Radical Reactions

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Enantioselective Cascade Radical Addition–Cyclization–Trapping Reactions**

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In recent years, studies on enantioselective radical reactions have achieved some remarkable success,[1] particularly in intermolecular addition reactions, allylations, and H-atom transfer reactions.[2,3] In contrast, only a handful of reports describe enantioselective radical cyclizations, which can be classified into three types by the nature of the coordination with a Lewis acid (**I**–**III**, Scheme 1).[4–7] A high degree of stereocontrol was achieved in type **II** cyclizations using α-radical species generated from a β-keto ester as a coordination site and was applied to cascade cyclization by Yang and co-workers.[7] However, there are no reports on enantioselective cascade reactions involving both inter- and intramolecular C–C bond-forming processes. Herein, we report a cascade type **IV** strategy that takes advantage of the hydroxamate ester.[5,8]

As most radical reactions proceed through early transition states, the structure of the substrate plays an important role;[9] thus, the control of the rotamer population would be crucial for achieving high selectivity in cascade reactions. We consider that the predominant formation of a single reactive

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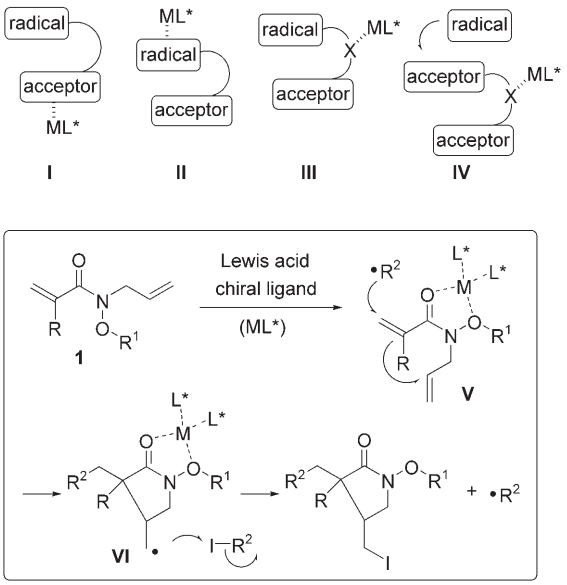
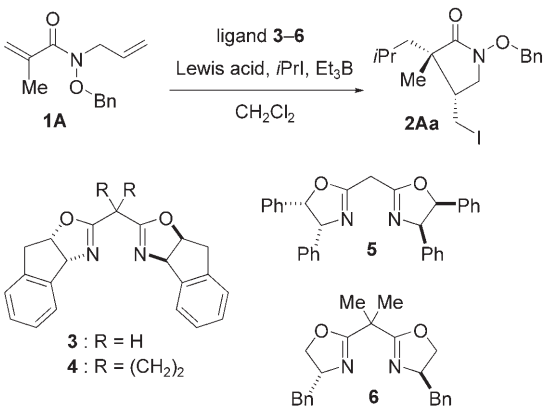


Scheme 1. Chiral Lewis acid mediated radical cyclization. ML* = chiral Lewis acid.

rotamer must be achieved by the type **IV** approach, which contains a coordination tether (X) inbetween two acceptors. Therefore, we selected a hydroxamate ester **1**, because rotamer **V** will prevail through a stable five-membered chelation.[10] We were also interested in probing the effect of the fluxional substituent of **1** (R^1) on the stereochemistry.[11]

A suitable combination of a chiral Lewis acid and hydroxamate ester would lead to the highly diastereo- and enantioselective reaction of **1A** (Scheme 2).[12] The radical reactions were initiated by triethylborane.[13] No reaction occurred in the absence of a Lewis acid (LA; Table 1, entry 1). In contrast, the addition of a Lewis acid promoted the reaction at 20 °C to give the 5-*exo* cyclization product **2Aa** along with recovered starting material **1A** (Table 1, entries 2 and 3), although the reaction did not proceed at −78 °C even with a Lewis acid (Table 1, entry 4). With a stoichiometric amount of the chiral Lewis acid prepared from $Zn(OTf)_2$ (Tf = trifluoromethanesulfonyl) and ligand **3**, the adduct **2Aa** was formed even at −78 °C with 71 % *ee* and high *cis*



Scheme 2. Radical addition–cyclization–trapping reaction of **1A**.

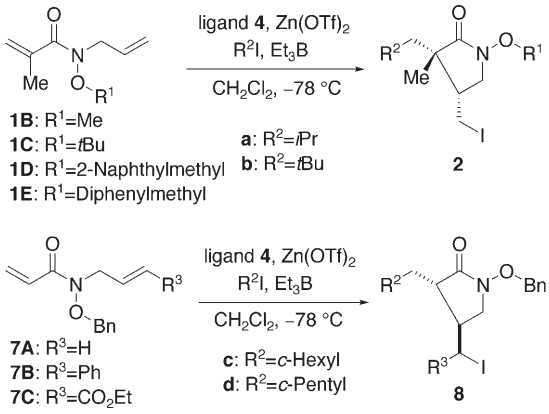
Table 1: Cascade radical reaction of **1A** with isopropyl iodide.[a]

Entry	LA	Ligand	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	–	–	20	–	–	–
2[e]	$Zn(OTf)_2$	–	20	41 (42)	>98:2	–
3[e]	$Mg(OTf)_2$	–	20	23 (69)	>98:2	–
4[e]	$Zn(OTf)_2$	–	−78	–	–	–
5[e]	$Zn(OTf)_2$	**3**	−78	76	>98:2	71
6[e]	$Zn(OTf)_2$	**4**	−78	81	>98:2	76
7[f]	$Zn(OTf)_2$	**4**	−78	71	>98:2	77
8[e]	$Zn(OTf)_2$	**5**	−78	81	>98:2	−69
9[e]	$Mg(OTf)_2$	**6**	−78	16 (79)	>98:2	racemic

[a] Reactions were carried out with **1A** (1 equiv), isopropyl iodide (30 equiv), and Et_3B in hexane (1.0 M, 2.5 equiv) with a Lewis acid (1 equiv) and ligand **3**–**6** (1 equiv). [b] Yield of the isolated product; the yield in parentheses is for the recovered starting material **1A**. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis. [e] In CH_2Cl_2. [f] In toluene/CH_2Cl_2 (4:1, v/v).

diastereoselectivity (Table 1, entry 5). These results suggest that the chelation with chiral Lewis acid led to decreased conformational flexibility and the expected rotamer **V** was present to a significant extent.[14] Somewhat better enantioselectivities were obtained by using ligand **4**, whereas the reaction with ligand **5** attenuated the enantiomeric excess, thus surprisingly resulting in the enantiomer of adduct **2Aa** (Table 1, entries 6–8).[15] In contrast, the combination of $Mg(OTf)_2$ and ligand **6** decreased the cyclization rate and gave the nearly racemic product (Table 1, entry 9).[16] A remarkable feature of this reaction is the construction of three bonds and tertiary and quaternary stereogenic centers through cascade inter- and intramolecular C−C bond-forming processes.

We next evaluated the effect of the substituent R^1 of **1B**–**E** on yield and selectivity (Scheme 3 and Table 2). The size of the substituent had an impact on enantioselectivity, with



Scheme 3. Radical reactions of **1B–E** and **7A–C**.

larger groups leading to lower *ee* values. Reaction of **1B**, which has a small methoxy group, lead to high enantio- and diastereoselectivity (Table 2, entry 1). More interestingly, the use of substrate **1E** with a diphenylmethyl group gave the nearly racemic product **2Ea**, probably as a result of dissonance between the chiral Lewis acid and bulky substituent

Table 2: Cascade reaction of **1B–E** and **7A–C** with alkyl iodides.[a]

Entry	Substrate	R^2	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1B**	*i*Pr	**2Ba**	75	>98:2	82
2	**1C**	*i*Pr	**2Ca**	71	>98:2	75
3	**1D**	*i*Pr	**2Da**	75	>98:2	73
4	**1E**	*i*Pr	**2Ea**	52	>98:2	racemic
5	**1B**	*t*Bu	**2Bb**	78	>98:2	88
6	**7A**	*i*Pr	**8Aa**	52	92:8	92
7	**7A**	cHex	**8Ac**	57	94:6	92
8	**7A**	*c*Pent	**8Ad**	35	94:6	91
9	**7B**	*i*Pr	–	–	–	–
10	**7C**	*i*Pr	complex mixture			

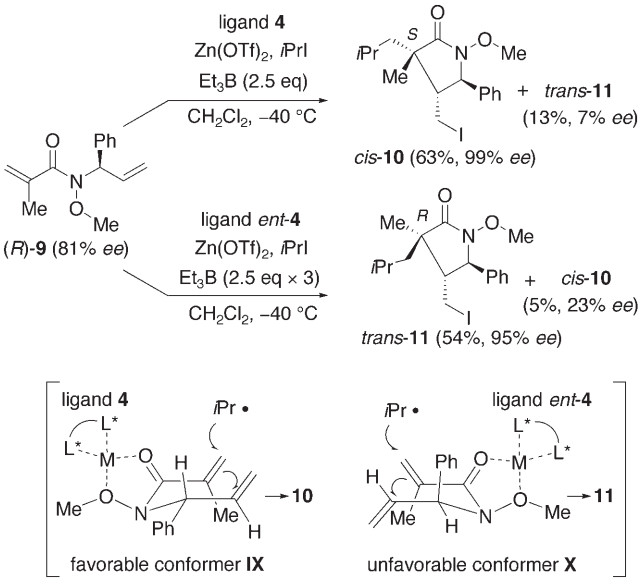
[a] Reactions were carried out with **1B–E** or **7A–C** (1 equiv), R^2I (30 equiv), and Et_3B in hexane (1.0 M, 2.5 equiv) with $Zn(OTf)_2$ (1 equiv) and ligand **4** (1 equiv). [b] Yield of the isolated product. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis.

(Table 2, entry 4). These observations clearly indicate that rigid conformation of the ternary complex formed from **1A**, $Zn(OTf)_2$, and ligand **4** is required for a good yield and high selectivity. Similarly, the reaction of **1B** with the *tert*-butyl radical gave **2Bb** with higher enantioselectivity (Table 2, entry 5). Outstanding levels of enantioselectivity were obtained in the reaction of acrylate substrate **7A** (Table 2, entries 6–8).[17] The reaction of **7A** with an isopropyl radical source gave 52% yield of the cyclic product **8Aa** with 92% *ee* and good *trans* diastereoselectivity (Table 2, entry 6). The moderate chemical yields of products **8** were attributed to competitive polymerization of **7A** through the acrylamide moiety.

The success of these reactions reflects the overall difference in the stability of the R^2 radical and a cyclic radical intermediate **VI**. Thus, the iodine atom-transfer process from secondary or tertiary alkyl iodide (R^2I) to unstable primary intermediate radical **VI** is a key step.[18] Indeed, the formation of cyclic products was not observed in the reaction of substrates **7B** and **7C**, which involves less effective iodine atom transfer to stable secondary radicals **VI** (Table 2, entries 9 and 10).

The cyclization of **1A–E** that leads to the major *cis* diastereomer occurs via the conformer **VII** (Scheme 4), in which two olefin units adopt a *cis* configuration, probably as a result of the effect of the orbital symmetry reported by Beckwith and Houk.[19] In marked contrast, the *trans* selectivity in the reaction of **7A** was regarded as being through the conformer **VIII** and the result of steric repulsion.

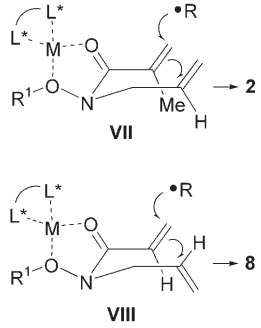
We next investigated the chiral substrate (*R*)-**9** (Scheme 5).[20] In the presence of ligand **4**, the reaction of (*R*)-**9** (81% *ee*) gave a 63% yield of (*S*)-*cis*-**10** with 99% *ee*,



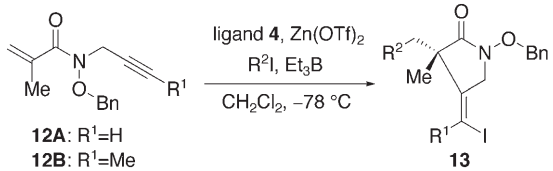
Scheme 5. Cascade radical reaction of chiral substrate (*R*)-**9**.

accompanied by a small amount of *trans*-**11** with low enantiomeric excess. The major cyclization proceeded via favorable conformer **IX**, thus minimizing the allylic 1,3-strain effect. The enhanced enantioselectivity of *cis*-**10** can be explained by kinetic resolution of an intermediate chiral radical. To substantiate this explanation, the enantiomer of ligand **4** (*ent*-**4**) was employed. Although the reaction using ligand *ent*-**4** required a large amount of Et_3B (3×2.5 equiv), the expected *R*-enriched *trans*-**11** (95% *ee*) was obtained via unfavorable conformer **X**, which carried an axial Ph group to avoid steric interaction with the allylic substituent. The absolute configuration was deduced from NOESY experiments of *cis*-**10** and *trans*-**11** with three chiral centers that assume an *R* configuration for the phenyl-substituted stereogenic carbon center.[21] Therefore, the absolute configuration at the quaternary carbon atom derived from substrates **1A–E** was also determined to be the *S* configuration.

We finally investigated the reaction of alkynes **12A** and **12B** (Scheme 6). The reactions gave high enantioselectivities



Scheme 4. Possible cyclic transition states **VII** and **VIII**.



Scheme 6. Cascade radical reaction of **12A** and **12B**.

(Table 3) and proceeded equally well with 30 mol% of chiral Lewis acid as with stoichiometric amounts. Further reduction of the catalyst load to 10 mol% resulted in a decrease of the chemical yield and enantioselectivity (Table 3, entry 4). The high *Z*/*E* selectivity of products **13** clearly indicates that the iodine atom transfer from R^2I to an intermediate radical proceeded efficiently.

Table 3: Cascade radical reaction of **12A** and **12B** with alkyl iodides.[a]

Entry	Substrate	R^2	LA [equiv]	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**12A**	*i*Pr	1.0	**13Aa**	87	>98:2	80
2	**12A**	*i*Pr	0.5	**13Aa**	85	>98:2	81
3	**12A**	*i*Pr	0.3	**13Aa**	82	>98:2	81
4	**12A**	*i*Pr	0.1	**13Aa**	49[e]	>98:2	47
5	**12A**	*t*Bu	1.0	**13Ab**	85	>98:2	92
6	**12A**	*c*Hex	1.0	**13Ac**	82	>98:2	81
7	**12B**	*i*Pr	1.0	**13Ba**	86	>98:2	83
8	**12B**	*i*Pr	0.3	**13Ba**	74	>98:2	81
9	**12B**	*t*Bu	1.0	**13Bb**	94	>98:2	90
10	**12B**	*c*Hex	1.0	**13Bc**	87	>98:2	85

[a] Reactions were carried out using **12A** or **12B** (1 equiv), R^2I (30 equiv), and Et_3B in hexane (1.0 M, 2.5 equiv) with $Zn(OTf)_2$ and ligand **4**. [b] Yield of the isolated product. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis. [e] Compound **12A** was recovered in 29% yield.

In conclusion, we have succeeded in performing the enantioselective radical addition–cyclization–trapping reaction that provides a powerful synthetic approach to chiral γ-lactams.

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[21] Details are provided in the Supporting Information.

