MANNICH TYPE REACTIONS OF ACYLHYDRAZONES WITH SILYL ENOLATES FOR THE SYNTHESIS OF β-AMINO ESTER, β-AMINO KETONE, β-LACTAM, PYRAZOLIDINONE, AND PYRAZOLONE DERIVATIVES#

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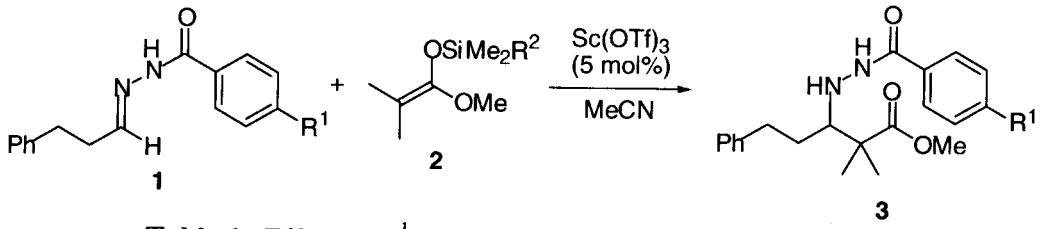
Abstract- In the presence of a catalytic amount of a rare earth triflate, acylhydrazones reacted with silyl enolates to afford the corresponding β-*N'*-acylhydrazino esters in high yields. A three-component reaction of an aldehyde, an acylhydrazine, and a silyl enolate was also performed successfully. The hydrazino esters thus obtained were readily converted to β-amino ester, β-amino ketone, β-lactam, pyrazolidinone, and pyrazolinone derivatives.

While Lewis acid-catalyzed reactions are of great current interest in organic synthesis,[1] catalytic activation of nitrogen-containing compounds are difficult because many Lewis acids are deactivated or decomposed by the nitrogen atoms of the starting materials or products. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are trapped by the nitrogen atoms.[2] From a synthetic point of view, development of new Lewis acid-catalyzed reactions of nitrogen-containing compounds is desired. Recently, we have found that rare earth triflates are effective for the catalytic activation of nitrogen-containing compounds.[3] For example, rare earth triflates activate aldehydes containing nitrogen atoms or aldimines catalytically, and efficient carbon-carbon bond-forming reactions have been realized using these catalytic systems. The catalytic use of rare earth triflates is rationalized by the equilibrium of the Lewis acids-nitrogen atoms coordination. This is similar to the equilibrium of rare earth triflates-water coordination, which enables the Lewis acids to be stable in water without hydrolysis.[4] In the course of our investigations to explore the utility of rare earth triflates in synthesis, we further studied the activation of other useful nitrogen-containing compounds by rare earth triflates. In this paper, we describe the catalytic activation of acylhydrazones by rare earth triflates, which react with silyl enolates smoothly to afford β-*N'*-acylhydrazino ester derivatives.[5] Facile syntheses of β-amino ester, β-amino ketone, β-lactam, pyrazolidinone, and pyrazolone derivatives using these reactions are also described.

Hydrazones are aldehyde and ketone equivalents as well as imines. Their stability is much higher than that of imines; for example, while aliphatic imines are known to be unstable, hydrazones derived from aliphatic aldehydes are often crystalline and can be isolated and stored at room temperature. However, their reactivity as electrophiles is low, and there have been much fewer reports on the reactions of hydrazones with nucleophiles than those of imines.[6,7] First we carefully examined the reactions of hydrazones with silyl enolates. While 3-phenylpropionaldehyde phenylhydrazone did not react with ketene silyl acetal (**2a**) (R^2 = *tert*-Bu) derived from methyl isobutyrate at all, 3-phenylpropionaldehyde acylhydrazones reacted with **2a** in the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$).[8] Among the acylhydrazones tested, 4-trifluoromethylbenzoylhydrazone (**1a**, $R^1 = CF_3$) gave the best yield (Table 1). It is noteworthy that the electronic effect of the benzoyl moieties influenced the yields dramatically. While hydrazones with electron-donating groups gave lower yields, higher yields were obtained using hydrazones with electron-withdrawing groups. As for Lewis acids, $Sc(OTf)_3$ gave an excellent yield,[9] and much lower yields were obtained by using typical Lewis acids such as $TiCl_4$, $SnCl_4$, and BF_3•OEt_2 (See also Table 2).



1 **2** **3**

Table 1. Effect of R^1 and Lewis Acids

Entry	Lewis Acid	R^1	R^2	Temp/°C	Yield/%
1	$Sc(OTf)_3$	H	*tert*-Bu	-20	37
2	$Sc(OTf)_3$	MeO	*tert*-Bu	-20	7
3	$Sc(OTf)_3$	NO_2	*tert*-Bu	-20	77
4	$Sc(OTf)_3$	CF_3	*tert*-Bu	-20	88
5	$Sc(OTf)_3$	CF_3	Me	-20	97 ($75^{a,b}$)
6	BF_3•OEt_2	CF_3	Me	0	4^a
7	$TiCl_4$	CF_3	Me	0	13^a
8	$SnCl_4$	CF_3	Me	0	46^a

[a]Dichloromethane was used as a solvent. [b]0 °C.

Several examples of the reactions of acylhydrazones with silyl enolates are shown in Table 3. Hydrazones derived from aromatic, aliphatic, and α,β-unsaturated aldehydes reacted with silyl enolates smoothly to afford the corresponding β-*N'*-acylhydrazinocarbonyl compounds in high yields. It is noted that several aliphatic hydrazones, readily prepared from aliphatic aldehydes, reacted with silyl enolates smoothly to afford the corresponding adducts in high yields.[10] All aliphatic acylhydrazones tested were crystalline and could be stored at room temperature. In addition,

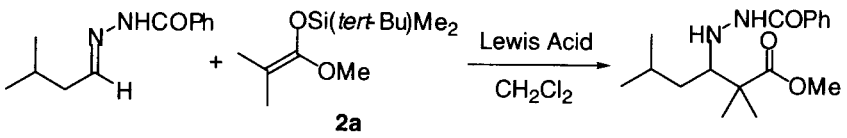


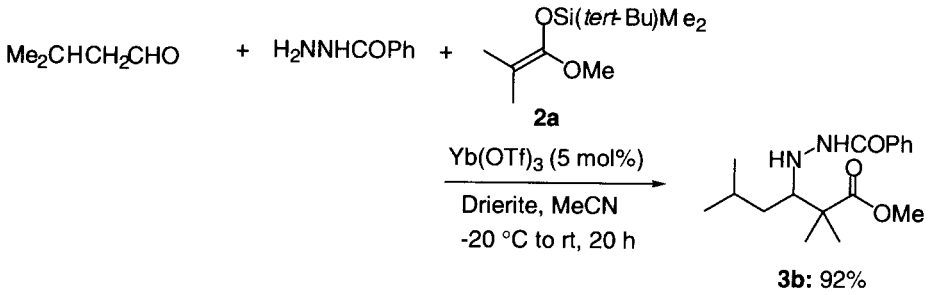
Table 2. Effect of Lewis Acids

Lewis Acid	Amount /mol%	Temp/°C	Time/h	Yield/%
$Sc(OTf)_3$	5	rt	1	quant[a]
$TiCl_4$	100	-20 to rt	12	trace[b]
$SnCl_4$	100	-20 to rt	12	10[c]
$BF_3•OEt_2$	100	-20 to rt	12	42[d]

[a]Acetonitrile was used as a solvent. [b]The starting material was recovered in 83%. [c]84%. [d]52%.

acylhydrazones derived from a glyoxylate and an α-keto ester, which were isolated as stable crystals, reacted with silyl enolates to afford the corresponding adducts in high yields. As for silyl enolates, the enolates derived from both esters and thioesters worked well. 1-Phenyl-1-trimethylsiloxyethene (a ketone-derived silyl enolate) also reacted with an aliphatic acylhydrazone to afford the desired product in a good yield.

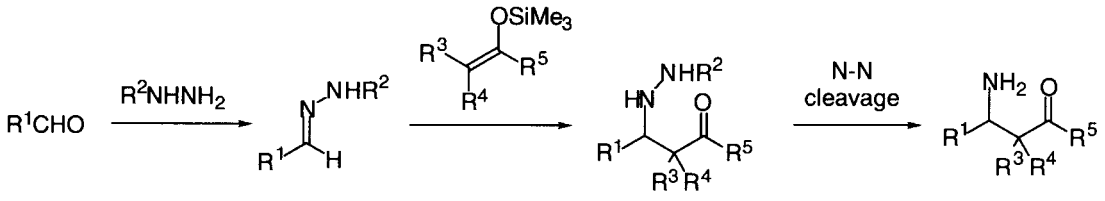
A three-component reaction of an aldehyde, a hydrazine, and a silyl enolate also proceeded smoothly. It was found that in the presence of a catalytic amount of $Yb(OTf)_3$ and Drierite, benzaldehyde reacted with benzoylhydrazine and the *tert*-butyldimethylsilyl enolate smoothly in acetonitrile at -20 °C to room temperature, to afford the desired β-*N'*-benzoylhydrazino ester in 92% yield (Scheme 1).[11] This three-component reaction would be useful for the synthesis of a compound library.[3c,12,13]



Scheme 1. A One-Pot Reaction of an Aldehyde, an Acylhydrazine, and a Silyl Enolate

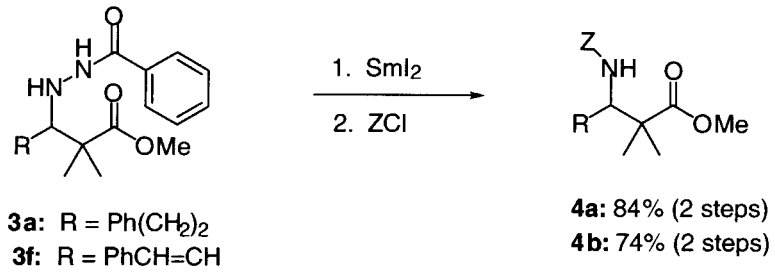
β-Aminocarbonyl Compounds

We then examined reductive cleavage of nitrogen-nitrogen bonds of the β-*N'*-acylhydrazinocarbonyl compounds. If the cleavage is successfully carried out, the two-step process can be regarded as a novel Mannich type reaction. Namely, hydrazones, readily prepared from aldehydes and acylhydrazines, react with silyl enolates to give β-*N'*-acylhydrazinocarbonyl compounds, and reductive cleavage of nitrogen-nitrogen bonds gives β-aminocarbonyl compounds (Scheme 2).



Scheme 2. Mannich Type Reactions Using Hydrazones

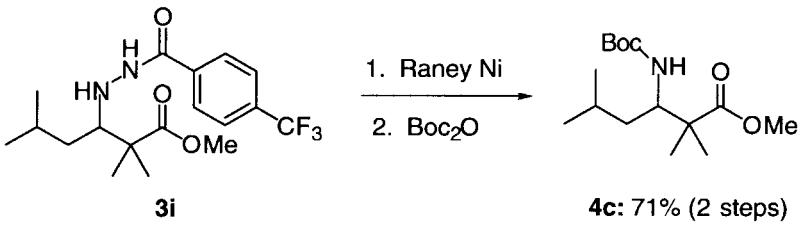
Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compound was successfully carried out using SmI_2 (Scheme 3).[14] Hydrazino ester (**3a** or **3f**) was treated with SmI_2 at -20 °C, and the resulting amino group was protected as its benzyl carbamate using benzyl chloroformate (ZCl) to afford *N*-Z-amino ester (**4a** or **4b**) in high yield. Alternatively, Raney Ni could cleave the nitrogen-nitrogen bond under H_2 atmosphere (Scheme 4).[15] Thus, adduct (**3i**) was treated with a catalytic amount of Raney Ni (W-3) under H_2 (1 atm) at ambient temperature. After cleavage of the nitrogen-nitrogen bond, the resulting amine was protected as its *tert*-butoxycarbonyl (Boc) group.



3a: R = $Ph(CH_2)_2$
3f: R = PhCH=CH

4a: 84% (2 steps)
4b: 74% (2 steps)

Scheme 3. Conversion to Amino Ester Derivative (1)



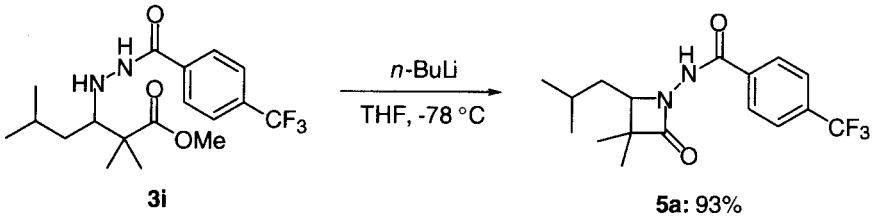
3i

4c: 71% (2 steps)

Scheme 4. Conversion to Amino Ester Derivative (2)

β-Lactams

β-*N'*-Acylhydrazinocarbonyl compounds are expected to be useful intermediates for the synthesis of some heterocyclic compounds. It was found that β-lactam (**5a**)[16] was obtained in an excellent yield by treatment of **3i** with *n*-BuLi at -78 °C (Scheme 5).



Scheme 5. Conversion to β-Lactam (1)

Alternatively, treatment of **3** with MeLi/CuI system gave the corresponding β-lactam derivatives in high yields. In the cases of a phenyl ester or an *S-tert*-butyl ester, use of a Grignard reagent instead of the lithium reagent gave better results (Table 4).

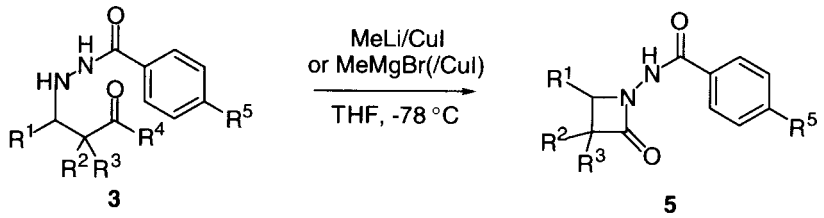
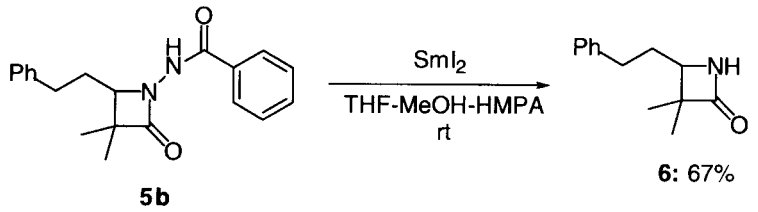


Table 4. Conversion to β-Lactams (2)

Base	Temp /°C	Time /h	R^1	R^2	R^3	R^4	R^5	Product	Yield/%
MeLi/CuI	rt	0.5	$Ph(CH_2)_2$	Me	Me	OMe	H	**5b**	79
MeLi/CuI	rt	0.5	Ph	Me	Me	OMe	H	**5c**	99
MeLi/CuI	rt	1	PhCH=CH	Me	Me	OMe	H	**5d**	72
MeMgBr	0	1	$Ph(CH_2)_2$	Me	H	OPh	CF_3	**5e**	89
MeMgBr/CuI	-20	1	$Ph(CH_2)_2$	H	H	S*tert*-Bu	CF_3	**5f**	55

The *N*-benzoyl group of **5** was readily removed by using SmI_2 (Scheme 6).



Scheme 6. Removal of *N*-Benzoyl Amino Group

Pyrazolidinones

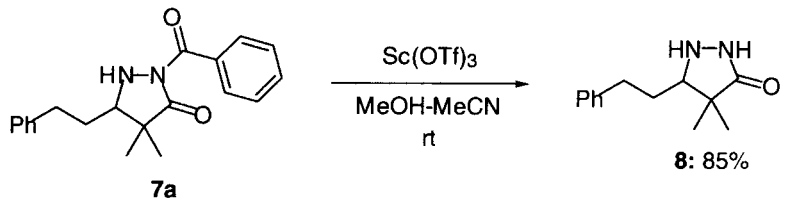
β-Lactams (**5**) were converted to pyrazolidinones under acidic conditions.[17] Thus, treatment of **5** with 4N HCl in ethyl acetate at room temperature afforded the corresponding pyrazolidinones (**7**) in excellent yields (Table 5).

5 7

Table 5. Conversion to Pyrazolidinones

R^1	R^2	R^3	R^4	Product	Yield/%
$Ph(CH_2)_2$	Me	Me	H	**7a**	99
Ph	Me	Me	H	**7b**	96
PhCH=CH	Me	Me	H	**7c**	73
$Ph(CH_2)_2$	Me	H	CF_3	**7d**	quant
$Ph(CH_2)_2$	H	H	CF_3	**7e**	quant

The amide protective group of **7** was readily removed by using $Sc(OTf)_3$ (Scheme 7).



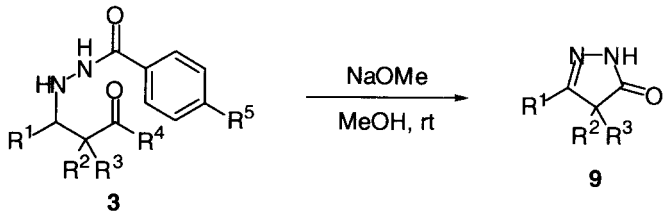
7a

Scheme 7. Removal of Benzoyl Group of **7a**

Pyrazolinones

Pyrazolone (**9**)[18,19] was produced from **3** in the presence of NaOMe at room temperature (Table 6). Since isomerization from **5** to **9** was observed under these conditions (NaOMe), **5** and **9** were expected to be kinetic and thermodynamic products, respectively.

In summary, Mannich type reactions of acylhydrazones with silyl enolates have been successfully carried out in the presence of a catalytic amount of a rare earth triflate, to afford the corresponding β-*N'*-acylhydrazino esters in high yields. A three-component reaction of an aldehyde, an acylhydrazine, and a silyl enolate also proceeded smoothly. The hydrazino esters thus obtained were readily converted to heterocyclic compounds such as β-amino ester, β-amino ketone, β-lactam, pyrazolidinone, and pyrazolinone derivatives in high yields..



3 9

Table 6. Conversion to Pylazolones

R^1	R^2	R^3	R^4	R^5	Product	Yield/%
$Ph(CH_2)_2$	Me	Me	OMe	H	**9a**	92
Ph	Me	Me	OMe	H	**9b**	92
$Ph(CH_2)_2$	Me	H	OPh	CF_3	**9c**	92

EXPERIMENTAL

General Methods: Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ = 0) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0) for ^{13}C NMR. IR spectra were measured with JASCO FT/IR-610 spectrophotometer. High-resolution MS spectra (HRMS) were measured with JEOL JMX-SX-102 Mass Spectrometer. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F.

Typical experimental procedure: A typical experimental procedure is described for the reaction of isovaleraldehyde 4-trifluoromethylbenzoylhydrazone (**1b**, $R^1 = Me_2CHCH_2$, R^2 = H, $R^3 = CF_3$ in Table 3) with ketene silyl acetal (**2b**, $R^4 = R^5$ = Me, R^6 = Me, R^7 = OMe in Table 3) (Table 3, Entry 10). To a solution of $Sc(OTf)_3$ (4.9 mg, 0.01 mmol) and **1b** (54 mg, 0.2 mmol) in acetonitrile (1.2 mL) was added a solution of **2b** (52.6 mg, 0.3 mmol) in acetonitrile (0.4 mL) at rt. After stirring for 4 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 2,2,5-trimethyl-3-[*N'*-(4'-trifluoromethylbenzoyl)hydrazino]hexanoate (**3i**, 65.9 mg, 88%) as a colorless powder.

In the cases of the three-component reactions, aldehydes, acylhydrazines, and silyl enolates were added successively in the presence of $Yb(OTf)_3$ or $Sc(OTf)_3$ (5 mol%) and Drierite in acetonitrile.

Methyl 3-*N'*-benzoylhydrazino-2,2-dimethyl-5-phenylpentanoate (3a): pale yellow oil. ^1H NMR δ 1.17 (s, 3H), 1.24 (s, 3H), 1.66-1.79 (m, 2H), 2.74-2.80 (m, 1H), 3.00-3.07 (m, 1H), 3.18 (dd, 1H, J = 2.2, 9.3 Hz), 3.56 (s, 3H), 4.80 (br s, 1H), 7.14-7.27 (m, 5H), 7.40-7.51 (m, 3H), 7.74-7.76 (m, 2H), 7.97 (s, 1H); ^{13}C NMR δ 20.5, 23.0, 31.2, 33.5, 46.7, 51.9, 66.3, 125.8, 126.7, 128.3, 128.4, 128.6, 131.7, 132.6, 141.9, 166.2, 178.7. HRMS Calcd for $C_{21}H_{26}N_2O_3$ (M^+) 354.1943, found 354.1962.

Methyl 3-*N'*-benzoylhydrazino-2,2,5-trimethylhexanoate (3b): colorless needles. mp 84.3-84.5 °C (hexane-ethyl acetate). ^{1}H NMR δ 0.91-0.96 (m, 6H), 1.35-1.11 (m, 8H), 1.97 (m, 1H), 3.27 (dd, 1H, *J* = 2.1, 9.6 Hz), 3.57 (s, 3H), 4.90 (br s, 1H), 7.50-7.39 (m, 3H), 7.75 (m, 2H), 8.01 (br s, 1H); ^{13}C NMR δ 20.0, 21.6, 22.8, 24.0, 25.2, 38.3, 46.3, 51.7, 64.3, 126.7, 128.4, 131.5, 132.5, 166.2, 178.9. HRMS Calcd for $C_{17}H_{26}N_2O_3$ (M^+) 306.1943, found 306.1924.

***S*-Ethyl 3-*N'*-benzoylhydrazino-2,2,5-trimethylthiohexanoate (3c):** pale yellow oil. ^{1}H NMR δ 0.94-1.01 (m, 7H), 1.16 (t, 3H, *J* = 7.3 Hz), 1.20 (s, 3H), 1.28-1.35 (m, 4H), 2.02 (br s, 1H), 2.77 (q, 2H, *J* = 7.3 Hz), 3.32 (dd, 1H, *J* = 1.5, 9.8 Hz), 4.80 (br s, 1H), 7.39-7.43 (m, 2H), 7.47-7.52 (m, 1H), 7.69-7.71(m, 3H); ^{13}C NMR δ 14.2, 20.2, 21.6, 23.1, 23.5, 24.1, 25.2, 38.5, 53.8, 65.3, 126.7, 128.5, 131.6, 132.8, 166.1, 207.9. HRMS Calcd for $C_{18}H_{28}N_2O_2S$ (M^+) 336.1872, found 336.1849.

Methyl 3-*N'*-benzoylhydrazino-2,2-dimethyl-3-phenylpropionate (3d): pale yellow oil. ^{1}H NMR δ 0.97 (s, 3H), 1.16 (s, 3H), 3.59 (s, 3H), 4.32 (s, 1H), 5.30 (br s, 1H), 7.20-7.40 (m, 11H); ^{13}C NMR δ 19.5, 23.8, 46.0, 52.1, 70.0, 126.7, 127.9, 128.0, 128.5, 129.1, 131.6, 132.6, 137.7, 166.9, 177.4. HRMS Calcd for $C_{19}H_{22}N_2O_3$ (M^+) 336.1630, found 336.1625. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.04; H, 6.73; N, 8.52.

Methyl 3-*N'*-benzoylhydrazino-2,2-dimethyl-5-phenyl-4-pentenoate (3e): pale yellow oil. ^{1}H NMR δ 1.28 (s, 3H), 1.31 (s, 3H), 3.67 (s, 3H), 3.81 (d, 1H, *J* = 9.3 Hz), 5.25 (br s, 1H), 6.15 (dd, 1H, *J* = 9.3, 15.6 Hz), 6.54 (dd, 1H, *J* = 9.3, 15.6 Hz), 7.20-7.44 (m, 8H), 7.67 (d, 2H, *J* = 7.3 Hz), 7.89 (s, 1H); ^{13}C NMR δ 20.3, 23.8, 45.4, 52.0, 69.9, 125.8, 126.5, 126.7, 127.7, 127.8, 128.5, 131.5, 132.7, 135.2, 136.5, 166.9, 177.2. HRMS Calcd for $C_{21}H_{24}N_2O_3$ (M^+) 352.1787, found 352.1791.

1-Ethyl methyl 2-*N'*-benzoylhydrazino-3,3-dimethylbutanedioate (3f): pale yellow oil. ^{1}H NMR δ 1.26 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.37 (s, 3H), 3.73 (s, 3H), 3.95 (s, 1H), 4.17-4.28 (m, 1H), 5.41 (br s, 1H), 7.40-7.53 (m, 3H), 7.71-7.74 (m, 2H), 7.89 (br s, 1H); ^{13}C NMR δ 14.1, 21.8, 21.9, 45.7, 52.1, 61.3, 69.4, 126.9, 128.6, 131.8, 132.6, 167.0, 171.3, 176.2. HRMS Calcd for $C_{16}H_{22}N_2O_5$ (M^+) 322.1529, found 322.1566.

Dimethyl 2-*N'*-benzoylhydrazino-2,3,3-trimethylbutandicarboxylate (3g): pale yellow oil. ^{1}H NMR δ 1.39 (s, 6H), 1.42 (s, 3H), 3.69 (s, 3H), 3.76 (s, 3H), 7.40-7.58 (m, 3H), 7.70-7.73 (m, 2H), 7.83 (br s, 1H); ^{13}C NMR δ 17.3, 21.4, 22.8, 48.4, 52.3, 52.4, 69.7, 126.9, 128.7, 131.8, 132.9, 166.6, 174.4, 176.5. HRMS Calcd for $C_{16}H_{22}N_2O_5$ (M^+) 322.1529, found 322.1519. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.61; H, 6.83; N, 8.56.

Methyl 2,2-dimethyl-5-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazino-pentanoate (3h): pale yellow oil. ^{1}H NMR δ 1.11 (s, 3H), 1.16 (s, 3H), 1.53-1.78 (m, 2H), 2.61-2.72 (m, 1H), 2.88-2.97 (m, 1H), 3.07 (dd, 1H, *J* = 2.6, 9.4 Hz), 3.51 (s, 3H), 7.05-7.19 (m, 5H), 7.59 (d, 2H, *J* = 8.3 Hz), 7.79 (d, 2H, *J* = 8.1 Hz), 8.30 (br s, 1H); ^{13}C NMR δ 20.6, 23.2, 30.9, 33.4, 46.8, 51.9, 66.2, 125.6 (q, *J* = 3.7 Hz), 125.9, 127.2, 128.3, 133.0, 133.4,

133.9, 135.9, 141.6, 164.4, 178.8. HRMS Calcd for $C_{22}H_{25}N_2O_3F_3$ (M^+) 422.1817, found 422.1822.

Methyl 3-*N'*-(4'-trifluoromethylbenzoyl)hydrazino-2,2,5-trimethylhexanoate (3i): colorless powder. mp 69-70 °C (hexane). ^{1}H NMR δ 0.89 (s, 3H), 0.91 (s, 3H), 1.07-1.33 (m, 8H), 1.85-1.94 (m, 1H), 3.20 (dd, 1H, *J* = 2.0, 9.7 Hz), 3.56 (s, 3H), 7.64 (d, 2H, *J* = 8.1 Hz), 7.83 (d, 2H, *J* = 8.1 Hz), 8.22 (br s, 1H); ^{13}C NMR δ 20.0, 21.5, 23.3, 24.0, 25.3, 38.2, 46.6, 51.9, 64.5, 125.6 (q, *J* = 3.7 Hz), 127.2, 129.3, 133.1, 133.5, 133.9, 135.9, 164.5, 179.2. HRMS Calcd for $C_{18}H_{25}N_2O_3F_3$ (M^+) 374.1817, found 374.1836.

***S*-Ethyl 2,2,5-trimethyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinothiohexanate (3j):** pale yellow oil. ^{1}H NMR δ 0.88-1.03 (m, 7H), 1.06-1.49 (m, 10H), 1.95-2.00 (m, 1H), 2.71-2.87 (m, 2H), 3.26-3.35 (m, 1H), 4.94 (br s, 1H), 7.65-7.91 (m, 5H); ^{13}C NMR δ 14.3, 20.1, 21.6, 23.2, 23.9, 24.1, 25.3, 38.4, 53.9, 65.4, 125.6 (q, *J* = 3.7 Hz), 127.2. 129.4, 133.5, 136.2, 164.4, 208.3.

Methyl 2,2-dimethyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinononanoate (3k): colorless needles. mp 97 °C (hexane). ^{1}H NMR δ 0.84-0.89 (m, 3H), 1.21-1.67 (m, 16H), 3.13 (dd, 1H, *J* = 1.7, 9.4 Hz), 3.61 (s, 3H), 5.05 (br s, 1H), 7.70 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.1 Hz), 8.02 (br s, 1H); ^{13}C NMR δ 14.0, 20.1, 22.6, 23.5, 27.2, 28.7, 29.4, 31.6, 46.7, 52.0, 66.9, 125.7 (q, *J* = 3.7 Hz), 127.2, 133.2, 133.5, 136.4, 164.3, 179.4. HRMS Calcd for $C_{20}H_{29}N_2O_3F_3$ (M^+) 402.2130, found 402.2101.

Methyl 2,2-dimethyl-3-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinopropanoate (3l): colorless needles. mp 93-95 °C (hexane). ^{1}H NMR δ 1.08 (s, 3H), 1.28 (s, 3H), 3.71 (s, 3H), 4.43 (s, 1H), 5.52 (br s, 1H), 7.28-7.38 (m, 5H), 7.56 (d, 2H, *J* = 8.3 Hz), 7.63 (d, 2H, *J* = 8.3 Hz), 7.84 (br s, 1H); ^{13}C NMR δ 19.5, 23.9, 46.2, 52.2, 70.1, 125.6 (q, *J* = 3.7 Hz), 127.3, 128.05, 129.08, 133.1, 133.5, 136.1, 137.6, 165.7, 177.5.

Methyl 2,2-dimethyl-5-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazino-4-pentenoate (3m): pale yellow oil. ^{1}H NMR δ 1.20 (s, 3H), 1.25 (s, 3H), 3.64 (s, 3H), 3.71 (dd, 1H, *J* = 5.1, 9.2 Hz), 5.18-5.22 (m, 1H), 6.08 (dd, 1H, *J* = 9.2, 15.8 Hz), 6.48 (d, 1H, *J* = 15.8 Hz), 7.14-7.36 (m, 5H), 7.56 (d, 2H, *J* = 8.6 Hz), 7.61 (d, 1H, *J* = 6.4 Hz), 7.69 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR δ 20.4, 24.0, 45.6, 52.2, 70.2, 125.6 (q, *J* = 3.7 Hz), 126.5, 127.2, 128.0, 128.6, 135.5, 136.3, 165.6, 177.3.

Methyl 2,2-dimethyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinohexenoate (3n): colorless needles. mp 84-86 °C (hexane). ^{1}H NMR δ 1.19 (s, 3H), 1.25 (s, 3H), 1.71 (dd, 3H, *J* = 1.5, 6.4 Hz), 3.57 (d, 1H, *J* = 8.1 Hz), 3.68 (s, 3H), 5.11 (br s, 1H), 5.40 (ddd, 1H, *J* = 1.5, 9.2, 15.2 Hz), 5.68 (dq, 1H, *J* = 6.4, 15.2 Hz), 7.56 (br s, 1H), 7.70 (d, 2H, *J* = 8.3 Hz), 7.82 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR δ 17.9, 20.0, 23.8, 45.2, 51.9, 69.7, 125.5 (q, *J* = 3.7 Hz), 126.7, 127.3, 131.9, 133.1, 133.4, 136.2, 165.3, 177.6.

Dimethyl 2,3,3-trimethyl-2-*N'*-(4'-trifluoromethylbenzoyl)butandicarboxylate (3o): pale yellow oil. ^{1}H NMR δ 1.39 (s, 3H), 1.42 (s, 3H), 3.70 (s, 3H), 3.76 (s, 3H), 5.30 (br s, 1H), 7.69 (d, 2H, *J* = 8.1 Hz), 7.84 (d, 2H, *J* = 8.1 Hz), 8.08 (br s, 1H); ^{13}C NMR δ 17.4, 21.4, 22.8,

48.4, 52.4, 52.5, 69.6, 125.7 (q, J = 3.8 Hz), 133.2, 133.7, 136.3, 138.7, 165.2, 174.5, 176.6. HRMS Calcd for $C_{17}H_{21}N_2O_5F_3$ (M^+) 390.1403, found 390.1391.

Phenyl 3-*N'*-benzoylhydrazino-2-methyl-5-phenylpentanoate (3p diastereomeric mixture): Diastereomers were not separable by silica gel column chromatography. pale yellow oil. ^1H NMR δ 1.26 (d, 1.5H, *J* = 7.1 Hz), 1.29 (d, 1.5H, *J* = 8.4 Hz), 1.74-1.96 (m, 2H), 2.70-2.95 (m, 3H), 3.22-3.28 (m, 0.5H), 3.44-3.50 (m, 0.5H), 5.04 (br s, 1H), 6.90-6.97 (m, 2H), 7.06-7.44 (m, 10H), 7.59-7.69 (m, 3H); ^{13}C NMR δ 10.9, 13.4, 31.8, 32.3, 32.5, 32.8, 42.1, 42.8, 62.3, 62.8, 121.53, 121.55, 125.77, 125.85, 125.96, 126.05, 126.86, 126.89, 128.41, 128.49, 128.63, 128.69, 129.28, 129.38, 129.54, 131.89, 132.34, 132.49, 141.09, 141.47, 141.71, 150.55, 150.67, 159.33, 167.17, 167.19, 174.39, 174.57. HRMS Calcd for $C_{25}H_{26}N_2O_3$ (M^+) 402.1943, found 402.1962.

Methyl 3-*N'*-benzoylhydrazino-2,5-dimethylhexanoate (3q diastereomeric mixture): Diastereomers were not separable by silica gel column chromatography. pale yellow oil. ^1H NMR δ 0.92-1.00 (m, 6H), 1.14-1.46 (m, 5H), 1.73-1.94 (m, 1H), 2.63-2.73 (m, 1H), 3.23-3.29 (m, 0.5H), 3.39-3.46 (m, 0.5H), 3.63 (s, 1.5H), 3.70 (s, 1.5H), 4.90 (br s, 1H), 7.40-7.53 (m, 3H), 7.74-7.79 (m, 2H), 7.92 (br s, 0.5H), 8.05 (br s, 0.5H); ^{13}C NMR δ 10.6, 12.5, 22.0, 22.4, 23.1, 23.6, 25.0, 25.1, 39.2, 39.8, 41.9, 42.7, 51.70, 51.73, 60.1, 60.8, 126.88, 126.92, 128.7, 131.78, 131.85, 132.6, 132.8, 166.86, 166.92, 176.2, 176.7. HRMS Calcd for $C_{16}H_{24}N_2O_3$ (M^+) 292.1787, found 292.1799.

***S*-Ethyl 3-*N'*-benzoylhydrazino-2,5-dimethylhexanoate (3r diastereomeric mixture):** Diastereomers were not separable by silica gel column chromatography. pale yellow oil. ^1H NMR δ 0.59-0.71 (m, 6H), 0.95-1.20 (m, 8H), 1.45-1.58 (m, 1H), 2.47-3.66 (m, 3H), 3.00-3.05 (m, 0.5H), 3.11-3.17 (m, 0.5H), 4.30 (br s, 1H), 7.11-7.23 (m, 3H), 7.43-7.50 (m, 2H), 7.61(br s, 0.5H), 7.81(br s, 0.5H); ^{13}C NMR δ 11.9, 13.6, 15.3, 15.5, 22.8, 23.3, 23.9, 24.1, 24.2, 24.6, 25.8, 26.0, 39.7, 40.9, 51.9, 52.2, 61.6, 62.2, 127.7, 127.8, 129.5, 123.6, 132.6, 133.6, 133.7, 167.6, 167.8, 203.9, 204.6.

Phenyl 2-methyl-5-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinopentanoate (3s *anti*) pale yellow oil. ^1H NMR δ 1.34 (d, 3H, *J* = 7.6 Hz), 1.79-1.97 (m, 2H), 2.71-2.97 (m, 3H), 3.34 (br s, 1H), 5.36 (br s, 1H), 6.80-7.33 (m, 10H), 7.60 (d, 2H, *J* = 8.1 Hz), 7.82 (d, 2H, *J* = 8.1 Hz), 8.30 (br s, 1H); ^{13}C NMR δ 13.2, 31.6, 32.0, 42.6, 62.4, 125.5 (q *J* = 3.7 Hz), 127.4, 128.4, 129.3, 133.1, 133.4, 133.8, 135.6, 141.5, 150.5, 165.6, 174.4.

Phenyl 2-methyl-5-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinopentanoate (3s *syn*) pale yellow oil. ^1H NMR δ 1.33 (d, 3H, *J* = 7.3 Hz), 1.79-1.97 (m, 2H), 2.71-2.97 (m, 3H), 3.56 (br s, 1H), 5.12 (br s, 1H), 6.80-7.33 (m, 10H), 7.54 (d, 2H, *J* = 8.3 Hz), 7.74 (d, 2H, *J* = 8.1 Hz), 8.17 (br s, 1H); ^{13}C NMR δ 10.6, 32.5, 32.6, 42.0, 61.9, 125.5 (q *J* = 3.7 Hz), 126.0, 127.4, 128.3, 128.4, 129.2, 133.1, 133.4, 133.8, 135.5, 141.2, 150.3, 165.8, 174.6. HRMS Calcd for $C_{26}H_{25}N_2O_3F_3$ (M^+) 470.1817, found 470.1838.

Isopropyl 2-benzyloxy-5-phenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinopentanoate (3t *anti*) pale yellow oil. ^1H NMR δ 1.26 (d, 6H, *J* = 6.2 Hz), 1.79-1.92 (m, 2H),

2.57-2.69 (m, 1H), 2.71-2.90 (m, 1H), 3.33 (br s, 1H), 4.16 (d, 1H, J = 2.8 Hz), 4.43 (d, 1H, J = 10.6 Hz), 4.69 (d, 1H, J = 10.6 Hz), 5.05-5.17 (m, 1H), 5.33 (br s, 1H), 6.89-7.61 (m, 14H), 8.20 (br s, 1H); ^{13}C NMR δ 21.6, 30.5, 32.3, 62.1, 68.3, 73.1, 80.8, 125.3 (q, J = 3.7 Hz), 125.9, 127.0, 128.3, 128.5, 131.6, 132.2, 132.6, 133.0, 136.0, 137.2, 141.2, 164.3, 170.5. HRMS Calcd for $C_{29}H_{31}N_2O_4F_3$ (M^+) 528.2236, found 528.2217.

Isopropyl 2-benzyloxy-5-phenyl-3-*N*'-(4'-trifluoromethylbenzoyl)hydrazinopentanoate (3t *syn*) pale yellow oil. ^{1}H NMR δ 1.22 (d, 6H, J = 6.2 Hz), 1.79-1.92 (m, 2H), 2.57-2.69 (m, 1H), 2.71-2.90 (m, 1H), 3.33 (br s, 1H), 4.06 (d, 1H, J = 3.9 Hz), 4.37 (d, 1H, J = 10.6 Hz), 4.77 (d, 1H, J = 10.6 Hz), 5.05-5.17 (m, 1H), 5.33 (br s, 1H), 6.89-7.61 (m, 14H), 8.08 (br s, 1H); ^{13}C NMR δ 21.6, 30.5, 32.2, 61.0, 69.0, 73.1, 80.9, 125.3 (q, J = 3.7 Hz), 125.9, 127.0, 128.3, 128.5, 131.6, 132.2, 132.6, 133.0, 135.8, 136.4, 141.2, 163.5, 170.7.

***S*-Ethyl 3-*N*'-benzoylhydrazino-5-methylhexanoate (3u):** pale yellow oil. ^{1}H NMR δ 0.92 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.17-1.21 (m, 3H), 1.26-1.33 (m, 1H), 1.41-1.48 (m, 1H), 1.75-1.84 (m, 1H), 2.64-2.78 (m, 2H), 2.84 (q, 2H, J = 7.3 Hz), 3.53 (m, 1H), 7.40-7.52 (m, 3H), 7.74-7.77 (m, 2H), 8.03(s, 1H); ^{13}C NMR δ 14.5, 22.4, 22.9, 23.4, 24.9, 42.2, 48.6, 56.4, 126.9, 128.6, 131.8, 132.6, 167.1, 198.7. HRMS Calcd for $C_{16}H_{24}N_2O_2S$ (M^+) 308.1559, found 308.1558.

***S*-*tert*-Butyl 3-*N*'-benzoylhydrazino-5-phenylthiopentanoate (3v):** pale yellow oil. ^{1}H NMR δ 1.33 (s, 9H), 1.73-1.78 (m, 2H), 2.58-2.72 (m, 4H), 3.4 (m, 1H), 7.07-7.22 (m, 5H), 7.31-7.42 (m, 3H), 7.64-7.67 (m, 3H); ^{13}C NMR δ 29.7, 32.1, 34.6, 48.3, 48.5, 58.0, 125.9, 126.9, 128.36, 128.42, 128.6, 131.8, 132.7, 141.6, 167.2, 199.1. HRMS Calcd for $C_{22}H_{28}N_2O_2S$ (M^+) 384.1872, found 384.1848.

***S*-Ethyl 5-phenyl-3-*N*'-(4'-trifluoromethylbenzoyl)hydrazinothiopentanoate (3w):** colorless powder. mp 120-122 °C (hexane). ^{1}H NMR δ 1.18 (t, 3H, J = 7.4 Hz), 1.73-1.93 (m, 2H), 2.70-2.92 (m, 6H), 3.49-3.53 (m, 1H), 5.19 (br s, 1H), 7.15-7.28 (m, 5H), 7.65 (d, 2H, J = 8.3 Hz), 7.84 (d, 2H, J = 8.1 Hz), 8.34 (s, 1H); ^{13}C NMR δ 14.4, 23.5, 32.0, 34.5, 47.8, 57.6, 125.5 (q, 3.7 Hz), 126.0, 127.4, 128.2, 128.4, 133.1, 133.6, 135.8, 141.3, 165.7, 198.5.

***S*-*tert*-Butyl 5-phenyl-3-*N*'-(4'-trifluoromethylbenzoyl)hydrazinothiopentanoate (3x):** pale yellow oil. ^{1}H NMR δ 1.42 (s, 9H), 1.77-1.92 (m, 2H), 2.62-2.79 (m, 4H), 3.46 (br s, 1H), 7.15-7.20 (m, 3H), 7.25-7.29 (m, 2H), 7.67 (d, 2H, J = 8.4 Hz), 7.86 (d, 2H, J = 8.2 Hz), 8.19 (br s, 1H); ^{13}C NMR δ 29.6, 32.0, 34.6, 48.3, 48.5, 57.6, 125.6 (q, J = 3.8 Hz), 126.0, 127.4, 128.3, 128.4, 133.2, 133.6, 135.9, 141.4, 165.6, 199.4. HRMS Calcd for $C_{23}H_{27}N_2O_2F_3S$ (M^+) 452.1745, found 452.1739. Anal. Calcd for $C_{23}H_{27}N_2O_2F_3S$: C, 61.04; H, 6.01; N, 6.19. Found: C, 60.76; H, 5.93; N, 5.94.

***S*-Ethyl 3-*N*'-(4'-trifluoromethylbenzoyl)hydrazinononanoate (3y):** colorless powder. mp 43-44 °C (hexane). ^{1}H NMR δ 0.88 (t, 3H, J = 6.4 Hz), 1.20 (t, 3H, J = 7.3 Hz), 1.28-1.62 (m, 10H), 2.73 (d, 2H, J = 6.1 Hz), 2.85 (dq, 2H, J = 1.7, 7.5 Hz), 3.46 (br s, 1H), 5.11 (br s, 1H), 7.70 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.6 Hz), 8.07 (s, 1H); ^{13}C NMR δ 14.0, 14.5,

22.5, 23.5, 25.8, 29.2, 31.6, 33.1, 48.2, 58.3, 125.6 (q, J = 3.7 Hz), 127.4, 133.3, 133.7, 135.9, 165.6, 199.0.

S-Ethyl 5-methyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinothiohexanoate (3z): pale yellow oil. ^{1}H NMR δ 0.93 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.20 (t, 3H, J = 7.4 Hz), 1.26-1.36 (m, 1H), 1.42-1.49 (m, 1H), 1.75-1.85 (m, 1H), 2.70 (dd, 1H, J = 14.8, 5.0 Hz), 2.75 (dd, 1H, J = 14.8, 6.7 Hz), 2.85(q, 2H, J = 7.4 Hz), 3.50-3.57(m, 1H), 5.06(br s, 1H), 7.70(d, 2H, J = 8.1 Hz), 7.88(d, 2H, J = 8.1 Hz), 8.09 (br s, 1H); ^{13}C NMR δ 14.5, 22.4, 22.8, 23.5, 24.9, 42.2, 48.6, 56.3, 125.7 (q, J = 3.7 Hz), 127.4, 133.2, 133.7, 135.9, 165.6, 199.0. HRMS Calcd for $C_{17}H_{23}N_2O_2F_3S$ (M^+) 376.1432, found 376.1451.

S-Ethyl 3-cyclohexyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazinopropanoate (3aa): colorless powder. mp 84-85 °C (hexane). ^{1}H NMR δ 1.05-1.27 (m, 5H), 1.18 (t, 3H, J = 7.3 Hz), 1.53-1.56 (m, 1H), 1.67-1.79 (m, 5H), 2.73-2.75 (m, 2H), 2.83 (dq, 2H, J = 3.7, 7.3 Hz), 3.30-3.35 (m, 1H), 5.18 (br s, 1H), 7.70 (d, 2H, J = 8.3 Hz), 7.86 (d, 2H, J = 8.1 Hz), 8.02 (s, 1H); ^{13}C NMR δ 14.5, 23.5, 26.2, 26.4, 28.7, 29.2, 40.6, 45.9, 62.8, 125.6 (q, J = 3.7 Hz), 127.3, 133.2, 133.6, 136.0, 165.2, 199.8.

1,5-Diphenyl-3-*N'*-(4'-trifluoromethylbenzoyl)hydrazino-1-pentanone (3bb): pale yellow oil. IR (neat) 1675 cm^{-1}, ^{1}H NMR δ 1.82-2.04 (m, 2H), 2.74-2.89 (m, 2H), 3.10 (dd, 1H, J = 4.6, 16.7 Hz), 3.24 (dd, 1H, J = 7.9, 16.7 Hz), 3.69 (br s, 1H), 7.13-7.93 (m, 14H), 8.38 (br s, 1H); ^{13}C NMR δ 32.3, 35.0, 42.8, 57.2, 125.6 (q, J = 3.7 Hz), 126.1, 127.3, 128.2, 128.4, 128.5, 128.7, 133.4, 135.9, 136.7, 141.5, 165.5, 199.8.

β-Aminocarbonyl compounds

Method A: A 0.1M THF solution of SmI_2 (10.4 mL, 1.04 mmol) was added to a MeOH (2.2 mL) solution of β-hydrazino ester (**3a**, 123 mg, 0.348 mmol) at –20 °C. The reaction mixture was stirred at the same temperature for 30 min and evaporated *in vacuo*. The residue was dissolved in a mixture of THF (3 mL) and saturated aqueous $NaHCO_3$ (3 mL), and benzyl chloroformate (119 mg, 0.698 mmol) was added at rt. After being stirred at the same temperature for 3 h, the reaction mixture was acidified with aqueous HCl and extracted with ethyl acetate (twice). The combined organic layers were washed with 5% aqueous solution of $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the *N*-*Z*-amino ester (**4a**, 129 mg, 84% yield) as a colorless oil.

Methyl 2,2-dimethyl-5-phenyl-3-phenylmethoxycarbonylaminopentanoate (4a): colorless oil. IR (neat) 1724 cm^{-1}; ^{1}H NMR δ 1.18 (s, 3H), 1.19 (s, 3H), 1.46-1.60 (m, 1H), 1.78-1.89(m, 1H), 2.54-2.78 (m, 2H), 3.62 (s, 3H), 3.77 (ddd, 1H, J = 10.6, 10.6, 2.3 Hz), 5.14 (s, 2H), 5.23 (d, 1H, J = 10.6 Hz), 7.07-7.40 (m, 10H); ^{13}C NMR δ 13.0, 23.2, 33.0, 33.7, 46.6, 51.9, 57.7, 66.8, 125.9, 128.07, 128.14, 128.38, 128.45, 128.55, 136.7, 141.7, 156.8, 177.0. HRMS Calcd for $C_{22}H_{27}NO_4$ (M^+) 369.1940, found 369.1923.

According to the same procedure, **4b** was obtained from **3f** (74% yield).

Methyl 2,2-dimethyl-5-phenyl-3-phenylmethoxycarbonylamino-4-pentenate (4b): colorless oil. IR (neat) 1726 cm^{-1}; ^1H NMR δ 1.25 (s, 3H), 1.29 (s, 3H), 3.67 (s, 3H), 4.37 (dd, 1H, *J* = 9.9, 7.7 Hz), 5.11 (s, 2H), 5.69 (d, 1H, *J* = 9.9 Hz), 6.10 (dd, 1H, *J* = 15.8, 7.7 Hz), 6.57 (d, 1H, *J* = 15.8 Hz), 7.20-7.45 (m, 10H); ^{13}C NMR δ 23.0, 23.6, 46.3, 52.0, 60.3, 66.8, 126.1, 126.5, 127.8, 128.1, 128.5, 133.0, 136.5, 156.0, 176.8. HRMS Calcd for $C_{22}H_{25}NO_4$ (M^+) 367.1784, found 367.1802.

Method B: To a solution of β-hydrazino ester (**3i**, 33 mg, 0.09 mmol) in ethanol (2 mL) was added a catalytic amount of Raney Ni (W-3) (*ca.* 10 mg). After stirring under H_2 at 1 atm for 24 h, a solution of di-*tert*-butyl dicarbonate (77 mg, 0.4 mmol) in ethanol (1 mL) was added under argon. After the solution was stirred at rt, for 15 h, Raney Ni was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel to give methyl 3-*tert*-butoxycarbonylamino-2,2,5-trimethylhexanoate (**4c**, 18 mg, 71%) as a colorless oil.

Methyl 3-*tert*-butoxycarbonylamino-2,2,5-trimethylhexanate (4c): colorless oil. IR (neat) 1716 cm^{-1}; ^1H NMR δ 0.91 (t, 6H, *J* = 6.8 Hz), 1.10-1.22 (m, 2H), 1.18 (d, 6H, *J* = 4.4 Hz), 1.44 (s, 9H), 1.53-1.68 (m, 1H), 3.67-3.92 (m, 1H), 3.68 (s, 3H), 4.74 (d, 1H, *J* = 10.6 Hz); ^{13}C NMR δ 21.4, 22.2, 23.1, 23.9, 25.1, 28.4, 40.8, 46.8, 51.7, 54.9, 78.9, 156.0, 177.3. HRMS Calcd for $C_{15}H_{29}NO_4$ (M^+) 287.2097, found 287.2072.

β-Lactams

Method A: To a solution of β-hydarazino ester (**3i**, 35 mg, 0.092 mmol) in THF (2 mL) was added a 1M *n*-BuLi THF solution (0.23 mmol) at –78 °C. The reaction mixture was stirred for 15 h and Et_2O and phosphate buffer (pH = 7) were added. The separated aqueous layer was extracted with Et_2O. The combined organic layeres were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired β-lactam (**5a**, 29 mg, 93%) as a colorless oil.

4-Isobutyl-3,3-dimethyl-1-(4'-trifluoromethylbenzoyl)aminoazetidin-2-one (5a): colorless oil. IR (neat) 1765, 1685, 1325 cm^{-1}; ^1H NMR δ 0.93 (dd, 6H, *J* = 6.4, 8.4 Hz), 1.26 (s, 3H), 1.42-1.51 (m, 1H), 1.49 (s, 3H), 1.56-1.72 (m, 2H), 3.92 (t, 1H, *J* = 6.6 Hz), 7.54 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 2H, *J* = 8.1 Hz), 9.81 (s, 1H); ^{13}C NMR δ 17.1, 22.46, 22.51, 23.1, 25.8, 37.9, 50.6, 67.6, 125.6 (q, *J* = 3.7 Hz), 127.6, 133.7, 150.7, 164.3, 176.5.

Manhood B: To a suspension of β-hydrazino ester (**3d**, 50 mg, 0.154 mmol) and CuI (73 mg, 0.385 mmol) in THF (1.5 mL) was added a 0.98 M MeLi ether solution (0.78 mL) at rt. The mixture was stirred at the same temperature for 30 min, and ethyl acetate and saturated aqueous NH_4Cl were added. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired β-lactam (**5c**, 45 mg, 99%) as a colorless oil.

4-Phenyl-3,3-dimethyl-1-benzoylaminoazetidin-2-one (5c): colorless oil. IR (neat) 1769, 1658 cm^{-1}; ^1H NMR δ 0.89 (s, 3H), 1.68 (s, 3H), 5.13 (s, 1H), 7.24-7.50 (m, 8H), 7.68 (d, 2H, *J* = 8.4 Hz), 9.90 (s, 1H); ^{13}C NMR δ 18.0, 22.6, 53.7, 71.5, 126.5, 127.3, 128.0, 128.5,

128.7, 130.6, 132.3, 135.5, 166.3, 176.9. HRMS Calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368, found 294.1384. According to the same procedure, **5b** was obtained from **3a** (79%) and **5d** was obtained form **3e** (72%).

1-Benzoylamino-3,3-dimethyl-4-(2'-phenylethyl)azetidin-2-one (5b): colorless oil. IR (neat) 1774, 1655, 1305 cm^{-1}; ^1H NMR δ 1.25 (s, 3H), 1.46 (s, 3H), 1.95-2.11 (m, 2H), 2.70 (t, 2H, *J* = 7.8 Hz), 3.87 (t, 1H, *J* = 6.6 Hz), 7.15-7.28 (m, 5H), 7.37-7.42 (m, 2H), 7.49-7.54 (m, 1H), 7.69 (d, 2H, *J* = 7.3 Hz), 8.31 (br s, 1H); ^{13}C NMR δ 16.9, 25.0, 31.5, 32.9, 50.5, 68.6, 126.2, 127.4, 128.27, 128.34, 128.5, 130.8, 132.3, 141.0, 166.0, 176.0. HRMS Calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.1681, found 322.1683. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.40; H, 6.86; N, 8.69.

1-Benzoylamino-3,3-dimethyl-4-(2'-phenylethenyl)azetidin-2-one (5d): colorless oil. IR (neat) 1766, 1677, 1659 cm^{-1}; ^1H NMR δ 1.29 (s, 3H), 1.54 (s, 3H), 4.49 (d, 1H, *J* = 9.0 Hz), 6.26 (dd, 1H, *J* = 15.8, 8.0 Hz), 6.68 (d, 1H, *J* = 15.8 Hz), 7.22-7.42 (m, 7H), 7.48-7.53 (m, 1H), 7.72-7.75 (m, 2H), 8.37 (br s, 1H); ^{13}C NMR δ 18.0, 22.3, 53.4, 70.9, 123.7, 126.7, 127.4, 128.3, 128.66, 128.70, 131.1, 132.5, 136.0, 136.1, 175.4, 181.8. HRMS Calcd for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, found 320.1509.

Method C: To a THF (2 mL) solution of β-hydrazino ester (**3s**, 49 mg, 0.105 mmol) was added a 0.93 M MeMgBr solution in THF (0.3 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h, and ethyl acetate and saturated aqueous NH_4Cl were added. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired β-lactam (**5e**, 35 mg, 89% yield).

3,4-*cis*-3-Methyl-4-(2'-phenylethyl)-1-(4'-trifluoromethylbenzoylamino)azetidin-2-one (5e *cis*): colorless oil. IR (neat) 1778, 1681, 1326 cm^{-1}; ^1H NMR δ 1.25 (d, 3H, *J* = 7.5 Hz), 1.89-2.10 (m, 2H), 2.61-2.79 (m, 2H), 3.39 (qd, 1H, *J* = 7.5, 6.4 Hz), 4.20 (td, 1H, *J* = 6.4, 6.4 Hz), 7.14-7.28 (m, 5H), 7.54 (d, 2H, *J* = 7.8 Hz), 7.74 (d, 2H, *J* = 7.8 Hz), 9.81 (br s, 1H); ^{13}C NMR δ 8.9, 30.8, 32.8, 44.4, 61.1, 125.5 (q, J = 3.5 Hz), 126.3, 127.8, 128.3, 128.6, 133.6, 133.7, 134.1, 140.8, 164.3, 173.4. HRMS Calcd for $C_{20}H_{19}N_2O_2F_3$ (M^+) 376.1399, found 376.1383.

3,4-*trans*-3-Methyl-4-(2'-phenylethyl)-1-(4'-trifluoromethylbenzoylamino)azetidin-2-one (5e *trans*): colorless oil. IR (neat) 1764, 1670, 1327 cm^{-1}; ^1H NMR δ 1.36 (d, 3H, *J* = 7.3 Hz), 2.13-2.24 (m, 2H), 2.63-2.86 (m, 3H), 3.77 (t, 1H, *J* = 5.3 Hz), 7.15-7.29 (m, 5H), 7.55 (d, 2H, *J* = 7.8 Hz), 7.73(d, 2H, *J* = 7.8Hz), 9.51(br s, 1H); ^{13}C NMR δ 13.1, 32.0, 33.9, 47.9, 65.6, 125.5 (q, *J* = 3.5 Hz), 126.3, 127.7, 128.3, 128.6, 133.6, 133.7, 134.1, 140.6, 164.3, 172.8.

Method D: To a suspension of β-hydrazino ester (**3x**, 47 mg, 0.104 mmol) and CuI (64 mg, 0.286 mmol) in THF (2 mL) was added a 0.93 M MeMgBr solution in THF (0.3 mL. 0.28 mmol) at -20 °C. The mixture was stirred for 30 min at the same temperature, and ethyl acetate and saturated aqueous NH_4Cl were added. The aqueous layer was extracted with ethyl acetate. The combined

organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired β-lactam (**5f**, 20 mg, 55%) as a pale yellow oil.

4-(2'-Phenylethyl)-1-(4'-trifluoromethylbenzoylamino)azetidin-2-one (5f): pale yellow oil. IR (neat) 1766, 1678, 1326 cm^{-1}; ^1H NMR δ 1.91-2.03 (m, 1H), 2.15-2.26 (m, 1H), 2.54 (dd, 1H, *J* = 14.8, 2.2 Hz), 2.60-2.78 (m, 2H), 3.07 (dd, 1H, *J* = 14.8, 5.2 Hz), 4.15 (m, 1H), 7.14-7.29 (m, 5H), 7.55 (d, 2H, *J* = 8.3 Hz), 7.71(m, 2H, *J* = 8.3 Hz), 9.58 (s, 1H); ^{13}C NMR δ 31.9, 34.3, 39.8, 57.4, 125.5 (q, J = 3.5 Hz), 126.3, 127.8, 128.3, 128.6, 133.5, 133.8, 134.2, 140.6, 164.4, 169.3. HRMS Calcd for $C_{19}H_{17}N_2O_2F_3$ (M^+) 362.1242, found 362.1230.

Removal of the *N*-benzoylamino group

A 0.1M THF solution of SmI_2 (7.0 mg, 0.7 mmol) was added to a mixture of a THF (6.0 mL) solution of the β-Lactam (**5b**, 77 mg, 0.237 mmol), MeOH (0.24 mL), and HMPA (0.24 mL) at -20 °C. The mixture was stirred at the same temperature for 20 min, and ethyl acetate and 1M HCl were added. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the desired β-lactam (**6**, 32 mg, 67%) as a colorless oil.

3,3-Dimethyl-4-(2'-phenylethyl)azetidin-2-one (6): colorless oil. IR (neat) 1746, 1385 cm^{-1}; ^1HNMR δ 1.18 (s, 3H), 1.30 (s, 3H), 1.79-1.86 (m, 1H), 1.91-1.96 (m, 1H), 2.59-2.74 (m, 2H), 3.33 (dd, 1H, *J* = 8.8, 4.6 Hz), 5.6 (br s, 1H), 7.17-7.32 (m, 5H); ^{13}C NMR δ 16.7, 22.6, 33.0, 33.3, 53.6, 60.2, 126.3, 128.3, 128.6, 141.0, 175.1. HRMS Calcd for $C_{13}H_{17}NO$ (M^+) 203.1310, found 203.1304.

Pyrazolidinones

The β-lactam (**5c**, 112 mg, 0.381 mmol) was dissolved in ethyl acetate (0.5 mL), and 4N HCl/ethyl acetate solution (4 mL) was added. After being stirred at rt for 4 h, the mixture was neutralized with saturated aqueous $NaHCO_3$. The separated aqueous layers were extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give 1-benzoylpyrazolidinone derivative (**7b**, 107 mg, 96%) as a colorless oil.

2-Benzoyl-4,4-dimethyl-5-phenyl-3-pyrazolidinone (7b): colorless oil. IR (neat) 1753, 1664, 1384 cm^{-1}; ^1H NMR δ 0.97 (s, 3H), 1.27 (s, 3H), 4.45 (d, 1H, *J* = 6.5 Hz), 6.15 (d, 1H, *J* = 6.5 Hz), 7.30-7.56 (m, 7H), 7.57-7.70 (m, 1H), 7.87-790 (m, 2H); ^{13}C NMR δ 18.8, 21.5, 47.5, 67.9, 127.5, 127.8, 128.5, 128.8, 129.1, 132.2, 132.9, 134.9, 165.6, 174.3. HRMS Calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368, found 294.1379. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.50; H, 6.20; N, 9.51.

According to the same procedure, β-lactams listed in Table 5 were converted to the corresponding pyrazolidinone derivatives (**7a**, **7c**, **7d**, and **7e**).

2-Benzoyl-4,4-dimethyl-5-(2'-phenylethyl)-3-pyrazolidinone (7a): colorless oil. IR (neat) 1750, 1649, 1307 cm^{-1}; ^1H NMR δ 1.06 (s, 3H), 1.12 (s, 3H), 1.76-1.84 (m, 2H), 2.65-2.71 (m, 1H), 2.81-2.86 (m, 1H), 3.24 (dd, 1H, *J* = 9.1 Hz, 4.0 Hz), 5.30 (br s, 1H), 7.12-7.54

(m, 10H); ^{13}C NMR δ 17.5, 21.8, 29.9, 32.7, 45.8, 63.1, 126.4, 127.8, 128.2, 128.7, 129.3, 132.3, 133.0, 140.9, 166.4, 176.4. HRMS Calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.1681, found 322.1683. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.36; H, 6.83; N, 8.67.

2-Benzoyl-5-(2'-phenylethenyl)-4,4-dimethyl-3-pyrazolidinone (7c): colorless oil. IR (neat) 1752, 1666, 1384 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s. 3H), 1.17 (s, 3H), 3.90 (dd, 1H, *J* = 7.3, 7.7Hz), 5.67 (d, 1H, *J* = 7.3 Hz), 6.10 (dd, 1H, *J* = 7.7, 15.9 Hz), 6.67 (d, 1H, *J* = 15.9 Hz), 7.13-7.37 (m. 7H), 7.42-7.48 (m, 1H), 7.56-7.60 (m, 2H); ^{13}C NMR δ 18.2, 21.4, 47.0, 66.4, 122.0, 126.6, 127.8, 128.3, 128.7, 129.2, 132.2, 132.9, 135.3, 135.9, 166.0, 175.2. HRMS Calcd for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, found 320.1532.

4,5-*cis*-4-Methyl-5-(2'-phenylethyl)-2-(4'-trifluorobenzoyl)-3-pyrazolidinone (7d *cis*): colorless oil. IR (neat) 1760, 1678, 1323 cm^{-1}; ^{1}H NMR δ 1.20 (d, 3H), 1.75-1.90 (m, 2H), 2.54-2.96 (m, 3H), 3.68 (q, 1H, *J* = 5.3 Hz), 5.36 (br s, 1H), 7.02-7.34 (m, 5H), 7.66-7.73 (m, 4H); ^{13}C NMR δ 9.6, 29.9, 32.2, 43.1, 56.9, 124.8 (q, *J* = 3.7 Hz), 126.4, 128.4, 128.7, 129.5, 133.3, 133.8, 136.6, 140.8, 165.4, 174.7. HRMS Calcd for $C_{20}H_{19}F_3N_2O_2$ (M^+) 376.1399, found 376.1393.

5-(2'-Phenylethyl)-2-(4'-trifuluorobenzoyl)-3-pyrazolidinone (7e): colorless oil. IR (neat) 1764, 1677, 1323 cm^{-1}; ^{1}H NMR δ 1.84-2.06 (m, 2H), 2.42-2.51 (m, 1H), 2.69-2.80 (m, 3H), 3.59-3.64 (m, 1H), 5.29 (br s, 1H), 7.12-7.28 (m, 5H), 7.58-7.66 (m, 4H); ^{13}C NMR δ 32.1, 35.2, 40.2, 53.6, 124.9 (q, *J* = 3.8 Hz), 126.5, 128.3, 128.7, 129.5, 133.3, 133.8, 136.4, 140.4, 165.0, 171.3. HRMS Calcd for $C_{19}H_{17}N_2O_2F_3$ (M^+) 362.1242, found 362.1229. Anal. Calcd for $C_{19}H_{17}N_2O_2F_3$: C, 62.98; H, 4.73; N, 7.73. Found: C, 62.77; H, 4.92; N, 7.48.

Removal of the amido group

To an acetonitrile (5 mL) solution of the 1-benzoylpyrazolidinone derivative (**7a**, 118 mg, 0.363 mmol) and $Sc(OTf)_3$ (9 mg, 0.0183 mmol, 5 mol%) was added MeOH (1 mL) at rt. After being stirred at the same temperature for 12 h, dichloromethane and saturated aqueous $NaHCO_3$ were added. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2CO_3, and evaporated *in vacuo*. The residue was dissolved in a 4N HCl solution in dioxane, and the solution was evaporated *in vacuo* again. The residue was triturated with Et_2O-hexane system to afford the desired debenzoylated pyrazolidinone as a HCl salt (**8**, 79 mg, 85% yield).

4,4-Dimethyl-5-(2'-phenylethyl)-3-pyrazolidinone (8 (free)): pale yellow oil. IR (neat) 1691 cm^{-1}; ^{1}H NMR δ 1.02 (s, 3H), 1.12 (s, 3H), 1.71-1.86 (m, 2H), 2.61-2.86 (m, 2H), 3.24 (dd, 1H, *J* = 9.7, 4.2 Hz), 7.02 (br s, 1H), 7.21-7.33 (m, 6H); ^{13}C NMR δ 16.7, 21.6, 29.8, 32.5, 42.5, 67.9, 126.1, 128.2, 128.5, 141.3, 182.2. HRMS Calcd for $C_{13}H_{18}N_2O$ (M^+) 218.1419, found 218.1430.

5-(2'-Phenylethyl)-4,4-dimethyl-3-pyrazolidinone hydrochloride salt (8 (HCL salt)): colorless powder. mp 157-159 °C (hexane). IR (KBr) 1752, 1288 cm^{-1}; ^{1}H NMR δ 1.17 (s, 3H), 1.25 (s, 3H), 1.98 (m, 1H), 2.44 (m, 1H), 2.77 (m, 1H), 3.01 (m, 1H), 3.82 (m, 1H),

7.18-7.27 (m, 6H); ^{13}C NMR δ 19.1, 21.8, 28.3, 32.1, 42.3, 67.7, 126.6, 128.5, 128.7, 139.7, 177.5.

Pyrazolinone

To a MeOH (3 mL) solution of β-hydrazino ester (**3s**, 23 mg, 0.049 mmol) was added NaOMe (7.9 mg, 0.146 mmol) at rt. The mixture was stirred at the same temperature for 12 h and Amberlite IRC-76 resin was added to quench the reaction. The resin was filtered off and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel chromatography to give the desired pyrazolone (**9c**, 10 mg, 92%) as a colorless oil.

5-(2'-Phenylethyl)-4-methyl-2-pyrazolin-5-one (9c): colorless oil. IR (neat) 1708 cm^{-1}; ^{1}H NMR δ 1.25 (s, 1H), 1.81 (s, 3H), 2.85 (br s, 4H), 7.12-7.29 (m, 5H); ^{13}C NMR δ 29.7, 31.0, 33.8, 91.2, 126.5, 128.4, 128.7, 140.1, 140.4.

Similarly, **9a** and **9b** were obtained.

4,4-Dimethyl-3-(2'-phenylethyl)-2-pyrazolin-5-one (9a): colorless oil. IR (neat) 1699, 1670 cm^{-1}; ^{1}H NMR δ 1.18 (s, 6H), 2.58-2.62 (m, 2H), 2.99-3.03 (m, 2H), 7.18-7.32 (m, 5H), 9.38 (s, 1H); ^{13}C NMR δ 20.6, 29.3, 31.1, 47.6, 126.2, 128.3, 128.5, 140.9, 167.6, 181.4. HRMS Calcd for $C_{13}H_{16}N_2O$ (M^+) 216.1263, found 216.1273.

4,4-Dimethyl-5-phenyl-2-pyrazolin-3-one (9b): colorless oil. IR (neat) 1704, 1661 cm^{-1};^{1}H NMR δ 1.49 (s, 6H), 7.42-7.45 (m, 3H), 7.79-7.82 (m, 2H), 9.79 (br s, 1H); ^{13}C NMR δ 22.4, 47.6, 126.2, 128.8, 130.1, 130.9, 163.6, 182.0. HRMS Calcd for $C_{11}H_{12}N_2O$ (M^+) 188.0950, found 188.0976.

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

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9. We also found that ytterbium triflate ($Yb(OTf)_3$) was effective for the activation of the acylhydrazone, although the yield was *ca.* 10% lower than that using $Sc(OTf)_3$ in a preliminary experiment.
10. It is also known that the imines derived from α,β-unsaturated aldehydes are often difficult to prepare due to their instability.
11. When $Sc(OTf)_3$ was used under the same reaction conditions, the desired product was obtained in a 72% yield (97% conversion).
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16. The structure was confirmed by X-Ray analysis of the corresponding *N*-benzoyl derivative.

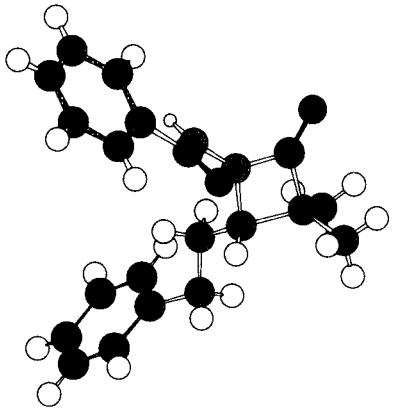

Chart 1. 3D Structure of the *N*-Benzoate of **5a** Based on X-Ray Analysis

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