Cascade radical reactions via carbon-carbon/heteroatom bond-forming process

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Abstract
This article highlights our recent efforts toward developing the cascade reactions constructing the carbon-carbon and carbon-heteroatom bond based on radical chemistry. The diethylzinc-promoted reaction of dehydroamino acid derivatives with acid anhydride or π-allyl palladium complex gave α,α-disubstituted amino acids via the radical and anionic carbon-carbon bond-forming process. This reaction was successfully expanded into the reductive transformation of N-phthaloyl dehydroalanine using BuSnH and Pd(PPh3)4. The chiral Lewis acid-mediated cascade radical addition-cyclization-trapping reaction proceeded smoothly with good enantioselectivities by using hydroxamate ester functionality as a chiral Lewis acid-coordinating tether between two radical acceptors. This method was applied into cascade reaction involving the unfavorable polarity-mismatched addition of electrophilic perfluoroalkyl radicals to electron-deficient acceptors. Additionally, cascade sequence terminated by radical-radical coupling was also reported.

Keywords: Cascade reaction, radical reaction, palladium, chiral Lewis acid, cyclization, perfluoroalkyl radical

Introduction
Strategies involving cascade process offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond-formation in a single operation. Radical chemistry has been developed as one of the most powerful tools for carbon-carbon bond formation in organic synthesis [1-11]. Particularly, the advantages for utilizing the radical methodologies are the high functional group tolerance and the mild reaction conditions because radical intermediates are not charged species. Therefore, a number of extensive investigations into sequential radical reactions have been reported over the last fifteen years and significant progress has been made in recent years [7-11].

We have also been interested in developing the new and efficient cascade approach for constructing carbon-carbon/heteroatom bond based on radical chemistry [12-15]. This review highlights our recent studies on cascade radical reactions, which can be classified into two types by the reaction mechanism (Figure 1).

Review
Cascade reactions via radical-ionic process
Compared to the sequential reactions only involving radical species, the cascade reactions involving both radical and ionic species are not well explored. The combination of radical process and ionic process is expected to allow further progress in the field of cascade carbon-carbon bond-forming chemistry. As an early work, Oshima's group has demonstrated that the radical addition-aldol condensation of enones or enals could be performed by Et3B as a radical initiator [16-18]. About ten years ago, several reactions involving radical and ionic process have been achieved [8,19-23]. In these reactions, the conversion of radical species into ionic species is a key step.

Dehydroamino acid derivatives are well known to be excellent radical acceptors [24-26]. We studied the synthesis of α,α-disubstituted amino acids based on the cascade radical and anionic reaction of dehydroamino acid derivatives [27,28]. At first, the reaction of dehydroamino acid derivative 1 was investigated by using acid anhydride as an electrophile (Scheme 1). As expected, dehydroamino acid 1 exhibited a good reactivity to give the desired α,α-disubstituted amino acid 2 in 63% yield, after hydrolysis of diphenylimino moiety. A remarkable feature of this reaction is the construction of two carbon-carbon bond and nitrogenated quaternary carbon-center via a cascade radical and ionic process. The combination of radical initiator Et2Zn and O2 was essential for successful reaction [29,30]. Initially, an ethyl radical was generated from Et2Zn and O2, and then, the ethyl radical added to 1 to give the intermediate radical A. In this reaction, Et2Zn also acted as an effective reducing agent. Thus, the initially formed radical A was rapidly converted into the zinc-enolate anion B and an ethyl radical. In marked contrast, the reaction did not proceed when Et3B was employed as a radical initiator due to the low reactivity of Et3B toward the radical α to an ester group [31,32]. In other words, the high reactivity of Et2Zn toward the alkoxycarbonyl-stabilized α-radical is a key factor for the successful transformation. The formation of zinc enolate from α,β-unsaturated ester in diethylzinc mediated...
radical reaction was also studied by Bertrand’s group [20].

On the basis of cascade acylation reaction, we next investigated the combination of radical reaction and transition metal-catalyzed allylation (Scheme 2). Since the electrophilic π-allyl palladium complex has shown excellent reactivity toward soft carbanion, we next studied the Et₂Zn-promoted reaction of 1 with π-allyl palladium complex based on our previous studies [33,34]. In this transformation, the branched acetates were found to be the efficient allylic reagent. To a solution of dehydroamino acid 1, the radical precursor (RI), the branched acetate (Ar=Ph) and Pd(PPh₃)₄ in CH₂Cl₂ was added Et₂Zn. As expected, three-component reaction proceeded smoothly to give the allylated products 3a-e after hydrolysis of diphenylimino moiety. As an alkyl radical precursor, i-PrI, c-pentyl-I, c-hexyl-I, s-BuI and t-BuI worked well. A favorable experimental feature is that the reaction proceeded smoothly even in the absence of toxic tin hydride or heavy metals via
the iodine atom transfer radical process. The reaction was also performed with other \( \pi \)-allyl palladium complexes to give the amino acids 3f-h allowing facile incorporation of structural variety. It is well known that the reaction of \( \pi \)-allyl palladium complex with Et\(_2\)Zn gives the allyl zinc reagent [35]. Therefore, it should be noted that all steps in this transformation must be faster than the competitive formation of allyl zinc reagent as a by-product.

Expansion into reductive transformation

The reductive aldol reaction is a synthetically attractive method, since a reductive method does not require the preformation of metal enolates or silyl enol ethers [36-38]. As an alternative approach to enolate anion, we investigated the reductive aldol reaction of \( N \)-phthaloyl dehydroalanine 4 (Scheme 3). In the presence of Bu\(_3\)SnH and Pd(PPh\(_3\))\(_4\), the reaction of 4 with benzaldehyde proceeded effectively to afford the desired product 5 in 65% yield. Next, this method was applied to the reductive allylation reaction involving two different Pd catalyzed process. As expected, the allylated product 6 was obtained in 48% yield by using the branched acetate, Bu\(_3\)SnH and Pd(PPh\(_3\))\(_4\). In this reaction, the enolate anions C and/or D were generated from Pd(PPh\(_3\))\(_4\) and Bu\(_3\)SnH. In addition to the radical-ionic reactions, these reductive reactions disclosed a broader aspect of the utility of dehydroamino acids for the synthesis of \( \alpha,\alpha \)-disubstituted amino acids.

Cascade reactions via radical-radical process

Free radical reaction has been a powerful method for constructing the multiple bonds via sequential radical-radical process. Particularly, our laboratory is interested in developing the cascade reaction involving the Lewis acid-mediated radical cyclization process for the synthesis of highly functionalized cyclic compounds [39,40]. For an efficient cyclization, the intramolecular radical cyclization must be faster than intermolecular trapping of the initially formed radical on a substrate. Therefore, the geometry of substrates should be crucial for the efficiency of cyclization process. We considered that the control of the rotamer population would be achieved by the introduction of a coordination tether into the middle of substrate (Figure 2). For this purpose, we paid attention to a hydroxamate ester as a coordination tether with chiral Lewis acid [41,42]. In this study, we also expected that the control of stereochemistry will been also achieved by this method. Recently, hydroxamic acid derivatives have been shown to be the useful achiral templates in enantioselective Diels-Alder reaction by Renaud's group [43,44]. In this cascade approach, it is also important to control the regiochemistry as well as stereochemistry. With the objective to control the regiochemistry, the substrate should have two kinds of polarity-different radical acceptors. Additionally, the activation of electron-deficient “acceptor 1” by Lewis acid could enhance the regioselectivity and may suppress the non-catalyzed reaction to give racemic products. Compared with the stereocontrol studies on intermolecular radical reactions, the enantiocontrol in radical cyclizations still remains a major challenge [45-52]. Therefore, we have started investigating the new type of chiral Lewis acid-mediated cyclization approach [53-55]. The radical addition-cyclization-trapping reaction of substrate 7 having methacryloyl moiety and the C-C triple bond was studied by using radical initiator Et\(_3\)B (Scheme 4) [56,57]. As expected, the regiochemistry was controlled to give the single product. The effect of chiral Lewis acid, generated from ligand L1 and Zn(OTf)\(_2\), is shown in Table 1. A stoichiometric amount of chiral Lewis acid promoted the reaction with an isopropyl radical at -78°C to form the product 8a in 87% yield with 80% ee (entry 1). Decreasing the amount of chiral Lewis acid to 0.5 or 0.3 equivalent did not affect both enantioselectivity and chemical efficiency (entries 2 and 3). These results indicate that the non-
Figure 2. Control of rotamer population, stereochemistry and regiochemistry.

Catalyzed background reaction giving the racemic product was suppressed. Similarly, cyclohexyl iodide worked well as a radical precursor (entry 4). High level of enantioselectivity was obtained in the reaction with t-butyl radical (entry 5). The rationale of the reaction pathway is that the nucleophilic alkyl radical initially reacted with electron-deficient acryloyl moiety of 7 to form carbonyl-stabilized radical E, which attacked intramolecularly to the carbon-carbon triple bond as a 5-exo cyclization manner. The products 8a-c were obtained via the iodine atom-transfer reaction from RI to vinyl radical F. Interestingly, high Z-selectivity of 8a-c was observed (Z:E = >98:2) in all cases. These observations indicate that the iodine atom-transfer to the reactive vinyl radical F is fast. The fast trapping reaction of F with RI would direct the Z selectivity without the isomerization.

The three-dimensional arrangement of two radical acceptors was controlled by a ternary complex of ligand, Lewis acid and substrate. Assuming that there is a tetrahedral or cis-octahedral geometry around the zinc center [58, 59], tentative model of octahedral complex is proposed (Figure 3). In this organization, two oxygen atoms of substrate 7 occupy two equatorial directions and the aryl group of ligand shields the C-C triple bond.

For the synthesis of the highly functionalized compounds,
the chiral substrate (R)-9 (81% ee) having a phenyl group at an allyl position was employed (Scheme 5). When the reaction with an isopropyl radical was carried out at -40°C, cis-10a was obtained in 63% yield with 99% ee as a major product. At the same time, a small amount of trans-11a was formed with low ee. The similar trend was also observed in the reaction of (R)-9 with t-butyl iodide. The enhanced enantioselectivity of cis-diastereomers cis-10a and cis-10b can be explained by kinetic resolution. A remarkable feature of this reaction is the construction of three bonds and three chiral centers via cascade process.

Cascade reactions involving the polarity-mismatched addition
Perfluoroalkyl radical is classified into electrophilic radical [60], thus, the polarity-mismatched addition of perfluoroalkyl radicals to electron-deficient alkenes is rare (Figure 4) [61-67]. We have been interested in the cascade transformation involving the polarity-mismatched perfluoroalkyl radical addition [68-70]. At first, we studied the regiochemistry of cascade reaction of substrate having two polarity-inverted acceptors with perfluoroalkyl radicals. In this reaction, two competitive reaction pathways (Mismatched path a and Matched path b) are presumed.

The enantioselective reaction of substrate 12 was performed at -78°C in the presence of chiral Lewis acid generated from ligand L1 and Zn(OTf)2 (Scheme 6). When n-C3F7I was employed as a primary perfluoroalkyl radical source, we found the polarity-mismatched perfluoroalkylation (path a) as a major course. The products 13a (cis/trans-mixture) and 14a were obtained in 97:3 ratio and the major product cis-13a was isolated with 87% ee. The enantioselectivities were increased by changing the perfluoroalkyl radical to secondary i-C3F7 and cyclo-C6F11 radicals. On the other hand, the regioselectivities decreased because the secondary perfluoroalkyl radicals exhibit greater electrophilicities than primary perfluoroalkyl radicals24.

The regiochemistry would be controlled mainly by the stability of intermediate radicals (Figure 5). The stabilization of an intermediate radical by resonance promotes the polarity-mismatched addition (path a) and leads to the major products 13a-c, whereas the matched radical addition (path b) gives the less stable radical.
Scheme 6. Polarity-mismatched perfluoroalkylation of 12.

Scheme 7. Cascade reaction terminated by radical-radical coupling.

Scheme 8. Radical addition to C=N bond and radical-radical coupling.

Cascade reactions terminated by radical-radical coupling
The accumulation of an intermediate radical frequently leads the additional radical-radical coupling reaction. In the case of bulky ketoxime ether 15, the trapping of an intermediate aminyl radical with Et₃B was suppressed owing to steric effect even when excess amounts of Et₃B were employed (Scheme 7) [71]. Therefore, N-isopropylated product 16 was obtained via the radical-radical coupling of an aminyl radical, which has enough time to couple with an isopropyl radical.

For another example, the radical-radical coupling was observed in the enantioselective radical addition to ketamine 17 using chiral Lewis acid derived from ligand L2 and Zn(OTf)₂ (Scheme 8) [72]. Interestingly, the diethylated product 18 was obtained as a major product with 80% ee. The formation of the diethylated product 18 results from the accumulation of an intermediate radical, which was not trapped by Et₃B probably due to the formation of stable complex with chiral Lewis acid.

Conclusion
The recent our studies on the cascade radical reactions are summarized in this review. At first, the cascade reaction involving both radical and ionic species is reported. Particularly,
the successful combination of radical reaction and Pd-catalyzed allylation is expected to allow further progress in the field of cascade chemistry. Next, the cascade reaction via the chiral Lewis acid-mediated radical cyclization process is reported. The radical addition-cyclization-trapping reaction proceeded with good enantioselectivities based on our strategy using hydroxamate ester as a coordination site with a chiral Lewis acid. Additionally, the cascade reaction involving the polarity-mismatched perfluoroalkylation is also developed. These studies offer opportunities for further exploration with intriguing possibilities in cascade transformations using radical reactions.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions                | HM | YT |
|--------------------------------------|----|----|
| Research concept and design          | ✓  | ✓  |
| Collection and/or assembly of data   | ✓  | -- |
| Data analysis and interpretation     | ✓  | -- |
| Writing the article                  | ✓  | ✓  |
| Critical revision of the article     | ✓  | -- |
| Final approval of article            | ✓  | ✓  |
| Statistical analysis                 | ✓  | -- |

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