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One-pot synthesis of five- or six-membered carbocycles through intramolecular cycloadditions by the use of ethyl chloroformate

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Abstract: The Michael addition reactions of β-nitrostyrenes **1** with 4-pentene-1-magnesium bromide **2a** or 3-butene-1-magnesium bromide **2b** generated nitronates **3** or **4**. Medium to high yields of isoxazolidine derivatives **9** and **10** were obtained when nitronates **3** or **4** were treated with ethyl chloroformate and catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature in one-pot and the ratios of *trans*-**9**:*cis*-**9** were from 1:3.00 to 1:4.06 and the ratios of *trans*-**10**:*cis*-**10** were >99:1. The formation of compounds **9** is proposed to proceed through intramolecular nitrile oxide-olefin cycloadditions (INOC) because compounds **14a-d**, obtained from the trapping of the nitrile oxides by ethyl chloroformate, could be isolated. The mechanism of the generation of compounds **10** is proposed to proceed through intramolecular alkoxycarbonyl nitronate-olefin cycloadditions (IAOC) to form intermediates *N*-(ethoxycarbonyl)isoxazolidines **13** and then eliminate EtOH and CO_2 (or $EtOCO_2H$) to yield the final products.

Introduction

Grignard reagents are the most important of the group IIA organometallics and always used as nucleophiles in the conjugate addition due to the high electron density on carbon. α,β-Unsaturated ketones, aldehydes, esters, nitriles, and nitro or sulfonyl compounds are the substrates most often used in this type reaction. Nitro olefins are useful intermediates in organic synthesis.[1] Due to the strong electron-withdrawing property of the nitro group, conjugated nitroalkenes are excellent Michael acceptors and the nitro group can be further transformed into a host of reactive intermediates, including silyl nitronates,[2] nitrile oxides,[3] and hydroximoyl chlorides.[4] Intramolecular 1,3-dipolar cycloadditions have been proved to be useful in synthetic utility.[5] Among these reactions, intramolecular nitrile oxide-olefin cycloadditions (INOC),[3,5] intramolecular silyl nitronate-olefin cycloadditions (ISOC),[2] and intramolecular oxime-olefin cycloadditions (IOOC)[6] are useful methods to generate [n.3.0] bicyclic compounds which can be converted into different products.

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Reactions of conjugate nitroalkenes with Grignard reagents to generate nitroalkanes or aldehydes have been reported.[7] Our previous study found that medium to high yields of nitroalkanes can be generated when nitronates were added to the dilute aqueous acid solution and high yields of hydroximoyl halides, nitrile oxides or carboxylic acids can be obtained when the same intermediates were treated with ice-cold concentrated aqueous hydrohalic or sulfuric acid solution.[8] The application of the use of nitrile oxides and olefin to undergo inter- or intramolecular 1,3-dipolar cycloadditions to yield [4.3.0] and [3.3.0] bicyclic products also has been reported in these studies.[8] In 1997, Hassner also have reported that the same five- and six-membered carbocycles can be prepared by treating the same nitronates with di-*tert*-butyl dicarbonate [$(t$-BuOCO)$_2$O] and 4-dimethylaminopyridine (DMAP) or with trimethylsilyl chloride.[9]

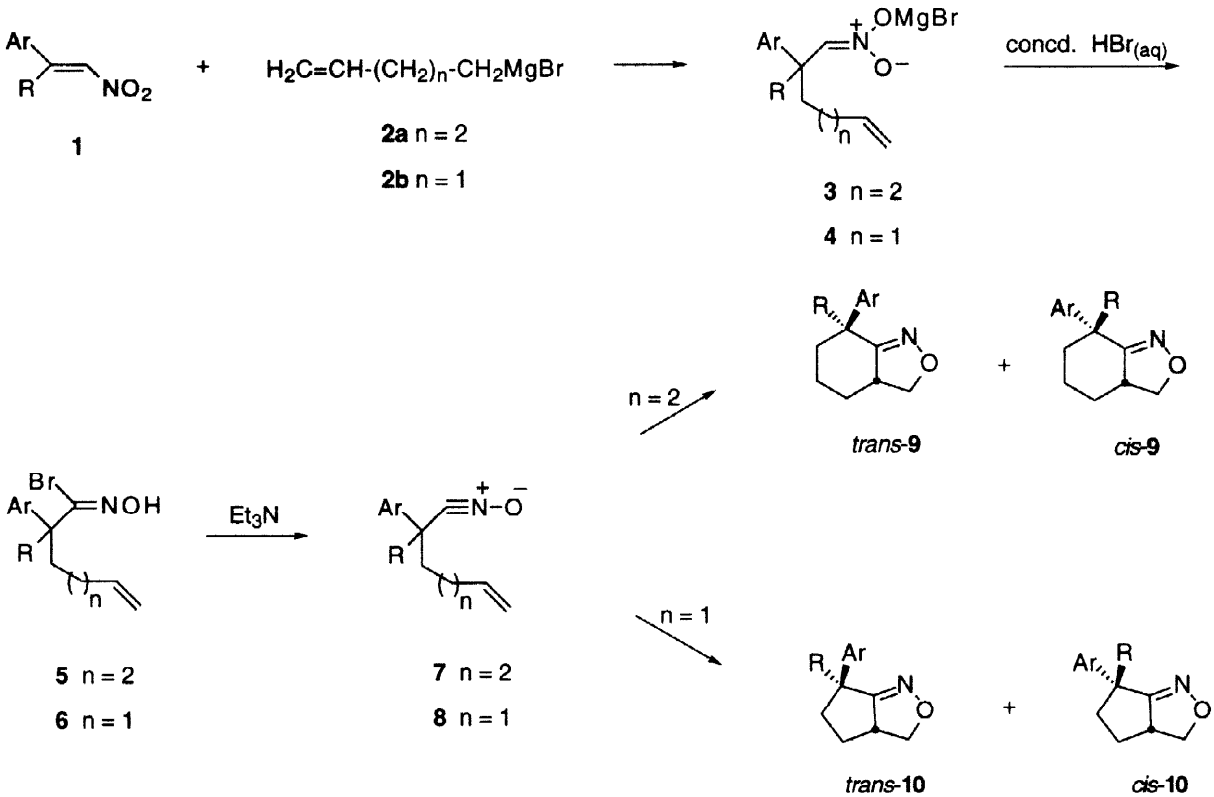
Nitrile oxides are important intermediates in the synthesis of isoxazoles and of many five-membered heterocyclic system via 1,3-dipolar cycloaddition reactions.[5] Two most widely used methods to generate nitrile oxides are: (1) reaction of aldoximes with oxidizing agents[10] or halogenating species[11] and (2) reaction of primary nitroalkanes with dehydrating agents,[3] e.g. aromatic isocyanates in the Mukaiyama-Hoshino method[3a] or ethyl chloroformate (or benzenesulfonyl chloride) in the Shimizu method.[12]

We wish to report an improved, easy and efficient method to afford medium to high yields of five- or six-membered carbocycles fused to isoxazolines from the reactions of β-nitrostyrenes **1** with alkenyl Grignard reagent **2a** or **2b** to generate nitronates **3** or **4** and then treat **3** or **4** with ethyl chloroformate and catalytic amount of DMAP in one-pot.

Results and Discussion

Although addition of Grignard reagents to aliphatic nitroalkenes always generates 1,4-addition, 1,2-addition, and diaddition products,[7] our previous study and literature report found that similar additions to the nitro olefins can proceed fairly smoothly.[8,9] Reaction of β-nitrostyrene **1a** (1 equivalent) with 4-pentene-1-magnesium bromide **2a** (2 equivalents) in THF at -10 ^{o}C generated nitronate **3a**. When **3a** was dropwise added to the ice-cold concentrated hydrobromic acid (48%) solution, 95% (NMR yield) of hydroximoyl bromide **5a** and trace amounts of *trans*-**9a** and *cis*-**9a** were generated. Similar result was also observed when **1a** reacted with 3-butene-1-magnesium bromide **2b** under similar conditions to generate 93% of **6a** (Scheme 1 and Table 1).[8]

[4.3.0] Bicyclic compounds *trans*-**9a** and *cis*-**9a** (88%) were generated and the ratio of *trans*-**9a**:*cis*-**9a** approximately equal to 1:4.50 according to the crude NMR and/or gas chromatography analysis when **3a** was workup with ice-cold concentrated hydrobromic acid solution and then the dichloromethane extract was treated with triethylamine at room temperature. Similarly, 80% of [3.3.0] bicyclic compounds *trans*-**10a** and *cis*-**10a** were produced and the ratio of *trans*-**10a**:*cis*-**10a** was 2.45:1 (GC analysis) when **4a** was treated with hydrobromic acid and triethylamine as described above (Table 2).[8]



1, 3-10

a Ar = Ph, R = H
b Ar = 4-$MeOC_6H_4$, R = H
c Ar = 4-FC_6H_4, R = H
d Ar = 2-thienyl, R = H
e Ar = 3-(*N*-phenyl)indolyl, R = H
f Ar = Ph, R = Ph
g Ar = $PhCH_2CH_2$, R = H

Scheme 1

Table 1. Reactions of Nitro Olefins with Grignard Reagents **2a** or **2b** in THF and Workup with Ice-Cold Concentrated Aqueous Hydrobromic Acid Solution

entry	substrate	Grignard reagent **2**	products	yields[a] (%)
1	**1a**	**2a**	**5a**	95[b,c]
2	**1d**	**2a**	**5d**	93[b]
3	**1a**	**2b**	**6a**	93
4	**1g**	**2b**	**6g**	90

[a] Yields were measured by ^1H NMR from integrations with a known amount of internal standard.
[b] Reference 8. [c] Product **5a** (90%) and trace amounts of *trans*-**9a** and *cis*-**9a** were isolated.

Table 2. Reactions of Nitro Olefins **1a-g** with Grignard Reagents **2a** or **2b** in THF and Workup with Ice-Cold Concentrated Aqueous Hydrobromic Acid Solution and then Triethylamine to Generate Products **9** or **10**

entry	substrate	Grignard reagent **2**	compounds	yields[a] (%)	*trans:cis*[b] **9** or **10**
1	**1a**	**2a**	**9a**	88	1 : 4.50
2	**1b**	**2a**	**9b**	98	1 : 3.84
3	**1c**	**2a**	**9c**	95	1 : 4.45
4	**1d**	**2a**	**9d**	85	1 : 1.00
5	**1e**	**2a**	**9e**	94	1 : 3.41
6	**1f**	**2a**	**9f**	92	–
7	**1g**	**2a**	**9g**	98	1 : 3.37
8	**1a**	**2b**	**10a**	80	2.45 : 1
9	**1b**	**2b**	**10b**	80	2.16 : 1
10	**1c**	**2b**	**10c**	60	2.24 : 1
11	**1d**	**2b**	**10d**	70	2.69 : 1
12	**1e**	**2b**	**10e**	55	2.80 : 1
13	**1f**	**2b**	**10f**	95	–
14	**1g**	**2b**	**10g**	73	2.40 : 1

[a] Yields were measured by ^{1}H NMR with a known amount of internal standard.
[b] Gas chromatography analysis.

The formation of the different isomers **9** and **10** can be explained by the generation of the nitrile oxide **7** or **8** to undergo intramolecular cycloaddition with olefin (INOC) to yield the final products as previously reported and the mechanism is shown as Scheme 1.[8]

It is reported that nitrile oxides can be effectively generated *in situ* by dehydration of the primary nitro compounds with ethyl chloroformate or benzenesulfonyl chloride in the presence of triethylamine or DMAP.[12] When ethyl chloroformate (ClCOOEt) and catalytic amount of DMAP were slowly added to nitronate **3a** at room temperature and stirred for 10 hours, 95% of **9a** were generated and the ratio of *trans*-**9a**:*cis*-**9a** was 1:4.06 (Table 3, entry 1). Not only 75% of **9b** but also 20% of **14a** and **14b** (almost equal amount) could be isolated when nitronate **3b** reacted with the same reagents (Table 3, entry 2). Similarly, 56% of **9c** and 30% of **14c** and **14d** (approximately equal amount) were generated when **1c** was used (Table 3, entry 3).

After obtaining high yields of products **9**, we also tried to react **4a** with ethyl chloroformate and DMAP as described above. Only *trans*-**10a** was isolated in 75% yield (80% NMR yield) and none of *cis*-**10a** was isolated after column purification (Table 3, entry 8). The crude NMR or gas chromatography analysis also indicated none of *cis*-**10a** could be detected. Similarly, only *trans*-**10b-g** (48-95%) were isolated when **1b-g**, respectively, reacted with **2b** under similar conditions and all the experimental results were shown in Table 3 (entries 9-14).

Table 3. One-Pot Reactions of Nitro Olefins **1a-g** with Grignard Reagents **2a** or **2b** in THF and then Ethyl Chloroformate and Catalytic Amount of DMAP Were Slowly Added to the Solution to Generate Products **9** or **10**

entry	substrate	Grignard reagent **2**	compounds	yields[a] (%)	*trans:cis*[b] **9** or **10**
1	**1a**	**2a**	**9a**	95	1:4.06
2	**1b**	**2a**	**9b**	75[c]	1:4.00
3	**1c**	**2a**	**9c**	56[d]	1:3.00
4	**1d**	**2a**	**9d**	97	1:3.10
5	**1e**	**2a**	**9e**	96	1:3.00
6	**1f**	**2a**	**9f**	95	–
7	**1g**	**2a**	**9g**	96	1:3.13
8	**1a**	**2b**	**10a**	80	> 99:1
9	**1b**	**2b**	**10b**	80	> 99:1
10	**1c**	**2b**	**10c**	60	> 99:1
11	**1d**	**2b**	**10d**	70	> 99:1
12	**1e**	**2b**	**10e**	48	> 99:1
13	**1f**	**2b**	**10f**	95	–
14	**1g**	**2b**	**10g**	60	> 99:1

[a] Yields were measured by ^{1}H NMR with a known amount of internal standard.

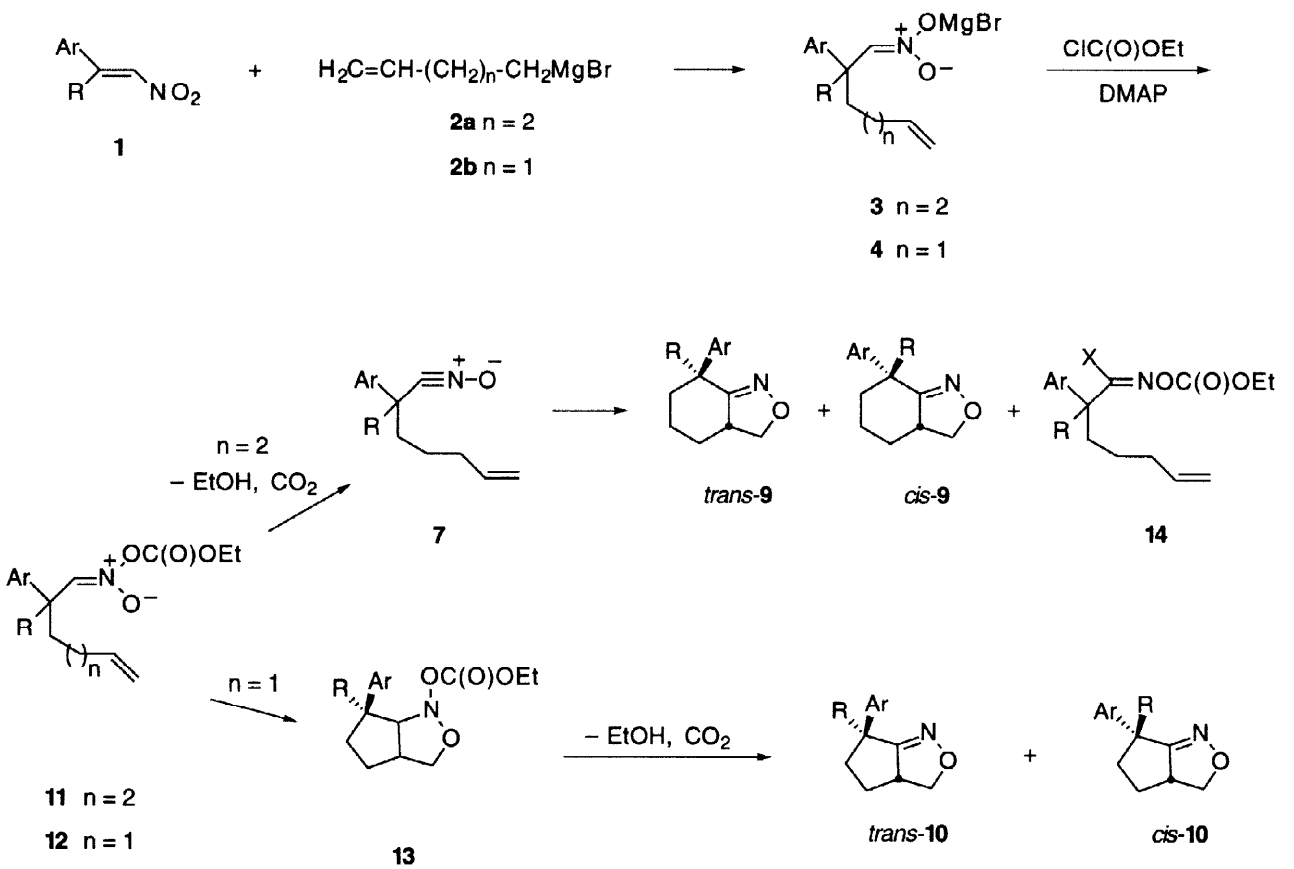
[b] Gas chromatography analysis.

[c] About 20% of **14a** and **14b** were isolated.

[d] About 30% of **14c** and **14d** were isolated.

Structure and stereochemistry of compounds **9** and **10** could be assigned by comparing the spectrum with the literature data.[8,9] The formation of compounds **9** is proposed to proceed through the generation of the nitrile oxides **7** as intermediates to undergo INOC reactions to yield the final products (Scheme 2). The following observations evidently support this proposed mechanism. First, the isolation of products **14a-d**, obtained from

the trapping of the nitrile oxides by ethyl chloroformate,[12] is the significant evidence to support this assumption. Second, the ratios of *trans*-**9**:*cis*-**9** which were observed by treating nitronates **3** with ethyl chloroformate and DMAP (Table 3, entries 1-7) were very close to the ratios of *trans*-**9**:*cis*-**9** when the same nitronates **3** were treated with concentrated hydrobromic acid solution and triethylamine (Table 2, entries 1-7). On the contrary, the generation of product **10** is proposed to proceed through IAOC step because only the *trans* isomers are formed under similar condition. The stereochemistry of the ethoxycarbonyl nitronate cycloaddition is proposed to be similar to the analogous nitrone and silyl nitronate cycloadditions because in these cases the transition states leading to *N*-substituted isoxazolidines can be assumed to have similar geometries.[9,13,14]



11-13

- **a** Ar = Ph, R = H
- **b** Ar = 4-MeOC$_6$H$_4$, R = H
- **c** Ar = 4-FC$_6$H$_4$, R = H
- **d** Ar = 2-thienyl, R = H
- **e** Ar = 3-(*N*-phenyl)indolyl, R = H
- **f** Ar = Ph, R = Ph
- **g** Ar = PhCH$_2$CH$_2$, R = H

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- **a** Ar = 4-MeOC$_6$H$_4$, R = H, X = Cl
- **b** Ar = 4-MeOC$_6$H$_4$, R = H, X = Br
- **c** Ar = 4-FC$_6$H$_4$, R = H, X = Cl
- **d** Ar = 4-FC$_6$H$_4$, R = H, X = Br

Scheme 2

It has been reported that only low yield of *trans*-**9a** and *cis*-**9a** (24%) and a complex mixture were generated when nitronate **3a** was treated with di-*tert*-butyl dicarbonate and DMAP.[9] Based on above results, we found ethyl chloroformate is a better reagent than di-*tert*-butyl dicarbonate to undergo nitronate transformation in one-pot condition. All experimental data also indicated that we have developed an improved, easy, and efficient method to synthesize high yields of five- and six-membered rings by using β-nitrostyrenes, alkenyl Grignard reagents, ethyl chloroformate and DMAP in one-pot. The advantages of this method are (a) the starting materials such as β-nitrostyrenes, ethyl chloroformate and DMAP are easily prepared or commercially available, (b) the use of the highly toxic and cancer suspect reagent such as HMPA or flammable and corrosive reagent such as TMSCl is avoidable,[9] (c) the reaction conditions are mild, for example, the transformation of the nitronates into ethoxycarbonyl nitronates and the entire sequences of IAOC or INOC reactions proceed smoothly at room temperature, (d) the experimental and workup procedures are simple and easy compared to the literature procedures, and (e) the yields of the products are excellent and the products are easily purified because the major byproducts such as CO_2 and EtOH (or EtOCOOH) are gas or soluble in water during the workup procedures.

Conclusion

An improved, convenient, and highly stereoselective method to afford high yields of five- or six-membered carbocycles involves 1,4-addition of alkenyl Grignard reagents, esterification of the nitronates, decarboxylation, and subsequent intramolecular 1,3-dipolar nitrile oxide-olefin cycloaddition (INOC) or involves 1,4-addition of alkenyl Grignard reagents, esterification of the nitronates, subsequent intramolecular 1,3-dipolar alkoxycarbonyl nitronate cycloaddition (IAOC), and decarboxylation, all in one pot. The intramolecular cycloadditions leading to six-membered rings favor *cis* isomers while such reactions leading to five-membered rings favor *trans* isomers.

Experimental Section

General. All reactions were performed in flame or oven-dried glassware under a positive pressure of nitrogen. Air and moisture sensitive compounds were introduced by the use of a syringe or cannula through a rubber septum. THF was distilled from sodium/benzophenone ketyl. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash column chromatography by the use of E. Merck silica gel 60 (230-400 mesh). GCMS were recorded on a HP 5890 GC/HP 5970B MSD, MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini-200 or JEOL EX-400 instrument. All NMR data were obtained in $CDCl_3$ solution and chemical shifts (δ) were given in ppm relative to TMS.

Materials. Compounds **1a-e**, 5-bromo-1-pentene, 4-bromo-1-butene, ethyl chloroformate, triethylamine, hydrobromic acid, and 4-dimethylaminopyridine (DMAP) were purchased from Aldrich Chemical Co and compounds **1a-e** were purified by flash column chromatography before used. Starting material **1f** and **1g** were prepared according to the literature procedures.[15,16]

Typical Experimental Procedure for the Grignard Reagents Addition to Nitro Olefins and INOC Reaction by use of Concentrated Hydrobromic Acid Solution and Triethylamine (Tables 1 and 2):[8] To a stirred solution of the Grignard reagent 4-pentene-1-magnesium bromide **2a** (4.0 mmol), prepared from 4-pentene-1-bromide (4.0 mmol) and magnesium (4.0 mmol), in dried THF 20 mL was added β-nitrostyrene **1a** (2 mmol) in THF 20 mL at -10 °C. After the starting material **1a** had disappeared by checking with TLC plate, the nitronate **3a** was slowly added to 100 mL of the ice-cold concentrated hydrobromic acid (48%) solution. The blue-green color was observed during the slow addition. The solution was stirred for 30 minutes, poured into the ice water, extracted with dichloromethane, dried over $MgSO_4$, filtered and the solvent was evaporated to obtain 95% (the yield was measured by NMR) of hydroximoyl bromide **5a** and trace amounts of bicyclic product *trans*-**9a** and *cis*-**9a** (Table 1, entry 1). Purification of the products was carried out by flash column chromatography (5:95 ethyl acetate/hexane) to obtain 90% pure product **5a** and trace amounts of *trans*-**9a** and *cis*-**9a**. Similarly, 93% of hydroximoyl bromide **6a** was generated when nitronate **4a**, generated from the reaction of **1a** with 3-butene-1-magnesium bromide **2b**, was treated with concentrated hydrobromic acid solution under similar experimental conditions and procedures (Table 1, entry 3). [4.3.0] Bicyclic products *trans*-**9a** and *cis*-**9a** (88% NMR yield) were generated when **3a** was treated with ice cold concentrated hydrobromic acid (48%) and then the dichloromethane solution was slowly added triethylamine at room temperature and the ratio of *trans*-**9a**:*cis*-**9a** was 1:4.50 (Table 2, entry 1) after workup. [3.3.0] Bicyclic products *trans*-**10a** and *cis*-**10a** (80% NMR yield) and the ratio of *trans*-**10a**:*cis*-**10a** was 2.45:1 when **4a** was workup with hydrobromic acid and triethylamine (Table 2, entry 8). The spectral data of compounds **5a**, **5d**, *trans*-**9a-b**, *trans*-**9d**, **9f**, *cis*-**9a-b**, *cis*-**9d**, *trans*-**10a-b**, **10f**, and *cis*-**10a-b** are all consistent with the literature reports.[8,9]

2-Phenyl-6-heptenohydroximoyl Bromide (5a):[8b] Brown liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 8.90 (s, 1H), 7.42-7.20 (m, 5H), 5.81-5.71 (m, 1H), 5.03-4.94 (m, 2H), 3.86 (t, J = 9.5 Hz, 1H), 2.18-1.78 (m, 4H), 1.50-1.26 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) 139.0, 138.6, 138.1, 128.5, 128.1, 127.4, 114.9, 54.0, 33.3, 32.4, 26.4. MS *m/z* (relative intensity) 283 [$(M+2)^+$, 2], 281 (M^+, 3), 202 (60), 185 (24), 170 (37), 143 (33), 117 (61), 102 (37), 91 (100), 77 (23). HRMS calcd for $C_{13}H_{13}BrNO$ [$(M+2)^+$] 283.0395, found 283.0416; calcd (M^+) 281.0415, found 281.0414.

2-(2-Thienyl)-6-heptenohydroximoyl Bromide (5d):[8b] Brown liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 8.35 (s, 1H), 7.23 (d, J = 3.4 Hz, 1H), 6.97 (dd, J = 3.4, 2.6 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 5.81-5.74 (m, 1H), 5.05-4.96 (m, 2H), 4.15 (dd, J = 6.8, 6.4 Hz, 1H), 2.22-1.84 (m, 4H), 1.52-1.36 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) 142.4, 138.0, 137.8, 126.7, 125.7, 124.7, 115.0, 48.6, 33.5, 33.2, 26.7. MS *m/z* (relative intensity) 289 [$(M+2)^+$, 5], 287 (M^+, 5), 272 (7), 270 (7), 256 (7), 254 (8), 220 (13), 218 (14), 208 (55), 177 (29), 149 (38), 138 (85), 123 (65), 108 (26), 97 (100). HRMS calcd for $C_{11}H_{14}BrNOS$ [$(M-1)^+$] 286.9980, found 287.0002.

2-Phenyl-5-hexenohydroximoyl Bromide (6a): This compound was brown liquid and unstable during the flash column purification and underwent dehydrobromination to generate compounds *trans*-**10a** and

cis-**10a**. The crude NMR data were described as the following. ^{1}H NMR (200 MHz, $CDCl_3$) 8.84 (s br, 1H), 7.36-7.22 (m, 5H), 5.88-5.68 (m, 1H), 5.06-4.95 (m, 2H), 3.87 (t, J = 7.2 Hz, 1H), 2.28-1.90 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) 138.9, 138.3, 137.4, 128.6, 128.2, 127.5, 115.6, 53.3, 32.1, 31.0. HRMS calcd for $C_{12}H_{14}BrNO$ [$(M+2)^+$] 270.0317 , found 270.0300; calcd 268.0337 (M^+), found 268.0334.

2-(2-Phenylethyl)-5-hexenohydroximoyl Bromide (6g): This compound was brown liquid and unstable during the flash column purification and underwent dehydrobromination to generate compounds *trans*-**10g** and *cis*-**10g**. The crude NMR data were described as the following. ^{1}H NMR (200 MHz, $CDCl_3$) 8.07 (s br, 1H), 7.32-7.14 (m, 5H), 5.86-5.66 (m, 1H), 5.05-4.92 (m, 2H), 2.70-1.39 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) 141.5, 140.1, 137.6, 128.4, 126.0, 115.3, 46.1, 34.7, 33.0, 32.1, 30.8.

***trans*-3,3a,4,5,6,7-Hexahydro-7-(4-fluorophenyl)cyclohexa[c]isoxazole (*trans*-9c):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.31-7.21 (m, 2H), 7.09-6.97 (m, 2H), 4.51 (dd, J = 10.6, 7.8 Hz, 1H), 4.21 (d, J = 5.0 Hz, 1H), 3.87 (dd, J = 9.8, 8.0 Hz, 1H), 3.27-3.08 (m, 1H), 2.59-2.47 (m, 1H), 2.15-1.26 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) 161.7 (d, J = 244.3 Hz), 161.2, 134.4 (d, J = 3.1 Hz), 128.8 (d, J = 7.6 Hz), 115.5 (d, J = 21.3 Hz), 73.7, 45.7, 37.1, 32.7, 29.9, 20.0. GCMS *m/z* (relative intensity) 219 (M^+, 39), 188 (70), 161 (55), 147 (26), 135 (44), 109 (100), 96 (30), 67 (55). HRMS calcd for $C_{13}H_{14}FNO$ 219.1059, found 219.1057.

***cis*-3,3a,4,5,6,7-Hexahydro-7-(4-fluorophenyl)cyclohexa[c]isoxazole (*cis*-9c):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.32-7.22 (m, 2H), 7.06-6.94 (m, 2H), 4.55 (dd, J = 10.6, 7.8 Hz, 1H), 3.85 (dd, J = 10.6, 7.8 Hz, 1H), 3.52 (dd, J = 12.2, 4.6 Hz, 1H), 3.36-3.17 (m, 1H), 2.25-1.37 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) 162.3, 161.8 (d, J = 244.0 Hz), 135.5 (d, J = 3.1 Hz), 129.7 (d, J = 7.6 Hz), 115.0 (d, J = 21.3 Hz), 73.6, 49.0, 43.7, 34.7, 32.0, 24.6. GCMS *m/z* (relative intensity) 219 (M^+, 21), 188 (85), 161 (60), 148 (27), 121 (38), 109 (100), 96 (28), 67 (64). HRMS calcd for $C_{13}H_{14}FNO$ 219.1059, found 219.1068.

***trans*-3,3a,4,5,6,7-Hexahydro-7-(*N*-phenyl-3-indolyl)cyclohexa[c]isoxazole (*trans*-9e):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.87-7.82 (m, 1H), 7.57-7.13 (m, 9H), 4.56 (d, J = 4.6 Hz, 1H), 4.45 (dd, J = 10.6, 8.0 Hz, 1H), 3.90 (t, J = 8.4 Hz, 1H), 3.43-3.24 (m, 1H), 2.65-2.54 (m, 1H), 2.20-1.36 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) 161.6, 139.7, 136.3, 129.7, 128.4, 126.5, 125.3, 124.4, 122.8, 120.3, 120.2, 115.2, 110.5, 73.6, 46.1, 33.1, 31.7, 30.9, 20.8. MS *m/z* (relative intensity) 316 (M^+, 100), 285 (45), 259 (64), 258 (57), 217 (55), 204 (69), 193 (39), 165 (24), 128 (39), 115 (54), 77 (74). HRMS calcd for $C_{21}H_{20}N_2O$ (M^+) 316.1576, found 316.1567. Anal. calcd : C, 82.28; H, 6.91; N, 5.05. Found: C, 82.72; H, 6.73; N, 4.79.

***cis*-3,3a,4,5,6,7-Hexahydro-7-(*N*-phenyl-3-indolyl)cyclohexa[c]isoxazole (*cis*-9e):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.87-7.82 (m, 1H), 7.57-7.13 (m, 9H), 4.58 (dd, J = 10.6, 8.0

Hz, 1H), 3.91 (dd, J = 10.6, 8.0 Hz, 1H), 3.90 (d, J = 7.0 Hz, 1H), 3.46-3.28 (m, 1H), 2.44-2.16 (m, 1H), 2.05-1.41 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) 161.7, 139.9, 136.0, 129.5, 128.2, 126.2, 126.0, 124.3, 122.4, 120.0, 119.6, 115.7, 110.7, 73.6, 49.4, 35.6, 34.8, 32.5, 25.0. MS *m/z* (relative intensity) 316 (M^+, 100), 285 (33), 259 (28), 258 (27), 217 (21), 204 (29), 193 (12), 165 (8), 128 (14), 115 (17), 77 (22). HRMS calcd for $C_{21}H_{20}N_2O$ (M^+) 316.1576, found 316.1578. Anal. calcd : C, 82.28; H, 6.91; N, 5.05. Found: C, 82.50; H, 6.79; N, 4.84.

***trans*-3,3a,4,5,6,7-Hexahydro-7-(2-phenylethyl)cyclohexa[c]isoxazole (*trans*-9g):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.28-7.08 (m, 5H), 4.38 (dd, J = 10.4, 7.8 Hz, 1H), 3.72 (dd, J = 9.2, 7.8 Hz, 1H), 3.11-2.92 (m, 1H), 2.88-2.65 (m, 2H), 2.33-1.02 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) 162.3, 141.9, 128.0, 127.9, 125.3, 72.7, 48.8, 36.8, 32.9, 32.7, 32.6, 32.2, 24.0. MS *m/z* (relative intensity) 202 (100), 201 (69), 171 (60), 170 (52), 143 (29), 115 (14), 103 (9), 91 (23). HRMS calcd for $C_{15}H_{19}NO$ (M^+) 229.1467, found 229.1465.

***cis*-3,3a,4,5,6,7-Hexahydro-7-(2-phenylethyl)cyclohexa[c]isoxazole (*cis*-9g):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.33-7.13 (m, 5H), 4.45 (dd, J = 10.4, 8.0 Hz, 1H), 3.82 (dd, J = 9.6, 8.0 Hz, 1H), 3.33-3.14 (m, 1H), 2.95-2.88 (m, 1H), 2.79-2.50 (m, 2H), 2.17-1.23 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) 162.2, 141.6, 128.5, 128.3, 125.9, 73.3, 45.3, 33.7, 33.5, 32.8, 32.6, 31.2, 19.7. MS *m/z* (relative intensity) 202 (100), 201 (69), 171 (60), 170 (52), 143 (29), 115 (14), 103 (9), 91 (23). HRMS calcd for $C_{15}H_{19}NO$ (M^+) 229.1467, found 229.1459.

***trans*-3a,4,5,6-Tetrahydro-6-(4-fluorophenyl)-3*H*-cyclopenta[*c*]isoxazole (*trans*-10c):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.29-7.19 (m, 2H), 7.07-6.95 (m, 2H), 4.66-4.51 (m, 1H), 4.01-3.80 (m, 3H), 2.91-2.75 (m, 1H), 2.35-2.12 (m, 2H), 1.70-1.49 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 173.4, 161.9 (d, J = 244.3 Hz), 136.3 (d, J = 3.1 Hz), 128.5 (d, J = 7.6 Hz), 115.5 (d, J = 21.3 Hz), 74.8, 55.6, 38.8, 38.7, 28.1. MS *m/z* (relative intensity) 205 (M^+, 74), 174 (48), 147 (39), 135 (31), 122 (100), 109 (76), 96 (41), 75 (27). HRMS calcd for $C_{12}H_{12}FNO$ (M^+) 205.0903, found 205.0898.

***cis*-3a,4,5,6-Tetrahydro-6-(4-fluorophenyl)-3*H*-cyclopenta[*c*]isoxazole (*cis*-10c):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.29-7.19 (m, 2H), 7.07-6.95 (m, 2H), 4.68-4.53 (m, 1H), 4.01-3.80 (m, 3H), 2.80-2.58 (m, 1H), 2.36-2.10 (m, 2H), 1.81-1.60 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 173.4, 161.9 (d, J = 244.3 Hz), 135.7 (d, J = 3.1 Hz), 129.5 (d, J = 7.6 Hz), 115.5 (d, J = 21.3 Hz), 75.5, 54.5, 39.9, 37.8, 26.1. MS *m/z* (relative intensity) 205 (M^+, 59), 175 (50), 147 (53), 133 (31), 122 (73), 96 (31), 75 (27). HRMS calcd for $C_{12}H_{12}FNO$ (M^+) 205.0903, found 205.0902.

***trans*-3a,4,5,6-Tetrahydro-6-(2-thienyl)-3*H*-cyclopenta[*c*]isoxazole (*trans*-10d):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.20 (dd, J = 2.4, 1.8 Hz, 1H), 6.97-6.92 (m, 2H), 4.66-4.50

(m, 1H), 4.19 (t, J = 8.0 Hz, 1H), 4.02-3.80 (m, 2H), 2.92-2.76 (m, 1H), 2.46-2.12 (m, 2H), 1.68-1.48 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.8, 142.1, 125.5, 122.8, 122.7, 73.6, 52.7, 37.3, 33.5, 26.2. MS *m/z* (relative intensity) 193 (M^+, 100), 162 (42), 136 (36), 122 (25), 110 (74), 96 (68), 91 (29). HRMS calcd for $C_{10}H_{11}NOS$ (M^+) 193.0561, found 193.0558.

***cis*-3a,4,5,6-Tetrahydro-6-(2-thienyl)-3*H*-cyclopenta[*c*]isoxazole (*cis*-10d):** Colorless liquid. NMR (200 MHz, $CDCl_3$) 7.20 (dd, J = 5.2, 1.4 Hz, 1H), 7.05 (dd, J = 3.4, 1.4 Hz, 1H), 6.96 (dd, J = 5.2, 3.4 Hz, 1H), 4.68-4.52 (m, 1H), 4.28 (dd, J = 10.0, 6.0 Hz, 1H), 4.00-3.78 (m, 2H), 2.82-2.63 (m, 1H), 2.45-2.29 (m, 1H), 2.22-2.06 (m, 1H), 1.83-1.61 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 172.9, 142.6, 126.7, 125.2, 124.2, 75.5, 54.5, 38.9, 35.8, 26.1. MS *m/z* (relative intensity) 193 (M^+, 100), 162 (42), 136 (45), 122 (30), 110 (72), 96 (99), 91 (42). HRMS calcd for $C_{10}H_{11}NOS$ (M^+) 193.0561, found 193.0554.

***trans*-3a,4,5,6-Tetrahydro-6-(*N*-phenyl-3-indolyl)-3*H*-cyclopenta[*c*]isoxazole (*trans*-10e):**[8b] Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.67-7.16 (m, 10H), 4.72-4.50 (m, 1H), 4.35 (dd, J = 10.2, 6.2 Hz, 1H), 4.06-3.87 (m, 2H), 2.95-2.75 (m, 1H), 2.51-2.34 (m, 1H), 2.25-2.06 (m, 1H), 1.80-1.65 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 173.0, 139.7, 136.7, 129.5, 128.1, 126.3, 125.9, 124.3, 122.6, 120.1, 119.3, 115.4, 110.7, 75.3, 54.9, 37.1, 32.0, 26.1. MS *m/z* (relative intensity) 302 (M^+, 100), 273 (35), 244 (18), 232 (37), 219 (65), 206 (18), 165 (14), 115 (39), 77 (29). HRMS calcd for $C_{20}H_{18}N_2O$ (M^+) 302.1419, found 302.1409.

***cis*-3a,4,5,6-Tetrahydro-6-(*N*-phenyl-3-indolyl)-3*H*-cyclopenta[*c*]isoxazole (*cis*-10e):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.76-7.12 (m, 10H), 4.68-4.48 (m, 1H), 4.25 (t, J = 8.0 Hz, 1H), 4.08-3.84 (m, 2H), 3.10-2.72 (m, 1H), 2.55-2.35 (m, 1H), 2.29-2.12 (m, 1H), 1.82-1.74 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 173.3, 139.6, 136.7, 129.6, 127.7, 126.4, 124.6, 124.3, 122.9, 120.3, 119.8, 116.2, 110.7, 74.9, 54.8, 37.1, 31.7, 28.1. MS *m/z* (relative intensity) 302 (M^+, 100), 273 (35), 244 (18), 232 (37), 219 (65), 206 (18), 165 (14), 115 (39), 77 (29). HRMS calcd for $C_{20}H_{18}N_2O$ (M^+) 302.1419, found 302.1419.

***trans*-3a,4,5,6-Tetrahydro-6-(2-phenylethyl)-3*H*-cyclopenta[*c*]isoxazole (*trans*-10g):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.33-7.14 (m, 5H), 4.59-4.43 (m, 1H), 3.90-3.68 (m, 2H), 2.86-2.60 (m, 3H), 2.57-2.39 (m, 1H), 2.13-2.00 (m, 1H), 1.96-1.70 (m, 1H), 1.54-1.34 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 174.3, 141.5, 128.6, 128.4, 126.0, 74.5, 55.0, 36.3, 35.4, 33.7, 28.0. GCMS *m/z* (relative intensity) 215 (M^+, 24), 187 (7), 169 (21), 156 (12), 137 (3), 124 (17), 117 (51), 91 (100), 77 (18), 65 (34), 55 (22). HRMS calcd for $C_{14}H_{17}NO$ (M^+) 215.1311, found 215.1310.

***cis*-3a,4,5,6-Tetrahydro-6-(2-phenylethyl)-3*H*-cyclopenta[*c*]isoxazole (*cis*-10g):** Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.33-7.14 (m, 5H), 4.58-4.41 (m, 1H), 3.87-3.65 (m, 2H),

2.93-2.61 (m, 3H), 2.46-2.26 (m, 1H), 2.17-1.70 (m, 4H), 1.62-1.42 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 174.5, 141.8, 128.6, 128.4, 126.0, 74.8, 55.3, 34.9, 34.1, 34.0, 33.8, 26.1. GCMS *m/z* (relative intensity) 215 (M^+, 3), 198 (2), 183 (3), 161 (24), 144 (8), 124 (27), 111 (100), 91 (85), 77 (21), 65 (36), 55 (15). HRMS calcd for $C_{14}H_{17}NO$ (M^+) 215.1311, found 215.1304.

1-Chloro-1-(ethoxycarbonyldioxyimino)-2-(4-methoxyphenyl)-6-heptene (14a): Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.25 (ddd, J = 8.6, 2.0, 1.0 Hz, 2H), 6.87 (ddd, J = 8.6, 2.0, 1.0 Hz, 2H), 5.76 (ddt, J = 17.0, 10.4, 6.6 Hz, 1H), 5.06-4.92 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.96 (t, J = 7.6 Hz, 1H), 3.80 (s, 3H), 2.21-1.84 (m, 4H), 1.48-1.34 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 159.3, 152.9, 152.4, 138.1, 129.7, 129.3, 115.0, 114.1, 65.3, 55.2, 51.1, 33.2, 31.2, 26.3, 14.1. GCMS *m/z* (relative intensity) 341 [$(M+2)^+$, 6], 339 (M^+, 19), 252 (5), 250 (17), 182 (15), 180 (35), 147 (49), 146 (100), 134 (52), 121 (69), 91 (11), 77 (6). HRMS calcd for $C_{17}H_{22}ClNO_4$ [$(M+2)^+$] 341.1208, found 341.1193; calcd (M^+) 339.1237, found 339.1248

1-Bromo-1-(ethoxycarbonyldioxyimino)-2-(4-methoxyphenyl)-6-heptene (14b): Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.25 (ddd, J = 8.6, 2.0, 1.0 Hz, 2H), 6.87 (ddd, J = 8.6, 2.0, 1.0 Hz, 2H), 5.76 (ddt, J = 17.0, 10.4, 6.6 Hz, 1H), 5.06-4.92 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.98 (t, J = 7.6 Hz, 1H), 3.80 (s, 3H), 2.27-1.83 (m, 4H), 1.48-1.34 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 159.2, 152.9, 146.8, 138.1, 129.8, 129.4, 115.0, 114.1, 65.4, 55.2, 52.8, 33.2, 31.8, 26.2, 14.1. GCMS *m/z* (relative intensity) 385 [$(M+2)^+$, 9], 385 (M^+, 8), 296 (8), 294 (8), 226 (11), 224 (12), 215 (19), 214 (33), 189 (12), 187 (11), 172 (19), 163 (23), 159 (21), 147 (29), 146 (100), 134 (40), 121 (65), 91 (10), 77 (5). HRMS calcd for $C_{17}H_{22}BrNO_4$ [$(M+2)^+$] 385.0712, found 385.0706; calcd (M^+) 383.0733, found 383.0720

1-Chloro-1-(ethoxycarbonyldioxyimino)-2-(4-fluorophenyl)-6-heptene (14c): Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.36-7.28 (m, 2H), 7.09-6.98 (m, 2H), 5.76 (ddt, J = 17.2, 10.4, 6.6 Hz, 1H), 5.06-4.93 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.96 (t, J = 7.8 Hz, 1H), 2.23-1.84 (m, 4H), 1.48-1.32 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 162.4 (d, J = 245.8 Hz), 152.8, 151.7, 137.9, 133.5 (d, J = 3.1 Hz), 129.7 (d, J = 7.6 Hz), 115.6 (d, J = 21.2 Hz), 115.1, 65.4, 51.2, 33.1, 31.2, 26.2, 14.1. GCMS *m/z* (relative intensity) 329 [$(M+2)^+$, tr], 327 (M^+, 1), 294 (tr), 292 (1), 240 (16), 238 (49), 202 (42), 187 (5), 186 (15), 185 (8), 175 (19), 170 (11), 169 (17), 160 (20), 150 (13), 147 (29), 146 (7), 143 (22), 135 (45), 134 (51), 133 (19), 122 (38), 109 (100). Anal. calcd for $C_{16}H_{19}ClFNO_3$: C, 58.63; H, 5.84. Found: C, 58.81; H, 5.78.

1-Bromo-1-(ethoxycarbonyldioxyimino)-2-(4-fluorophenyl)-6-heptene (14d): Colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$) 7.36-7.25 (m, 2H), 7.09-6.98 (m, 2H), 5.76 (ddt, J = 17.2, 10.4, 6.6 Hz, 1H), 5.07-4.93 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 4.02 (t, J = 7.8 Hz, 1H), 2.24-1.83 (m, 4H), 1.52-1.31 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 162.4 (d, J = 245.8 Hz), 152.8, 146.2

(d, J = 1.5 Hz),, 138.0, 133.7 (d, J = 3.0 Hz), 129.9 (d, J = 8.3 Hz), 115.6 (d, J = 21.5 Hz), 115.2, 65.5, 53.0, 33.2, 31.9, 26.2, 14.1. GCMS *m/z* (relative intensity) 373 [$(M+2)^+$, tr], 371 (M^+, tr), 284 (14), 282 (13), 203 (24), 202 (29), 175 (13), 160 (18), 151 (11), 147 (28), 135 (19), 134 (52), 133 (14), 122 (27), 109 (100). Anal. calcd for $C_{16}H_{19}BrFNO_3$: C, 51.63; H, 5.14. Found: C, 51.80; H, 5.08.

Typical Experimental Procedure for the One-Pot Grignard Addition to Nitro Olefins and IAOC Reaction by Using Ethyl Chloroformate and in the Presence of Catalytic Amounts of 4-Dimethylaminopyridine (DMAP) (Table 3): To a stirred solution of the Grignard reagent **2a** (4 mmol), prepared from 4-pentene-1-bromide (4.0 mmol) and magnesium (4.0 mmol), in dried THF 20 mL was added β-nitrostyrene **1a** (2 mmol) in THF 20 mL at -10 °C. After the starting material **1a** had disappeared, ethyl chloroformate (4 mmol) and catalytic amount of DMAP (0.2 mmol) were added to the solution and stirred for 10 hours at room temperature. The solution was poured into the brine and extracted with dichloromethane, dried over $MgSO_4$, filtered and the solvent was evaporated to obtain 95% (the yield was determined by NMR) of *trans*-**9a** and *cis*-**9a** and the ratio of *trans*-**9a**:*cis*-**9a** was 1.00:4.06. Purification of the products was carried out by flash column chromatography (5-20% ethyl acetate/hexane) to obtain 85% of pure *trans*-**9a** and *cis*-**9a**. Similar procedures were repeated when substrate **1a** reacted with **2b** to obtain 80% (NMR yield) of *trans*-**10a** only and all the experimental results were shown in Table 3.

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