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TiF_4-catalyzed direct amidation of carboxylic acids and amino acids with amines†

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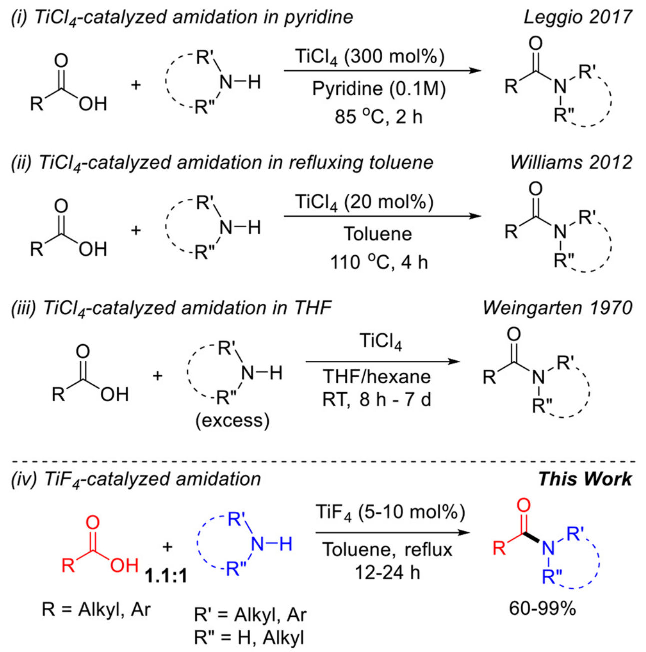
Unlike other metal fluorides, catalytic titanium tetrafluoride enhances the direct amidation of aromatic and aliphatic carboxylic acids and *N*-protected amino acids in refluxing toluene. While aromatic acids were converted to amides with 10 mol% of the catalyst within 24 h, aliphatic acids underwent a faster reaction (12 h), with lower catalyst loading (5 mol%). This protocol is equally efficient with alkyl and aryl amines providing a variety of carboxamides and peptides in 60–99% yields.

Introduction

The prevalence of amides in organic molecules and biomolecules has made their preparation, structure, and reactivity a much-discussed subject. The direct amidation of carboxylic acids is the most straightforward protocol to access them, although it is a challenging reaction[1] due to the formation of ammonium salt. Dehydration of the salt to an amide can be achieved at high temperatures. For milder reactions, the conversion of the acid to a derivative capable of undergoing facile nucleophilic acyl substitution, such as an acid chloride or anhydride, is opted for. Also, a variety of carbodiimide reagents, such as dicyclohexylcarbodiimide (DCC),[2] 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC),[3] and 1,1′-carbonyldiimidazole (CDI)[4] or phosphate agents, such as benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP),[5] Castro's reagent (BOP),[6] T3P,[7] HBTU,[8] HATU,[9] *etc.* have been developed for the dehydrative coupling of an acid with an amine.[10,11] However, in addition to the reagent cost, the need for additional equivalents of amines and excess reagents adds to the difficulties in the separation of the amides from stoichiometric quantities of the side products. Leading the intense activity in developing alternate catalyzed direct amidation protocols[12,13] are boron-[14] and silicon-based[15] catalysts as well as transition metal salts, particularly those of Ti,[16–18] Mn,[19] Fe,[20] Zn,[21,22] Zr,[17,23,24] In,[25] Hf,[26] Ta,[27,28] *etc.* Indeed, some of these reactions are carried out in sealed tubes and are effective only for aliphatic acids and several of these protocols are inefficient for amidation with anilines.

We have recently reported the effect of catalytic titanium tetrachloride ($TiCl_4$) for the borane-amine mediated reduction of ketones,[29] acids,[30] amides,[31] and nitriles,[32] deoxygenation of esters to ethers[33] and deoxyhalogenation of carbonyl compounds.[34] During these projects, we undertook a systematic evaluation of the catalytic ability of several metal halides and established that the reaction depended on the Lewis acidity of these halides and $TiCl_4$ is a critical and superior catalyst. Interested in $TiCl_4$'s applicability for amidation, a literature search was undertaken, which led to a recent, impractical process with 300 mol% of $TiCl_4$ in pyridine as the solvent (Scheme 1(i)).[18] A prior report comparing several Lewis acids



Scheme 1 Comparison of titanium halide mediated amidation catalyzed amidation.

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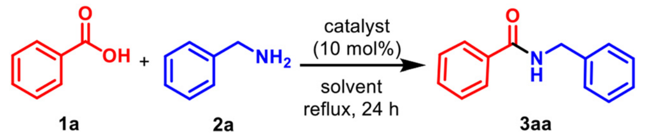
for amidation reported that $ZrCl_4$ is superior to $TiCl_4$ (Scheme 1(ii)).[17] The first report from half a century ago using large excess of amines is inconclusive (Scheme 1(iii)).[16]

Results and discussion

After attempting an amidation of benzoic acid (**1a**) with benzylamine (**2a**) without any catalyst in refluxing toluene (24 h, 15% yield; Table 1, entry 1), a similar reaction in the presence of 10 mol% $TiCl_4$ provided 89% yield of the corresponding amide **3aa**[35] (Table 1, entry 2). $TiBr_4$ was equally effective (91% yield, entry 3). Other group 4 metal chlorides, such as $ZrCl_4$ and $HfCl_4$, were poor amidation catalysts (entries 4 and 5) under similar conditions. Mader and Helquist have reported that titanium isopropoxide (TIPO) is a poor catalyst for intermolecular amidation.[36] However, Adolfsson and coworkers reported successful amidation in THF in a sealed tube with 1.5 equiv. of the acid and catalytic TIPO or Ti(*n*-BuO)$_4$.[37] Attempts to scale-up the reaction with $TiCl_4$ and $TiBr_4$ were unrealistic due to the corrosive nature of the reagents, so we turned our attention to TiF_4.

We had observed during our earlier-mentioned deoxyhalogenation of carbonyls[34] using $TiCl_4$ and $TiBr_4$ that the corresponding fluoride did not participate in the nucleophilic transfer of the fluoride. This led us to believe that TiF_4 might be a stable catalyst for Lewis acid-mediated reactions. Surprisingly, there are only scarce reports on direct amidation using metal fluorides as catalysts. Metal fluoride salts, such as ZnF_2 and AlF_3, are ineffective compared to chlorides for the formylation of amines.[21] Also, a recent report on the screening of different fluoride salts such as CsF, NaF, KF, $AgSbF_6$, and KPF_6 as promoters for a similar esterification produced poor results with all of them, except KPF_6.[38] The hexafluorophosphate was effective for amidation as well.[38] Our long-time interest in the chemistry of fluorinated molecules stimulated us to examine TiF_4 for the direct amidation of carboxylic acids. The literature suggested that unlike the chloride analog, TiF_4 is easier to handle, stable in air and water,[39] and has excellent solubility in dimethoxyethane and THF.[40,41] Our concerns were the possible complexation of TiF_4 with amines,[42] which could be detrimental to their nucleophilicity. The results documented herein unequivocally confirm that 5–10% of TiF_4 is a catalytic promoter for the direct amidation of both aliphatic and aromatic carboxylic acids with both classes of amines (Scheme 1(iv)).

Table 1 Optimization of amidation conditions



Entry	LA	Solvent	Yield,[a] %
1	None	Toluene	15
2	$TiCl_4$	Toluene	89
3	$TiBr_4$	Toluene	91
4	$ZrCl_4$	Toluene	45
5	$HfCl_4$	Toluene	47
6	TiF_4	Toluene	77[b]
7	TiF_4	Toluene	96
8	TiF_4	Toluene	28[c]
9	TiF_4	Toluene	NR[d]
10	TiF_4	Xylene	69
11	TiF_4	Benzene	NR[c]
12	TiF_4	Cyclohexane	NR[c]
13	TiF_4	THF	NR[c]
14	TiF_4	CH_3CN	NR[c]
15	BF_3-Et_2O	Toluene	79 (83)[e]
16	ZnF_2	Toluene	43
17	ZrF_4	Toluene	41

[a] Isolated yields for reactions using 1.1 equiv. of **1a** and 1.0 equiv. of **2a**. [b] 1.0 equiv. of carboxylic acid. [c] 5 mol% of TiF_4 used. [d] Reaction at 80 °C. [e] From ref. 43 in refluxing benzene (100 h) in the presence of Et_3N. NR = No reaction.

A reaction of an equivalent each of **1a** with **2a** in refluxing toluene in the presence of 10 mol% TiF_4 for 24 h provided 77% of **3aa**[35] (entry 6), which was increased to 96% with an additional 10% of the acid (entry 7). A large scale 50 mmol reaction was carried out for the synthesis of *N*-benzylbenzamide (**3aa**), which resulted in a slightly reduced yield of 77%. We then explored the limitations of the process by varying the catalyst loading, solvent, reaction temperature, *etc.* (entries 8–14) and concluded that 10% catalyst with 1.1 equiv. of the acid provided the optimal yield. BF_3-Et_2O,[43] ZnF_2 and, ZrF_4, were also compared (entries 15–17), which gave unsatisfactory results.

Having determined the optimal conditions for the amidation of **1a** with **2a**, the generality of the protocol was examined by varying the acids and amines (Fig. 1 and 2). In all cases, pure amides were isolated after a simple acid–base workup. Initially, we maintained the amine (benzylamine) and focused on the effect of the aromatic acid (Fig. 1). Substitutions on the benzene ring of **1a** were examined with benzoic acid substituents bearing electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) (**1b–1j**). All of the amides were obtained in good to excellent yields. However, moderate yield was realized with *ortho*-substituted benzoic acids **1b** and **1g**, probably due to the increased steric effects. Among those tested, 4-nitrobenzoic acid failed to undergo amidation. Cinnamic acid (**1k**) and nicotinic acid (**1l**) were also treated with **2a** to yield the corresponding amides **3ka** and **3la** in 99% and 93% yields, respectively. Replacing benzylamine with cyclohexylamine (**2c**) resulted in 24% yield of the amide **3ac**. However, increasing the catalyst to 50 mol% afforded 90% yield of the product.

Preparation of tertiary amides from aromatic acids was examined using morpholine (**2d**) as the representative secondary amine. Thus, benzoic acids with EWGs and EDGs were amidated with **2d** in 90–98% yield, except 2-methoxybenzoic acid **1g**, which, as with **2a**, provided **3gd** in 61% yield. Significantly, amidations of benzoic acids and anilines each bearing EDGs and EWGs were complete within 24 h, and the products were isolated in 77–96% yields. It is noteworthy that

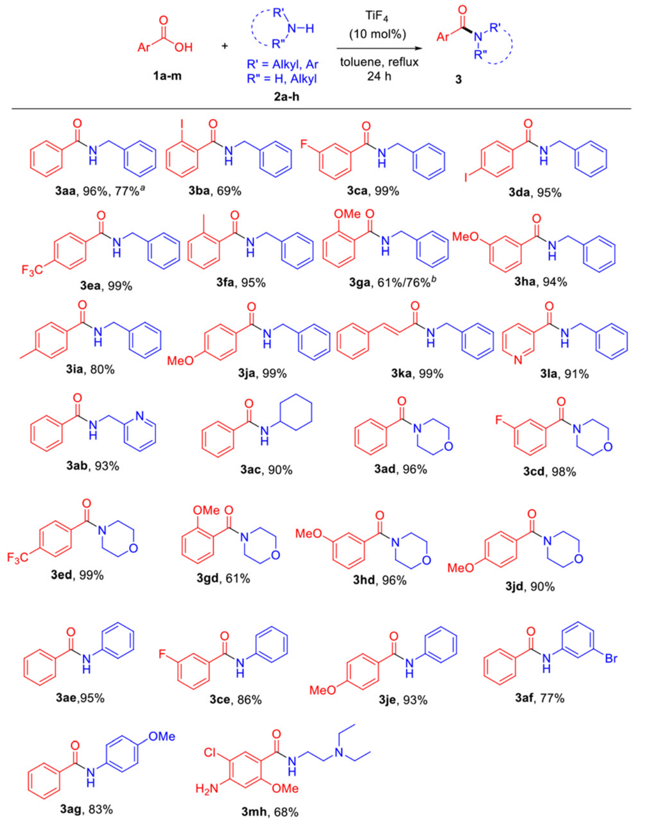


Fig. 1 Amidation of aryl carboxylic acids using 10 mol% TiF_4, 1.1 equiv. of carboxylic acid and 1 equiv. of amine. Isolated yields shown. [a]Yield for the 50 mmol scale reaction. [b]Yield with 50 mol% catalyst.

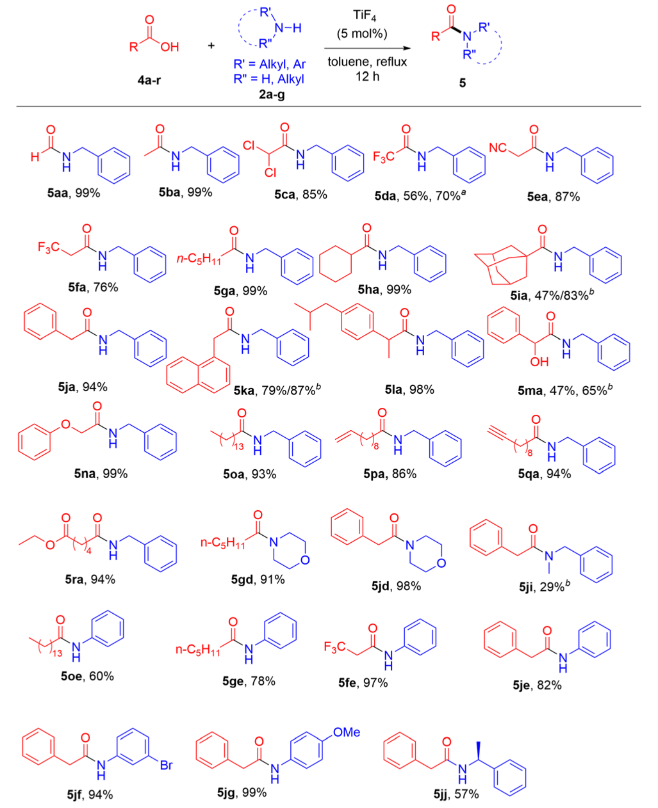


Fig. 2 Amidation of alkyl carboxylic acids using 5 mol% TiF_4, 1.1 equiv. of carboxylic acid and 1 equiv. of amine. Isolated yields shown. [a]Indicates product yield with 20% catalyst loading. [b]Yield with 50 mol% catalyst.

amidations with anilines are seldom reported for several of the procedures described in the literature. Under similar conditions, metoclopramide (**3mh**), an antiemetic and gut motility stimulator,[44] was synthesized from 4-amino-5-chloro-2-methoxybenzoic acid (**1m**) and *N,N*-diethylethane-1,2-diamine (**2h**).

The direct amidation of aliphatic acids (**4a–4r**) required only 5 mol% TiF_4 and were faster (12 h) (Fig. 2). Formic, acetic, cyclic, linear, and arylacetic acids reacted smoothly and the amides (**5**)[35] were obtained in good to excellent yields (Fig. 2). The amide **5ia** from adamantylcarboxylic acid (**4i**) and benzylamine (**2a**) was obtained in only 47% yield under the standard conditions. However, it improved to 83% with 50 mol% of the catalyst.

The reaction of the anti-inflammatory drug ibuprofen (**4l**) and **2a** produced the corresponding amide **5la** in 98% yield. A decreased yield of 47% was observed for amide **5ma** from mandelic acid (**4m**) under the standard conditions, which was improved to 65% with 50 mol% of the catalyst. The need for excess catalyst could be due to the reaction of the hydroxyl group with the catalyst. No side reaction was observed with substrates having distal double (**4p**) and triple (**4q**) bonds in the carboxylic acids and amides **5pa** and **5qa** were obtained in 86% and 94% yields, respectively. Nevertheless, the yield of the amide **5ji** was low (29%) when phenylacetic acid (**4j**) was reacted with a secondary amine (**2i**). An optically pure amine, (*R*)-(+)-α-methylbenzylamine (**2j**), was treated with **4j** to examine the stereochemical retention during the amidation. The chiral amide **5jj**, which was isolated in 57% yield, revealed an optical rotation comparable to the pure chiral amide reported in the literature,[45] demonstrating the applicability of this process for chiral substrates.

The new amidation protocol was next examined to prepare peptides from amino acids. The amidation of the sterically hindered *N*-Fmoc and *N*-Boc protected glycine (**6a** and **6b**) with benzylamine **2a** (Fig. 3) yielded the target amides **7aa**[35] and **7ba** in 62% and 88% yields, respectively.

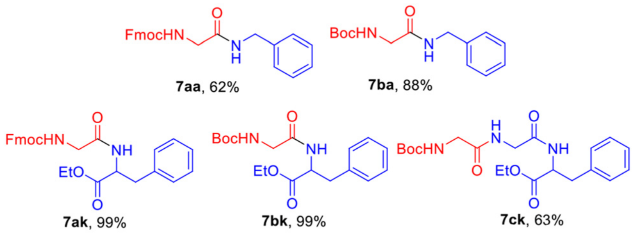


Fig. 3 Direct amidation of amino acids and primary amines using catalytic TiF_4 (5%).

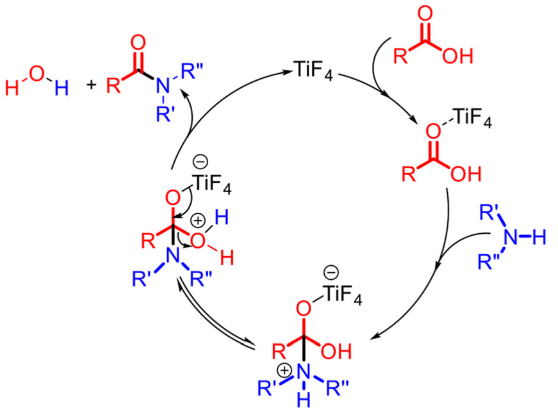


Fig. 4 Proposed mechanism of titanium tetrafluoride-catalyzed amidation of carboxylic acids.

More challenging di- and tripeptide couplings were also successfully achieved *via* the combination of *N*-Fmoc-Gly-OH (**6a**) and *N*-Boc-Gly-OH (**6b**), with ethyl α-amino esters of phenylalanine **2k** under the described conditions when the amides **7ak** and **7bk** were obtained in excellent (99%) yields. Subsequently, dipeptide **7bk** was deprotected to give the intermediate Gly-Phe-OEt, which was further reacted with *N*-Boc-Gly-OH (**6b**) to furnish the tripeptide *N*-Boc-Gly-Gly-Phe-OEt **7ck** in 63% yield, demonstrating the capability of the reaction for sequential amidation reactions.

The TiF_4-mediated amidation is believed to proceed *via* the coordination of the catalyst with the acid, which prepared the carbonyl for the nucleophilic attack by the amine, which was followed by a proton transfer, elimination of water and regeneration of the catalyst (Fig. 4). A similar mechanism proposed for the amidation of carboxylic acids with catalytic $ZrCl_4$[46] forms the basis of our hypothesis. TiF_4 is known to complex with amines.[42] It is known to complex with ketones and carboxylic acids as well.[41] However, the formation of an ammonium salt upon the mixing of the carboxylic acid and amine may preclude the formation of the amine–titanium complex. In refluxing toluene, the ammonium salt is probably cleaved, and the amine attacks the Ti-complexed carbonyl carbon.

Conclusion

In conclusion, we have described a direct amidation protocol using catalytic TiF_4 (10 mol% for aromatic or 5 mol% for aliphatic acids) in refluxing toluene. The former is amidated within 24 h, while the latter requires only 12 h. This procedure can provide secondary and tertiary amides from both aliphatic and aromatic acids and amines in very high yields. This is applicable for the synthesis of peptides from amino esters and *N*-protected amino acids and has several advantages, such as: (i) ready availability and (ii) very low molecular weight of the catalyst, (iii) non-chromatographic purification, (iv) no requirement of removal of water using azeotropic/molecular sieves for small scale reactions, and (v) consistently high yields. We continue to explore ways to improve and extend this amidation procedure.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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