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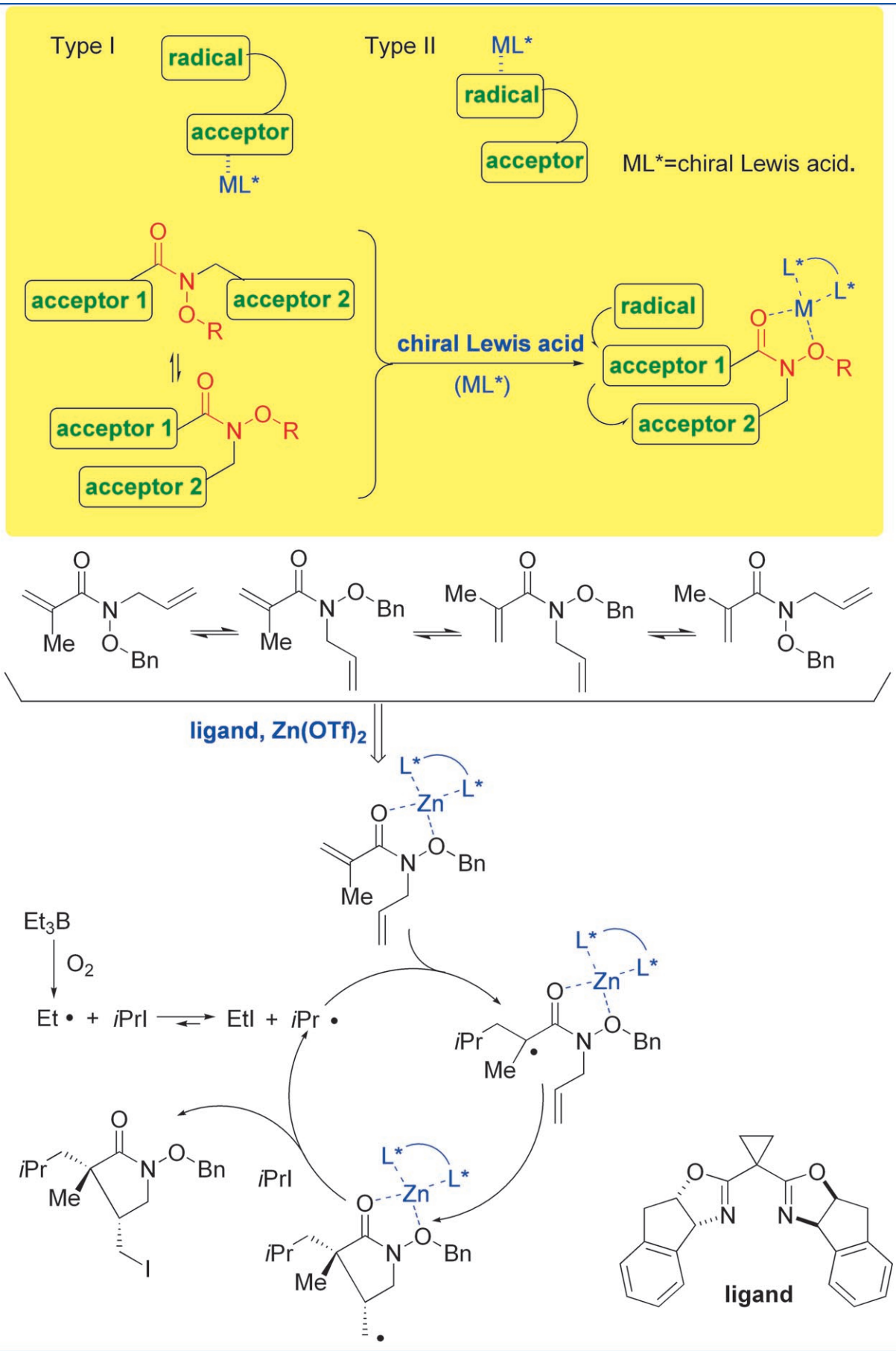

Enantioselective Radical Cyclizations: A New Approach to Stereocontrol of Cascade Reactions

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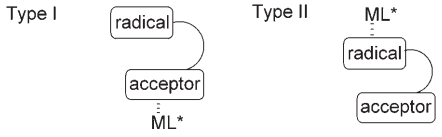
Dedicated to the memory of the late Professor Yoshihiko Ito

Abstract: Stereocontrol in a cascade radical addition–cyclization–trapping reaction was achieved by a new approach, which utilizes a hydroxamate ester moiety as a coordinating chiral Lewis acid tether between two radical acceptors. A remarkable feature of this reaction is the construction of three bonds and tertiary and quaternary stereogenic centers through both inter- and intramolecular carbon–carbon bond-forming processes. The chiral Lewis acid mediated reaction of oxime ethers also proceeded smoothly with good enantio- and diastereoselectivities, indicating the usefulness of the cascade approach for the asymmetric synthesis of various γ-lactams.

Keywords: cascade reactions · enantioselectivity · Lewis acids · oxime ether · radicals

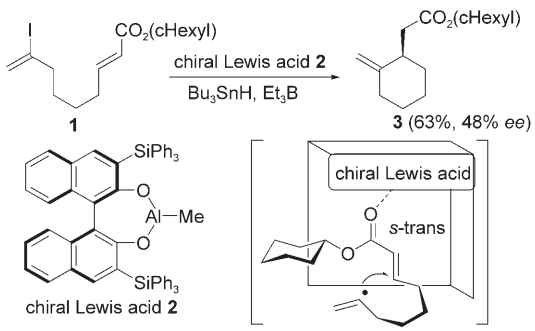
Introduction

The control of stereochemistry in free-radical-mediated reactions has been of great importance to organic synthesis.[1] Hence, in recent years, significant progress has been made in enantioselective radical addition reactions, allylation, and hydrogen-atom transfer reactions.[2–4] Particularly, enantioselective carbon–carbon bond construction from radical intermediates is a subject of current interest.[5] However, studies on enantioselective radical carbon–carbon bond-forming reactions have concentrated on intermolecular reactions, and stereocontrol in intramolecular construction still remains a major challenge. Only a handful of reports describes enantioselective radical cyclization reactions mediated by chiral Lewis acids; these reactions can be classified into two types by the nature of coordination with a Lewis acid (Type I and Type II, ML* = chiral Lewis acid).[6–8]



Enantioselective Radical Cyclizations

Early work on enantioselective type I cyclization reactions was reported by Nishida's group (Scheme 1).[6] The 6-*exo* cyclization of **1** was performed by using chiral aluminum Lewis acid **2** derived from $AlMe_3$ and BINOL (BINOL = 2,2-dihydroxy-1,1-binaphthyl). With use of four equivalents of **2**, the desired cyclic product **3** was obtained in 48% *ee*; the use of one equivalent of **2** gave low selectivity.



Scheme 1. Type I cyclization.

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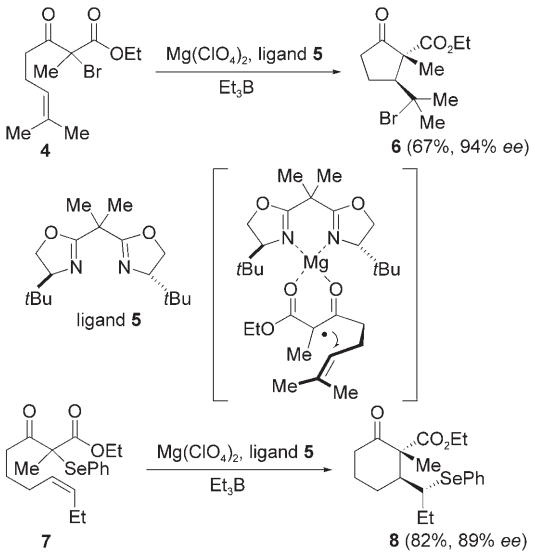
A high degree of stereocontrol was achieved by Yang and co-workers in type II cyclizations by using α-radical species generated from a β-keto ester as a coordination site (Scheme 2).[7] Atom-transfer cyclization of **4** proceeded

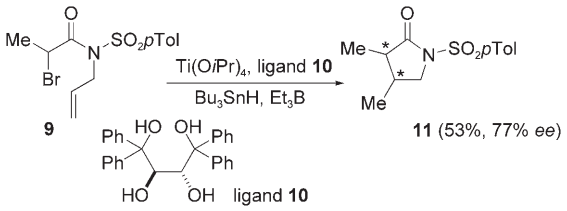


4 **6** (67%, 94% *ee*) **7** **8** (82%, 89% *ee*)

Scheme 2. Type II cyclization.

smoothly to give the cyclized product **6** in good enantioselectivity when chiral ligand **5** and $Mg(ClO_4)_2$ were employed.[7a] As a solvent effect, toluene generally gave higher enantioselectivities than CH_2Cl_2. PhSe-group-transfer radical cyclization of **7** also proceeded with 89% *ee*.[7c] High enantioselectivity was attained even when using 0.3 equivalents of the chiral Lewis acid catalyst.

Enantioselective cyclization of α-bromo-*N*-allylamides was studied by Ishii's group (Scheme 3).[8] Among several

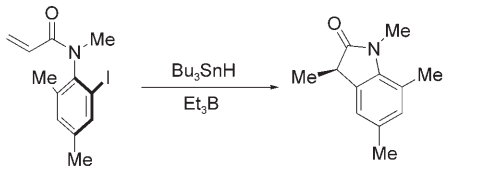


9 **11** (53%, 77% *ee*)

Scheme 3. Radical cyclization.

substrates evaluated, only sulfonamide **9** with a *p*-tolyl sulfonyl substituent gave reasonable enantioselectivity. In the presence of $Ti(OiPr)_4$ and chiral ligand **10**, the product **11** was obtained in 77% *ee*.

As a related example, transfer of chirality was also investigated in radical cyclization by Curran's group (Scheme 4).[9] In this unique cyclization procedure, axial chirality was transferred into a new stereocenter with retention of chirality as a result of the almost complete absence of racemization of radical intermediates.

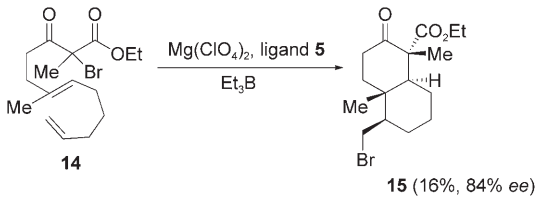


12 (97% *ee*) **13** (84% *ee*)

Scheme 4. Transfer of chirality.

The enantioselective radical cyclization was also achieved by Bach's group, who relied on an unique chiral Brønsted acid catalyst.[10] However, this reaction cannot be categorized as direct stereocontrol in radical cyclizations, because the stereodetermining step is hydrogen transfer from Bu_3SnH to the intermediate radical.

Strategies involving tandem or cascade process offer the advantage of multiple carbon–carbon bond formations in a single operation; thus, a number of extensive investigations into sequential radical reactions were reported in recent years.[11,12] Enantioselective tandem or cascade radical cyclizations continue to attract much interest, since highly functionalized compounds with multiple stereocenters are provided. The type II cyclization has been applied to tandem cyclization (Scheme 5).[7b] Tandem reaction of **14** could be

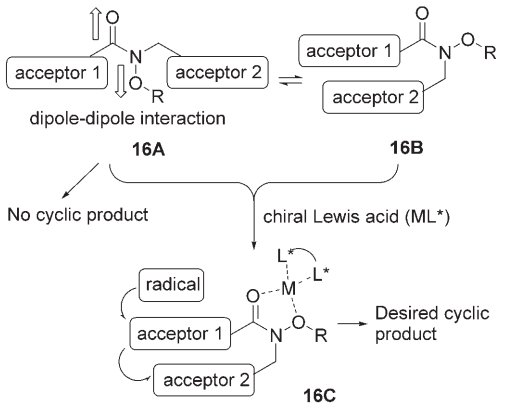


14 **15** (16%, 84% *ee*)

Scheme 5. Tandem reaction through type II cyclization.

performed with ligand **5** and $Mg(ClO_4)_2$. Although reaction of **14** in toluene at −78 °C gave poor enantioselectivity, good enantioselectivity was observed when reaction was carried out in toluene at −20 °C, but the yield of the product **15** was low. Recently, Yang et al. also reported that the PhSe-group-transfer reaction was ideal in terms of both reaction efficiency and enantioselectivity for the tandem cyclization.[7c]

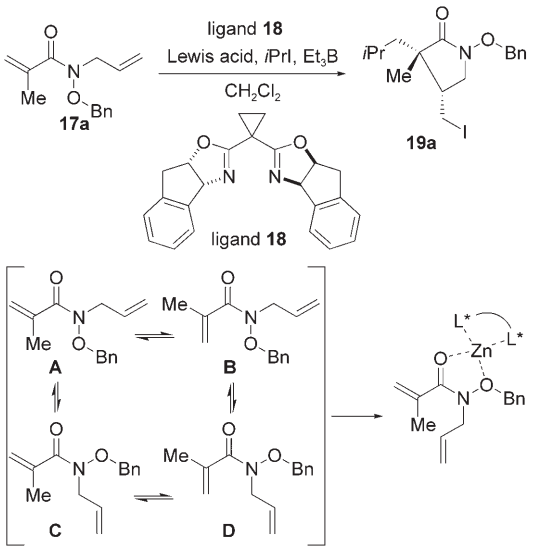
Despite such significant advances, the difficulty in achieving the enantioselective tandem or cascade radical cyclizations has remained unresolved and there are no reports on enantioselective reactions involving both inter- and intramolecular carbon–carbon bond-forming processes. The goal of our work is to develop a highly efficient and stereoselective cascade carbon–carbon bond-forming method. Therefore, we have designed new approaches to control stereochemistry of cascade radical addition–cyclization reactions by making use of hydroxamate esters (Scheme 6).[13]



Scheme 6. Radical addition–cyclization–trapping reaction of **17a**.

Since most radical reactions proceed through early transition states, the geometry of substrates play an important role;[14] thus, the control of the rotamer population such as **16A** and **16B** would be crucial for achieving both excellent chemical efficiency and high selectivity in cascade reactions (Scheme 6). The principal function of a Lewis acid is to control the rotamer populations of substrates.[15] We have considered that the predominant formation of a single reactive rotamer **16C** must be achieved by the approach that involves a coordination tether in the middle of two acceptors. Additionally, we also expected that the activation of radical acceptor 1 on reactive rotamer **16C** by Lewis acid could suppress the noncatalyzed reaction giving racemic products. Therefore, we have been interested in exploring tethers such that the substrate has the potential for the formation of a five-membered chelate with the chiral Lewis acid. Recently, hydroxamic acid derivatives have been shown to be useful achiral templates by Renaud's group in enantioselective Diels–Alder reaction.[16] Therefore, we selected a hydroxamate ester moiety as a coordination tether for the chiral Lewis acid. In our concept, the hydroxamate ester moiety could control the rotamer population of substrates through a stable five-membered chelation.

First, the isopropyl radical addition-cyclization-trapping reaction of hydroxamate ester **17a** was studied (Scheme 7). We expected that a proper combination of chiral ligand, Lewis acid, and hydroxamate ester would allow highly enantioselective cyclization as a result of the control of the several possible rotamers **A**–**D**. Representative results of an experiment to probe the utility of hydroxamate ester functionality are shown in Table 1.[17] While practically no reaction occurred in the absence of a Lewis acid additive (entry 1), the addition of a zinc Lewis acid accelerated the reaction at 20 °C to give the 5-*exo* cyclization product **19a** in 41 % yield accompanied by the recovered starting material **17a**; the equilibrium population of reactive rotamer was increased by coordination of Lewis acid (entry 2). It is important to note that the zinc-mediated reaction did not proceed at −78 °C (entry 3). The use of chiral ligand led to an enhancement in chemical yield even at −78 °C. In the presence of stoichiometric amounts of the chiral Lewis acid prepared from Zn-



Scheme 7. Concept of enantioselective cascade reaction.

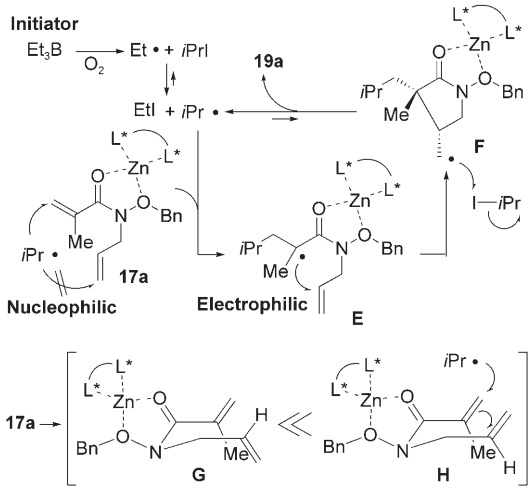
Table 1. Radical reaction of **17a** with isopropyl iodide.[a]

Entry	LA	Ligand	T [°C]	Yield [%]	dr[b]	*ee* [%][c]
1	none	none	20	NR[d]		
2	$Zn(OTf)_2$	none	20	41 (42)[e]	>98:2	
3	$Zn(OTf)_2$	none	−78	NR[d]		
4	$Zn(OTf)_2$	**18**	−78	81	>98:2	76

[a] Reactions were carried out with **17a** (1 equiv), isopropyl iodide (30 equiv), 1.0 M Et_3B in hexane (2.5 equiv), Lewis acid (1 equiv) and ligand **18** (1 equiv). [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis. [d] No reaction. [e] Yield in parentheses is for the recovered starting material **17a**.

$(OTf)_2$ and box ligand **18**, the product **19a** was formed in 81 % yield with good enantioselectivity and high *cis* diastereoselectivity (entry 4). These results suggest that the chelation with a chiral Lewis acid led to reduced conformation flexibility and the expected chiral Lewis acid coordinating rotamer was present to a significant extent to enhance the cyclizations rates. As a general trend, the combination of a phenyl-substituted box ligand and zinc Lewis acid gives high selectivity, whereas the aliphatic substituted box ligands give high selectivity in combination with magnesium Lewis acid.[18] Indeed, enantioselectivity was remarkably decreased when $Mg(OTf)_2$ was used instead of $Zn(OTf)_2$.

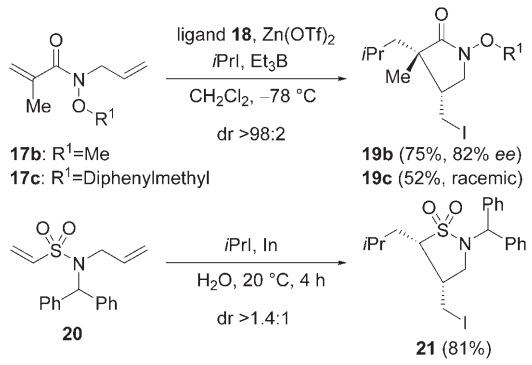
The rationale of the reaction pathway of this reaction is that the nucleophilic isopropyl radical initially reacts with electron-deficient methacryloyl moiety of **17a** to form electrophilic carbonyl-stabilized radical **E**, which undergoes intramolecular attack at the olefin moiety, that is, a 5-*exo-trig* radical cyclization (Scheme 8). The cyclic product **19a** was obtained by an iodine-atom-transfer reaction from isopropyl iodide to the primary radical **F**. The success of this reaction reflects the overall difference in the stability of the isopropyl radical and an intermediate radical **F**. Thus, the iodine-atom-transfer process from a secondary alkyl iodide to an unstable primary intermediate radical **F** is a key step.[19] Cyc-



Scheme 8. Effect of substituent R^1 on yield and selectivity.

lization leading to the major *cis*-diastereomer occurs via the conformer **H**, in which two olefin units adopt a *cis* arrangement, probably due to the effect of orbital symmetry reported by Beckwith and Houk.[20] In the case of **17a**, which has a methyl group, the effect of orbital symmetry can be assumed to be more significant the steric factor between **G** and **H**.

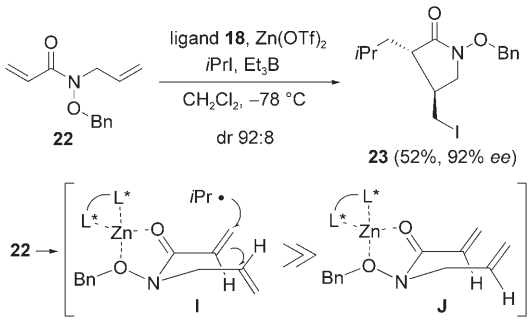
We are interested in probing the effect of the fluxional substituent R^1 of the hydroxamate ester moiety on yield and selectivity (Scheme 9).[21] The steric factor of the substituent



Scheme 9. Possible reaction pathway and possible cyclic transition states.

R^1 had an impact on enantioselectivity. Reaction of **17b**, which has a small methoxy group, was both highly enantio- and diastereoselective. In contrast, increasing the size of R^1 affected the reactivity and selectivity, and the use of substrate **17c**, with a diphenylmethyl group, gave the nearly racemic product **19c**, probably due to dissociation between chiral Lewis acid and bulky substituent. These observations clearly indicate that rigid conformation of the ternary complex of substrate, $Zn(OTf)_2$ and ligand **18** was required for good yield and high stereoselectivity. The size of the fluxional substituent was important for efficiency of radical cyclization without Lewis acid. In our previous work on indium-mediated radical reaction of sulfonamides,[22] the bulky substituent was essential to achieve good conversions. Sulfonamide **20**, with a bulky diphenylmethyl group, exhibited good reactivity to give good yield of the cyclic product **21** after being stirred at 20 °C for 4 h. Compared with the case of **20**, substrates **17a** and **17b** exhibited excellent reactivities in the presence of chiral Lewis acid as a result of the predominant formation of reactive rotamer by chelation.

An outstanding level of enantioselectivity was obtained in the cascade reaction of acrylated substrate **22** (Scheme 10).

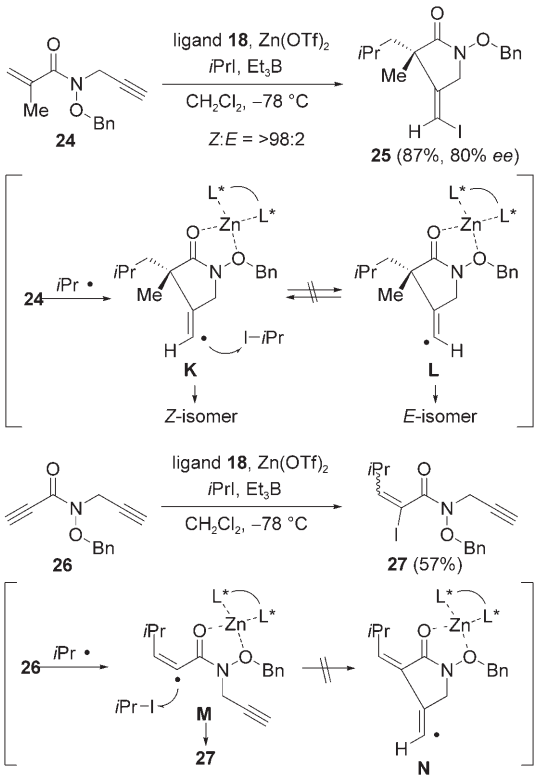


Scheme 10. Radical reaction of acrylated substrate **22**.

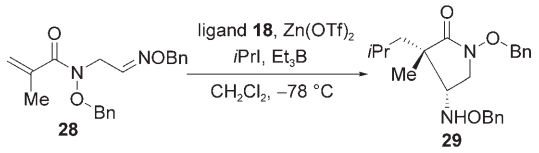
In marked contrast to methacrylated substrates **17a–c**, *trans* diastereoselectivity was observed. The *trans* selectivity in reaction of **22** was regarded as the result of steric repulsion between two olefin units and the reaction proceeded via the stable conformer **I**.

To understand the generality and practicality of the present cascade reaction, the next substrates of choice were substrates **24** and **26** having carbon-carbon triple bond (Scheme 11). As expected, the chiral Lewis acid promoted the reaction of **24** to afford the cyclized product **25** in high yield and with enantioselectivity. The high *Z*/*E* selectivity of product **25** indicates that the iodine atom transfer from *i*PrI to reactive vinyl radical **K** was effective and directed the *Z* selectivity. The catalytic nature of the reaction of **24** was also examined. The reaction proceeded equally well with 30 mol% of chiral Lewis acid as with stoichiometric amounts. In contrast to substrate **24**, the desired product was not formed when substrate **26**, with two carbon–carbon triple bonds, was employed. The adduct **27** was only obtained as a result of the quick trapping reaction of vinyl radical **M** with *i*PrI.

The carbon–nitrogen double bond of imine derivatives has emerged as a radical acceptor.[23–26] However, nothing is known about the enantioselective radical cyclization of imines.[27] The oxime ether **28** was found to undergo a radical addition–cyclization reaction mediated by chiral Lewis acids, based on our strategy by using hydroxamate ester as a coordination site (Scheme 12).[28] In the presence of $Zn(OTf)_2$, the use of ligand **18** led to not only an enhancement in chemical yield, but also an improvement in *cis/trans* diastereoselectivity (compare entry 1 with entry 2 in Table 2).[29] A careful reaction analysis showed that the amount of tri-



Scheme 11. Radical reaction of **24** and **26**.



Scheme 12. Radical addition–cyclization reaction of oxime ether **28**.

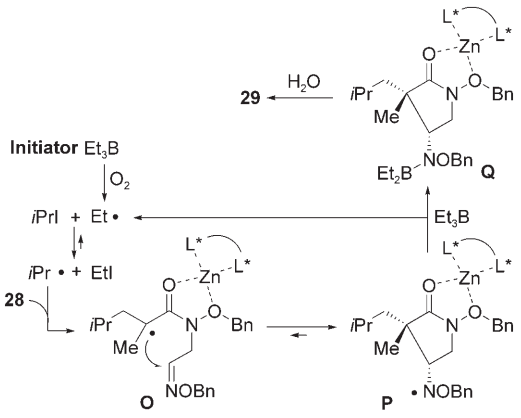
Table 2. Radical reaction of **28** with isopropyl iodide.[a]

Entry	Ligand	Et_3B [equiv]	t [h]	Yield [%]	ratio[b]	*ee* [%][c]
1	none	2.5×2	15	22 (25)[d]	78:22	
2	**18**	2.5	3	69	84:16	68
3	**18**	20	3	70	82:18	85
4	**18**	2.5	1	17	89:11	77
5	**18**	2.5	24	91	76:24	64

[a] Reactions were carried out with **28** (1 equiv), isopropyl iodide (30 equiv), 1.0 M Et_3B in hexane, $Zn(OTf)_2$ (1 equiv) and ligand **18** (1 equiv). [b] Ratio for *cis*- and *trans*-isomers; determined by ^1H NMR analysis. [c] Enantioselectivity of *cis*-isomer was determined by HPLC analysis. [d] Yield in parentheses is for the recovered starting material **28**.

ethylborane and the reaction time had an impact on enantioselectivity. Increasing the amount of triethylborane to 20 equivalents improved the enantioselectivity (entry 3). Improvement of enantioselectivity was also observed by changing the reaction time from 3 h to 1 h (entry 4), although a prolonged reaction led to lower selectivity (entry 5).

Result from these studies shows that trapping step of an aminyl radical **P** with triethylborane is relatively slow (Scheme 13). We assume that the slow trapping reaction



Scheme 13. Possible reaction pathway.

would allow the reversibility between intermediate **O** and aminyl radical **P**, leading to erosion of enantioselectivity.

Conclusion

We have shown that the cascade radical reaction involving cyclization process proceeded with good enantioselectivities based on our strategy of using a hydroxamate ester as a coordination site with a chiral Lewis acid. The present new approach offers opportunities for further exploration with intriguing possibilities in enantioselective radical cyclization.

Acknowledgements

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