Pergamon

Tetrahedron 55 (1999) 13285–13300

TETRAHEDRON

Synthesis of *Meta*-Substituted Aniline Derivatives by Nucleophilic Substitution

Andrew J Belfield, George R Brown,* Alan J Foubister and Paul D Ratcliffe

AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG

Received 19 July 1999; revised 19 August 1999; accepted 9 September 1999

Abstract: Substitution by amines of fluorobenzenes containing a *meta*-substituted electron withdrawing group (EWG), in DMSO at 100 °C over 60 h gave *meta*-substituted aniline derivatives in isolated yields of up to 98%. The scope of the reaction is explored in terms of reaction conditions and substrates. It is postulated that facile *meta*-substitutions are facilitated through field stabilisation of the intermediate anion by EWG substituents.

Keywords : Amination, Aryl halides, Substituent effects

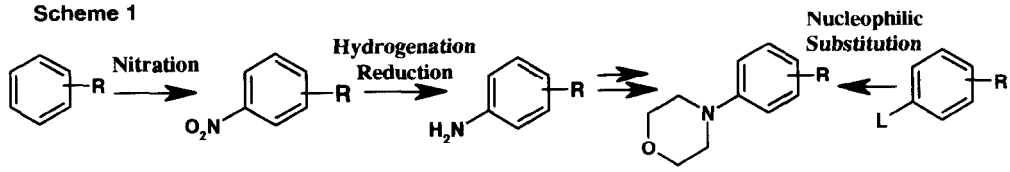
Introduction

Anilines are very important synthetic intermediates and are used widely in the preparation of pharmaceuticals, dyes, pesticides and heterocyclic compounds. It is therefore important that methods exist for the efficient synthesis of novel anilines on laboratory to manufacturing scales, and that new methods are developed for the synthesis of less accessible derivatives. Historically,[1] aniline synthesis was carried out mainly by electrophilic aromatic substitution in two steps (Scheme 1): nitration or nitrosation, followed by catalytic hydrogenation or reduction with a metal salt. These procedures have found large scale use, but have some limitations, such as the use of strong acidic or oxidizing reaction conditions, and *ortho/para* mixtures may be obtained. Aromatic nucleophilic substitution[2] has the potential advantage of being a single reaction step, but until recently was restricted[2] in synthetic use to substrates containing an electron withdrawing group (EWG), and also in most cases to *ortho/para* substitution patterns, with *meta*-substitution giving poor synthetic yields. In recent years however, the nucleophilic substitution approach has been much developed by the discovery[3, 4, 5] of metal-catalyzed carbon-nitrogen bond forming reactions, which do not require the presence of EWGs, and the continued development of the existing S_NAr substitution process. This paper describes the synthesis of *meta*-substituted anilines in high yields under modified S_NAr reaction conditions, and compares these yields with the known palladium catalyzed methods. This work has appeared[6] in part as a preliminary communication.

We required an efficient synthesis of the morpholine-substituted benzoic acids **1a-c**, which preferably

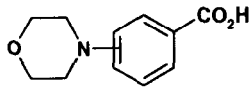
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00818-2

Scheme 1



R = variety of groups; L = leaving group

could be operated cost effectively on larger scales, and did not require palladium catalysts or the presence of phosphine ligands. In this situation there is an even greater advantage in employing nucleophilic substitution



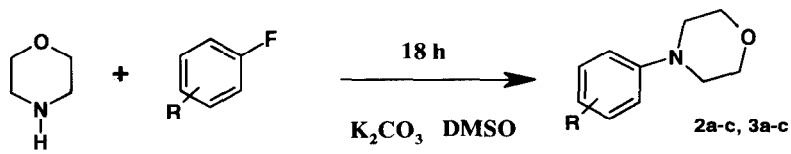
1a, 2-substituted
1b, 3-substituted
1c, 4-substituted

with morpholine, rather than electrophilic substitution, because with electrophilic substitution the amine substituent obtained after the reduction step requires elaboration to the morpholine ring system, which is known[7] to be a lengthy process involving several synthetic steps. The morpholine-substituted acids **1a-c** were conveniently sought *via* the synthesis of their corresponding esters **2a-c** and nitriles **3a-c** (Table 1).

Results and Discussion

Reaction of morpholine (Table1) with ethyl fluorobenzoates or benzonitriles at 100 °C in DMSO solvent for 18 h and with anhydrous K_2CO_3 present, gave adequate yields of the *ortho*- and *para*-substituted derivatives **2a**, **2c**, **3a**, and **3c**, but in line with expectations[1] it failed to afford any *meta*-substituted **2b**, and gave only a poor 14% yield of **3b**. Two approaches were followed in order to seek a more efficient *meta*-substitution: palladium catalysed C-N bond formation was briefly examined, and secondly despite the poor precedent,[1] nucleophilic substitution in the *meta*-position to an EWG was explored. These two approaches were subsequently compared.

Table 1 Nucleophilic substitution reactions at 100 °C in the presence of K_2CO_3.



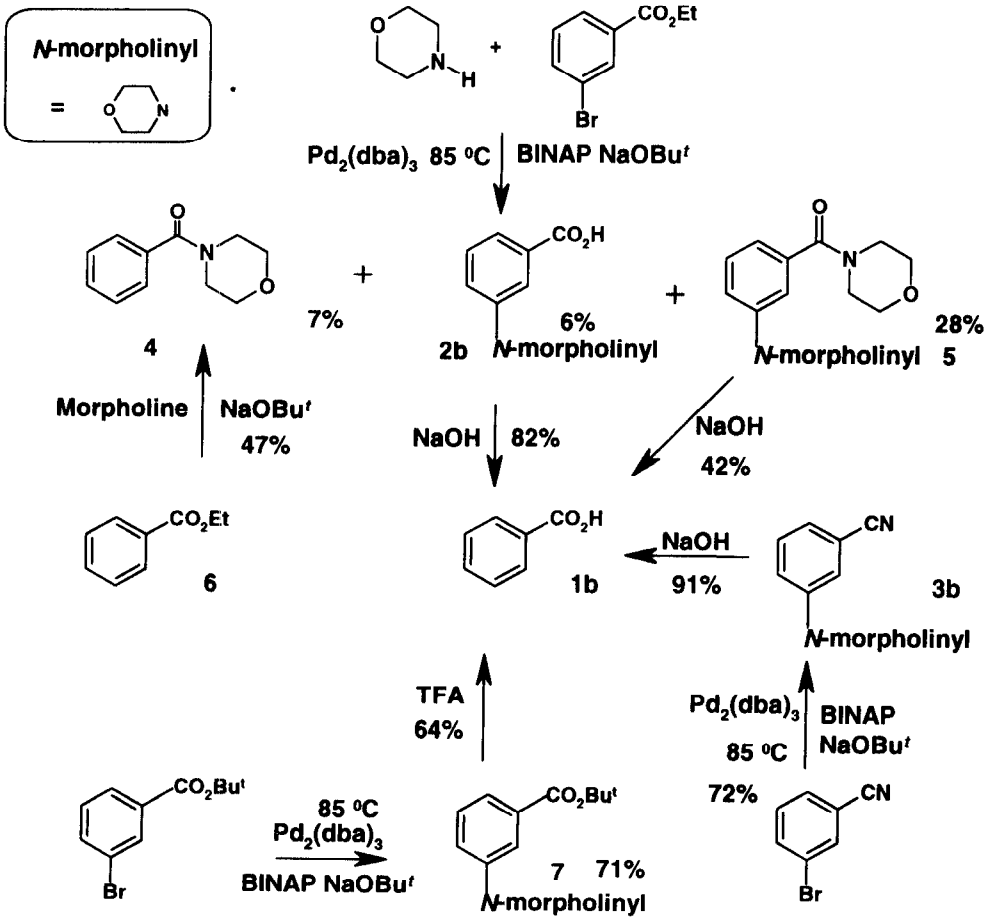
2a-c, 3a-c

Substituent	R = CO_2Et	Yield %	R = CN	Yield %
2-F	**2a**	28	**3a**	82
3-F	**2b**	0	**3b**	14
4-F	**2c**	47	**3c**	94

Palladium catalyzed substitution

The palladium catalyzed reaction (Scheme 2) was employed using the optimal reported[8] reaction conditions: with bromide as the leaving group, NaOBu^t as the base, tris(dibenzylideneacetone) dipalladium(0) as the catalyst, and BINAP as the ligand. *N*-benzoylmorpholine **4** and the desired product **2b** were obtained in very poor yield, but the major product was the morpholinobenzamide **5**. Both the amide **5** and the morpholine **2b** were hydrolysed with 5M NaOH to give good yields of **1b**.

Scheme 2



To ascertain which reagent had led to the formation of the unwanted morpholinoamide **5**, morpholine was allowed to react with ethyl benzoate **6** (Scheme 2) at 85 °C in toluene for 18 h. In the presence of morpholine alone, none of the ethyl benzoate was converted to the morpholinobenzamide **4**. When NaOBu^t was added however, a 47% yield of **4** was obtained, which increased to only 56% in a reaction containing the

palladium catalyst as well. On the basis of these experiments, amide formation was attributed to the presence of butoxide ion. When the weaker and more soluble base caesium carbonate was used in place of NaOBu^t in a reaction with ethyl 3-bromobenzoate under the same palladium catalyzed reaction conditions[8] as above, an improved 38% yield of **2b** was obtained, without amide formation occurring.

Morpholine amide formation was more successfully avoided under palladium catalysis[8] with NaOBu^t, by using the corresponding *t*-butyl ester or by use of the analogous nitrile. Thus *t*-butyl 3-bromobenzoate gave the morpholine derivative **7**, (71%), which hydrolysed in TFA to **1b** (64%). Secondly, reaction with 3-bromobenzonitrile afforded **3b** (72%), which hydrolysed readily with NaOH in *n*-BuOH to give **1b** (91%).

Substitutions without palladium catalysis

These modified palladium catalyzed reactions described above gave the *meta*-substituted products in good yields, and the amide formation issue had been successfully addressed. Nevertheless, the nucleophilic substitution reactions were re-examined to discover if reaction conditions could be found for larger scale experiments, that did not involve palladium reagents or BINAP. Some support for attempting this approach came from the observation that the stronger electron withdrawing CN-group gave a 14% yield of **3b** (Table 1) in replacement reactions with morpholine, and an early report[9] of a mechanistic study, which showed that *meta*-nucleophilic substitutions could proceed when there were two strong EWGs *meta*-disposed to the leaving group.

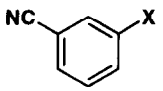
Exploration of the reaction conditions for *meta*-substitution was first restricted to the synthesis of **3b**, using 3-fluorobenzonitrile and morpholine as substrates, in K_2CO_3/DMSO at 100 ^{0}C during 18 h. Extending the reaction time from 18 to 60 h increased the yield of **3b**, to 29%, and in an attempt to obtain a further yield improvement, homogeneous reaction conditions were explored with the K_2CO_3 replaced as base by an equivalent amount of morpholine (*ie.* a total of 5.5 equivalents); here the yield of **3b** was increased to 62%. The structure of this material was carefully considered, because of the unexpectedly high yield; was it correct, and were other regioisomers present? The ^{1}H-NMR spectroscopic data for **3b** indicated that only the *meta*-product had been formed, and this was supported by TLC comparisons with authentic samples of **3a** and **3c**. Examination of the proton splitting patterns and chemical shifts obtained from the *ortho*-, and *para*-morpholinobenzonitriles **3a, 3c**, also showed there were no signals in the **3b** 60h/DMSO reaction product spectrum consistent with the presence of *ortho*- or *para*-substitution. The ^{13}C-NMR spectrum of **3b** confirmed that it was *meta*-substituted with no *ortho* or *para* products present, and the spectra were consistent with carbon chemical shift predictions.[10]

Neither increasing the reaction time to 90 h (58%), increasing the reaction temperature to 130 °C (60%), changing the solvent to dimethylacetamide (18%), NMP (17%) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, 51%), employing DABCO catalysis (55%), nor increasing the amount of morpholine to an excess of 15 equivalents (46%), could significantly increase the 62% yield of **3b**. These experiments indicated that the substitution conditions employing a 5.5 equivalent excess of morpholine in DMSO for 60 h

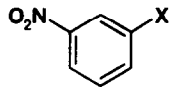
were optimum, and they gave reproducible yields of **3b** even on a 150 g scale. These reaction conditions were used in all of the investigations concerning: the leaving group, substrate and nucleophile variation.

Leaving group variation

Halogen, nitro and triflate leaving groups were examined in compounds **8-12** with morpholine as the nucleophile, and reaction did not proceed except for the triflate **10**, (48%) indicating that with a single EWG



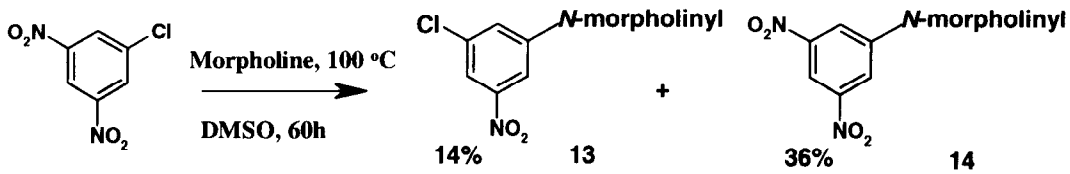
8, X = Cl
9, X = Br



10, X = OTf
11, X = NO_2
12, X = Cl

substituent, fluoride and triflate were the only viable leaving groups. It was anticipated that a second *meta*-substituted EWG would give sufficient electron withdrawal for amination to proceed with the poorer leaving groups, and this was the case (Scheme 3). 3,5-Dinitrochlorobenzene afforded a mixture with two isolable

Scheme 3

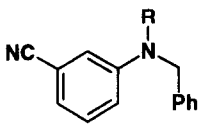


products: **13**, (14%) resulting from replacement of a nitro substituent, and **14** (36%) the major product resulting from chloride substitution. In addition 4% of starting halide was recovered, with the remainder being decomposed material.

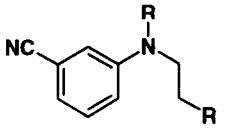
Nature of the amine nucleophile

Good yields were obtained when 3-fluorobenzonitrile was allowed to react with cyclic secondary amines: morpholine (62%, **3b**), piperidine (68%, **15**), *N*-methylpiperazine (69%, **16**), and pyrrolidine (64%, sealed tube **17**), but with the benzylamine **18a** a poor 22% yield was obtained and its more hindered homologue failed to afford **18b**. No reaction was observed with 3-fluorobenzonitrile and cyclohexylamine or *t*-butylamine indicating that branching on the α-carbon of the alkylamine caused a steric effect, but *n*-butylamine afforded a low 10% yield of **19a**. Higher isolated yields were obtained when the amine component contained a hetero-substituent, as in **19b-20c** (31-58%).

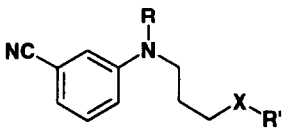
Reaction of 3-fluorobenzonitrile with 2 equivalents of piperazine (Scheme 4) gave the *N*-mono-substituted product **21** in 57% yield, with none of the disubstituted **22**. With 5.5 equivalents of piperazine this



18a R = Me, **22%**
18b R = Et, **0%**



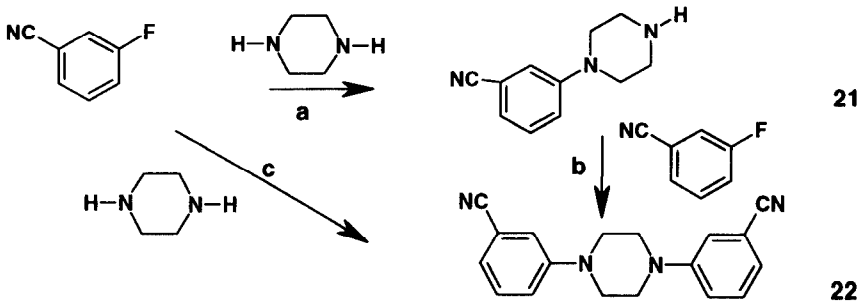
19a R = H, R' = Et **10%**
19b R = Me, R' = CH_2NMe_2 **58%**
19c R = H, R' = NMe2 **34%**
19d R = H, R' = CH_2NMe_2 **36%**
19e R = H, R' = $(CH_2)_2NMe_2$ **39%**



20a X = O, R = H, R' = Me **42%**
20b X = O, R = H, R' = ^nBu **38%**
20c X = S, R = H, R' = Me **31%**

yield increased to 68%, with still none (by TLC/isolation) of **22** being present in the reaction product. Attempts to prepare **22** directly from piperazine and 2 equivalents of 3-fluorobenzonitrile in the presence of 3 equivalents of K_2CO_3 afforded mixtures containing only traces of **22**, but a 17% yield was obtained when equimolar amounts of 3-fluorobenzonitrile and **21**, were allowed to react with 3 equivalents of K_2CO_3.

Scheme 4

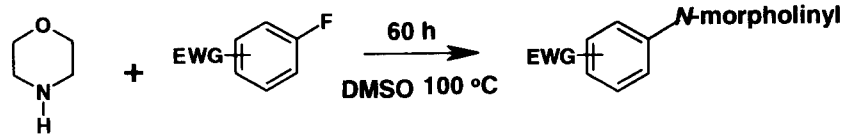


Yields : a = 57 and 68%; b = 17%; c = 0%

Fluoro-substituted substrates

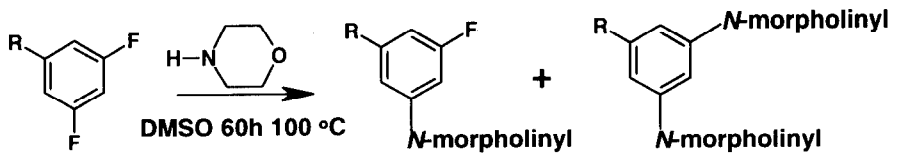
The extent to which fluorobenzenes (Table 2) reacted with morpholine in DMSO at 100 °C depended principally on the ring EWG, as yields of over 70% were obtained with substituents having Hammett *σ-meta* substituent values[11] >0.7, whereas values < 0.4 gave yields of <10%. The nitro and cyano-substituted compounds **31-34** gave poor yields with the electron donating methyl group being present as a substituent. When two fluoro leaving groups were present mixtures of mono- and di-substituted products were obtained (Table 3) with the mono-substituted product predominating. In a ^{1}H-NMR experiment in DMSO-d_6 at 100 °C, 3,5-difluoronitrobenzene was completely converted to **37** after 1h and the disubstituted **38** was only detectable after 3h. This experiment indicated that formation of the disubstituted products was a two step process. Reaction of 3,5-difluoronitrobenzene and morpholine at room temperature over 60h gave a 91% isolated yield of **37** and none of **38**. In **39** the ester EWG was not sufficiently electron withdrawing for reaction to di-substituted

Table 2 Substratc variation in reactions with morpholine at 100 °C during 60 h



Compd	EWG	% Yield	Compd	EWG	% Yield
23	3-NO_2	98	**29**	H	0
24	3-CO_2Et, 5-CF_3	74	**30**	F	8
25	3-CN, 5-CF_3	97	**31**	2-Me, 5-NO_2	1
26	3-CF_3	19	**32**	2-Me, 3-NO_2	0
27	3-CO_2Et	3	**33**	3-NO_2, 4-Me	20
28	3-CO_2H	0	**34**	3-CN, 4-Me	4

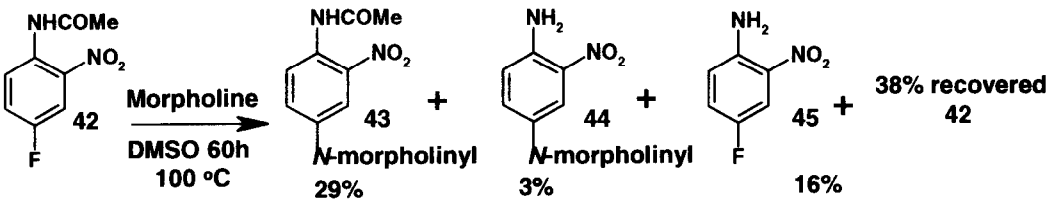
Table 3 Substitution of 3, 5-difluoro-compounds



R	Compd	% yield	Compd	% yield
		Mono-substitution		Di-substitution
CN	**35**	62	**36**	37
NO_2	**37**	78	**38**	16
CO_2Et	**39**	77	-	-

products. A subsequent experiment where **35**, and **37** were allowed to react with morpholine under the same standard reaction conditions, gave poor yields of **36** (8%) and **38** (19%). Reaction of ethyl 3,5-difluorobenzoate (in a sealed tube, but otherwise using the standard DMSO/60h/100 °C reaction conditions)

Scheme 5

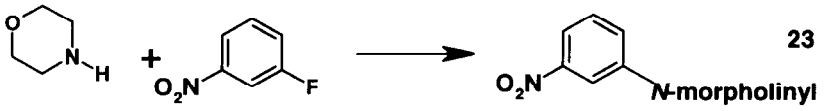


with pyrrolidine gave 68% of the mono-substituted product **40**, but also afforded the amide **41** of **40** in 32% yield. Cleavage of the acetamido group during the substitution of **42** led to mixtures of products (Scheme 5).

Nucleophilic amination at a *meta*-substituted leaving group

The *meta*-amination yields were considerably increased under these modified reaction conditions for nucleophilic substitution and were superior to literature precedents[1] (Table 4), except those for indoles and indolines.[12] Consideration was thus given as to whether an alternative reaction mechanism was involved. The three main mechanisms used[1,2] to explain nucleophilic aromatic substitution reactions were not supported by the experimental evidence above. The S_N1 mechanism is inappropriate, and radical and photochemical mechanisms were rejected because no radical initiator was present, and reaction proceeded in the dark to give the same amination yields. The involvement of a benzyne intermediate was discounted because: a) the base used

Table 4 Comparison with literature[13] substitutions for the synthesis of **23**

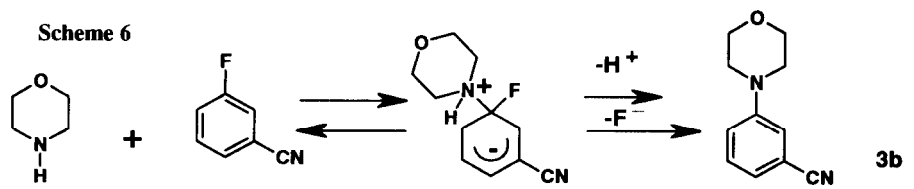


Reaction conditions	% Yield of 23
24 h reflux, MeCN, (ref. 12)	0
62 h, 10 kbar, MeCN, (ref. 12)	77
60 h, 100 °C, DMSO	98

(morpholine) was too weak; b) fluoride is too poor a leaving group; and c) there was no evidence by TLC, ^{1}H-NMR or ^{13}C-NMR of *cine*-substituted reaction products in any of these substitutions.

In conventional *ortho*/*para* nucleophilic substitutions the intermediate anion is stabilised[1] *via* both canonical resonance structures and the field effects of the EWG. With the *meta*-substituted substrates described

Scheme 6



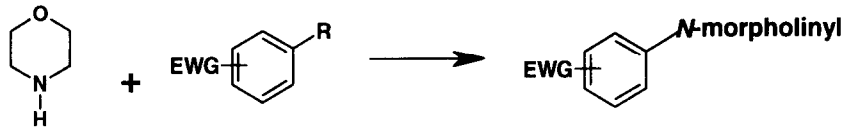
in this paper resonance is restricted, and mainly the field effect remains for the stabilisation of the postulated cyclohexadienyl anion reaction intermediate (Scheme 6). This hypothesis of field effect stabilisation is supported by: a) the yield variation (Table 3) being related to the Hammett σ-*meta* substituent values of the EWGs e.g. NO_2 >CN >CF_3 , which explains the restriction of the reaction to strong EWGs such as cyano and nitro or

combinations of EWGs with a similar capacity for stabilisation; b) the known[14, 15] substitution by the stronger (and anionic) oxygen nucleophiles (such as phenoxide ions) in the presence of strong EWGs. Thus, pending further kinetic investigation, the S_NAr mechanism was retained as an explanation for the high yielding *meta*-aminations reported herein, with the EWGs stabilising the intermediate cyclohexadienyl anion by field effects.

Conclusions

The enhanced yields of *meta*-substituted products in these nucleophilic amination reactions were based on the identification of favourable reaction conditions, because the precedented poor nucleophilic substitution yields were obtained in our preliminary work (Table 1). The high yielding, but slow substitution process was influenced by: the amine concentration; the nature of the substrate EWG; the leaving group (fluoro being preferred to triflate) and the choice of solvent. Best yields were obtained with cyclic secondary amines, but primary alkylamines containing a δ-substituted heteroatom also afforded adequate yields. The reported general procedure represents an alternative synthetic approach to the well established palladium catalyzed amination methods, but is restricted to benzenes substituted with an EWG. The yields obtained in this laboratory (with an

Table 5 A comparison of catalyzed and non-catalyzed substitutions



Pd-catalyzed			Uncatalyzed 60 h, DMSO		
EWG	**R**	**% Yield**	**EWG**	**R**	**% Yield**
2-CN	Br	**3a** 90	2-CN	F	**3a** 90
3-CN	Br	**3b** 72	3-CN	F	**3b** 62
4-CN	Br	**3c** 84	4-CN	F	**3c** 97

optimal leaving group, but without using specialist organometallic chemistry apparatus or optimising the palladium catalyst) were very similar for both sets of reaction conditions (Table 5). The nitro- and cyano-substituted products described above offer scope for further transformations to other C- and N-ring substituted aniline derivatives.

Experimental

Melting points were determined with a Buchi apparatus and are uncorrected. The ^{1}H-NMR spectra were determined with a Bruker AM (300 MHz) spectrometer and the ^{13}C-NMR with a Bruker DPX (400 MHz) instrument. Mass spectra were measured on a Platform Micromass (electrospray) instrument, and IR spectra as

Nujol mulls on a Perkin Elmer series 1600 FTIR instrument. Reactions were carried out under an atmosphere of argon and column chromatography was on E. Merck silica gel (Kieselgel 60, 230-400 mesh). All compounds analysed correctly for C, H, and N, (±0.4%), and the ^{1}H- and ^{13}C-NMR spectra were consistent with the assigned structures.

Example of the uncatalyzed substitution method used in Table 1

3-(4-Morpholino)benzonitrile (3b).

Morpholine (0.39 mL, 4.5 mmol) was added to a stirred suspension of K_2CO_3 (0.840 g, 6 mmol), 3-fluorobenzonitrile (0.363 g, 3 mmol) in DMSO (5 ml) at 20 °C. The reaction mixture was flushed with argon and heated to 105 °C for 18 h, cooled and water (50 mL) added. The aqueous was extracted with diethyl ether (3 x 40 mL). The organic layers were combined, washed with saturated brine (2 x 40 mL), dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with ethyl acetate-isohexane (1:9 v/v) to give **3b**, as a cream solid, (0.08 g, 14%), mp 102-103 °C; Rf 0.31 silica gel (ethyl acetate-isohexane 1:3 v/v); [Found: C, 70.2; H, 6.6; N, 14.9. $C_{11}H_{12}N_2O$ requires C, 70.0; H, 6.4; N, 15.0 %]; δ_H ($CDCl_3$) 7.12 (m, 1H), 7.02 (m, 3H), 3.78 (t, 4H, J = 4.8 Hz), 3.10 (t, 4H, J = 5.1 Hz); δ_C (400 MHz; $DMSOd_6$) 151.3 (s), 129.9 (s), 122.8 (s), 119.5 (s), 119.1 (s), 118.1 (s), 113.0 (s), 66.5 (s), 48.4 (s); IR (cm^{-1}) 2226, 1599, 1573, 1307, 1270, 1244, 1116, 994, 961; m/z (M+H) 189.

Ethyl 3-(4-morpholino)benzoate, palladium-catalyzed method (2b).

Ethyl 3-bromobenzoate(1.92 mL, 12 mmol) was added to a stirred, degassed, anhydrous solution of BINAP (0.336 g, 4.5 mol%), $NaOBu^t$ (1.615 g, 16.8 mmol), tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$ (0.33 g, 3 mol%) and morpholine (1.25 mL, 14.4 mmol), in toluene (30 mL). The reaction mixture was stirred at 90 °C for 20 h under argon. The solution was cooled, and extracted with 1 M HCl (2 x 40 mL), the aqueous phase was basified with aqueous Na_2CO_3 and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with saturated brine (1 x 50 mL), dried and concentrated to give a brown oil. The oil was purified by chromatography on silica gel. Elution with methanol-dichloromethane (1:50 v/v) gave **4** as a brown oil, (0.10 g, 7 %); δ_H ($CDCl_3$) 7.39 (m, 5H), 3.65 (broad t, 4H), 3.53 (broad t, 4H); m/z (M+H) 192. Further elution with methanol-dichloromethane (1:25 v/v) gave, as a yellow oil **2b**; (0.15 g, 6 %); δ_H ($CDCl_3$) 7.51 (s, 1H), 7.48(d, 1H, J = 2.8 Hz), 7.25 (t, 1H, J = 4.8 Hz), 7.0 (dd, 1H, J = 7.8 and 1.9 Hz), 4.3 (q, 2H, J = 7.1 Hz), 3.8 (t, 4H, J = 5.1 Hz), 3.13 (t, 4H, J = 4.7 Hz), 1.33 (t, 3H, J = 7.1 Hz); m/z (M+H) 236. Further elution with methanol-dichloromethane (1:12 v/v) gave **5**, as a dark brown oil (0.45 g, 28%); δ_H ($CDCl_3$) 7.30 (m, 1H), 6.97 (m, 2H), 6.83 (d, 1H, J = 5.9 Hz), 3.85 (t, 4H, J = 4.7 Hz), 3.68 (m, 8H), 3.20 (t, 4H, J = 5.2 Hz); m/z (M+H) 277.

3-(4-Morpholino)benzonitrile, palladium-catalyzed method (3b).

3-Bromobenzonitrile (10 g, 55 mmol) was added to a stirred, degassed, solution of BINAP (1.54 g, 4.5 mol%), $NaOBu^t$ (7.4 g, 77 mmol), $Pd_2(dba)_3$ (1.51 g, 3 mol%) and morpholine (5.74 mL, 66 mmoles), in anhydrous toluene (150 mL). The reaction mixture was stirred at 90 °C for 20 h under argon. On cooling the mixture was extracted with 1 M HCl (3 x 50 mL), the aqueous phase was basified with aqueous Na_2CO_3 and extracted with ethyl acetate. The combined extracts were washed with saturated brine (1 x 50 mL), dried and concentrated to give a brown solid. The original toluene organic phase was exaporated and the residue combined with the brown solid and was purified by flash column chromatography. The column was eluted with ethyl acetate-isohexane (1:5 v/v) giving **3b** as a cream solid, (7.48 g, 72%); mp 102-103 °C; δ_H ($CDCl_3$) 7.29 (dd, 1H, J = 7.1 and 8.9Hz), 7.08 (s, 1H), 7.03 (m, 2H), 3.81 (t, 4H, J = 4.9 Hz), 3.11 (t, 4H, J = 5.0 Hz); m/z (M+H) 189.

t-Butyl 3-(4-morpholino)benzoate (7).

t-Butyl 3-bromobenzoate (0.77 g, 3 mmol) was added to a stirred, degassed, solution of BINAP (0.084 g, 4.5 mol%), $NaOBu^t$ (0.4 g, 4.2 mmol), $Pd_2(dba)_3$ (0.082 g, 3 mol%) and morpholine (0.30 g, 3.3 mmol), in anhydrous toluene (30 mL). The reaction mixture was stirred at 90 °C for 20 h under argon. On cooling the mixture was filtered and the solvent evaporated to give a dark brown residue. The residue was triturated in ethyl acetate-isohexane (1:9 v/v) and refiltered. The filtrate was evaporated to give an oil which was purified by column chromatography on a IST Bond Elut (25 g silica gel). The column was eluted with ethyl acetate-isohexane (1:9 v/v) to give **7** as an oil, (0.556 g, 71%); δ_H ($CDCl_3$) 7.48 (t, 1H, J = 1.9 Hz), 7.42 (d, 1H, J = 5.3 Hz), 7.23 (t, 1H, J = 7.5 Hz), 6.98 (dd, 1H, J = 9.0 and 2.5 Hz), 3.80 (t, 4H, J = 4.8 Hz), 3.11 (t, 4H, J = 4.9 Hz) 1.52 (s, 9H); m/z (M+H) 264.

3-(4-Morpholino)benzoic acid (1b).

a) Trifluoroacetic acid (5 mL, 64.9 mmol), was added dropwise to a stirred solution of t-butyl-3-(4-morpholino)benzoate (0.50 g, 1.89 mmol) in dichloromethane (10 mL), at 0 °C under argon. The mixture was stirred for 1 h, evaporated to an oil, and toluene (30 mL) was added. Evaporation gave an oil which solidified to give **1b** (0.43 g, 68.5 %) as the trifluoroacetate salt; m/z (M-H) 206.

b) 5M NaOH (33.87 mL, 169.4 mmol) was added to a stirred suspension of **3b** (6.37 g, 33.7 mmol) in butan-1-ol (30 mL) and the mixture stirred at 115 °C under argon for 9 h. On cooling the butanol was evaporated and the reaction mixture neutralised with an equivalent amount of 1M HCl (169 mL, 169 mmol). The resulting colourless precipitate was filtered, washed with water, diethyl ether and dried to give **1b** as a colourless solid (6.443 g, 92%) 164-165 °C; [Found : C, 63.4; H, 6.3; N, 6.6 $C_{11}H_{13}NO_3$ requires C, 63.7; H, 6.2; N, 6.8%]; δ_H (DMSO-d_6) 12.8 (s, 1H), 7.44 (s, 1H), 7.32 (t, 1H, J = 8.0 Hz), 7.20 (d, 2H, J = 7.3 Hz), 3.77 (t, 4H, J = 4.8 Hz), 3.13 (t, 4H, J = 5.0 Hz); m/z (M-H) 206.

Example of the General Procedure for uncatalyzed substitution in DMSO at 100 °C for 60h.

3-(4-Morpholino)benzonitrile (3b).

Morpholine (72 mL, 0.742 mol), was added to a solution of 3-fluorobenzonitrile (16.34 g, 0.135 mol) in DMSO (112 mL) and the mixture heated for 60 h at 100 °C. The reaction mixture was cooled and poured into water (1200 mL). The solid product was filtered, washed with water and dried *in vacuo* giving a pale pink solid (14.69 g). The residual aqueous filtrate was extracted with diethyl ether (2 x 400 mL). The combined organic phases were washed with saturated brine, dried ($MgSO_4$) and the extracts evaporated giving an oil (6.7 g). The oil was purified by filtration chromatography on silica gel. Elution with ethyl acetate-isohexane (1:9 v/v) gave **3b** as a colourless solid (1.02 g). (15.71 g 62%); mp 102-103 °C; [Found: C, 70.0; H, 6.4; N, 15.0. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.6; N, 14.9 %]; δ_H ($CDCl_3$) 7.29 (dd, 1H, J = 9.0 and 7.2 Hz), 7.08 (s, 1H), 7.03 (m, 2H), 3.81 (t, 4H, J = 4.5 Hz), 3.11 (t, 4H, J = 4.8 Hz); m/z (M+H) 189.

This General Procedure was used to synthesize the compounds in Table 6 below.

Table 6 Reactions of morpholine under the General Procedure

Cmpd	mp °C	yield %	m/z M+H	cmpd	mp °C	yield %	m/z M+H
3a	59-60	90	189	**24**	105-106	74	304
3c	81-82[a]	97	189	**25**	165-166	97	257
13	109-110	14	243	**26**	oil	19	232
14	221-223	36	253 (M+)	**27**	oil	3	236
15	oil	68	187	**30**	103-104[c]	8	182
16	oil	69	202	**31**	75-77	1	223
17	84-85	64	173	**33**	75-77	20	223
18a	oil	22	223	**34**	72-73	4	203
19a	oil	10	174	**35**	103-104	78	207
19b	oil	58	217	**36**	195-196	16	274
19c	oil	34	190	**37**	135-136	62	225
19d	oil	36	204	**38**	205-206	37	294
19e	oil	39	217 (M+)	**39**	67-68	77	254
20a	oil	42	191	**40**	91-93	68	263
20b	oil	38	231	**41**	53-55	32	238
20c	oil	31	206 (M+)	**43**	181-183[d]	29	266
21	236-237	68	186	**44**	164-165	3	224
22	234-235	17	288	**45**	91-93	16	157
23	103-105[b]	98	181				

[a] i Reference 12a mp 75-76.5 °C; ii Wolfe, J. P.; Buchwald, S. L. *J.Org.Chem.* **1997**, *62*, 1264-1267, mp 54-55 °C. [b] Hurst, D. T. *Heterocycles*, **1988**, *27*, 371-376, mp 106.5 °C. [c] Popp, F.D.; et al. *J. Med. Chem.* **1967**, *10*, 481-484 , mp 100-105 °C. [d] Ainsworth, D. P.; Suschitzky, H. *J Chem Soc. C.* 1966, 111-113. mp 160 °C.

2-(4-Morpholino)benzonitrile (3a).

In a similar manner 2-fluorobenzonitrile was reacted with morpholine, to give **3a**, as a cream solid, (0.462 g, 82 %); which was crystallised from isohexane; mp 59-60 °C; R_f 0.39 silica gel (ethyl acetate-isohexane 1:3 v/v);

Table 7 Microanalyses for compounds in Table 6

	Found %				Reqd %		
Compd	**C**	**H**	**N**	**Formulae**	**C**	**H**	**N**
3a	69.9	6.4	14.8	$C_{11}H_{12}N_2O$	70.0	6.4	15.0
3c	70.0	6.7	14.9	$C_{11}H_{12}N_2O$	70.0	6.4	15.0
13	49.7	4.7	11.3	$C_{10}H_{11}N_2O_2Cl$	49.6	4.5	11.6
14	47.1	4.1	16.3	$C_{10}H_{11}N_3O_4$	47.2	4.3	16.1
15	76.5	7.4	14.9	$C_{12}H_{14}N_2.0.1H_2O$	76.5	7.5	14.8
16	69.9	7.0	20.3	$C_{12}H_{15}N_3.0.25H_2O$	70.0	7.4	20.4
17	76.4	7.2	16.2	$C_{11}H_{12}N_2$	76.7	7.0	16.3
18a	80.7	6.4	12.5	$C_{15}H_{14}N_2$	81.1	6.3	12.6
19a	76.2	8.1	16.0	$C_{11}H_{14}N_2$	75.8	8.0	16.3
19b	72.0	9.2	19.7	$C_{13}H_{19}N_3$	71.3	8.8	19.4
19c	69.6	8.1	22.1	$C_{11}H_{15}N_3$	69.8	7.9	22.2
19d	68.9	8.7	19.8	$C_{12}H_{17}N_3.0.25H_2O$	69.3	8.7	20.2
19e	60.4	8.9	19.3	$C_{13}H_{19}N_3$	60.8	8.8	19.4
20a	69.2	7.5	14.4	$C_{11}H_{14}N_2O$	69.5	7.4	14.7
20b	72.3	8.8	12.0	$C_{14}H_{20}N_2O$	72.4	8.6	12.1
20c	64.0	6.9	13.4	$C_{11}H_{14}N_2S$	64.1	6.8	13.6
21	50.9	6.0	16.5	$C_{11}H_{13}N_3$	50.8	5.8	16.2
22	72.1	5.6	19.0	$C_{18}H_{16}N_4.0.7H_2O$	71.8	5.8	18.6
23	57.5	5.7	13.3	$C_{10}H_{12}N_2O_3$	57.6	5.8	13.5
24	55.4	5.3	4.4	$C_{14}H_{16}FNO_3$	55.4	5.3	4.6
25	55.9	4.4	10.8	$C_{12}H_{11}F_3N_2O$	56.3	4.3	10.9
26	56.4	5.0	5.8	$C_{11}H_{12}F_3NO$	56.7	5.2	6.0
27	66.0	7.0	6.1	$C_{13}H_{17}NO_3$	66.4	7.2	6.0

Table 7 contd

30	66.6	6.5	7.5	$C_{10}H_{12}FNO$	66.3	6.6	7.7
31	59.3	6.4	12.5	$C_{11}H_{14}N_2O_3$	59.5	6.3	12.6
33	59.1	6.3	12.4	$C_{11}H_{14}N_2O_3$	59.5	6.3	12.6
34	69.8	7.1	13.5	$C_{12}H_{14}N_2O.0.1H_2O$	69.7	7.0	13.6
35	64.1	5.4	13.5	$C_{11}H_{11}FN_2O$	64.0	5.4	13.6
36	65.9	7.0	15.4	$C_{15}H_{19}N_3O_2$	65.8	6.8	15.2
37	53.2	4.7	12.1	$C_{10}H_{11}FN_2O_3$	53.1	4.9	12.3
38	52.0	6.2	14.2	$C_{14}H_{19}N_3O_4$	52.3	6.5	14.3
39	61.8	6.4	5.5	$C_{13}H_{16}FNO_3$	61.7	6.3	5.5
40	65.6	6.9	6.0	$C_{13}H_{16}FNO_2$	65.8	6.8	6.0
41	68.3	7.3	10.4	$C_{15}H_{19}FNO_2$	68.7	7.3	10.7
43	54.6	5.7	15.6	$C_{12}H_{15}N_3O_4$	54.3	5.7	15.8
44	53.6	5.6	18.5	$C_{10}H_{13}N_3O_4$	53.8	5.8	18.8
45	46.0	3.4	17.8	$C_6H_5FN_2O_2$	46.1	3.2	17.9

[Found: C, 69.9; H, 6.4; N, 14.8. $C_{11}H_{12}N_2O$ requires C, 70.0; H, 6.4; N, 15.0 %]; δ_H ($CDCl_3$) 7.53 (dd, 1H, *J* = 8.0 and 1.9 Hz), 7.42 (td, 1H, *J* = 7.6 and 1.4 Hz), 6.95 (m, 2H), 3.83 (t, 4H, *J* = 4.8 Hz), 3.16 (t, 4H, *J* = 4.7 Hz); IR (cm^{-1}) 2217, 1594, 1484, 1283, 1255, 1224, 1112, 1937, 936, 922, 758; m/z (M+H) 189.

4-(4-Morpholino)benzonitrile (3c).

In a similar manner 4-fluorobenzonitrile was reacted with morpholine, to give **3c**, as a cream solid, (0.523 g, 94 %); which was crystallised from ethyl acetate-isohexane (1:10 v/v); mp 82-83 °C; R_f 0.23 silica gel (ethyl acetate-isohexane 1:3 v/v); [Found: C, 70.0; H, 6.7; N, 14.9. $C_{11}H_{12}N_2O$ requires C, 70.0; H, 6.4; N, 15.0%]; δ_H ($CDCl_3$) 7.42 (d, 2H, *J* = 8.9 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 3.78 (t, 4H, *J* = 5.0 Hz), 3.21 (t, 4H, *J* = 4.8 Hz); IR (cm^{-1}) 2216, 1605, 1515, 1244, 1181, 1115, 928; m/z (M+H) 189.

***N*-4-(3-chloro-5-nitro)morpholine and *N*-4-(3,5-dinitrophenyl)morpholine (13 and 14).**

Morpholine (0.718 mL, 8.25 mmol) was added to a stirred solution of 3,5-dinitro chlorobenzene (0.292 g, 1.43 mmol) in DMSO (2.5 mL), causing a colour change from cream to purple. The mixture was heated at 100 °C and stirred for 60 h under an argon atmosphere. The cooled reaction mixture was poured into water (25 mL), and the aqueous phase extracted with ethyl acetate. The combined extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated *in vacuo* giving an orange solid. The residue was purified on a 10g silica Bond Elut, eluting with ethyl acetate-isohexane (1:9 v/v), gave **13**, as an orange solid, (0.047 g, 14 %); mp 109 - 110°C; [Found: C, 49.7; H, 4.7; N, 11.3. $C_{10}H_{11}FN_2O_2Cl$ requires C, 49.6; H, 4.5; N, 11.6%]; δ_H ($CDCl_3$) 7.58 (d, 1H, *J* = 1.9 Hz), 7.50 (d, 1H, *J* = 2.0 Hz), 7.02 (d, 1H, *J* = 1.9 Hz), 3.78 (t, 4H, *J* = 1.8 and 3.3 Hz), 3.18

(t, 4H, J = 1.8 and 3.3 Hz); m/z (M+H) 243. Further elution with ethyl acetate-isohexane (1:3 v/v) gave, as an orange solid, **14** (0.127 g, 35 %); mp 221-223°C; [Found: C, 47.1; H, 4.1; N, 16.3. $C_{10}H_{11}N_3O_4$ requires C, 47.2; H, 4.3; N, 16.1%]; δ_H ($CDCl_3$) 8.35 (s, 1H), 7.88 (s, 2H), 3.82 (t, 4H, J = 4.8 Hz), 3.30 (t, 4H, J = 4.6 Hz); m/z (M^+) 253.

3-Fluoro-5-morpholinobenzonitrile (35) and 3,5-dimorpholinobenzonitrile (36).

In a similar manner and on the same scale as **37** below, eluting with ethyl acetate-isohexane (1:4 v/v), gave **35**, as a colourless solid, (0.484 g, 78 %); mp 112.5 -113.5 °C; [Found: C, 64.1; H, 5.4; N, 13.5. $C_{11}H_{11}FN_2O$ requires C, 64.0; H, 5.4; N, 13.6 %]; δ_H ($CDCl_3$) 7.54 (s, 1H), 7.29 (d, 1H, J = 2.0 Hz), 6.82 (d, 1H, J = 2.1 Hz), 3.88 (t, 4H, J = 5.1 Hz), 3.23 (t, 4H, J = 4.8 Hz); m/z (M+H) 207.4. Further elution with ethyl acetate-isohexane (1:1 v/v) gave, as a colourless solid, **36** (0.13 g, 16 %); mp 196-198 °C; [Found: C, 65.9; H, 7.0; N, 15.4. $C_{15}H_{19}N_3O_2$ requires C, 65.8; H, 6.8; N, 15.2%]; δ_H ($CDCl_3$) 6.65 (d, 2H, J = 1.8 Hz), 6.58 (t, 1H, J = 2.0 and 1.9 Hz), 3.83 (t, 8H, J = 4.9 Hz), 3.17 (t, 8H, J = 5.1 Hz); m/z (M+H) 274.5.

***N*-4-(3-fluoro-5-nitrophenyl)morpholine (37) and 3,5-dimorpholinonitrobenzene (38).**

Morpholine (1.437 mL, 6.5 mmol), was added to a solution of 3,5-difluoronitrobenzene (0.477 g, 3 mmol) in DMSO (5 mL) and the mixture heated for 60 h at 100 °C. After cooling, the reaction mixture was poured into water (50 mL) and an orange solid product collected. The residual aqueous filtrate was extracted with diethyl ether (3x50 mL) and the combined extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated giving orange solid. The solids were combined and purified by silica filtration chromatography. Elution with ethyl acetate-isohexane (1:4 v/v) gave, as an orange solid, **37** (0.42 g; 62 %); mp 134-135 °C; [Found: C, 53.2; H, 4.7; N, 12.1. $C_{10}H_{11}FN_2O_3$ requires C, 53.1; H, 4.9; N, 12.3 %]; δ_H ($CDCl_3$) 7.54 (s, 1H), 7.29 (d, 1H, J = 5.1 Hz), 6.82 (d, 1H, J = 5.8 Hz), 3.88 (t, 4H, J = 4.9 Hz), 3.23 (t, 4H, J = 5.0 Hz); m/z (M+H) 227. Further elution with ethyl acetate-isohexane (1:1 v/v) gave, as an orange solid, **38** (0.325 g, 37 %); mp 207-209 °C; [Found: C, 52.0; H, 6.2; N, 14.2. $C_{14}H_{19}N_3O_4$ requires C, 52.3; H, 6.5; N, 14.3 %]; δ_H ($CDCl_3$) 7.26 (s, 2H), 6.63 (s, 1H), 3.90 (t, 8H, J = 4.8 Hz), 3.21 (t, 8H, J = 5.0 Hz); m/z (M+H) 294.

References and Notes

1. March, J. *Advanced Organic Chemistry : Reactions, Mechanisms and Structure*, 4th edition, **1992**, p641.
2. Terrier, F. *Nucleophilic Aromatic Displacement*, **1991**, VCH Publishers Inc., New York, pp376.
3. Wolfe, J. P., Wagaw, S., Marcoux, J-F., and Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805-818.
4. a) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2046-2067. b) Hartwig, J. F. *Synlett* **1997**, 329-340.
5. Belfield, A. J., Brown, G.R., and Foubister, A.J. *Tetrahedron*, **1999**, in press.

6. Brown, G. R., Foubister, A. J., and Ratcliffe, P. D. *Tetrahedron Lett.* **1999**, *40*, 1219-1222.

7. Brown, G. R., Foubister, and A. J., Stribling, D. *J. Chem. Soc. PerkinTrans I*, **1987**, 547-551.

8 a) Guram, A. S., Rennels, R. A. and Buchwald S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348-1350; b) Wolfe, J. P., Wagaw, S., and Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215-7216.

9 Bevan, C. W. L., Foley, J. A., Hirst, J., and Uwamu, W. O. *J. Chem. Soc. (B)*, **1970**, 794-797.

10 Predictions for the ^{13}C NMR spectra were made from SpecInfo 3.1.6, a product of Chemical Concepts Germany.

11 Hansch, C., Leo, A., and Hoekman, D. *Exploring QSAR, Hydrophobic, Electronic and Steric Constants*, ACS Professional Reference Book, **1995**, American Chemical Society, Washington, DC.

12 a) Glankowski, E. J.; Fortunato, J. M.; Spaulding, T. C.; Wilker, J. C.; Ellis, D. B. *J. Med. Chem.* **1985**, *28*, 66-73. b) Smith III, W. J.; Sawyer, J. S. *Tetrahedron Lett.*, **1996**, *37*, 292-302.

13 a) Kotsuki, H., Kobayashi, S., Suenga, H., and Nishizawa, H. *Synthesis* **1990**, 1145-1146. b) Kotsuki, H.; Kobayashi, S., Matsumoto, K., Suenga, H., and Nishizawa, H. *Synthesis* **1990**, 1147-1148.

14 Idoux, J. P., Madenwald, M. L., Garcia, B. S., Gupton, J. T., and Chu, D-L. *J. Org. Chem*, **1985**, *50*, 1876-1878.

15 Boswell Jr., R. F., Helsley, G. C., Duncan Jr., R. L.., Funderburk, W. H., and Johnson, D. N. *J. Med. Chem.* **1974**, *17*, 1000-1008.