Titanium(IV) Isopropoxide as an Efficient Catalyst for Direct Amidation of Nonactivated Carboxylic Acids

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Abstract: Secondary and tertiary amides are formed in high yields, in an efficient and environmentally benign titanium(IV) isopropoxide catalyzed direct amidation of carboxylic acids with primary and secondary amines.

Key words: amides, titanium, catalysis, carboxylic acids, amines

The amide bond is a common functional group in both natural and synthetic compounds. Approximately 25% of all pharmaceuticals available on the global market are estimated to contain at least one amide bond,¹ and environmentally benign and inexpensive methods for amide-bond synthesis are highly valuable. Amides can be synthesized from the corresponding ammonium salts at high temperatures.² Substrates with stereocenters or sensitive functional groups are, however, likely to racemize or decompose under harsh thermal conditions, and a multitude of different coupling reagents utilizing milder reaction conditions have been developed for the formation of amides.³ All coupling-reagent methods are based on activation of the carboxylic acid using stoichiometric amounts of reagents, which leads to a poor atom economy for the processes. The extensive use of coupling reagents on industrial scale, resulting in stoichiometric amounts of waste, is one of the reasons to why the formation of amides without poor atom-economy reagents, was ranked as the most challenging task in organic chemistry by the American Chemical Society Green Chemistry Institute.⁴ A limited number of catalytic protocols for direct amidation of nonactivated carboxylic acids and amines have been reported. Various boron-based catalysts have been shown to allow for milder reaction conditions and, in general, most secondary and certain tertiary amides can be prepared in good to excellent yields. However, partial racemization of enantiomerically pure starting materials is a general drawback with these catalysts.⁵ There are also reports on enzymatic protocols with a limited substrate scope⁶ and a few reported protocols on metal catalysis at high reaction temperatures,^{7,8} where the thermal background reaction can be expected to be significant. We have recently demonstrated that zirconium(IV) chloride is an efficient catalyst for the direct amidation of nonactivated carboxylic acids with both primary and secondary amines.⁹ The operationally simple reactions resulted in excellent yields of a range of

SYNLETT 2012, 23, 2201–2204 Advanced online publication: 17.08.2012 DOI: 10.1055/s-0032-1316993; Art ID: ST-2012-B0452-L © Georg Thieme Verlag Stuttgart · New York amides without any racemization of chiral starting materials at 70 °C in THF in the presence of molecular sieves as a water scavenger. During the same time and in parallel to our work, Williams and co-workers also reported that ZrCl₄ along with ZrCp₂Cl₂ were efficient catalysts for the direct amidation between carboxylic acids and primary and secondary amines, at 110 °C in toluene.⁸ The group of Yamamoto has previously reported that group IV metal complexes can be used as catalysts for catalytic esterification of carboxylic acids with alcohols.^{5j,10}

In our previous study on direct amidation of carboxylic acids with primary and secondary amines, we found that zirconium tetrachloride efficiently catalyzed the transformation. We became interested to see if this was a general feature of early transition-metal complexes and decided to evaluate a series of metal chlorides and alkoxides as catalysts for the formation of *N*-benzyl phenylacetamide (**3a**, Scheme 1 and Table 1), under the reaction conditions and workup methods we have reported earlier.⁹

Scheme 1 Direct catalytic amide formation of nonactivated carboxylic acids

Interestingly, it was found that several of the examined Lewis acids were active catalysts, with seven complexes giving rise to isolated yields around 90% (Table 1, entries 2–8). Titanium tetrachloride displayed lower activity (Table 1, entry 1), and $Y(Oi-Pr)_3$ (Table 1, entry 9) did not show any activity at all. In the latter case, the yield is in the same range as the thermal background reaction (Table 1, entry 11). The use of the vanadium complex VO(OEt)₃ resulted in low conversion and a mixture of products (Table 1, entry 10).

The possibility of using several different Lewis acid catalysts in this user-friendly amidation protocol, where the reaction mixture is simply filtered through a pad of silica to yield analytically pure amides in most cases, makes this amidation methodology highly attractive and practical. Since titanium isopropoxide is an inexpensive and widely used chemical compound found in most research laboratories, we decided to further evaluate this complex as a catalyst for the direct amide formation. The amidation reaction was found to proceed smoothly in several solvents at a concentration of 0.4 M, and worked best under an

 Table 1
 Lewis Acid Catalyst Screen for the Direct Amidation of Phenyl Acetic Acid with Benzylamine^a

Entry	Catalyst	Isolated yield (%)
1	TiCl ₄	68
2	Ti(O <i>i</i> -Pr) ₄	91
3	Ti(OBu) ₄	89
4	$ZrCl_4$	>99
5	Zr(OEt) ₄	93
6	Zr(Ot-Bu) ₄	93
7	Hf(Ot-Bu) ₄	89
8	Nb(OEt) ₅	88
9	Y(Oi-Pr) ₃	13 ^b
10	VO(OEt) ₃	21 ^{b,c}
11	_	10

^a Reaction conditions: phenylacetic acid (1.2 mmol), benzylamine (1 mmol), catalyst (10 mol%), and activated 4 Å MS (0.5 g) in dry THF (amine concentration 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere. Reaction time 24 h.

^b NMR yield.
^c Mixture of products.

· Mixture of products.

inert atmosphere (Table 2, entry 2 vs. 3). No significant difference in yield was seen when the amidation was performed in a sealed tube or under regular reflux conditions in a round-bottomed flask equipped with condenser (Table 2, entries 1 and 2, respectively) under nitrogen atmosphere. Furthermore, it was found that the reaction

Table 2 Solvent Screening^a

Entry	Solvent	Isolated yield (%)
1	THF	91
2 ^b	THF	90
3 ^{b,c}	THF	67
4 ^d	THF	91
5	MeCN	75
6	toluene	89
7	DMSO	68
8	CH_2Cl_2	93
9	DMF	63
10	1,4-dioxane	86

^a Reaction conditions: phenylacetic acid (1.2 mmol), benzylamine (1 mmol), Ti(O*i*-Pr)₄ (10 mol%), and 4 Å MS (0.5 g), in dry solvent (amine concentration 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere.

^b Reflux conditions in round-bottomed flask with condenser.

^c Regular atmosphere.

^d Phenylacetic acid (20 mmol), benzylamine (24 mmol), Ti(Oi-Pr)₄

(10 mol%) and 4 Å MS (5 g) in dry THF (amine concentration 1.6 M) at 70 $^\circ C$ in a sealed tube under N_2 atmosphere.

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could be scaled up to 20 mmol at a concentration of 1.6 M with respect to the amine without any decrease in yield (Table 2, entry 4).

The relatively nontoxic solvent THF was chosen as reaction medium for a substrate screening (Table 3). As can be seen in Table 3, secondary and tertiary amides with different functional groups were formed in good to excellent yields with catalytic amounts of Ti(Oi-Pr)₄. The enantiomerical excess of the chiral starting materials was fully retained in the formed amides 3r, 3s, and 3t (Table 3, entries 18-20), as determined by chiral HPLC. However, the more labile stereocenter in ibuprofen, situated in both α position and benzylic position, underwent partial racemization, and the resulting amide **3q** was found to have an enantiomeric excess of 83% (Table 3, entry 17). The formation of tertiary amides required a higher reaction temperature (100 °C), and a catalyst loading of 20 mol%. Under these conditions, compounds 3aa-ac were isolated in good yields (Table 3, entries 27–29). Unfortunately, even at these conditions, the bulky N_N-dihexylamine as well as aniline turned out to be problematic substrates when reacted with phenylacetic acid, resulting in 20% of amide product and trace amounts, respectively. Benzoic acid as well as the sterically hindered Boc-protected amino acids required 20 mol% catalyst loading and 1.5 equivalents of acid in order to reach good yields (Table 3, entries 9, 18, and 19). Cyclohexanecarboxylic acid, adamantanecarboxylic acid, and cinnamic acid were all run at 100 °C to generate good to moderate yields (Table 3, entries 11–13). The thermal background reaction in the amidation reactions depends strongly on the nature of the substrates, the choice of solvent and, most importantly, the reaction temperature. This observation was also reported by Williams and co-workers, who described that substantial thermal background reactions occur for a large number of substrates at temperatures of 110 °C and above.¹⁰ To determine the extent of thermal amidation occurring for amide 3a under the reaction conditions presented in this study, a control experiment was performed, resulting in a 10% yield (Table 1, entry 11). This result can be compared to 69% yield of the same amide, formed under thermal conditions, as reported by Grosjean et al. for the same substrate,¹¹ indicating that the high yields of amides in Table 3 at 70 °C is the result of true catalysis.¹²

 Table 3
 Substrate Screening^a



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Table 3	Substrate Screening ^a	(continued)
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 Table 3
 Substrate Screening^a (continued)

Entry	Amide	Number	Isolated yield (%) ^a
3	Br O N Ph	3c	85
4	Ph ^O N Ph	3d	99
5	O H H Ph	3e	99
6	Ph ^S N Ph	3f	94
7	S O N Ph	3g	88
8	O H H Ph	3h	72
9	Ph N Ph	3i	82°
10	N H Ph	3ј	81
11	N H H H	3k	80 ^e
12	H Ph	31	65°
13	Ph N Ph	3m	61 ^e
14		3n	75
15	F ₃ C N Ph	30	92
16	Boc ^N N H H H	3р	93
17	O N H Ph	3q	80 ^f

Entry	Amide	Number	Isolated yield (%) ^a
18 ^b	O N H Boc	3r	78°
19 ^b	O HN Boc	3s	78°
20 ^b	Ph N Ph	3t	81
21	Ph N S	3u	97
22	Ph N O H	3v	96
23	Ph N O	3w	91
24	PhN	3x	88
25	Ph N O	3у	71
26	PhN10	3z	79
27	Ph N O	3aa	74 ^d
28	Ph	3ab	69 ^d
29	PhNO	3ac	76 ^d

^a Reaction conditions: carboxylic acid (1.2 mmol), benzyl amine (1 mmol), Ti(O*i*-Pr)₄ (10 mol%), and 4 Å MS (0.5 g), in dry THF (substrate concentrations 0.4 M) at 70 °C in a sealed tube under N_2 atmosphere.

^b No racemization was detected with chiral HPLC (AD column).

^c Carboxylic acid (1.5 mmol) and Ti(O*i*-Pr)₄ (20 mol%).

^d Carboxylic acid (1.5 mmol) and Ti(O*i*-Pr)₄ (20 mol%) at 100 °C. ^e Reaction temperature 100 °C.

^f Carboxylic acid ($c \ 0.2 \ M$) and Ti(O*i*-Pr)₄ (20 mol%). Product ee (83%) was determined with chiral HPLC (IA column).

To conclude, we have demonstrated that several early transition-metal complexes are efficient catalysts for the direct amidation of nonactivated carboxylic acids with amines. Secondary and tertiary amides were readily formed in good to excellent yields with a general and operationally simple protocol using the easily handled and inexpensive titanium(IV) isopropoxide as catalyst.

General Catalytic Amidation Procedure

Phenylacetic acid (163 mg, 1.2 mmol) and flame-dried 4 Å MS (500 mg) was placed in an oven-dried vial equipped with a stirring bar and sealed with a crimp-on cap. The atmosphere was exchanged for N₂, dry THF (2.5 mL) was added, and the reaction vessel was put in an oil bath at 70 °C. After 5 min, Ti(O*i*Pr)₄ (30 μ L, 0.1 mmol) was added, and the mixture was stirred for an additional 15 min. Benzylamine (0.11 mL, 1 mmol) was added, and after 24 h, the reaction mixture was filtered through a pad of silica, eluted with 100 mL solvent (EtOAc–Et₃N = 200:1) and concentrated under reduced pressure to afford analytically pure amide **3a** (205 mg, 91%).

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