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Hydroxy-Directed Amidation of Carboxylic Acid Esters Using a Tantalum Alkoxide Catalyst

Hiroaki Tsuji* and Hisashi Yamamoto*

Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi 487-8501, Japan

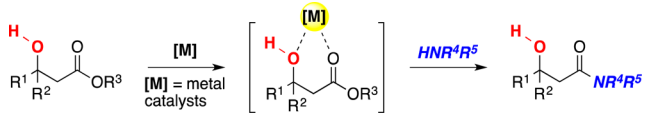
Supporting Information

ABSTRACT: We describe herein a new strategy for the chemoselective synthesis of amides by using a metal-catalyzed hydroxy-directed reaction. A hydroxy group located at the β-position of an ester group promoted the activation of a carbonyl group with a tantalum alkoxide catalyst followed by amidation reactions, leading to a wide variety of β-hydroxyamides with excellent chemeselectivity. The chemoselective amidation strategy can be extended to the catalytic synthesis of dipeptide derivatives, which remains challenging research subjects in modern organic synthesis.

Amides are the most important functional groups found in natural products, pharmaceuticals, polymers, and proteins. Owing to their importance, the development of efficient amidation processes that avoid the use of wasteful peptide coupling reagents is an urgent research subject in synthetic organic chemistry.[1] In this context, catalytic approaches to the synthesis of amides have been attracting considerable attention, and a number of elegant catalytic methods have been established to date.[2] However, developed strategies for the chemoselective catalytic amidation reaction are scarce despite its utility in the chemical ligation of peptides and proteins and the manipulation of complex organic molecules. Herein, we describe a new strategy for the synthesis of amides in a metal-catalyzed hydroxy-directed amidation of β-hydroxycarboxylic acid esters, providing the corresponding β-hydroxyamides in good yields and with high chemoselectivities. The hydroxy-directed amidation approach we developed has been extended to the catalytic synthesis of dipeptide derivatives, which remains a challenging research subject in modern organic synthesis.

Substrate-directed reactions are versatile methods for the construction of organic molecules in chemo- and stereoselective manners.[3] The metal-catalyzed hydroxy-directed reaction is an important substrate-directed reaction and provides remarkable synthetic tools, as exemplified by asymmetric epoxidation[4] and hydrogenation reactions.[5] Thus, these processes expand the horizon of organic synthesis as substrate-controlled reactions. Indeed, the directing effect of the hydroxy group in metal catalysis has been exhibited in cross-coupling reactions,[6] ring-opening reactions,[7] cyclization reactions,[8] hydroacylation reactions,[9] azirizination reactions,[10] and C−H bond functionalization reactions.[11] Inspired by the high efficiency of a hydroxy group in metal catalysis as a directing group, we envisioned that a hydroxy group situated at the β-position of the carbonyl group would promote the activation of the carbonyl group by metal catalysts and subsequent amidation reactions, allowing for the efficient and chemoselective amidation of carboxylic acid esters with amines (Scheme 1).

Scheme 1. Metal-Catalyzed Hydroxy-Directed Amidation of β-Hydroxy Carboxylic Acid Esters



To verify our hypothesis, we initially assessed the directing effect of a hydroxy group in the metal-catalyzed amidation reaction of carboxylic acid esters.[12] The reaction of an equimolar mixture of phenyl β-hydroxypropanoate (**1a**) and phenyl propanoate (**2a**) with *p*-toluidine (**3a**) was carried out in toluene at room temperature for 24 h in the presence of various metal catalysts (Table 1). Although a $La(OTf)_3$-catalyzed amidation reaction of esters has been reported,[12b] self-condensation reactions of **1a** occurred predominantly as a side reaction in our reaction system (entry 1). Other metal triflate catalysts, such as $Sc(OTf)_3$, $In(OTf)_3$, and $Bi(OTf)_3$, were also employed (entries 2−4). In these cases, the desired β-hydroxyamide **4aa** was obtained in a moderate yield. However, the amidation reaction of nonhydroxy-containing ester **2a** also took place, resulting in low chemoselectivity. Next, we examined several metal alkoxides as catalysts. Although Parco reported the amidation reaction of esters catalyzed by $Zr(Ot\text{-}Bu)_4$,[12a] the catalyst did not effectively work under our reaction conditions (entry 5). $Ti(OEt)_4$, $Hf(Ot\text{-}Bu)_4$, $VO(Oi\text{-}Pr)_3$, and lanthanum isopropoxides also showed no efficiency for the hydroxy-directed amidation reaction (entries 6−11). On the other hand, when $Nb(OEt)_5$ was used as the catalyst, the yield of **4aa** slightly improved to 54% (entry 12). Gratifyingly, we found that $Ta(OEt)_5$ efficiently catalyzed the hydroxy-directed amidation reaction to give the desired product **4aa** in an 88% NMR yield (84% isolated yield) with excellent chemoselectivity (entry 13). We observed that the use of phenyl β-methoxypropanoate instead of **1a** gave the desired β-methoxyamide in only 9% yield. We also tested the other tantalum sources under the reaction conditions. $TaCl_5$ and $TaBr_5$ also showed efficient catalytic activity for the amidation reaction, but a trace amount of **5aa** was also formed (entries 14 and 15).

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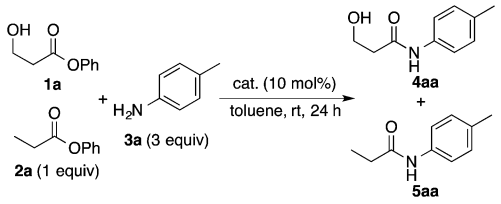
Table 1. Screening of Metal Catalysts

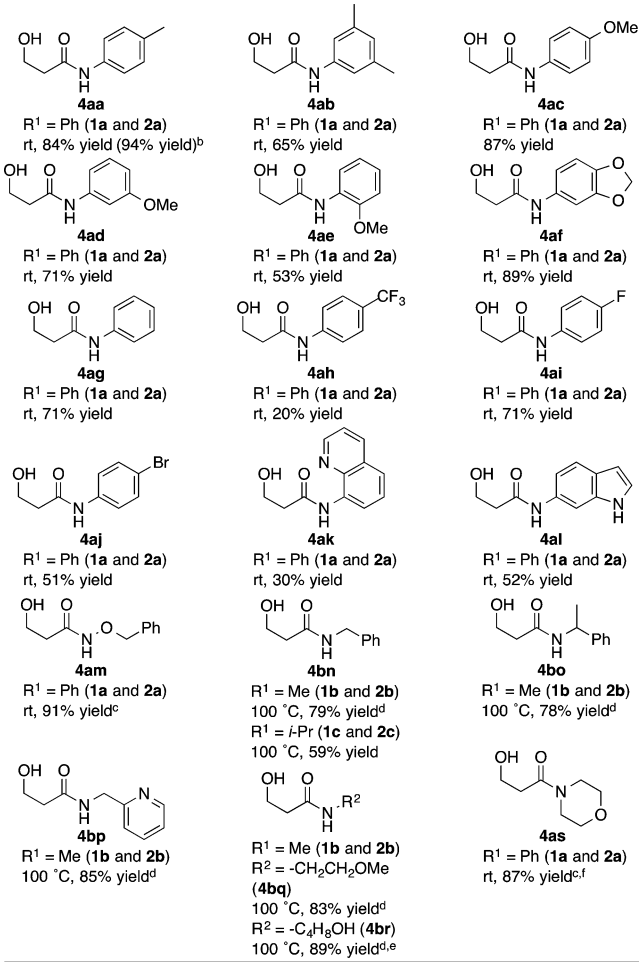


entry	cat.	yield of **4aa** (%)[a]	yield of **5aa** (%)[a]	**4aa**:**5aa**[b]
1[c]	$La(OTf)_3$	–	–	–
2	$Sc(OTf)_3$	53	15	78:22
3	$In(OTf)_3$	41	12	77:23
4	$Bi(OTf)_3$	47	13	78:22
5	$Zr(O\textit{t}\text{-Bu})_4$	11	<1	>99:1
6	$Ti(OEt)_4$	31	<1	>99:1
7	$Hf(O\textit{t}\text{-Bu})_4$	9	<1	>99:1
8	$VO(O\textit{i}\text{-Pr})_3$	24	<1	>99:1
9[c]	$La(O\textit{i}\text{-Pr})_3$	–	–	–
10[c]	$Ga(O\textit{i}\text{-Pr})_3$	–	–	–
11[c]	$Yb(O\textit{i}\text{-Pr})_3$	–	–	–
12	$Nb(OEt)_5$	54	<1	>99:1
13	$Ta(OEt)_5$	88(84)[d]	<1	>99:1
14	$TaCl_5$	84	<9[e]	>90:10
15	$TaBr_5$	94	<5[e]	>95:5

[a]The yields were determined by ^{1}H NMR analyses using 1,1,2,2-tetrachloroethane as an internal standard. [b]The chemoselectivities were determied by ^{1}H NMR analyses of crude mixtures. [c]Complex mixtures of **4aa**, self-condensed products of **1a**, and the other unidentified byproducts were observed in ^{1}H NMR of crude mixtures. [d]Isolated yield. [e]With a trace amount of impurities.

With the optimized reaction conditions in hand, we investigated the scope of amines in the hydroxy-directed amidation reaction of esters (Scheme 2). A wide variety of amines, including aromatic (**3a**–**j**), heteroaromatic (**3k**, **3l**), and aliphatic amines (**3m**–**3s**), were smoothly reacted with *β*-hydroxycarboxylic acid esters (**1a**–**1c**) to give the corresponding *β*-hydroxyamides **4aa**–**4as** in up to a 91% yield with >98:2 chemoselectivities. The amidation of **1a** could be conducted on a gram scale with slightly improved yield (94%) and without loss of chemoselectivity (>99:1). While the reaction using aromatic amines bearing an electron-donating group (**3a**–**f**) proceeded well, the use of electron-deficient aromatic amine (**3h**) led to a slight decrease in the yield. Aniline derivatives **3i** and **3j** bearing fluoro and bromo atoms on their phenyl rings gave *β*-hydroxyamides **4ai** and **4aj** in 71% and 51% yields with excellent chemoselectivities. The amidation reaction using aniline derivatives having heteroaromatic rings (**3k**, **3l**) took place chemoselectively to deliver the desired products **4ak** and **4al** in 30% and 52% yields, respectively. *O*-Benzylhydroxyamine (**3m**) underwent the reaction to afford *β*-hydroxyamide **4am** in a 91% yield with perfect chemoselectivity, which can be converted into valuable hydroxamic acids and primary amides by a simple reduction.[13] Although the use of highly reactive aliphatic amines **3n**–**3q** and a high reaction temperature were required, methyl ester (**1b**) or isopropyl ester (**1c**) in place of phenyl ester (**1a**) were applicable to this catalytic system, providing the corresponding *β*-hydroxyamides **4bn**–**4bq** in high yields and with high chemoselectivities. A free hydroxy group in the amine substrate was compatible with the amidation, giving *β*-hydroxyamides **4br** in 89% yield with 93:7 chemoselectivity. When methyl *β*-methoxypropanoate was subjected to the reaction conditions instead of **1b**, the desired *β*-methoxyamide was formed in 32% yield with 75:25 chemoselectivity. Morpholine (**3s**) gave the desired product **4as** in an 87% yield with slight formation of amide **5as**.

Scheme 2. Scope of Amines in the Hydroxy-Directed Amidation of Carboxylic Acid Esters[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), **3** (0.75 mmol), $Ta(OEt)_5$ (0.025 mmol) in toluene (1 mL) at rt or 100 °C for 24 h. The chemoselectivities were determied by ^{1}H NMR analyses of crude mixtures. [b]1.0 g of **1a** was used. [c]With 1.2 equiv of amines. [d]Methyl butyrate was used as **2b**. [e]**4br**:**5br** = 93:7. [f]**4as**:**5as** = 98:2.

We next examined the scope with respect to *β*-hydroxycarboxylic acid esters **1** (Scheme 3). A series of *β*-mono- and *β*-disubstituted *β*-hydroxycarboxylic acid esters **1** were efficiently transformed into the corresponding *β*-hydroxyamides **4da**–**4on** in moderate to high yields with excellent chemoselectivities. The reaction of phenyl *β*-hydroxy *β*-phenylpropanoate (**1d**) and phenyl butanoate (**2d**) with *p*-toluidine (**3a**) proceeded in the presence of 10 mol % $Ta(OEt)_5$ to afford the amide **4da** in a 97% yield with complete chemoselectivity. Aromatic substituents bearing methoxy, trifluoromethyl, and bromo groups were well tolerated, giving the amides **4ea**–**4ga** in

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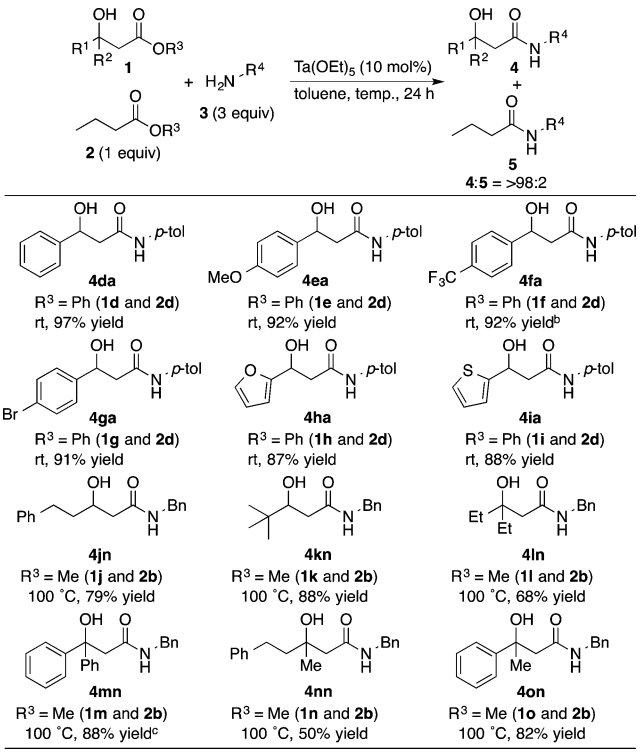
Scheme 3. Scope of β-Hydroxy Esters in the Hydroxy-Directed Amidation of Carboxylic Acid Esters[a]

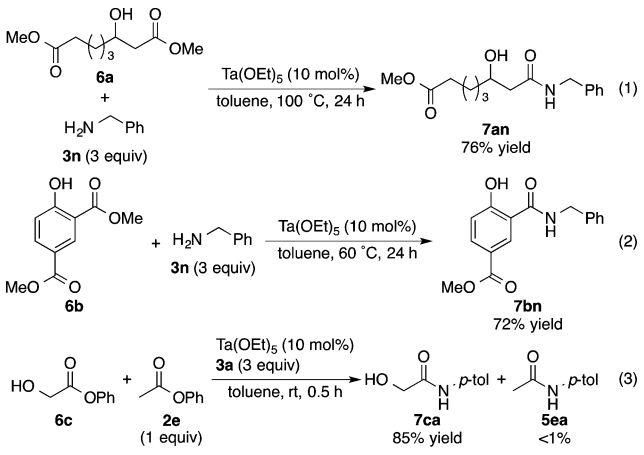


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), **3** (0.75 mmol), $Ta(OEt)_5$ (0.025 mmol) in toluene (1 mL) at rt or 100 °C for 24 h. The chemoselectivities were determied by ^1H NMR analyses of crude mixtures. [b]**4fa**:**5da** = 97:3. [c]**4mn**:**5da** = 98:2.

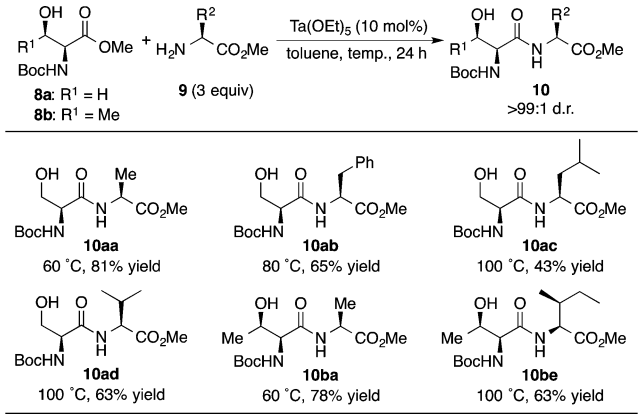
high yields and chemoselectivities. β-Hydroxyamides **4ha** and **4ia** having 2-furyl and 2-thienyl substituents were obtained in 87% and 88% yields, respectively. The reaction of β-alkyl β-hydroxycarboxylic acid esters **1j** and **1k** underwent the reaction to deliver the β-alkyl β-hydroxyamides **4jn** and **4kn** in 79% and 88% yields, respectively. The reaction of β,β-diethyl β-hydroxycarboxylic acid ester **1l** took place to give β-hydroxyamide **4ln** in a 68% yield. β,β-Diphenyl β-hydroxycarboxylic acid ester **1m** afforded the amide **4mn** in a high yield. β-Hydroxycarboxylic acid esters **1n** and **1o** bearing two different substituents at their β-position were also applicable to our reaction conditions, giving the desired amides **4nn** and **4on** in 50% and 82% yields, respectively.

Next, we extended our protocol toward the amidation of esters, which have two methyl ester groups on different positions from the hydroxy group and also α-hydroxyesters. The reaction of ester **6a** with benzylamine (**3n**) took place chemoselectively to give amide **7an** in a 76% yield (eq 1). A phenolic hydroxy group also exhibited a directing effect for the amidation reaction; thus, amide **7bn** was obtained in a 72% yield (eq 2). Furthermore, the catalyst system can be applicable to the amidation of α-hydroxyesters **6c**, providing α-hydroxyamide **7ca** in 85% yield with excellent chemoselectivity (eq 3).[14]

To demonstrate the synthetic utility of the hydroxy-directed amidation reaction, we turned our attention to the catalytic synthesis of dipeptide derivatives without the use of enzymatic methods,[15] which still remains challenging in modern organic chemistry (Scheme 4).[16] To our delight, the reaction of *N*-Boc-serine methyl ester (**8a**) with amino acid methyl esters **9a**–**d**



Scheme 4. Catalytic Synthesis of Dipeptide Derivatives



[a]Reaction conditions: **8** (0.25 mmol), **9** (0.75 mmol), $Ta(OEt)_5$ (0.025 mmol) in toluene (1 mL) at 60–100 °C for 24 h. The diastereomeric ratios (d.r.'s) were determined by ^1H NMR analyses of crude mixtures.

derived from L-alanine, L-phenylalanine, L-leucine, and L-valine proceeded in the presence of $Ta(OEt)_5$ as the catalyst to provide the corresponding dipeptide derivatives **10aa**–**ad** in 43–81% yields with excellent diastereoselectivities.[17] Furthermore, *N*-Boc-threonine methyl ester (**8b**) was also transformed into dipeptide derivatives **10ba** and **10be** in 78% and 63% yields, respectively. Fortunately, we did not observe any epimerization of the amino acid moiety, which is due to the use of simple methyl ester rather than highly activated carboxylic acids of the previous peptide coupling reagents.

In conclusion, we have developed a new strategy toward the chemoselective synthesis of amides by a tantalum ethoxide catalyzed hydroxy-directed amidation reaction of β-hydroxycarboxylic acid esters with amines, leading to an array of β-hydroxyamides in good yields with high chemoselectivity. The protocol allowed for the catalytic synthesis of dipeptide derivatives, which is still in its infancy in modern organic chemistry. The development of a method for the catalytic peptide synthesis using our directed amidation strategy and its application to the synthesis of peptide pharmaceuticals are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

AUTHOR INFORMATION

Corresponding Authors

*tsuji@isc.chubu.ac.jp

*hyamamoto@isc.chubu.ac.jp

Notes

The authors declare no competing financial interest.

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(14) Based on reviewers' suggestions, we examined the amidation of γ- and δ-hydroxyesters. Fortunately, these substrates were reacted with benzylamine at 60 °C under our catalyst system to give the corresponding γ- and δ-hydroxyamides in 23% and 27% yields, respectively, with >99:1 chemoselectivity. More detailed experiments of these substrates are in due course.

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(17) We also tested *N*-Boc-cysteine methyl ester as the substrate to assess the directing effect of a thiol group, but the desired dipeptide derivative was not formed.

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