Synthesis of Quinolines and 2*H*-Dihydropyrroles by Nucleophilic Substitution at the Nitrogen Atom of Oxime Derivatives

Mitsuru Kitamura, Masayuki Yoshida, Takashi Kikuchi, Koichi Narasaka*

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Fax +81(3)58006891.; E-mail: narasaka@chem.s.u-tokyo.ac.jp.

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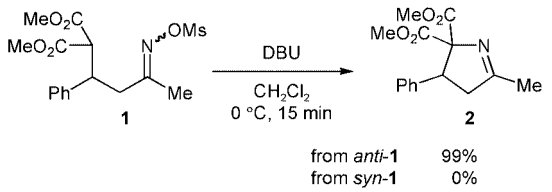
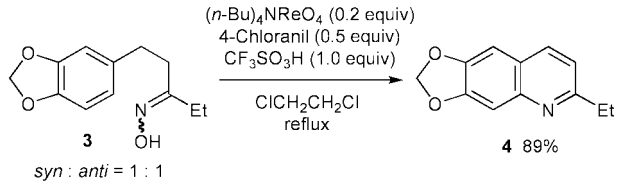
Abstract: Isomerization of oxime derivatives was researched in detail to find out the methods for the *syn-anti* isomerization of *O*-substituted oximes. Based on these findings were developed simple methods for the preparation of aza-heterocycles from both stereoisomers of oximes. Quinolines were synthesized from β-aryl ketone oximes by treatment with trifluoroacetic anhydride and 4-chloranil. γ,δ-Unsaturated *O*-methoxyacetyloximes were transformed to 2*H*-dihydropyrroles by reaction with methoxy-acetic acid.

Key words: nucleophilic substitution, oxime derivatives, quinolines, tetrahydroquinolines, 2*H*-dihydropyrroles

We have been engaged in the synthesis of aza-heterocycles from oxime derivatives based on the substitution at the sp^2 nitrogen of oximes.[1–3] That is, intramolecular nucleophilic moieties such as active methine and aryl groups attack the oxime nitrogen to give cyclization products as shown in Equations 1,[3] 2, and 3[1] and these reactions were revealed to proceed via S_N2-type mechanism.[1–4] Due to the stereospecificity of S_N2-type reaction, only the *anti*-isomer[5] of *O*-mesyloxime **1** was converted to imine **2** while the *syn*-isomer **1** was recovered under the same reaction conditions.[3] This stereospecificity, however, causes a serious drawback in applying this reaction to organic synthesis, because it is quite hard to prepare oxime derivatives in a stereoselective manner.[6]



Equation 1



Equation 2

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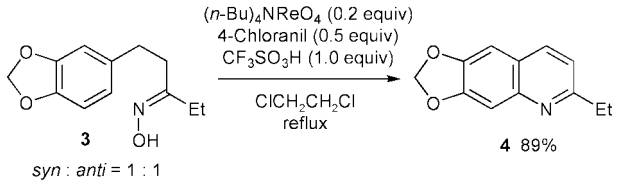
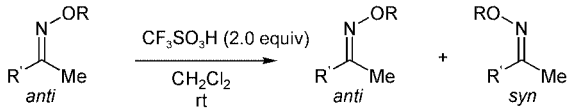


Equation 3

It was considered that both oximes stereoisomers can be employed for the cyclization if the *syn-anti* isomerization of oxime derivatives occurs under the cyclization conditions. Actually, quinoline derivative **4** was obtained in high yield from a 1:1 mixture of the *syn*- and *anti*-β-aryl ketone oximes **3** by treatment with tetrabutylammonium perrhenate and trifluoromethanesulfonic acid,[1] because the oxime itself was easily isomerized under acidic conditions (Equations 2 and 3).[7,8] Although both stereoisomers of oximes could be employed in this rhenium-catalyzed cyclization, it is desirable to carry out the transformation by employing common reagents under milder reaction conditions.

To carry out a substitution at the sp^2 nitrogen of the oxime, it is necessary to convert the hydroxy group into an appropriate leaving group. As mentioned, isomerization of oxime itself readily proceeds under acidic conditions, whereas *O*-substituted oxime hardly isomerizes under mild conditions.[7–11] For example, 4-phenylbutan-2-one oxime (**5**) isomerized by the treatment with trifluoromethanesulfonic acid, while the *O*-methyloxime **6** underwent very little isomerization under the same conditions (Scheme 1).

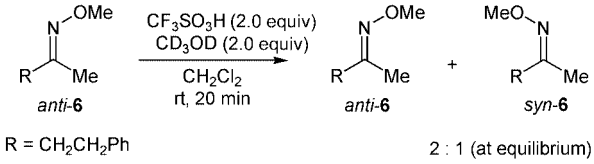


OR	Time	*anti* : *syn*
OH	<20 min	2 : 1 (at equilibrium)
OMe	12 h	>99 : <1 (no isomerisation)

Scheme 1

O-Methyloxime **6** was found to isomerize by the combined use of trifluoromethanesulfonic acid and a nucleophile such as methanol-d_4. As no substitution product

such as *O*-(methyl-d_3)oxime was obtained, isomerization of *O*-methyloxime **6** occurred by protonation onto the oxime nitrogen and the successive addition-elimination of methanol (Equation 4).[9c]



Equation 4

O-Acyloximes were isomerized by the action of carboxylic acid however this occurred slowly. The treatment of *O*-acetyloxime *anti*-**7** with benzoic acid caused the isomerization at 80 °C in toluene, and the isomer ratio attained at equilibrium after 6 hours was 3:1 (*anti*/*syn*). Probably, this isomerization proceeds by addition-elimination of benzoic acid to the imino group (Equation 5).

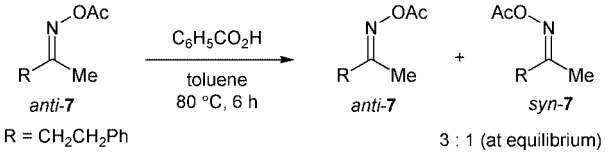
Biographical Sketches

Mitsuru Kitamura was born in Takamatsu, Japan, in 1971 and received his BSc in 1994 and MSc in 1996 from Keio University. After receiving his PhD in 1999 from Tokyo Institute of Technology under the guidance of Prof. K. Suzuki, he was appointed as a research associate in Prof. Narasaka's group at The University of Tokyo. He received The Inoue Research Award for Young Scientists (2000) and a Toray Award of the Synthetic Organic Chemical Society (2001). His research interests are the synthesis of nitrogen heterocycles and the total synthesis of natural products.

Masayuki Yoshida was born in Nagoya, Japan in 1975. He studied chemistry at Department of Chemistry, The University of Tokyo, where he received his BSc in 1998 and PhD in 2003 under the under the guidance of Prof. K. Narasaka. He currently works at the Research Institute of Sankyo Co., Ltd.

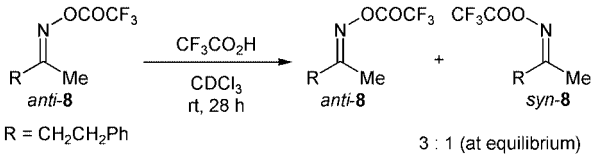
Takashi Kikuchi was born in Kumagaya, Japan in 1980. He was trained as a chemist at The University of Tokyo and received his BSc in 2002. He is currently studying as a graduate student at the same university under the guidance of Prof. K. Narasaka.

Koichi Narasaka was born in Miyagi, Japan, in 1944 and received his BSc in 1967 from Tokyo Institute of Technology. He received his PhD in 1972 under the guidance of Prof. T. Mukaiyama. He became a research associate of the same group in 1972, and then in 1975, moved with Prof. Mukaiyama to The University of Tokyo, where he became a lecturer. His postdoctoral work was with Prof. E. J. Corey at Harvard University from 1975 to 1976. He was appointed to the position of associate professor in 1978, and has been a professor since 1987. He received The Chemical Society of Japan Award for Young Chemists (1979), The Chemical Society of Japan Award (2000), Louis Pasteur Medal (France, 2001), Merck Schuchardt-Lectureship (Germany, 2002), IAP Lectureship (Columbia University, USA, 2002), Boehringer-Ingelheim Lecture Award (University of Toronto, Canada, 2003). His research interests are in the area of development of new methods of organic synthesis.



Equation 5

Furthermore, *O*-acyloxime **8** having a more labile acyl group such as trifluoroacetyl group, isomerized by treatment with trifluoroacetic acid at room temperature to attain at equilibrium, giving an *anti*/*syn* mixture of 3:1 (Equation 6). The isomerization of this labile *O*-acyloxime is supposed to proceed not only by the above mentioned addition-elimination mechanism but also by the following pathways. As another observation, the treatment of acetone *O*-chlorodifluoroacetyloxime with trifluoroacetic acid resulted in the generation of a mixture of acetone *O*-trifluoroacetyl- and *O*-chlorodifluoroacetyloximes. This scrambling of the acyl groups indicated that the isomerisation may also occur by S_N2 substitution at the oxime nitrogen with acids and/or acyl exchange, through the formation of a mixed anhydride and the free oxime.

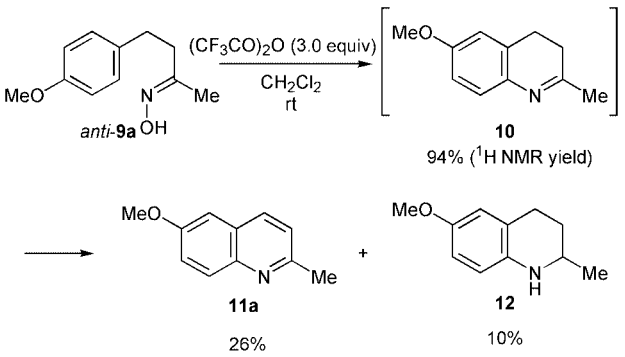


Equation 6

Based on these findings on the isomerization, we considered that treatment of a *syn*- and *anti*-mixture of β-aryl oxime with trifluoroacetic anhydride would generate the *O*-trifluoroacetyloxime,[1] in which the *anti*-isomer would cyclize to quinoline through activation by *O*-protonation of the acyl group. The remaining *syn*-isomer would be isomerized to the *anti*-isomer by the trifluoroacetic acid generated.

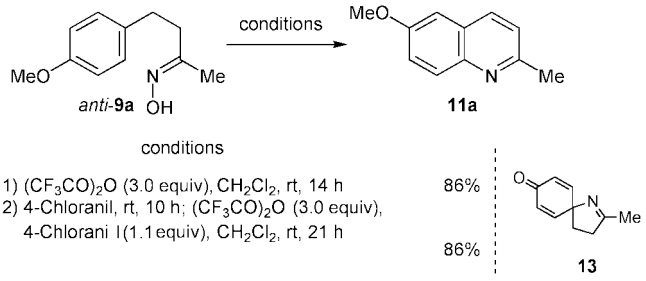
To examine the above hypothesis, 4-(4-methoxyphenyl) butan-2-one *(E)*-oxime (*anti*-**9a**), was treated with 3 equivalents of trifluoroacetic anhydride at room temperature (Scheme 2). The cyclization occurred as expected to give quinoline **11a** and 1,2,3,4-tetrahydroquinoline **12** in 26% and 10% yields, respectively, as the disproportionated products of the preliminary formed dihydroquinoline **10**.[12] By the analysis of the ^1H and ^{13}C NMR spectra of the crude reaction mixture, 3,4-dihydroquinoline **10** was found to be formed in 94% yield, whereas the isolated yield of **11a** and **12** was low. To obtain quinoline **11a** in good yield as a sole product, the conversion of 3,4-dihydroquinoline **10** into quinoline **11a** by oxidation was examined.[1]

In fact, oxidation of the crude reaction mixture with 4-chloranil gave quinoline **11a** in 86% yield with a trace amount of spiro compound **13** (Scheme 3). Furthermore,



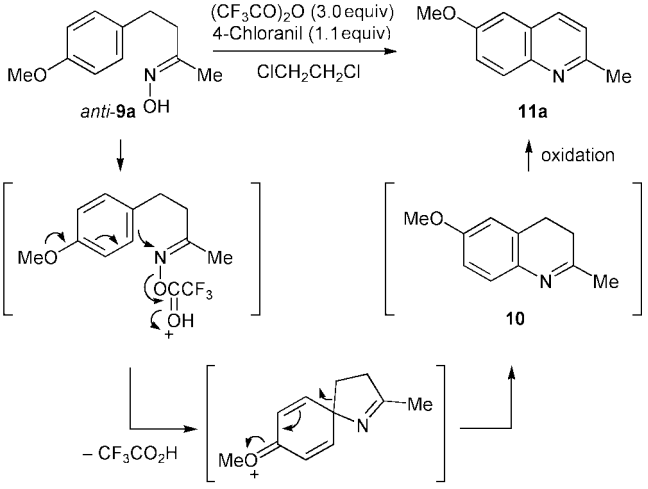
Scheme 2 $(CF_3CO)_2O$-mediated cyclization of *anti*-**9a**

the treatment of **9a** with a mixture of trifluoroacetic anhydride and 4-chloranil, resulted in smooth cyclization of *anti*-**9a**, affording **11a** in the same yield. The use of other oxidants, such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, 4-methylmorpholine *N*-oxide, MnO_2, gave the desired quinoline **11a** in poor to moderate yields.



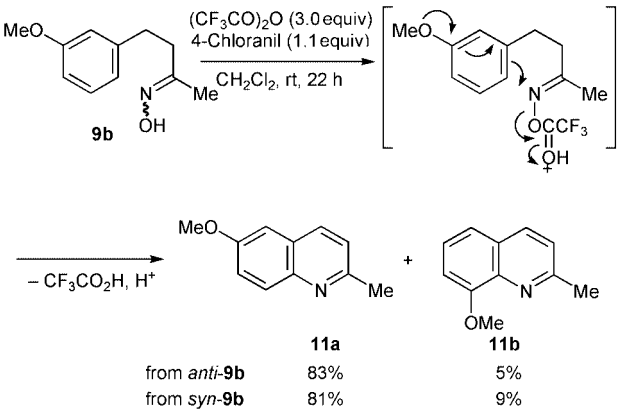
Scheme 3

A plausible mechanism for this cyclization is shown in Scheme 4. After trifluoroacetylation of the oxime **9a**, nucleophilic attack by the aryl moiety occurs onto the oxime nitrogen to form azaspirotrienes. Then successive cyclohexadienone-phenol-type rearrangement[13] and oxidation of the generated 3,4-dihydroquinoline **10** with 4-chloranil yielded **11a**.



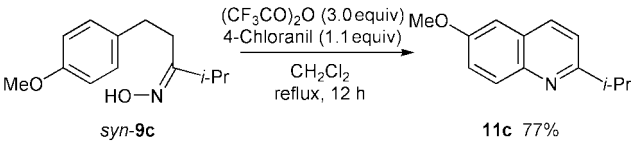
Scheme 4 Plausible mechanism of formation of quinoline **11a**

As explained above, *anti*-oxime *anti*-**9a** could be converted to quinoline **11a** by the simple treatment with trifluoroacetic anhydride and 4-chloranil at room temperature. Then, we examined the influence of the stereochemistry of oximes on the cyclization. Because it was hard to isolate the *syn*-isomer of **9a** in a pure form, we studied the cyclization of both the stereoisomers of *m*-methoxyphenylethyl ketone oxime **9b** (Scheme 5). From the *anti*-**9b**, 6-methoxy-2-methylquinoline (**11a**) and 8-methoxy-2-methylquinoline (**11b**), which correspond to *para*- and *ortho*-cyclization products, were obtained in 83% and 5% yields, respectively. Even from the *syn*-**9b**, quinolines **11a** and **11b** were also formed in 81% and 9% yield, respectively. Thus the cyclization proceeds irrespective of the stereochemistry of oximes, due to the isomerization of the oxime **9b** and the intermediate *O*-trifluoroacetyloxime, under the reaction conditions.



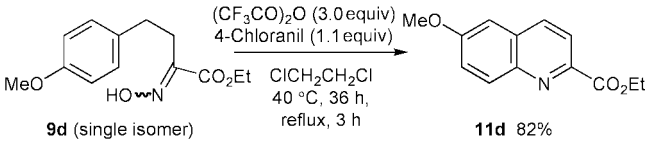
Scheme 5 Influence of *syn*/*anti*-stereochemistry

Then secondary oxime **9c** was prepared to confirm the generality for the cyclization of sterically unfavorable *syn*-isomers. This oxime exist almost exclusively in the *syn*-form at equilibrium, due to steric repulsion. Though the cyclization of *syn*-**9c** required refluxing in dichloromethane, quinoline **11c** was obtained in 77% yield (Equation 6). And it is noteworthy that no Beckmann rearrangement product was detected, although the secondary alkyl ketone oxime readily undergoes the rearrangement.

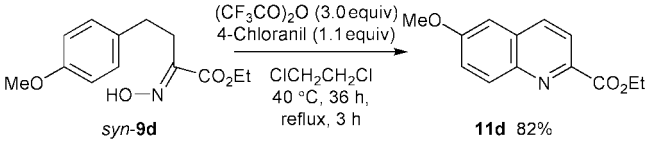


Equation 7

The oxime of α-keto ester **9d**[14] was also successfully transformed to quinoline **11d** at 40 °C in 82% yield (Equations 8 and 9), which was obtained in poor yield in the previous rhenium-trifluoromethanesulfonic acid method.[1b]



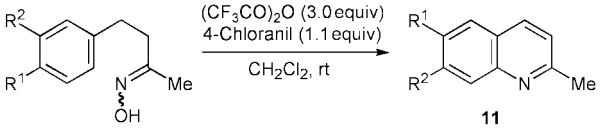
Equation 8



Equation 9

Since it became apparent that both *anti*- and even *syn*-oximes could be transformed to quinolines by this simple procedure, the cyclization of several β-aryl ketone oximes was examined as shown in Table 1. *p*-Methyl and non-substituted phenethyl ketone oximes *anti*-**9e** and **5** were converted to the corresponding quinolines **11e** and **11f** in refluxing 1,2-dichloro-ethane in 76% and 72% yields, respectively (entries 1 and 2). Though the reaction of oximes having acetamido and *N*,*N*-dimethylamino groups on the β-phenyl group, did not give fruitful results, benzyloxycarbonyl(methyl)amino derivative **9g** was transformed to the desired quinoline **11g** in 72% yield (entry 3). The introduction of bromo substituent to methoxyphenyl group led to a slowing down of the cyclization, but the quinoline **11h** was obtained in good yield (82%, entry 4).

Table 1 Synthesis of Various Qunolines **11** from β-Aryl Ketone Oximes



Entry	R^1	R^2	*anti*:*syn*	Substrate	Time (h)	Yield (%)
1[a]	Me	H	>99:<1	**9e**	24	77 (**11e**)
2[b,c]	H	H	>99:<1	**5**	24	72 (**11f**)
3[d]	CBzMeN	H	3:2	**9g**	24	72 (**11g**)
4[e]	MeO	Br	9:1	**9h**	48	82 (**11h**)

[a] Compound **14** (Figure 1) was obtained in 7%.
[b] 1,2-Dichloroethane was used as solvent at refluxing temperature.
[c] Beckmann rearrangement product **15** was obtained in 10% yield.
[d] Compound **13** was obtained in 5% yield.
[e] Compound **16** was obtained in 4% yield.

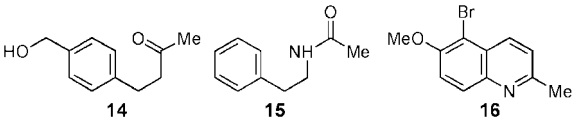
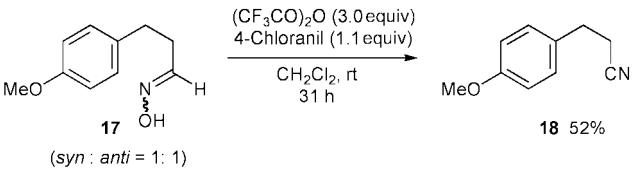


Figure 1

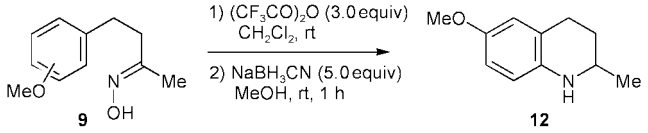
Thus, the cyclization of β-aryl ketone oximes proceeded successfully, whereas aldoxime **17** did not cyclize but gave nitrile **18** by Beckmann fragmentation (Equation 10).[15]



Equation 10

As described above, β-aryl ketone oximes are transformed to quinolines by reaction with trifluoroacetic anhydride and 4-chloranil via the intermediate, 3,4-dihydroquinolines. Accordingly, it was expected that 1,2,3,4-tetrahydroquinolines would be formed by the reduction of the intermediate. In fact, treatment of β-aryl ketone oximes **9a** and **9b** with trifluoroacetic anhydride followed by the reduction with sodium cyanoborohydride in methanol afforded 1,2,3,4-tetrahydroquinoline **12** in 85% and 73% yield, respectively (Table 2).

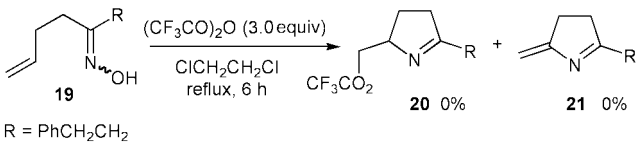
Table 2 Synthesis of Tetrahydroqunoline **12** from β-Aryl Oximes



Entry	Oxime **9**	Time (h)[a]	Yield (%)
1	*anti*-**9a**	17	85
2	*anti*-**9b**	24	73

[a] 1st step.

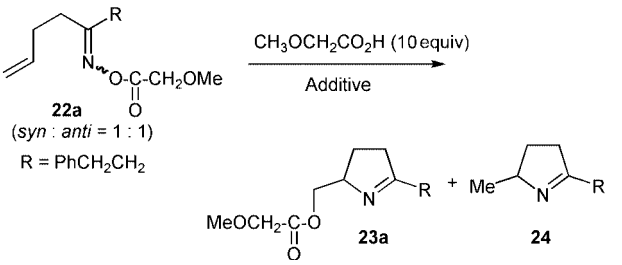
In the above quinoline synthesis, aryl groups play the role as intramolecular nucleophiles for the cyclization. A similar intramolecular substitution was attempted by introducing an olefinic moiety as a nucleophile instead of an aryl group. γ,δ-Unsaturated ketone oxime **19** was treated similarly with trifluoroacetic anhydride, we expected the formation of cyclic imine **20** and/or **21** (Equation 11). We, however, could not observe the formation of cyclic imine **20**, which was found to react with trifluoroacetic anhydride and decompose. Because the use of acid anhydride has to be avoided for the preparation of cyclic imines, we tried the cyclization starting from *O*-acyloximes of γ,δ-unsaturated ketones.



Equation 11

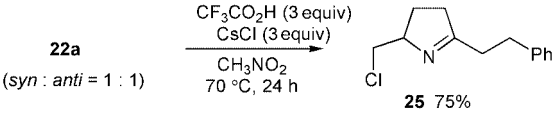
γ,δ-Unsaturated ketone *O*-methoxyacetyl oxime **22a** was treated with methoxyacetic acid in refluxing 1,2-dichloroethane to form the imine.[16] The expected dihydropyrrole **23a** having 2-methoxyacetoxymethyl group was obtained in 22% yield with 2-methyldihydropyrrol **24**, which was formed by a radical process[17] (Table 3, entry 1). In a polar solvent like nitromethane at 70 °C, the reaction proceeded smoothly by treatment with 10 equivalents of methoxyacetic acid, and the addition of 4 Å molecular sieves increased the yield of **23a** up to 83% (entries 2–4).

Table 3 Synthesis of dihydropyrrole **23a** from oxime **22a**



Entry	Solvent	Temp	Additive	Time (h)	Yield **23a** (%)	Yield **24** (%)
1	$ClCH_2CH_2Cl$	reflux	–	12	22	11
2	CH_3NO_2	reflux	–	2	45	7
3	CH_3NO_2	reflux	MS 4 Å	2	55	7
4	CH_3NO_2	70 °C	MS 4 Å	24	83	5

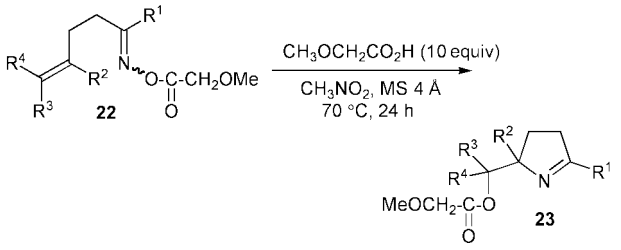
Because the cyclization proceeded via an S_N2-type ionic process, a chlorine atom could be introduced instead of the acyloxy group by performing the reaction under modified conditions with CsCl and trifluoroacetic acid (Equation 12).



Equation 12

The transformation proceeded with wide generality as shown in Table 4. Various γ,δ-unsaturated *O*-methoxyacetyloximes **22** having a variety of olefinic moieties, terminal mono- and di-δ-substituted, mono- and di-γ-substituted, and terminal vinyl, were successfully converted to the corresponding dihydropyrroles **23** in good yields.

Table 4 Synthesis of Various Dihydropyrroles **23** from Oximes **22**



Run	R^1	R^2	R^3	R^4	Substrate	Yield/%
1	$PhCH_2CH_2$	H	H	H	**22a**	83 (**23a**)
2	$PhCH_2CH_2$	Me	H	H	**22b**	59 (**23b**)
3	$PhCH_2CH_2$	H	Me	H	**22c**	72 (**23c**)[a]
4	Me	H	Ph	H	**22d**	72 (**23d**)[b]
5[c,d]	$PhCH_2CH_2$	H	Me	Me	**22e**	88 (**23e**)

[a] Diastereomer mixture (3:2).
[b] Single diastereomer.
[c] The reaction was carried out for 12 h.
[d] 2-isopropenyl-5-phenylethyl-3,4-Dihydro-2*H*-pyrrole (**26**) was formed in 5% yield.

In conclusion, convenient methods for the transformations of phenylethyl ketone oximes to quinolines and γ,δ-unsaturated ketone *O*-methoxyacetyl oximes to dihydropyrroles have been developed based on the intramolecular S_N2-type reaction. In these reactions, both stereoisomers of oximes can be employed for the preparation of these aza-heterocycles.

IR spectra were recorded on Horiba FT-300S. ^{1}H NMR spectra were recorded with a Bruker Avance 500 (500 MHz) and a Bruker DRX 500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded with a Bruker Avance 500 (125 MHz) and a Bruker DRX 500 (125 MHz) spectrometer. Chemical shift values were given in ppm relative to tetramethylsilane for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. High resolution mass spectra were taken with a JEOL JMS-700M spectrometer. Melting points (mp) were uncorrected. Silica Gel 60 N (spherical, neutral) (Kanto Chemical) was used for column chromatography, and Wakogel® B-5F (Wako Pure Chemical Industries) was used for preparative thin-layer chromatography. All the solvents were stored over MS 4 Å after purification. Dichloromethane and 1,2-dichloroethane were distilled from phosphorous pentoxide and calcium hydride, successively. Toluene was dried over calcium chloride and distilled after decantation. Nitromethane was distilled from calcium chloride. Methanol-d_4 (Aldrich) and chloroform-*d* (Nippon Sanso) were used as received. Trifluoroacetic anhydride, trifluoroacetic acid, and trifluoromethanesulfonic acid were distilled from phosphorous pentoxide before use. Benzoic acid (Tokyo Chemical Industry) was used as received. Methoxyacetic acid was distilled from calcium chloride. Triethylamine was distilled from calcium hydride before use. 4-Chloranil was recrystallized from dry toluene. Configurations of oximes (*syn* or *anti*) were determined by the ^{13}C NMR.[18]

4-Phenylbutan-2-one (*E*)-Oxime (*anti*-5)[1b]
To a solution of 4-phenylbutan-2-one (4.05 g, 27.0 mmol) in MeOH (30 mL), hydroxylamine hydrochloride (3.80 g, 54.0 mmol) and pyridine (4.42 g, 54.0 mmol) were added, and the mixture was stirred for 12 h at r.t. After removal of the solvent in vacuo, water was added, and organic materials were extracted with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the obtained solid was recrystallized from hexane–Et_2O to afford 4-phenylbutan-2-one (*E*)-oxime (2.46 g, 15.1 mmol) in 56% yield; colorless crystals; mp 86 °C.

IR (KBr): 3220, 1681, 1602, 1452, 1361, 950, 746, 698 cm^{-1}.

^{1}H NMR: δ = 1.91 (3 H, s), 2.51 (2 H, t, *J* = 8.2 Hz), 2.83 (2 H, t, *J* = 8.2 Hz), 7.18–7.30 (5 H, m), 8.81 (1 H, br s).

^{13}C NMR: δ = 13.8, 32.6, 37.7, 126.1, 128.3, 128.4, 141.0, 157.9.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.80; H, 8.11; N, 8.60.

4-Phenylbutan-2-one (*Z*)-Oxime (*syn*-5)
Colorless oil.

IR (ZnSe): 3215, 2864, 1662, 1603, 1495, 1454, 1377, 1038, 950, 746, 696 cm^{-1}.

^{1}H NMR: δ = 1.82 (3 H, s), 2.66–2.69 (2 H, m), 2.82–2.86 (2 H, m), 7.18–7.30 (5 H, m), 9.30 (1 H, br s).

^{13}C NMR: δ = 20.2, 30.7, 31.4, 126.1, 128.3, 128.4, 141.2, 158.3.

4-Phenylbutan-2-one (*E*)-*O*-Methyloxime (*anti*-6)
To a solution of 4-phenylbutan-2-one (1.48 g, 10.0 mmol) in MeOH (20 mL), *O*-methylhydroxylamine hydrochloride (1.60 g, 20.0 mmol) and pyridine (1.58 g, 20.0 mmol) was added, and the mixture was stirred for 12 h at r.t. After removal of the solvent in vacuo, water was added, and organic materials were extracted with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane–EtOAc) to afford 4-phenylbutan-2-one (*E*)-*O*-methyloxime (0.76 g, 4.3 mmol) as less polar compounds than (*Z*)-oxime in 43% yield; colorless oil.

IR (ZnSe): 2937, 1637, 1603, 1454, 1367, 1052, 746, 698 cm^{-1}.

^{1}H NMR: δ = 1.85 (3 H, s), 2.47 (2 H, t, *J* = 8.0 Hz), 2.82 (2 H, t, *J* = 8.0 Hz), 3.83 (3 H, s), 7.19–7.20 (3 H, m), 7.27–7.28 (2 H, m).

^{13}C NMR: δ = 14.1, 32.9, 37.7, 61.1, 126.0, 128.3, 128.4, 141.1, 156.8.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.58; N, 7.70.

4-Phenylbutan-2-one (*Z*)-*O*-Methyloxime (*syn*-6)
Colorless oil.

IR (ZnSe): 3336, 2937, 1768, 1602, 1454, 1377, 1058, 891, 746, 698 cm^{-1}.

^{1}H NMR: δ = 1.80 (3 H, s), 2.60 (2 H, t, *J* = 8.0 Hz), 2.79 (2 H, t, *J* = 8.0 Hz), 3.81 (3 H, s), 7.19–7.21 (3 H, m), 7.27–7.30 (2 H, m).

^{13}C NMR: δ = 20.2, 31.2, 31.6, 61.1, 126.0, 128.2, 128.4, 141.1, 157.5.

4-Phenylbutan-2-one (*E*)-*O*-Acetyloxime (*anti*-7)
To a solution of 4-phenylbutan-2-one (*E*)-oxime (1.63 g, 10.0 mmol) in CH_2Cl_2 (50 mL), Et_3N (3.22 g, 30.0 mmol) and Ac_2O (2.17 g, 20.0 mmol) was added, and the mixture was stirred for 12 h at r.t. The reaction was quenched with sat. aq $NaHCO_3$, and organic materials were extracted with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane–EtOAc) to afford

4-phenylbutan-2-one (*E*)-*O*-acetyloxime (*anti*-**7**) (1.75 g, 8.53 mmol) in 85% yield; colorless oil.

IR (ZnSe): 3028, 1763, 1641, 1365, 1200, 912, 727, 698 cm^{-1}.

^1H NMR: δ = 1.99 (3 H, s), 2.21 (3 H, s), 2.63 (2 H, t, *J* = 8.1 Hz), 2.89 (2 H, t, *J* = 8.1 Hz), 7.21–7.30 (5 H, m).

^{13}C NMR: δ = 15.6, 19.5, 32.4, 37.4, 126.2, 128.1, 128.4, 140.2, 165.5, 166.7.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.44; H, 7.59; N, 6.82.

4-Phenylbutan-2-one (*Z*)-*O*-Acetyloxime (*syn*-7)
Colorless oil.

IR (ZnSe): 3026, 1755, 1365, 1201, 914, 746, 698 cm^{-1}.

^1H NMR: δ = 1.98 (3 H, s), 2.11 (3 H, s), 2.71 (2 H, t, *J* = 7.6 Hz), 2.85 (2 H, t, *J* = 7.6 Hz), 7.18–7.32 (5 H, m).

^{13}C NMR: δ = 19.5, 20.4, 31.8, 32.5, 126.4, 128.1, 128.3, 128.5, 140.0, 166.1.

Isomerization of Oximes 5–7 (Scheme 1 or Equations 4, 5)
4-Phenylbutan-2-one (*E*)-oxime (5); Typical Procedure
To a solution of 4-phenylbutan-2-one (*E*)-oxime (15.3 mg, 0.104 mmol) in CH_2Cl_2 (0.75 mL), trifluoromethanesulfonic acid (31.2 mg, 0.208 mmol) was added at r.t., and the reaction was followed by ^1H NMR. After the reaction mixture was stirred for 2 h, the reaction was quenched with sat. aq Na_2CO_3. Organic materials were extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by preparative thin-layer chromatography (hexane–EtOAc, 3:1) to afford 4-phenylbutan-2-one oxime (*E*/*Z* = 2:1) (14.7 mg, 0.101 mmol) in 97% yield.

Isomerization of 4-Phenylbutan-2-one (*E*)-*O*-Trifluoroacetyloxime (Equation 6)
To a solution of 4-phenylbutan-2-one (*E*)-oxime (11.8 mg, 0.0723 mmol) in $CDCl_3$ (0.75 mL), Et_3N (31 μL, 0.22 mmol) and trifluoroacetic anhydride (31 μL, 0.22 mmol) were added successively at r.t., and the mixture was left to stand for 30 min to generate 4-phenylbutan-2-one (*E*)-*O*-trifluoroacetyloxime in situ. Then trifluoroacetic acid (23 μL, 0.30 mmol) was added to the mixture, the progress of the reaction was followed ^1H NMR.

4-(3-Methoxyphenyl)butan-2-one (*E*)-oxime (9b); Typical Procedure
To a solution of 3-methoxybenzaldehyde (6.80 g, 49.4 mmol) in acetone (38 mL) was added 1 M aq NaOH (100 mL) dropwise over 30 min, and the mixture was stirred for 1 h. After neutralization with 6 M aq HCl, acetone was removed by evaporation. The remaining aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane–EtOAc) to afford 4-(3-methoxyphenyl)-3-buten-2-one (7.22 g, 41.0 mmol) in 82% yield.

A suspension of 4-(3-methoxyphenyl)-3-buten-2-one (7.22 g, 41.0 mmol), 5% Pd/C (732 mg) and HOAc (ca 80 mg) in EtOH (40 mL) was stirred under H_2 atmosphere for 1 d. After purging the H_2 with argon, the reaction mixture was filtered through a celite pad. The solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc) to give 4-(3-methoxyphenyl)butan-2-one (5.36 g, 30.1 mmol) in 73% yield.

To a solution of 4-(3-methoxyphenyl)butan-2-one (5.42 g, 30.4 mmol) in EtOH (57 mL), a solution of hydroxylamine hydrochloride (4.22 g, 60.7 mmol) and pyridine (4.96 g, 62.7 mmol) in EtOH (27 mL) was added, and the mixture was stirred for 1 d. After addition of water, organic materials were extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation, and the residue was recrystallized from EtOH to afford 4-(3-methoxyphenyl)butan-2-one (*E*)-oxime (**9b**) (2.60 g, 13.5 mmol) in 44% yield.

4-(4-Methoxyphenyl)butan-2-one (*E*)-Oxime (*anti*-9a)[1b]
Colorless crystals; mp 77 °C.

IR (KBr): 3240, 1678, 1610, 1512, 1242 cm^{-1}.

^1H NMR: δ = 1.91 (3 H, s), 2.47 (2 H, t, *J* = 8.5 Hz), 2.78 (2 H, t, *J* = 8.5 Hz), 3.78 (3 H, s), 6.83 (2 H, d, *J* = 8.6 Hz), 7.11 (2 H, d, *J* = 8.6 Hz), 8.72 (1 H, br s).

^{13}C NMR: δ = 13.7, 31.7, 38.0, 55.2, 113.8, 129.2, 133.1, 157.9, 158.0.

4-(3-Methoxyphenyl)butan-2-one (*E*)-oxime (*anti*-9b)[1b]
Colorless crystals; mp 59 °C.

IR (KBr): 3240, 1603, 1493, 1259, 1169, 1039, 764, 700 cm^{-1}.

^1H NMR: δ = 1.92 (3 H, s), 2.51 (2 H, t, *J* = 8.1 Hz), 2.81 (2 H, t, *J* = 8.1 Hz), 3.79 (3 H, s), 6.74–6.79 (3 H, m), 7.19–7.22 (1 H, m), 8.33 (1 H, br s).

^{13}C NMR: δ = 13.7, 32.6, 37.6, 55.1, 111.4, 114.0, 120.6, 129.4, 142.7, 158.0, 159.6.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.49; H, 8.02; N, 7.04.

4-(3-Methoxyphenyl)butan-2-one (*Z*)-Oxime (*syn*-9b)
Colorless oil.

IR (ZnSe): 3217, 1660, 1601, 1583, 1489, 1257, 1151, 1038, 775, 692 cm^{-1}.

^1H NMR: δ = 1.92 (3 H, s), 2.50 (2 H, t, *J* = 8.1 Hz), 2.82 (2 H, t, *J* = 8.1 Hz), 3.79 (3 H, s), 6.74–6.83 (3 H, m), 7.19–7.22 (1 H, m), 9.37 (1 H, br s).

^{13}C NMR: δ = 20.2, 30.5, 31.4, 55.1, 111.4, 113.9, 120.6, 129.4, 142.8, 158.2, 159.6.

1-(4-Methoxyphenyl)-4-methylpentan-3-one (*E*)-Oxime (*syn*-9c)
Colorless crystals; mp 71–72 °C.

IR (KBr): 3248, 2964, 1612, 1510, 1244, 1176, 1036, 939, 806 cm^{-1}.

^1H NMR: δ = 1.08 (6 H, d, *J* = 6.9 Hz), 2.41 (1 H, septet, *J* = 6.9 Hz), 2.55 (2 H, t, *J* = 8.2 Hz), 2.83 (2 H, t, *J* = 8.2 Hz), 3.79 (3 H, s), 6.84 (2 H, d, *J* = 8.7 Hz), 7.16 (2 H, d, *J* = 8.7 Hz), 8.14 (1 H, br s).

^{13}C NMR: δ = 19.8, 29.3, 31.0, 33.9, 55.2, 113.8, 129.2, 134.0, 157.9, 165.0.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.37; H, 8.69; N, 6.11.

Ethyl 2-Hydroxyimino-4-(4-methoxyphenyl)butyrate (9d)
Colorless crystals; mp 91–92 °C.

IR (ZnSe): 3228, 1724, 1610, 1512, 1441, 1246, 1194, 1007, 827, 766 cm^{-1}.

^1H NMR: δ = 1.31 (3 H, t, *J* = 7.1 Hz), 2.79 (2 H, t, *J* = 7.9 Hz), 2.89 (2 H, t, *J* = 7.9 Hz), 3.79 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 6.84 (2 H, d, *J* = 11.5 Hz), 7.16 (2 H, d, *J* = 11.5 Hz), 9.54 (1 H, br s).

^{13}C NMR: δ = 14.1, 27.0, 30.9, 55.2, 61.8, 113.8, 129.3, 132.9, 152.5, 158.0, 163.3.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.23; H, 6.77; N, 5.51.

4-(4-Methyphenyl)butan-2-one (*E*)-Oxime (*anti*-9e)
Colorless crystals; mp 90–92 °C.

IR (ZnSe): 3228, 2925, 1676, 1512, 1367, 1211, 951, 862, 810, 754, 644 cm^{-1}.

^1H NMR: δ = 1.91 (3 H, s), 2.31 (3 H, s), 2.48 (2 H, t, *J* = 8.2 Hz), 2.79 (2 H, t, *J* = 8.2 Hz), 7.07–7.09 (4 H, m), 8.05 (1 H, br s).

^{13}C NMR: δ = 13.7, 21.0, 32.2, 37.9, 128.1, 129.1, 135.6, 138.0, 158.0.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.57; H, 8.63; N, 7.81.

Benzyl *N*-[4-(3-Hydroxyiminobutyl)phenyl]-*N*-methylcarbamate (9g)
Colorless crystal; mp 63–65 °C; *E*/*Z* = 2:1.

IR (ZnSe): 3365, 2920, 1699, 1684, 1689, 1514, 1346, 1149 cm^{-1}.

^1H NMR: δ = 1.81 (1 H, s), 1.91 (2 H, s), 2.50 (1.3 H, t, *J* = 8.4 Hz), 2.66 (0.7 H, t, *J* = 8.4 Hz), 2.81 (2 H, t, *J* = 8.4 Hz), 3.30 (3 H, s), 5.15 (2 H, s), 7.16–7.29 (9 H, m), 8.86 (1 H, br s).

^{13}C NMR: δ = 13.7, 20.3, 30.5, 30.9, 32.0, 37.5, 37.8, 67.2, 125.7, 127.6, 127.8, 128.3, 128.7, 128.8, 136.6, 139.0, 139.1, 141.2, 155.5, 157.6, 158.1.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.12; H, 6.93; N, 8.47.

4-(3-Bromo-4-methoxyphenyl)butan-2-one Oxime (9h)
Colorless crystal; mp 76–84 °C; *E*/*Z* = 9:1.

IR (ZnSe): 3224, 3116, 2943, 1604, 1495, 1281, 1254, 1053, 806, 725 cm^{-1}.

^1H NMR: δ = 1.82 (0.3 H, s), 1.91 (2.7 H, s), 2.47 (1.8 H, t, *J* = 8.1 Hz), 2.62 (0.2 H, t, *J* = 8. 1 Hz), 2.76 (2 H, t, *J* = 8.1 Hz), 3.86 (3 H, s), 6.81 (1 H, d, *J* = 8.4 Hz), 7.08 (0.9 H, dd, *J* = 2.2, 8.4 Hz), 7.09 (0.1 H, dd, *J* = 2.2, 8.4 Hz), 7.38 (0.9 H, d, *J* = 2.2 Hz), 7.42 (0.1 H, d, *J* = 2.2 Hz), 8.91 (1 H, br s).

^{13}C NMR: δ = 13.8, 20.3, 30.3, 30.7, 31.3, 37.7, 56.2, 111.5, 111.9, 128.2, 133.0, 134.6, 154.2, 157.6.

Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.72; H, 5.28; N, 4.88.

3-(4-Methoxyphenyl)propanal Oxime (17)
Colorless crystal; mp 108 °C; *E*/*Z* = 1:1.

IR(KBr): 3174, 3080, 2839, 1610, 1514, 1437, 1244, 1032, 833, 815 cm^{-1}.

^1H NMR: δ = 2.49 (1 H, dt, *J* = 4.8, 7.7 Hz), 2.68 (1 H, dt, *J* = 4.8, 7.7 Hz), 2.76 (2 H, t, *J* = 7.7 Hz), 3.79 (3 H, s), 6.74 (0.5 H, t, *J* = 4.8 Hz), 6.84 (2 H, d, *J* = 8.6 Hz), 7.12 (2 H, d, *J* = 8.6 Hz), 7.45 (0.5 H, t, *J* = 4.8 Hz), 7.86 (0.5 H, br s), 8.32 (0.5 H, br s).

^{13}C NMR: δ = 26.6, 31.1, 31.4, 31.9, 55.2, 113.9, 129.2, 129.3, 132.6, 132.7, 151.5, 151.9, 158.0.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.28; H, 7.41; N, 7.65.

Cyclization of *anti*-9a;Typical Procedure
To a solution of 4-(4-methoxyphenyl)butan-2-one (*E*)-oxime (*anti*-**9a**) (96.3 mg, 0.498 mmol) in CH_2Cl_2 (4 mL), trifluoroacetic anhydride (317 mg, 1.51 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 3 min at r.t. 4-Chloranil (135 mg, 0.550 mmol) was added immediately to the mixture, which was stirred for 21 h. 1 M aq NaOH (? mL) was added to the reaction mixture, and the mixture was stirred for 1 h. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine and dried over Na_2SO_4. Na_2SO_4 was filtered off, and the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel, hexane–EtOAc, 1:1) to afford 6-methoxy-2-methylquinoline **11a** (73.4 mg, 42.4 mmol) in 86% yield.

6-Methoxy-2-methylquinoline (11a)[1b]
Colorless crystal; mp 65 °C.

IR (KBr): 2964, 1624, 1603, 1498, 1238, 1113, 1030, 879 cm^{-1}.

^1H NMR: δ = 2.69 (3 H, s), 3.88 (3 H, s), 7.00 (1 H, d, *J* = 2.8 Hz), 7.20 (1 H, d, *J* = 8.4 Hz), 7.32 (1 H, dd, *J* = 2.8, 9.2 Hz), 7.90 (1 H, d, *J* = 8.4 Hz), 7.91 (1 H, d, *J* = 9.2 Hz).

^{13}C NMR: δ = 24.9, 55.3, 105.1, 121.7, 122.1, 127.2, 129.9, 134.9, 143.7, 156.2, 157.0.

8-Methoxy-2-methylquinoline (11b)[1b]
Colorless crystal; mp 117–119 °C.

IR (KBr): 2960, 1603, 1263, 1111, 1074 cm^{-1}.

^1H NMR: δ = 2.80 (3 H, s), 4.08 (3 H, s), 7.04 (1, dd, *J* = 1.4, 7.5 Hz), 7.32 (1 H, d, *J* = 8.5 Hz), 7.35 (1 H, dd, *J* = 1.4, 7.8 Hz), 7.40 (1 H, dd, *J* = 7.5, 7.8 Hz), 8.02 (1 H, *J* = 8.5 Hz).

^{13}C NMR: δ = 25.7, 56.0, 107.6, 119.4, 122.6, 125.7, 127.5, 136.1, 139.7, 154.8, 158.1.

2-Isopropyl-6-methoxyquinoline (11c)
Colorless oil.

IR (KBr): 2962, 1624, 1601, 1500, 1464, 1379, 1163, 1031, 933 cm^{-1}.

^1H NMR: δ = 1.38 (6 H, d, *J* = 6.9 Hz), 3.88 (3 H, s), 3.22 (1 H, septet, *J* = 6.9 Hz), 7.01 (1 H, d, *J* = 2.9 Hz), 7.25 (1 H, d, *J* = 8.5 Hz), 7.33 (1 H, dd, *J* = 2.9, 9.2 Hz), 7.95 (1 H, d, *J* = 9.2 Hz), 7.95 (1 H, *J* = 8.5 Hz).

^{13}C NMR: δ = 22.5, 36.9, 55.3, 105.0, 119.2, 121.6, 127.6, 130.3, 135.1, 143.6, 157.0, 165.0.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.52; H, 7.46; N, 6.87.

Ethyl 6-Methoxyquinoline-2-carboxylate (11d)
Colorless crystals; mp 127–128 °C.

IR (ZnSe): 2983, 2217, 1724, 1620, 1385, 1274, 1225, 1159, 1105, 1018, 831, 723 cm^{-1}.

^1H NMR: δ = 1.46 (3 H, t, *J* = 7.2 Hz), 3.94 (3 H, s), 4.52 (2 H, q, *J* = 7.2 Hz), 7.08 (1 H, d, *J* = 2.8 Hz), 7.40 (1 H, dd, *J* = 2.8, 9.3 Hz), 8.12 (1 H, d, *J* = 9.9 Hz), 8.14 (1 H, d, *J* = 9.9 Hz), 8.19 (1 H, d, *J* = 9.3 Hz).

^{13}C NMR: δ = 14.4, 55.6, 62.0, 104.6, 121.5, 123.4, 130.8, 132.3, 135.6, 143.8, 145.8, 159.4, 165.6.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.67; H, 5.77; N, 5.92.

2,6-Dimethylquinoline (11e)[19]
Colorless crystals; mp 57–58 °C.

IR (KBr): 3388, 2951, 1601, 1496, 1309, 1222, 1119, 831 cm^{-1}.

^1H NMR: δ = 2.52 (3 H, s), 2.73 (3 H, s), 7.25 (1 H, d, *J* = 8.4 Hz), 7.51 (1 H, dd, *J* = 1.7, 8.6 Hz), 7.53 (1 H, d, *J* = 1.7 Hz), 7.91 (1 H, d, *J* = 8.6 Hz), 7.96 (1 H, d, *J* = 8.4 Hz).

^{13}C NMR: δ = 21.4, 25.3, 121.9, 126.4, 126.5, 128.3, 131.6, 135.4, 135.5, 146.4, 158.0.

2-Methylquinoline (11f)[1b]
Colorless oil.

IR (ZnSe): 3055, 1623, 1601, 1506, 1423 cm^{-1}.

^1H NMR: δ = 3.01 (3 H, s), 7.25 (1 H, d, *J* = 8.4 Hz), 7.45 (1 H, dd, *J* = 6.9, 8.2 Hz), 7.65 (1 H, dd, *J* = 6.9, 8.4 Hz), 7.74 (1 H, d, *J* = 8.2 Hz), 8.00 (1 H, d, *J* = 8.4 Hz), 8.01 (1 H, d, *J* = 8.4 Hz).

^{13}C NMR: δ = 25.4, 122.0, 125.6, 126.4, 127.4, 128.6, 129.4, 136.1, 147.9, 159.0.

Benzyl *N*-Methyl-*N*-(2-methylquinolin-6-yl)carbamate (11g)
Yellow oil.

IR (ZnSe): 3032, 1699, 1623, 1601, 1496, 1321, 1143, 1005, 835, 748, 696 cm^{-1}.

^1H NMR: δ = 2.74 (3 H, s), 3.42 (3 H, s), 5.19 (2 H, s), 7.26–7.31 (6 H, m), 7.61 (2 H, m), 7.97–7.99 (2 H, m).

^{13}C NMR: δ = 25.3, 37.8, 67.4, 122.4, 122.7, 126.4, 127.7, 127.9, 128.1, 128.4, 129.2, 135.8, 136.4, 140.4, 146.0, 155.4, 159.0.

HRMS (FAB^+): *m*/*z* calcd for $C_{19}H_{19}N_2O_2$: $(M + H)^+$, 307.1447; found, 307.1466.

7-Bromo-6-methoxy-2-methylquinoline (11h)
Colorless crystals; mp 84–85 °C.

IR (ZnSe): 2935, 1597, 1471, 1344, 1238, 1134, 1039, 847 cm^{-1}.

^1H NMR: δ = 2.70 (3 H, s), 4.00 (3 H, s), 7.05 (1 H, s), 7.26 (1 H, d, *J* = 8.4 Hz), 7.92 (1 H, d, *J* = 8.4 Hz), 8.26 (1 H, s).

^{13}C NMR: δ = 25.1, 56.4, 105.5, 116.8, 122.5, 126.4, 133.2, 134.8, 143.8, 153.3, 157.4.

Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.35; H, 4.06; N, 5.34.

2-Methyl-1-azaspiro[4.5]deca-1,6,9-trien-8-one (13)[1b]
Colorless oil.

IR (ZnSe): 2944, 1664, 1624, 914, 858, 744 cm^{-1}.

^1H NMR: δ = 2.06 (2 H, t, *J* = 8.0 Hz), 2.13 (3 H, s), 2.81 (2 H, t, *J* = 8.0 Hz), 6.23 (2 H, d, *J* = 10.0 Hz), 6.62 (2 H, d, *J* = 10.0 Hz).

^{13}C NMR: δ = 20.0, 33.9, 40.1, 74.8, 127.9, 150.4, 179.4, 182.9.

4-(4-Hydroxymethylphenyl)butan-2-one (14)
Colorless oil.

IR (KBr): 3340, 2924, 1705, 1508, 1362, 1161, 1012 cm^{-1}.

^1H NMR: δ = 2.14 (3 H, s), 2.75 (2 H, t, *J* = 7.3 Hz), 2.89 (2 H, t, *J* = 7.3 Hz), 4.65 (2 H, s), 7.19 (2 H, d, *J* = 6.9 Hz), 7.28 (2 H, d, *J* = 6.9 Hz).

^{13}C NMR: δ = 29.4, 30.0, 45.1, 65.1, 127.3, 128.5, 138.7, 140.5, 207.9.

HRMS (FAB^+): *m*/*z* calcd for $C_{11}H_{15}O_2$ $(M + H)^+$, 179.1072; found, 179.1102.

***N*-Phenethylacetamide (15)[20]**
Colorless oil.

^1H NMR: δ = 1.91 (3 H, s), 2.78 (2 H, t, *J* = 7.0 Hz), 3.50 (2 H, t, *J* = 7.0 Hz), 5.44 (1 H, br s), 7.17–7.31 (5 H, m).

5-Bromo-6-methoxy-2-methylquinoline (16)
Yellow oil.

IR (ZnSe): 2935, 2842, 1612, 1597, 1493, 1340, 1265, 1128, 1066, 813 cm^{-1}.

^1H NMR: δ = 2.74 (3 H, s), 4.05 (3 H, s), 7.35 (1 H, d, *J* = 8.7 Hz), 7.48 (1 H, d, *J* = 9.2 Hz), 8.01 (1 H, d, *J* = 9.2 Hz), 8.41 (1 H, d, *J* = 8.7 Hz).

^{13}C NMR: δ = 24.9, 57.1, 107.5, 116.4, 123.4, 126.9, 129.4, 134.7, 143.9, 153.4, 157.4.

HRMS (FAB^+): *m*/*z* calcd for $C_{11}H_{11}BrNO$, $(M + H)^+$, 252.0024; found, 252.0040.

3-(4-Methoxyphenyl)propanenitrile (18)[21]
Colorless oil.

IR (ZnSe): 2935, 2245, 1610, 1510, 1244, 1178, 1030, 833 cm^{-1}.

^1H NMR: δ = 2.57 (2 H, t, *J* = 7.3 Hz), 2.89 (2 H, t, *J* = 7.3 Hz), 3.79 (3 H, s), 6.87 (2 H, d, *J* = 8.7 Hz),7.15 (2 H, d, *J* = 8.7 Hz).

^{13}C NMR: δ = 19.6, 30.7, 55.2, 114.2, 119.2, 129.3, 130.1, 158.7.

6-Methoxy-2-methyl-3,4-Dihydroquinoline (10)[22]
^1H NMR: δ = 2.50 (3H, s), 2.86-2.94 (4H, m), 3.75 (3H, s), 6.68 (1H, d, *J* = 2.5 Hz), 6.74 (1H, dd, *J* = 2.5, 8.6 Hz), 7.38 (1H, d, *J* = 8.6 Hz); ^{13}C NMR δ 21.2, 23.8, 29.3, 55.6, 113.1, 114.4, 122.9, 126.0, 127.8, 161.3, 180.2.

6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (12)[23]
To a solution of 4-(4-methoxyphenyl)butan-2-one (*E*)-oxime (**9a**) (103 mg, 0.533 mmol) in CH_2Cl_2 (2 mL), trifluoroacetic anhydride (336 mg, 1.56 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 3 min at r.t. After the mixture was stirred for 14 h, $NaBH_3CN$ (178 mg, 2.83 mmol) in MeOH (2 mL) was added to the mixture. The mixture was stirred for 1 h, and the reaction was quenched with 1 M aq NaOH. Then, organic materials were extracted with CH_2Cl_2, and the combined extracts were washed with brine, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by preparative thin-layer chromatography (silica gel) to afford 6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline **12** (79.6 mg, 0.450 mmol) in 85% yield.

Colorless crystals; mp 65 °C.

IR (KBr): 2960, 1504, 1441, 1240, 1153, 1041, 808 cm^{-1}.

^1H NMR: δ = 1.20 (3 H, d, *J* = 6.3 Hz), 1.57 (1 H, m), 1.91 (1 H, m), 2.70 (1 H, m), 2.84 (1 H, m), 3.33 (1 H, m), 3.72 (3 H, s), 6.44 (1 H, d, *J* = 8.4 Hz), 6.57 (1 H, d, *J* = 2.9 Hz), 6.59 (1 H, dd, *J* = 2.9, 8.4 Hz).

^{13}C NMR: δ = 22.5, 26.9, 30.3, 47.5, 55.8, 112.8, 114.6, 115.3, 122.5, 138.9, 151.8.

γ,δ-Unsaturated Ketone *O*-Methoxyacetyloximes 22; Typical Procedure
To a solution of 3-phenylpropionic acid (25.0 g, 166.5 mmol) in CH_2Cl_2 (50 mL), oxalyl chloride (21.16 g, 166.7 mmol) was added, and the mixture was stirred for 5 h. CH_2Cl_2 was removed under reduced pressure to afford 3-phenylpropionyl chloride in quantitative yield.

The crude acid chloride (9.3 g, 55 mmol) and Et_3N (15.1 mL, 110 mmol) was added to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (5.3 g, 55 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred overnight. After the reaction was quenched with water, organic materials were extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$. Solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel (hexane–EtOAc) to give *N*-methoxy-*N*-methyl-3-phenylpropionamide (7.7 g, 55 mmol) in 79% yield.

To a suspension of Mg (0.73 g, 30 mmol) in THF (10 mL), a small amount of I_2 was added, and then 1-bromo-3-butene (3.67 g, 27 mmol) was added dropwise. The reaction mixture was refluxed for 1.5 h, and then cooled to 0 °C. *N*-Methoxy-*N*-methyl-3-phenylpro-

pionamide (3.79 g, 20.9 mmol) in THF (10 mL) was added to the reaction mixture, which was refluxed for 30 min. After adding 2 M aq HCl to the reaction mixture, organic materials were extracted with Et_2O. The combined organic extracts were washed with sat. aq $NaHCO_3$ and brine, successively, and dried over $MgSO_4$. After removal of Et_2O under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc) to give1-phenyl-7-hepten-3-one (2.98 g, 15.5 mmol) in 76% yield.

To a solution of 1-phenyl-7-hepten-3-one (4.3 g, 23 mmol) in MeOH (46 mL), hydroxylamine hydrochloride (8.0 g, 0.12 mol) and pyridine (10 mL, 0.12 mol) was added, and the mixture was stirred overnight. The reaction was quenched with water, and organic materials were extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to give crude product 1-phenyl-7-heptene-3-one oxime (4.6 g, 23 mmol).

To a solution of the crude product (298 mg, 1.47 mmol) in CH_2Cl_2 (8 mL), Et_3N (602 μL, 4.40 mmol) and methoxyacetyl chloride (319 mg, 2.94 mmol) was added successively at 0 °C, and the mixture was stirred overnight. The reaction was quenched with sat. aq Na_2CO_3, and organic materials were extracted with CH_2Cl_2. The combined organic extracts were dried over $NaSO_4$. After removal of the solvent under reduced pressure, the residue was purified by chromatography on silica gel (hexane–EtOAc) to afford 1-phenyl-7-heptene-3-one *O*-methoxyacetyloxime (**22a**) (*E*/*Z* = 1:1) (315 mg, 1.14 mmol) in 78% yield (2 steps).

1-Phenylhept-6-en-3-one *O*-Methoxyacetyloxime (22a)
Colorless oil; *E*/*Z* = 1:1.

IR (ZnSe): 2929, 1770, 1637, 1454, 1373, 1113, 1012, 993, 933, 924, 748, 700 cm^{-1}.

^1H NMR: δ = 2.25–2.39 (3 H, m), 2.49–2.52 (1 H, m), 2.64–2.70 (2 H, m), 2.82–2.85 (1 H, m), 2.89–2.93 (1 H, m), 3.48 (1.5 H, s), 3.48 (1.5 H, s), 4.14 (1 H, s), 4.17 (1 H, s), 5.00–5.07 (2 H, m), 5.73 (1 H, m), 7.18–7.23 (3 H, m), 7.28–7.32 (2 H, m).

^{13}C NMR: δ = 29.0, 29.8, 30.0, 31.4, 31.9, 32.1, 33.7, 35.9, 59.4, 59.4, 69.1, 69.1, 115.7, 116.0, 126.3, 126.5, 136.2, 136.5, 140.1, 140.4, 168.4, 168.7, 168.8, 168.8.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.69; H, 7.82; N, 4.97.

6-Methyl-1-phenylhept-6-en-3-one *O*-Methoxyacetyloxime (22b)
Colorless oil; *E*/*Z* = 1:1.

IR (ZnSe): 2931, 2343, 1772, 1647, 1456, 1169, 1114, 935, 746, 700 cm^{-1}.

^1H NMR: δ = 1.74 (3 H, d, *J* = 9.1 Hz), 2.19–2.28 (2 H, m), 2.40–2.43 (1 H, m), 2.53–2.56 (1 H, m), 2.64–2.71 (2 H, m), 2.83–2.86 (1 H, m), 2.89–2.93 (1 H, m), 3.48 (1.5 H, s), 3.49 (1.5 H, s), 4.14 (1 H, s), 4.18 (1 H, s), 4.69 (1 H, s), 4.76 (1 H, d, *J* = 9.1 Hz), 7.18–7.24 (3 H, m), 7.29–7.32 (2 H, m).

^{13}C NMR: δ = 22.2, 22.3, 28.1, 31.4, 32.0, 32.2, 32.7, 33.6, 33.8, 35.9, 59.5, 69.1, 69.2, 110.9, 111.1, 126.3, 126.5, 128.2, 128.3, 128.5, 128.6, 140.1, 140.5, 143.7, 144.0, 168.5, 168.7, 169.2.

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.46; H, 8.17; N, 4.65.

(6*E*)-1-Phenyloct-6-en-3-one *O*-methoxyacetyloxime (22c)
Colorless oil; *E*/*Z* = 1:1.

IR (ZnSe): 2931, 1772, 1637, 1603, 1452, 1117, 748, 700 cm^{-1}.

^1H NMR: δ = 1.60-1.65 (3 H, m), 2.17–2.29 (2 H, m), 2.32–2.35 (1 H, m), 2.43–2.50 (1 H, m), 2.60–2.71 (2 H, m), 2.84 (1 H, t, *J* = 7.5 Hz), 2.90 (1 H, t, *J* = 7.5 Hz), 3.48 (1.5 H, s), 3.49 (1.5 H, s), 4.14 (1 H, s), 4.18 (1 H, s), 5.31–5.42 (1 H, m), 5.43–5.54 (1 H, m), 7.17–7.22 (3 H, m), 7.26–7.31 (2 H, m).

^{13}C NMR: δ = 17.8, 28.8, 29.1, 29.7, 31.5, 32.0, 32.2, 34.2, 36.0, 59.5, 69.1, 69.2, 126.3, 126.4, 126.5, 126.7, 128.2, 128.3, 128.5, 128.6, 128.8, 129.1, 140.2, 140.5, 168.5, 168.7, 169.1, 169.1.

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.83; H, 8.31; N, 4.91.

(5*E*)-6-Phenylhex-5-en-2-one (*E*)-*O*-Methoxyacetyloxime (22d)
Colorless oil.

IR (ZnSe): 2925, 1770, 1647, 1448, 1369, 1163, 1117, 935, 744, 694 cm^{-1}.

^1H NMR: δ = 2.00 (3 H, s), 2.48–2.53 (4 H, m), 3.47 (3 H, s), 4.18 (2 H, s), 6.15–6.20 (1 H, m), 6.41–6.44 (1 H, m), 7.18–7.33 (5 H, m).

^{13}C NMR: δ = 15.5, 29.5, 35.4, 59.4, 69.1, 126.0, 127.2, 128.1, 128.5, 131.2, 137.2, 166.4, 168.5.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.67; H, 7.47; N, 5.24.

1-Phenyl-7-methyloct-6-en-3-one *O*-Methoxyacetyloxime (22e)
Colorless oil; *E*/*Z* = 1:1.

IR (ZnSe): 2925, 1770, 1450, 1111, 933, 746, 700 cm^{-1}.

^1H NMR: δ = 1.60 (3 H, s), 1.69 (3 H, s), 2.19–2.32 (3 H, m), 2.41–2.44 (1 H, m), 2.63–2.71 (2 H, m), 2.83 (1 H, t, *J* = 8.0 Hz), 2.91 (1 H, t, *J* = 8.0 Hz), 3.48 (1.5 H, s), 3.49 (1.5 H, s), 4.14 (1 H, s), 4.18 (1 H, s), 5.06–5.09 (1 H, m), 7.17–7.22 (3 H, m), 7.26–7.31 (2 H, m).

^{13}C NMR δ 17.6, 17.7, 24.5, 24.7, 25.6, 25.6, 29.8, 31.5, 32.1, 32.3, 34.5, 36.2, 59.5, 69.2, 69.2, 122.1, 122.3, 126.3, 126.5, 128.2, 128.3, 128.5, 128.6, 133.1, 133.6, 140.2, 140.6, 168.6, 168.6, 169.3, 169.4.

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.49; H, 8.57; N, 4.59.

2*H*-Dihydropyrroles; Typical Procedure
Under an argon atmosphere, to a solution of 1-phenyl-6-hepten-3-one *O*-methoxyacetyloxime (**22a**) (67.5 mg, 0.245 mmol) in nitromethane (4 mL), MS 4 Å (270 mg) and methoxyacetic acid (221 mg, 2.45 mmol) was added, and the mixture was stirred at 70 °C for 24 h. The reaction was quenched with sat. aq Na_2CO_3, and organic materials were extracted with EtOAc. The combined organic extracts were dried over $NaSO_4$. The solvents were removed under reduced pressure, and the residue was purified by preparative TLC (silica gel, hexane–EtOAc, 1:2) to afford 2-(methoxyacetoxy)methyl-5-phenyl-3,4-dihydro-2*H*-pyrrole **23a** (56.0 mg, 0.204 mmol) in 83% yield.

2-(Methoxyacetoxy)methyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (23a)
[5-(2-phenylethyl)-3,4-dihydro-2*H*-pyrrol-2-yl]methyl methoxyacetate
Colorless oil.

IR (ZnSe): 2927, 1751, 1734, 1641, 1456, 1192, 1126, 752, 702 cm^{-1}.

^1H NMR: δ = 1.54–1.62 (1 H, m), 2.01–2.08 (1 H, m), 2.43–2.58 (2 H, m), 2.66–2.69 (2 H, m), 2.87–2.98 (2 H, m), 3.45 (3 H, s), 4.05 (2 H, s), 4.19–4.32 (3 H, m), 7.20–7.30 (5 H, m).

^{13}C NMR: δ = 25.2, 32.5, 35.1, 37.6, 59.1, 67.2, 69.5, 70.6, 125.9, 128.1, 128.3, 141.0, 170.2, 179.1.

HRMS (FAB^+): *m*/*z* calcd for $C_{16}H_{22}NO_3$ $(M + H)^+$, 276.1600; found, 276.1624,

2-(Methoxyacetoxy)methyl-2-methyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (23b)
Colorless oil.

IR (ZnSe): 2929, 1753, 1734, 1645, 1454, 1192, 1126, 750, 700 cm^{-1}.

^1H NMR: δ = 1.24 (3 H, s), 1.58–1.64 (1 H, m), 1.83–1.87 (1 H, m), 2.54 (2 H, t, *J* = 7.9 Hz), 2.63–2.66 (2 H, m), 2.91 (2 H, t, *J* = 7.9 Hz), 3.42 (3 H, s), 4.00 (2 H, s), 4.09–4.16 (2 H, m), 7.18–7.22 (3 H, m), 7.27–7.30 (2 H, m).

^{13}C NMR: δ = 24.2, 31.8, 32.7, 35.2, 38.0, 59.3, 69.6, 70.8, 74.7, 126.1, 128.2, 128.4, 141.0, 170.2, 177.1.

HRMS (FAB^+): *m*/*z* calcd for $C_{17}H_{24}NO_3$ $(M + H)^+$, 290.1756; found, 290.1759.

2-(1-Methoxyacetoxy)ethyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (23c)
Colorless oil; (dr 3:2).

IR (ZnSe): 2933, 1749, 1731, 1645, 1454, 1192, 1124, 752, 700 cm^{-1}.

^1H NMR: δ = 1.27–1.28 (3 H, m), 1.53–1.60 (0.4 H, m), 1.61–1.69 (0.6 H, m), 1.92–2.01 (1 H, m), 2.40–2.56 (2 H, m), 2.61–2.71 (2 H, m), 2.86–2.96 (2 H, m), 3.42 (1.8 H, s), 3.45 (1.2 H, s), 3.97–4.01 (2 H, m), 4.09–4.16 (1 H, m), 5.08–5.16 (1 H, m), 7.18–7.22 (3 H, m), 7.27–7.30 (2 H, m).

^{13}C NMR: δ = 16.6, 16.9, 24.2, 24.6, 32.5, 32.7, 35.3, 35.4, 37.5, 37.8, 59.2, 59.3, 69.9, 73.5, 73.5, 75.3, 75.9, 126.0, 126.0, 128.2, 128.2, 128.4, 128.4, 141.1, 141.3, 169.7, 169.9, 178.8, 179.0.

HRMS (FAB^+): *m*/*z* calcd for $C_{17}H_{24}NO_3$ $(M + H)^+$, 290.1756; found, 290.1740.

2-(1-Methoxyacetoxy-1-methyl)ethyl-5-phenylethyl-3,4-dihyro-2*H*-pyrrole (23e)
Colorless oil.

IR (ZnSe): 2933, 1745, 1726, 1645, 1452, 1369, 1298, 1196, 1120m, 741, 700 cm^{-1}.

^1H NMR: δ = 1.40 (3 H, s), 1.60 (3 H, s), 1.65–1.72 (1 H, m), 1.88–1.95 (1 H, m), 2.38–2.54 (2 H, m), 2.63–2.73 (2 H, m), 2.87–2.97 (2 H, m), 3.42 (3 H, s), 3.89 (2 H, s), 4.31–4.34 (1 H, m), 7.18–7.22 (3 H, m), 7.26–7.29 (2 H, m).

^{13}C NMR: δ = 22.0, 23.7, 23.8, 32.6, 35.2, 37.8, 59.1, 79.8, 85.2, 126.0, 128.3, 128.4, 141.2, 169.5, 178.4, 178.4.

HRMS (FAB^+): *m*/*z* calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$, 304.1913; found, 304.1905

2-(1-Methoxyacetoxy-1-phenyl)methyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (23d)
Colorless oil; single isomer, the stereochemistry was not determined.

IR (ZnSe): 2947, 1749, 1647, 1456, 1379, 1186, 1124, 962, 701 cm^{-1}.

^1H NMR: δ = 1.47–1.54 (1 H, m), 1.72–1.83 (1 H, m), 2.01 (3 H, s), 2.23–2.48 (2 H, m), 3.43 (3 H, s), 4.04 (1 H, d, *J* = 16.4 Hz), 4.17 (1 H, d, *J* = 16.4 Hz), 4.36–4.47 (1 H, m), 5.77 (1 H, d, *J* = 7.5 Hz), 7.25–7.42 (5 H, m).

^{13}C NMR: δ = 19.7, 25.5, 38.7, 59.2, 69.8, 75.6, 78.6, 127.0, 127.4, 128.1, 128.2, 137.7, 169.5, 176.9.; HRMS (FAB^+): *m*/*z* calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$, 262.1443; found, 262.1466

2-Methyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (24)[24]
Yellow oil.

IR (neat): 2960, 1643, 1603, 1496, 1454, 906, 750, 700 cm^{-1}.

^1H NMR: δ = 1.24–1.25 (3 H, m), 1.30–1.39 (1 H, m), 2.02–2.09 (1 H, m), 2.40–2.44 (1 H, m), 2.47–2.54 (1 H, m), 2.60–2.64 (2 H, m), 2.91–2.95 (2 H, m), 4.01–4.07 (1 H, m), 7.15–7.20 (3 H, m), 7.24–7.28 (2 H, m).

^{13}C NMR: δ = 22.0, 30.6, 32.7, 35.3, 37.7, 67.7, 125.9, 128.2, 128.3, 141.4, 176.1.

2-Chloromethyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (25)
Colorless oil.

IR (ZnSe): 2951, 1641, 1602, 1495, 1454, 1427, 1290, 748, 700 cm^{-1}.

^1H NMR: δ = 1.75–1.77 (1 H, m), 2.06–2.08 (1 H, m), 2.47–2.51 (1 H, m), 2.55–2.62 (1 H, m), 2.65–2.70 (2 H, m), 2.92–2.98 (2 H, m), 3.63–3.67 (1 H, m), 3.74–3.78 (1 H, m), 4.33–4.36 (1 H, m), 7.18–7.22 (3 H, m), 7.26–7.30 (2 H, m).

^{13}C NMR: δ = 26.0, 32.6, 35.2, 38.1, 48.6, 72.9, 126.0, 128.2, 128.4, 141,1, 179.5.

HRMS (FAB^+): *m*/*z* calcd for $C_{13}H_{17}ClN$ $(M + H)^+$, 222.1050; found, 222.1049.

2-Isopropenyl-5-phenylethyl-3,4-dihydro-2*H*-pyrrole (26)
Colorless oil.

IR (KBr): 2915, 1720, 1496, 1454, 894, 750, 700 cm^{-1}.

^1H NMR: δ = 1.59–1.64 (1 H, m), 1.67 (3 H, s), 2.08–2.10 (1 H, m), 2.40–2.47 (1 H, m), 2.50–2.56 (1 H, m), 2.69 (2 H, t, *J* = 8.1 Hz), 2.92–3.02 (2 H, m), 4.48 (1 H, t, *J* = 7.2 Hz), 4.76 (1 H, s), 4.82 (1 H, s), 7.17–7.29 (5H, m).

^{13}C NMR: δ = 19.3 28.2, 32.7, 35.3, 37.8, 77.1, 109.9, 126.0, 128.4, 141.4, 146.8, 177.5.

HRMS (FAB^+): *m*/*z* calcd for $C_{15}H_{20}N$ $(M + H)^+$, 214.1596; found, 214.1619.

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