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The mono-functionalization of symmetrical polyamines

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Dedicated to the victims, firefighters, policemen and service people who lost their lives as a consequence of the tragedies that occurred on 11 September 2001

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Contents

1. Introduction

Differentially substituted symmetrical amine moieties, particularly piperazines, are found as either a key pharmacophoric element or an important structural scaffold in a large number of drugs and drug candidates that encompass a wide range of biochemical targets across all therapeutic areas. Representative examples include the vasodilator flunarizine[1] (**1**), the histamine antagonist cetirizine[2] (**2**), the sedative–hypnotic trifluoperazine[3] (**3**), the quinolone antibacterial ciprofloxacin[4] (**4**), the anti-psychotic olanzapine[5] (**5**), the anxiolytic busprione[6] (**6**) and the cardiotonic agent vesnarinone[7] (**7**). Whilst the development of synthetic approaches suitable for the large scale production of such compounds does not appear to have presented a significant practical challenge, there remains an abiding interest in developing methods for selectively discriminating symmetric polyamine functionality.[8–11] Although the de novo construction of unsymmetrical diamines is a potentially useful and unequivocal approach, it is inherently circuitous in nature. Consequently, a more direct and practical strategy comprising the mono-functionalization of symmetrical polyamines has found frequent application. However, deficiencies associated with the available procedures clearly provide an opportunity for further process refinement. The two principal preparative methods that have been developed rely upon a strategy of either selective protection followed by modification and deprotection or that of simply employing the polyamine in considerable excess. The former process is less concise while the latter is often more practical but inherently less elegant, particularly if the amine is structurally complex and difficult to access. Indeed, as the molecular complexity of synthetic targets increases and awareness of the concepts of atom economy and environmentally considerate chemistry is heightened,[12] the quest for complete control over efficient and selective introduction of functionality will continue to be a challenging problem. In this review, we focus upon the progress that has been realized towards the direct and selective derivatization of symmetrical polyamines without resorting to the inefficiencies associated with the common tactics of discrete protection/deprotection strategies or the use of a significant (>3-fold) excess of amine. The narrative is organized such that summaries of selected reactions producing unsymmetrical polyamines derivatized with sp^3, sp^2 and other electrophiles, primarily sulfur derivatives, will be discussed in sequence.

2. Chemistry

2.1. Reactions of polyamines with sp^3 electrophiles

(i) Alkylation with halides and tosylates

The selective mono-alkylation of simple polyamines such as ethylene diamine (**8**) or piperazine is a particularly difficult

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Keywords: acylation; alkylation; arylation; diamines; desymmetrization; aza macrocycles; cyclen; cyclam; piperazines; regiocontrol.

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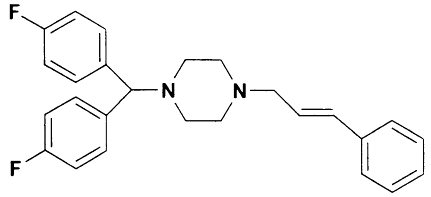

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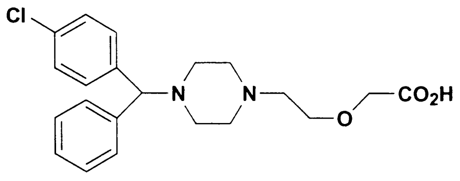
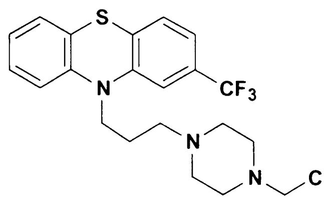
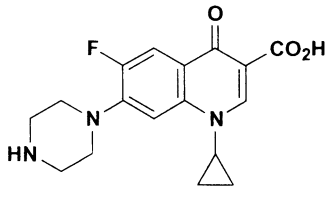
Flunarizine



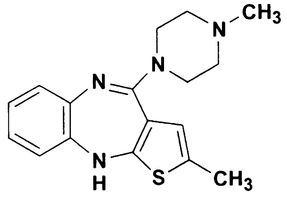
2
Cetirizine



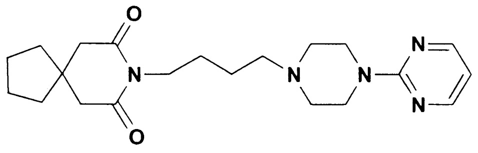
3
Trifluoperazine



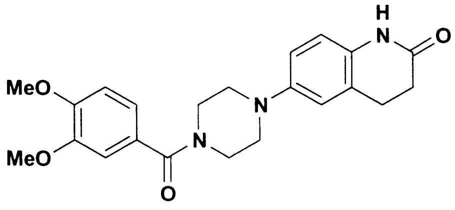
4
Ciprofloxacin



5
Olanzapine



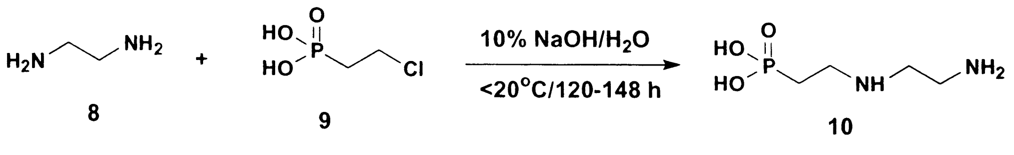
6
Buspirone



7
Vesnarinone

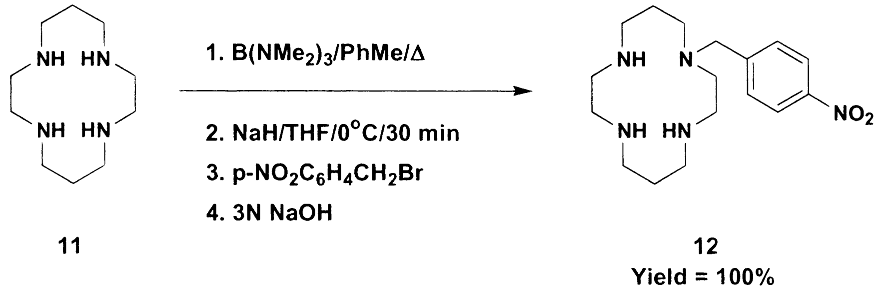
transformation to accomplish without resorting to the use of a substantial excess of amine or indirect methods. In addition to the problem of influencing the inherent statistical bias between unreacted starting material, and mono- and dialkylated products, the production of quaternized derivatives adds considerably to the complexity of potential products. Nevertheless, there are several isolated examples of success in this endeavor,[13–15] although none appear to have been refined to the level of being generally applicable and reliable. There is clearly a significant opportunity for the development of improved methodology that would avoid the more typical result of a complex mixture that necessitates difficult and indirect purification procedures.[16] However, Scheme 1 provides an example where using only a modest, 25%, excess of ethylene diamine (**8**) relative to the chloride **9** was sufficient to provide a high yield of the alkylated product **10**.[13] The optimized conditions described called for the inclusion of a catalytic quantity of KI, a common additive for accelerating alkylation reactions, whilst maintaining the temperature of the reaction mixture below 20°C in order to achieve an impressively high yield. Although it is not clear why the presence of KI should exert such a profound influence on product distribution, in the absence of KI the 47% yield of **10** reported essentially reflects that expected in a reaction proceeding under statistical control. See note added in proof (Section 4).

Azamacrocycles, of value to the chemistry community because of their spectrum of physical and biochemical properties, represent a unique circumstance because they often permit the convenience of a temporary in situ protection that capitalizes on either overt tridentate reactivity or the inherent polydentate coordination properties. To this end, boron-,[17,18] silicon-,[19] phosphorus-[20,21] and metal-based[8,22–24] approaches have been applied with excellent efficiency and practicality. The processes described in Schemes 2[18] and 3[21] are illustrative examples of high yielding, one-pot, convenient procedures that rely upon the

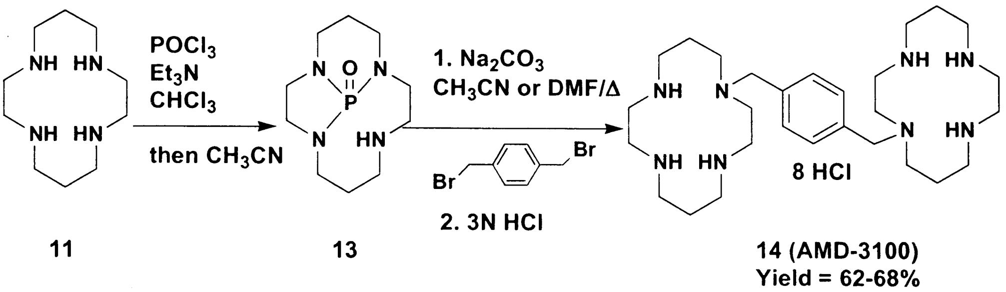


Yield = 86% with KI
47% without KI

Scheme 1.



Scheme 2.

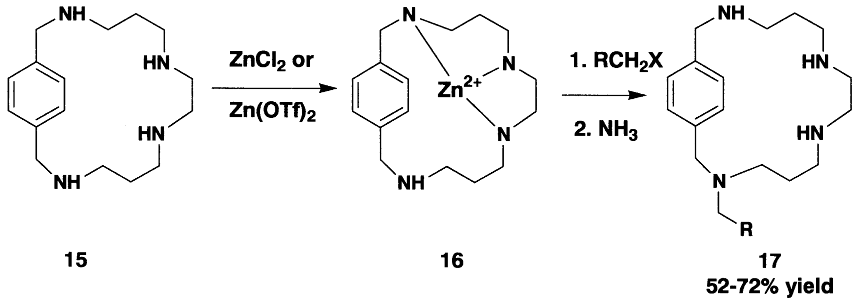


Scheme 3.

temporary, simultaneous protection of three nitrogen atoms by boron- and phosphorus-based reagents, respectively. The mild conditions for the mono-alkylation of cyclam **11** using NaH, unique amongst a series of bases examined, described in Scheme 2 were specifically developed for *p*-nitrobenzyl bromide because the more commonly used lithium counterion[17] was found to be incompatible with this sensitive alkylating agent.[18] This reaction may proceed by a process of initial alkylation of the secondary amine and subsequent deprotonation by NaH since it has been demonstrated that the intermediate tri-coordinated boron complex of cyclam **11** is not deprotonated upon exposure to NaH in THF, even at reflux.[25]

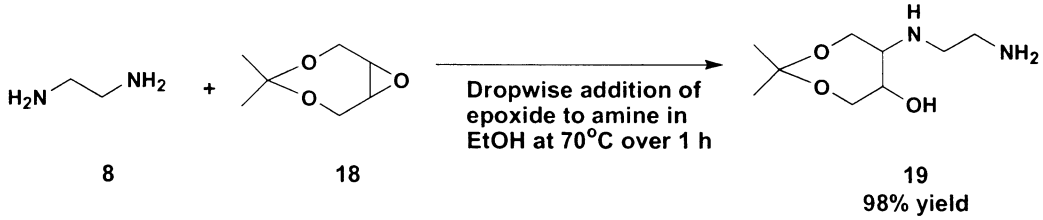
Scheme 3 presents a particularly powerful example of this concept that describes a simple, efficient and inexpensive preparative procedure for the synthesis of AMD-3100 (**14**), a CXCR4 receptor antagonist recently advanced into clinical trials for the treatment of HIV.[26,27] The phosphoric triamide **13** is prepared in situ from cyclam **11** and alkylated under mild conditions using Na_2CO_3 as the base.[21] Aqueous acidic hydrolysis of the mono-alkylated phosphoric triamide intermediate completes the sequence, ultimately providing the product **14** as its HCl salt in 62–68% yield.[21]

These processes involving an in situ protection protocol provide practical and elegant preparative procedures for the selective alkylation of polyazamacrocycles. In the absence of internal protection, alkylation produces complex mixtures of mono- and disubstituted derivatives from which the mono-alkylated products are typically isolated in poor yield.[22,28,29] Although the direct alkylation of cyclophane **15** under elementary conditions produced such mixtures, it was found that the inclusion of a stoichiometric amount of $ZnCl_2$ or $Zn(OTf)_2$ in the reaction mixture markedly altered the course of the reaction.[22] Thus, stirring molar equivalents of **15**, the zinc reagent and an alkylating agent at 0°C to room temperature provided good yields of the mono-derivatized product **17**, specifically alkylated on a single benzylic amine moiety, as summarized in Scheme 4.[22]



R = Ph, *p*-$NO_2C_6H_4$, *p*-$CH_3C_6H_4$, EtO_2C, CH_2=CH

Scheme 4.



Scheme 5.

Only minor amounts of the dialkylated product and unreacted starting material were detected in the crude reaction mixture under these conditions; however, conducting the reaction at higher temperatures led to an increase in the production of dialkylated material. The intermediacy of complex **16** in which three nitrogen atoms are complexed to the Zn^{2+} atom was invoked to rationalize the observed regiospecificity. The simultaneous complexation of the Zn^{2+} atom by all four nitrogen atoms is precluded by conformational constraints imposed by the *para*-substituted aromatic ring.

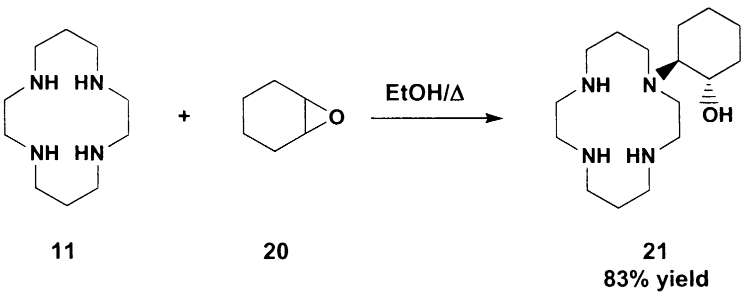
(ii) Alkylation with epoxides and aziridines

Epoxides are reactive electrophiles towards polyamines but general reaction principles that allow for the predictable control of mono-alkylation, either through specific reaction conditions or the application of custom-designed reagents, have not been described. Several examples of desymmetrization have been described that, although apparently of limited general applicability, provide background context and reaction conditions that may be of some value in future design.[30–32] The reaction of ethylene diamine (**8**) with a stoichiometric quantity of epoxide **18** afforded the mono-alkylated amino alcohol **19**, presumed to be of the *trans* disposition, in excellent yield, provided that **18** was carefully added in a dropwise fashion to the amine in ethanol at 70°C over a period of 1 h (Scheme 5).[30] These conditions appeared to be general for polyamines reacting with **18** since two additional examples described afforded similar outcomes. In contrast, the act of simply combining stoichiometric quantities of **8** and **18** in ethanol afforded a mixture of mono- and dialkylated products with incomplete consumption of **8**.[30]

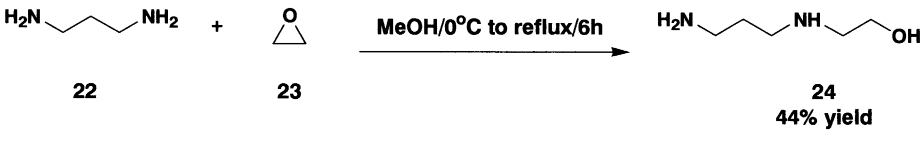
The reaction of polyazamacrocyles with epoxides provides a notable exception to the anticipated production of statistically distributed products, even in the absence of additives.[31] The tetra-amine **11** reacts with a 4-fold excess of cyclohexene oxide (**20**) in EtOH at reflux to afford only the racemic mono-alkylated adduct **21** in an excellent 83% yield (Scheme 6).[31]

Under similar circumstances, stoichiometric amounts of the structurally less complex reaction partners propylene diamine (**22**) and ethylene oxide (**23**) combine to afford the mono-adduct **24** in only 44% yield, as summarized in Scheme 7.[32] In this case the observed result is that anticipated of a reaction controlled by the simple principle of statistical distribution.

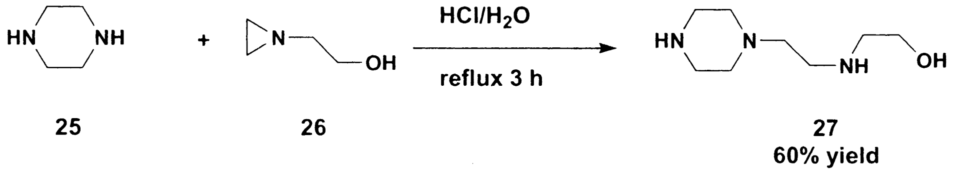
The reaction of aziridines with diamines has not been extensively explored and representative examples are relatively sparse. The combination of piperazine (**25**) and aziridine **26** in hot water containing a catalytic amount of HCl reportedly provides the adduct **27** in 60% yield, as depicted in Scheme 8.[33] However, a significant excess of piperazine was used in this protocol and no attempt appears to have been made to further optimize the conditions.



Scheme 6.



Scheme 7.



Scheme 8.

2.2. Reactions of polyamines with sp^2 electrophiles

(i) Reductive amination of polyamines

The selective reductive amination of polyamines using either $NaBH_4$ or $NaBH_3CN$ has been examined as a means of accessing mono-alkylated derivatives. However, procedures employing stoichiometric quantities of reactant are rare and the yields generally poor. One example drawn from the literature, in which just a 20% excess of ethylenediamine (**8**) was employed, is depicted in Scheme 9 in which in situ reduction of the imine derived from diamine **8** and pyruvate **28** affords product **29**.[34] Although only a modest 23% yield is reported the procedure is unoptimized, providing some basis for anticipating improved preparative protocols.

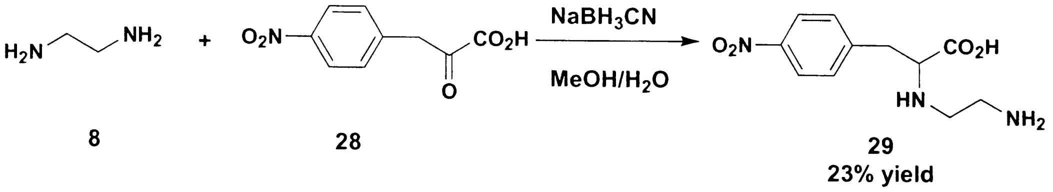
(ii) Michael addition reactions of polyamines

Diamines readily participate as donors in Michael addition reactions with olefin partners that are activated by ester,[35–37] nitrile,[35,38] amide[35] or phosphine oxide[39] functionality. Representative is the reaction of the structurally simple ethylenediamine (**8**) with a molar equivalent of acrylonitrile (**30**) to afford the corresponding adduct **31**, a useful synthetic precursor to substituted derivatives of cyclam **11**, in 46% yield (Scheme 10).[38] Although this result appears to be encouraging, it should be noted that the outcome is that expected if the products are statistically distributed.

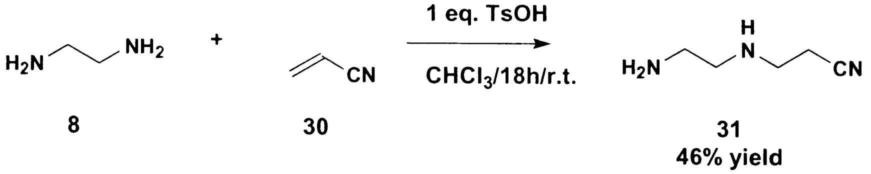
Whilst the use of excess polyamine is more typical, the azamacrocycle **11** once again reacts in a fashion that represents a unique departure from convention.[35] Thus, coupling of **11** with an equimolar amount of acrylamide (**32**) in the presence of one equivalent of *p*-toluenesulfonic acid affords adduct **33** in an excellent 81% yield (Scheme 11).[35] Several additional examples using a series of Michael acceptors demonstrated the generality of the protocol with isolated yields ranging from 25 to 69%.[35]

(iii) Acylation reactions of polyamines

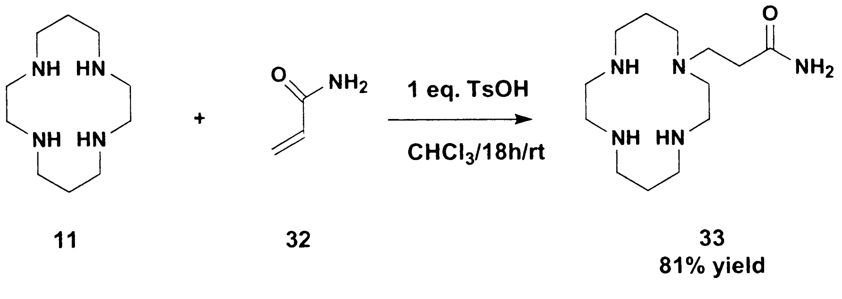
Acylated diamines are prevalent throughout the organic



Scheme 9.



Scheme 10.



Scheme 11.

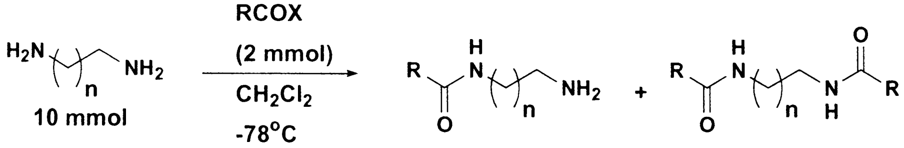
chemistry literature as intermediates in the synthesis of a myriad of natural and unnatural compounds encompassing a wide range of interests. Attractive synthetic approaches often rely upon the incorporation of such elements by selective acylation of one of the two amine functionalities, a relatively routine task if the two amines are unsymmetrical since small steric and/or electronic effects can exert a pronounced influence on the selective formation of mono-acylated products. There is considerable literature precedent demonstrating that primary amines can be acylated with excellent selectivity over secondary amines and that proximate electron withdrawing groups can kinetically impede the acylation of an amine. In addition, sterically demanding elements adjacent to the nitrogen atom of a piperazine will frequently and strongly favor acylation at the unencumbered amine functionality. However, the mono-acylation of symmetrical polyamines is considerably more challenging and methods for their selective mono-acylation have been studied in some detail. This is primarily because of the synthetic utility of the products as precursors to mono-functionalized derivatives via the conventionally applied protocol that relies upon protection, derivatization and deprotection.

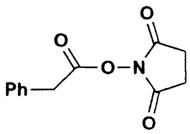
In the absence of inherent steric or electronic influences, treating a symmetrical diamine with one equivalent of an acylating agent would be expected to yield a statistical distribution of products comprising unreacted starting diamine and the mono- and diacylated products. Under these circumstances, the maximum theoretical yield of the mono-acylated product would be 50% with the yield of diacylated material not exceeding 25%. However, in practice the diacylated products are quite often isolated in much higher yields than mono-acylated products, even in the presence of a large excess of diamine.[40] As summarized in Table 1, the exposure of an 0.1 M solution of a symmetrical diamine to just 0.2 equiv. of a highly reactive acylating agent affords high yields of the diacylated product.[40] However, a careful analysis of the reaction kinetics demonstrated that the first acylation event proceeded much more rapidly than the second. The relative reaction rate ratios were determined to be between 3 and 20, dependent upon the length of the alkyl chain separating the diamine moieties. The formation of the diacylated product in quantities greater than that anticipated based on statistical grounds was attributed to inadequate dispersion of the reagents. This hypothesis relies upon the concept that a high local concentration of acylating agent completes the acylation of both amine elements before it is uniformly distributed throughout the reaction solution. In fact, the kinetic data suggested that should the mixing problem be eliminated, a better than statistical distribution of mono-acylated product would be anticipated. As a consequence, conditions that appropriately combine the use of less reactive acylating agents, lower temperatures to control reactivity, high dilution and rapid stirring of reaction mixtures are effective in producing mono-acylated products in preparatively useful yields, as summarized in Table 1.[40]

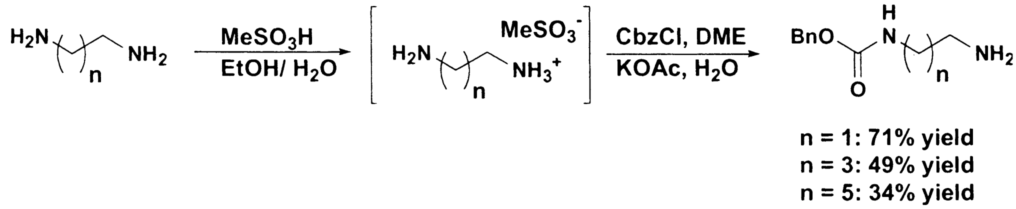
The introduction of a single acyl group to a diamine markedly reduces the nucleophilicity of the remaining amine element providing a generally applicable principle that is the foundation of several practical preparative protocols.[40] The earliest such method that has found widespread use takes advantage of dynamic protection of one amine moiety by protonation and is dependent upon the difference in basicity of a mono-acylated amine compared to that of a diprotonated diamine.[40–48] However, this effect is lessened as the separation between the two amine moieties increases and the effects of intramolecular interactions are reduced. A representative example of this general preparative procedure in which methanesulfonic acid is utilized to protect one amine moiety of a series of diamines whilst the other amine is derivatized with CbzCl is summarized in Scheme 12. Aqueous KOAc was included in the acylation step to neutralize the HCl generated and maintain the pH of the reaction mixture at ~4.0.[44]

The use of AcOH as the solvent appears to be a particularly convenient method, although the conditions described are somewhat harsh.[43] Less convenient but milder conditions utilize indicators to monitor pH, which is continuously adjusted by the addition of base as the derivatizing agent is introduced.[41,44] Barrett has extended this concept by

Table 1. The reaction of diamines with acylating agents



n	RCOX	% Diacyl product	
		0.1 M (RCOX)	5 mM (RCOX)
1	PhCOCl	99	22
1	$(PhCO)_2O$	24	14
1	$PhCH_2COCl$	89	56
1	$(PhCH_2CO)_2O$	29	7
1		7	6
3	PhCOCl	79	35
3	$(PhCO)_2O$	27	9



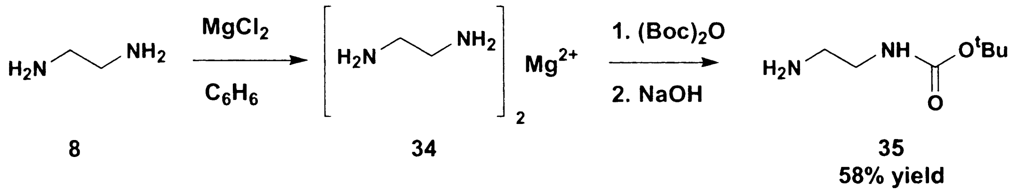
Scheme 12.

taking advantage of the propensity of 18-crown-6 to form a complex with protonated primary amines in a dynamic process.[49,50] However, the optimized conditions require two equivalents of this toxic and expensive reagent[49,50] and the use of either $MgCl_2$ or $AlCl_3$ appears to offer a cheaper and equally effective alternative.[51] Stirring ethylenediamine (**8**) with a 50% molar equivalent of anhydrous $MgCl_2$ in benzene afforded the isolable magnesium complex **34**, shown in Scheme 13. Exposure of **34** to a stoichiometric amount of di-*tert*-butyldicarbonate followed by alkaline hydrolysis delivered the mono-protected derivative **35** in 58% yield.[51] A comparative summary of the yields associated with the use of $MgCl_2$ and $AlCl_3$ to discriminate between the degenerate amines of the homologous series of diamines is presented in Table 2.[51]

More recent studies have focused on two alternative and mutually complementary approaches that rely upon the development of acylating agents with reduced intrinsic reactivity or a strategy of enhancing amine nucleophilicity. Success associated with the former method is based on kinetic differentiation due to the reduced reactivity of the remaining amine in a mono-acylated product coupled with a more discriminating acylating agent. In contrast, the latter strategy is in essence a kinetic inversion in which enhancing the nucleophilicity of an amine is designed to rapidly consume the substrate.

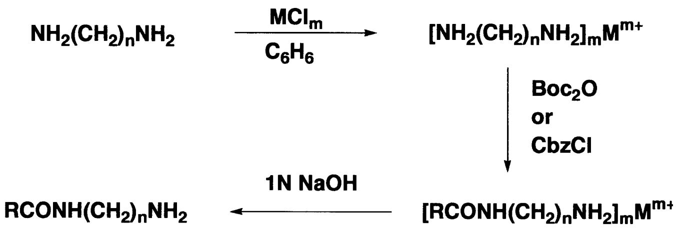
A variety of acylating reagents and conditions, many the result of careful consideration of reactivity in the design process, have been explored with generally good results and the most prominent examples are summarized in Table 3.[52–60] The structurally homologous diacylated ureas compiled in entries 2–5 are particularly effective reagents for the mono-acetylation of piperazine under mild reaction conditions.[53] 1,3-Dihydro-1,3-diacetyl-2*H*-benzimidazolone (**37**) emerged as the preferred reagent, superior in its reactivity to three more common but structurally disparate acetylating agents. Moreover, **37** is easily prepared from the commercially available cyclic urea **36** and the mono-acetylated by-product **38** is readily separated from product amides **39** by virtue of its limited solubility in common organic solvents (Scheme 14).[53]

Of the other reagents listed in Table 3, ethyl trifluoroacetate



Scheme 13.

Table 2. The mono-acylation of diamines under the influence of metal additives



	Yield (%) with $AlCl_3$		Yield (%) with $MgCl_2$	
n	R=OtBu	R=OBn	R=OtBu	R=OBn
2	44	21	58	42
3	55	53	78	35
4	44	73	75	68
5	36	65	64	61
6	39		57	

Table 3. Reaction of polyamines with diverse acylating agents

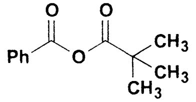
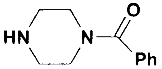
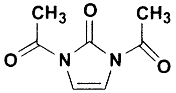
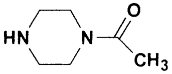
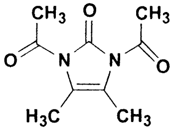
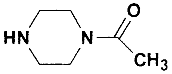
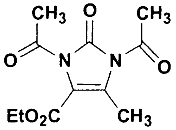
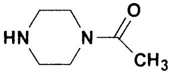
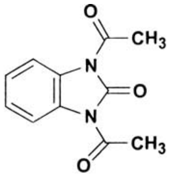
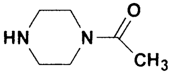
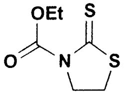
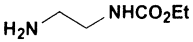
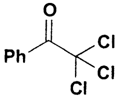
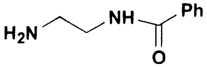
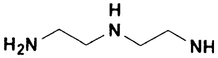
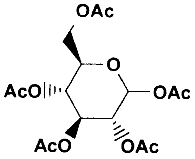
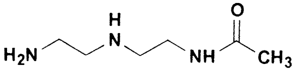
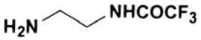
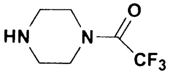
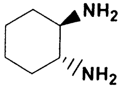
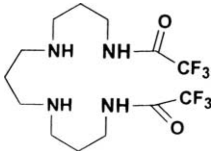
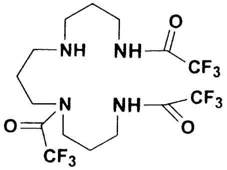
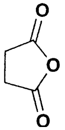
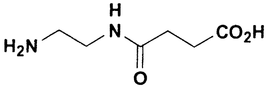
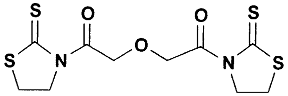
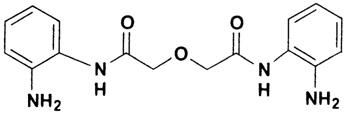
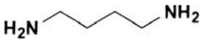
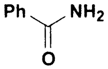
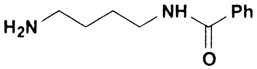
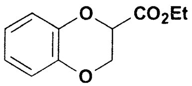
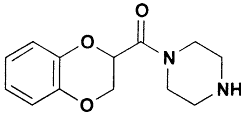
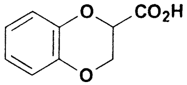
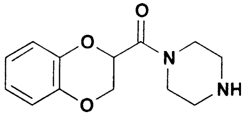
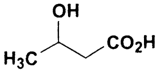
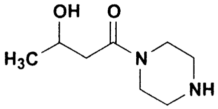
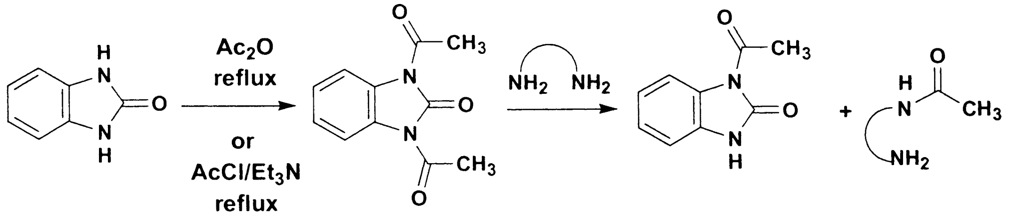
Entry	Substrate	Reagent	Product	Comments	Yield (%)	Reference
1	Piperazine			Anhydride prepared in situ in CH_2Cl_2; 2 equiv piperazine added and rt for 3 h	71	52
2	Piperazine				85	53
3	Piperazine			CH_2Cl_2/25°C	88	53
4	Piperazine				94	53
5	Piperazine				93	53
6	Ethylenediamine			CH_2Cl_2/10 min/rt	97	54
7	Ethylenediamine			1.5 equiv. amine in hexane at rt	100	55
8				0.2 mol of pentaacetate in EtOH at 25°C	41	56
9	Ethylenediamine	CF_3CO_2Et		12.6:1 mono to bis at −70°C in EtOH; poorer selectivity in CH_3CN		57

Table 3. (*continued*)

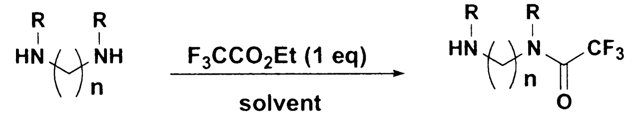
Entry	Substrate	Reagent	Product	Comments	Yield (%)	Reference
10	Piperazine	CF_3CO_2Et		5.8:1 in THF at rt		57
11		CF_3CO_2Et	Statistical mixture—due to cooperativity between amines	1.8:1 mono to bis		57
12		CF_3CO_2Et			96	58
13	Ethylenediamine			Mono-acylation in THF at rt but diacylation in EtOH at rt to 70°C	50	50
14	1,2-Phenylenediamine				80	51
15				Reflux at 159°C for 15 h	70	52
16	Piperazine			Reflux in xylenes with 2 equiv. piperazine for 26.5 h Heat neat ester with 1.2 equiv. piperazine at 110°C for 3 h	77 94	53 54
17	Piperazine			Reflux in xylenes with 2 equiv. piperazine for 75 h	50	53
18	Piperazine			Heat at 110°C for 20 h in the presence of 2 equiv. hexamethyldisilazane	83	55



36 37 38 39

Scheme 14.

Table 4. The reaction of symmetrical diamines with ethyl trifluoroacetate



n	R	Reaction temperature	Solvent	Mono/bis
2	H	0°C	MeCN	3.0
2	H	−70°C	EtOH	12.6
2	CH_3	rt	THF	43.7
3	CH_3	rt	THF	8.3
6	CH_3	rt	THF	3.6
2	$-CH_2CH_2-$	rt	THF	5.8

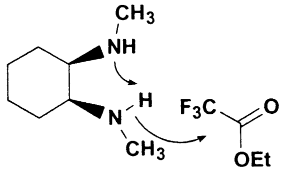
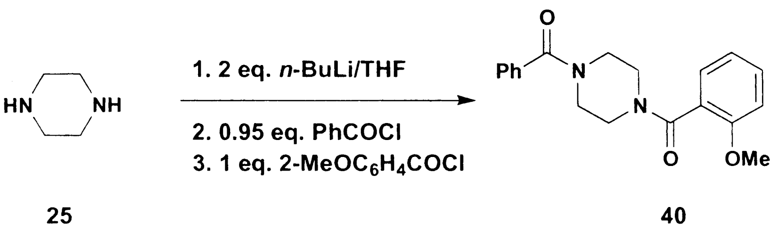


Figure 1.

(entries 9–12) combines the benefits of low cost and ready availability with ease of removal, providing a convenient substrate for further derivatization. However, the selective reaction of ethyl trifluoroacetate with diamines exhibited some dependency upon substrate and the reaction temperature, as summarized in Table 4. At 0°C, ethylenediamine (**8**) yielded a near statistical 3:1 ratio of mono- to bis-acylated products but lowering the reaction temperature to −70°C markedly increased this ratio to a preparatively useful 12.6:1.[57] The use of more sterically hindered secondary amines resulted in further enhancement and a ratio of 43.7:1 was obtained even under the more convenient conditions associated with conducting the reaction at room temperature. However, the increase in selectivity was diminished as the distance between the two secondary amines was increased and a very interesting observation was that *cis*- and *trans*-1,2-diaminocyclohexanes gave ratios of mono- to bis-acylated products of 68.0:1 and 1.8:1, respectively. These results were explained by invoking intramolecular hydrogen bonding between the amines, favored by proximity, which results in a concerted activation and deactivation, summarized schematically in Fig. 1.

Other methods offering advantage involve heating a primary amide (Table 3, entry 15),[61] ester (Table 3, entry 16)[62,63] or acid (Table 3, entry 17)[62] with a diamine or heating a carboxylic acid and a diamine in the presence of 1–2 equiv. of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) at 110°C, a reaction that proceeds via the intermediacy of a silyl ester (Table 3, entry 18).[64] The latter conditions are highly selective, producing small amounts of diacylated product only with reactive aromatic acids. Indeed, subjecting the mono-acylated diamines to the conditions under which they formed failed to produce detectable diacylated product.[64] All of these procedures take advantage of the poor electrophilicity of the carboxylic acid derivative (relative to e.g. acyl chlorides) to reduce the propensity for derivatization of the second, less nucleophilic amine after mono-acylation of the diamine.

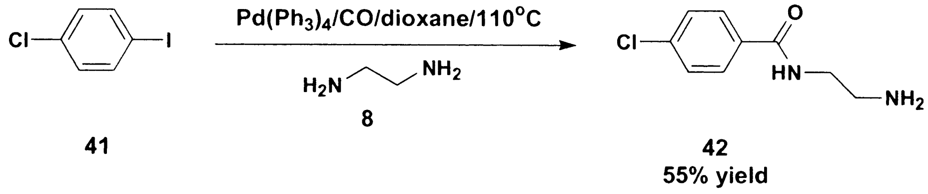
The concept of controlling acylation by enhancing the reactivity of diamines that are spatially proximate has also been explored.[19,65] By generating the dianion of piperazine (**25**) and related cyclic and acyclic diamines using BuLi, Wang et al. were able to accomplish mono-acylation with benzoyl chloride quickly and in high yield.[65] Under these conditions, benzoyl chloride was consumed rapidly at room temperature to afford the mono-benzoylated derivatives in yields ranging from 78 to 91% for the examples reported. However, this method was only examined in the context of aroyl chlorides and the inherent basicity of the lithium amides may preclude the use of enolizable acylating agents. Nevertheless, piperazine (**25**) was effectively and efficiently desymmetrized in a single operation to provide



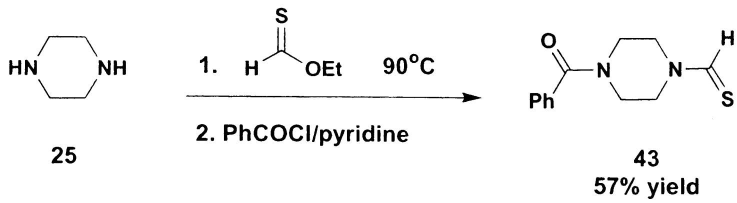
25

40
100% yield

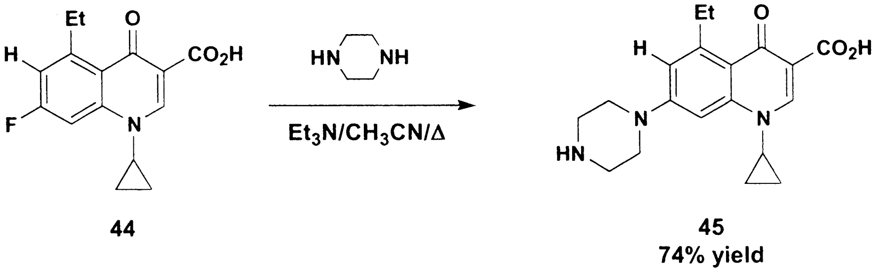
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

a quantitative yield of the unsymmetrical diaroyl derivative **40**, as summarized in Scheme 15.[65]

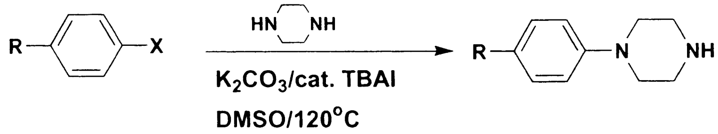
The use of metal-catalyzed carbonylation processes has also been examined with both ruthenium- and palladium-mediated procedures developed.[66,67] Ru-catalyzed carbonylation has been used to produce *N*-formyl piperazine but the preparative value is questionable given the poor overall yield of 23%.[66] Palladium-catalyzed carbonylation of 1-chloro-4-iodo-benzene (**41**) in the presence of 2 equiv. of ethylenediamine (**8**) afforded the amide **42** in an isolated 55% yield, as summarized in Scheme 16.[67]

An alternative strategy reacts piperazine (**25**) with *O*-ethyl thioformate to afford the unstable mono-thioformate intermediate which is exposed in situ to an acyl chloride or an anhydride to afford the disubstituted product.[68] When benzoyl chloride was employed in the second step of this procedure, benzamide **43** was isolated in an overall yield of 57%, as depicted in Scheme 17.

(iv) Reaction of polyamines with aromatic and heteroaromatic sp^2 electrophiles

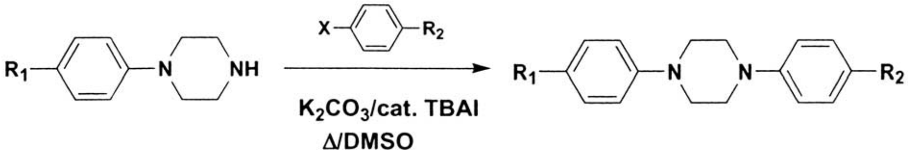
Arylated and heteroarylated diamines are pharmacophoric elements common to several important drugs, including the anti-bacterial quinolone ciprofloxacin (**4**),[4] the anxiolytic buspirone (**6**)[6] and the cardiac stimulant vesnarinone (**7**).[7]

Table 5. The reaction of substituted benzenes with piperazine



R	X	Yield of product (%)
NO_2	Br	98
NO_2	Cl	91
NO_2	NO_2	76
CN	Cl	80
$COCH_3$	Cl	49
OCH_3	Br	0

Table 6. The reaction of arylated piperazines with aryl halides



R_1	X	R_2	Yield of product (%)
NO_2	Cl	NO_2	0
NO_2	Cl	CN	0
CN	Cl	NO_2	81
$COCH_3$	Cl	NO_2	76
NH_2	Br	NO_2	85
NH_2	Cl	NO_2	77
OCH_3	Br	NO_2	77

In a typical experimental protocol for assembling molecules of this kind, a substituted benzene or electrophilic heterocycle derivative is exposed to an excess of the diamine, frequently at elevated temperatures, to complete the S_NAr reaction.[69] However, if the diamine is expensive, the electrophile can be used in excess under circumstances where a second S_NAr reaction is slow for steric or electronic reasons.[70] A successful example taken from the quinolone anti-bacterial literature in which only a slight excess of piperazine was used is shown in Scheme 18. Heating the fluoroquinolone **44** and 1.1 equiv. of piperazine (**25**) in the presence two equivalents of Et_3N at reflux in CH_3CN afforded the target compound **45** in 74% yield.[71]

In an effort to illuminate mechanistic aspects of this reaction, a recent study probed the arylation of unprotected piperazine in detail as part of an effort to identify practical conditions for the large scale preparation of an anti-fungal drug candidate.[72,73] The reaction of piperazine with a series of substituted benzenes provided adducts in yields that were found to be dependent upon the electronic nature of the electrophile, as summarized in Table 5. Attempts to arylate both nitrogen atoms of piperazine with 1-chloro-4-nitrobenzene were unsuccessful, even under forcing conditions with excess aryl halide and the addition of exogenous base.[72] In general, piperazines arylated with highly electron deficient nitro-aromatic moieties were resistant to further reaction. However, arylation of the second nitrogen atom did proceed smoothly with more modestly electron withdrawing aryl substituents or after reduction of the nitro moiety to an amine, data that is compiled in Table 6.[72]

These results led to the development of a theory focused on the effects of electron density at the substituted piperazine nitrogen and its role in providing anchimeric assistance by hydrogen bonding to the secondary amine and thereby enhancing nucleophilicity of this nitrogen atom, as depicted in Fig. 2(A).[73] Recognizing the potential for the nitro substituent to function as a H-bond acceptor, as depicted in Fig. 2(B), the reaction of piperazine with 1-chloro-2-nitrobenzene produced a mixture of *N*-arylated and *N*,*N′*-bis-arylated derivatives whilst 2-chlorobenzonitrile, constrained from engaging in intramolecular hydrogen bonding as a consequence of geometrical considerations, produced only the mono-arylated product under similar conditions. In addition, the dipolar aprotic solvents DMSO

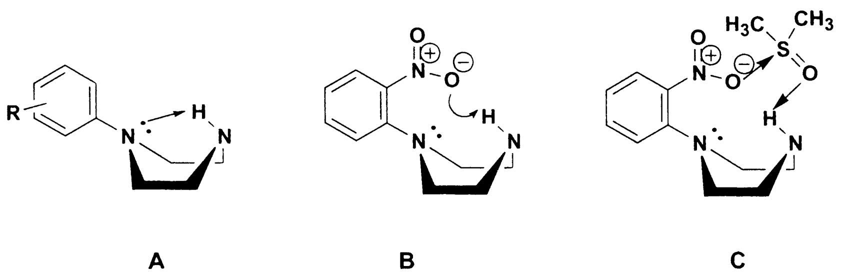
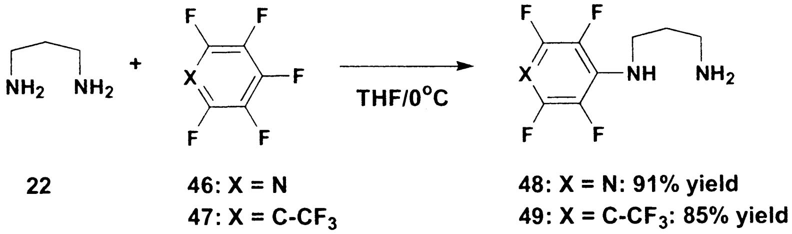


Figure 2.



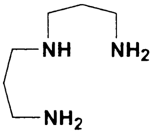
Scheme 19.

and *N*-methylpyrrolidinone (NMP) promoted the second arylation whereas in CH_3CN this reaction was sluggish. These results suggested the participation of solvent as a mediator of anchimeric assistance through hydrogen bonding, as depicted in Fig. 2(C) for DMSO.

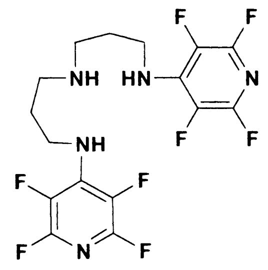
The polyfluoro-aromatic derivatives perfluoropyridine (**46**) and perfluorotoluene (**47**) react with stoichiometric amounts of 1,3-diaminopropane (**22**) in THF at 0°C to afford excellent yields of the mono-arylated products **48** and **49**, respectively, Scheme 19.[74]

The less reactive perfluorobenzene, C_6F_6, requires harsher conditions (DMF, 100°C and 2 equiv. of diamine) and produces the mono-arylated product **50** in a relatively modest yield, Scheme 20.[74] Production of bis-arylated and cyclized products detracted from the selective production of **50**. However, the bis-arylated product **51** was readily produced using just a stoichiometric amount of 1,3-diaminopropane (**22**).

Extension of this process to the selective mono-arylation of triamines such as **52** was not optimized and the bis-arylated product **53** was readily obtained at 0°C.[74]

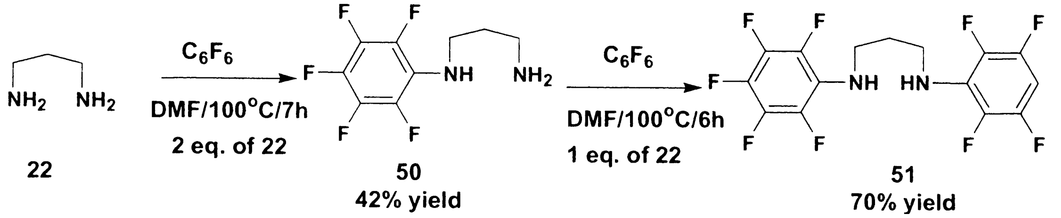


52

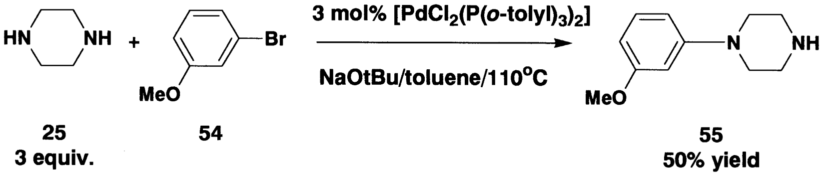


53

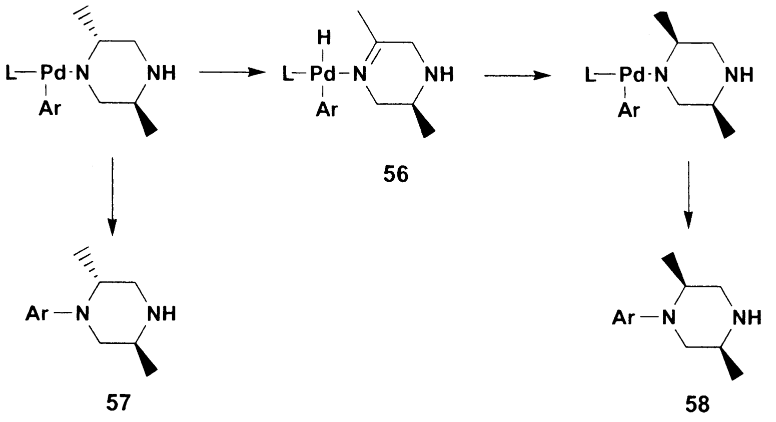
Palladium-mediated arylation of diamines has also been examined,[75–78] following the original disclosures of the potential for catalysis by Buchwald[79] and Hartwig.[80] Reaction of a slight excess of piperazine (**25**) with 3-bromoanisole (**54**) in the presence of 3 mol% of $[PdCl_2(P(o\text{-tolyl})_3)_2]$ and 1.4 equiv. of NaOtBu in toluene at 100°C afforded a mixture of *N*-mono- and *N*,*N*′-bis-arylated derivatives.[75] The *N*,*N*′-bis-arylated product was isolated in 46% yield by employing half an equivalent of piperazine but using a three molar excess of piperazine (**25**) increased the yield of the *N*-mono-arylated material **55** to 50% at the expense of the bis-substituted product (<5%), Scheme 21.



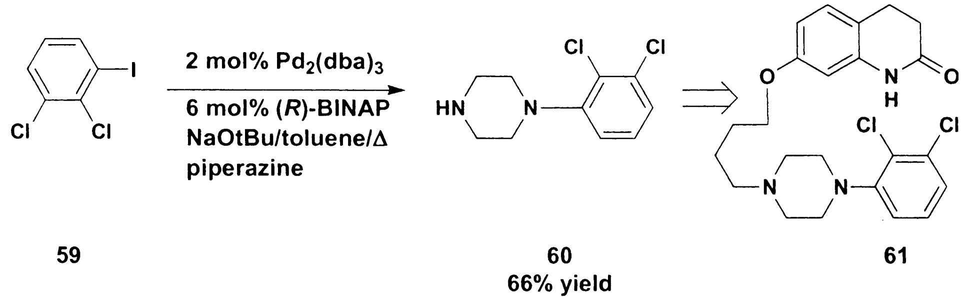
Scheme 20.



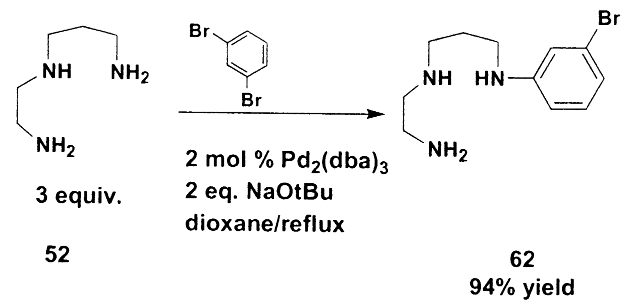
Scheme 21.



Scheme 22.



Scheme 23.

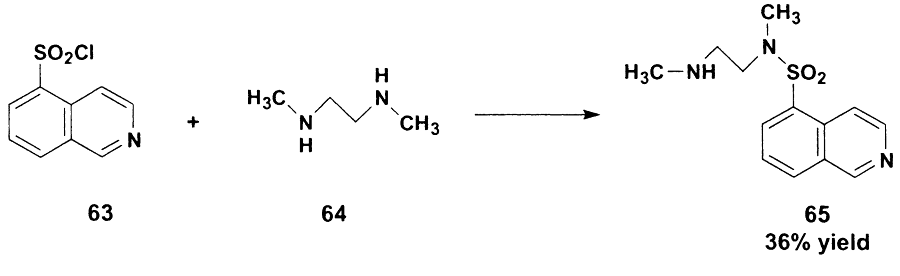


Scheme 24.

In general, although this procedure is useful for *N*-arylation using unactivated arene derivatives, yields are poor to modest and showed sensitivity to steric effects, both on the aromatic substrate and the piperazine. For example, *ortho*-substituted iodo- or bromo-benzene derivatives afforded low yields of products whilst C-methylated piperazines reacted exclusively at the sterically less encumbered nitrogen and gave none of the bis-arylpiperazine derivative. Interestingly, although *trans*-2,5-dimethylpiperazine coupled in poor (19%) yield, the product was isolated as a 5:1 mixture of *trans* and *cis* products **57** and **58**, respectively, indicative of epimerization. This was postulated to occur via a sequential β-hydride elimination and insertion process to afford a Pd-coordinated imine intermediate **56**, Scheme 22.[75]

Specific conditions were developed for the synthesis of 2,3-dichlorophenylpiperazine (**60**), an intermediate in the synthesis of the anti-psychotic agent aripiprazole (**61**), optimally using piperazine (**25**), 1-iodo-2,3-dichlorobenzene (**59**), 2 mol% $Pd_2(dba)_3$, 6 mol% (*R*)-BINAP and NaOtBu in toluene at reflux (Scheme 23).[76] 1-Bromo-2,3-dichlorobenzene participated almost as effectively but the triflate analog with *N*-methylpiperazine gave only traces of coupled product.

Acyclic polyamines are readily arylated using $PdCl_2(dppf)$ or $Pd_2(dba)_3$ as catalysts, producing the mono-substituted products in yields ranging from poor to excellent.[77,78] The success of this process is largely dependent upon the substitution pattern of the aromatic substrate. For example, 1,3-diaminopropane (**22**) reacted with bromobenzene to afford the mono-phenyl derivative in 70% yield. However, yields were lower using *p*-bromoanisole (5%) or *o*-bromoanisole (20%), although both could be improved by increasing catalyst loading from 0.5 mol% to 5 or 10 mol%.[77] This procedure was successfully extended to poly-halogenated benzenes where generally excellent yields were recorded for the coupling of aliphatic di- and tri-amine derivatives in the presence of 2–4 mol% of catalyst. For example, the



Scheme 25.

Scheme 26.

reaction of 1,3-dibromobenzene with *N*-(3-aminopropyl)-1,3-diaminopropane (**52**) afforded the mono-arylated product **62** in 94% yield, Scheme 24.[78]

2.3. Reactions of polyamines with other electrophiles

The mono-sulfonylation of diamines has not received extensive study and most procedures rely upon the use of excess diamine to maximize the yield of mono-substituted derivatives.[81–83] For example, the reaction of the isoquinolylsulfonyl choride **63** with 1.5 equiv. of diamine **64** affords the sulfonamide **65** in a modest 36% yield (Scheme 25).[82]

In a more compelling example, the sulfamide **66** was readily obtained under mild conditions in 73% yield after recrystallization using only a 66% excess of piperazine (**25**) relative to the sulfamoyl chloride.[83] Further derivatization of **66** afforded compounds that were determined to be inhibitors of sorbitol dehydrogenase[83] (Scheme 26).

3. Conclusion

Considerable progress has been made over recent years towards the development of practical and efficient methods for selectively derivatizing one amine moiety in the context of symmetrically disposed polyamines. Several protocols represent practical and useful methodologies that are reasonably broad in scope and have demonstrated general applicability. These processes, which are based on a number of conceptually different and complementary themes, are beginning to find utility in a range of synthetic endeavors. However, it is clear that more general and reliable methods that do not rely on the kind of reactivity bias conferred by unique, inherent structural elements and their relative disposition are required in order to further advance this area of organic synthetic methodology.

4. Note added in proof

A recent advance has provided a useful and practical experimental protocol for the mono-alkylation of symmetrical and unsymmetrical primary diamines.[84] The use of sub-stoichiometric amounts of CsOH, a base that has previously shown uniquely high selectivity for the mono-alkylation of primary amines uncomplicated by the production of significant amounts of tertiary amine product, has been extended to the mono-alkylation of symmetrical primary diamines. Carefully optimized conditions expose the diamine to a molar quantity of halide and 0.5 equivalents of CsOH in DMF in the presence of powdered 4 Å molecular sieves, an ingredient that accelerates the process whilst optimizing yield. The reaction is generally performed at room temperature and is effective even with poorly reactive alkylating agents although for more reactive halides lowering the temperature to 0°C minimizes over-alkylation. In a representative example, the reaction of 1,3-diaminopropane (**22**) with 1-bromo-3-phenylpropane (**67**) afforded the mono-alkylated product **68** in 65% yield after 24 hours (Scheme 27).[84]

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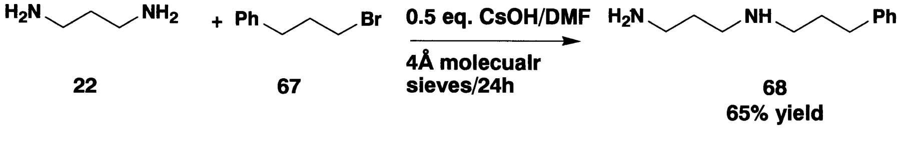

Scheme 27.

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Nicholas Meanwell is currently Director of Chemistry at the Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, Connecticut. He received his PhD degree in 1979 from the University of Sheffield for studies conducted under the supervision of Dr D. Neville Jones that focused on the application of alkenyl sulfoxides as synthetic precursors of prostaglandin analogs. A post-doctoral fellowship (1979–1982) with Professor Carl R. Johnson at Wayne State University was devoted to the development of new synthetic methodology based on sulfur chemistry and its application to total synthesis. In 1982, he joined Bristol-Myers Squibb where he designed and synthesized inhibitors of blood platelet aggregation as part of the cardiovascular therapeutic focus before contributing to the identification and development of neuroprotective agents. The large-conductance, Ca^{2+}-dependent potassium channel opener Maxipost™, currently in Phase 3 clinical trials, emerged from those studies. Since 1994, he has been responsible for a team of chemists designing and synthesizing anti-viral agents directed towards new developing therapeutic options for the treatment of HIV, HCV, RSV and influenza.

Tao Wang is currently a Senior Research Investigator at the Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, Connecticut. He received his B.S. degree in Organic Chemistry in 1990 from Peking University in Beijing, China. In 1996 he obtained his PhD degree under the supervision of Professor Kang Zhao at New York University in New York City for an analysis of stereocontrolled S_N2' cyclizations. From 1996 to 1998 he worked as a postdoctoral associate with Professor Gilbert Stork at Columbia University, investigating asymmetric dihydroxylation reactions and developing routes towards the total synthesis of (−)-tetracycline. In May 1998, he joined the anti-viral chemistry department of Bristol-Myers Squibb Pharmaceutical Research Institute. His research interests are in the areas of the design and synthesis of anti-viral drug candidates, the application of new technology and the development of novel synthetic methodology, particularly involving heterocycles and new synthons, for the acceleration of drug candidate optimization.