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Bis(phenolate)–Titanium(IV) Catalysts for Efficient and Sustainable Direct Amide Bond Formation

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ABSTRACT

Amides are fundamental and hugely widespread functional groups in key bioactive and industrially relevant molecules. However, conventional methods for amide bond formation, particularly in peptide synthesis, are challenging in terms of environmental impact, waste, and production costs. The most commonly used method for amide bond formation involves activating carboxylic acids with excess coupling agents, heavily affecting the atom economy of the process. Despite the need for more sustainable alternatives, research on catalytic methodologies to minimize such drawbacks remains limited. In this study, we explored the use of titanium alkoxides of general formula $Ti(OAr)_2(OiPr)_2$, as efficient and environmentally friendly catalysts for amide bond formation. Our results indicated that the replacement of isopropoxide ligands with the less basic phenolates 2,4-dimethylphenolate and 2,6-dimethylphenolate significantly improved the reactivity of the Ti-center. Indeed, by using 5% mol of titanium bis(2,6-dimethylphenoxy)diisopropoxy (**Ti2**), or 10% mol of titanium bis(2,4-dimethylphenoxy)diisopropoxy (**Ti1**), we achieved efficient direct amidation between benzylamine and various carboxylic acids, including *N*-protected amino acids for which limited data are available in the literature. This work highlights the potential of titanium-based catalysis as a sustainable and effective solution for amide bond formation, particularly in peptide synthesis.

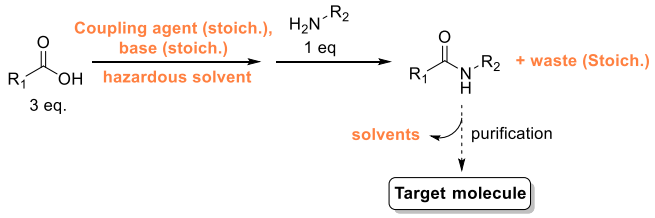
1 | Introduction

The formation of amide bonds is a fundamental process in organic chemistry, due to its broad application in the synthesis of a wide range of industrially relevant compounds, such as pharmaceutical drugs [1–3], agrochemicals [4–7], cosmetics [8–10], and materials [11].

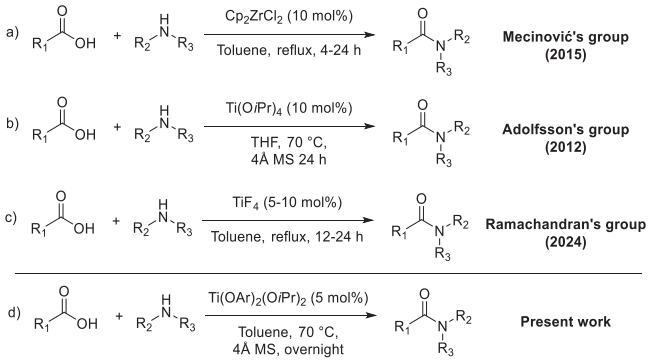
However, the formation of the amide by direct condensation of an amine with a carboxylic acid is hampered by the protonation of the amine and requires drastic conditions to promote the nucleophilic addition of the amine to the carbonyl group. For this reason, several synthetic alternatives have been developed through the years primarily based on the pre-activation of the carboxylic acid functionality using specific coupling agents such as carbodiimides (e.g. DCC, DIC) [12, 13], benzotriazoles (e.g. HOBt) [14, 15], and their derivative phosphonium (e.g. PyBOP) and uronium salts (e.g. HATU) [16].

While the use of these coupling reagents is critical for increasing the reaction rate and minimizing the occurrence of unwanted side reactions (e.g. racemization of carboxylic acids containing an α-stereocenter), their application in at least stoichiometric amounts leads to the generation of large quantities of by-products. This

Gioele Colombo and Elettra Fasola contributed equally to the work.



SCHEME 1 | Traditional methods of amide bond formation.



SCHEME 2 | Metal-based direct amidation of carboxylic acids and amines.

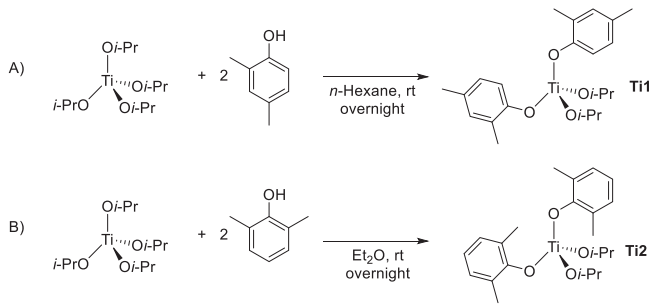
results in a poor atom economy and a significant production of waste per kilogram of product (high E factor, Scheme 1) [17]. The additional involvement of hazardous solvents such as *N,N'*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and dichloromethane (DCM) definitely makes the chemistry of the amide bond one of the heaviest in terms of economic costs, environmental impact, and production of waste [18].

This is particularly relevant in the synthesis of peptides and peptidomimetics, which play a crucial role in numerous physiological and biological processes and hold significant potential as therapeutic agents. In this context, peptide bond formation (formally an amide bond) typically occurs on a solid support during the elongation of the peptide chain. This approach reduces the number of purification steps and accelerates the overall synthetic process. However, solid-phase peptide synthesis (SPPS) often requires extensive use of hazardous solvents and a super-stoichiometric amount of reagents at each step, which poses considerable environmental and safety challenges from an industrial perspective [19]. For these reasons, during the last years, the development of "greener" methodologies aimed at the formation of amide bonds has become crucial, as demonstrated by the increasing literature centered on new sustainable amide synthesis procedures [20]. One of the main focuses is the substitution of the classical hazardous solvents with more environmentally friendly media (i.e., water, organic solvents from sustainable sources, etc.) [21–23], with the final aim to make these synthetic processes safer. On the other hand, the challenges associated with the formation of large quantities of byproducts, arising from the use of activating agents, could potentially be addressed through a catalytic activation of the carboxylate or amine counterparts. This area of chemistry has been extensively explored over the past few decades with the development of many new homogeneous methodologies based on the use of boronic acid catalysis [24], organocatalysis [25], and ester amidation [26].

Among these approaches, the most common is based on the use of boron catalysts, first presented in 1996 by Yamamoto's group and still representing an active area of research [27, 28]. The structure refinement of the boron-catalysts allowed milder reaction conditions [29], but these compounds are often not compatible with some functional groups, and, additionally, they require complex synthetic routes. More recently, silicon-based catalysts presenting simpler structures showed promising results [30], but they also proved limited tolerance for complex substrates and are sometimes still required in stoichiometric amounts [31]. The latter problem is also faced with most examples of organocatalysts (e.g., phosphines or diselenides) [31, 32].

The alternative approach of using transition metals to promote the formation of amide bonds starting from non-activated carboxylic acids has received less attention so far. In this strategy, the reaction partners are brought into close proximity by coordination to the metal, which also activates them for the subsequent condensation [33]. On the other hand, catalysts are often composed of less abundant precious metals (e.g., Pd, Ru, Zr, and Hf), needed in relatively high loadings (up to 10%), and harsh or refluxing conditions are required, which are incompatible with many substrates (e.g., Scheme 2a) [34–38]. Only a few examples reported safer conditions and/or the use of more available metals for direct amide bond catalysis [39]. In this perspective, the independent work of Adolfsson and Williams paved the way for the use of Group IV metals, in particular titanium and hafnium, in milder reaction conditions and a larger scope (Scheme 2b) [40, 41]. In fact, among the oxophilic early transition metals, titanium represents a valid alternative for direct amidation catalysis in homogeneous conditions [42, 43], due to its relatively high abundance—ranking as the ninth most abundant element in the Earth's crust [44]—as well as its cost-effectiveness and nontoxicity. In the literature, the use of titanium alkoxides to activate the carboxylic group has primarily been reported for transesterification reactions (as in the controlled polymerization of lactide) [45] but has also been applied in the formation of amide bonds. The group of Ramachandran recently reported successful direct amide bond formation between various carboxylic acids and amines using catalytic amounts of titanium (IV) fluoride, which apparently behaves exclusively as a Lewis acid (Scheme 2c) [46]. Indeed, the oxophilic nature of titanium would activate the carboxyl group, facilitating the nucleophilic addition and promoting substitution reactions on the Ti-center [31].

However, the use of titanium(IV) halides often requires careful handling due to their sensitivity to moisture which leads to the release of hydrogen halides. Also, titanium *iso*propoxide, $Ti(OiPr)_4$, has been reported as a promising catalyst for direct amidation of non-activated carboxylic acids [40]. In the search of more active catalysts, we report herein our investigations into the use of mixed titanium alkoxides with general formula $Ti(OAr)_2(OiPr)_2$, as safer and more efficient catalysts for amide bond formation. Particular attention is given to the coupling reactions between amines and *N*-protected amino acids, an area where limited data is available in literature (Scheme 2d). The introduction of aryloxide ligands, which are less basic than *iso*propoxide, is expected to enhance the stability of the



SCHEME 3 | Synthesis of the two titanium diphenolate diisopropoxide catalysts **Ti1** and **Ti2**.

corresponding catalysts to decomposition by protonation of the ligands, as well as their reactivity. This enhancement can be attributed to the electron-withdrawing effect of the aromatic substituents, which increase the electrophilicity of the titanium center [47].

2 | Results and Discussion

2,4-Dimethylphenol and 2,6-dimethylphenol were chosen as ligands. Two different titanium-based catalysts, **Ti1** [(2,4-dimethylphenoxy)$_2$Ti(O*i*-Pr)$_2$] and **Ti2** [(2,6-dimethylphenoxy)$_2$Ti(O*i*-Pr)$_2$], were synthesized, and the effect of the different aryloxide ligands on the catalytic activity was investigated, also with respect to Ti(O*i*-Pr)$_4$. As shown in Scheme 3, the titanium complexes were obtained by mixing Ti(O*i*Pr)$_4$ with 2 equiv of dimethylphenol in diethyl ether or *n*-hexane overnight, then thoroughly evaporating volatiles [48]. Viscous oils were obtained in both cases, which were then subjected to characterization to confirm the formation of the disubstituted aryloxy-titanium catalysts. NMR spectra of **Ti1** (see Figure S1, for both ^{1}H and ^{13}C-NMR) were in accordance with literature data [47], while CHN analysis was not fully reliable due to the high tendency of this catalyst to hydrolyze, which compromised the analysis. (Table S1). However, the experimental results yielded a C:H ratio of 1:1.40, close to the theoretical value of 1:1.45, thus providing partial support for the proposed structure. The fluxional nature of the ligands of **Ti2** in solution impaired its NMR characterization (Figure S2), while its CHN analysis revealed close C and H content, notwithstanding the limited stability of these compounds towards hydrolysis. The residues were dissolved in dry toluene or THF to form stock solutions, which were stored under an inert atmosphere and subsequently used in the catalytic tests without further purification. (Scheme 3).

We began our study using the conditions established by Adolfsson and coworkers, in which the coupling between 1.2 equiv of Boc-glycine and 1 equiv of benzylamine was carried out with different amounts of Ti(O*i*Pr)$_4$ in dry THF at 70 °C for 24 h and in the presence of molecular sieves to trap the water formed during the reaction. The use of molecular sieves is necessary to avoid catalyst deactivation and generation of titanium oxides (Scheme 2b) [40]. Running the reaction in toluene rather than THF, proved to be beneficial, since it significantly improved the final yield from 69% to 94% (entries 1 and 2, Table 1). The lower efficiency of the catalyst in oxygenated solvents (see also Table S2 for further examples) might be due to interactions between the oxophilic titanium center and the solvent, or to the hydrophobicity of toluene, which allows for a more efficient elimination of water. Similarly, working with an excess of amine rather than acid, as well as lowering the temperature to 50 °C and 30 °C, or removing/reducing the amounts of molecular sieves proved to be detrimental to the good outcome of the reaction (Table S2).

Thus, 1.2 equiv *N*-Boc-glycine was reacted with 1.0 equiv of benzylamine in the presence of 20% of the synthesized catalysts **Ti1** or **Ti2**, at 70 °C for 24 h using dry toluene as solvent, and adding the optimized amounts of molecular sieves (see Table S2 for amounts of molecular sieves). Both reactions yielded the final amide products with conversions of 78% and 86%, respectively, demonstrating that under these reaction conditions, the two new aryloxy-based catalysts exhibit similar activity to Ti(O*i*Pr)$_4$, with **Ti2** showing slightly higher activity. As expected, the use of dry THF as a solvent slightly decreased the yields to 65% and 76% for **Ti1** and **Ti2,** respectively (entries 5 and 6, Table 1), whereas decreasing the reaction temperatures was again not sustainable for the success of the reaction (Table S2, entries 12–15).

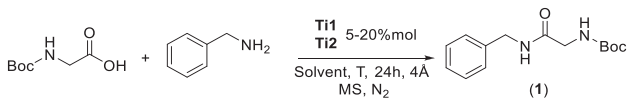
Catalyst loading was then investigated: interestingly, a significant improvement in product yields was observed with both catalysts **Ti1** and **Ti2** reducing the catalyst to 10% and 5%, whereas Ti(O*i*Pr)$_4$ showed lower yields with 10% catalyst and only trace amounts of the final amide product at the catalytic amounts of 5% mol (entries 7–12, Table 1). This comparison highlights the enhanced catalytic efficiency and robustness of the phenolate-based catalysts, particularly **Ti2**, under reduced catalyst loading conditions. The difference in the activity of the newly synthesized catalysts may be due to the higher steric hindrance of the two methyl substituents on the metal center in **Ti2** (2,6-dimethyl substituents) compared to **Ti1** (2,4-dimethyl). To further investigate the effect of the phenolate ligands on the catalytic performances of **Ti1** and **Ti2**, we synthesized and tested the tetrakis-phenolate Ti catalyst (**Ti3**), featuring 2,6-dimethylphenol as a ligand, and designed to form stronger and, consequently, more stable Ti—O bonds. In particular, **Ti3** was synthesized from Ti(O*i*Pr)$_4$ and 4 equiv of 2,6-dimethylphenol (Scheme 4). ^{1}H NMR spectrum of **Ti3** was in accordance with literature data (Figure S3) [48].

Rather unexpectedly, **Ti3** showed only moderate activity in the direct amidation of *N*-Boc-glycine with benzylamine, under the usual conditions (1.0 equiv of amine and 1.2 equiv of acid, 5% of **Ti3**, in dry toluene), resulting in a low isolated yield of 23% for product **1** (Scheme 5). This reduced activity of the catalyst bearing 4 phenolate ligands might be due to an increased steric hindrance as well as to the stronger acidity of the phenols with respect to alcohols, which makes the metal ion less easily accessible by both the carboxylic acid and the amine.

Based on these results, catalyst **Ti2** was chosen to investigate the scope of the direct amidation reaction using different carboxylic acids.

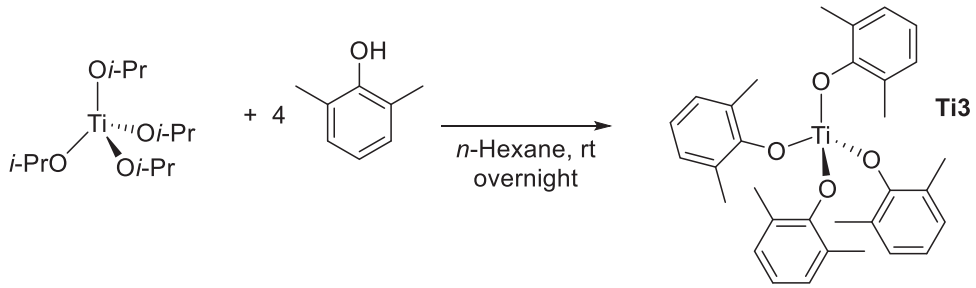
Although our primary interest was in amide bond formation for peptide synthesis, we started to investigate the ability of **Ti2** to promote amide bond formation between benzylamine and aromatic acids for a direct comparison with the results previously obtained by other groups [36, 40, 46]. Thus, benzylamine was

TABLE 1 | Screening reaction conditions in the direct amidation reaction of Boc-glycine and benzylamine using different **Ti1**, **Ti2**, and Ti(O*i*Pr)$_4$ catalysts.

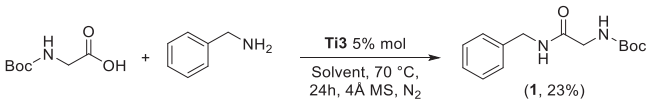


#	Catalyst	Cat %	*T* (°C)	Solvent	Yield[a]	TON	TOF (h^{-1})
1	Ti(O*i*Pr)$_4$	20%	70	Dry THF	69%	3.45	0.14
2	Ti(O*i*Pr)$_4$	20%	70	Dry toluene	94%	4.70	0.20
3	**Ti1**	20%	70	Dry toluene	78%	3.90	0.16
4	**Ti2**	20%	70	Dry toluene	86%	4.30	0.18
5	**Ti1**	20%	70	Dry THF	65%	3.25	0.14
6	**Ti2**	20%	70	Dry THF	76%	3.80	0.16
7	Ti(O*i*Pr)$_4$	10%	70	Dry toluene	74%	7.40	0.31
8	**Ti1**	10%	70	Dry toluene	91%	9.10	0.38
9	**Ti2**	10%	70	Dry toluene	74%	7.40	0.31
10	Ti(O*i*Pr)$_4$	5%	70	Dry toluene	5%	1.00	0.04
11	**Ti1**	5%	70	Dry toluene	78%	15.6	0.65
12	**Ti2**	5%	70	Dry toluene	99%	19.8	0.83

[a]Isolated yields.

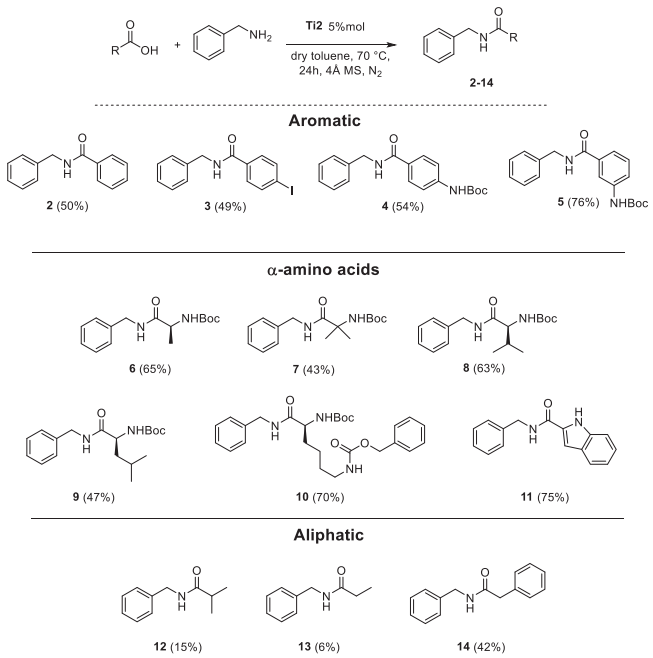


SCHEME 4 | Synthesis of the titanium tetra-phenolate catalyst **Ti3**.



SCHEME 5 | Direct amidation reaction of Boc-glycine and benzylamine using **Ti3** tetrakis catalyst.

reacted with benzoic acid three para and meta substituted derivatives by using 5% mol of **Ti2** in dry toluene for 24 h and in presence of molecular sieves. As shown in Scheme 6, all the final compounds were successfully obtained in satisfactory yields ranging from 50% to 76% of isolated product (compounds **2**–**5**). In these conditions we were generally able to achieve comparable yields to Ramachandran's protocol with 10% TiF_4 (61%–99%) and to Mecinović's one with 10% of $ZrCp_2Cl_2$ (44%–77%) [36, 46], by using a nontoxic and more handily catalyst. These positive results prompted us to test our catalytic protocol with a series of *N*-protected-*α*-amino acids, for which only few examples are reported in the literature [36, 40, 41, 46]. The best results were obtained with the *N*-Boc-Lysine(Cbz) with an isolated yield of 70% (compound **10**, Scheme 6), followed by *N*-Boc-Alanine and *N*-Boc-Valine (65% and 63%, respectively, **6** and **8**, Scheme 6). By contrast, when *N*-Boc-amino-*iso*butyric acid (Aib) was coupled to benzylamine, the amide **7** was obtained in 43% yield, suggesting that the steric hindrance of the amino acid side chain plays a relevant role in the interaction with the Ti center. Apparently, the good results obtained with amino acids (and in particular with *N*-Boc-Lys) claim for an active role of the amino group in directing the carboxylate towards the metal center. Indeed, the group of Kol and others showed that the coordination of amine ligands might lead to a tuning of the metal geometry, thereby changing its electronic and steric parameters [45, 49, 50]. In fact, substitution of *α*-amino-*iso*butyric acid with *iso*butyric acid, lead to product **12** in only 15% yield; similarly, when alanine was replaced by propionic acid, the corresponding amide **13** was isolated in trace amount (6% yield). These results support the idea that the *α*-amino group may interact with the titanium center, facilitating the substrate's approach to the Ti-catalyst. The high yield obtained with the highly sterically hindered indole-2-carboxylic acid (**11**, 75%), as well as the lower yield obtained with the phenyl acetic acid as carboxylate source (compound **14**, 42%) further corroborated our hypothesis of a possible positive



SCHEME 6 | Scope of the direct amidation reaction between benzylamine and different carboxylic acids.

effect deriving from a nitrogen atom in a close position to the carboxylic acid group. Although direct evidence for a specific N-Ti interaction in the transition state of Ti-catalyzed amidation is not yet reported, homoleptic early transition metal α-amino acid complex X-ray structures reveal the bidentate nature of α-amino acid coordination [51, 52]. On the other hand, when benzylamine was replaced with more sterically hindered substrates, such as the α-branched 1-phenylethylamine, no reaction was observed with *N*-Boc-glycine.

Finally, an attempt to build simple di- and tri- peptides with this protocol was performed. In this case, the solvent was changed from toluene to THF in order to achieve complete solubility of the peptides. Both catalyst **Ti1** and **Ti2** were tested for the formation of the dipeptide *N*-Boc-Gly-Gly-Bn (**16,** Scheme 7), with **Ti1** showing slightly higher performance over **Ti2** in the formation of *N*-Boc-Gly-Gly-Bn (65% vs 52%, see also Table S3). Moderate yields were also obtained in the coupling of *N*-Boc-Ala to deprotected compound **1** (NH_2-Gly-Bn) to form the dipeptide *N*-Boc-Ala-Gly-Bn, **17,** while, the tripeptide *N*-Boc-Gly-Gly-Gly-Bn **18** was obtained with an isolated yield of 13% (Table S3).

To assess whether the integrity of an α-stereocenter of the coupled amino acid was affected by this protocol, the optical rotation ($[\alpha]_D$) of compound **6** was measured, comparing the values obtained using our novel Ti catalyst, **Ti2**, and those produced with a traditional coupling reagent (HATU). In both cases, the optical rotation values were similar (−26.2 for the compound synthesized *via* direct amidation and −25.1 in the case of coupling with HATU) and closely aligned with those reported in the literature (−22.0 to −24.7, Table S4) [36, 53–56]. These results suggest that the Ti-catalyzed direct amidation does not induce epimerization of the α-stereocenter.

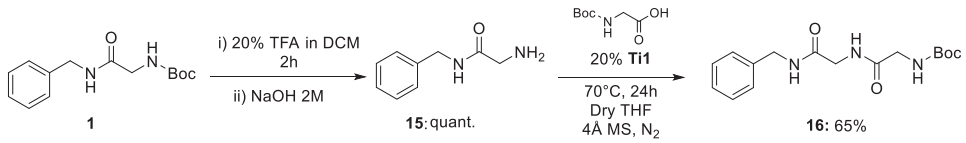
In agreement with the literature on group IV metal complexes as catalysts for direct amidation [57], a working hypothesis for the catalytic cycle for direct amidation using titanium complexes **Ti1** and **Ti2** is proposed and illustrated in Scheme 8. Briefly, one or more *iso*propoxide ligands on the *bis*[phenolate]-titanium catalyst undergo ligand exchange with an equivalent number of carboxylates (I) after an acid-base reaction, where the alkoxides are protonated due to their higher basicity. This exchange activates the carbonyl carbon through coordination, facilitating a nucleophilic attack by the nitrogen atom of the amine (II). A subsequent proton transfer (III) promotes the formation and release of the desired amide along with uncharacterized oxygenated titanium species. These species further participate in an acid-base reaction, producing water as a byproduct and regenerating the catalyst.

3 | Conclusion

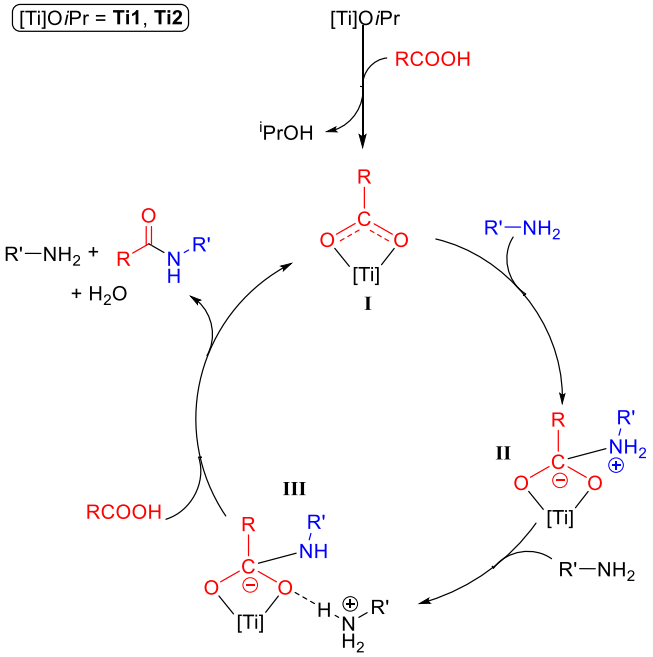
In conclusion, we investigated titanium(IV) *bis*-phenolates as catalysts for amide bond formation directly from a carboxylic acid and an amine with the final aim to find sustainable alternatives to the usual coupling agent methodologies, and overcome environmental, waste, and production costs issues of these conventional methods, mainly in peptide synthesis. For this reason, the complexes were obtained titanium *bis*(2,4-dimethylphenoxy)di*iso*propoxy (**Ti1**) and titanium *bis*(2,6-dimethylphenoxy)di*iso*propoxy (**Ti2**) reacting Ti(O*i*Pr)$_4$ with 2 equiv of 2,4-dimethylphenol and 2,6-dimethylphenol, respectively. Remarkably, **Ti2** gave almost quantitative yields at 5% loading when benzylamine was reacted with the *N*-Boc-glycine (entry 12, Table 1) in toluene at 70 °C in presence of molecular sieves, whereas **Ti1** required 10% of loading to provide over 90% of yield (entry 8, Table 1). Thus, both catalysts significantly improved the reaction outcome compared to the one catalyzed by Ti(O*i*Pr)$_4$, which required 20% catalyst loading to reach similar efficiencies. Interestingly, complete substitution of *iso*propoxides with phenolates in the herein synthesized **Ti3** catalyst dramatically reduced the activity, likely due to the higher stability of the resulting coordination complex.

Expanding the reaction scope by modifying the carboxylic acid counterpart and using 5% of **Ti2**, we demonstrated that aromatic and amino acids consistently yielded superior results compared to their aliphatic counterparts, likely due to N-Ti interactions (to underline the sensitiveness of the reaction to the studied key parameters in an intuitive, user-friendly manner, all the results are summarized in radar diagrams in Figure S4) [58]. Optical rotation measurements for compound **6** aligned with reported values, suggesting preservation of the stereochemical integrity at the α-amino stereocenter.

Furthermore, the catalytic system developed herein represents a significant step forward in sustainable amide bond formation, aligning with the core principles of green chemistry. By employing earth-abundant and low-toxicity titanium(IV) complexes, this methodology circumvents the need for hazardous and waste-intensive stoichiometric coupling agents. The process exhibits a high degree of atom economy, as it generates water as the sole byproduct, thereby substantially reducing the overall E-factor compared to traditional amidation protocols. Furthermore, this



SCHEME 7 | Synthetic route for the deprotection and elongation of compound (**1**) to build the di-peptide **16**.



SCHEME 8 | Proposed catalytic cycle for direct amidation using titanium complexes **Ti1** and **Ti2**.

approach addresses the environmental impact of solvents by moving away from hazardous media such as DMF or DCM.

Finally, catalyst **Ti1** was chosen to catalyze a simple peptide chain elongation for its better performance in THF, a required solvent for solubilizing peptides. The best result was obtained with the synthesis of the Bn-Gly-Gly-*N*-Boc dipeptide **16**, which was obtained in 65% yield. By contrast, the dipeptide Bn-Gly-Ala-*N*-Boc **17** and the tripeptide Bn-Gly-Gly-Gly-*N*-Boc **18** were obtained in lower yields, indicating a possible negative effect of the steric hindrance on the catalytic performance of the catalyst.

Overall, this study introduces a titanium-based protocol for direct amidation reaction based on non-toxic and economic phenolate-Ti catalysts that is applicable under milder conditions than previous Ti-based systems and/or with a significant reduction of the catalyst loading. While the method proved to be effective, further research is required to deepen the understanding of the catalytic mechanism, stereochemistry, and long-term stability. These findings pave the way for broader applications in peptide synthesis and other sensitive amide-containing molecules.

4 | Materials and Methods

NMR spectra were recorded with an AVANCE 400 Bruker spectrometer at 400 MHz for ^{1}H NMR. Chemical shifts are given as δ values in ppm relative to residual solvent peaks as the internal reference. *J* values are given in Hz. Commercially available reagents were used as purchased from Sigma-Aldrich, Fluorochem, and TCI without further purification. High-resolution masses were achieved with Thermo Fisher Scientific Orbitrap Exploris 120 equipped with UHPLC and a C18 column. Optical rotation was measured at 298 K by a Jasco P-2000 polarimeter in a 10 mL cuvette filled with a 1 mg/mL solution in $CHCl_3$ of the compounds. Elemental analysis was obtained with a Perkin-Elmer CHN Analyzer 2400 Series II.

4.1 | Synthesis of the Catalysts

Ti1: The synthesis was performed as reported in the literature [47]—2,4-dimethylphenol (2 equiv, 1.5 mmol) was dissolved in 2 mL of dry *n*-hexane under an inert atmosphere. Subsequently, titanium *iso*propoxide [Ti(O*i*Pr)$_4$] (1 equiv, 0.75 mmol) was added, leading to a color change from pale yellow to intense red. The reaction mixture was stirred overnight at room temperature. Afterward, the solvent and the isopropanol byproduct were thoroughly removed under reduced pressure, yielding a red oil in high yield (96%). This oil was then dissolved in 4 mL of dry toluene, producing the desired solution for subsequent catalytic reactions, and stored under an inert atmosphere to prevent hydrolysis. Elemental analysis: calculated for $C_{22}H_{32}O_4Ti$: C 64.71%, H 7.90%; found C 58.98%, H 6.99%.

Ti2: 2,6-Dimethylphenol (2 equiv, 1.5 mmol) was dissolved in 2 mL of dry diethyl ether under an inert atmosphere. Subsequently, titanium *iso*propoxide [Ti(O*i*Pr)$_4$] (1 equiv, 0.75 mmol) was added, leading to a color change from light yellow to orange. The reaction mixture was stirred overnight at room temperature. Afterward, the solvent and the isopropanol byproduct were thoroughly removed under reduced pressure, yielding an orange oil in almost quantitative yield (98%). This oil was then dissolved in 4 mL of dry toluene, producing the desired solution for subsequent catalytic reactions, and stored under an inert atmosphere to prevent hydrolysis. Elemental analysis: calculated for $C_{22}H_{32}O_4Ti$: C 64.71%, H 7.90%; found C 63.55%, H 7.78%.

Ti3: The synthesis was performed as reported in the literature [48]—2,6-dimethylphenol (4 equiv, 24 mmol) was dissolved in 40 mL of dry *n*-hexane under an inert atmosphere. Subsequently, titanium *iso*propoxide [Ti(O*i*Pr)$_4$] (1 equiv, 6.0 mmol) was added dropwise, leading to a yellow solution. The reaction mixture was stirred overnight at room temperature. Afterward, the solvent and the isopropanol byproduct were thoroughly removed under reduced pressure, yielding a red oil. Adding 5 mL of *n*-hexane and heating to 50 °C for 1 h led to the precipitation of the desired compound as a yellow solid. Yield: 85%. The solid was then stored under an inert atmosphere to prevent hydrolysis.

Elemental analysis: calculated for $C_{32}H_{36}O_4Ti$: C 72.18%, H 6.81%; found C 70.41%, H 6.88%.

4.2 | General N-Protection of Amino Acids

The amino acid (2 mmol) was suspended in 6.7 mL of a 1:1 dioxane/water mixture and cooled to 0 °C. To this suspension, di-*tert*-butyl dicarbonate (Boc_2O, 2.6 mmol) and triethylamine (6 mmol) were added. The mixture was then stirred at room temperature overnight. The pH of the mixture was subsequently adjusted to 3 by adding an aqueous solution of potassium bisulfate ($KHSO_4$). The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and then washed with brine. The organic phase was dried, and the solvent was removed under reduced pressure to yield the final product.

Boc-Alanine: Yield 99%. ^{1}H NMR (400 MHz, DMSO d_6) δ 12.36 (b, 1H), 7.07 (d, 1H), 3.92 (q, 1H), 1.38 (s, 9H), 1,21 (d, 3H).

Boc-Valine: Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, J = 9.0 Hz, 1H), 4.25 (dd, J = 9.3, 4.6 Hz, 1H), 2.21 (dd, J = 13.4, 6.8 Hz, 1H), 1.45 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H).

Boc-Leucine: Yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, J = 7.3 Hz, 1H), 4.33 (d, J = 3.7 Hz, 1H), 1.84-1.62 (m, 2H), 1.61-1.50 (m, 1H), 1.47 (s, 9H) 0.98 (d, J = 6.4 Hz, 6H).

4.3 | General N-Protection of Aminobenzoic Acids

The aminobenzoic acid (2 mmol) was suspended in 10 mL of a 1:1 dioxane/water mixture. To this suspension, di-*tert*-butyl dicarbonate (Boc_2O, 2.6 mmol) and triethylamine (6 mmol) were added. The mixture was then stirred at room temperature overnight. The pH of the mixture was subsequently adjusted to 5 by adding an aqueous solution of 3 M hydrochloric acid (HCl), leading to product precipitation. The solid was then filtered, washed with cold water, and dried.

Boc-4-aminobenzoic acid: Yield 83%. ^{1}H NMR (400 MHz, MeOD) δ 7.93 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 1.54 (s, 9H).

Boc-3-aminobenzoic acid: Yield 84%. ^{1}H NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.69 – 7.62 (m, 2H), 7.36 (t, J = 7.9 Hz, 1H), 1.54 (s, 9H).

4.4 | General Procedure for the Catalytic Tests

Molecular sieves (4 Å, 0.75 g per mmol of amine) were activated in a Schlenk flask through vacuum/nitrogen cycles heating at 250 °C. Subsequently, the carboxylic acid and 2 mL of solvent were added, and the solution was heated to 70 °C. The catalyst was introduced into the solution, which was then stirred for 15 min. Afterward, the amine was added, and the reaction was allowed to proceed at 70 °C for 24 h. The mixture was then filtered over a Celite pad and washed with ethyl acetate and methanol. The solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography using a dichloromethane/methanol mixture as the eluent to yield the final product.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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