Supporting Information for Catalytic Cyclopropanation of Alkenes using Diazo Compounds Generated In Situ. A novel route to 2-Arylcyclopropylamines

Varinder K. Aggarwal,*[†] Javier de Vicente[†] and Roger V. Bonnert[‡]

School of Chemistry, Bristol University, Cantock's Close, Bristol BS8 1TS, UK

v.aggarwal@bristol.ac.uk

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General methods: Flash chromatography was performed on silica gel (Merck Kiesegel 60 F_{254} 230-400 mesh). TLC was performed on aluminium backed silica plates (60 F_{254}) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), molybdic acid / Δ, anisaldehyde / Δ, permanganate / Δ. Melting points were determined on a Khöfler hot stage. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Only selected absorbencies (ν_{max}) are reported. ^{1}H NMR spectra were recorded at 250, 270 or 400 MHz on Bruker AC-250, Delta GX/270 or Delta GX/400 instruments, respectively. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to TMS. ^{13}C NMR spectra were recorded at either 68 or 100 MHz on Delta GX/270 or Delta GX/400 instruments, respectively. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak and are assigned as s, d, t, q for C, CH, CH_2 and CH_3. Degenerate peaks are prefixed by the number of carbons. Low resolution mass spectra (m/z) were recorded on a Micromass Analytical Autospec spectrometer with only molecular ions (M^+), and major peaks being reported with intensities quoted as percentages of the base peak. High-resolution mass spectra were recorded on a Micromass Analytical Autospec spectrometer. Microanalyses were performed using a Carlo Erba EA1108. All chemicals were purchased from Aldrich, Fluka or Lancaster, and used as delivered. THF and toluene were pre-dried over sodium wire and then purified by passing through a solvent column prior to use.[1]

Representative procedure for the preparation of tosyl hydrazones.

To a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (5.0 g, 26.79 mmol) in methanol (10 mL) was added benzaldehyde (2.36 mL, 23.30 mmol) dropwise. A mildly exothermic reaction ensued and the hydrazide dissolved. Within 5-10 minutes the tosyl hydrazone began to precipitate. After approximately 30 min the mixture was cooled to 0°C and the product removed by filtration, washed with a small quantity of cold methanol and then crystallized from hot methanol to give 5.809 g (91%) benzaldehyde tosyl hydrazone[2] as white needles; m.p. 127-128°C (methanol) (lit.,[2] 128-129°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s, CH_3), 7.29-7.36 (5H, m, Aryl H), 7.52-7.57 (2H, m, Aryl H), 7.78 (1H, s, CHN), 7.89 (2H, d, *J* = 8.3 Hz, Aryl H), 8.29 (1H, br. s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (q), 127.3 (2d), 127.9 (2d), 128.6 (2d), 129.7 (2d), 130.4 (d), 133.1 (s), 135.2 (s), 144.3 (s), 147.9 (d).

***p*-Fluorobenzaldehyde tosyl hydrazone[3]**

Yield 85%; white needles; m.p. 133-134°C (methanol) (lit.,[3] 134-136°C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.39 (3H, s, C*H*$_3$), 7.00 (2H, t, *J* = 8.6 Hz, Aryl H), 7.30 (2H, d, *J* = 7.9 Hz, Aryl H), 7.54 (2H, dd, *J* = 8.9 and 5.6 Hz, Aryl H), 7.78 (1H, s, C*H*N), 7.88 (2H, d, *J* = 8.6 Hz, Aryl H), 8.56 (1H, br. s, N*H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5 (q), 115.7 (2d, $J_{C\text{-}F}$ = 22.3 Hz), 127.9 (2d), 129.2 (2d, $J_{C\text{-}F}$ = 8.3 Hz), 129.5 (s), 129.7 (2d), 135.3 (s), 144.2 (s), 148.4 (d), 165.5 (s, $J_{C\text{-}F}$ = 251.2 Hz); IR (thin film) ν_{max}/cm^{-1} 3437, 1643, 1602, 1511, 1167.

† School of Chemistry, Bristol University, Cantock's Close, Bristol BS8 1TS, UK.

‡ AstraZeneca R&D Charnwood, Medicinal Chemistry, Bakewell Road, Loughborough, Leics LE11 5RH, UK.

[1] The solvent column is composed of activated alumina (A-2). For toluene a supported copper redox catalyst (Q-5 reactant) is also employed. See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

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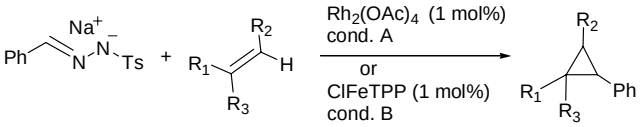
***p*-Methoxybenzaldehyde tosyl hydrazone**[4]

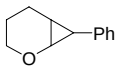
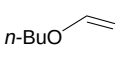
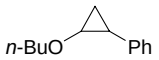
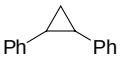
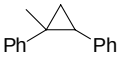
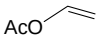
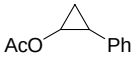
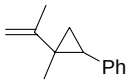
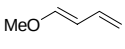
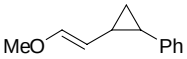
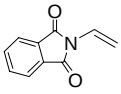
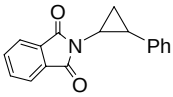
Yield 83%; white needles; m.p. 110-112°C (lit.,[4] 110-112°C); (methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.85 (2H, d, J = 8.7 Hz, Aryl H), 7.29 (2H, d, J = 8.3 Hz, Aryl H), 7.50 (2H, d, J = 8.7 Hz, Aryl H), 7.74 (1H, s, C*H*N), 7.87 (2H, d, J = 8.3 Hz, Aryl H), 8.24 (1H, br. s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (q), 55.4 (q), 114.2 (2d), 126.1 (s), 128.0 (2d), 129.0 (2d), 129.7 (2d), 135.5 (s), 144.2 (s), 148.4 (d), 165.5 (s).

Benzaldehyde tosyl hydrazone sodium salt[5]

A 1M sodium methoxide solution was prepared by adding sodium (423 mg, 18.39 mmol) to anhydrous methanol (19 mL) with external cooling. Once all of the metal was dissolved, benzaldehyde tosyl hydrazone (4.80 g, 17.51 mmol) was added and the mixture stirred until the entire solid was dissolved. After stirring for a further 15 min at room temperature the methanol was removed under reduced pressure (at room temperature). The last traces of methanol were removed under high vacuum. The salt was then ground to give a free flowing powder using a mortar and pestle to afford 5.21 g (99%) of a white powder (the product was stored in a cool place in absence of direct light). ^{1}H NMR (400 MHz, D_2O) δ 2.17 (3H, s, CH_3), 7.15-7.23 (5H, m, Aryl H), 7.35-7.40 (2H, m, Aryl H), 7.60 (2H, d, J = 8.4 Hz, Aryl H), 7.83 (1H, s, CHN); ^{13}C NMR (100 MHz, D_2O) δ 20.7 (q), 126.6 (2d), 126.7 (2d), 128.8 (2d), 129.5 (2d), 129.6 (d), 135.8 (s), 139.2 (s), 142.8 (s), 145.9 (d).

Table 1. Catalytic cyclopropanation of alkenes using diazo compounds generated in situ



alkene	cyclopropane.	
		**a**
		**b**
		**c**
		**d**
		**e**
		**f**
		**g**
		**h**

Conditions A = 1,4-dioxane, 10 mol% PTC, 30ºC.
B = toluene, 5 mol% PTC, 40ºC.

Representative procedure for the catalytic cyclopropanation of alkenes using diazo compounds generated in situ (table 1).

A mixture of benzaldehyde tosyl hydrazone sodium salt (300 mg, 1.01 mmol), benzyltriethylammonium chloride (23 mg, 0.1 mmol), rhodium acetate (4 mg, 0.01 mmol), styrene (576 µl, 5 mmol) and dry 1,4-dioxane (2.5 mL) was vigorously stirred for 2 days at 30°C. Water (7 mL) was added to the mixture, which was then washed with DCM (2×15 mL) and the combined layers dried over Na_2SO_4. Evaporation gave the residue, which was purified by flash chromatography (eluent petroleum

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ether/ethyl acetate 10:1) to afford *cis* and *trans*-**c** (93 mg, 49%) as a mixture of isomers (77/23).

7-Phenyl-2-oxa-bicyclo[4.1.0]heptane (a)[6]

cis-**a**; eluent petroleum ether/ethyl acetate 30:1, R_f = 0.35; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.40-0.60 (1H, m), 1.02-1.13 (1H, m), 1.18-1.29 (1H, m), 1.72-1.99 (3H, m), 3.24 (1H, ddd, *J* = 11.9, 10.7 and 2.6 Hz, OCH_2CH$_2$), 3.42 (1H, ddd, *J* = 10.7, 2.6 and 0.9 Hz, OC*H*H), 3.86 (dd, *J* = 7.0 and 6.1 Hz, OC*H*CHPh), 7.18-7.43 (5H, m, Aryl H).

2-Butoxy-1-phenyl-cyclopropane (b)[7]

trans-**b**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.1 Hz, CH_3), 0.75-1.60 (6H, m, 3×CH$_2$), 2.07 (1H, ddd, *J* = 10.1, 6.4 and 2.4 Hz, C*H*Ph), 3.29-3.36 (1H, m, OC*H*), 3.55 (2H, t, *J* = 6.7 Hz, OCH_2CH$_2$), 6.99-7.35 (5H, m, Aryl H).

cis-**b**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75 (3H, t, *J* = 7.3 Hz, CH_3), 1.00-1.60 (6H, m, 3×CH$_2$), 1.95 (1H, ddd, *J* = 9.4, 7.5 and 6.4 Hz, C*H*Ph), 3.08 (1H, dt, *J* = 9.4, 6.4 Hz, OC*H*H), 3.32 (1H, dt, *J* = 9.4 and 6.4 Hz, OC*H*H), 3.48 (1H, td, *J* = 6.4 and 4.0 Hz, OC*H*), 7.22 (5H, m, Aryl H).

1,2-Phenylcyclopropane (c)[8]

trans-**c**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (2H, t, *J* = 7.4 Hz, CH_2), 2.15 (2H, t, *J* = 7.4 Hz, C*H*Ph), 7.10-7.32 (10H, m, Aryl H).

cis-**c**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33-1.52 (2H, m, CH_2), 2.48 (1H, dd, *J* = 8.6 and 6.5 Hz, C*H*Ph), 6.92-7.28 (10H, m, Aryl H).

1, 2-Diphenyl-1-methyl-cyclopropane (d)[9]

trans-**d**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.49 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (1H, dd, *J* = 6.2 and 5.1 Hz, C*H*H), 1.15 (3H, s, CH_3), 1.48 (1H, dd, *J* = 8.7 and 5.1 Hz, C*H*H), 2.44 (1H, dd, *J* = 8.7 and 6.2 Hz, C*H*Ph), 7.43-7.21 (10H, m, Aryl H).

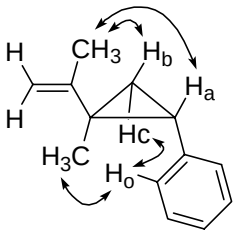
cis-**d**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.49; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (1H, dd, *J* = 8.6 and 5.8 Hz, C*H*H), 1.52 (1H, t, *J* = 5.8 Hz, C*H*H), 1.56 (3H, s, CH_3), 2.24 (1H, dd, *J* = 8.6 and 5.8 Hz, C*H*Ph), 6.74-6.79 (2H, m, Aryl H), 7.00-7.20 (8H, m, Aryl H).

1-Acetoxy-2-phenyl-cyclopropane (e)[7]

cis-**e**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.23; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23-1.37 (2H, m, CH_2), 1.81 (3H, s, CH_3), 2.28 (1H, dt, *J* = 9.2 and 7.0 Hz, C*H*Ph), 4.33 (1H, td, *J* = 7.0 and 4.0 Hz, C*H*OAc), 7.17-7.33 (5H, m, Aryl H).

2-Isopropenyl-2-methyl-1-phenylcyclopropane (f)

trans-**f**; eluent petroleum ether, R_f = 0.50; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.87 (3H, s, CH_3), 0.94 (1H, dd, *J* = 6.3 and 4.9 Hz, CH_2), 1.23 (1H, dd, *J* = 8.9 and 4.9 Hz, CH_2), 1.82 (3H, s, CH_3), 2.16 (1H, dd, *J* = 8.9 and 6.3 Hz, C*H*Ph), 4.78 (1H, m, CH_2=C), 4.85 (1H, m, CH_2=C), 7.18-7.32 (5H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1 (t), 18.5 (q), 20.3 (q), 25.7 (s), 29.2 (d), 109.3 (t), 125.8 (d), 127.9 (2d), 129.1 (2d), 139.4 (s), 150.6 (s); MS m/z (EI) 172 (M^+, 34), 157 (100), 129 (52), 105 (76), 91 (61), 77 (95), 57 (84); HRMS: found 172.1250, $C_{13}H_{16}$ requires 172.1252.



Proton (δ)	NOE observations
H_a(2.16 ppm)	CH_3C=C
H_b(1.23 ppm)	CH_3C=C
H_c(0.94 ppm)	CH_3C, H_o
H_o(7.22 ppm)	CH_3C

cis-**f**; eluent petroleum ether, R_f = 0.50; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (1H, dd, *J* = 8.6 and 5.2 Hz, C*H*H), 1.34 (3H, s, CH_3), 1.33-1.37 (1H, m, C*H*H), 1.53 (3H, s, CH_3), 1.97 (1H, dd, *J* = 8.3 and 5.8 Hz, C*H*Ph), 4.78 (1H, m, CH_2=C), 4.85 (1H, m, CH_2=C), 7.18-7.32 (5H, m, Aryl H).

2-[2-Phenyl-(cyclopropyl)]-1-methoxy-ethene (g)[10]

trans-**g**; eluent petroleum ether/ethyl acetate 95:5, R_f = 0.50; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (1H, dt, *J* = 8.5 and 5.6 Hz, C*H*H), 1.11 (1H, dt, *J* = 8.5 and 5.6 Hz, C*H*H), 1.54 (1H, m, C*H*CH=CH), 1.78 (1H, m, C*H*Ph), 3.50 (3H, s, CH_3O), 4.62 (1H, dd, *J* = 12.5 and 7.3 Hz, CH_3OC*H*=CH), 6.42 (1H, d, *J* = 12.5 Hz, CH_3OCH=C*H*), 7.21-7.29 (5H, m, Aryl H).

cis-**g**; eluent petroleum ether/ethyl acetate 95.5, R_f = 0.50; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (1H, q, *J* = 5.9 Hz, C*H*H), 1.22 (1H, td, *J* = 8.6 and 5.9 Hz, C*H*H), 1.78 (1H, m, C*H*CH=CH), 2.22 (1H, td, *J* = 8.6 and 5.9 Hz, C*H*Ph), 3.30 (3H, s, CH_3O), 4.16 (1H, dd, *J* = 12.8 and 8.3 Hz, CH_3OC*H*=CH), 6.36 (1H, d, *J* = 12.8 Hz, CH_3OCH=C*H*), 7.01-7.29 (5H, m, Aryl H).

2-(2-Phenyl-cyclopropyl) -1,3-isoindoledione (h)

trans-**h**; White solid; eluent petroleum ether/ethyl acetate 9:1, R_f = 0.38; m.p. 80-82°C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.59 (1H, m, C*H*H), 1.63-1.69 (1H, m, C*H*H), 2.55 (1H, ddd, *J* = 9.9, 7.0 and 3.5 Hz, C*H*Ph), 2.84 (1H, ddd, *J* = 7.7, 4.4 an 3.5 Hz, C*H*N), 7.20-7.34 (5H, m, Aryl H), 7.71-7.75 (2H, m, Aryl H), 7.83-7.87 (2H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (t), 23.1 (d), 30.3 (d), 123.3 (2d), 126.6 (d), 127.2 (2d), 128.5 (2d), 131.8 (s), 134.1 (2d), 139.8 (2s), 168.6 (2s); IR ($CHCl_3$) ν_{max}/cm^{-1} 1776, 1718, 1604, 1500, 1398; MS m/z (EI) 263 (M^+, 34), 245 (83), 234 (43), 218 (33),

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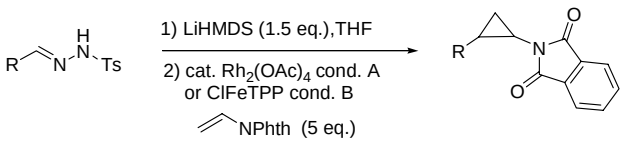
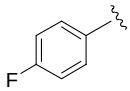
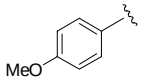
206 (28), 148 (42), 116 (100), 84 (36), 76 (32); HRMS: found 263.0938, $C_{17}H_{13}NO_2$ requires 263.0946. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.48; H, 5.39; N, 5.35.

cis-**h**; White solid; eluent petroleum ether/ethyl acetate 9:1, R_f = 0.32; m.p. 122-124°C (petroleum ether/ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.56-1.65 (1H, m, C*H*H), 2.21 (1H, td, *J* = 8.4 and 4.9 Hz, C*H*H), 2.53 (1H, dt, *J* = 8.4 and 7.3 Hz, C*H*Ph), 3.09 (1H, ddd, *J* = 8.3, 7.3 an 4.9 Hz, C*H*N), 7.15-7.02 (5H, m, Aryl H), 7.59-7.69 (4H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (t), 22.0 (d), 29.0 (d), 123.0 (2d), 126.2 (d), 127.7 (2d), 127.9 (2d), 131.3 (s), 133.8 (2d), 136.0 (2s), 168.8 (2s); IR (thin film) ν_{max}/cm^{-1} 1769, 1712, 1460, 1395, 1137, 931, 864, 706; MS m/z (EI) 263 (M^+, 11), 148 (45), 116 (100), 130 (32), 104 (51), 76 (63); HRMS: found 263.0941, $C_{17}H_{13}NO_2$ requires 263.0946. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 76.91; H, 4.90; N, 5.09.

Table 2. Catalytic cyclopropanation of alkenes via in situ generation of diazo compounds from tosyl hydrazones



R	catalyst	yield (%)[a]	*trans:cis*[b]	cy.
	$Rh_2(OAc)_4$	52	4:96	**h**
	ClFeTPP	71	33:67	
	$Rh_2(OAc)_4$	49	3:97	**i**
	ClFeTPP	53	32:68	
	$Rh_2(OAc)_4$	14	3:97	**j**
	ClFeTPP	51	25:75	

Conditions A = 1,4-dioxane, 10 mol% PTC, 30ºC.
B = toluene, 5 mol% PTC, 40ºC.

Representative procedure for the catalytic cyclopropanation of alkenes via in situ generation of diazo compounds from tosyl hydrazones (table 2).

To a solution of benzaldehyde tosyl hydrazone (206 mg, 0.75 mmol) in dry THF (3 mL) at -78°C was added under nitrogen a solution 1M of LiHMDS in THF (750 µl). After stirring at -78°C for 15 min the mixture was warmed up to room temperature and the solvent was evaporated under reduced pressure. To the formed salt was added benzyltriethylammonium chloride (8 mg, 0.037 mmol), ClFeTPP (5 mg, 0.007 mmol), *N*-vinylphthalimide (650 mg, 3.75 mmol) and dry toluene (4 mL). The mixture was vigorously stirred for 2 days at 40°C. Water (7 mL) was added to the mixture, which was then washed with CH_2Cl_2 (2×20 mL) and dried over Na_2SO_4. Evaporation gave a residue, which was purified by flash chromatography (eluent petroleum ether/ethyl acetate 10:1) to afford 46 mg (23%) of *trans*-**h** and 93 mg (48%) of *cis*-**h**.

2-[2-(4-Fluoro-phenyl)-cyclopropyl]-1,3-isoindoledione (i)

trans-**i**; White solid; eluent petroleum ether/ethyl acetate 10:1, R_f = 0.26; m.p. 97-98°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (1H, q, *J* = 7.0 Hz, C*H*H), 1.65 (1H, ddd, *J* = 10.2, 7.0 and 4.1 Hz, C*H*H), 2.49 (1H, ddd, *J* = 10.2, 7.0 and 4.1 Hz, C*H*Ph), 2.75 (1H, dt, *J* = 7.0 and 4.1 Hz, C*H*N), 7.01 (1H, t, *J* = 8.4 Hz, 2H, Aryl H), 7.32 (2H, dd, *J* = 8.4 and 5.5 Hz, Aryl H), 7.73 (m, 2H, Aryl H), 7.85 (m, 2H, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (t), 22.5 (d), 29.9 (d), 115.3 (2d), 123.2 (2d), 128.8 (2d), 131.7 (2s), 134.1 (2d), 135.3 (s), 161.7 (s, $J_{C\text{-}F}$ = 245.2 Hz), 168.6 (2s); IR (thin film) ν_{max}/cm^{-1} 3043, 1774, 1717, 1513, 1399, 1144, 839, 717; MS m/z (EI) 281 (M^+, 38), 263 (75), 148 (87), 134 (100), 104 (44), 76 (62); HRMS: found 281.0846, $C_{17}H_{12}NO_2F$ requires 281.0852. Anal. Calcd for $C_{17}H_{12}NO_2F$: C, 72.59; H, 4.30; N, 4.98. Found: C, 72.05; H, 4.32; N, 5.00.

cis-**i**; White solid; eluent petroleum ether/ethyl acetate 10:1, R_f = 0.21; m.p. 136-138°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (1H, q, *J* = 7.7 Hz, C*H*H), 2.19 (1H, ddd, *J* = 7.7, 7.3 and 4.9 Hz, C*H*H), 2.51 (1H, q, *J* = 7.3 Hz, C*H*Ph), 3.08 (1H, td, *J* = 7.7 an 4.9 Hz, C*H*N), 6.81 (2H, t, *J* = 8.8 Hz, Aryl H), 7.06 (2H, dd, *J* = 8.8 and 5.1 Hz, Aryl H), 7.62-7.71 (4H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (t), 21.3 (d), 28.8 (d), 114.8 (2d), 123.0 (2d), 129.3 (2d), 131.5 (2s), 131.6 (s), 134.0 (2d), 161.4 (s, $J_{C\text{-}F}$ = 244.5 Hz), 168.8 (2s); IR (thin film) ν_{max}/cm^{-1} 3024, 1774, 1705, 1509, 1397, 976, 923, 716; MS m/z (EI) 281 (M^+, 43), 263 (86), 148 (93), 134 (100), 104 (46), 76 (67); HRMS: found 281.0849, $C_{17}H_{12}NO_2F$ requires 281.0852.

2-[2-(4-Methoxy-phenyl)-cyclopropyl]-1,3-isoindoledione (j)

trans-**j**; White solid; eluent petroleum ether/ethyl acetate 3:1, R_f = 0.43; m.p. 99-101°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (1H, q, *J* = 6.8 Hz, C*H*H), 1.60 (1H, m, C*H*H), 2.48 (1H, ddd, *J* = 9.8, 6.8 and 3.4 Hz, C*H*Ph), 2.74 (1H, ddd, *J* = 6.8, 3.9 an 3.4 Hz, C*H*N), 3.80 (3H, s, OCH_3), 6.87 (2H, m, Aryl H), 7.29 (2H, m, Aryl H), 7.72 (m, 2H, Aryl H), 7.85 (m, 2H, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2 (t), 22.5 (d), 29.9 (d), 55.4 (q), 114.0 (2d), 123.3 (2d), 128.5 (2d), 131.8 (s), 131.9 (2s), 134.1 (2d), 158.4 (s), 168.7 (2s); IR (thin film) ν_{max}/cm^{-1} 2964, 1773, 1717, 1515, 1398, 1248, 1144, 1030, 719; MS m/z (EI) 293 (M^+, 87), 260 (23), 146 (100), 76 (24); HRMS: found

293.1045, $C_{18}H_{15}NO_3$ requires 293.1051. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.53; H, 5.25; N, 4.77.

cis-**j**; White solid; eluent petroleum ether/ethyl acetate 3:1, R_f = 0.36; m.p. 106-108°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (1H, q, *J* = 7.5 Hz, C*H*H), 2.16 (1H, td, *J* = 9.3 and 7.5 Hz, C*H*H), 2.48 (1H, dt, *J* = 9.3 and 7.5 Hz, C*H*Ph), 3.04 (1H, td, *J* = 7.5 an 4.9 Hz, C*H*N), 3.66 (3H, s, OCH_3), 6.66 (2H, t, *J* = 8.8 Hz, Aryl H), 7.02 (2H, d, *J* = 8.8 Hz, Aryl H), 7.62 (2H, m, Aryl H), 7.68 (2H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9 (t), 21.3 (d), 28.8 (d), 55.2 (q), 113.5 (2d), 123.3 (2d), 127.9 (s), 129.0 (2d), 131.5 (2s), 133.9 (2d), 158.1 (s), 169.0 (2s); IR (thin film) ν_{max}/cm^{-1} 1772, 1713, 1515, 1396, 1250, 1035, 718; MS m/z (EI) 293 (M^+, 70), 146 (100), 84 (18), 76 (26); HRMS: found 293.1048, $C_{18}H_{15}NO_3$ requires 293.1051. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.75; H, 5.20; N, 4.80.

***cis*-2-Phenyl-cyclopropylamine**[11]

A solution of hydrazine monohydrated (16 µl, 0.32 mmol) in ethanol (2 mL) was added to a suspension of *cis*-**h** in ethanol (1 mL). After stirring for 10 h at 40°C a solution 1N HCl (0.1 mL) was added and the mixture was stirred for further 3h at the same temperature. After the mixture was cooled the precipitated was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in 1N HCl (2 mL) and the aqueous solution was washed with ether (2×6 mL). 2N NaOH was added to the aqueous layer until alkaline pH and then extracted with CH_2Cl_2 (2×6 mL). The organic layer was dried over Na_2SO_4, and evaporated under vacuum to afford 32 mg (79%) of a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.69-0.75 (1H, m, C*H*H), 0.85-1.18 (3H, m, NH_2 and C*H*H), 1.98 (1H, td, *J* = 8.2 and 6.9 Hz, C*H*Ph), 2.54 (1H, td, *J* = 8.2 and 4.2 Hz, C*H*N), 7.09-7.29 (5H, m, Aryl H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.4 (t), 23.3 (d), 30.8 (d), 125.9 (d), 128.1 (2d), 129.1 (2d), 137.8 (s).

Synthesis of the HIV-1 reverse transcriptase inhibitor 6

4-Chloro-1-ethoxy-2-fluoro-benzene (1)

4-Chloro-2-fluorophenol (7.315 g, 49.91 mmol), ethyl iodide (7.984 mL, 51.18), K_2CO_3 (13.797 g, 99.82 mmol) in dry acetone (100 mL) were stirred under nitrogen at 55°C overnight. The evaporation gave 8.68 g (100%) of 4-chloro-1-ethoxy-2-fluoro-benzene as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, t, *J* = 7.0 Hz, CH_3), 4.07 (2H, q, *J* = 7.0 Hz, CH_2), 6.86 (1H, t, *J* = 8.8 Hz, Aryl H), 7.01 (1H, m, Aryl H), 7.09 (1H, dd, *J* = 11.0 and 2.6 Hz, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (q), 65.3 (t), 115.5 (d), 116.9 (d, $J_{C\text{-}F}$ = 27.2 Hz), 124.2 (d), 125.2 (s), 145.9 (s), 152.5 (s, $J_{C\text{-}F}$ = 247.7 Hz); IR ν_{max}/cm^{-1} (thin film) 3079, 2985, 2933, 1583, 1477, 1305, 1208, 1132, 1043, 886, 779, 657; MS m/z (EI) 174 (M^+, 71), 146 (62), 84 (100); HRMS: found 174.0246, $C_8H_8O_2FCl$ requires 174.0247. Anal. Calcd for C_8H_8OFCl: C, 55.03; H, 4.62. Found: C, 54.52; H, 4.60.

6-Chloro-3-ethoxy-2-fluoro-benzaldehyde (2)

n-BuLi (1.6M in *n*-hexanes, 33.4 mL, 53.44 mmol) was added under nitrogen to a solution of **1** (8.48 g, 48.56 mmol) in dry THF cooled at -65°C. After stirring for 45 min at -65°C, DMF (4.137 mL, 53.44 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was poured onto ice and extracted with diethyl ether (100 mL). The organic layer was washed with 0.01N HCl (60 mL), H_2O (50 mL), and brine (50 mL), dried over $MgSO_4$ and evaporated. Crystallization from *n*-hexane gave 8.46 g (87%) of the aldehyde **2** as a yellow solid, m.p. 58-60°C (*n*-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 6.9 Hz, CH_3), 4.12 (2H, q, *J* = 6.9 Hz, OCH_2CH$_3$), 7.10 (1H, t, *J* = 8.6 Hz, Aryl H), 7.17 (1H, dd, *J* = 8.6 and 1.5 Hz, Aryl H), 10.43 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (q), 65.8 (t), 119.7 (d), 121.9 (s), 125.9 (d), 126.3 (s), 146.6 (s), 153.5 (s, $J_{C\text{-}F}$ = 266.0 Hz), 187.2 (d); IR ν_{max}/cm^{-1} (thin film) 2500, 2159, 1693, 1470, 1267, 1005, 908, 874, 818; MS m/z (CI with CH_4) 203 ([(M+H)]$^+$, 100); HRMS: found [(M+H)]$^+$ 203.0275, $C_9H_9O_2FCl$ requires 203.0269. Anal. Calcd for $C_9H_8O_2FCl$: C, 53.35; H, 3.98. Found: C, 53.58; H, 4.23.

6-Chloro-3-ethoxy-2-fluoro-benzaldehyde tosyl hydrazone (3)

A solution of **2** (4.222 g, 20.90 mmol) in methanol (15 mL) was added dropwise to a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (4.095 g, 21.94 mmol) in methanol (35 mL) at room temperature. After 1.5 h of continuous stirring the solvent was remover under reduced pressure and the solid was crystallised from methanol to give 5.567 g (72%) of the hydrazone **3** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, *J* = 7.0 Hz, OCH$_2$CH_3), 2.33 (3H, s, CH_3C$_6$H$_4$), 4.05 (2H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 7.14 (1H, t, *J* = 8.8 Hz, Aryl H), 7.20 (1H, dd, *J* = 8.8 and 1.1 Hz, Aryl H), 7.38 (2H, d, *J* = 8.4 Hz, Ts), 7.71 (2H, d, *J* = 8.4 Hz, Ts), 8.00 (1H, s, C*H*N), 11.77 (1H, br. s, N*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4 (q), 21.0 (q), 64.8 (t), 116.1 (d), 120.2 (s), 123.4 (s), 125.3 (d), 127.2 (2d), 129.6 (2d), 136.0 (s), 139.8 (d), 143.6 (s), 146.0 (s), 149.7 (s, $J_{C\text{-}F}$ = 257.5 Hz); IR ν_{max}/cm^{-1} (thin film) 3152, 1598, 1572, 1472, 1310, 1156, 932, 802, 703, 661; MS m/z (CI with CH_4) 371 ([(M+H)]$^+$, 44), 343 (40), 203 (76), 157 (46), 139 (64), 93 (56); HRMS: found [(M+H)]$^+$ 371.0635, $C_{19}H_{17}N_2O_3SClF$ requires 371.0632. Anal. Calcd for $C_{19}H_{16}N_2O_3SClF$: C, 51.82; H, 4.35; N, 7.55. Found: C, 51.94; H, 4.36; N, 7.61.

2-[2-(6-Chloro-3-ethoxy-2-fluoro-phenyl)-cyclopropyl]-1,3-isoindoledione (4)

To a solution of **3** (556 mg, 1.502 mmol) in dry THF (8 mL) at -78°C was added under nitrogen a solution 1M of LiHMDS in THF (1.5 mL). After stirring at -78°C for 15 min the mixture was warmed up to room temperature. The solvent was evaporated under reduced pressure and benzyltriethylammonium chloride (34 mg, 0.150 mmol),

[11] Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* **1977**, *20*, 771.

rhodium acetate (7 mg, 0.015 mmol), *N*-vinylphthalimide (1.300 g, 7.51 mmol) and 1,4-dioxane (8 mL) were added. The resulting mixture was vigorously stirred for 2 days at room temperature. Water (7 mL) was added to the mixture, which was then washed with CH_2Cl_2 (2×25 mL) and dried over Na_2SO_4. Evaporation gave a residue, which was purified by flash chromatography (eluent petroleum ether/ethyl acetate 10:1) to afford 61 mg (11%) of *trans*-**4** and 348 mg (65%) of *cis*-**4**.

trans-**4**; White solid; eluent petroleum ether/ethyl acetate 10:1, R_f = 0.35; m.p. 97-98°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, t, *J* = 6.8 Hz, C*H*$_3$), 1.64 (1H, q, *J* = 7.6 Hz, C*H*H), 1.89 (1H, m, C*H*H), 2.83 (1H, ddd, *J* = 10.7, 7.6 and 4.6 Hz, C*H*Ar), 3.58 (1H, dt, *J* = 7.6 and 4.6 Hz, C*H*N), 4.07 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 6.77 (1H, t, *J* = 8.8 Hz, Aryl H), 7.09 (1H, dd, *J* = 8.8 and 2.0 Hz, Aryl H), 7.72 (2H, m, Aryl H) , 7.84 (2H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (t), 14.8 (q), 16.9 (d), 30.1 (d), 65.2 (t), 113.0 (d), 123.3 (2d), 124.4 (d), 125.9 (s), 127.1 (s), 131.8 (2s), 134.0 (2d), 146.3 (s), 151.9 (s, J_{C-F} = 249.0 Hz), 168.3 (2s); IR (thin film) ν_{max}/cm^{-1} 2985, 1775, 1720, 1469, 1394, 883, 797, 718; MS m/z (EI) 359 (M$^+$, 40), 339 (40), 324 (88), 310 (46), 296 (52), 276 (30), 177 (62), 172 (48), 130 (34), 104 (94), 76 (100); HRMS: found 359.0735, $C_{19}H_{15}NO_3ClF$ requires 359.0724. Anal. Calcd for $C_{19}H_{15}NO_3ClF$: C, 63.43; H, 420; N, 3.89. Found: C, 63.44; H, 4.17; N, 3.91.

cis-**4**; White solid; eluent petroleum ether/ethyl acetate 10:1, R_f = 0.27; m.p. 123-125°C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* = 6.8 Hz, C*H*$_3$), 1.58 (1H, m, C*H*H), 2.49 (1H, dt, *J* = 9.3 and 7.3 Hz, C*H*H), 2.98 (1H, td, *J* = 7.3 and 5.4 Hz, C*H*Ar), 3.56 (1H, m, C*H*N), 3.86 (2H, q, *J* = 6.8 Hz, OC*H*$_2$CH$_3$), 6.66 (1H, t, *J* = 8.3 Hz, Aryl H), 7.06 (1H, dd, *J* = 8.8 and 2.0 Hz, Aryl H), 7.61-7.73 (4H, m, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9 (t), 14.6 (q), 17.1 (d), 29.0 (d), 65.4 (t), 113.9 (d), 123.0 (2d), 124.3 (d), 128.2 (s), 131.6 (3s), 133.8 (2d), 146.0 (s), 152.6 (s, J_{C-F} = 249.1 Hz), 168.4 (2s); IR (thin film) ν_{max}/cm^{-1} 2983, 1775, 1717, 1468, 1392, 1207, 884, 797, 720; MS m/z (EI) 359 (M$^+$, 46), 339 (56), 324 (100), 310 (60), 296 (62), 276 (36), 177 (68), 172 (56), 149 (98), 130 (44), 104 (90), 76 (97); HRMS: found 359.0735, $C_{19}H_{15}NO_3ClF$ requires 359.0724. Anal. Calcd for $C_{19}H_{15}NO_3ClF$: C, 63.43; H, 420; N, 3.89. Found: C, 63.04; H, 4.06; N, 4.00.

***cis*-2-(6-Chloro-3-ethoxy-2-fluoro-phenyl)-cyclopropylamine (5)**

To a suspension of *cis*-**4** (170 mg, 0.47 mmol) in ethanol (2 mL) was added hydrazine monohydrated (115 μl, 2.36 mmol). After 5 min of stirring at 40°C the solid was dissolved and the solution was stirred for further 55 min. After the mixture was cooled the precipitated was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in 1N HCl (5 mL). The aqueous solution was washed with ether (2×15 mL). The aqueous layer was treated with 2N NaOH until alkaline pH and then extracted with DCM (2×15 mL). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to afford 85 mg (78%) of the amine **5** as a colorless oil.[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92-0.97 (1H, m, C*H*H), 1.30 (1H, ddd, *J* = 9.3, 7.1 and 6.3 Hz, C*H*H), 1.34 (2H, br. s, N*H*$_2$) 1.45 (3H, t, *J* = 6.9 Hz, C*H*$_3$), 1.72 (1H, dt, *J* = 9.3 and 7.1 Hz, C*H*Ar), 2.76-2.82 (1H, m, C*H*H), 4.02-4.09 (2H, m, OC*H*$_2$CH$_3$), 6.76 (1H, t, *J* = 9.0 Hz, Aryl H), 7.08 (1H, dd, *J* = 9.0 and 2.2 Hz, Aryl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (t), 14.7 (q), 17.2 (d), 29.5 (d), 64.9 (t), 112.7 (d), 124.0 (d), 125.1 (s), 128.2 (s), 146.3 (s), 153.3 (s, J_{C-F} = 247.5 Hz).

2-Amino-5-cyanopyridine[13]

A solution of 2-amino-5-bromopyridine (1.500 g, 8.67 mmol) and CuCN (1.164 g, 13.00 mmol) in dry DMF (17 mL) was stirred at reflux for 48 h. The solvent was removed reduced pressure vacuum and the remaining oil was treated with a 25% concentrated ammonia solution in a saturated NH_4Cl solution (70 mL). The mixture was stirred for 1h and then extracted with EtOAc (4×50 mL). The organic layer was dried over Na_2SO_4, evaporated, purified by flash chromatography (eluent petroleum ether/ethyl acetate 1:1) and then crystallized from EtOAc to give 720 mg (70%) of 2-amino-5-cyanopyridine as pale yellow needles; eluent petroleum ether/ethyl acetate 1:1, R_f = 0.28; m.p. 154-156°C (ethyl acetate) (lit.,[14] 158-160°C, *n*-hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (2H, br. s, N*H*$_2$), 6.50 (1H, dd, *J* = 8.8 and 0.8 Hz, *H*-3), 7.61 (1H, dd, *J* = 8.8 and 2.2 Hz, *H*-4), 8.36 (1H, m, *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.5 (s), 107.9 (d), 118.1 (s), 140.2 (d), 153.1 (d), 160.1 (s); IR (thin film) ν_{max}/cm^{-1} 3410, 3141, 2210, 1652, 1599, 1508, 1407, 1289, 830, 757; MS m/z (EI) 119 (M$^+$, 100), 92 (86), 88 (36), 73 (34), 70 (50), 61 (88). Anal. Calcd for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.37; H, 3.82; N, 34.90.

***N*-[cis-2-(6-Chloro-3-ethoxy-2-fluorophenyl) cyclopropyl]-*N'*-[2-(5-cyanopyridyl)]urea (6)[15]**

To a solution of triphosgene (43 mg, 0.144 mmol) in dry THF (2mL) at -78°C was added under nitrogen *via* cannula a solution of 2-amino-5-cyanopyridine (51 mg, 0.428 mmol) and dry triethylamine (120 μl, 0.862 mmol) in THF (2 mL) over a period of 8 min with continuous stirring. After addition the mixture was left stirring for 10 min at -78°C and then allowed to reach room temperature within 20 min (the initial pale yellow solution became red). To the mixture was added slowly *via* cannula a solution of **5** (66 mg, 0.287 mmol) and dry

[12] The amine **5** was shown to be unstable and therefore the product was used in the following step without further purification.

[13] Sundberg, R. J.; Biswas, S.; Murthi, K. K.; Rowe, D. *J. Med. Chem.* **1998**, *41*, 4317.

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[15] Högberg, M.; Sahlberg, C.; Engelhardt, P.; Noréen, R.; Kangasmetsä, J.; Johansson, N. G.; Öberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B-L.; Unge, T.; Lövgren, S.; Fridborg, K.; Bäckbro, K. *J. Med. Chem.* **1999**, *42*, 4150-4160.

triethylamine (60 μl, 0.431 mmol) in THF (2 mL) over a period of 8 min. After addition the mixture was left stirring at room temperature for 2h. Then diethyl ether was added to the mixture, which was washed with 0.01N HCl, dried over Na_2SO_4 and evaporated. The crude material was purified by column chromatography (silica gel, EtOAc) and then crystallized from EtOAc to give 61 mg (56%) of a pale yellow solid; eluent ethyl acetate, R_f = 0.50; m.p. 214-216°C (ethyl acetate) (lit.,[15] 211-212°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-1.34 (1H, m, C*H*H), 1.47 (3H, t, *J* = 6.9 Hz, CH_3), 1.64 (1H, dt, *J* = 9.3 and 6.9 Hz, C*H*H), 2.11 (1H, q, *J* = 7.3 Hz, C*H*Ar), 3.31 (1H, m, C*H*N), 4.07 (2H, m, OCH_2CH$_3$), 6.84 (1H, t, *J* = 8.8 Hz, Aryl H), 6.92 (1H, m, Aryl H), 7.15 (1H, dd, *J* = 8.6 and 1.5 Hz, Aryl H), 7.71 (1H, dd, *J* = 8.6 and 2.2 Hz, Aryl H), 8.16 (1H, m, Aryl H), 9.32 (1H, br. s, N*H*), 9.65 (1H, br. s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (t), 14.9 (q), 15.6 (d), 28.0 (d), 65.0 (t), 101.6 (s), 112.0 (d), 113.1 (d), 117.2 (s), 124.3 (d), 128.0 (s), 140.2 (d), 146.5 (s), 150.3 (d), 152.7 (s, $J_{C\text{-}F}$ = 249.0 Hz), 155.1 (s), 155.2 (s), 156.3 (s); IR (thin film) ν_{max}/cm^{-1} 3200, 3107, 2978, 2223, 1698, 1547, 1465, 1387, 1300, 850, 798, 752, 707, 659; MS m/z (CI with CH_4) 375 ([(M+H)]$^+$, 38), 194 (62), 146 (100), 120 (52); HRMS: found [(M+H)]$^+$ 375.1025, $C_{18}H_{17}N_4O_2ClF$ requires 375.1024. Anal. Calcd for $C_{18}H_{16}N_4O_2ClF$: C, 57.68; H, 4.30; N, 14.95. Found: C, 57.89; H, 4.27; N, 14.77.