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Zinc-mediated radical reaction of glyoxylic oxime ether and hydrazone in aqueous media: asymmetric synthesis of α-amino acids

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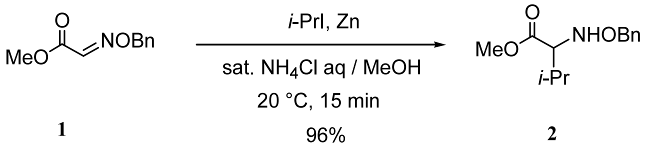
Abstract—Alkyl radical addition to glyoxylic oxime ether and hydrazone in aqueous media was studied using zinc dust as a radical initiator. The zinc-mediated radical reaction of the hydrazone bearing a chiral camphorsultam provided the corresponding alkylated products with good diastereoselectivities, which could be converted into enantiomerically pure α-amino acids.

Zinc-mediated carbon–carbon bond-forming reactions in aqueous media have attracted considerable interest from both economical and environmental points of view.[1] Among various types of known zinc-mediated reactions,[1] zinc-mediated radical reactions have captured much recent attention, because of the exceptional tolerance of functional groups.[2]

The carbon–nitrogen double bond has emerged as a radical acceptor.[3] However, zinc-mediated radical reactions of imine derivatives have not been widely studied so far. Our recent studies show that *N*-sulfonylimines are excellent radical acceptors for the aqueous-medium reaction using zinc as a single-electron transfer radical initiator.[4] As part of our program directed toward the development of environmentally benign synthetic reaction in aqueous media[5] employing imines as a substrate, we now report for the first time zinc-mediated radical addition to the Oppolzer's camphorsultam derivatives of water-resistant glyoxylic oxime ethers and hydrazones for asymmetric synthesis of α-amino acids.

As a preliminary experiment, we first examined the zinc-mediated isopropyl radical addition to achiral glyoxylic oxime ether **1**, because it has shown high reactivity toward radical additions in our recent studies (Scheme 1).[6] To a suspension of oxime ether **1**, metallic unactivated Zn, and *i*-PrI in MeOH was added dropwise saturated aq. NH_4Cl at 20°C. After the reaction mixture has been stirred at 20°C for 15 min, the desired isopropylated product **2** was obtained in 96% yield. The reaction probably proceeds through the radical pathway based on a single-electron transfer from zinc as reported previously.[4] It is noteworthy that reduction and hydrolysis of the oxime ether group were not observed under present reaction conditions.



Scheme 1.

Expecting that the comparison of zinc-mediated reactions with indium-mediated reactions[5a,b] would lead to instructive suggestions regarding radical initiators such as zinc and indium, we next investigated diastereoselective radical additions to oxime ether **3** having camphorsultam as a chiral auxiliary (Scheme 2 and Table 1). We recently reported indium-mediated alkyl radical addition to oxime ether **3** in aqueous media.[5a,b] The addition reactions to **3** were run in saturated aq. NH_4Cl even in the absence of an organic co-solvent. In contrast to indium-mediated reactions,[5b] the zinc-mediated reaction of **3** with an isopropyl radical proceeded smoothly to give the isopropylated product **4a** in 64% yield, after being stirred for only 0.5 h (entry 1).

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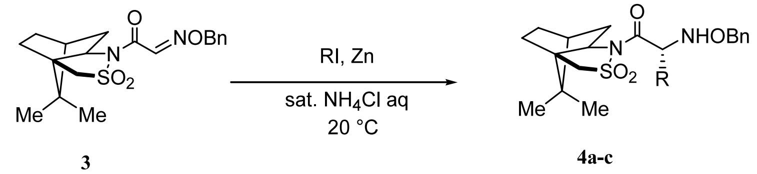


Scheme 2.

Table 1. Alkyl radical addition to chiral oxime ether **3**

Entry	R	Time (h)	Product	Yield (%)[a]	De (%)[b]
1[c]	*i*-Pr	0.5	**4a**	64	75
2[d]	c-Pentyl	2	**4b**	74 (11)	78
3[c]	*t*-Bu	1	**4c**	81	73

[a] Combined yields of diastereomers. Yield in parentheses was for the recovered starting material **3**.

[b] Diastereoselectivities were determined by ^{1}H NMR analysis of crude product.

[c] Reactions of oxime ether **3** (0.11 mmol) were carried out with RI (0.55 mmol) and Zn (0.77 mmmol) in sat. aq. NH_4Cl (0.4 mL).

[d] Reaction of oxime ether **3** (0.11 mmol) was carried out with c-pentyl iodide (0.55 mmol×2) and Zn (0.77 mmmol) in sat. aq. NH_4Cl (0.4 mL).

However, the diastereoselectivity of the zinc-mediated reactions was lower than that obtained by previous indium-mediated reactions. The absolute configuration at the newly formed stereocenter of major product **4a** was determined to be *R* by conversion into authentic *N*-Cbz-D-valine.[7] Other alkyl iodides were also examined as an alkyl radical precursor. Not only a secondary cyclopentyl radical but also a bulky tertiary butyl radical worked well under similar reaction conditions to give the corresponding adducts **4b** and **4c** in good yields (entries 2 and 3).

Expecting that the bulky diphenyl amino group on the imino nitrogen atom of **5** would enhance the diastereoselectivities, we next examined the diastereoselective radical addition to hydrazone **5** as a congener of radical acceptor (Scheme 3). The hydrazone **5** was easily prepared by condensation of methyl (*E*)-diphenylhydrazono acetate with (1*R*)-(+)-2,10-camphorsultam in the presence of trimethylaluminum. Screening the reaction conditions showed that the biphasic reaction conditions using saturated aq. NH_4Cl and CH_2Cl_2 were effective for the radical reaction of hydrazone **5**. As expected, the diastereoselectivities observed in the reaction of hydzone **5** were better than those obtained by the reaction of oxime ether **3** (Table 2). The isopropyl radical addition to hydrazone **5** gave the isopropylated product **6a** in 73% yield with 86% de, accompanying with 7% yield of the starting material **5** (entry 1). A cyclopentyl radical worked well (entry 2). In the case of *tert*-butyl radical addition, 84% yield of the desired product **6c** was obtained as a single diastereomer (entry 3).[8]

Table 2. Alkyl radical addition to chiral hydrazone **5**[a]

Entry	R	Product	Yield (%)[b]	De (%)[c]
1	*i*-Pr	**6a**	73 (7)	86
2	c-Pentyl	**6b**	58 (40)	86
3	*t*-Bu	**6c**	84	>95

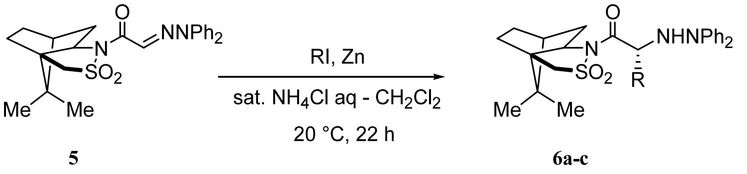
[a] Reactions of hydrazone **5** (0.11 mmol) were carried out with RI (0.55 mmol), Zn (0.77 mmmol) in sat. aq. NH_4Cl (0.4 mL) and CH_2Cl_2 (0.1 mL).

[b] Combined yields of diastereomers. Yields in parentheses were for the recovered starting material **5**.

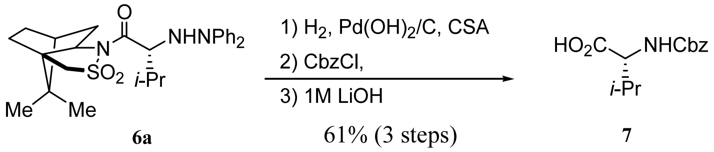
[c] Diastereoselectivities were determined by ^{1}H NMR analysis.

We finally converted the isopropylated product **6a** into α-amino acid **7** (Scheme 4). The cleavage of the N–N bond of diastereomerically pure product **6a** which was readily obtained by preparative TLC was successfully achieved by hydrogenolysis in the presence of Pearlman's catalyst and camphorsulfonic acid. Subsequently, protection with CbzCl and hydrolysis using 1M LiOH gave *N*-Cbz-D-valine **7** in 61% yield from **6a** without any loss of enantiomeric excess.

In conclusion, we have established the diastereoselective zinc-mediated alkyl radical addition to imine derivatives such as oxime ether and hydrazone in aqueous media. The reactions proceeded with good diastereoselectivities, providing access to a range of α-amino acid.



Scheme 3.



Scheme 4.

Acknowledgements

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8. A typical experimental procedure of alkyl radical addition to hydrazone **5**: To a suspension of hydrazone **5** (0.11 mmol), RI (0.55 mmol), Zn (0.77 mmmol) and CH_2Cl_2 (0.1 mL) was added dropwise aqueous sat. NH_4Cl (0.4 mL) at 20°C. After being vigorously stirred at the same temperature for 22 h, the reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1) afforded desired product **6** in the yields shown in Table 2.