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Lewis acid-catalyzed atom transfer radical cyclization of unsaturated β-keto amides

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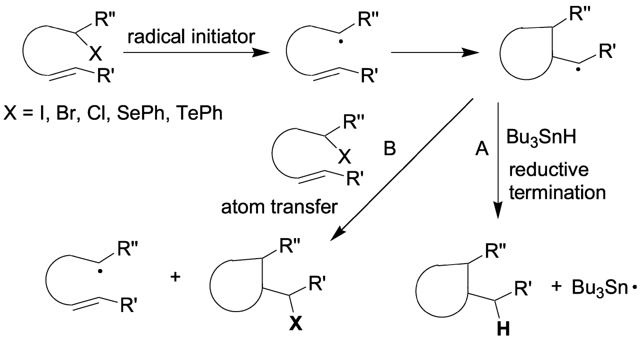
Abstract—The Lewis acid-catalyzed atom transfer radical cyclization reactions of olefinic α-bromo β-keto amides were investigated. It was found Lewis acid $Yb(OTf)_3$ or $Mg(ClO_4)_2$ not only promoted the cyclization reactions, but also resulted in excellent *trans* stereocontrol in the cyclization products. With the catalysis of Lewis acid $Yb(OTf)_3$ or $Mg(ClO_4)_2$ at −78°C in the presence of Et_3B/O_2, the cyclization reactions of *C*-olefinic β-keto amides provided cyclic ketones, while the cyclization reactions of *N*-olefinic β-keto amides led to the formation of γ-lactams, which could be converted to 3-aza-bicyclo[3,1,0]hexan-2-ones.

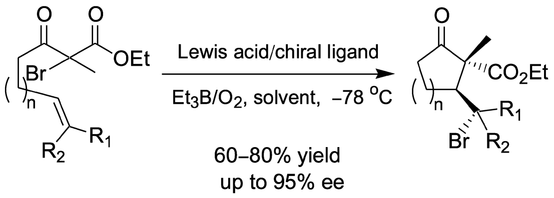
1. Introduction

Atom transfer radical cyclization reactions are versatile and powerful tools for the synthesis of cyclic compounds.[1] Compared with the reductive reactions using Bu_3SnH to terminate the radicals (Path A, Scheme 1), atom transfer radical cyclization reactions keep the transfer group (X) in the products, thereby allowing for further functionalization (Path B).[2]



Scheme 1.

In recent years, Lewis acids have been increasingly used to accelerate radical reactions.[3] While Lewis acids such as lanthanide triflates have shown great promise in reductive radical addition reactions,[4] there are only a few reports about the effect of Lewis acids on the atom transfer radical reactions.[5] Guindon and co-workers demonstrated that Lewis acid complexation resulted in excellent stereocontrol of an atom transfer radical allylation reaction.[5a] Porter and co-workers found that Lewis acids such as $MgBr_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$ could accelerate the intermolecular atom transfer radical addition of α-bromo oxazolidinones to alkenes.[5b] We previously investigated the effect of Lewis acids on the atom transfer radical mono and tandem cyclization reactions of unsaturated α-bromo β-keto esters.[6] We found that the cyclization reactions catalyzed by Lewis acid $Yb(OTf)_3$ or $Mg(ClO_4)_2$ provided exclusively *trans* 2,3-disubstituted cyclic ketones, and a highly enantioselective version (up to 95% ee) of such reactions was developed by using Lewis acid $Mg(ClO_4)_2$ or $Yb(OTf)_3$ combined with a chiral oxazoline ligand (Eq. (1)).[6] These cyclization reactions required the presence of an α-alkyl substituent since α-monobromo β-keto esters without an α-alkyl substituent were unstable during column purification and upon storage.[7,8] In contrast, α-bromo β-keto amides were found to be rather stable and readily accessible.[8] A literature survey revealed that, while α-halo β-keto esters[9] and α-halo malonates[10] had been particularly studied, there was no report on the atom transfer radical reactions of olefinic α-bromo β-keto amides. Therefore, we decided to explore the effect of Lewis acids on the atom transfer radical cyclization reactions of unsaturated α-bromo β-keto amides.



(1)

Keywords: Lewis acid; radical cyclization; keto amide.
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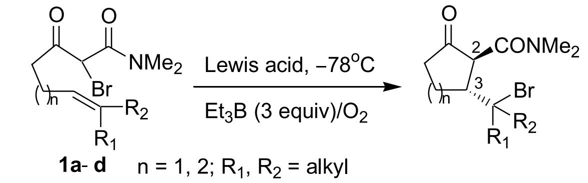
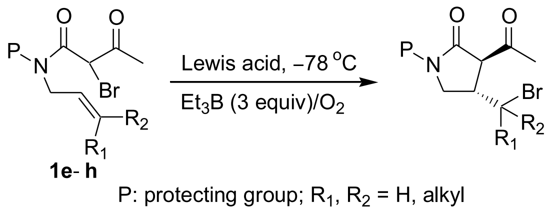
Two types of unsaturated α-bromo β-keto amides were investigated. The first type of substrates included *C*-alkenyl α-bromo β-keto amides (**1a–d**), which contain an all carbon backbone (Scheme 2). The cyclization of this type of substrates would result in the formation of 2,3-disubstituted cyclic ketones. The second type of substrates, *N*-alkenyl α-bromo β-keto amides (**1e–h**) in which the olefin tethers were attached to the nitrogen of the amide group, were expected to form γ-lactams (2-pyrrolidinones) in the cyclization reactions (Scheme 3).



Scheme 2.



Scheme 3.

In this paper, we report that Lewis acids such as $Yb(OTf)_3$ and $Mg(ClO_4)_2$ significantly accelerate the atom transfer radical cyclization reactions of both *C*- and *N*-alkenyl α-bromo β-keto amides.

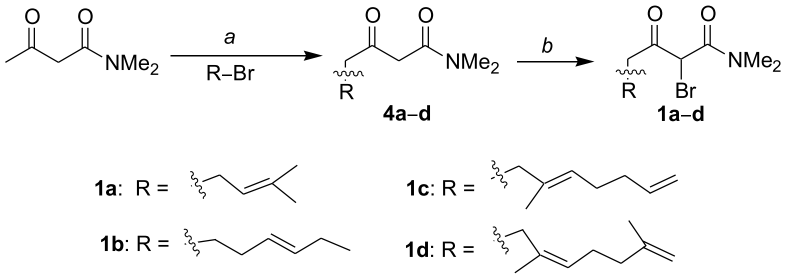
2. Results and discussion

2.1. Preparation of alkenyl α-bromo β-keto amides

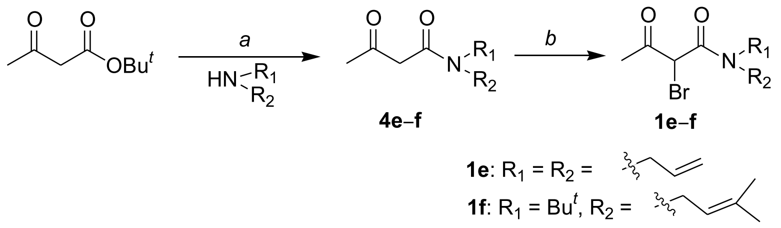
The olefinic tethers of *C*-alkenyl β-keto amides (**1a–d**) were introduced via alkylation of the dianion of *N*,*N*-dimethyl acetoacetamide with various alkenyl bromides (Scheme 4). *N*-Alkenyl β-keto amides (**1e–h**) were prepared by a transamidation reaction of a β-keto ester with an unsaturated amine[11] (Schemes 5 and 6). All the β-keto amides (**4a–h**) were brominated with *N*-bromosuccinimide (NBS) in EtOAc in high yield (Schemes 4–6).[8]

2.2. Atom transfer radical cyclization reactions of *C*-alkenyl α-bromo β-keto amides 1a–d

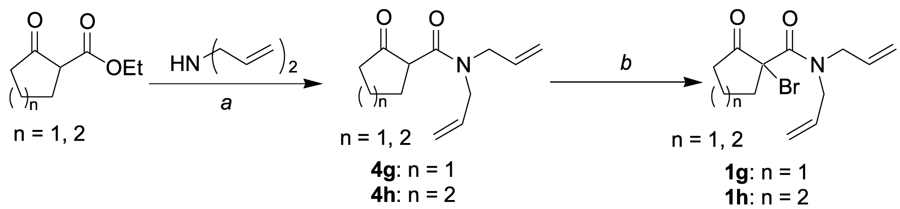
In our investigation of Lewis acid-catalyzed atom transfer radical cyclization of olefinic β-keto esters, Lewis acids $Yb(OTf)_3$ and $Mg(ClO_4)_2$ were found to be the most efficient catalysts. Therefore, those optimal conditions were first applied to the cyclization of *C*-alkenyl α-bromo β-keto amides **1a–d**. All reactions were conducted at −78°C with Et_3B/O_2 as the radical initiator (Scheme 2 and Table 1).



Scheme 4. *Reagents and conditions*: (a) NaH, *n*-BuLi, THF, alkyl bromide, 0°C to rt, 50–60% yield; (c) NBS (1.1 equiv.), EtOAc, rt, 70–90% yield.

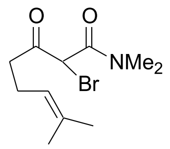
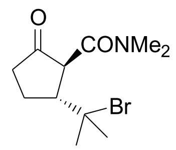
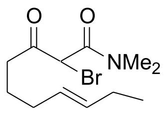
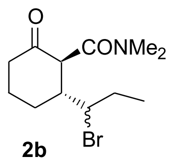
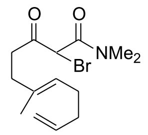
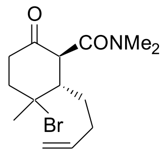
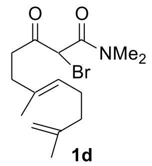
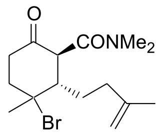


Scheme 5. *Reagents and conditions*: (a) amine, DMAP (0.5 equiv.), toluene, reflux, 38–45% yield; (b) NBS (1.1 equiv.), EtOAc, rt, 80–85% yield.



Scheme 6. *Reagents and conditions*: (a) amine, DMAP (0.5 equiv.), toluene, reflux, 98% yield for **4g**, 78% for **4h**; (b) NBS (1.1 equiv.), NaH, THF, 41–42% yield.

Table 1. Lewis acid-catalyzed atom transfer radical cyclization of *C*-alkenyl substrates **1a–d**[a]

Entry	Substrate	Lewis acid (equiv.)	Solvent	Time (h)	Product	Isolated yield (%)
1	 **1a**	–	CH_2Cl_2	3	 **2a**	0[b]
2		$Yb(OTf)_3$ (0.3)	CH_2Cl_2	1		74
3		$Mg(ClO_4)_2$ (0.3)	CH_2Cl_2	1		57
4	 **1b**	$Yb(OTf)_3$ (0.3)	CH_2Cl_2	2	 **2b**	62 (1/1.8)[c]
5		$Mg(ClO_4)_2$ (0.3)	CH_2Cl_2	2		78 (1/1.6)[c]
6	 **1c**	$Yb(OTf)_3$ (0.5)	Et_2O	4	 **2c**	40[d]
7	 **1d**	$Mg(ClO_4)_2$ (0.3)	CH_2Cl_2	4	 **2d**	28[d]

[a] The reactions were carried out with 0.5 mmol (for **1a** and **1b**) or 0.3 mmol (for **1c** and **1d**) of substrate at 30 mM concentration in the indicated anhydrous solvent at −78°C.
[b] Reduction product **4a** was isolated in 66% yield and the conversion of **1a** was 88%.
[c] Diastereomeric ratios.
[d] Only one diastereomer was isolated. The stereochemistry at the carbon bearing a bromo atom could not be clearly determined from the NOESY experiment due to peak overlap. The reaction conducted at a higher temperature (−40°C) gave a similar result.

Without any Lewis acid, the cyclization reaction of substrate **1a** failed to give the desired product **2a**, and only reduction product **4a** was isolated in 66% yield with 88% conversion (entry 1). In the presence of a Lewis acid catalyst (entries 2–7), cyclization of olefinic β-keto amides **1a–d** resulted in the exclusive formation of the *trans* cyclization products (the 2-amide group *trans* to the 3-alkyl group), similar to the case of olefinic α-bromo β-keto esters.[6a] In particular, upon the addition of 0.3 equiv. of Lewis acid $Mg(ClO_4)_2$ or $Yb(OTf)_3$, cyclization of **1a** afforded **2a** in 57–74% yield (entries 2 and 3). It is worth pointing out that cyclization product **2a** was formed via a radical process rather than an ionic pathway[12] because substrate **1a** was stable toward $Mg(ClO_4)_2$ or $Yb(OTf)_3$ in CH_2Cl_2 at room temperature without the radical initiator. In the cyclization of substrate **1b**, two epimeric bromides **2b** (ratio 1:1.6–1.8) were obtained in 60–80% yield (entries 4 and 5). These results clearly indicated that the Lewis acid not only promoted the atom transfer radical cyclization reactions, but also resulted in excellent *trans* stereocontrol in the cyclization products.

Tandem cyclization reactions of substrates **1c** and **1d** were attempted under the usual conditions. However, no desired tandem cyclization product was isolated despite of the fact that analogous β-keto esters underwent tandem radical cyclization products in moderate yields.[6b] The cyclization of **1c** under the $Yb(OTf)_3/Et_2O$ condition only gave a monocyclization product **2c** in 40% yield (entry 6). In the cyclization of **1d** with $Mg(ClO_4)_2$ as the catalyst in CH_2Cl_2, monocyclization product **2d** was obtained in 28% yield (entry 7). The major side products of these cyclization reactions were the reduction products **4c** and **4d**, respectively. The tandem cyclization reactions of **1c** and **1d** were also tested at a higher temperature (−40°C), but similar results were obtained as at −78°C. The reason why olefinic α-bromo β-keto amides failed to give tandem cyclization products remains unknown.

The stereochemistry of product **2a** was assigned by comparing the NMR spectral data of **2a** and a corresponding phenylseleno compound reported in literature.[13] The 2,3-*trans* relationship of the products **2b**, **2c** and **2d** was determined by the large coupling constant (J=10–12 Hz) between the H-2 and H-3. The stereochemistry of the major isomer of product **2b** was confirmed by X-ray crystallographic analysis (Fig. 1).

2.3. Lactam formation via atom transfer radical cyclization reactions of *N*-alkenyl α-bromo β-keto amides 1e–h

γ-Lactams (2-pyrrolidinones) are a class of versatile

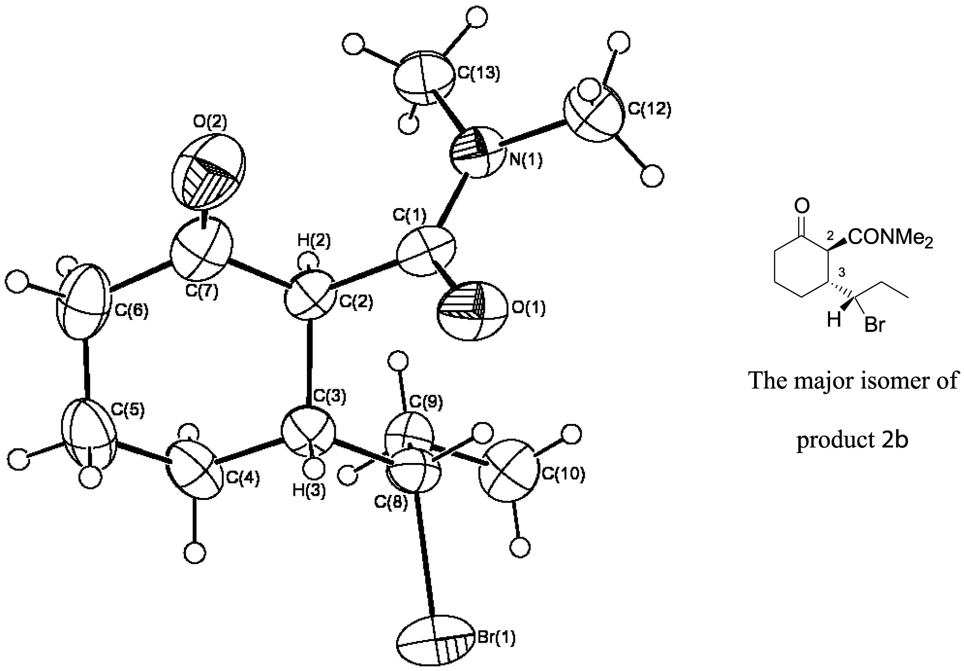


Figure 1. X-ray structure of the major isomer of product **2b**.

compounds. They not only show various biological activities, but also are excellent starting materials for the synthesis of biologically active 5-membered-ring nitrogen heterocyclic compounds such as (+)-α-allokainic acid,[14] (+)-α-kainic acid,[15] acromelic acid,[16] and isocynometrine.[17] Consequently, it has stimulated great interest of organic chemists to develop new methods for the syntheses of this type of compounds with diverse structural features.[18] The Lewis acid-catalyzed atom transfer radical cyclization reactions were found to be useful for the synthesis of γ-lactams. In our study, *N*-alkenyl α-bromo β-keto amides **1e–h** were subjected to the optimized atom transfer radical cyclization conditions (Scheme 3), and the results are tabulated in Table 2.

The cyclization of substrate **1e** with 0.5 equiv. of $Mg(ClO_4)_2$ or $Yb(OTf)_3$ as the catalyst led to the formation of γ-lactam **2e** along with a cyclopropanation product **3e** in 60–70% total yield, and the ratios of these two products varied according to the reaction conditions (Table 2, entries 2–4). In contrast, no cyclization product was obtained in the absence of a Lewis acid (entry 1). The formation of product **3e** could be explained by the subsequent intramolecular cyclopropanation via 1,3-elimination of HBr from product **2e** (Scheme 7). Cyclopropanation product **3e** could also be directly obtained from **1e** in 43% overall yield by treating the cyclization reaction mixture with 2 equiv. of NaH (entry 8).

The cyclization of substrate **1f** with Lewis acid catalysis resulted in the formation of γ-lactam **2f** in 70–80% yield (Table 2, entries 5–7). Further treatment of product **2f** with NaH in THF gave a cyclopropanation product **3f** in 80% yield (Scheme 8). The cyclopropanation reaction could also be finished in one pot by treating the cyclization product mixture with NaH, providing **3f** in 60% overall yield (entry 9).

The 2,3-*trans* relationships of products **2e** and **2f** were determined by the coupling constants (J=6–9 Hz) of the α-protons according to the literature reports.[19,20]

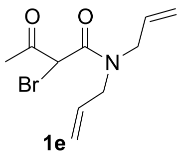
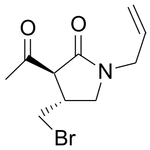
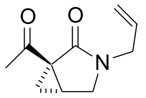
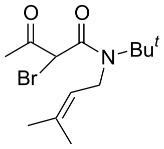
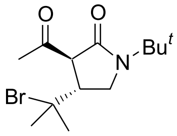
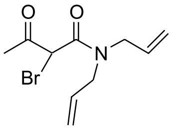
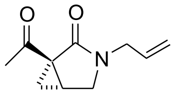
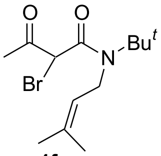
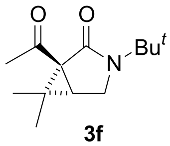
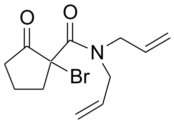
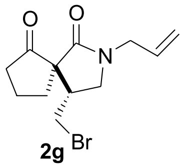
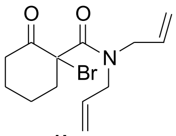
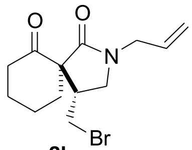
3-Aza-2-bicyclo[3.1.0]hexan-2-one derivatives (Fig. 2) are suitable starting materials for the preparation of cyclopropyl nucleosides[21] and conformationally restricted amino acids.[22] In addition, 3-azabicyclo[3,1,0]hexane unit is also found in some biologically active compounds such as *trovafloxacin*.[23] The formation of products **3e** and **3f** indicated that atom transfer radical cyclization of *N*-alkenyl α-bromo β-keto amides and subsequent intramolecular cyclopropanation provided a new pathway for the synthesis of 3-aza-bicyclo[3.1.0]hexan-2-one derivatives.[24]

Spirolactams are useful building blocks for the synthesis of natural products such as spirostaphylotrichin[25] and some natural alkaloids including sibirine, nitramine, or isonitramine.[26] Therefore, the development of new methods for the synthesis of spirolactams has caught increased attention of organic chemists. The reported methods include thermolysis of *N*-unsaturated β-keto amides[27a] and enamino carboxamides,[27b] and manganese (III) salt promoted radical cyclization of β-keto carboxamides.[27c] The cyclization reactions of substrates **1g** and **1h** provided spirolactams in 59 and 39% yield, respectively (entries 11 and 12). The stereochemistries of products **2g** and **2h** were determined from NOESY experiment (Fig. 3). Compared with the reported synthesis of spirolactams,[27] the Lewis acid-catalyzed atom transfer radical cyclization reactions were conducted under very mild condition at low temperature, leading to the formation of products with excellent stereocontrol.

2.4. Explanation for the stereochemistry

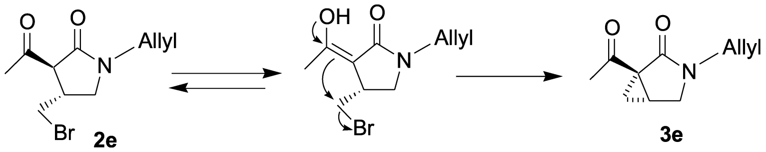
Similar to the *trans* stereocontrol in the Lewis

Table 2. Lewis acid-catalyzed atom radical cyclization of *N*-alkenyl substrates **1e**–**h**[a]

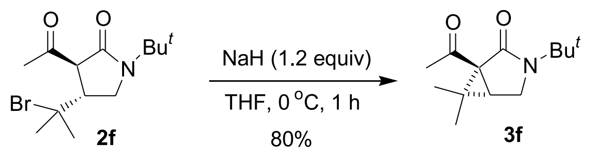
Entry	Substrate	Lewis acid (equiv.)	Solvent	Time (h)	Product	Isolated yield (%)
1	 **1e**	–	CH_2Cl_2	5	 **2e** +  **3e**	0[b]
2		$Yb(OTf)_3$ (0.5)	Et_2O	1.5		68 (3/1)[c]
3		$Yb(OTf)_3$ (0.5)	CH_2Cl_2	2		64 (1/1.6)[c]
4		$Mg(ClO_4)_2$ (0.5)	CH_2Cl_2	2		73 (1/1.9)[c]
5	 **1f**	$Yb(OTf)_3$ (0.3)	Et_2O	2	 **2f**	79
6		$Yb(OTf)_3$ (0.3)	CH_2Cl_2	2		76
7		$Mg(ClO_4)_2$ (0.5)	CH_2Cl_2	2		73
8	 **1e**	$Yb(OTf)_3$ (0.5)	Et_2O	1	 **3e**	43[d]
9	 **1f**	$Mg(ClO_4)_2$ (0.5)	CH_2Cl_2	1	 **3f**	60[d]
10	 **1g**	–	Et_2O	3	 **2g**	0[e]
11		$Yb(OTf)_3$ (0.5)	Et_2O	3		59
12	 **1h**	$Yb(OTf)_3$ (0.5)	Et_2O	3	 **2h**	39

[a] The reactions were carried out at −78°C with 0.4 mmol (for **1e** and **1g**–**h**) or 0.5 mmol (for **1f**) of substrate at 30 mM concentration in the indicated dry solvent.
[b] Reductive debromination product **4e** was obtained in 72% yield.
[c] Ratios of the two products **2e/3e**.
[d] Overall yield of two reactions. After the radical cyclization reaction, the product mixture was treated with 2 equiv. of NaH at 0°C for 0.5–2 h.
[e] Reductive debromination product **4g** was isolated in 99% yield.

acid-catalyzed atom transfer radical cyclization reactions of alkenyl α-bromo β-keto esters,[6] the excellent stereocontrol in the cyclization reactions of unsaturated β-keto amides was rationalized by the chelation effect of the Lewis acids. As illustrated for the cyclization reaction of substrate **1b** (Scheme 9), the two carbonyl groups were locked in the *syn* orientation by chelation to a Lewis acid. In transition state **TS1**, the steric interaction between the olefinic group and the locked dicarbonyl group was highly unfavorable. Therefore, the cyclization proceeded exclusively via



Scheme 7.



Scheme 8.

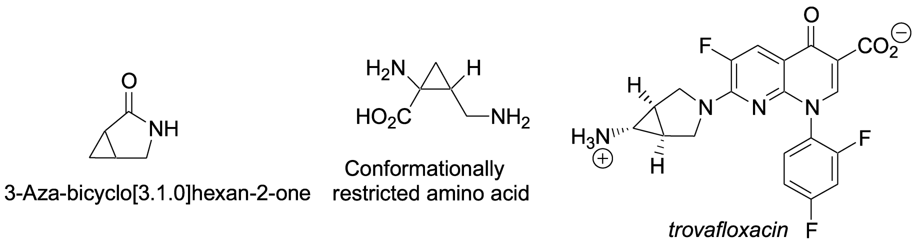


Figure 2.

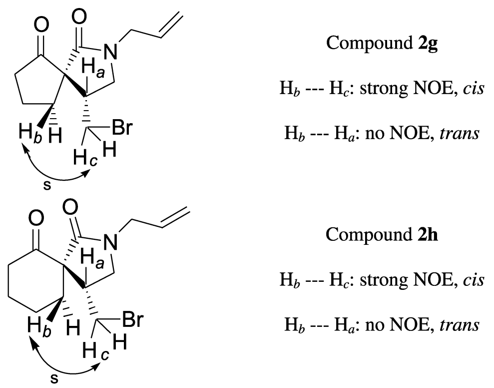


Figure 3. NOESY analysis of compounds **2g** and **2h**. The assignments of protons were made on the basis of ^{1}H NMR, ^{13}C NMR, DEPT, and CH-COSY spectra.

transition state **TS2**, which resulted in the exclusive formation of *trans* product **2b**. The *trans* stereocontrol in the formation of spirolactam **2h** could be similarly explained (Scheme 10).

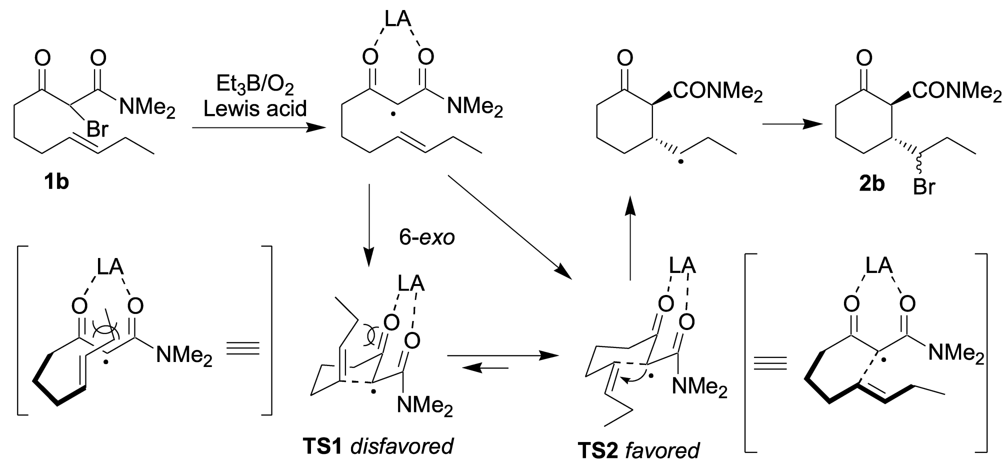
3. Conclusion

In summary, Lewis acids such as ytterbium triflates and magnesium perchlorate significantly accelerated the atom transfer radical cyclization reactions of two types of olefinic β-keto amides with excellent stereocontrol. As the cyclization products were highly functionalized, these reactions should be very useful in the construction of disubstituted cyclic ketones, γ-lactams, spirolactams, and 3-aza-2-bicyclo[3.1.0]hexan-2-one derivatives.

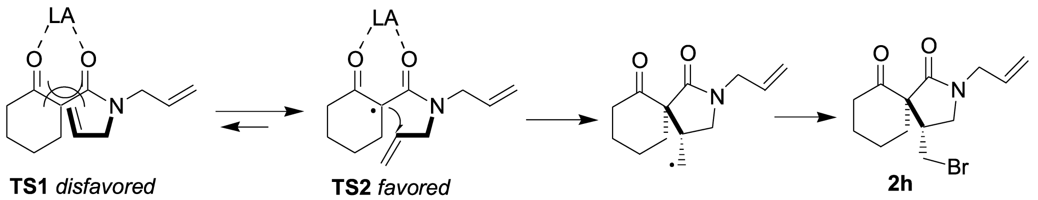
4. Experimental

4.1. General methods

All reactions were performed in oven-dried flasks. Air and



Scheme 9. Mechanism of stereocontrol.



Scheme 10.

moisture-sensitive compounds were introduced via syringes through a rubber septum. THF and Et_2O were distilled from sodium metal-benzophenone ketyl before use. Dichloromethane and toluene were distilled over calcium hydride. Flash column chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM) using ethyl acetate/*n*-hexane as eluting solvents.

Nuclear magnetic resonance spectra were recorded in deuteriochloroform ($CDCl_3$) unless otherwise indicated, with tetramethylsilane (TMS) as internal standard at ambient temperature on a Bruker Avance DPX 300 or 400 Fourier Transform Spectrometer. Infrared absorption spectra were recorded as a solution in CH_2Cl_2 with a Bio-Rad FTS 165 Fourier Transform Spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra. Melting points were determined by Axiolab ZEISS microscope apparatus and were uncorrected. Optical rotations were recorded on a Perkin–Elmer 343 Polarimeter.

4.1.1. Preparation of 7-methyl-3-oxo-oct-6-enoic acid dimethylamide (4a). To a suspension of NaH (60% oil dispersion, 960 mg, 24 mmol) in THF (50 mL) was added *N*,*N*-dimethyl-3-oxo-butyramide (2.58 g, 20 mmol) slowly at 0°C. After 30 min, *n*-BuLi (2.4 M in *n*-hexane, 9 mL, 22 mmol) was added slowly at 0°C. 4-Bromo-2-methyl-2-butene (96%, 2.6 mL, 22 mmol) was added dropwise 0.5 h later. The reaction was then stirred at room temperature for 4 h. After removal of solvents, the residue was diluted with water and extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$, and then concentrated. The crude product was purified by flash column chromatography to give **4a** (2.41 g, 12.2 mmol, 61%) as a light yellow oil. Analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, R_f=0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.8 (s, 0.2×1H, enol), 5.11 (s, 0.2×1H, enol), 5.06 (t, *J*=7.1 Hz, 1H), 3.54 (s, 0.8×2H), 2.99 (s, 3H), 2.97 (s, 3H), 2.59 (t, *J*=7.4 Hz, 2H), 2.27 (q, *J*=7.2 Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 204.6 (C), 177.8 (C, enol), 167 (C), 133.1 (C), 122.6 (CH), 86.5 (CH, enol), 49.6 (CH_2), 43.1 (CH_2), 38.1 (CH_3), 36.2 (CH_2, enol), 35.6 (CH_3), 25.9 (CH_3), 25.3 (CH_2, enol), 22.5 (CH_2), 17.9 (CH_3); IR (CH_2Cl_2) 2927, 1720, 1645 cm^{-1}; LRMS for $C_{11}H_{19}NO_2$ (EI, 20 eV) *m/z* 198 (M^++H, 5), 197 (M^+, 38), 154 (43), 129 (100); HRMS (EI) for $C_{11}H_{19}NO_2$ (M^+): calcd 197.1416, found 197.1412.

4.1.2. 3-Oxo-dec-7-enoic acid dimethylamide (4b). Prepared similarly to **4a**. Yield 50%; a light yellow oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.8 (s, 0.4×1H, enol), 5.49–5.30 (m, 2H), 5.10 (s, 0.4×1H, enol), 3.53 (s, 0.6×2H, keto), 3.04–2.97 (4 s, 2×CH_3, keto and enol), 2.56 (t, *J*=7.3 Hz, 1H) 2.18 (t, *J*=7.5 Hz, 1H), 2.04–1.95 (m, 4H), 1.70–1.61 (m, 2H), 0.96 (2t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 204.9 (C), 178.2 (C), 172.5 (C, enol), 167.1 (C, enol), 133.4 (CH), 133.2 (CH, enol), 128.6 (CH, enol), 127.8 (CH), 86.5 (CH, enol), 49.6 (CH), 42.5 (CH_2), 38.2 (CH_3), 35.7 (CH_3), 35.6 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 26.7 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 23.6 (CH_2), 14.2 (CH_3); IR (CH_2Cl_2) 3669, 3055, 2964, 2948, 1719, 1649, 1589 cm^{-1}; LRMS for $C_{12}H_{21}NO_2$ (EI, 20 eV) *m/z* 212 (M^++H, 2), 211 (M^+, 8), 142 (11), 129 (100); HRMS (EI) for $C_{12}H_{21}NO_2$ (M^+): calcd 211.1572, found 211.1564.

4.1.3. 6-Methyl-3-oxo-undeca-6,10-dienoic acid dimethylamide (4c). Prepared similarly to **4a**. Yield 65%; a light yellow oil; analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, R_f=0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.8 (s, 0.2×1H, enol), 5.87–5.73 (m, 1H), 5.22–5.08 (m, 1H), 5.10 (s, 0.2×1H, enol), 5.03–4.93 (m, 2H), 3.54 (s, 0.8×2H, keto), 2.99 (s, 3H), 2.97 (s, 3H), 2.67 (t, *J*=7.3 Hz, 2H), 2.27 (t, *J*=7.5 Hz, 2H), 2.08–2.06 (m, 4H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 204.6 (C), 167.0 (C), 138.8 (CH), 134.0 (C), 124.8 (CH), 114.8 (CH_2), 49.6 (CH_2), 41.9 (CH_2), 38.2 (CH_3), 35.7 (CH_3), 34.1 (CH_2), 33.5 (CH_3), 27.6 (CH_2), 16.4 (CH_3); IR (CH_2Cl_2) 2929, 1721, 1644 cm^{-1}; LRMS for $C_{14}H_{23}NO_2$ (EI, 20 eV) *m/z* 237 (M^+, 6), 219 (5), 178 (15), 141 (16), 129 (100); HRMS (EI) for $C_{14}H_{23}NO_2$ (M^+): calcd 237.1729, found 237.1731.

4.1.4. 6,10-Dimethyl-3-oxo-undeca-6,10-dienoic acid dimethylamide (4d). Prepared similarly as **4a**. Yield 63%; a light yellow oil; analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, R_f=0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.8 (s, 0.3×1H, enol), 5.20–5.11 (m, 1H), 5.11 (s, 0.3×1H, enol), 4.70 (s, 1H), 4.66 (s, 1H), 3.54 (s, 0.7×2H, keto), 3.00–2.97 (4 s, 2×CH_3, keto and enol), 2.67 (t, *J*=7.3 Hz, 2H), 2.27 (t, *J*=7.6 Hz, 2H), 2.11 (q, *J*=7.3 Hz, 2H), 2.04–1.99 (m, 2H), 1.72 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 204.6 (C), 167.0 (C), 146.0 (C), 138.8 (C), 125.1 (CH), 110.2 (CH_2), 49.7 (CH_2), 42.0 (CH_2), 38.3 (CH_3), 38.0 (CH_2), 35.8 (CH_3), 33.5 (CH_2), 26.5 (CH_2), 22.8 (CH_3), 16.4 (CH_3); IR (CH_2Cl_2) 3055, 2938, 1721, 1645 cm^{-1}; LRMS for $C_{15}H_{25}NO_2$ (EI, 20 eV) *m/z* 252 (M^++H, 3), 251 (M^+, 9), 208 (17), 170 (52), 129 (100); HRMS (EI) for $C_{15}H_{25}NO_2$ (M^+): calcd 251.1885, found 251.1896.

4.1.5. Preparation of *N*,*N*-diallyl-3-oxo-butyramide (4e). *tert*-Butyl acetoacetate (6.0 mL, 97%, 35 mmol), diallylamine (5.2 mL, 42 mmol) and DMAP (2.2 g, 18 mmol) were mixed in toluene (30 mL). The mixture was heated to reflux for 6 h. After removal of solvent, the residue was extracted with Et_2O. The extract was washed successively with diluted HCl (2N) and water, and then dried over $MgSO_4$. After concentration, the crude product was purified by flash column chromatography to give **4e** (2.87 g, 45%) as a light yellow oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f=0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.65 (s, 0.3×1H, enol), 5.83–5.70 (m, 2H), 5.25–5.13 (m, 4H), 5.06 (s, 0.3×1H), 4.00 (d, *J*=5.7 Hz, 2H), 3.85 (d, *J*=4.8 Hz, 2H), 3.53 (s, 0.7×2H, keto), 2.28 (s, 0.7×3H, keto), 1.94 (s, 0.3×3H, enol); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 202.8 (C), 175.4 (C, enol), 172.3 (C), 167.0 (C), 132.9 (2×CH), 117.9 (CH_2), 117.3 (CH_2), 87.4 (CH, enol), 50.1 (CH_2), 48.3 (CH_2), 30.6 (CH_3), 22.3 (CH_3); IR (CH_2Cl_2) 3056, 2988, 1732, 1651 cm^{-1}; LRMS for $C_{10}H_{15}NO_2$ (EI, 20 eV) *m/z* 181 (M^+, 2), 166 (7), 153 (100), 140 (5), 136 (84), 107 (69); HRMS (EI) for $C_7H_{10}NO_2$ ($M^+-C_3H_5$): calcd 140.0711, found 140.0724.

4.1.6. *N-tert*-Butyl-*N*-(3-methyl-but-2-enyl)-3-oxo-butyramide (4f). Prepared similarly as **4e**. Yield 38%; a light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.41; ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.21 (s, 0.15×1H, enol), 5.07–5.02 (m, 1H), 5.00 (s, 0.15×1H, enol), 3.85 (d, *J*=5.6 Hz, 2H), 3.46 (s, 0.85×2H, keto), 2.26 (s, 0.85×3H, keto), 1.92 (s, 0.15×3H, enol), 1.73 (s, 3H), 1.62 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) major δ 203.7 (C), 167.9 (C), 134.0 (C), 123.1 (CH), 58.0 (C), 53.1 (CH_2), 44.5 (CH_2), 30.4 (CH_3), 29.1 (3×CH_3), 25.8 (CH_3), 18.2 (CH_3); IR (CH_2Cl_2) 3056, 2975, 1722, 1637 cm^{-1}; LRMS for $C_{13}H_{23}NO_2$ (EI, 20 eV) *m/z* 226 (M^++H, 4), 225 (M^+, 20), 169 (21), 168 (100), 126 (34); HRMS (EI) for $C_{13}H_{23}NO_2$ (M^+): calcd 225.1729, found 225.1722.

4.1.7. 2-Oxo-cyclopentanecarboxylic acid diallylamide (4g). Prepared similarly as **4e**. Yield 98%; a light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.65 (m, 2H), 5.25–5.10 (m, 4H), 4.40– 4.25 (m, 2H), 3.83 (dd, *J*=15.5, 2.5 Hz, 1H), 3.69 (dd, *J*=15.1, 6.0 Hz, 1H), 3.40 (t, *J*=7.5 Hz, 1H), 2.55–2.45 (m, 1H), 2.32–2.28 (m, 2H), 2.22–2.09 (m, 2H), 1.87–1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 212.0 (C), 169.2 (C), 133.5 (CH), 132.9 (CH), 117.1 (CH_2), 116.6 (CH_2), 52.2 (CH), 49.5 (CH_2), 48.4 (CH_2), 38.8 (CH_2), 27.7 (CH_2), 21.22 (CH_2); IR (CH_2Cl_2) 3058, 2981, 2884, 1740, 1637 cm^{-1}; LRMS for $C_{12}H_{17}NO_2$ (EI, 20 eV) *m/z* 207 (M^+, 47), 166 (100); HRMS (EI) for $C_{12}H_{17}NO_2$ (M^+): calcd 207.1259, found 207.1262.

4.1.8. 2-Oxo-cyclohexanecarboxylic acid diallylamide (4h). Prepared similarly as **4e**. Yield 78%; a yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84–5.71 (m, 2H), 5.30–5.15 (m, 4H), 4.34–4.26 (m, 1H), 3.88–3.81 (m, 1H), 3.76–3.73 (m, 1H), 3.70–3.69 (m, 1H), 3.51 (ddd, *J*=10.0, 5.1, 1.2 Hz, 1H), 2.60–2.53 (m, 1H), 2.37–2.19 (m, 2H), 2.08–1.96 (m, 3H), 1.88–1.79 (m, 1H), 1.71–1.62 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$; DEPT) δ 207.5 (C), 169.6 (C), 133.3 (CH), 132.8 (CH), 117.0 (CH_2), 116.5 (CH_2), 54.3 (CH), 49.1 (CH_2), 48.0 (CH_2), 41.8 (CH_2), 30.3 (CH_2), 26.8 (CH_2), 23.4 (CH_2); IR (CH_2Cl_2) 3086, 2949, 1711, 1651 cm^{-1}; LRMS for $C_{13}H_{19}NO_2$ (EI, 20 eV) *m/z* 221 (M^+, 100), 206 (10), 193 (25), 180 (33); HRMS (EI) for $C_{13}H_{19}NO_2$ (M^+): calcd 221.1415, found 221.1416.

4.2. Typical procedure for the α-bromination of olefinic β-keto amides

4.2.1. Preparation of 2-bromo-7-methyl-3-oxo-oct-6-enoic acid dimethylamide (1a). To a stirred solution of **4a** (1.00 g, 5.06 mmol) in EtOAc (30 mL) was added solid *N*-bromosuccinimide (0.99 g, 5.60 mmol) at room temperature. The reaction completed in around 1 h. The reaction mixture was diluted with Et_2O, then washed with water and dried over $MgSO_4$. After concentration, the crude product was purified by flash column chromatography to give **1a** (1.01 g, 72%). A light yellow oil; analytical TLC (silica gel 60), 70% EtOAc in *n*-hexane, R_f=0.56; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (t, *J*=7.1 Hz, 1H), 4.98 (s, 1H), 3.07 (s, 3H), 3.00 (s, 3H), 2.83 (m, 2H), 2.25 (q, *J*=7.2 Hz, 2H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 200.1 (C), 165.5 (C), 133.5 (C), 122.6 (CH), 49.2 (CH), 39.8 (CH_2), 38.4 (CH_3), 36.7 (CH_3), 26.0 (CH_3), 23.1 (CH_2), 18.0 (CH_3); IR (CH_2Cl_2) 2987, 2938, 1746, 1716, 1645 cm^{-1}; LRMS for $C_{11}H_{18}BrNO_2$ (EI, 20 eV) *m/z* 276 (M^+−H, 5), 274 (M^+−H, 7), 196 (40), 114 (100); HRMS (EI) for $C_{11}H_{18}BrNO_2$ (M^+): calcd 275.0521, found 275.0515.

4.2.2. 2-Bromo-3-oxo-dec-7-enoic acid dimethylamide (1b). Prepared similarly to **1a**. Yield 89%; a colorless oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51–5.44 (m, 1H), 5.39–5.31 (m, 1H), 4.98 (s, 1H), 3.09 (s, 3H), 3.00 (s, 3H), 2.87–2.71 (m, 2H), 2.04–1.69 (m, 4H), 1.69 (m, 2H), 0.96 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 200.5 (C), 165.5 (C), 133.4 (CH), 128.3 (CH), 49.0 (CH), 39.0 (CH_2), 38.4 (CH_3), 36.6 (CH_3), 31.9 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 14.2 (CH_3); IR (CH_2Cl_2) 2964, 2942, 1740, 1714, 1654 cm^{-1}; LRMS for $C_{12}H_{20}BrNO_2$ (EI, 20 eV) *m/z* 210 (M^+−Br, 100), 165 (14), 129 (44), 113 (13); HRMS (EI) for $C_{12}H_{20}NO_2$ (M^+−Br): calcd 210.1494, found 210.1505.

4.2.3. 2-Bromo-6-methyl-3-oxo-undeca-6,10-dienoic acid dimethylamide (1c). Prepared similarly to **1a**. Yield 84%; a light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84–5.76 (m, 1H), 5.17 (m, 1H), 4.98 (s, 1H), 5.03–4.94 (m, 2H), 3.09 (s, 3H), 3.00 (s, 3H), 2.97– 2.85 (m, 2H), 2.30 (t, *J*=7.7 Hz, 2H), 2.07 (t, *J*=3.1 Hz, 4H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 200.1 (C), 165.5 (C), 138.8 (CH), 133.9 (C), 125.1 (CH), 114.8 (CH_2), 49.0 (CH), 38.5 (CH_2), 38.4 (CH_3), 36.7 (CH_3), 34.1 (CH_2), 34.0 (CH_2), 27.7 (CH_2), 16.4 (CH_3); IR (CH_2Cl_2) 2934, 1736, 1713, 1653 cm^{-1}; LRMS for $C_{14}H_{22}BrNO_2$ (EI, 20 eV) *m/z* 236 (M^+−Br, 64), 191 (6), 129 (13), 114 (100); HRMS (EI) for $C_{14}H_{22}NO_2$ (M^+−Br): calcd 236.1650, found 236.1639.

4.2.4. 2-Bromo-6,10-dimethyl-3-oxo-undeca-6,10-dienoic acid dimethylamide (1d). Prepared similarly to **1a**. Yield 63%; a light yellow oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (t, *J*=6.7 Hz, 1H), 4.97 (s, 1H), 4.70 (d, *J*=0.7 Hz, 1H), 4.66 (d, *J*=0.7 Hz, 1H), 3.09 (s, 3H), 3.00 (s, 3H), 2.84–2.98 (m, 2H), 2.30 (t, *J*=7.6 Hz, 2H), 2.12 (q, *J*=7.0 Hz, 2H), 2.02 (t, *J*=7.5 Hz, 2H), 1.72 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 200.1 (C), 165.5 (C), 145.9 (C), 137.7 (C), 125.3 (CH), 110.2 (CH_2), 49.0 (CH), 38.5 (CH_3), 38.4 (CH_2), 37.9 (CH_2), 36.6 (CH_3), 34.0 (CH_2), 26.5 (CH_2), 22.7 (CH_3), 16.3 (CH_3); IR (CH_2Cl_2) 2939, 1741, 1715, 1651 cm^{-1}; LRMS for $C_{15}H_{24}BrNO_2$ (EI, 20 eV) *m/z* 330 (M^+−H, 15), 328 (M^+−H, 19), 250 (35), 121 (17), 114 (100); HRMS (EI) for $C_{15}H_{23}BrNO_2$ (M^+−H): calcd 328.0912, found 328.0907.

4.2.5. *N,N*-Diallyl-2-bromo-3-oxo-butyramide (1e). Prepared similarly to **1a**. Yield 78%; a light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.70 (m, 2H), 5.32–5.16 (m, 4H), 4.88 (s, 1H), 4.20–3.82 (m, 4H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 198.1 (C), 165.8 (C), 132.5 (CH), 132.1 (CH), 118.3 (CH_2), 117.9 (CH_2), 50.3 (CH_2), 48.9 (CH_2), 48.6 (CH), 27.4 (CH_3); IR (CH_2Cl_2) 3063, 2988, 1748, 1716, 1656 cm^{-1}; LRMS for $C_{10}H_{14}BrNO_2$ (EI, 20 eV) *m/z* 261 (M^+, 100), 259 (M^+, 72), 180 (31), 153 (77), 136 (67); HRMS (EI) for $C_{10}H_{14}BrNO_2$ (M^+): calcd 259.0208, found 259.0216.

4.2.6. 2-Bromo-*N*-*tert*-butyl-*N*-(3-methyl-but-2-enyl)-3-oxo-butyramide (1f). Prepared similarly to **1a**. Yield 82%; a light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14–5.09 (m, 1H), 4.84 (s, 1H), 3.99 (d, J=5.6 Hz, 2H), 2.43 (s, 3H), 1.76 (s, 3H), 1.67 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) major δ 198.3 (C), 166.4 (C), 135.2 (C), 122.8 (CH), 59.0 (C), 52.0 (CH), 44.5 (CH_2), 28.8 (3×CH_3), 27.4 (CH_3), 25.9 (CH_3), 18.3 (CH_3); IR (CH_2Cl_2) 3063, 2978, 1743, 1715, 1647 cm^{-1}; LRMS for $C_{13}H_{22}BrNO_2$ (EI, 20 eV) m/z 305 (M^+, 6), 303 (M^+, 6), 223 (11), 208 (15), 140 (100); HRMS (EI) for $C_{13}H_{22}BrNO_2$ (M^+): calcd 303.0834, found 303.0834.

4.2.7. 1-Bromo-2-oxo-cyclopentanecarboxylic acid diallylamide (1g). Yield 43%; a light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.59; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.74 (m, 2H), 5.22–5.13 (m, 4H), 4.31–4.15 (m, 2H), 4.07–3.96 (m, 2H), 2.96 (ddd, J=14.3, 7.2, 7.1 Hz, 1H), 2.51–2.33 (m, 3H), 2.19–2.08 (m, 1H), 2.07–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 206.4 (C), 162.3 (C), 133.3 (CH), 131.8 (CH), 118.2 (CH_2), 117.2 (CH_2), 61.6 (C), 51.0 (CH_2), 48.1 (CH_2), 39.2 (CH_2), 34.9 (CH_2), 18.6 (CH_2); IR (CH_2Cl_2) 3055, 2988, 2306, 1743, 1637 cm^{-1}; LRMS (EI, 20 eV) for $C_{12}H_{16}NO_2Br$, m/z 287 (M^+, 16), 285 (M^+, 18), 232 (50), 206 (68), 192 (100); HRMS (EI) for $C_{12}H_{16}NO_2$ (M^+-Br): calcd 206.1181, found 206.1180.

4.2.8. 1-Bromo-2-oxo-cyclohexanecarboxylic acid diallylamide (1h). Yield 42%; a light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.61 (m, 2H), 5.22–5.12 (m, 4H), 4.17 (dd, J=15.2, 4.3 Hz, 1H), 4.03 (dd, J=16.7, 4.9 Hz, 1H), 3.81–3.74 (m, 2H), 3.11–3.05 (m, 1H), 2.86–2.80 (m, 1H), 2.50–2.43 (m, 1H), 2.24–2.17 (m, 1H), 2.05–1.94 (m, 2H), 1.87–1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 206.1 (C), 165.6 (C), 133.6 (CH), 131.9 (CH), 118.8 (CH_2), 117.9 (CH_2), 69.0 (C), 50.8 (CH_2), 48.6 (CH_2), 44.8 (CH_2), 40.9 (CH_2), 29.2 (CH_2), 24.4 (CH_2); IR (CH_2Cl_2) 3055, 2987, 2953, 2254, 1726, 1714, 1651 cm^{-1}; LRMS (EI, 20 eV) for $C_{13}H_{18}NO_2Br$, m/z 301 (M^+, 22) 299 (M^+, 22), 260 (46), 258 (49), 220 (100), 192 (89); HRMS (EI) for $C_{13}H_{18}NO_2Br$ (M^+): calcd 299.0521, found 299.0511.

4.2.9. Typical procedure for Lewis acid-catalyzed atom transfer radical cyclization reactions of olefinic β-keto amides (Table 1, entry 2). To a stirred solution of **1a** (138.1 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL) was added $Yb(OTf)_3$ (93 mg, 0.15 mmol) at room temperature. Then the mixture was cooled to −78°C. Half an hour later, Et_3B (1 M in hexane, 1.5 mL, 1.5 mmol) and O_2 gas (5.0 mL) were added via syringe. The reaction mixture was stirred at −78°C and was followed by TLC. The reaction completed after 1 h. The mixture was filtered through a thin pad of silica gel and then concentrated. The crude product was purified by flash column chromatography to give **2a** (102 mg, 74%) as a light yellow oil. Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, J=9.9 Hz, 1H), 3.24 (s, 3H), 3.02 (s, 3H), 2.86 (dt, J=7.0, 10.7 Hz, 1H), 2.50–2.34 (m, 2H), 2.32–2.22 (m, 1H), 1.95 (dt, J=8.9, 11.1 Hz, 1H), 1.83 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 213.1 (C), 169.1 (C), 73.7 (C), 56.9 (CH), 52.9 (CH), 39.2 (CH_2), 38.1 (CH_3), 36.5 (CH_3), 34.8 (CH_3), 33.0 (CH_3), 24.9 (CH_2); IR (CH_2Cl_2) 2976, 2938, 1773, 1744, 1651 cm^{-1}; LRMS for $C_{11}H_{18}BrNO_2$ (EI, 20 eV) m/z 277 (M^+, 4), 275 (M^+, 3), 196 (100), 167 (70), 154 (65); HRMS (EI) for $C_{11}H_{18}BrNO_2$ (M^+): calcd 275.0521, found 275.0515.

4.2.10. 2-(1-Bromo-propyl)-6-oxo-cyclohexanecarboxylic acid dimethylamide (2b) (the minor isomer of product 2b). A white solid, mp 128–129°C (Et_2O); analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.26; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (ddd, J=2.1, 4.4, 9.6 Hz, 1H), 3.88 (d, J=11.1 Hz, 1H), 3.04 (s, 3H), 2.99 (s, 3H), 2.56–2.49 (m, 2H), 2.36–2.28 (m, 1H), 2.16–2.10 (m, 1H), 2.05–1.93 (m, 2H), 1.90–1.83 (m, 1H), 1.81–1.72 (m, 2H), 1.03 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 206.7 (C), 168.9 (C), 66.1 (CH), 59.2 (CH), 46.2 (CH), 41.7 (CH_2), 37.7 (CH_3), 36.2 (CH_3), 31.1 (CH_2), 24.0 (CH_2), 24.0 (CH_2), 13.3 (CH_3); IR (CH_2Cl_2) 2971, 2940, 1712, 1647cm^{-1}; LRMS for $C_{12}H_{20}BrNO_2$ (EI, 20 eV) m/z 291 (M^+, 7), 289 (M^+, 7), 210 (100), 209 (18), 129 (78); HRMS (EI) for $C_{12}H_{20}BrNO_2$ (M^+): calcd 289.0677, found 289.0667.

4.2.11. 2-(1-Bromo-propyl)-6-oxo-cyclohexanecarboxylic acid dimethylamide (2b) (the major isomer of product 2b). A white solid, mp 125–126°C (Et_2O); analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (dt, J=3.1, 10.4 Hz, 1H), 3.84 (d, J=10.0 Hz, 1H), 3.06 (s, 3H), 3.02 (s, 3H), 2.86–2.80 (m, 1H), 2.60–2.50 (m, 1H), 2.31–2.22 (m, 1H), 2.07–1.96 (m, 2H), 1.88–1.72 (m, 3H), 1.69–1.54 (m, 1H), 1.03 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 207.2 (C), 169.7 (C), 67.3 (CH), 56.6 (CH), 46.2 (CH), 41.0 (CH_2), 38.0 (CH_3), 36.4 (CH_3), 30.4 (CH_2), 28.9 (CH_2), 23.0 (CH_2), 13.8 (CH_3); IR (CH_2Cl_2) 2971, 2940, 1712, 1647 cm^{-1}; LRMS for $C_{12}H_{20}BrNO_2$ (EI, 20 eV) m/z 291 (M^+, 4), 289 (M^+, 4), 210 (100), 192 (14), 129 (41); HRMS (EI) for $C_{12}H_{20}BrNO_2$ (M^+): calcd 289.0677, found 289.0669.

4.2.12. 3-Bromo-2-but-3-enyl-3-methyl-6-oxo-cyclohexanecarboxylic acid dimethylamide (2c). A light yellow oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.72 (m, 1H), 5.03–4.93 (m, 2H), 3.72 (d, J=10.8 Hz, 1H), 3.03 (s, 3H), 3.02 (s, 3H), 2.95–2.86 (m, 1H), 2.51 (ddd, J=2.1, 5.2, 16.1 Hz, 1H), 2.38 (ddd, J=2.1, 6.6, 14.7 Hz, 1H), 2.28–2.16 (m, 2H), 2.14–2.01 (m, 2H), 1.92 (s, 3H), 1.91–1.82 (m, 1H), 1.21–1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT, CH COSY) δ 205.8 (C), 169.2 (C), 138.5 (CH), 115.2 (CH_2), 75.0 (C), 59.1 (CH), 50.6 (CH), 42.2 (CH_2), 39.1 (CH_2), 38.0 (CH_3), 36.3 (CH_3), 34.2 (CH_2), 33.4 (CH_2), 32.7 (CH_3); IR (CH_2Cl_2) 2936, 1712, 1678, 1641 cm^{-1}; LRMS for $C_{14}H_{22}BrNO_2$ (EI, 20 eV) m/z 236 (M^+-Br, 22), 235 (M^+-HBr, 36), 207 (40), 191 (39), 162 (41), 121 (100); HRMS (EI) for $C_{14}H_{22}NO_2$ (M^+-Br): calcd 236.1651, found 236.1646.

4.2.13. 3-Bromo-3-methyl-2-(3-methyl-but-3-enyl)-6-oxo-cyclohexanecarboxylic acid dimethylamide (2d). A light yellow oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f=0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.66 (s, 1H), 3.74 (d, J=10.8 Hz, 1H), 3.03 (s, 3H), 3.02 (s, 3H), 2.91 (m, 1H), 2.52 (ddd, J=2.1, 5.2, 16.6 Hz, 1H), 2.38 (ddd, J=2.1, 6.6, 14.7 Hz, 1H), 2.24–1.87 (m, 5H), 1.92 (s, 3H), 1.70 (s, 3H), 1.24–1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 205.8 (C), 169.2 (C), 145.9 (C), 110.3 (CH_2), 75.0 (C), 59.1 (CH), 51.0 (CH), 42.3 (CH_2), 39.2 (CH_2), 38.1 (CH_3), 37.5 (CH_2), 36.3 (CH_3), 33.3 (CH_2), 32.6 (CH_3), 22.8 (CH_3); IR (CH_2Cl_2) 2938, 1714, 1647 cm^{-1}; LRMS for $C_{15}H_{24}BrNO_2$ (EI, 20 eV) *m/z* 250 (M^+−Br, 100), 221 (45), 205 (59), 189 (68), 121 (93); HRMS (EI) for $C_{15}H_{24}NO_2$ (M^+−Br): calcd 250.1807, found 250.1809.

4.2.14. 3-Acetyl-1-allyl-4-bromomethyl-pyrrolidin-2-one (2e). A light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 0.02×1H, enol), 5.76–5.63 (m, 1H), 5.25–5.18 (m, 2H), 3.89 (d, J=6.1 Hz, 2H), 3.54 (d, J=7.0 Hz, 0.98×1H, keto), 3.52–3.41 (m, 3H), 3.33–3.28 (m, 1H), 3.16 (dd, J=6.2, 8.9 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 202.7 (C), 168.3 (C), 131.8 (CH), 119.0 (CH_2), 60.7 (CH), 49.4 (CH_2), 45.9 (CH_2), 37.7 (CH_2), 36.5 (CH), 32.6 (CH_3); IR (CH_2Cl_2) 3055, 2986, 1716, 1691, 1645 cm^{-1}; LRMS for $C_{10}H_{14}BrNO_2$ (EI, 20 eV) *m/z* 261 (M^+, 34), 259 (M^+, 37), 218 (25), 216 (27), 180 (100); HRMS (EI) for $C_{10}H_{14}BrNO_2$ (M^+): calcd 259.0208, found 259.0198.

4.2.15. 1-Acetyl-3-allyl-3-aza-bicyclo[3.1.0]hexan-2-one (3e). A light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77–5.64 (m, 1H), 5.30–5.15 (m, 2H), 3.90–3.77 (m, 2H), 3.50 (dd, J=5.9, 10.5 Hz, 1H), 3.23 (d, J=10.5 Hz, 1H), 2.58 (s, 3H), 2.44–2.39 (m, 1H), 1.94 (dd, J=3.9, 8.0 Hz, 1H), 1.12 (dd, J=4.0, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 203.7 (C), 171.2 (C), 132.5 (CH), 118.7 (CH_2), 47.1 (CH_2), 45.4 (CH_2), 39.5 (C), 29.9 (CH_3), 25.4 (CH), 24.8 (CH_2); IR (CH_2Cl_2) 3056, 2923, 1711, 1691, 1645 cm^{-1}; LRMS for $C_{10}H_{13}NO_2$ (EI, 20 eV) *m/z* 180 (M^++H, 14), 179 (M^+, 100), 178 (M^+−H, 20), 164 (52); HRMS (EI) for $C_{10}H_{13}NO_2$ (M^+): calcd 179.0946, found 179.0944.

4.2.16. 3-Acetyl-4-(1-bromo-1-methyl-ethyl)-1-*tert*-butyl-pyrrolidin-2-one (2f). A light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (d, J=7.7 Hz, 1H), 3.58 (t, J=9.5 Hz, 1H), 3.43–3.35 (m, 1H), 2.93–2.85 (m, 1H), 2.48 (s, 3H), 1.72 (s, 3H), 1.59 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 204.1 (C), 168.6 (C), 70.2 (C), 61.6 (CH), 55.2 (C), 47.7 (CH_2), 44.1 (CH), 33.2 (CH_3), 32.4 (CH_3), 31.1 (CH_3), 27.9 (3×CH_3); IR (CH_2Cl_2) 2980, 1717, 1680, 1627 cm^{-1}; LRMS for $C_{13}H_{22}BrNO_2$ (EI, 20 eV) *m/z* 305 (M^+, 16), 303 (M^+, 17), 290 (61), 288 (62), 208 (100); HRMS (EI) for $C_{13}H_{22}BrNO_2$ (M^+): calcd 303.0834, found 303.0823.

4.2.17. 2-Allyl-4-bromomethyl-2-aza-spiro[4.4]nonane-1,6-dione (2g). A light yellow oil; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f=0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71–5.58 (m, 1H), 5.20–5.12 (m, 2H), 3.90–3.74 (m, 2H), 3.66 (dd, J=14.6, 7.5 Hz, 1H), 3.37–3.31 (m, 1H), 3.25–3.19 (m, 1H), 3.11–3.06 (m, 1H), 2.95–2.86 (m, 1H), 2.48–2.16 (m, 4H), 2.00–1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 216.2 (C), 171.9 (C), 132.0 (CH), 118.8 (CH_2), 62.3 (C), 49.8 (CH_2), 45.8 (CH_2), 40.4 (CH), 37.6 (CH_2), 32.5 (CH_2), 28.3 (CH_2), 19.8 (CH_2); IR (CH_2Cl_2) 3055, 2987, 2306, 1739, 1686 cm^{-1}; LRMS (EI, 20 eV) for $C_{12}H_{16}NO_2Br$, *m/z* 287 (M^+, 47), 285 (M^+, 40), 230 (52); 192 (100); HRMS (EI) for $C_{12}H_{16}NO_2$ Br (M^+): calcd 285.0365, found 285.0350.

4.2.18. 2-Allyl-4-bromomethyl-2-aza-spiro[4.5]decane-1,6-dione (2h). A light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77–5.64 (m, 1H), 5.24–5.16 (m, 2H), 3.88 (dd, J=6.1, 1.3 Hz, 2H), 3.39–3.56 (m, 3H), 3.29–3.22 (m, 1H), 3.15–3.04 (m, 2H), 2.52–2.45 (m, 1H), 2.35–2.28 (m, 1H), 2.15–2.05 (m, 2H), 1.60–1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 206.9 (C), 171.5 (C), 131.6 (CH), 118.6 (CH_2), 61.8 (C), 48.6 (CH_2), 45.6 (CH_2), 40.2 (CH_2), 38.7 (CH), 31.4 (CH_2), 30.7 (CH_2), 26.8 (CH_2), 20.5 (CH_2); IR (CH_2Cl_2) 3055, 2986, 2950, 1709, 1686 cm^{-1}; LRMS (EI, 20 eV) for $C_{13}H_{18}NO_2$ Br *m/z* 301 (M^+, 24), 299 (M^+, 26), 220 (67); 192 (100); HRMS (EI) for $C_{13}H_{18}NO_2$ Br (M^+): calcd 299.0521, found 299.0518.

4.3. Typical procedure for cyclopropanation reaction of atom transfer radical cyclization product

4.3.1. Preparation of 2-allyl-4-bromomethyl-2-aza-spiro[4.5]decane-1,6-dione (3f) from 2f. To a stirred of solution of cyclization product **2f** (152 mg, 0.5 mmol) in dry THF (20 mL) at 0°C was added NaH (60% oil dispersion, 24 mg, 0.6 mmol). The mixture was stirred at 0°C for 1 h. After removal of THF, the residue was extracted with Et_2O. The organic extract was washed with water then dried over $MgSO_4$. After concentration, the crude product was purified by flash column chromatography to give **3f** (89 mg, 80%). A light yellow oil; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, R_f=0.42; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (dd, J=6.6, 10.9 Hz, 1H), 3.23 (d, J=10.9 Hz, 1H), 2.49 (s, 3H), 2.15 (d, J=6.6 Hz, 1H), 1.38 (s, 9H), 1.21 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 203.9 (C), 169.6 (C), 54.6 (C), 52.2 (C), 42.9 (CH_2), 32.2 (C), 30.9 (CH), 28.5 (CH_3), 27.9 (3×CH_3), 21.1 (CH_3), 15.4 (CH_3); IR (CH_2Cl_2) 2985, 1673, 1666 cm^{-1}; LRMS for $C_{13}H_{21}NO_2$ (EI, 20 eV) *m/z* 223 (M^+, 24), 209 (13), 208 (100), 138 (31); HRMS (EI) for $C_{13}H_{21}NO_2$ (M^+): calcd 223.1572, found 223.1572.

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