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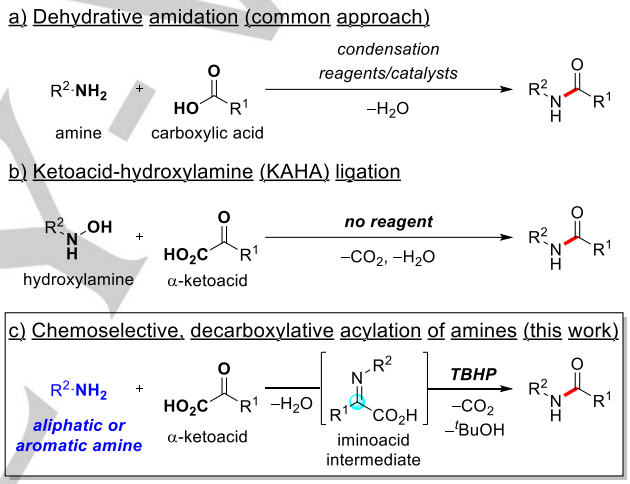
A Hydroperoxide-Mediated Decarboxylation of α-Ketoacids Enables the Chemoselective Acylation of Amines

Takeshi Nanjo, Natsuki Kato, Xuan Zhang, and Yoshiji Takemoto*

Abstract: Strategies for the formation of amide bonds, i.e., one of the most basic and important transformations in organic synthesis, have so far focused predominantly on dehydration reactions. Herein, we report and demonstrate the practical utility of a novel decarboxylative amidation of α-ketoacids using inexpensive *t*-butyl hydroperoxide (TBHP), which is characterized by high yields, a broad substrate scope, mild reaction conditions, and a unique chemoselectivity. These features enable the synthesis of peptides from amino-acid-derived α-ketoacids under preservation of the stereochemical information.

Amide-containing molecules are ubiquitous in natural products, pharmaceuticals, and organic materials. Due to the rapidly increasing interest in peptides, i.e., important amide-containing biopolymers in biological organisms, methods for the efficient formation of amide bonds have been pursued intensively.[1] Among these, dehydrative condensation reactions based on carboxylic acids and amines represent the most common approach (Scheme 1a).[2] While a catalytic amidation method using organoborane derivatives has recently attracted attention,[3,4] another major route to amide bonds proceeds via the use of stoichiometric amounts of condensation agents such as HATU[5] and COMU,[6] which have been developed in order to form amide bonds under epimerization-free, mild reaction conditions.

Moreover, decarboxylative amidations using α-ketoacids, which are converted into acyl-coenzyme As (CoAs) by thiamine pyrophosphate (TPP), have attracted substantial attention as a new type of acylation reactions.[7,8] In 2006, Bode and co-workers described ketoacid-hydroxylamine (KAHA) ligation, which merely requires the mixing of α-ketoacids and hydroxylamines, to afford the corresponding amides in the absence of any condensation agents (Scheme 1b).[7] This bioorthogonal transformation has been used for the chemoselective coupling of long peptide fragments, albeit that the preparation of hydroxylamines is needed.[7d] More recently, Lan, Lei, and co-workers have reported a photo-induced decarboxylative amidation, in which aniline is effectively acylated under an atmosphere of O_2.[8a] Despite these brilliant preceding studies, there are no reported examples of high-yielding decarboxylative acylations of simple aliphatic amines including amino acids or peptides as nucleophiles.[9] We envisioned that iminoacids, which are intermediates in radical-mediated decarboxylative amidations,[8b] may have highly electrophilic properties and thus nucleophilic oxidants such as hydroperoxides could smoothly accelerate their oxidative decarboxylation (Scheme 1c). Herein, we report a novel strategy for the formation of amide bonds using α-ketoacids and a wide range of amines. The transformation is mediated by the inexpensive agent *t*-butyl hydroperoxide (TBHP) and provides the corresponding amides and anilides chemoselectively in high yield under mild reaction conditions.



Scheme 1. Different strategies for the formation of amide bonds.

Initially, we explored the reaction conditions for the decarboxylative amidation of 2-phenethylamine (**1**) and 2-oxo-4-phenylbutyric acid (**2**) as model substrates. The screening of oxidants revealed that TBHP effectively provided the desired amide **3** in 92% yield (Table 1, entry 1). This reaction requires merely an approximately equimolar mixture of amine and α-ketoacid and proceeds at room temperature under neutral conditions. While cumene hydroperoxide (CHP) also provided **3** in 79% yield (entry 2), peroxyacids such as *m*CPBA were not effective for this decarboxylative amidation, which is probably due to its low nucleophilicity (entry 3). The reaction proceeds in different polar solvents of varying polarity, including DMF, DMSO and EtOH, i.e., the reaction medium can be tailored to the solubility requirements of the substrates (entries 4-6). Additionally, amine hydrochloride salt **1**·HCl also afforded **3** by adding potassium carbonate to the reaction mixture as a base (entry 7). Finally, we compared this new TBHP-mediated procedure with previously established conditions and found that under photo-induced decarboxylative amidation conditions, **1** and **2** provided amide **3** in lower yield (entries 8 and 9).[8a,b]

With the optimal conditions established, we investigated the substrate scope of this decarboxylative amidation (Scheme 2).

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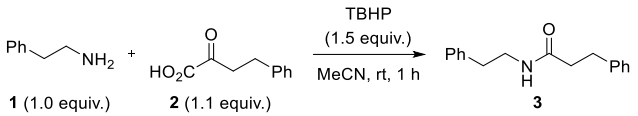
Initially, we examined different amines and α-ketoacids in order to evaluate the general potential of the transformation (Scheme 2a). Both benzyl and 1-phenethyl amine provided the corresponding amides in 86% (**4**) and 77% yield (**5**). Cyclohexylamine also afforded the corresponding amide (**6**) in excellent yield (81%). Subsequently, we focused on secondary amines and discovered that both cyclic and acyclic amines provided the corresponding amides (**7** and **8**) in good yield. Furthermore, the reaction could also be applied to aliphatic amines and anilines, and the reaction of *p*-toluidine afforded anilide **9** in 70% yield, albeit that a longer reaction time is required. Then, we examined several α-ketoacids, which provided amides **10**–**13**. A β-branched ketoacid provided **10** in good yield, and even sterically hindered pivalamide **11** was obtained in 53% yield. The corresponding benzoylation and formylation products (**12** and **13**) were also obtained by using commercially available α-ketoacids, respectively.

Table 1. Optimizing the reaction conditions[a]



1 (1.0 equiv.) **2** (1.1 equiv.) **3**

Entry	Deviation from entry 1	Yield (%)[b]
1	none	92
2	CHP instead of TBHP	79
3	*m*CPBA instead of TBHP	8[c]
4	DMF instead of MeCN	88
5	DMSO instead of MeCN	83
6	EtOH instead of MeCN	88
7	**1**·**HCl** and K_2CO_3 (1.5 equiv.) instead of **1**	96
8	$[Ru(phen)_3]Cl_2$, O_2, DMSO, light, 48 h	32[c]
9	O_2, 1,4-dioxane, H_2O, light, 48 h	0[c]

[a] **1** (0.1 mmol), **2** (0.11 mmol), and TBHP (0.15 mmol) in MeCN at room temperature for 1 h. [b] Isolated yield of **3**. [c] Yields were determined by ^1H NMR spectroscopy using dimethylterephthalate as an internal standard.

Subsequently, we focused on the compatibility of various functional groups, considering the uniqueness of the oxidative acylation conditions (Scheme 2b). Terminal alkenes and alkynes are fully compatible under the applied decarboxylative amidation conditions, and the corresponding amides (**14** and **15**) were obtained in excellent yield. Thioether and a tertiary amine moieties did not affect the yield of amides **16** and **17**. Heterocycles are also applicable and amides **18**-**21**, which contain pyridine, furan, thiophene, and indole rings, were obtained in excellent yield. Then, we applied the acylation conditions to amines bearing nucleophilic sites, which can potentially be acylated, and found that aliphatic amino groups reacted preferentially in the presence of unprotected aniline, phenol, and alcohol (**22**–**24**). In addition, we discovered that this decarboxylative amidation protocol can differentiate between different carboxy groups in the same molecule (**25** and **26**). Using α-ketoglutaric acid, which bears both α-ketocarboxy and conventional carboxy groups, chemoselectively afforded amide **25** in 66% yield under preservation of the terminal carboxy group. This feature also enabled the acylation of gabapentin, which furnished amide **26** in 81% yield without affecting the unprotected carboxy group.

Following this basic analysis of this transformation, we attempted the chemoselective acylation of more complex amines (**27** and **28**). The introduction of hydrophobic motifs, such as a fatty acid chain, in amines may induce dramatic changes in both their biological activity and pharmacokinetics. A fatty acid chain could be easily introduced in good yield in Baclofen (**27**), which is a GABA agonist that contains an unprotected carboxy group. Pyridoxamine, which contains phenolic or aliphatic hydroxyl groups and a nucleophilic pyridine moiety, was predominantly acylated on the primary amine nitrogen to provide the corresponding palmitoyl amide **28** in 67% yield.

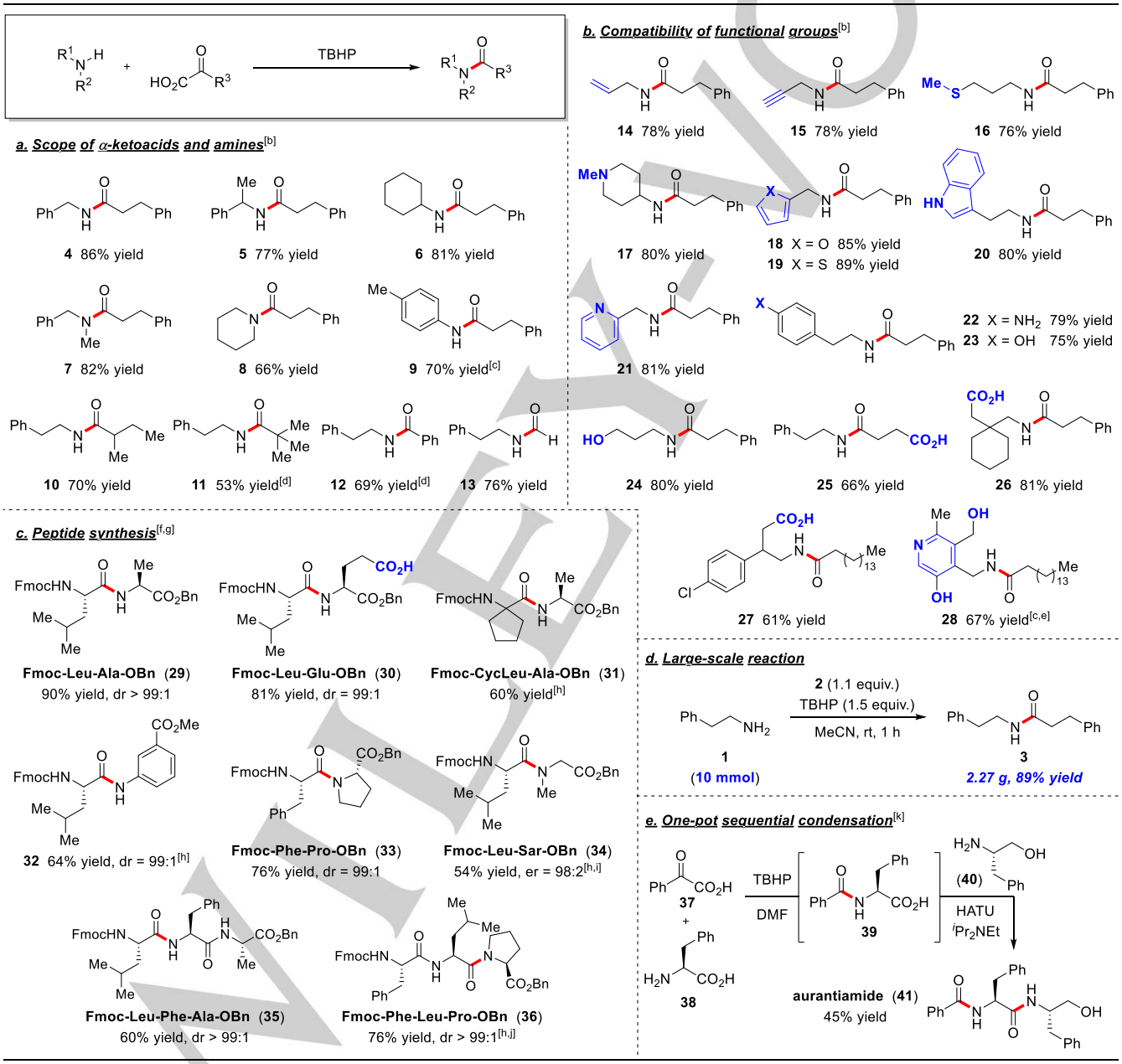
Subsequently, we demonstrated the formation of peptides (Scheme 2c). The decarboxylative amidation of Fmoc-leucine-derived α-ketoacid[7c] and alanine benzyl ester successfully proceeded to afford dipeptide **29** in 90% yield under stereoretention at the α position relative to the carbonyl group (dr > 99:1). As described above, the presence of an unprotected carboxy group in a glutamic acid residue did not significantly influence the yield of dipeptide **30**. Coupling of an α,α-disubstituted amino acid, which is a medicinally important type of unnatural amino acids, provided dipeptide **31** in 60% yield. Furthermore, a less electrophilic aromatic amino acid provided peptide **32** in 64% yield under retention of the stereochemical information. Tertiary amides, which are not accessible by KAHA ligation,[7] were effectively formed, and the reaction of proline and *N*-methyl amino acid afforded dipeptides **33** and **34** in good yield. In the same way, tripeptides **35** and **36** were successfully prepared by this decarboxylative amidation. It is noteworthy that **36** was obtained as a single diastereomer, despite the general concerns regarding epimerization upon formation of tertiary amide bonds on the C-terminus of a peptide.[2]

We also investigated the scalability of this transformation (Scheme 2d). The reaction conditions could be easily carried out on a 10-mmol scale and the use of inexpensive TBHP and α-ketoacid **2** smoothly converted amine **1** into the amide **3** in excellent yield without any precautions.

Moreover, a one-pot sequential condensation was carried out taking advantage of the α-ketocarboxy-selectivity (Scheme 2e). The TBHP-assisted coupling of phenylglyoxylic acid **37** and unprotected phenylalanine **38** predominantly afforded amide **39**. The following addition of phenylalaninol **40**, HATU, and amine to the reaction mixture successfully provided biologically active aurantiamide[10] **41** in a one-pot fashion.

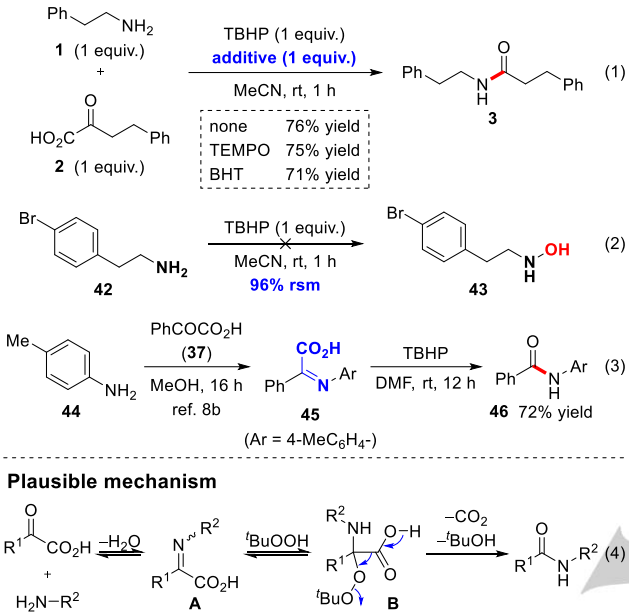
Lastly, we conducted a mechanistic analysis of the decarboxylative amidation (Scheme 3). TBHP is generally recognized as a radical initiator at high temperature, and previously established photo-induced decarboxylative

amidations of α-ketoacids have been proposed to proceed via radical intermediates.[8a,b] Therefore, we initially tested the addition of radical scavengers in order to determine if radical intermediates are involved in the TBHP-mediated amidation (Scheme 3, eq 1). When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or di-*t*-butyl hydroxytoluene (BHT) were added to the standard reaction conditions, a significant influence on the yield of amide **3** was not observed. These results indicate that the reaction does not proceed via a radical but through an ionic pathway.[11] Then, we considered the possibility that the oxidation of the amine with TBHP could afford a hydroxylamine intermediate that could engage in a KAHA ligation with the α-ketoacid. However, TBHP did not react with aliphatic amine **42** in the absence of the α-ketoacid, and therefore, hydroxylamine intermediate **43** was excluded (Scheme 3, eq 2).[12,13] In addition, iminoacid **45**, derived from aniline **44** and phenylglyoxylic acid **37**, was isolated.[8b] Addition of TBHP to a solution of **45** in DMF (Scheme 3, eq 3) yielded anilide **46** in 72% yield, which strongly indicates that the iminoacid is an intermediate of the decarboxylative amidation.



Scheme 2. Substrate scope [a] Isolate yield. [b] Amine (1.0 equiv.), α-ketoacid (1.1 equiv.), and TBHP (1.2-1.5 equiv.) in MeCN or DMF at room temperature for 1 h. [c] The reaction proceeded for 12 h. [d] α-Ketoacid (1.5 equiv.) and TBHP (2.0 equiv.) were used. [e] MeOH was used as the solvent. [f] Amine (1.0 equiv.), α-ketoacid (1.2 equiv.), and TBHP (1.5 equiv.) in DMF at 0 ºC for 12 h. [g] Er and dr values were estimated by chiral SFC analysis. [h] The reaction was carried out at room temperature. [i] The reaction proceeded for 48 h. [j] The reaction proceeded for 24 h. [k] **37** (1.2 equiv.), **38** (1.0 equiv.), and TBHP (1.5 equiv.) in DMF at room temperature for 12 h; **40** (1.5 equiv.), HATU (1.5 equiv.), and $^{i}Pr_2NEt$ (3.0 equiv.) at room temperature for 16 h.

Based on the experimental results, a plausible mechanism is proposed in Scheme 3 (eq 4). The α-ketoacid and the amine couple to afford iminoacid intermediate **A**, before the addition of TBHP to the highly electrophilic imino group occurs. The resulting tetrahedral intermediate **B** could then be converted into the desired amide under concomitant release of carbon dioxide and *t*-butyl alcohol.



Scheme 3. Mechanistic studies.

In summary, we have described a novel decarboxylative acylation reaction for aliphatic and aromatic amines, which employs α-ketoacids as acylating agents. The formation of the amide bond proceeds, in contrast to previously reported acylation reactions, under mild conditions and exhibits unique chemoselectivity. Taking advantage of these characteristic features allowed efficiently synthesizing complex amides including peptides and amide analogues of bioactive molecules. The obtained results demonstrate the synthetic potential of this approach for the chemoselective late-stage amidation of complex amines in total synthesis and the chemical ligation of peptides. We are currently exploring further applications of this strategy and investigating mechanistic details of the transformation.

Acknowledgements

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Keywords: peroxides • decarboxylation • α-ketoacids • amides • peptides

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[11] In contrast to the TBHP-mediated acylation conditions, photo-mediated decarboxylative amidations are inhibited by the addition of a stoichiometric amount of TEMPO; for details, see: ref. 8b.

[12] The addition of 1 equiv. of AcOH did not have influence on the control experiment. This results could exclude the possibility that an acid accelerates the oxidation of amines. See Supporting Information for details.

[13] KAHA ligation was reported to proceed effectively at approximately 40 °C. Conversely, the TBHP-mediated acylation proceeds even at 0 °C. This result corroborates that the amidation does not proceed *via* an amine oxidation followed by KAHA ligation.

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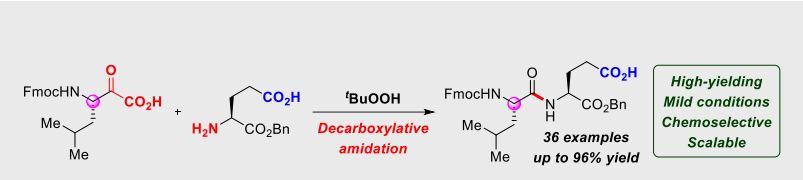

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