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FULL PAPER

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Direct amidation of non-activated carboxylic acid and amine derivatives catalyzed by $TiCp_2Cl_2$

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This paper described a mild and efficient direct amidation of non-activated carboxylic acid and amine derivatives catalyzed by $TiCp_2Cl_2$. Arylacetic acid derivatives reacted with different amines to afford the corresponding amides in good to excellent yield except of aniline. Aryl formic acids failed to react with aniline but smoothly reacted with aliphatic amines and benzylamine in moderate to good yield, fatty acids reacting with benzyl and aliphatic amines give amides in good to excellent yield. Chiral amino acids derivatives were transformed into amides without racemization in moderate yield. The possible mechanism of direct amidation catalyzed by $TiCp_2Cl_2$ was discussed. This catalytic method is very suitable for the amidation of low sterically hindered arylacetic acid, fatty acids with different low sterically hindered amines except aniline, as well as the amidation of aryl formic acid with benzyl and aliphatic amines.

KEYWORDS

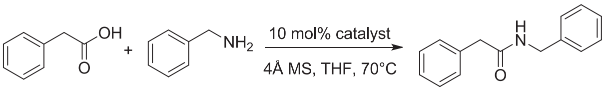
amine derivatives, chiral amino acids, direct amidation, non-activated carboxylic acid derivatives, without racemization

1 | INTRODUCTION

Amide bonds, which form proteins and polypeptides of the cornerstone of life, exist widely in natural and synthetic compounds such as drugs,[1–3] agrochemicals, biomacromolecules and food additives.[4–8] The high stability of amide bonds has led to their extensive applications in materials such as nylon and artificial silk.[9,10] Therefore, the formation of amide bonds is one of the most important reactions for organic synthesis. Although there are many different ways to obtain amides, most of them suffer from complicated purification process and poor atom economy. The formation of amides with high atom economy process was ranked as the most challenging task in organic chemistry by the ACS Green Chemistry Institute.[11] Catalytic direct amidation of carboxylic acid and amine is highly attractive as it would lead to cost-effective and atom economy processes with water as the only by-product.

In the past 10 years, catalytic direct amidations by organo-boron derivatives have emerged.[12–29] However, the acquisition of organo-boron compounds often requires long reaction steps, harsh reaction conditions and tedious purification.[12,14,15,17,19,21–28] Direct amidation catalyzed by Group IV metal or early transition metal complexes have received increasing attention in recent years. In 2015, Adolfsson *et al*. reported the direct amidation of acids and amines at room temperature with good to excellent yields by using expensive $HfCp_2Cl_2$ as catalyst.[30] In 2012, Adolfsson *et al*. reported the direct amidation by using 2–10 mol% moisture sensitive $ZrCl_4$ with good yields and elucidated the possible mechanism in 2017.[31,32] These methods are novel, however, zirconium and hafnium are both rare metals and coexist in nature, which result in difficulties in separation. Their high cost and sensitivity to humidity and air limited their application in large scale. Using titanium compounds as amidation catalyst is more attractive since it is cheap and abundant in nature. Nordahl and Carlson[33] reported the direct amidation of benzoic acid with different amines in toluene with reflux by using a catalytic amount of $TiCl_4$ (30 mol%). In the same year, Mader and Helquist[34] reported that 50 mol% of Ti $(Oi\text{-}Pr)_4$ can mediate lactamisations of amino acids in 1,2-dichloroethane at reflux with good yields. Adolfsson *et al.* reported that catalytic direct amidation of non-activated carboxylic acids with amines in good yield by using 10 mol% of Ti $(Oi\text{-}Pr)_4$ as catalyst.[35] However, these titanium salts or complex are sensitive to moisture or air (smoke under the air) and hard to handle in lab or industry. Developing stable Ti complex as direct amidation's catalyst becomes critical and meaningful. As our program to develop amidation catalysts continues,[36] here we present a more stable catalyst-$TiCp_2Cl_2$ which can efficiently carry out direct amidation of non-active carboxylic acids and amines. To the best of our knowledge, this is the first report of using $TiCp_2Cl_2$ as catalyst for direct amidation.

2 | RESULTS AND DISCUSSION



Phenylacetic acid and benzylamine were selected as model compounds to investigate the performance of the different catalysts including Ti $(Oi\text{-}Pr)_4$, $TiCl_4$ and $TiCp_2Cl_2$. To verify the role of these catalysts, control experiment was performed in the absence of the catalysts. Adolfsson's Ti $(Oi\text{-}Pr)_4$ catalyzed direct amidation protocol[35] was used to investigate the performance of the different catalysts. The reaction was monitored by Gas Chromatography-Mass Spectrometer (GC–MS). As showed in Figure 1, only one by-product peak was found in the reaction catalyzed by $TiCl_4$, whereas three by-products peaks, two of which was identified as 1,3-diphenylpropan-2-one, N-benzylidene-1-phenylmethan amine and one unknown product were found in the reaction catalyzed by Ti $(Oi\text{-}Pr)_4$. The structures of the by-products were identified by matching mass spectrometry libraries and confirmed by comparing their retention time and mass spectral data with those of standards under the same GC–MS experimental conditions. Interestingly, almost no any by-product peak was observed in the reaction of amidation catalyzed by $TiCp_2Cl_2$. The yield of the target amide was showed in Figure 2. The target product can be obtained in 11% yield without catalyst which is similar to the result reported by Adolfsson *et al.*[35] When $TiCl_4$ was used as catalyst, the isolated yield of the amide was 84%, the competition reaction is the condensation of the phenylacetic acid affording 1,3-diphenylpropan-2-on. The isolated yield of the amidation reaction catalyzed by $TiCp_2Cl_2$ was up to 96% which is higher than the reaction catalyzed by Ti $(Oi\text{-}Pr)_4$ (81% yield) and $TiCl_4$. The results show that titanium salt or complex can truly catalyze the formation of amide bond and $TiCp_2Cl_2$ is the best among the three catalysts.

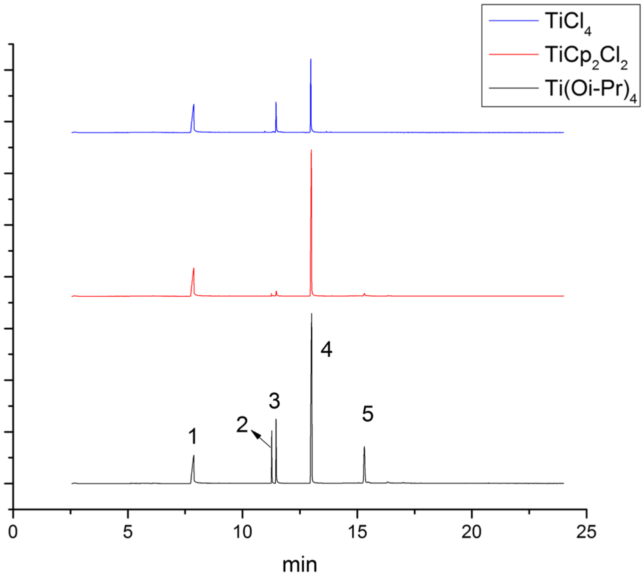


FIGURE 1 The GC of amide reaction catalyzed by $TiCl_4$, Ti $(Oi\text{-}Pr)_4$ and $TiCp_2Cl_2$

Peak 1: phenylacetic acid. Peak 2: N-benzylidene-1-phenyl-methanamine. Peak 3: 1,3-diphenylpropan-2-one. Peak 4: target

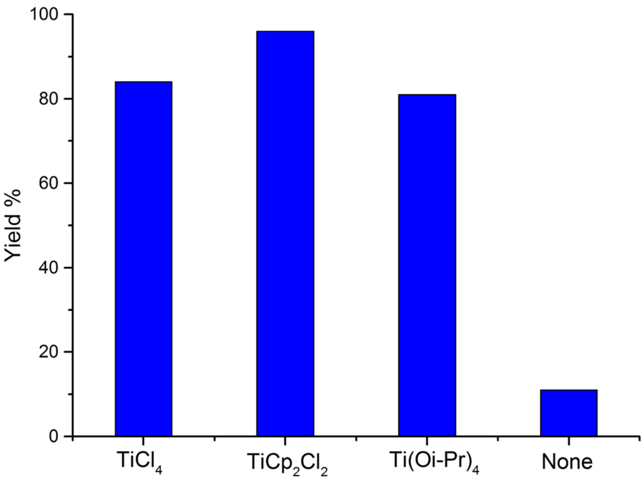


FIGURE 2 The yield of amidation of phenylacetic acid with benzylamine catalyzed by Ti complex

amide. Peak 5: unknown by-product. Reaction condition: phenylacetic acid (1.2 mmol), benzyl-amine (1.0 mmol), cat. (10 mol%), solvent (10 mL), 0.75 g 4 Å MS.

In our catalytic amidation procedure, the reactants, molecule sieves, catalyst and solvent together under Ar were mixed in a sealed tube and heated for 24, 36 or 48 hr. This procedure is simpler than that reported by Adolfsson using Ti (Oi-Pr)$_4$ as catalyst.[35]

Table 1 showed the amidation yield by TiCp$_2$Cl$_2$ in different solvents such as DCM, THF, toluene, 1,4-dioxane, MeCN and DMSO. In DCM under 40 °C, the yield was 50% for 36 hours and 60% for 48 hr (Table 1, entry 1 and 2). When the temperature was increased to 70 °C, the yield increased to 95% and 94% for 24 hr (Table 1, entry 3 and 4). However, when toluene, 1,4-dioxane, MeCN was used as the solvent, the yield decreased (88%, 89% and 63%, respectively, Table 1, entry 7, 8, 9), especially DMSO, the yield decreased dramatically (32%, Table 1, entry 10). The best yield by TiCp$_2$Cl$_2$ was obtained in THF at 24 hours in 96% with a slight excess of the amine (Table 1, entry 5). Furthermore, the reaction was rather insensitive to the stoichiometry of reactants because equally good results were obtained by using either a slight excess of the acid or of the amine and the use of an excess of the amine was beneficial due to the yield of product (Table 1, entries 3–4, 5–6) and the excess of the acid may lead to the formation of a small amount of by-product 1,3-diphenylpropan-2-one, which increases the difficulty of product purification.

TABLE 1 The effects of different solvents on the direct amidation of phenylacetic acid with benzylamine catalyzed by TiCp$_2$Cl$_2$

Entry	Solvent[a]	Time	Temp. (°C)[a]	Yield (%)[b]
1	DCM[a]	36	40	50
2	DCM[a]	48	40	60
3	DCM[a]	24	70	95
4	DCM[c]	24	70	94
5	THF[a]	24	70	96
6	THF[c]	24	70	94
7	Toluene[a]	24	70	88
8	1,4-dioxane[a]	24	70	89
9	MeCN[a]	24	70	63
10	DMSO[a]	24	70	32

[a] Reaction condition: phenylacetic acid (2 mmol), benzylamine (2.4 mmol), cat. (10 mol%), solvent (20 mL), 1.5 g 4 Å MS.

[b] Isolated yields.

[c] Phenylacetic acid (2.4 mmol), benzylamine (2.0 mmol), cat. (10 mol%), solvent (20 mL), 1.5 g 4 Å MS.

The catalyst loading was evaluated by using phenylacetic acid and benzylamine as substrates. When the amount of catalyst was 10 mol%, the yield of amidation was 96% (Table 2, entry 2). Reducing the catalyst loading to 5 mol%, the isolated yield was significantly reduced to 58% (Table 2, entry 1), increasing the catalyst loading to 20 mol%, the yield is 95% (Table 2, entry 3). The results showed that 10 mol% catalysts loading are enough for the direct amidation.

The results also revealed that water played an important role in the process of catalytic direct amidation, as showed in Figure 3, the isolated yield of amide was strictly dependent on the amounts of 4 Å powdered molecular sieves when all other parameters are equal. When the amount of molecular sieve was increased to 0.75 g/mmol substrate, the best yield of amide was obtained; an increase in the amount of 4 Å powdered molecular sieves resulted in the lower product yield. This finding indicated the dual role of water in the reaction which was first proposed by Adolfsson.[19,30]

As shown Table 3, Table 4 and Table 5, different non-activated carboxylic acids including aryl acetic acid, aryl formic acid, fatty acid and amine derivatives were used to

TABLE 2 Effect of the amount of catalyst on the reaction

Entry	TiCp$_2$Cl$_2$ (mol%)	Yield (%)
1	5	58
2	10	96
3	20	95

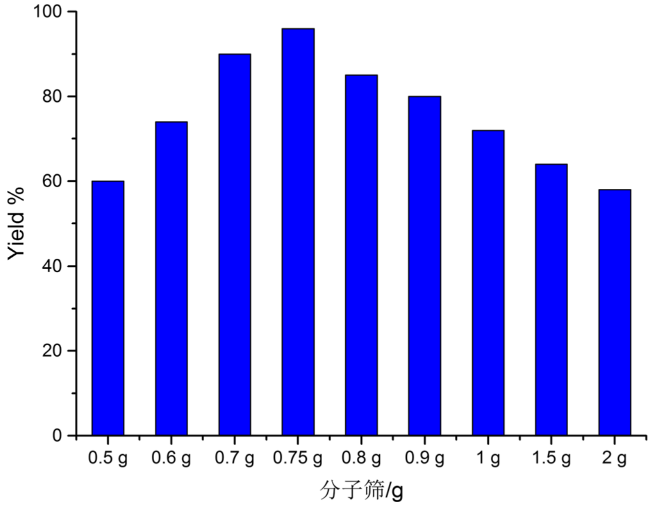
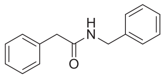
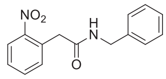
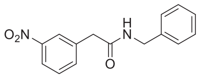


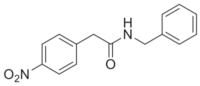
FIGURE 3 Effect of the amount of molecular sieve in the reaction mixture on the amide yield

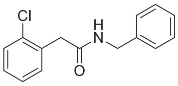
TABLE 3 Synthesis of amide derivatives from different substituents of phenylacetic acids and amines using TiCp$_2$Cl$_2$ as catalyst

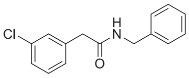

3aa, 96%[a]

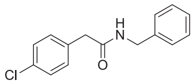

3ab, 27%[a]


3ac, 57%[a]


3ad, 74%[a]


3ae, 37%[a]


3af, 77%[a]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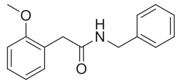
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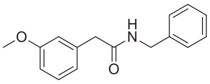
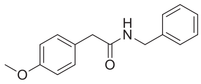

3ai, 71%[a]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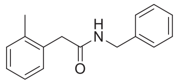
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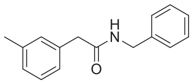
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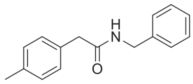
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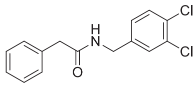
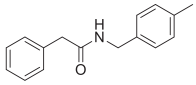
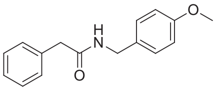

3an, 95%[a]


3ao, 80%[a]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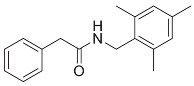
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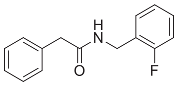
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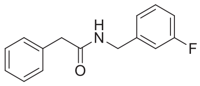
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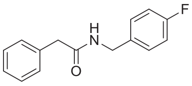
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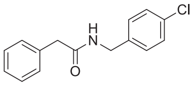
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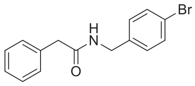
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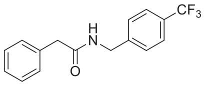
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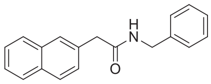
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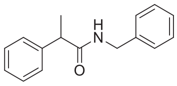
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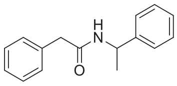
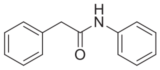
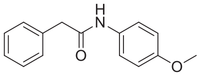
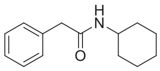

3az, 28%[a]


3ba, nd%[a], trace[c]


3bb, 10%[a], 50%[b]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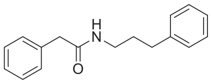
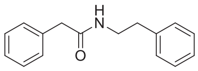
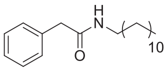
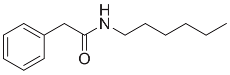
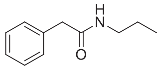
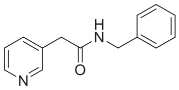

3bd, 31%[a], 92%[b]

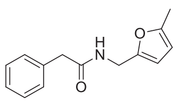

3be, 41%[a], 96%[b]


3bf, 26%[a], 87%[b]


3bg, 46%[a], 85%[b]


3bh, 52%[a], 89%[b]


3bi, 71%[a]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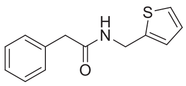
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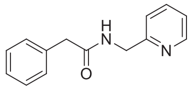
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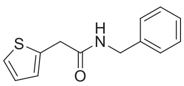
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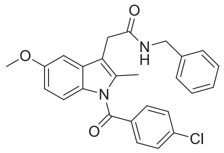
3bn, 85%[a]

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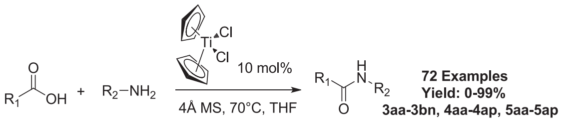
[a] Reaction condition: acid (1 mmol), amine (1.2 mmol), cat. (10 mol%), 075 g 4 Å MS, dry THF (10 mL), at 70 °C in a sealed tube under Ar, 24 hr.

[b] cat. (20 mol%), acid (1 mmol), amine (2.0 mmol), 80 °C, 36 hr.

[c] cat. (20 mol%), 80 °C, 48 hr, determined by GC–MS.

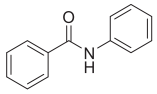
investigate the efficiency of the $TiCp_2Cl_2$-catalyzed direct amidation.

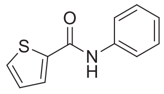


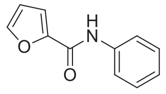
According to the results in Table 3, the substitute groups on the aromatic ring of the phenylacetic acid derivatives played crucial roles for the direct amidation with benzylamine. The yield was affected by the steric and electronic effect of the substitute groups on the aromatic ring and the steric effect was more important. With the same substitute on the different positions of the aromatic ring, the order of the amidation yield was para>meta>ortho (Table 3, **3ab-3ad**, **3ae-3ag**, **3ah-3aj**, **3ak-3am**). The ortho substitution has strong steric bulk effect, resulting in significantly decreased yield (Table 3, **3ab**, **3ae**, **3ah**, **3ak**). The amidation yield of the acid substrate with electron-donating group (s) on the aromatic ring is generally higher than that of the substrate with electron-withdrawing group (s) (Table 3, **3aa-3 am**). The substitute groups on the aromatic ring of the benzyl amine derivatives affected the amidation yield and the electron-withdrawing group on the aromatic rings was favorable for the reaction (Table 3, **3an-3aw**). The reaction of sterically hindered 1-phenylethanamine with phenylacetic acid afforded the amide in 28% yield (Table 3, **3az**). The amidation reaction of heteroaryl methylamine or heteroaryl acetic acid derivatives carried out smoothly and the corresponding amides were obtained in good yield (Table 3, **3bi-3bm**). The reaction of more complex anti-inflammatory drug indomethacin with benzylamine produced the corresponding amide successfully in the yield of 85% (Table 3, **3bn**). 1-Naphthaleneacetic acid reacted with benzylamine to afford the amide in 70% yield (Table 3, **3ax**). The reaction of phenylacetic acid with aliphatic amines required 20 mol% catalyst loading, two equivalent amine and longer reaction time in order to reach good yields (Table 3, **3bd-3bh**). Aniline (weak basicity) failed to react with phenylacetic acid but p-methoxyaniline afforded the amide in 10% yield (Table 3, **3ba-3bb**), however, the yield of **3bb** was increased to 50% and the yield of **3ba** was trace under the optimized reaction condition.

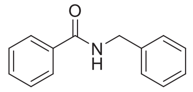
Under $TiCp_2Cl_2$-catalyzed direct amidation condition, examining the aryl formic acid's reactivity is similarly intriguing. Benzoic acid, 2-furancarboxylic acid and 2-thiophenecarboxylic acid failed to react with aniline even using 20 mol% $TiCp_2Cl_2$ (Table 4, **4aa-4ac**). The reaction of benzoic acid with aliphatic amines and benzyl amine derivatives required 20 mol% catalyst loading, two

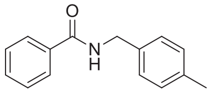
TABLE 4 Synthesis of amide derivatives from aryl formic acids and amines using $TiCp_2Cl_2$ as catalyst

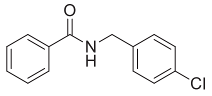

4aa, nd[a], nd[b]

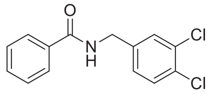

4ab, nd[a], nd[b]

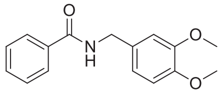

4ac, nd[a], nd[b]

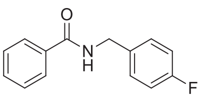

4ad, 43%[a], 83%[b]

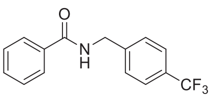

4ae, 23%[a], 85%[b]

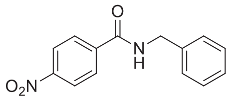

4af, 22%[a], 87%[b]

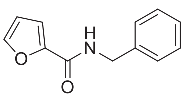

4ag, 35%[a], 93%[b]

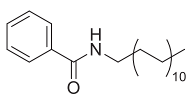

4ah, 37%[a], 90%[b]

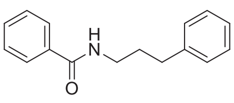

4ai, 14%[a], 87%[b]

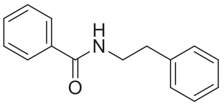

4aj, 22%[a], 88%[b]

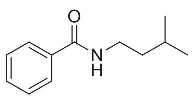

4ak, 55%[a]


4al, 45%[a]


4am, 3%[c], 74%[b]


4an, 5%[c], 71%[b]


4ao, 2%[c], 68%[b]


4ap, 77%[b]

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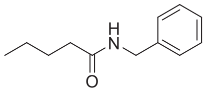
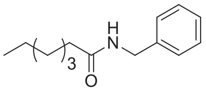
[a] Reaction condition:acid (1 mmol), amine (1.2 mmol), cat. (10 mol%), 075 g 4 Å MS, dry THF (10 mL), at 70 °C in a sealed tube under Ar, 24 hr.

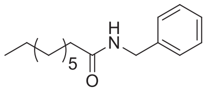
[b] cat. (20 mol%), acid (1 mmol), amine (2 mmol), 80 °C, 36 hr.

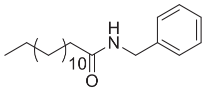
[c] acid (1 mmol), amine (1.2 mmol), cat. (10 mol%), yield was determined by GC–MS.

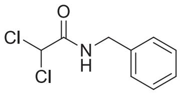
TABLE 5 Synthesis of amide derivatives from fatty acids and amino acids with amines using $TiCp_2Cl_2$ as catalyst

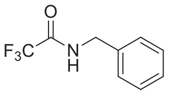

5aa, 62%[a]

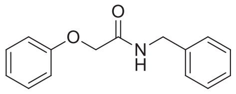

5ab, 65%[a]

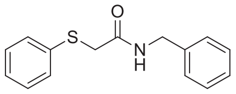

5ac, 71%[a]

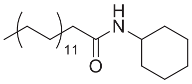

5ad, 82%[a]

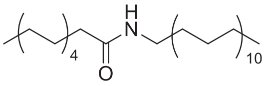

5ae, >99%[b]

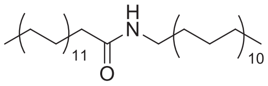

5af, >99%[b]

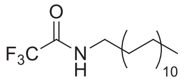

5ag, >99%[a]

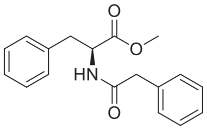

5ah, 92%[a]

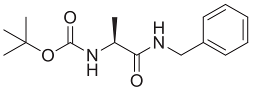

5ai, 30%[a], 81%[c]

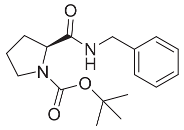

5aj, 23%[a], 90%[c]

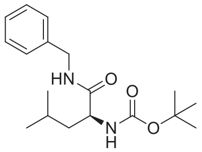

5ak, 35%[a], 95%[c]


5al, >99%[b]


5am, 54%[a]


5an, 56%[a]


5ao, 60%[a]


5ap, 51%[a]

[a] Reaction condition: acid (1 mmol), amine (1.2 mmol), cat. (10 mol%), 075 g 4 Å MS, dry THF (10 mL), at 70 °C in a sealed tube under Ar, 24 hr.

[b] 8 h.

[c] cat. (20 mol%), acid (1 mmol), amine (2 mmol), 80 °C, 36 hr.

equivalent amine and longer reaction time to reach good yields and benzylamine derivatives afforded the amides in higher yield (Table 4, **4ad-4ap**). 4-nitrobenzoic acid with strong electron-withdrawing nitro group reacted with benzylamine to afford the corresponding amide in 55% yield (Table 4, **4ak**), 2-furancarboxylic acid reacted with benzylamine in 45% yield (Table 4, **4al**). The results indicated that benzylamine derivatives possess higher reactivity to aryl formic acids and this enhanced reactivity of benzylamine- "benzylic effect" have been also observed by Andrew Whiting[37] and André Loupy[38] in the uncatalyzed direct amide formation reaction.

When fatty acids with different chain lengths and benzylamine were used as substrates, the amidation yield was moderate to good. Moreover, the yield of amidation increased with the increasement of the length of carbon chains (Table 5, **5aa-5ad**, 62–82%). When the acid is dichloroacetic acid or trifluoroacetic acid with strong acidity, the yield was over 99% in 8 hours (Table 5, **5ae-5af**). Fatty acids reacted with aliphatic amines to afford the corresponding amides in 81–95% yield by using 20 mol% catalyst and two equivalent amine (Table 5, **5ai-5ak**). However, trifluoroacetic acid reacted with dodecylamine to afford the amide in excellent yield with 10 mol% catalyst loading and 1.2 equivalent amine (Table 5, **5al**, >99%). Ether and thioether groups on the α position of acetic acid were unaffected by the amidation reaction and very favorable for the amidation yields (Table 5, **5ag** >99%, **5ah** 92%).

When the chiral starting materials such as L-phenylalanine methyl ester, Boc-L-alanine, Boc-L-proline and Boc-L-leucine were used as the substrate, the target amides were obtained in the yield of 54%, 56%, 60% and 51%, without racemization (Table 5, **5am-5aq**). By using **5 am** as the example, the enantiomeric excess of the target amide was determined by comparison of chiral HPLC of target amide with the racemic amide compound (Figure 4, (a) and (b), **5 am**).

In 2011, Whiting *et al.* proposed the possible mechanism of uncatalyzed direct amidation through hydrogen-bonded dimeric carboxylic acid,[37] in 2017, Adolfsson *et al.* elucidated the mechanism of zirconium-catalyzed direct amidation through a dinuclear zirconium species.[32] The normal Lewis acid mechanism of Ti $(OBu)_4$-catalyzed esterification of acid and alcohol was proposed by Bonora *et al.* in 1985.[39] As showed in Figure 5, when the phenylacetic acid was

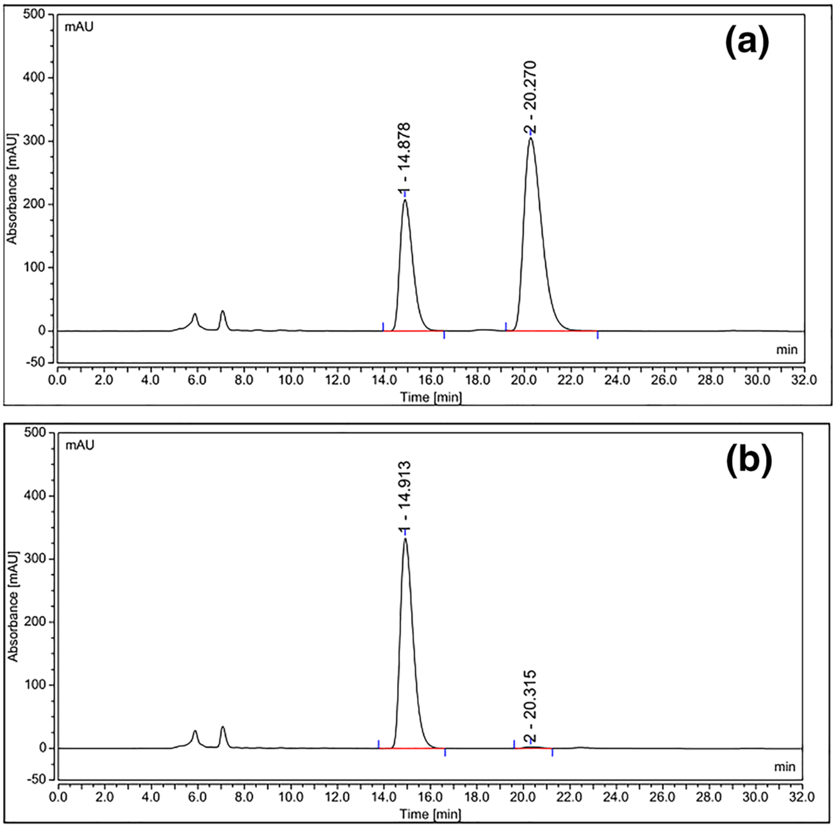
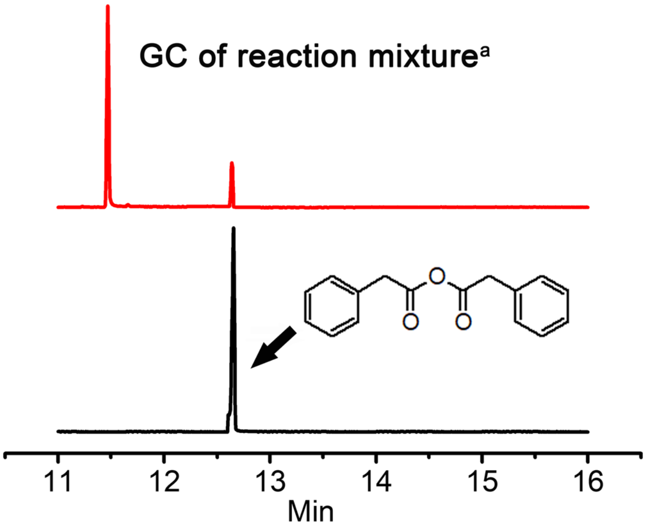


FIGURE 4 Chiral HPLC of compound **5 am** (b) and racemic compound **5 am** (a)

heated in THF under 70 °C in the presence of 10 mol% catalyst and 4 Å molecule sieves to afford a small amount of the anhydride of phenylacetic acid after 10 hr. The result suggested that the $TiCp_2Cl_2$-catalyzed direct amidation is possibly through anhydride intermediate (thermal amidation) and Lewis acid-catalyzed mechanism simultaneously. The titanium atom in the complex easily coordinated with oxygen atom and the crystal structure of the adduct of titanium complex and ester formed from ethyl lactate and acrylic acid has been solved.[40] The possible mechanism of amidation catalyzed by $TiCp_2Cl_2$ was proposed based on the results mentioned above, in our Lewis acid-catalyzed reaction, the acid reacts with catalyst $TiCp_2Cl_2$ to afford the six member ring intermediate,[39,40] then the carbon of carbonyl group of the acid becomes electropositive enough in the intermediate for subsequent attack by the amine to afford the target amide and water (Figure 6).



Reaction condition: phenylacetic acid (1 mmol), cat. (10 mol%), 0.75 g 4Å MS, dry THF (10 mL), at 70 °C in a sealed tube under Ar, 10 hr.

FIGURE 5 The GC of reaction of phenylacetic acid catalyzed by $TiCp_2Cl_2$ and of phenylacetic acid anhydride

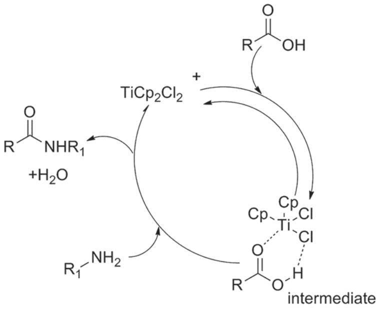


FIGURE 6 The possible mechanism of the direct amidation catalyzed by $TiCp_2Cl_2$

3 | EXPERIMENTAL

Flame-dried 4 Å MS (0.75 g), acid derivative (1 mmol), amine derivative (1.2 mmol), $TiCp_2Cl_2$ (10 mol% of the acid) and dry THF (10 mL) was placed in an oven-dried vial equipped with a stirring bar and sealed with a crimp-on cap. The atmosphere was exchanged for Ar. The resulting mixture was stirred at 70 °C for 24 hr, after that, the mixture was cooled to room temperature, filtered, the filter cake was washed with dichloromethane (3 × 5 mL), the filtrate was combined and evaporated to dryness, the residue was purified by flash column to gain the pure amide.

The characterization data of amides as well as the ^1H, ^{13}CNMR and mass spectrum are given in the supporting information.

4 | CONCLUSION

Due to its mild and environmentally friendly features, catalytic direct amidation using cheap, eco-friendly and stable catalyst is of great interest in the industry and lab scale synthesis of amide. The method presented herein is the first report of $TiCp_2Cl_2$-catalyzed protocol for the direct amidation of non-activated carboxylic acid derivatives with amines. The method afforded amides in moderate to excellent yields depending on the type of substrate acids and amines, and the enantiomeric purity of the asymmetric starting materials was retained. The reaction yield was significantly affected by the steric and electronic nature of the phenylacetic acid substrates, types of the acids and amines as well as the amount of 4 Å molecular sieves. The reaction conditions tolerate a significant number of structurally different acid substrates including heteroaromatic, aliphatic, α-halogenerate and α-substituted carboxylic acids, as well as aminoacids. The possible mechanism of the catalytic direct amidation by $TiCp_2Cl_2$ is possibly through simultaneous thermal amidation and Lewis acid-catalysis.

NOTES

The authors declare no competing financial interest.

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SUPPORTING INFORMATION AVAILABLE

Experimental procedures, compound characterization data and original NMR and HRMS spectrum.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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