Tandem Reactions

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Tandem Radical-Addition–Aldol-Type Reaction of an α,β-Unsaturated Oxime Ether**

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Conjugate addition of radical species has been recognized as a versatile tool for introducing an alkyl group into the β position of α,β-unsaturated carbonyl compounds,[1] and the subsequent trapping of the intermediate radical species with allyltin compounds has been widely studied.[2,3] Tandem reactions are among the most efficient synthetic methods. However, those that proceed sequentially through ionic species sometimes exhibit problematic drawbacks such as the need for exacting reaction conditions, whereas undesired polymerization may result from tandem radical reactions. A combination of radical and ionic processes may alleviate these problems and could thus be a promising approach. Oshima and co-workers first demonstrated that a tandem radical addition–aldol condensation of enones or enals could be performed via the formation of an intermediate boryl enolate.[4] Other groups have recently reported tandem reactions involving radical and ionic processes for the convenient synthesis of highly complex molecules.[5] However, there are only limited examples which employ enolate intermediates formed by a radical addition reaction. The goal of our work is to develop a highly efficient carbon–carbon bond-construction method by taking advantage of a novel hybrid radical–ionic reaction involving the radical addition to α,β-unsaturated oxime ethers and subsequent ionic trapping of the resulting *N*-boryl enamine by aldehydes.

Building upon our syntheses of α- and β-amino acids by radical addition to oxime ethers,[6] we extended our use of α,β-unsaturated oxime ether **1** bearing Oppolzer's camphorsultam to the synthesis of γ-amino acids (Figure 1). Recent studies on the radical addition to imines showed that aminoboranes were effectively formed by trapping of intermediate aminyl radicals with triethylborane.[7–10] Thus, we expected

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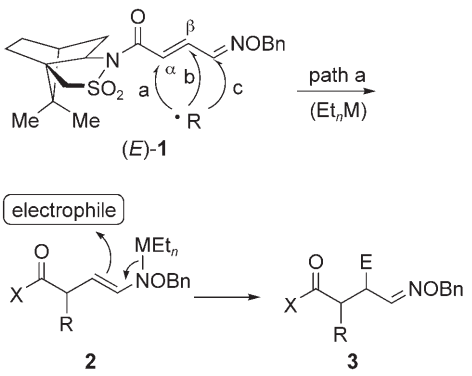
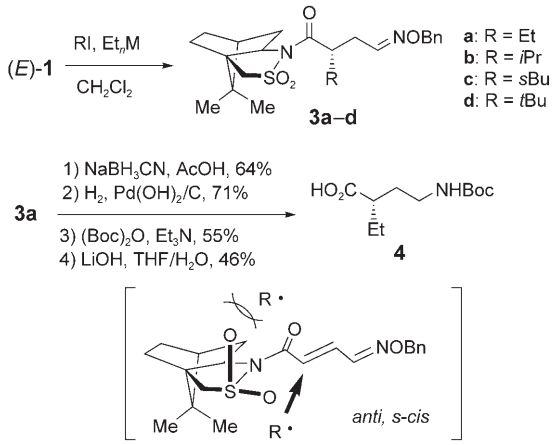


Figure 1. Tandem reaction involving both radical and ionic processes (X = (1*R*)-camphorsultam). Bn = benzyl.

that the boryl enamine **2** could be formed by the triethylborane-promoted radical addition to (*E*)-**1**, if the reaction proceeds regioselectively by path a.

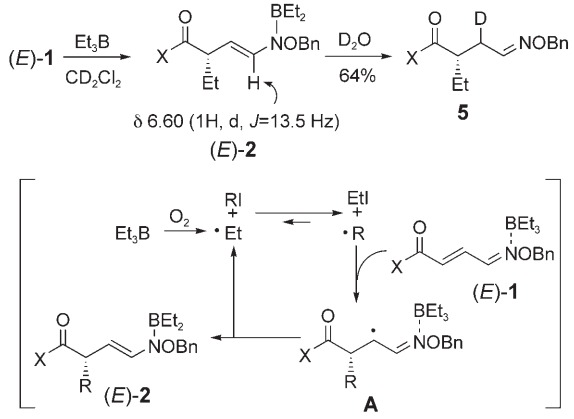
Prior to exploring issues of the tandem process, we first investigated the regioselectivity in the carbon-radical addition to conjugated oxime ether (*E*)-**1**, which possesses three radicophilic centers (Scheme 1). The addition of ethyl radical



Scheme 1. Radical addition to conjugated oxime ether (*E*)-**1**. Boc = *tert*-butyloxycarbonyl.

to (*E*)-**1** was performed in CH_2Cl_2 at 20 °C for 20 min with triethylborane (Table 1, entry 1). The reaction took place regioselectively at the α position of the carbonyl group (path a as shown in Figure 1) to give the desired product **3a** in 97 % yield without formation of other regioisomers (paths b or c). This is the first example of a regioselective radical addition to a conjugated oxime ether that involves four electrophilic positions. The diastereomeric purity of **3a** was found to be no less than 97.5:2.5 d.r. by ^{1}H NMR spectroscopic analysis of the crude product. The absolute configuration at the newly formed stereocenter was determined to be *S* by converting the adduct **3a** into the authentic γ-amino acid **4**.[11] The stereochemical preference of this reaction can be rationalized as follows. With regard to the conformation of (*E*)-**1**, the *anti* (sulfonyl and carbonyl groups) and *s-cis* (carbonyl group and C=C bond) planar rotamer shown in Scheme 1 should be favored over other rotamers. Therefore, the alkyl-radical addition to the *re* (bottom) face is favored, presumably resulting from steric interactions with the axial oxygen of the sulfonyl group.[6c] In marked contrast, the ethylated product **3a** was not formed with the use of diethylzinc as a radical initiator (Table 1, entry 2).[12] The high diastereoselectivities and good chemical yields were observed in the addition of secondary alkyl radicals to (*E*)-**1** (Table 1, entries 3 and 4). A lower chemical yield was attained with a bulky *tert*-butyl radical, but the reaction still proceeded with high d.r. (> 97.5:2.5; Table 1, entry 5). These observations indicate that triethylborane acts as an effective reagent for trapping the intermediate enaminyl radical to form the boryl enamine **2**.

To confirm the formation of boryl enamine **2**, we studied the ^{1}H NMR spectra and the trapping reaction of boryl enamine **2** with D_2O (Scheme 2). The ^{1}H NMR spectra of the



Scheme 2. Trapping reaction of boryl enamine with D_2O (X = (1*R*)-camphorsultam).

Table 1: Alkyl-radical addition to conjugated oxime ether (*E*)-**1**.[a]

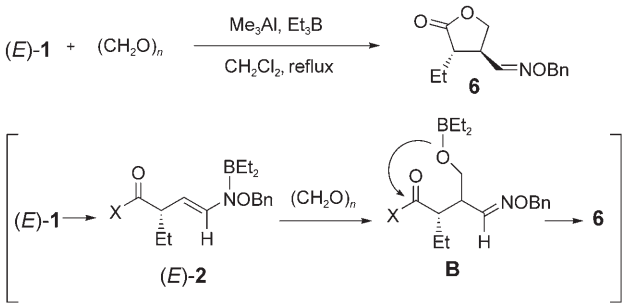
Entry	Initiator	RI	Product	Yield [%][b]	d.r.[c]
1	Et_3B	none	**3a**	97	> 97.5:2.5
2	Et_2Zn	none	–	ND	
3	Et_3B	*i*PrI	**3b**	56	> 97.5:2.5
4	Et_3B	*s*BuI	**3c**	69	> 97.5:2.5
5	Et_3B	*t*BuI	**3d**	28	> 97.5:2.5

[a] Reactions were carried out using RI (30 equiv) and Et_3B or Et_2Zn in hexane (1.0 M, 5 equiv) in CH_2Cl_2 for 20 min. [b] Isolated yield of the desired alkylated product (ND = not detected). [c] Diastereomeric ratios were determined by ^{1}H NMR analysis.

reaction mixture of **1** with triethylborane in CD_2Cl_2 suggested the formation of (*E*)-enamine **2** as shown in Scheme 2. The deuteration of boryl enamine **2** took place at the β position (relative to the carbonyl group) to give the product **5** in 64 % yield. Thus, the rationale of the reaction pathway is that the alkyl radical adds to the α position of the carbonyl group in (*E*)-**1** to form the intermediate radical **A**, which is captured by triethylborane to afford the (*E*)-boryl enamine **2** and regenerate an ethyl radical.

With these results in mind, we next investigated the tandem radical-addition–aldol-type reaction of an α,β-unsa-

turated oxime ether by using paraformaldehyde (Scheme 3). Triethylborane was added to a mixture of **1** and paraformaldehyde. The resulting products were the ethylated product **3a** and *trans*-γ-butyrolactone **6** in 53 and 44% yields, respectively (Table 2, entry 1). The γ-butyrolactone **6** was presumably



Scheme 3. Tandem radical-addition–trapping reaction of boryl enamine with paraformaldehyde (X = (1*R*)-camphorsultam).

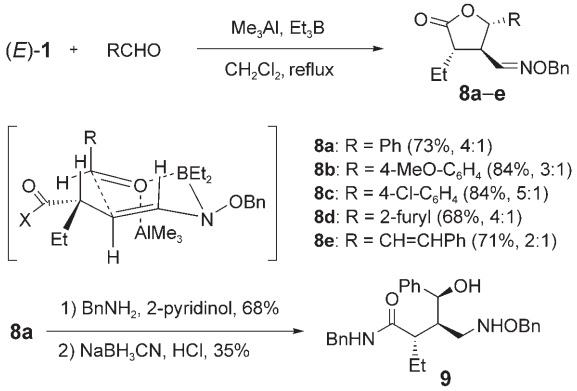
Table 2: Radical–aldol-type reaction of (*E*)-**1** with paraformaldehyde.[a]

Entry	Lewis acid	*T* [°C]	Yield [%][b]		Selectivity[c]
			6	**3a**	*trans*:*cis*
1	None	reflux	44	53	10:2
2	Me_3Al	20	41	42	10:3
3	Me_3Al	reflux	72	–	10:3[d]

[a] Reactions were carried out with Et_3B in hexane (1.0 M, 5 equiv), Me_3Al in hexane (1.0 M, 1.2 equiv), and $(CH_2O)_n$ (1.2 equiv) in CH_2Cl_2. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Enantiomeric purity of the *trans* isomer was found to be 90% *ee* by HPLC analysis.

formed through the diastereoselective addition of ethyl radical to **1**, trapping of boryl enamine **2** with paraformaldehyde, and intramolecular lactonization with concomitant removal of the chiral auxiliary. The relative configuration of the two substituents on lactone **6** was determined by NOE interaction experiments. To the best of our knowledge, this reaction represents the first reported example of the electrophilic trapping reaction of an unstable *N*-boryl enamine generated through a radical process. This tandem reaction was promoted in the presence of Me_3Al (1.2 equiv) as a Lewis acid. The reaction using Me_3Al under reflux gave the desired lactone **6** exclusively in 72% yield (Table 2, entry 3). The enantiomeric purity of *trans*-γ-butyrolactone **6** was found to be 90% *ee* by chiral HPLC analysis. The lower stereoselectivity of the tandem reaction (90% *ee*) than that of the simple ethyl-radical addition (> 97.5:2.5 d.r.) was attributed to the higher reaction temperature (reflux) used in the initial radical reaction step.

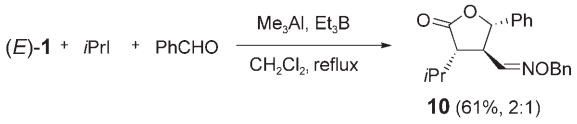
The utility of this new tandem radical–ionic reaction was tested in the asymmetric synthesis of various types of γ-butyrolactones. Thus, we investigated the reaction with different kinds of aldehydes (Scheme 4). The trapping reaction of boryl enamine **2** with benzaldehyde gave the *trans*,*trans* isomer **8a** as the major product, accompanied by small amounts of other diastereomers. γ-Butyrolactone **8a** was easily converted into γ-amino acid derivative **9**. Treat-



Scheme 4. Radical-addition–aldol-type reaction of (*E*)-**1** (ratio in parentheses is for the yield of the major isomer to that of all other isomers combined; X = (1*R*)-camphorsultam).

ment of **8a** with benzylamine in the presence of 2-pyridinol gave an acyclic oxime ether which was reduced to the amino acid amide **9**.[13] The electron-donating and electron-withdrawing substituents on the aromatic ring of the aldehyde exhibited no apparent effects on either the chemical yield or the stereoselectivity, and good yields were attained for both **8b** and **8c**. 2-Furfural and cinnamaldehyde also worked well under similar reaction conditions. The *trans*,*trans* stereoselectivity observed for the reaction can be explained by invoking a six-membered-ring transition state. The sterically more stable conformer of (*E*)-boryl enamine reacted with the Me_3Al-activated aldehyde in such a way that 1,3-diaxial interactions were minimized, and an unfavorable steric interaction with allylic substituents was avoided.[14]

Finally, we examined the tandem reaction involving an addition of isopropyl radical, which occurred by way of an iodine atom-transfer process, followed by an aldol-type reaction (Scheme 5). With the use of isopropyl iodide



Scheme 5. Isopropyl-radical-addition–aldol-type reaction of (*E*)-**1** (ratio in parentheses is for the yield of the major isomer to that of all other isomers combined).

(20 equiv) as radical precursor and benzaldehyde as trapping agent, the tandem reaction of (*E*)-**1** proceeded smoothly to give isopropyl-substituted γ-butyrolactone **10** in 61% yield.

In conclusion, we have developed a hybrid type of reaction that involves a radical addition and an aldol condensation. This tandem reaction of an α,β-unsaturated oxime ether provides a powerful synthetic approach to chiral γ-butyrolactones and γ-amino acids.

Experimental Section

General procedure for radical-addition–aldol-type reaction of α,β-unsaturated oxime ether (*E*)-**1**: Aldehyde (0.148 mmol) and Me_3Al

(1.0 M in hexane, 0.148 mL, 0.148 mmol) were added to a solution of (*E*)-**1** (50 mg, 0.124 mmol) in CH_2Cl_2 (5 mL) at room temperature under a N_2 atmosphere. Et_3B (1.0 M in hexane, 0.62 mL, 0.62 mmol) was then added dropwise to the reaction mixture at reflux. After stirring at reflux for 3 h, the reaction mixture was diluted with saturated aqueous $NaHSO_3$ and then extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated at decreased pressure. Purification of the residue by preparative TLC (hexane/EtOAc 5:1) afforded the desired γ-butyrolactones.

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