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TETRAHEDRON

Trifluoromethanesulfonic acid catalyzed Friedel–Crafts acylation of aromatics with β-lactams

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Abstract—*N*-Protected and unprotected 2-azetidinones, protolytically activated by superacidic trifluoromethanesulfonic acid, react with aromatic compounds to give β-amino aromatic ketones in good to excellent yields (65–98%). Non-benzenoid aromatics (pyrrole and ferrocene) produced good yield (64–89%) of the corresponding ketones.

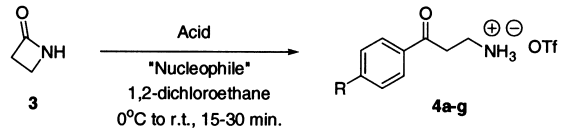
1. Introduction

Friedel–Crafts reactions are among the most common and important transformations in organic chemistry for electrophilic aromatic alkylations and acylations.[1] A significant number of Lewis acid catalysts ($AlCl_3$, $FeCl_3$, $SnCl_4$, $BF_3{\cdot}OEt_2$) have been shown to be very successful for the acylation of aromatic substrates with acid chlorides or anhydrides.[2] Aromatic ketones can also be prepared by the reaction of carboxylic acids with aromatic hydrocarbons catalyzed by methanesulfonic acid,[3] polyphosphoric acid,[4] and Nafion-H.[5] In addition, aromatic acylations have been achieved with methyl benzoate and various aromatic compounds (both electron-rich and electron-poor) protolytically activated by the superacidic trifluoromethanesulfonic acid, to produce benzophenone derivatives in good yields.[6] Considering the proven generality and usefulness of Friedel–Crafts acylations in organic synthesis, as well as the easy access to a wide range of substituted β-lactams, we envisioned that the β-lactam would be a good substrate for acylating aromatics, due to its high ring strain, to produce β-amino aromatic ketone derivatives. We previously reported a very mild procedure for the intermolecular acylation of aromatic substrates with 2-azetidinones and *N*-substituted 2-azetidinones with trifluoromethanesulfonic acid to give the corresponding β-amino aromatic ketones in good to excellent yields.[7] Herein, we report these results and extensions to this methodology to include heteroaromatic substrates.

2. Results and discussion

The efficacy of 2-azetidinone **1** as a Friedel–Crafts substrate for a variety of aromatic compounds, including bromobenzene, chlorobenzene, fluorobenzene, toluene, and anisole, is illustrated in Table 1. Thus, 2-azetidinone **1** and the corresponding aromatic compound (10.0 equiv.) were mixed with trifluoromethanesulfonic acid (1.1 equiv.) in 1,2-dichloroethane at 0°C and the mixture was allowed to warm to room temperature and was stirred for 15–30 min. With the exception of the highly deactivated nitrobenzene, all trifluoromethanesulfonic acid (pK_a (H_2O)=−14; pK_a (DMSO)=−0.3)[8] catalyzed reactions provided the β-amino aromatic ketone derivatives **4a–f** as their triflate salt in good

Table 1. Acylation of aromatics with 2-azetidinone using trifluoromethanesulfonic acid



3 4a-g

Nucleophile	Acid[a]	Product	R	Yield (%)[b]
Bromobenzene	TfOH	**4a**	Br	92[c]
Chlorobenzene	TfOH	**4b**	Cl	92
Fluorobenzene	TfOH	**4c**	F	91
Benzene	TfOH	**4d**	H	98
Anisole	TfOH	**4e**	OMe	95
Toluene	TfOH	**4f**	Me	93
Toluene	MSA	**4f**	Me	0[d]
Toluene	TFA	**4f**	Me	0[d]
Nitrobenzene	TfOH	**4g**	NO_2	0[d]

[a] TfOH=trifluoromethanesulfonic acid; MSA=methanesulfonic acid; TFA=trifluoroacetic acid.
[b] Isolated yields.
[c] Optimal yields obtained when heated to 80°C for 2 h.
[d] Reaction was heated to reflux with no desired product isolated.

Keywords: pyrrole; Friedel–Crafts acylation; aromatic hydrocarbons.

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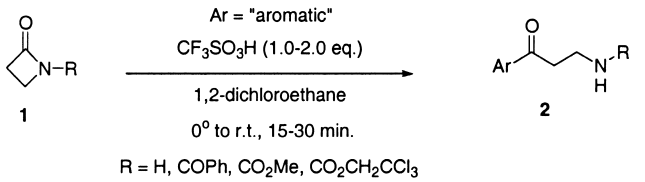
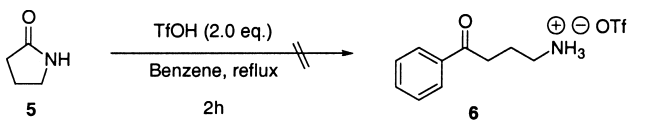
to excellent yields (Eq. (1)), see also Table 1). The protic acids, methanesulfonic acid (pK_a (H_2O)=−0.6; pK_a (DMSO)=1.6) and trifluoroacetic acid (pK_a (H_2O)=−0.25; pK_a (DMSO)=3.45)[8] proved to be too weak to catalyze the Friedel–Crafts acylation with 2-azetidinone even under more vigorous conditions (5.0 equiv., 80°C).



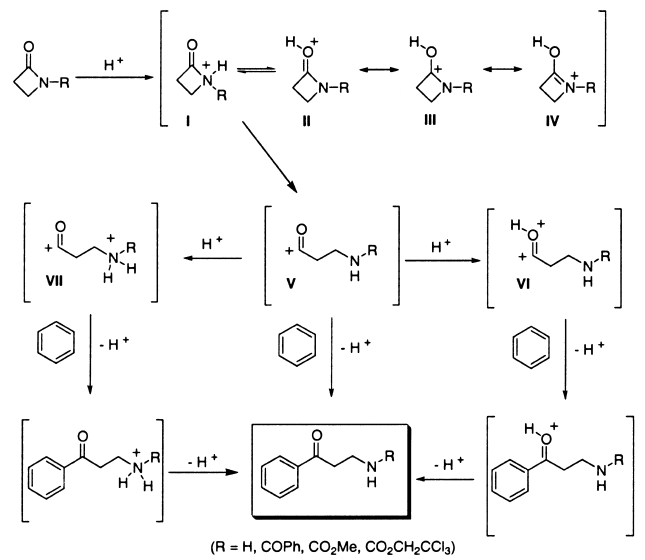
(1)



(2)

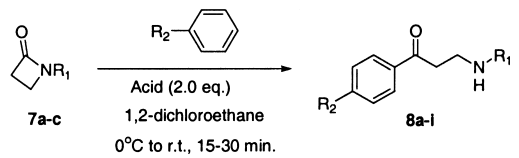
Also, the less strained β-butyrolactam **5** failed to undergo the Friedel–Crafts reaction with benzene under forcing conditions.

A possible mechanism of acylation consistent with previous reported studies is an acid catalyzed, *N*-protonated, unimolecular (A_N1) mechanism where the rate-limiting step involves formation of the acylium ion **V** as shown in Scheme 1.[9] The A_N1 mechanism is favored due to the enhanced rate of C–N bond fission that occurs in 2-azetidinones, resulting from the relief in ring strain (~119.4 kJ/mol).[10] The formation of dicationic intermediates such as **VI** are known and have been well explored in superacidic media, however, a possible second protonation is anticipated to occur on the more basic nitrogen atom providing intermediate **VII**.[11] The highly reactive acyl carbonium ion **V** or **VII** then react with the aromatic substrate, providing the acylated product (Scheme 1).



Scheme 1. Proposed mechanism for Friedel–Crafts acylation with β-lactams.

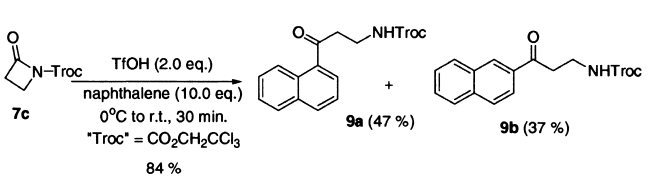
Table 2. Actylation of aromatics with *N*-protected 2-azetidinones with trifluoromethanesulfonic acid



Substrate **7**	R_1	R_2	Acid[a]	Product	Yield (%)[b]
7a	COPh	Me	TfOH	**8a**	70
7b	CO_2Me	H	TfOH	**8b**	65
7c	$CO_2CH_2CCl_3$	Br	TfOH	**8c**	84
7c	$CO_2CH_2CCl_3$	Cl	TfOH	**8d**	87
7c	$CO_2CH_2CCl_3$	F	TfOH	**8e**	85
7c	$CO_2CH_2CCl_3$	CMe	TfOH	**8f**	86
7c	$CO_2CH_2CCl_3$	Me	TfOH	**8g**	85
7c	$CO_2CH_2CCl_3$	H	TfOH	**8h**	91
7c	$CO_2CH_2CCl_3$	H	MSA	**8h**	0[c]
7c	$CO_2CH_2CCl_3$	H	TFA	**8h**	0[c]
7c	$CO_2CH_2CCl_3$	H	$AlCl_3$	**8h**	0[c]
7c	$CO_2CH_2CCl_3$	H	$BF_3{\cdot}OEt_2$	**8h**	0[c]
7c	$CO_2CH_2CCl_3$	H	$SnCl_4$	**8h**	0[c]
7c	$CO_2CH_2CCl_3$	NO_2	TfOH	**8i**	0[c]

[a] TfOH=trifluoromethanesulfonic acid; MSA=methanesulfonic acid; TFA=trifluoroacetic acid.
[b] Isolated yields.
[c] No reaction at room temperature; reaction was heated to reflux with no desired product isolated.

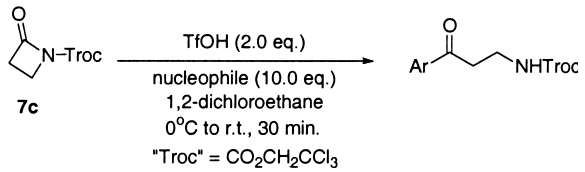
The Friedel–Crafts acylation of various *N*-acylated 2-azetidinones **7** with a variety of aromatics was subsequently investigated. The results are shown in Table 2. Treatment of 2-azetidinones **7a–c** and the aromatic substrate (10.0 equiv.) with trifluoromethanesulfonic acid (2.0 equiv.) in 1,2-dichloroethane at 0°C to room temperature over 30 min provided the corresponding products **8a–h** in excellent yields. Treatment of the 2-azetidinone **7c** with traditional Lewis acids ($AlCl_3$, $SnCl_4$, $BF_3{\cdot}OEt_2$) and protic acids (MSA, TFA) did not result in any Friedel–Crafts acylation of benzene, not even under more forcing conditions (refluxing conditions for several hours). Treatment of *N*-Troc (2,2,2-trichloroethoxycarbonyl)-2-azetidinone **7c**, under the reaction conditions, in the presence of naphthalene (10.0 equiv.) provided a mixture of the 1- and 2-substituted naphthalene isomers in overall 84% yield (Eq. (3)). Using ferrocene as the aromatic substrate, acylation was accomplished to give ferrocene-ketone **10** in 89% yield (Table 3).

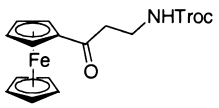
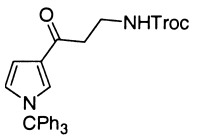
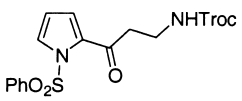


(3)

All attempts to di-acylate ferrocene by using an excess of 2-azetidinone **7c** failed, giving only single acylation of ferrocene. The 2-azetidinones also proved to be substrates for the acylation of aromatic heterocycles. The *N*-protected pyrroles, *N*-trityl-pyrrole and *N*-phenylsulfonyl-pyrrole (Table 3), were also examined, under the same reaction conditions, giving the corresponding 3-substituted **11** and 2-substituted **12** pyrroles in moderate yields (Table 3).

Table 3. Acylation of ferrocene and *N*-substituted pyrroles with *N*-(Troc)-2-azetidinone using trifluoromethanesulfonic acid

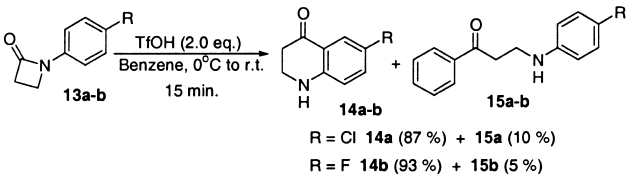


Nucleophile		Product	Yield (%)[a]
	**10**		89
	**11**		65
	**12**		64

[a] Isolated yields.

In addition, we examined the *N*-aryl 2-azetidinones (*p*-Cl, *p*-F, *p*-H, *p*-OMe, *p*-NO_2) **13a–e** under the same mild reaction conditions due to their high propensity to suffer CO–N bond cleavage under both acidic and basic conditions.[12] The *N*-aryl 2-azetidinones were prepared by standard protocols.[13] *N*-Aryl 2-azetidinones **13** have previously been shown to undergo a Fries-type rearrangement (intramolecular Friedel–Crafts), resulting in the corresponding 2,3-dihydro-4(1*H*)-quinolones **14** under forcing conditions (reflux in trifluoroacetic acid for 2 h).[14] We report here a significantly milder method for the preparation of quinolones **14a–e** using trifluoromethanesulfonic acid (1.0–2.0 equiv.) in 1,2-dichloroethane (0°C to room temperature over 15 min) in excellent yields (Table 4).

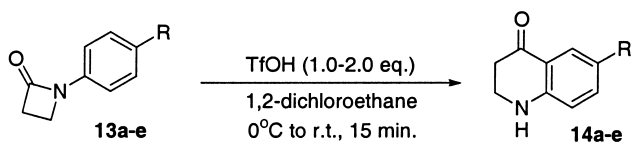
We also examined the competition between the intramolecular Fries-type rearrangement and intermolecular Friedel–Crafts reaction by running the reaction using benzene as the solvent.



(4)

As anticipated, the intramolecular Fries-type rearrangement giving quinolones **14a** (87%) and **14b** (93%) was favored over the intermolecular Friedel–Crafts reaction to give **15a** (10%) and **15b** (5%) in excellent combined overall yield.

Table 4. Fries-type rearrangement of aryl 2-azetidinones with trifluoromethanesulfonic acid



Substrate **13**	R	Yield **14** (%)[a]
13a	Cl	97
13b	F	98
13c	H	96[b]
13d	OMe	97[b]
13e	NO_2	0

[a] Isolated yields.
[b] 2 equiv. trifluoromethanesulfonic acid were required for optimal yield.

3. Conclusions

In summary, we have shown that 2-azetidinones can be activated by trifluoromethanesulfonic acid to undergo Friedel–Crafts acylation of aromatic and heteroaromatics to give their respective β-amino aromatic ketones in preparatively good yields.

4. Experimental

Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without further purification. All solvents were reagent grade. THF was freshly distilled from sodium/benzophenone under nitrogen. All reactions were magnetically stirred and monitored by thin layer chromatography with Analtech 0.25-mm pre-coated silica gel plates. Column chromatography was carried out on silica gel 60 (230–400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory devices) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton, carbon, and fluorine NMR spectra were recorded on a Varian Gemini-300 spectrometer or a Varian VXR-500 spectrometer. Chemical shifts are reported relative to the residue peaks of solvent chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C) and dimethyl sulfoxide (δ 2.49 for ^{1}H and δ 39.5 for ^{13}C). High-resolution mass spectra were obtained at the Mass Spectrometry Laboratory of the University of South Carolina, Department of Chemistry & Biochemistry with a Micromass VG-70S mass spectrometer. Gas chromatography/low-resolution mass spectra were recorded on a Hewlet–Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. Microanalyses were recorded on a Perkin–Elmer Series II CHNS/O 2400 Analyzer. All chemicals were obtained from Aldrich Chemical Co. and used as received. 1-trityl-pyrrole,[15] 1-phenylsulfonyl-pyrrole,[16] and *N*-(benzoyl)-2-azetidinone[17] were prepared by literature protocols. *Caution*: trifluoromethanesulfonic acid is a corrosive and hygroscopic liquid that should be handled with care under a dry atmosphere.

4.1. Preparation of 3-amino-1-phenyl-propan-1-one trifluoromethylsulfonate (4d) from 2-azetidinone and benzene under trifluoromethanesulfonic acid catalysis (typical procedure for 4a–4f)

Trifluoromethanesulfonic acid (1.5 mmol, 232 mg) was added slowly to a solution of 2-azetidinone (1.4 mmol, 100 mg) in benzene (14.0 mmol, 1.25 mL) and 1,2-dichloroethane (0.5 mL) at 0°C under a dry nitrogen atmosphere. The solution was stirred at room temperature for 15–30 min. The reaction mixture was then carefully neutralized with ice-water (10 mL) containing saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was separated, washed with water, brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give product **4d** as a white flaky solid, which was re-crystallized in ethyl acetate (412 mg, 98%).

4.1.1. 3-Amino-1-(4-bromo-phenyl)-propan-1-one trifluoromethylsulfonate (4a). 92%; mp 163°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 3.17 (t, 2H, J=6 Hz), 3.37 (t, 2H, J=6 Hz), 7.5–7.8 (br-s, 3H), 7.75 (d, 2H, J=9 Hz), 7.90 (d, 2H, J=9 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 197.2 (CO), 135.6, 132.6, 130.6, 128.5, 123.5 (q, CF_3, J=318 Hz), 36.3, 34.7; ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ −22075.24; IR: (NaCl) 3300–3215 (NH), 1684 (CO), 1261 (SO_2); LRMS (%) 229 (M, 20), 210 (24), 198 (20), 183 (100), 155 (60). Anal. calcd for $C_{10}H_{11}BrF_3NO_4S$: C, 31.76; H, 2.93; N, 3.70. Found: C, 32.09; H, 3.05; N, 3.47.

4.1.2. 3-Amino-1-(4-chloro-phenyl)-propan-1-one trifluoromethylsulfonate (4b). 92%; mp 148°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 3.17 (t, 2H, J=6 Hz), 3.37 (t, 2H, J=6 Hz), 7.34 (br-s, 3H), 7.58 (d, 2H, J=9 Hz), 7.97 (d, 2H, J=9 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 196.9 (CO), 139.3, 135.2, 130.5, 129.6, 123.5 (q, CF_3, J=317 Hz), 36.4, 34.8; ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ −22084.40; IR: (NaCl) 3291–3209 (NH), 1684 (CO), 1281 (SO_2); LRMS (%) 184 (12), 163 (19) 139 (100), 75 (42), 44 (69). Anal. calcd for $C_{10}H_{11}ClF_3NO_4S$: C, 35.99; H, 3.32; N, 4.20. Found: C, 36.28; H, 3.48; N, 4.10.

4.1.3. 3-Amino-1-(4-fluoro-phenyl)-propan-1-one trifluoromethylsulfonate (4c). 91%; mp 132°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 3.16 (t, 2H, J=6 Hz), 3.37 (t, 2H, J=6 Hz), 7.0–7.7 (br-s, 3H), 7.37 (t, 2H, J=9 Hz), 8.06 (t, 2H, J=9 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 196.0 (CO), 167.0, 163.7, 132.7, 131.1, 131.0, 122.9 (q, CF_3, J=318 Hz), 116.1, 115.8, 35.8, 34.2; ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ −22087.45, −29845.49; IR: (NaCl) 3291–3209 (NH), 1682 (CO), 1236 (SO_2); LRMS (%) 167 (M, 10), 150 (13), 138 (13), 123 (100), 95 (70), 74 (28), 44 (78). Anal. calcd for $C_{10}H_{11}F_4NO_4S$: C, 37.86; H, 3.49; N, 4.41. Found: C, 38.21; H, 3.64; N, 4.15.

4.1.4. 3-Amino-1-phenyl-propan-1-one trifluoromethyl sulfonate (4d). 98%; mp 122°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 3.17 (t, 2H, J=6 Hz), 3.39 (t, 2H, J=6 Hz), 7.41 (br-s, 3H), 7.56 (t, 2H, J=7 Hz), 7.67 (t, 1H, J=7 Hz), 7.98 (d, 2H, J=7 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 198.0 (CO), 136.4, 134.4, 129.5, 128.6, 123.5 (q, CF_3, J=318 Hz), 36.4, 34.8; ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ −22078.29; IR: (NaCl) 3221 (NH), 1682 (CO), 1288 (SO_2); LRMS (%) 149 (M, 10), 132 (20), 105 (100), 77 (78), 51 (43), 44 (85). Anal. calcd for $C_{10}H_{12}F_3NO_4S$: C, 40.13; H, 4.04; N, 4.68. Found: C, 40.56; H, 3.81; N, 4.13.

4.1.5. 3-Amino-1-(4-methoxy-phenyl)-propan-1-one trifluoromethylsulfonate (4e). 95%; mp 155°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 3.13 (t, 2H, J=6 Hz), 3.30 (t, 2H, J=6 Hz), 3.85 (s, 3H), 6.2 (br-s, 3H), 7.07 (d, 2H, J=9 Hz), 7.96 (d, 2H, J=9 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 196.3 (CO), 164.2, 130.9, 129.6, 114.7, 123.5 (q, CF_3, J=318 Hz), 56.3, 35.9, 34.9; ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ; IR: (NaCl) 3250–3171 (NH), 1670 (CO), 1249 (SO_2); LRMS 179 (M). Anal. calcd for $C_{11}H_{14}F_3NO_5S$: C, 40.12; H, 4.29; N, 4.25. Found: C, 40.40; H, 4.53; N, 4.14.

4.1.6. 3-Amino-1-(4-methyl-phenyl)-propan-1-one trifluoromethylsulfonate (4f). 93%; mp 160°C; ^{1}H NMR: (300 MHz) (d^6-DMSO) δ TMS: 2.38 (s, 3H), 3.16 (t, 2H, J=6 Hz), 3.35 (t, 2H, J=6 Hz), 7.36 (d, 2H, J=8 Hz), 7.40 (br-s, 3H), 7.88 (d, 2H, J=8 Hz); ^{13}C NMR: (74.47 MHz) (d^6-DMSO) δ 197.5 (CO), 144.9, 134.2, 130.1, 128.8, 123.5 (q, CF_3, J=318 Hz), 36.3, 34.9, 21.8 (Me); ^{19}F NMR: (282.35 MHz) (d^6-DMSO) δ −22075.24; IR: (NaCl) 3288–3220 (NH), 1680 (CO), 1263 (SO_2); LRMS (%) 163 (M, 12), 146 (18), 134 (22), 119 (100), 91 (83), 65 (39), 44 (51). Anal. calcd for $C_{11}H_{14}F_3NO_4S$: C, 42.17; H, 4.50; N, 4.47. Found: C, 42.46; H, 4.71; N, 4.32.

4.1.7. 2-Oxo-azetidine-1-carboxylic acid methyl ester (7b). In a 100 mL round bottom flask under dry N_2, 2-azetidinone (7.03 mmol, 513 mg) was dissolved in anhydrous tetrahydrofuran (23 mL). The solution was then cooled to −78°C (acetone/dry ice bath) causing precipitation of the insoluble lactams, and then *n*-butyl lithium (7.86 mmol, 0.785 mL) was carefully and slowly added dropwise with stirring. After 30 min of stirring, a solution of methyl chloroformate (7.86 mmol, 0.61 mL) in anhydrous tetrahydrofuran (7 mL) was added dropwise. The reaction mixture was stirred at −78°C for 1 h and allowed to warm to room temperature for 1 h after which it was quenched with 20 mL aqueous saturated ammonium chloride. The solution was then washed with diethyl-ether (3×20 mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was further purified by column chromatography on silica gel (dichloromethane/ethanol, 99:1) to yield **7b** (700 mg, 77%). Mp 64°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.92 (t, 2H, J=5 Hz), 3.48 (t, 2H, J=5 Hz), 3.69 (s, 3H); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 164.4 (CO), 149.4 (OCON), 53.1 (Me), 37.6, 36.4; IR: (NaCl) 1801 (CO), 1724 (OCON). Anal. calcd for $C_5H_7NO_3$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.82; H, 5.64; N, 10.67.

4.1.8. 2-Oxo-azetidine-1-carboxylic acid-2,2,2-trichloroethyl ester (7c). In a 100 mL round bottom flask under dry N_2, 2-azetidinone (4.22 mmol, 300 mg) was dissolved in anhydrous tetrahydrofuran (14 mL). The solution was then cooled to −78°C (acetone/dry ice bath) causing

precipitation of the insoluble lactams, and then *n*-butyl lithium (4.64 mmol, 0.46 mL) was carefully and slowly added dropwise with stirring. After 30 min of stirring, a solution of 2,2,2-trichloroethyl chloroformate (4.64 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise. The reaction mixture was stirred at −78°C for 1.5 h and allowed to warm to room temperature for 1 h after which it was quenched with 15 mL aqueous saturated ammonium chloride. The solution was then washed with diethyl-ether (3×20 mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown oil. The crude material was further purified by column chromatography on silica gel (hexanes/ethyl acetate, 6:4) and re-crystallized with diethyl ether to yield **7b** (890 mg, 86%). Mp 98°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.14 (t, 2H, *J*=5 Hz), 3.73 (t, 2H, *J*=5 Hz), 4.83 (s, 2H); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 164.0 (CO), 147.0 (OCON), 94.3 (CCl_3), 74.7, 38.2, 37.2; IR: (NaCl) 1790 (CO), 1730 (OCON). Anal. calcd for $C_6H_6Cl_3NO_3$: C, 29.24; H, 2.45; N, 5.68. Found: C, 29.60; H, 2.55; N, 5.64.

4.2. Preparation of (3-oxo-3-phenyl-propyl)-carbamic acid-2,2,2-trichloro-ethyl ester (8h) from *N*-(2,2,2-trichloroethoxycarbonyl)-2-azetidinone and benzene under trifluoromethanesulfonic acid catalysis (typical procedure for 8a–8h, 9–12)

Trifluoromethanesulfonic acid (0.82 mmol, 222 mg) was added slowly to a solution of *N*-(2,2,2-trichloroethoxy-carbonyl)-2-azetidinone **7c** (0.41 mmol, 100 mg) in benzene (4.4 mmol, 0.4 mL) and 1,2-dichloroethane (0.4 mL) at 0°C under a dry nitrogen atmosphere. The solution was stirred at room temperature for 15–30 min. The reaction mixture was then carefully neutralized with ice-water (10 mL) containing saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated, washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was re-crystallized in diethyl-ether to give pure product (121 mg, 91%) or purified by column chromatography on silica gel (hexane/ethyl acetate, 7:3).

4.2.1. *N*-(3-Oxo-3-*p*-tolyl-propyl)-benzamide (8a). 70%; mp 109°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.81 (s, 3H), 3.28 (t, 2H, *J*=6 Hz), 3.86 (q, 2H, *J*=6 Hz), 7.23 (d, 2H, *J*=8 Hz), 7.23 (br-s, 1H), 7.34–7.47 (m, 3H), 7.76 (d, 2H, *J*=8 Hz), 7.84 (d, 2H, *J*=8 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 199.2 (CO), 167.4 (CON), 144.3, 134.4, 133.9, 131.3, 129.3, 128.4, 128.1, 126.9, 37.9, 34.9, 21.6 (Me); IR: (NaCl) 3333 (NH), 1680 (CO), 1639 (CON); LRMS (%) 167 (M, 13), 148 (32), 119 (100), 105 (75), 91 (31), 77 (43). Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.33; H, 6.26; N, 5.18.

4.2.2. (3-Oxo-3-phenyl-propyl)-carbamic acid methyl ester (8b). 65%; oil; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.21 (t, 2H, *J*=6 Hz), 3.59 (q, 2H, *J*=6 Hz), 3.63 (s, 3H), 5.42 (br-s, 1H), 7.49 (t, 2H, *J*=7 Hz), 7.61 (t, 1H, *J*=7 Hz), 7.98 (d, 2H, *J*=7 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 199.4 (CO), 157.4 (OCON), 136.7, 133.7, 128.9, 128.2, 52.3 (Me), 38.7, 36.1; IR: (NaCl) 3350 (NH), 1718 (OCON), 1684 (CO); HRMS *m/e* calcd for $C_{11}H_{13}NO_3$ (M) 230.0793, found 230.0791.

4.2.3. [(3-(4-Bromo-phenyl)-3-oxo-propyl)]-carbamic acid-2,2,2-trichloro-ethyl ester (8c). 84%; mp 84°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.26 (t, 2H, *J*=6 Hz), 3.68 (q, 2H, *J*=6 Hz), 4.72 (s, 2H), 5.70 (br-s, 1H), 7.63 (d, 2H, *J*=9 Hz), 7.83 (d, 2H, *J*=9 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 197.8 (CO), 154.6 (OCON), 134.9, 132.0, 129.5, 128.7, 95.4 (CCl_3), 74.4, 38.1, 35.9; IR: (NaCl) 3354 (NH), 1734 (OCON), 1684 (CO); LRMS (%) 403 (M, 1), 367 (1), 270 (8), 254 (12), 226 (14), 210 (49), 183 (100), 157 (28), 131 (27), 76 (33). Anal. calcd for $C_{12}H_{11}BrCl_3NO_3$: C, 35.72; H, 2.75; N, 3.47. Found C, 35.65; H, 2.69; N, 3.40.

4.2.4. [(3-(4-Chloro-phenyl)-3-oxo-propyl)]-carbamic acid-2,2,2-trichloro-ethyl ester (8d). 87%; mp 87°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.23 (t, 2H, *J*=6 Hz), 3.65 (q, 2H, *J*=6 Hz), 4.70 (s, 2H), 5.76 (br-s, 1H), 7.44 (d, 2H, *J*=9 Hz), 7.87 (d, 2H, *J*=9 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 198.0 (CO), 154.9 (OCON), 140.3, 134.9, 129.7, 129.3, 95.8 (CCl_3), 74.7, 38.5, 36.3; IR: (NaCl) 3352 (NH), 1734 (OCON), 1684 (CO); LRMS (%) 359 (M). Anal. calcd for $C_{12}H_{11}Cl_4NO_3$: C, 40.14; H, 3.09; N, 3.90. Found C, 41.22; H, 3.23; N, 3.81.

4.2.5. [(3-(4-Fluoro-phenyl)-3-oxo-propyl)]-carbamic acid-2,2,2-trichloro-ethyl ester (8e). 85%; mp 81°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.24 (t, 2H, *J*=6 Hz), 3.64 (q, 2H, *J*=6 Hz), 4.72 (s, 2H), 5.74 (br-s, 1H), 7.15 (m, 2H), 7.99 (m, 2H); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 197.3 (CO), 167.6, 164.3, 154.6 (OCON), 132.7, 130.7, 130.6, 116.0, 115.7, 95.4 (CCl_3), 74.4, 38.1, 36.0; ^{19}F NMR: (282.35 MHz) ($CDCl_3$) δ −29500.42; IR: (NaCl) 3356 (NH), 1734 (OCON), 1684 (CO); LRMS (%) 342 (M). Anal. calcd for $C_{12}H_{11}Cl_3FNO_3$: C, 42.07; H, 3.24; N, 4.09. Found C, 41.22; H, 3.29; N, 4.07.

4.2.6. [(3-(4-Methoxy-phenyl)-3-oxo-propyl)]-carbamic acid-2,2,2-trichloro-ethyl ester (8f). 86%; mp 75°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.20 (t, 2H, *J*=6 Hz), 3.64 (q, 2H, *J*=6 Hz), 3.87 (s, 3H), 4.71 (s, 2H), 5.81 (br-s, 1H), 6.93 (d, 2H, *J*=9 Hz), 7.93 (d, 2H, *J*=9 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 197.4 (CO), 163.8, 154.9 (OCON), 130.3, 129.4, 113.8, 95.5 (CCl_3), 74.4, 55.4 (OMe), 37.7, 36.2; IR: (NaCl) 3350 (NH), 1734 (OCON), 1670 (CO); LRMS (%) 354 (M, 10), 317 (3), 205 (31), 177 (38), 134 (100), 91 (92), 77 (89) 63 (35). Anal. calcd for $C_{13}H_{14}Cl_3NO_4$: C, 44.03; H, 3.98; N, 3.95. Found C, 43.75; H, 3.98; N, 3.92.

4.2.7. (3-Oxo-3-*p*-tolyl-propyl)-carbamic acid-2,2,2-trichloro-ethyl ester (8g). 85%; mp 98°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.42 (s, 3H), 3.23 (t, 2H, *J*=6 Hz), 3.65 (q, 2H, *J*=6 Hz), 4.71 (s, 2H), 5.78 (br-s, 1H), 7.27 (d, 2H, *J*=8 Hz), 7.85 (d, 2H, *J*=8 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 198.9 (CO), 154.9 (OCON), 144.8, 134.2, 129.7, 128.4, 95.8 (CCl_3), 74.7, 38.3, 36.4; IR: (NaCl) 3356 (NH), 1734 (OCON), 1680 (CO); LRMS (%) 338 (M, 15). Anal. calcd for $C_{13}H_{14}Cl_3NO_3$: C, 46.11; H, 4.17; N, 4.14. Found: C, 46.09; H, 4.20; N, 4.07.

4.2.8. (3-Oxo-3-phenyl-propyl)-carbamic acid-2,2,2-trichloro-ethyl ester (8h). 91%; mp 75°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.27 (t, 2H, J=6 Hz), 3.67 (q, 2H, J=6 Hz), 4.71 (s, 2H), 5.74 (br-s, 1H), 7.48 (t, 2H, J=7 Hz), 7.59 (t, 1H, J=7 Hz), 7.96 (d, 2H, J=7 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 198.9 (CO), 154.6 (OCON), 136.3, 133.6, 128.7, 127.9, 95.5 (CCl_3), 74.4, 38.1, 36.0; IR: (NaCl) 3427 (NH), 1716 (OCON), 1678 (CO); LRMS (%) 224 (M). Anal. calcd for $C_{12}H_{12}Cl_3NO_3$: C, 44.40; H, 3.73; N, 4.32. Found: C, 44.45; H, 3.78; N, 4.25.

4.2.9. (3-Naphthalen-1-yl-3-oxo-propyl)-carbamic acid 2,2,2-trichloro-ethyl ester (9a) and (3-naphthalen-2-yl-3-oxo-propyl)-carbamic acid 2,2,2-trichloro-ethyl ester (9b). 47% **9a**; 37% **9b**; ^{1}H NMR: (500 MHz) ($CDCl_3$) δ TMS: 3.33 (t, 2H, J=6 Hz), 3.36 (t, 2H, J=6 Hz), 3.70 (4H, q, J=6 Hz), 4.72 (s, 2H), 4.73 (s, 2H), 5.78 (br-s, 2H), 7.45–7.62 (m, 5H), 7.85–7.88 (m, 4H), 7.93 (d, 1H, J=8 Hz), 7.98–7.99 (m, 2H), 8.43 (s, 1H), 8.71 (d, 1H, J=9 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 202.9 (CO), 199.1 (CO), 154.9 (OCON), 136.0, 134.9, 134.3, 134.0, 133.7, 132.7, 130.4, 130.2, 129.9, 128.9, 128.84, 128.8, 128.7, 128.5, 128.0, 127.2, 126.8, 125.9, 124.6, 123.7, 95.9 (CCl_3), 74.8, 41.4, 38.5, 36.9, 36.6; IR: (NaCl) 3352 (NH), 1736 (OCON), 1676 (CO); HRMS *m/e* calcd for $C_{16}H_{14}Cl_3NO_3$ (M) 373.0039, found 373.0030.

4.2.10. (3-Oxo-3-ferrocenyl-propyl)-carbamic acid-2,2,2-trichloro-ethyl ester (10). 89%; mp 94°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.97 (t, 2H, J=6 Hz), 3.58 (q, 2H, J=6 Hz), 4.16 (m, 5H), 4.50 (s, 2H), 4.69 (m, 2H), 4.76 (m, 2H), 5.78 (br-s, 1H); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 203.2 (CO), 154.6 (OCON), 95.5 (CCl_3), 78.3, 74.4, 72.6, 69.9, 69.2, 38.9, 36.1; IR: (NaCl) 3341 (NH), 1734 (OCON), 1660 (CO); LRMS (%) 432 (M). Anal. calcd for $C_{16}H_{16}Cl_3FeNO_3$: C, 44.43; H, 3.73; N, 3.24. Found C, 44.44; H, 3.59; N, 3.14.

4.2.11. [3-Oxo-3-(1-trityl-1*H*-pyrrol-3-yl)-propyl]-carbamic acid-2,2,2-trichloro-ethyl ester (11). 63%; mp 51°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.94 (t, 2H, J=6 Hz), 3.56 (q, 2H, J=6 Hz), 4.68 (s, 2H), 5.71 (br-s, 1H), 6.58 (m, 2H), 7.13 (m, 6H), 7.3 (m, 10H); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 194.5 (CO), 154.6 (OCON), 142.4, 129.8, 128.0, 127.7, 125.4, 123.9, 108.1, 95.6 (CCl_3), 76.9 (CPh_3), 74.4, 38.5, 36.2; IR: (NaCl) 3337 (NH), 1736 (OCON), 1657 (CO); LRMS (%) 554 (M). Anal. calcd for $C_{29}H_{25}Cl_3N_2O_3$: C, 62.66; H, 4.53; N, 5.04. Found C, 61.51; H, 4.55; N, 4.83.

4.2.12. 3-Chloro-2,3-dihydro-4(1*H*)-quinolone (14a). 97%; mp 126°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.67 (t, 2H, J=7 Hz), 3.56 (t, 2H, J=7 Hz), 4.70 (br-s, 1H), 6.64 (d, 1H, J=9 Hz), 7.20 (dd, 1H, J=8, 3 Hz), 7.75 (d, 1H, J=3 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 192.7 (CO), 150.5, 134.9, 126.6, 122.9, 119.7, 117.5, 41.9, 37.6; IR: (NaCl) 3356 (NH), 1647 (CO). Anal. calcd for C_9H_8NOCl: C, 59.52; H, 4.44; N, 7.71. Found C, 59.74; H, 4.43; N, 7.46.

4.2.13. 3-Fluoro-2,3-dihydro-4(1*H*)-quinolone (14b). 98%; mp 71°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.66 (t, 2H, J=7 Hz), 3.54 (t, 2H, J=7 Hz), 4.58 (br-s, 1H), 6.65 (dd, 1H, J=9, 3 Hz), 7.02 (td, 1H, J=3, 9 Hz), 7.46 (dd, 1H, J=9, 3 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 193.1 (CO), 157.0, 153.9, 148.8, 123.3, 122.9, 120.3, 119.3, 119.2, 117.4, 117.3, 112.2, 111.9, 42.3, 37.8; IR: (NaCl) 3341 (NH), 1651 (CO). Anal. calcd for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48. Found C, 65.57; H, 5.19; N, 7.99.

4.2.14. 2,3-Dihydro-4(1*H*)-quinolone (14c). 96%; mp 44°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.66 (t, 2H, J=7 Hz), 3.53 (t, 2H, J=7 Hz), 4.79 (br-s, 1H), 6.69 (d, 2H, J=9 Hz), 7.26 (t, 1H, J=7 Hz), 7.81 (d, 1H, J=8 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 194.0 (CO), 152.3, 135.2, 127.4, 119.0, 117.6, 115.9, 42.0, 37.9; IR: (NaCl) 3348 (NH), 1660 (CO). Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found C, 72.22; H, 6.08; N, 9.16.

4.2.15. 3-Methoxy-2,3-dihydro-4(1*H*)-quinolone (14d). 97%; mp 111°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 2.66 (t, 2H, J=7 Hz), 3.51 (t, 2H, J=7 Hz), 4.41 (br-s, 1H), 3.74 (s, 3H), 6.63 (d, 1H, J=9 Hz), 6.95 (dd, 1H, J=9, 3 Hz), 7.29 (d, 1H, J=3 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 193.7 (CO), 151.9, 147.4, 125.2, 119.1, 117.6, 107.6, 55.6 (Me), 42.7, 38.0; IR: (NaCl) 3331 (NH), 1647 (CO). Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.20; N, 7.90. Found C, 67.81; H, 6.22; N, 7.83.

4.2.16. 3-(4-Chloro-phenylamino)-1-phenyl-propan-1-one (15a). 10%; mp 135°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.29 (t, 2H, J=6 Hz), 3.60 (t, 2H, J=6 Hz), 4.10 (br-s, 1H), 6.58 (d, 2H, J=9 Hz), 7.14 (d, 2H, J=9 Hz), 7.49 (t, 2H, J=8 Hz), 7.58 (t, 1H, J=8 Hz), 7.96 (d, 2H, J=8 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 199.1 (CO), 146.2, 136.5, 133.4, 129.1, 128.6, 127.9, 122.0, 114.0, 38.7, 37.3; IR: (NaCl) 3370 (NH), 1672 (CO). Anal. calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found C, 69.02; H, 5.69; N, 5.21.

4.2.17. 3-(4-Fluoro-phenylamino)-1-phenyl-propan-1-one (15b). 5%; mp 115°C; ^{1}H NMR: (300 MHz) ($CDCl_3$) δ TMS: 3.29 (t, 2H, J=6 Hz), 3.59 (t, 2H, J=6 Hz), 4.05 (br-s, 1H), 6.61 (dd, 2H, J=4, 9 Hz), 6.91 (t, 2H, J=9 Hz), 7.49 (t, 2H, J=8 Hz), 7.60 (t, 1H, J=8 Hz), 7.97 (d, 2H, J=8 Hz); ^{13}C NMR: (74.47 MHz) ($CDCl_3$) δ 199.2 (CO), 157.4, 154.3, 144.0, 136.6, 133.4, 128.6, 127.9, 120.3, 115.8, 115.5, 113.9, 39.4, 37.4; IR: (NaCl) 3366 (NH), 1672 (CO). Anal. calcd for $C_{15}H_{14}FNO$: C, 74.06; H, 5.80; N, 5.76. Found C, 74.83; H, 5.50; N, 4.85.

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References

1. (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley-Interscience: New York, 1965; Vols. I–IV. (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, 1973.
2. (a) Effenberger, F.; Steegmuller, D. *Chem. Ber.* **1988**, *121*,

117. (b) Mukaiyama, T.; Suzuki, K.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1992**, 435. (c) Takagi, K.; Shimoishi, Y.; Sasaki, K. *Chem. Lett.* **1994**, 2055. (d) Evans, P. A.; Nelson, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298. (e) Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197. (f) Desmurs, J. R.; Labrouillere, M.; Le Roux, C. L.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871.
3. Cho, H.; Matsuki, S.; Mizuno, A.; Annoura, H.; Tatsuoka, T. *J. Heterocycl. Chem.* **1997**, *34*, 87.
4. Mizuno, A.; Miya, M.; Kamei, T.; Shibata, M.; Tatsuoka, T.; Nakanishi, K.; Takiguchi, C.; Hidaka, T.; Yamaki, A.; Inomata, N. *Chem. Pharm. Bull.* **2000**, *48*, 1129.
5. Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *36*, 3955.
6. Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199.
7. Anderson, K. W.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 459.
8. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
9. (a) Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144. (b) Cox, R. A.; Yates, K. *Can. J. Chem.* **1981**, *59*, 2853. (c) Abboud, J.-L. M.; Canada, T.; Homan, H.; Notario, R.; Cativiela, C.; Diaz de Villegas, M. D.; Bordeje, M. C.; Mo, O.; Yanez, M. *J. Am. Chem. Soc.* **1992**, *114*, 4728. (d) Wan, P.; Modro, T. A.; Yates, K. *Can. J. Chem.* **1980**, *58*, 2423.
10. Roux, M. V.; Jimenez, P.; Davalos, J. Z.; Castano, O.; Molina, M. T.; Notario, R.; Herreros, M.; Abboud, J.-L. M. *J. Am. Chem. Soc.* **1996**, *118*, 12735.
11. (a) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364. (b) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081. (c) Olah, G. A.; Hartz, N.; Rasul, G.; Burrichter, A.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 6421.
12. (a) Fischer, M.; Mattheus, A. *Chem. Ber.* **1969**, *102*, 342. (b) Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1366. (c) Bird, P. G.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2664. (d) Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 981.
13. (a) Takahata, H.; Ohnishi, Y.; Takehara, H.; Tsuritani, K.; Yamazaki, T. *Chem. Pharm. Bull.* **1981**, *29*, 1063. (b) Manhas, M. S.; Jeng, S. J. *J. Org. Chem.* **1967**, *32*, 1246.
14. (a) Kano, S.; Ebata, T.; Shibuya, S. *Heterocycles* **1976**, *4*, 1649. (b) Kano, S.; Ebata, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2105. (c) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1981**, *15*, 1011.
15. Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 93.
16. Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379.
17. Freihammer, P. M.; Detty, M. R. *J. Org. Chem.* **2000**, *65*, 7203.