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SHORT COMMUNICATION

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Metal–Organocatalytic Tandem Azide Addition/Oxyamination of Aldehydes for the Enantioselective Synthesis of β-Amino α-Hydroxy Esters

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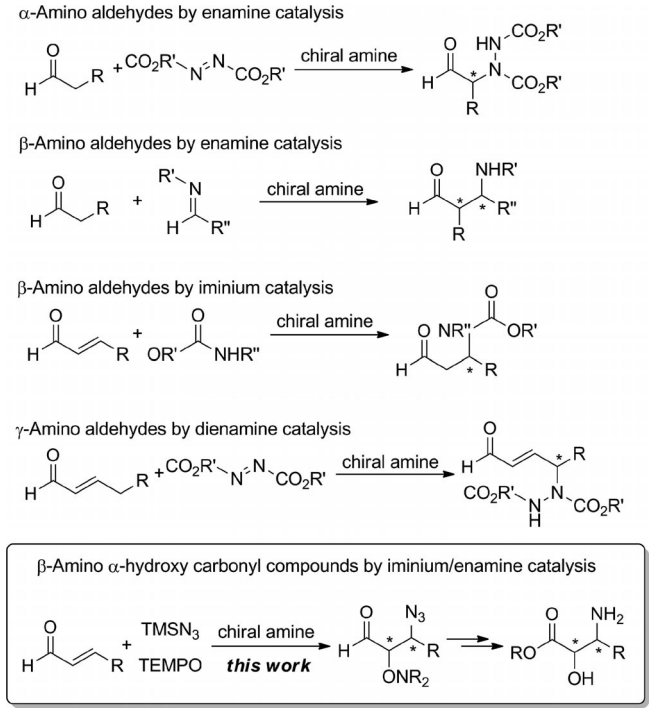
The tandem reaction of α,β-unsaturated aldehydes with trimethylsilyl azide and 2,2,6,6-tetramethylpiperidin-1-yloxy in the presence of chiral amines and iron complexes as the catalysts in a one-pot reaction enantioselectively afforded β-azido α-oxyaminated aldehydes. Further synthetic modification of the product afforded β-amino α-hydroxy esters in good yields with good diastereo- and enantioselectivities.

Introduction

A tremendous amount of effort has been devoted to developing synthetic methods for optically active α-, β-, and γ-amino aldehydes and their derivatives, such as amino acids, owing to their broad utility in natural product synthesis and in the pharmaceutical industries.[1,2] In particular, the chiral amine catalyzed synthesis of amino aldehydes has received great attention, for which the direct and highly enantioselective addition of an amine group at different positions of an aldehyde has been made possible under environmentally benign conditions (Scheme 1). Depending on the catalytically competent species (enamine, iminium, or dienamine), different amine sources have been used to afford various amino aldehydes with good enantioselectivities.[3–5]

Among the organocatalyzed syntheses of amino aldehydes, the synthesis of β-amino aldehydes through the Michael addition of a nitrogen nucleophile to an iminium intermediate has attracted our interest, because we have been involved in the study of asymmetric cascade organocatalytic reactions involving the iminium-catalyzed Michael addition of various nucleophiles to α,β-unsaturated aldehydes.[6–8] The cascade reaction conditions involving 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and azide may afford synthetically and pharmaceutically useful β-amino α-hydroxy carbonyl compounds (Scheme 1),[9] which have been synthesized by various methods,[10,11] for example, the oxyamination of alkenes,[10] hydroxylation of β-amino enolates,[11h] amination of keto esters,[11i] Henry reaction of carbonyl compounds,[11j,11k,11l] Mannich reaction of α-oxyaldehydes,[11m,11n] reduction of α-acetoxy-β-enamino esters,[11o] and reduction of β-amino α-keto esters.[11p] In comparison to the previously reported methods, the proposed organocatalyzed tandem addition approach may afford enantiomerically enriched β-amino α-hydroxy carbonyl precursors from commercially available starting materials with step economy without the use of expensive and highly air- and moisture-sensitive metal complexes. In addition to the synthesis of β-amino α-hydroxy carbonyl compounds, β-azido α-oxyaminated aldehydes, formed from organocatalytic reactions, contain easily manipulated and versatile az-



Scheme 1. Syntheses of amino aldehydes by organocatalysis.

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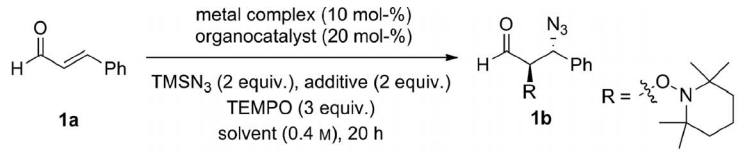
ide and aldehyde functional groups, which can be converted into various other functional groups.

Although the Michael addition of azides to ketones, esters, carboxylic acids, amides, and electron-deficient nitro compounds has been reported,[12] the Michael addition of azides to α,β-unsaturated aldehydes has been rarely reported because of competitive 1,2-addition and the polymerization of aldehydes in the presence of nitrogen nucleophiles.[13] The catalytic version of the enantioselective Michael addition of azides to α,β-unsaturated aldehydes has not been reported yet. In this study, the enantioselective tandem iminium-catalyzed azide addition and enamine/iron-catalyzed oxyamination of α,β-unsaturated aldehydes afforded optically active α,β-disubstituted aldehydes, which were further modified to biologically important β-amino α-hydroxy esters.

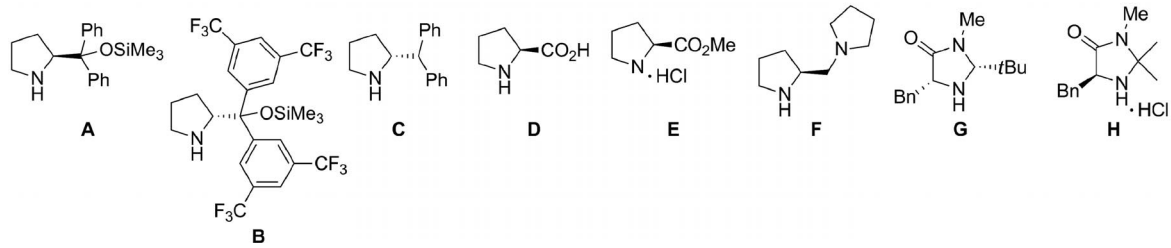
Results and Discussion

The asymmetric tandem addition of azide and TEMPO to cinnamaldehyde (**1a**) was investigated in the presence of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**A**) and metal catalysts.[14] As the azide source, trimethylsilyl azide ($TMSN_3$) was used along with benzoic acid to afford HN_3. Suitable metal catalysts for the addition of TEMPO were investigated; the use of $FeCl_3·6H_2O$ as the catalyst afforded **1b** in good yield (Table 1, entry 2). To increase the stereoselectivity of the reaction, the sterically bulky organocatalyst (*R*)-2-{bis[3,5-bis(trifluoromethyl)phenyl][(trimethylsilyl)oxy]methyl}pyrrolidine (**B**) was used to afford **1b** in higher yield and enantioselectivity (Table 1, entry 5). If the reaction temperature was lowered to –15 °C, the enantioselectivity slightly increased (Table 1, entry 6). Then, various carboxylic acids, bases, and F^- sources [CsF and tetrabutylammonium fluoride (TBAF)] were investigated to generate the azide nucleophile (Table 1, entries 7–12). Trifluoroacetic acid (TFA) catalyzed the reaction to afford **1b** with slightly lower diastereo- and enantioselectivity than other acids and the base. CsF did not promote the reaction at all, and TBAF induced the highest enantioselectivity, albeit in a low yield (3%). Upon screening the metal catalysts, higher yields were obtained with the use of hydrated iron complexes. Therefore, water (1 equiv.) was added to the reaction mixture containing $FeCl_3·6H_2O$; however, a lower

Table 1. Optimization of the enantioselective tandem addition of azide and TEMPO to **1a**.



Entry	Metal complex	Organocatalyst	Additive	Solvent	Temp. [°C]	Yield [%]	*de* [%]	*ee* [%]
1	CuBr	**A**	$PhCO_2H$	CH_3CN	0	48	>95	71
2	$FeCl_3·6H_2O$	**A**	$PhCO_2H$	CH_3CN	0	51	>95	71
3	$FeCl_3$	**A**	$PhCO_2H$	CH_3CN	0	39	>95	77
4	$FeCl_2·4H_2O$	**A**	$PhCO_2H$	CH_3CN	0	40	>95	73
5	$FeCl_3·6H_2O$	**B**	$PhCO_2H$	CH_3CN	0	66	>95	82
6	$FeCl_3·6H_2O$	**B**	$PhCO_2H$	CH_3CN	–15	61	>95	85
7	$FeCl_3·6H_2O$	**B**	HOAc	CH_3CN	–15	38	>95	87
8	$FeCl_3·6H_2O$	**B**	TFA	CH_3CN	–15	56	82	46
9	$FeCl_3·6H_2O$	**B**	pivalic acid	CH_3CN	–15	34	>95	86
10	$FeCl_3·6H_2O$	**B**	LiOAc	CH_3CN	–15	14	>95	87
11	$FeCl_3·6H_2O$	**B**	CsF	CH_3CN	–15	–	–	–
12	$FeCl_3·6H_2O$	**B**	TBAF	CH_3CN	–15	3	>95	90
13	$FeCl_3·6H_2O$	**B**	$PhCO_2H$	CH_3CN[a]	–15	44	>95	80
14	$FeCl_3·6H_2O$	**C**	$PhCO_2H$	CH_3CN	–15	24	>95	69
15	$FeCl_3·6H_2O$	**D**	$PhCO_2H$	CH_3CN	–15	31	>95	1
16	$FeCl_3·6H_2O$	**E**	$PhCO_2H$	CH_3CN	–15	43	>95	6
17	$FeCl_3·6H_2O$	**F**	$PhCO_2H$	CH_3CN	–15	33	>95	2
18	$FeCl_3·6H_2O$	**G**	$PhCO_2H$	CH_3CN	–15	5	>95	10
19	$FeCl_3·6H_2O$	**H**	$PhCO_2H$	CH_3CN	–15	13	>95	10



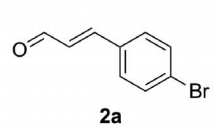
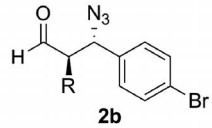
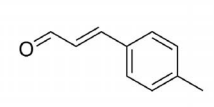
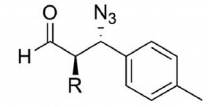
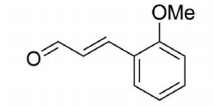
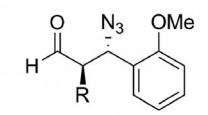
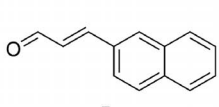
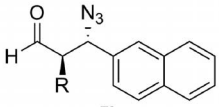
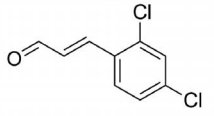
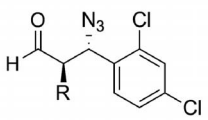
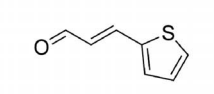
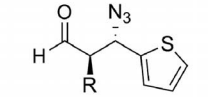
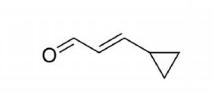
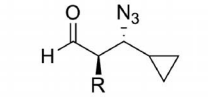
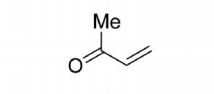
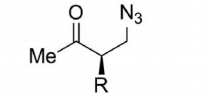
[a] H_2O (1 equiv.).

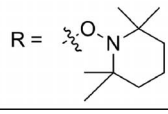
yield and selectivity were obtained (Table 1, entry 13). In addition to catalysts **A** and **B**, diverse proline derivatives (e.g., **C**, **E**, and **F**), proline (**D**), and imidazolidinone catalysts (e.g., **G** and **H**) were investigated, all of which afforded **1b** in low yields with low enantioselectivities (Table 1, entries 14–19). Catalysts **B**, **C**, **E**, and **F** generated (2*R*,3*R*)-**1b**, and catalysts **A**, **D**, **G**, and **H** afforded (2*S*,3*S*)-**1b**. Moreover, other solvents (THF, toluene, DMF, $CHCl_3$, and CH_2Cl_2) were used; however, **1b** was formed in less than 5% yield (THF: 2%, toluene: 5%, DMF: 1%, $CHCl_3$: 4%, CH_2Cl_2: 3%). As an azido source, NaN_3 was used instead of $TMSN_3$ under the optimized conditions, and desired tandem addition product **1b** was not isolated. Because this tandem reaction comprises both Michael addition and oxyamination, the formation of a simple azide addition product from the simple Michael addition of **1a** was attempted in the absence of both TEMPO and the metal complex. In the absence of only TEMPO, however, no simple Michael addition product was isolated. Presumably, the azide addition product may not be stable under the asymmetric iminium catalysis conditions, and thus no asymmetric azide addition to the α,β-unsaturated aldehydes would occur, as reported. Upon combining both the azide addition and oxyamination protocols, α,β-unsaturated aldehyde **1a** was smoothly converted into **1b**. Furthermore, chiral amine catalysts and the stereocontrolled azido group at the β-position cooperatively controlled the stereochemistry of the α-position to afford **1b** with excellent diastereo- and enantioselectivity.

Next, a diverse array of α,β-unsaturated aldehydes were subjected to the optimized reaction conditions for the tandem azide/TEMPO addition. As listed in Table 2, 4-bromocinnamaldehyde (**2a**) was converted into **2b** in 51% yield with 84% enantiomeric excess (*ee*; Table 2, entry 1). The transformation of 4-methylcinnamaldehyde (**3a**) into **3b** resulted in a yield and enantioselectivity that was similar to that obtained with **1b** (Table 2, entry 2). Relative to the enantioselectivity obtained with *para*-substituted cinnamaldehyde derivatives, the reaction of *ortho*-methoxycinnamaldehyde (**4a**) resulted in slightly reduced enantioselectivity (Table 2, entry 3). The reactions of naphthalene- and dichlorophenyl-substituted aldehydes **5a** and **6a** afforded **5b** and **6b** in 49% yield (80% *ee*) and 59% yield (82% *ee*), respectively (Table 2, entries 4 and 5). The reaction of thiophenyl aldehyde **7a** afforded **7b** in 45% yield with the highest enantioselectivity (90% *ee*; Table 2, entry 6). The reaction of cyclopropyl-substituted aldehyde **8a** resulted in a lower yield and a lower enantioselectivity relative to that of the aromatic substituted aldehydes (Table 2, entry 7). Methyl vinyl ketone (**9a**) was subjected to the reaction conditions to afford **9b** in 60% yield; however, no enantioselectivity was achieved. In the reaction of **9a**, chiral catalyst **B** was not involved in the oxyamination step. Instead, an enol intermediate that was formed by the reaction of the ketone with the acid reacted with the Fe–TEMPO complex.

The utility of our protocol was shown by the synthesis of optically active β-amino α-hydroxy esters from **1b** (Scheme 2). The conversion of aldehyde **1b** into the corresponding esters successfully afforded **1c** and **1c′** in 80 and 62% yield, respectively. A combination of zinc metal (Zn) and acetic acid was used to cleave the O–N bond of TEMPO. To our delight, cleavage of the O–N bond and azide reduction occurred simultaneously to afford β-amino α-hydroxy esters **1d** and **1d′** in 50 and 51% yield, respectively. The absolute and relative stereochemistry of **1d′** was

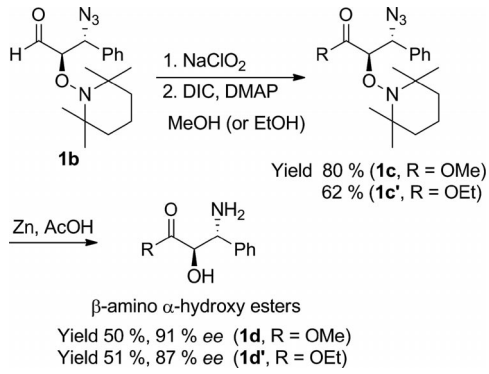
Table 2. Tandem addition of azide and TEMPO to α,β-unsaturated carbonyl compounds.[a]

Entry	Reactant	Product	Yield [%] (*de* [%], *ee* [%])
1	 **2a**	 **2b**	51 (>95, 84)
2	 **3a**	 **3b**	71 (>95, 82)
3	 **4a**	 **4b**	65 (>95, 75)
4	 **5a**	 **5b**	49 (>95, 80)
5	 **6a**	 **6b**	59 (>95, 82)
6	 **7a**	 **7b**	45 (>95, 90)
7	 **8a**	 **8b**	42 (>95, 71)
8	 **9a**	 **9b**	60 (0)

R = 

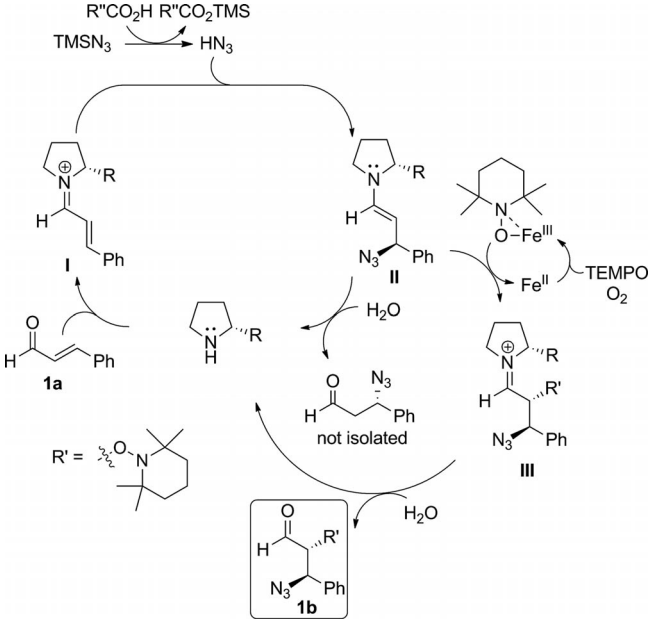
[a] Reaction conditions: aldehyde (0.25 mmol) was added to a solution of (*R*)-2-[bis(3,5-bis(trifluoromethyl)phenyl(trimethylsilyloxy)-methyl]pyrrolidine (20 mol%), $FeCl_3 \cdot 6H_2O$ (10 mol%), benzoic acid (0.5 mmol), $TMSN_3$ (0.5 mmol), and TEMPO (0.5 mmol) in CH_3CN. The reaction mixture was stirred in the air at –15 °C for 20 h.

established by comparing its optical rotation and ^{1}H NMR spectroscopic data with the reported data.[11p] The enantioselectivity of **1d** and **1d′** was measured by HPLC analysis, which indicated no decrease in the enantioselectivity during the synthetic modification of **1b**.



Scheme 2. Synthesis of β-amino α-hydroxy esters; DIC = *N*,*N*′-diisopropylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

A reaction mechanism for the tandem addition of azide and TEMPO to α,β-unsaturated aldehydes is proposed, as shown in Scheme 3. It comprises two catalytic cycles: (1) a catalytic cycle for the iminium-mediated azide addition and (2) a cycle for the enamine-mediated TEMPO addition. The first catalytic cycle begins with the formation of iminium salt **I** from cinnamaldehyde and catalyst **B**. The subsequent Michael addition of an azide nucleophile to iminium **I** affords enamine intermediate **II**, which undergoes Fe^{III}–TEMPO addition. The presence of a Fe^{III}–TEMPO complex was proposed in the Fe^{III}-complex-catalyzed α-oxyamination of aldehydes.[15] The reduced Fe^{II} species is then oxidized by TEMPO or oxygen and adds to the catalytic cycle. Because the reaction runs in air and uses 3 equiv. of TEMPO, the oxidation of Fe^{II} to Fe^{III} is possible by both



Scheme 3. A plausible reaction mechanism.

oxidants. The mechanism involving the participation of azido radicals generated from $TMSN_3$ and TEMPO was also considered.[16] However, in the absence of metal catalysts, the reaction did not proceed, and this indicates that this reaction cannot occur through a simple radical process.

Conclusions

Herein, we reported a tandem reaction involving the iminium-catalyzed Michael addition of azides and the iron-catalyzed TEMPO addition to α,β-unsaturated aldehydes. A diverse array of β-azido α-oxyaminated aldehydes were prepared in good yields with good diastereo- and enantioselectivities under environmentally benign conditions. Further synthetic modification of the product afforded β-amino α-hydroxy esters from easily accessible reactants in four steps. The potential application of this protocol for the syntheses of biologically and pharmaceutically important building blocks was demonstrated. In addition, we showed for the first time that azide nucleophiles can be used in the chiral amine catalyzed Michael addition of α,β-unsaturated aldehydes. Problems associated with the Michael addition of azides to α,β-unsaturated aldehydes were solved by a tandem reaction protocol. Subsequent organocatalyzed α-oxyamination of β-azido aldehydes solved the problems related to azide addition to α,β-unsaturated aldehydes.

Experimental Section

General: Anhydrous solvents were transferred by an oven-dried syringe. Dichloromethane was distilled from calcium hydride. ^{1}H NMR spectra were recorded with a Varian Mercury plus (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane. ^{13}C NMR spectra were recorded with a Varian Mercury plus (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at δ = 77.00 ppm for deuteriochloroform. TEMPO and the chiral amine catalysts were purchased from Aldrich, and $FeCl_3{\cdot}6H_2O$ was purchased from Kanto Chemical (97.0% purity). These chemicals were used without purification.

General Procedure for the Catalytic Reaction: A mixture of aldehyde (0.25 mmol), trimethylsilyl azide (0.50 mmol), benzoic acid (0.50 mmol), TEMPO (0.75 mmol), $FeCl_3{\cdot}6H_2O$ (0.025 mmol), and (*R*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (0.05 mmol) in CH_3CN (0.625 mL) was stirred in the air at –15 °C for 16–22 h. The solvent was removed under reduced pressure to produce a residue that was purified by column chromatography on a silica gel (hexane/diethyl ether = 99:1) to obtain the final pure product.

Supporting Information (see footnote on the first page of this article): Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra

Acknowledgments

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