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Asymmetric synthesis of α-amino acids: indium-mediated reactions of glyoxylic oxime ether in aqueous media†

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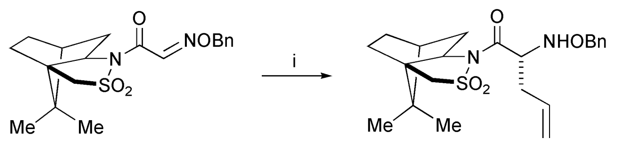
Received (in Cambridge, UK) 9th April 2002, Accepted 16th May 2002
First published as an Advance Article on the web 6th June 2002

The indium-mediated allylation and alkylation reactions of the Oppolzer camphorsultam derivative of glyoxylic oxime ether proceeded with excellent diastereoselectivity in aqueous media, providing a variety of enantiomerically pure α-amino acids.

The indium-mediated allylation reactions of carbonyl compounds in aqueous media have been of great importance from both economical and environmental points of view.[1] In contrast, the corresponding reaction of imine derivatives has not been widely studied; therefore, the development of the indium-mediated reaction of imines in aqueous media has been a subject of current interest. Chan's group reported the first studies on the indium-mediated allylation of *N*-sulfonylimines in aqueous media through an allylindium(I) intermediate.[2] As a part of our program directed toward the development of reactions of imines in aqueous media,[3] we recently reported the indium-mediated alkylation reactions of imine derivatives by using indium as a single-electron transfer radical initiator.[4] We now report an asymmetric synthesis of α-amino acids based on indium-mediated allylation and alkylation reactions of glyoxylic oxime ether.

We examined the reaction of Oppolzer's camphorsultam derivative of glyoxylic oxime ether **1**, which would allow access to a variety of enantiomerically pure α-amino acids (Scheme 1). In our previous work on triethylborane-induced radical reactions in organic solvents,[5] oxime ether **1** has shown excellent reactivity; thus, we expected that the direct comparison of indium-mediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding the reactivity and stereochemical course of indium-mediated reactions. The reaction of **1** with allyl bromide (2.5 equiv.) in the presence of indium (2.5 equiv.) in H_2O–MeOH (2 : 1, v/v) proceeded smoothly at 20 °C to give 98% of the desired product **2a** with 88% de (Table 1, entry 1). The enantiomerically pure product **2a** could be obtained after recrystallisation. The replacement of H_2O–MeOH (2 : 1, v/v) with H_2O–THF (1 : 1, v/v) led to similar chemical yield and selectivity, which are comparable to or better than those obtained by zinc-mediated reaction reported by Hanessian's group (entry 2).[6] An excellent selectivity was observed in the reaction of **1** with allyl bromide in H_2O–THF at 0 °C (entry 3). The biphasic reaction using allyl iodide in H_2O–CH_2Cl_2 (4 : 1, v/v) proceeded slowly to give **2a** in 93% yield with 90% de after being stirred at 20 °C for 23 h (entry 4). The absolute configuration at the newly formed chiral center of the major product, which can be converted into allylglycine, was assigned to be *R* by comparing with authentic spectral data.[6]



1 2a

Scheme 1 *Reagents and conditions*: i, CH_2=$CHCH_2X$ (2.5 equiv.), In (2.5 equiv.).

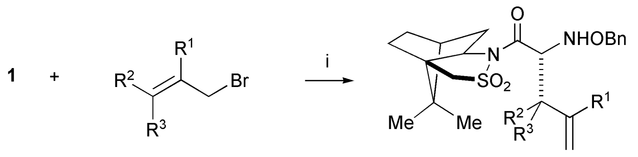
Table 1 In-mediated allylation of **1** in aqueous media

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)[a]	de (%)[b]
1[c]	H_2O–MeOH (2 : 1)	20	2	98	88 (> 98)
2[c]	H_2O–THF (1 : 1)	20	2	98	88
3[c]	H_2O–THF (1 : 1)	0	2	97	91
4[d]	H_2O–CH_2Cl_2 (4 : 1)	20	23	93	90

[a] Isolated yields. [b] Diastereoselectivities were determined by ^1H NMR analysis. Diastereoselectivity in parentheses is for selectivity after recrystallisation. [c] Reactions were carried out with allyl bromide. [d] Reaction was carried out with allyl iodide.

Other substituted allyl bromides worked well under similar reaction conditions and the reactions took place at the γ-position of allyl bromides *via* the chelated six-membered ring transition state (Scheme 2). The stereoselectivity was shown to be dependent on the position of the substituent in allyl bromides (Table 2). The reaction of **1** with the γ-substituted allyl bromides such as cinnamyl bromide **3b** and 4-bromo-2-methyl-2-butene **3c** gave the single diastereomers **2b** and **2c** in 91 and 90% yields, respectively (entries 1 and 2). In contrast, the reaction with the β-substituted allyl bromides **3d** and **3e** gave products **2d** and **2e** with a moderate diastereoselectivities even at 0 °C (entries 3–6). A similar trend has been reported by Hanessian's group in zinc-mediated allylation reaction in aqueous ammonium chloride.[6]

We recently reported the indium-mediated alkyl radical addition to electron-deficient C=N and C=C bonds in aqueous media.[4] Based on these studies, we next investigated the alkylation method for the synthesis of aliphatic α-amino acids by using indium as a single-electron transfer radical initiator (Scheme 3). The treatment of **1** with isopropyl iodide (5 × 2 equiv.) and indium (7 equiv.) in H_2O–MeOH (2 : 1, v/v) gave the desired product **2f** in 18% yield with 84% de, accompanied with 68% of the starting compound **1** after being stirred at 20 °C for 1 h (Table 3, entry 1). After being stirred at 20 °C for 72 h, 43% of the desired product **2f** was obtained in 84% de (entry 2). The biphasic reaction of **1** in H_2O–CH_2Cl_2 (4 : 1, v/v) proceeded slowly to give 44% yield of **2f** with 81% de after being stirred



3b : R^1=H, R^2=Ph, R^3=H
3c : R^1=H, R^2=Me, R^3=Me
3d : R^1=Me, R^2=H, R^3=H
3e : R^1=CO_2Me, R^2=H, R^3=H

2b-e

Scheme 2 *Reagents and conditions*: i, **3b**–**e** (2.5 equiv.), In (2.5 equiv.), H_2O–THF (1 : 1), 20 °C, 2 h.

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† Electronic supplementary information (ESI) available: typical procedures for allylation reaction and isopropyl radical addition reaction. See http://www.rsc.org/suppdata/cc/b2/b203493j/

DOI: 10.1039/b203493j

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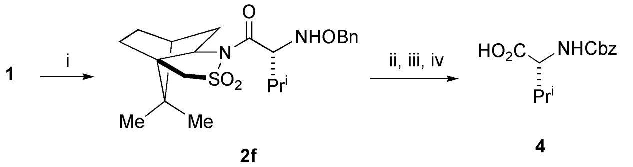
Table 2 In-mediated reaction of **1** in aqueous media

Entry	Reagent	Product	Yield (%)[a]	de (%)[b]
1	**3b**	**2b**	91[c]	> 98
2	**3c**	**2c**	90	> 98
3	**3d**	**2d**	93	63
4[d]	**3d**	**2d**	95	64
5	**3e**	**2e**	96	58
6[d]	**3e**	**2e**	96	59

[a] Isolated yields. [b] Diastereoselectivities were determined by ^{1}H NMR analysis. [c] The *threo*-isomer was selectively obtained. [d] Reactions were carried out at 0 °C for 2 h.

for 72 h (entry 3). These selectivities are slightly better than that obtained by triethylborane-induced radical reaction in organic solvent at 20 °C reported by our group.[5] As the best result, the treatment with isopropyl iodide (10 equiv.) and indium (10 equiv.) in H_2O gave the desired product **2f** in 53% yield with 84% de, accompanied with 21% of the starting compound **1** after being stirred at 20 °C for 48 h (Table 3, entry 5). These reactions would proceed *via* a tin-free radical process including the single-electron transfer (SET) reaction from indium as shown in our previous report.[4] The product **2f** could be converted into (*R*)-*N*-Cbz-valine **4**. Thus, the absolute stereochemical course of the radical addition to **1** was found to be the same as that for the allylation of **1** and triethylborane-induced radical reaction of **1**.[5] Although the indium-mediated alkylation reaction of **1** was slower than the indium-mediated allylation reaction of **1**, it is important to note that aliphatic α-amino acids would not be readily synthesized by applying the known reactions of organometallic reagents.[7] Thus, the synthesis of aliphatic α-amino acids using the radical addition to glyoxylic imines complements the synthesis of allylic and aromatic α-amino acids using the nucleophilic addition of organometallic reagents to glyoxylic imines.

Modest chemical yield and good diastereoselectivity were obtained in reaction of **1** with a cyclopentyl radical in H_2O after being stirred at 20 °C for 48 h, (Scheme 4). Particularly, the nucleophilic *tert*-butyl radical worked well to give 79% yield of the desired product **2h** with 98% de. In our previous studies, the triethylborane-induced alkyl radical addition to imine derivatives is frequently plagued by the formation of an ethylated by-product as a result of competitive addition of an ethyl radical generated from triethylborane.[5,8] It should be noted that the indium-mediated radical reaction gave selectively the desired alkylated products.

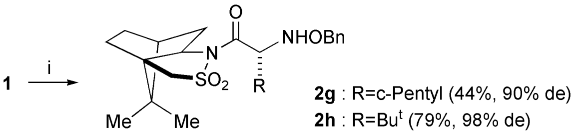


Scheme 3 *Reagents and conditions*: i, $\mathrm{Pr^iI}$, In, 20 °C, ii, H_2, $Pd(OH)_2$, MeOH, 20 °C (77%); iii, CbzCl, Na_2CO_3, acetone–H_2O, 0 °C (92%); iv, 1 N LiOH, THF, 20 °C (73%).

Table 3 In-mediated isopropyl radical addition to **1** in aqueous media

Entry	Solvent	Lewis acid	Time (h)	Yield (%)[a]	de (%)[b]
1[c]	H_2O–MeOH (2:1)	None	1	18 (68)	84
2[d]	H_2O–MeOH (2:1)	None	72	43 (12)	84
3[d]	H_2O–CH_2Cl_2 (4:1)	None	72	44 (7)	81
4[e]	H_2O	None	24	48 (21)	82
5[f]	H_2O	None	48	53 (21)	84
6[g]	H_2O	$InCl_3$	24	50 (25)	81

[a] Isolated yields. Yields in parentheses are for the recovered starting material **1**. [b] Diastereoselectivities were determined by ^{1}H NMR analysis. [c] Reaction was carried out with $\mathrm{Pr^iI}$ (5 × 2 equiv.) and In (7 equiv.) at 20 °C. [d] Reactions were carried out with $\mathrm{Pr^iI}$ (10 × 3 equiv.) and In (20 equiv.) at 20 °C. [e] Reaction was carried out with $\mathrm{Pr^iI}$ (10 × 2 equiv.) and In (10 equiv.) at 20 °C. [f] Reaction was carried out with $\mathrm{Pr^iI}$ (10 equiv.) and In (10 equiv.) at 20 °C. [g] Reaction was carried out with $\mathrm{Pr^iI}$ (10 equiv.), In (10 equiv.), and $InCl_3$ (1 equiv.) at 20 °C.



Scheme 4 *Reagents and conditions*: i, c-Pentyl I (40 equiv.) or $\mathrm{Bu^tI}$ (10 equiv.), In (10 equiv.), H_2O, 20 °C, 48 h.

In addition to the previously reported asymmetric synthesis of α-amino acids *via* triethylborane-induced alkyl radical addition to glyoxylic oxime ether in organic solvent,[5] the indium-mediated allylation and alkylation method in aqueous media disclosed a broader aspect of the utility of glyoxylic oxime ether for the synthesis of various types of α-amino acid derivatives.

We thank a Grant-in-aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants. H.M. gratefully acknowledges the financial support from Takeda Science Foundation and The Mochida Memorial Foundation, Japan.

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