ZrCl_4$	10
6	$[NH_4][H_2NCO_2]$	$TiCl_4$	99
7[e]	$[NH_4][H_2NCO_2]$	$TiCl_4$	99
8	$[NH_4][H_2NCO_2]$	$Ti(O\text{-}i\text{-}Pr)_4$	27
9	$[NH_4][H_2NCO_2]$	$Ti(OBu)_4$	28
10	$[NH_4][H_2NCO_2]$	$ZrCl_4$	75
11[d]	$[NH_4][H_2NCO_2]$	$Zr(O\text{-}t\text{-}Bu)_4$	53
12[d]	$[NH_4][H_2NCO_2]$	$Hf(O\text{-}t\text{-}Bu)_4$	53
13	$[NH_4][H_2NCO_2]$	$HfCl_4$	70
14	$[NH_4][H_2NCO_2]$	$PhB(OH)_2$	10
15	$[NH_4][H_2NCO_2]$	$2\text{-I-}C_6H_4B(OH)_2$	17
16	$[NH_4][H_2NCO_2]$	–	2

[a] *Reaction conditions:* phenylacetic acid (1.0 mmol), ammonia equivalent (2–3 mmol), catalyst (20 mol%), and activated 4 Å molecular sieves (0.5 g) in dry THF (acid concentration 0.4 M at 100 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h. $[NH_4][HCO_2]$ or $[NH_4][HCO_3]$ (2 mmol) at 0.4 M acid concentration, $[NH_4][H_2NCO_2]$ (3 mmol) at 0.4 M acid concentration.
[b] Isolated yields.
[c] Ammonia (6 mmol).
[d] Yield determined by ^1H NMR.
[e] Acid concentration 0.067 M.

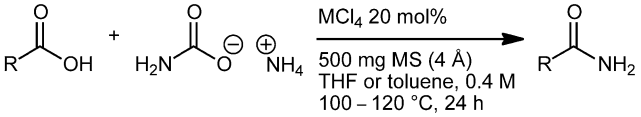
built up inside the reaction vessel. Therefore, the amidation reactions were performed in either Ace pressure tubes, suitable for pressures up to 150 psig, or in vials equipped with caps and septa.

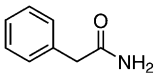
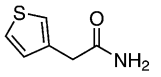
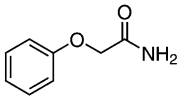
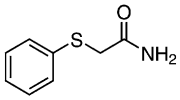
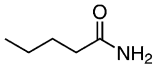
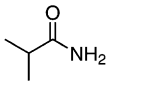
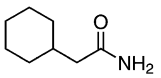
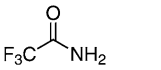
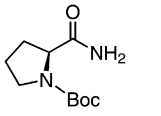
Boronic acids,[6] and especially 2-iodophenylboronic acid [2-I-$C_6H_4B(OH)_2$],[6b] are reported to be efficient catalysts for the formation of secondary and tertiary amides from non-activated carboxylic acids. The use of phenylboronic acid or 2-iodophenylboronic acid as catalysts for the formation of primary amides under the reaction conditions described above, resulted in poor yields of amide **5** (Table 1, entries 14 and 15). The thermal reaction using ammonium carbamate without catalyst present, resulted in essentially no conversion of the acid into the amide (Table 1, entry 16). In addition to the ammonia sources presented in Table 1, other potential amine equivalents such as formamide, sulfamic acid, urea and ammonium chloride were evaluated. However, no or poor conversion to amide **5**, along with the formation several by-products were observed. In the microwave heated amidations presented by Reddy and co-workers,[15] urea was used as amine source together with zirconyl chloride or cerium ammonium nitrate as catalysts. However, in our hands the reported protocol did not result in the formation of any primary amide products.

From the above investigation it was evident that the best results for the formation of primary amides were obtained using three equivalents of ammonium carbamate in the presence of a catalytic amount of either titanium(IV), zirconium(IV) or hafnium(IV) chloride. Hafnium(IV) chloride is significantly more expensive in comparison to its titanium and zirconium counterparts,[18] and therefore we chose to continue our investigation using the optimized conditions described in Table 1 and the two latter group IV chlorides. We performed a series of amidations of different carboxylic acids using ammonium carbamate as amine source (Table 2). The formation of the thiophene-containing amide **7a** along with the phenoxy-substituted amide **7b** worked well and the amide products were isolated in good yields (Table 2, entries 2 and 3). In the latter case we found that an increase of the reaction temperature to 120 °C, and changing the solvent from THF to toluene resulted in higher yield of the product. For all substrates containing an aromatic substituent, titanium(IV) chloride proved to be superior over the zirconium catalyst (Table 2, entries 1–4). Different aliphatic carboxylic acids were successfully converted into their corresponding amides in good yields (Table 2, entries 5–9). In our previous findings for the zirconium-catalyzed amidations, the enantiopurity of chiral starting material was fully retained. Unfortunately, the harsher reaction conditions required for the direct formation of primary amides resulted in some racemization of *N*-Boc protected L-prolineamide **7h**, which was isolated with 59% and 64% enantiomeric excess, employing $TiCl_4$ and $ZrCl_4$, respectively. The amides presented in Table 2 were isolated using a most convenient and straightforward work-up. Analytically pure products were obtained after a simple filtration of the reaction mixture through a short path of Celite™ followed by removal of the solvent.

The successful results obtained for the catalytic formation of primary amides presented above, encouraged us to further our investigations towards the formation of other amides, where the use of proper car-

Table 2. Titanium- or zirconium-catalyzed formation of primary amides from carboxylic acids and ammonium carbamate.[a]



Entry	Amide		Isolated yields [%]		
			$TiCl_4$	$ZrCl_4$	Thermal
1[b]		**5**	99	75	2
2[b]		**7a**	90	87	4
3[c]		**7b**	91	81	5
4[c]		**7c**	99	82	7
5[b]		**7d**	88	96	14
6[c]		**7e**	72	42	11
7[c]		**7f**	86	60	7
8[c]		**7g**	50	67	4
9[c]		**7h**	67[d]	89[e]	14

[a] *Reaction conditions:* carboxylic acid (1 mmol), ammonium carbamate **4** (3 mmol), MCl_4 (20 mol%), and activated 4 Å molecular sieves (0.5 g), in dry solvent (acid concentration 0.4 M) at 100 or 120 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h.
[b] THF, 100 °C.
[c] Toluene, 120 °C.
[d] 59% *ee* determined by optical rotation.
[e] 64% *ee* determined by optical rotation.

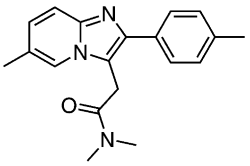


Figure 2. The top-selling drug Zolpidem, containing the *N,N*-dimethylamide functionality.

bamates would provide suitable and practical substitutes for gaseous amines. We decided to evaluate dimethylammonium dimethylcarbamate **8**, as an equivalent of dimethylamine, which upon reaction with carboxylic acids would generate *N,N*-dimethyl amides. The latter functionality is important and is for example found in the top-selling drug Zolpidem, used for the treatment of insomnia (Figure 2).[18]

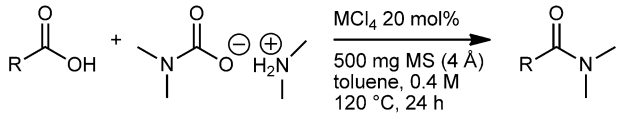
Dimethylammonium dimethylcarbamate **8** is commercially available, and using this reagent under the conditions described above would allow for the direct formation of tertiary amides. Gratifyingly, a series of *N,N*-dimethylamides was formed in good to excellent yields when structurally different carboxylic acids were reacted with 2 equivalents of **8**, using 20 mol% titanium(IV) or zirconium(IV) chloride as catalysts (Table 3). For comparative reasons, dimethylamine in THF (2 M) 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 below. The resulting isolated yield of amide **9a** was found to be somewhat lower compared to that described in Table 3, entry 1, with the same catalyst (74% *vs.* 85%).

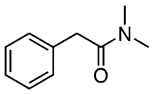
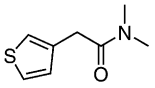
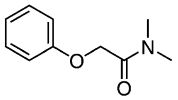
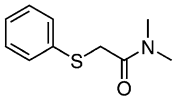
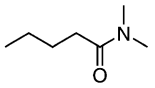
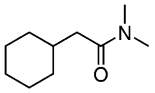
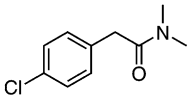
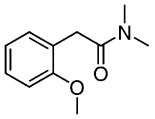
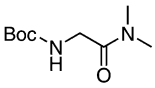
The non-catalyzed thermal amidations using **8** resulted in 5–14% yields of the corresponding *N,N*-dimethylamides, demonstrating that even though there is a certain background reaction, the major amount of amides formed in the catalytic set-up is mediated by the transition metal complex. Moreover, phenylboronic acid and 2-iodophenylboronic acid were evaluated as catalysts for the formation of *N,N*-dimethyl-2-phenylacetamide (**9a**) using **8** as the amine source. However, employing the boronic acid catalysts resulted in in poor yields of the target amide (42% and 31% respectively).

In conclusion, we have demonstrated that the direct formation of primary amides can be accomplished by reacting non-activated carboxylic acids with ammonium carbamate in the presence of either titanium(IV) or zirconium(IV) chloride. The method stands as a significantly greener protocol for amide formations in comparison to classic amidation methods using various coupling reagents. Based on the same catalytic strategy, we have presented a direct method for the formation of *N,N*-dimethylamides, simply by employing the commercially available dimethylammonium dimethylcarbamate as amine source.

To date, there are only few catalytic protocols available for the direct transformation of carboxylic acids into primary amides, and none known for the direct formation of *N,N*-dimethylamides. We have shown that the use of zirconium(IV) or titanium(IV) chloride is far superior as catalysts for these transformations, in comparison to the well-established boronic acid catalysts. Furthermore, we have demonstrated that the group IV transition metals efficiently can be

Table 3. Direct zirconium-catalyzed formation of *N,N*-dimethylamides from carboxylic acids.[a]



Entry	Amide		Isolated yields [%] $TiCl_4$	$ZrCl_4$	Thermal
1		**9a**	81	85	14
2		**9b**	89	74	11
3		**9c**	90	94	8
4		**9d**	83	85	5
5		**9e**	51	76	6
6		**9f**	61	45	17
7		**9g**	58	99	12
8		**9h**	81	67	8
9		**9i**	56	69	12

[a] *Reaction conditions:* carboxylic acid (1 mmol), dimethylammonium dimethylcarbamate **8** (2 mmol), MCl_4 (20 mol%), and activated 4 Å molecular sieves (0.5 g), in dry toluene (acid concentration 0.4 M) at 120 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h.

employed as catalysts for the formation of all classes of amides.

Experimental Section

Typical Procedure for the Formation of Primary Amides Catalyzed by $ZrCl_4$

An oven-dried 15-mL Ace pressure tube with a stirring bar was charged with the carboxylic acid (1.0 mmol), molecular sieves 4 Å (0.5 g), $ZrCl_4$ (0.2 mmol, 0.0466 g), ammonium carbamate (3.0 mmol, 0.234 g) and dry toluene (2.5 mL) under a nitrogen atmosphere. The pressure tube was sealed and put in a preheated oil bath. The mixture was stirred at 120 °C for 24 h and then cooled to room temperature. The reaction mixture was passed through a plug of Celite™ (4 × 4 cm) eluted with 200 mL EtOAc. The solvent was removed under reduced pressure affording in most cases the analytically pure product.

Typical Procedure for the Formation of *N*,*N*-Dimethylamides Catalyzed by $ZrCl_4$

An oven-dried 15-mL Ace pressure tube with a stirring bar was charged with the carboxylic acid (1.0 mmol), molecular sieves 4 Å (0.5 g), $ZrCl_4$ (0.2 mmol, 0.0466 g), dimethylammonium dimethylcarbamate (2.0 mmol, 0.268 g) and dry toluene (2.5 mL) under a nitrogen atmosphere. The pressure tube was sealed and put in a preheated oil bath. The mixture was stirred at 120 °C for 24 h and then cooled to room temperature. The reaction mixture was passed through a plug of silica (4 × 4 cm) eluted with 100 mL EtOAc:Et_3N (200:1). The solvent was removed under reduced pressure affording in most cases the analytically pure product.

Acknowledgements

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Direct Catalytic Formation of Primary and Tertiary Amides from Non-Activated Carboxylic Acids, Employing Carbamates as Amine Source

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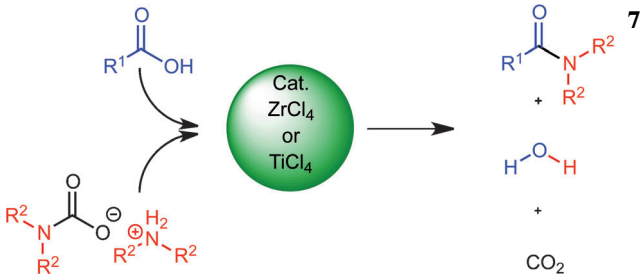

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