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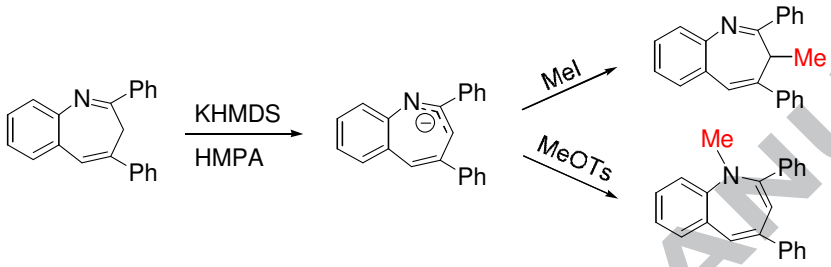
Graphical Abstract



Regioselective Alkylation Reactions of 2,4-Diphenyl-3*H*-1-benzazepine give either 3-Alkyl-3*H*-1-benzazepines or 1-Alkyl-1*H*-1-benzazepines

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Abstract: 2,4-Diphenyl-3*H*-1-benzazepine is deprotonated with either LDA or KHMDS. The resulting anion is alkylated with alkyl halides or MeOTs, giving either products of alkylation at C3, or at N, or a mixture of both. The regioselectivity depends on the base, presence of the complexing agent HMPA, and the leaving group of the alkylating agent. Using MeI as alkylating agent gives exclusively the C3-methylated product, while using MeOTs gives exclusively the N-methylated product. The N-alkylated products show evidence of stereodynamic behavior in their NMR spectra.

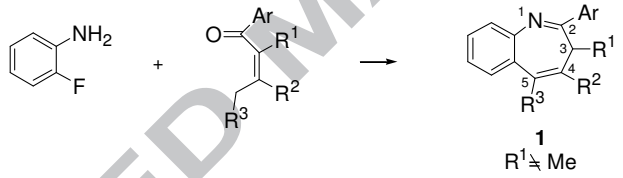
Keywords: 1-benzazepine, regioselective, alkylation, stereodynamic

INTRODUCTION

The stereodynamic properties of conformationally chiral nitrogen-atom-containing medium-ring heterocycles, typified by 1-benzazepine derivatives, are a subject of much current interest.[1] The sense of conformational chirality can affect the biological activity of these molecules. If the sense of conformational chirality changes with time, this must be taken into account if the molecule is to be developed into a drug.[2,3] Placement of an alkyl group on the ring, which creates a chiral center, can quicken or slow the rate of conformational exchange; more importantly, this new chiral center can bias the conformational chirality and result

in preferential formation of a particular diastereomer.[1,4-9] Thus, studies of the effects of substitution are gaining importance in the development of new heterocyclic drugs of this class.

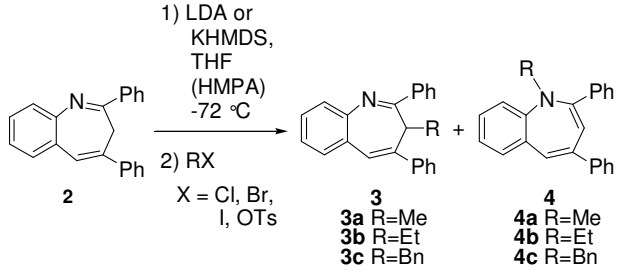
We have reported a synthesis of 2-aryl-3*H*-1-benzazepines **1** which allows placement of alkyl groups at C4 and C5 (Scheme 1).[10] However, attempted placement of a methyl group at C3 failed. To overcome this limitation, we envisioned a deprotonation at C3 of a benzazepine, followed by an S_N2-type reaction with an akyl halide. Streef et al.[11] have reported that 3*H*-azepines can be deprotonated, and the resulting anion alkylated to give 3-alkyl-3*H*-azepines. Similarly, we have reported that 2,4-diphenyl-3*H*-1-benzazepine (**2**) can be deprotonated with LDA and the resulting anion alkylated with methyl iodide, giving exclusively the 3-alkylated product, albeit in low yield.[12] We report here that the yield of this reaction can be improved, and the regioselectivity altered to favor the novel N-alkylated isomers, by varying the base, complexing agent, and the alkylating agent.



Scheme 1. Limitation in a synthesis of 2-arylbenzazepines.

RESULTS AND DISCUSSION

Treatment of benzazepine **2**[13] with LDA or KHMDS, either with or without the complexing agent HMPA, in THF at -72 °C, for either one hour (LDA) or 10 minutes (KHMDS), gives a deeply colored anion. To this solution is added an alkyl halide, followed by warming to room temperature. Standard extractive aqueous work-up and chromatographic purification gives the 3-alkylated products **3**, and N-alkylated products **4** (Scheme 2).[14] The 5-alkylated products were not seen in any of the reactions. NMR yields were calculated based on the mass of crude product, which contained the two alkylated products and sometimes starting benzazepine.



Scheme 2. Alkylation of benzazepine **2** to give 3-alkylated **3** and N-alkylated **4**.

Table 1 shows the results of our attempts at methylation, ethylation, and benzylation. Use of LDA as base and MeI as alkylating agent gave exclusively 3-methyl **3a** albeit in low yield (entry 1); use of excess MeI did not give an improved yield. Use of excess KHMDS in place of LDA resulted in only recovered starting material (entry 2); this surprising negative result was confirmed by repetition. Inclusion of the complexing agent HMPA gave a mixture of 3-methyl **3a** and N-methyl **4a**, favoring the former (entry 3). By the principles of HSAB theory,[15] we reasoned that use of the harder alkylating agent MeOTs may promote reaction at the harder nitrogen atom of the deprotonated benzazepine. This proved to be the case, as no 3-methyl **3a** could be detected in the crude reaction mixture of entry 4. As in methylation, the selectivity of the ethylation reactions (entries 5-8) showed sensitivity to inclusion of HMPA (6 vs. 7), and choice of leaving group in the alkylating agent (entry 7 vs 8).

The regioselectivity is also affected by the size of alkylating agent. As the steric bulk of the alkyl halide increased, the selectivity for 3-alkylated **3** decreased (compare entries 3 and 7). This effect was especially prominent in benzylation reactions (entries 9-13) which showed the least regioselectivity. The first attempt at benzylation (entry 9), using the conditions from entry 1, gave only stilbene, 2-bromo-1,2-diphenylethane and recovered starting benzazepine; stilbene and 2-bromo-1,2-diphenylethane are both products of base-induced self-condensation of benzyl bromide. Use of KHMDS as base either without (entry 11) or with HMPA present (entry 12) still resulted in a mixture of 3- and N-alkylated products. Unlike the methylation and ethylation reactions, the selectivity of benzylation did not change much with a change of leaving group in the alkyl halide (entry 12 vs. entry 13).

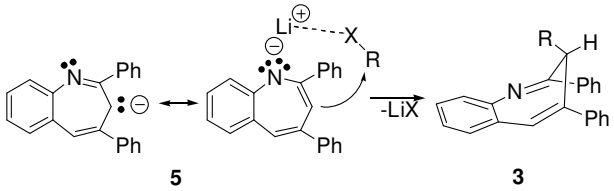
Finally, to maximize the yields, we used the system of Carlier et al.,[16] consisting of 2.4 equivalents of KHMDS/HMPA. We found, as they did, that the superstoichiometric amount of base is needed for acceptable yields.

					Isolated yields	
entry	base (eq.)	eq. HMPA	R-X (eq.)	NMR yield (**3**:**4**)	**3**	**4**
1	LDA (2.0)	0	MeI (1)	63 (100:0)	31	0
2	KHMDS (2.4)	0	MeI (1)	0 (-)	0	0
3	KHMDS (2.4)	12	MeI (5)	83 (89:11)	49	8
4	KHMDS (2.4)	12	MeOTs (5)	70 (0:100)	0	49
5	LDA (2.4)	0	EtI (1)	42 (90:10)	n.d.	n.d.
6	KHMDS (2.4)	0	EtI (1)	n.d. (80:20)	n.d.	n.d.
7	KHMDS (2.4)	12	EtI (1)	86 (68:32)	40	21
8	KHMDS (2.4)	12	EtBr (1)	87 (30:70)	22	43
9	LDA (2.0)	0	BnBr (4)	0 (-)	0	0
10	LDA (2.4)	12	BnBr (1)	n.d. (58:42)	n.d.	n.d.
11	KHMDS (2.4)	0	BnBr (1)	83 (67:33)	35	13
12	KHMDS (2.4)	12	BnBr (1)	98 (50:50)	34	33
13	KHMDS (2.4)	12	BnCl (1)	95 (46:54)	32	33

Table 1. Alkylation reactions of benzazepine **2**, to go with Scheme 2.

The regioselectivity seen in the alkylation reactions can be explained in the following way. After deprotonation by LDA, a resonance-stabilized anion such as **5** would be the result. The lithium ion may be more tightly bound to the nitrogen atom. When an alkyl halide approaches, a cyclic transition state can be envisioned, where the alkyl group of the alkyl halide will end up being attached to C3 because of complexation of the lithium ion with the halogen atom. Thus, 3-alkylation is favored. As the counterion is switched from lithium to potassium, and then to potassium/HMPA, the anion becomes more and more naked. In this case, most of the negative charge will reside on the N atom, causing it to be more nucleophilic than C3. Especially in the presence of HMPA, the metal ion is not available to

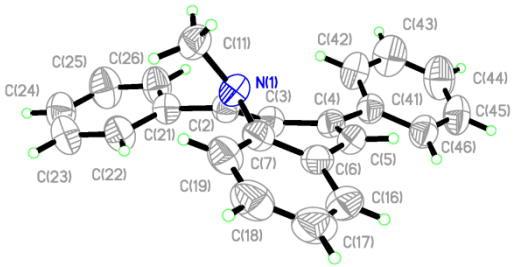
orient the incoming alkyl halide, so N-alkylation is favored, or at least 3-alkylation is slightly less favored. In either case, the alkyl group of the products **3** and **4** is expected to be oriented in the axial sense, initially at least, based on stereoelectronic considerations proposed in a closely related system.[17]



5 **3**

Scheme 3. Rationalization of C3-alkylation in anion **5** when lithium is the counterion.

(a)



(b)

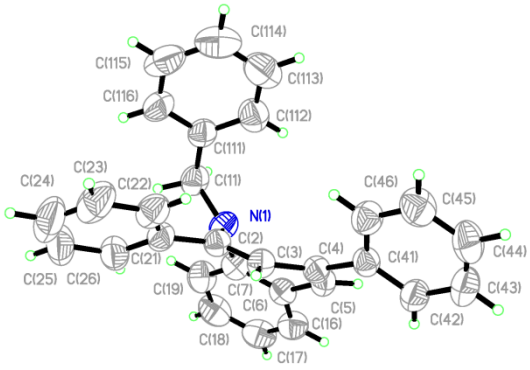


Figure 1. ORTEP diagrams of (a) N-methyl **4a**, and (b) N-benzyl **4c**. One enantiomer of the two present in each compound is shown arbitrarily.

The regiochemical and stereochemical assignments were done by both X-ray crystallography and 1H NMR analyses. The X-ray crystal structures of N-alkylated **4a** and **4c** (Figure 1) show, in addition to puckered azepine rings, considerably flattened nitrogen atoms which are out of the planes of their respective benzo groups; in **4a** the sum of the three C-N-C bond angles is 353°, while the C19-C11-N-C7 dihedral angle is 30°.[18] The alkyl groups of both are oriented in the pseudoequatorial manner, although there is not much of a distinction between axial and equatorial, as the hybridization of the nitrogen atom must be close to sp^2.

The 3-alkylated compounds **3b** and **3c** are solid, but crystals suitable for X-ray analysis could not be obtained. Since the expected NMR spectra of the possible 5-alkylated benzazepines would be similar to those of their 3-alkylated isomers, a detailed NMR study was undertaken to confirm the proposed structures of **3b** and **3c**. This was done by analyzing the coupling pattern, chemical shifts, and NOE data. For example, doublets in the aromatic region of the proton spectrum that integrate to two protons are markers for the ortho protons of the 2- and 4- phenyl groups, while doublets that integrate to one proton each are assigned to H6 and H9 of the benzazepines. This information when coupled with the observed NOEs from H3 to the ortho protons of the 2- and 4- phenyl groups, and also from H5 to H6, unequivocally confirmed the structures of **3b** and **3c** (see

supplementary data). The pseudoaxial orientation can be assigned to the alkyl groups in these two based on similarities in their 1H NMR spectra when compared to the 1H NMR spectra of 3-methyl **3a** and benzazepine **2**, which are well characterized.[12] In 3-methyl **3a**, which is known to have its methyl group in the pseudoaxial orientation,[12] the chemical shift of the pseudoequatorial H3 is 5.00 ppm; the corresponding values for 3-ethyl **3b** and 3-benzyl **3c** match well, at 4.81 and 5.00 ppm, respectively. For comparison, the chemical shift of the pseudoequatorial H3 in benzazepine **2** is 4.97 ppm, while the chemical shift of the pseudoaxial H3 is much lower, at 1.98 ppm.[10,19]

The N-alkylated benzazepines provide an interesting contrast to their 3-alkylated isomers. Both N-alkylated and 3-alkylated benzazepines contain two elements of chirality, a chiral center and the conformationally chiral seven-membered ring. A ring-flip, which inverts the seven-membered ring, converts 3-methyl **3a** to a diastereomer of the original structure, as the chiral center is not inverted. In an earlier study,[12] we found that 3-methyl **3a** exists as the major isomer (1,400:1) in equilibrium with its ring-flipped diastereomer, and that their interconversion is fast (Gibbs free energy of activation ($\Delta G^{\ddagger}$) = 16.4 kcal/mol for ring-flip of **3a**) at room temperature. The situation may be much different for the N-alkylated isomers **4a**-**c**, as both chiral elements have the possibility of inverting. Enantiomerization of the N-alkylated benzazepines would require both a ring-flip of the azepine ring, and inversion of the N atom; these two processes could be concomitant or occur independently of each other.

When a solution of N-benzyl **4c** in $CDCl_3$ is cooled below room temperature, the singlet in the 1H NMR spectrum assigned to the diastereotopic benzylic protons begins to broaden and eventually decoalesces at 278 K into a pair of doublets. No other broadening of peaks is seen. This is an indication that a dynamic stereochemical process is occurring, which is causing exchange between the benzylic protons. Using the chemical shift difference (78.6 Hz) and the geminal coupling constant (15.0 Hz), the $\Delta G^{\ddagger}$ of the dynamic process at the coalescence temperature can be calculated.[20] For N-benzyl **4c**, the $\Delta G^{\ddagger}$ is found to be 13.8 kcal/mol.

In conclusion, regioselective alkylation of a 3*H*-1-benzazepine provides access to 1-alkyl-1*H*-1-benzazepines, which present some very interesting stereochemical

features. The puckered azepine ring has planar chirality. Also, the nitrogen atom in principle is a chiral center, although the X-ray crystal structure indicates considerable deviation from pyramidal geometry towards trigonal planar. Preliminary NMR evidence suggests that these molecules show dynamic stereochemistry of some type. We plan a full computational and NMR spectroscopic study that will allow assignment of free energy barriers to the various stereodynamic processes that occur during enantiomerization of the N-alkylated benzazepines. These processes include a ring-flip, inversion of the nitrogen atom, rotations within the alkyl group, and rotation of the phenyl groups. We expect our studies to add to the growing literature of medium-ring nitrogen-atom-containing heterocycles, some important members of which exhibit planar chirality and contain a chiral nitrogen atom.[21-25]

Supplementary data available: Experimental procedures for **3b**, **3c**, **4b**, and **4c**; 1H and 13C NMR spectra of **3b**, **3c**, and **4a-c**; variable-temperature 1H NMR spectra of **4b** and **4c**; NOE data for **3b** and **3c**; crystallographic data and information about the data collection for **4a** and **4c**. Crystallographic data (excluding structure factors) for **4a** and **4c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 999481 (**4a**) and CCDC 999482 (**4c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.Uk).

Acknowledgments

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14) Experimental procedures for 2,4-diphenyl-3-methyl-3*H*-1-benzazepine (**3a**) and 2,4-diphenyl-1-methyl-1*H*-1-benzazepine (**4a**): To a solution of 2,4-diphenyl-3*H*-1-benzazepine (**2**) (296 mg, 1.00 mmol) and HMPA (2.0 mL, 12 mmol) in 10 mL anhydrous THF at -72 °C under N_2 was added dropwise potassium hexamethyldisilazide (2.4 mL, 2.4 mmol; 1.0 *M* in THF), giving a dark-brown solution. After 10 min, methyl iodide (0.310 mL, 4.98 mmol) was added dropwise, and the color of the solution changed to red-orange. The cold bath was removed, and after 25 min of warming to room temperature, the solution changed to a milky yellow color. The solution was partitioned between 8 mL H_2O and 8 mL Et_2O. The aqueous layer was extracted with 2 x 8 mL Et_2O, and the combined organic layer was washed

with 2 x 8 mL 1.0 *M* aqueous HCl. Drying of the organic layer over $MgSO_4$ and rotary evaporation gave 271 mg crude product, which contained an 89:11 ratio of 3-methyl **3a**:N-methyl **4a**, as judged by relative 1H NMR peak areas of the quartet at 5.00 ppm due to H3 in 3-methyl **3a**, and the doublet at 5.84 ppm due to H3 in N-methyl **4a**. Purification by radial chromatography (silica gel, 1-mm rotor, 1% EtOAc/hexane) gave two fractions: N-methyl **4a** (25 mg, 8% yield) as an orange solid, mp = 101-103 °C, R_f = 0.50 in 5% EtOAc/hexane; and 3-methyl **3a**[12] (152 mg, 49% yield). 2,4-diphenyl-1-methyl-1*H*-1-benzazepine (**4a**): 1H NMR (500 MHz, $CDCl_3$) δ 2.93 (s, 3H), 5.84 (d, *J* = 0.8 Hz, 1H), 6.94 (s, 1H), 7.01-7.05 (m, 2H), 7.09 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.28-7.42 (m, 9H), 7.58 (dd, *J* = 8.4, 1.4 Hz, 2H); 13C NMR (125 MHz, $CDCl_3$) δ 39.1, 118.0, 119.4, 123.5, 126.2 (2), 127.5, 127.7, 128.2 (4), 128.4 (2), 129.2, 129.9, 130.5, 134.8, 139.1, 141.1, 141.8, 152.8, 153.2; HRMS (CI) calcd. for $C_{23}H_{19}N$+H *m/z* 310.1590, found 310.1581. Slow recrystallization from 10% EtOAc/hexane gave crystals of N-methyl **4a** suitable for X-ray analysis. A crystal of N-methyl **4a** was mounted on the end of a glass fiber. Data collected at room temperature indicated orthorhombic symmetry and systematic absences consistent with space group *Pbca*. This space group was used for the solution and refinement of the structure. Crystal data and information about the data collection are provided in the supplementary data.

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18) The corresponding values for **4c** are 353° and 34°.

19) The chemical shifts for the protons of the methylene group in benzazepine **2** aren't strictly comparable to the chemical shifts of the H3 protons in the others, as the solvents and temperatures are different. The two diastereotopic methylene protons in benzazepine **2** are only distinguishable at low temperature; at room temperature they appear together as a singlet due to a fast ring-flip. Also, we have found the effect of solvent to be minimal on the chemicals shifts of these types of protons.

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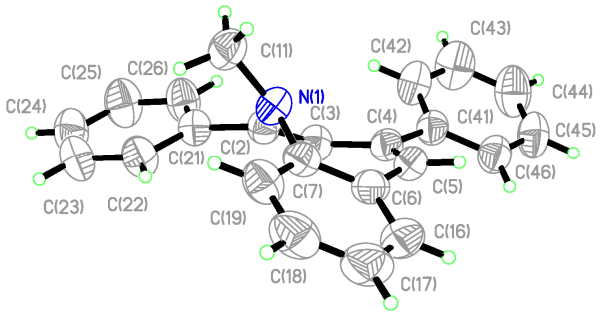
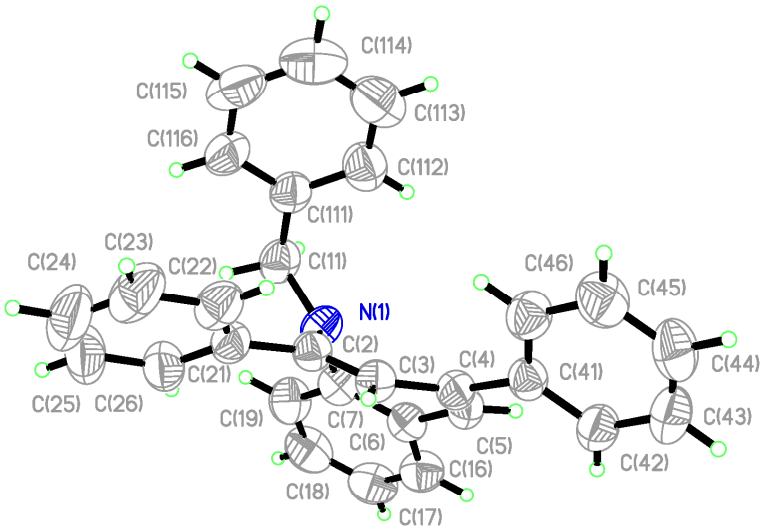
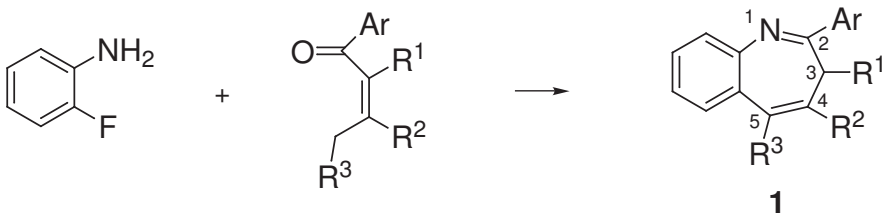
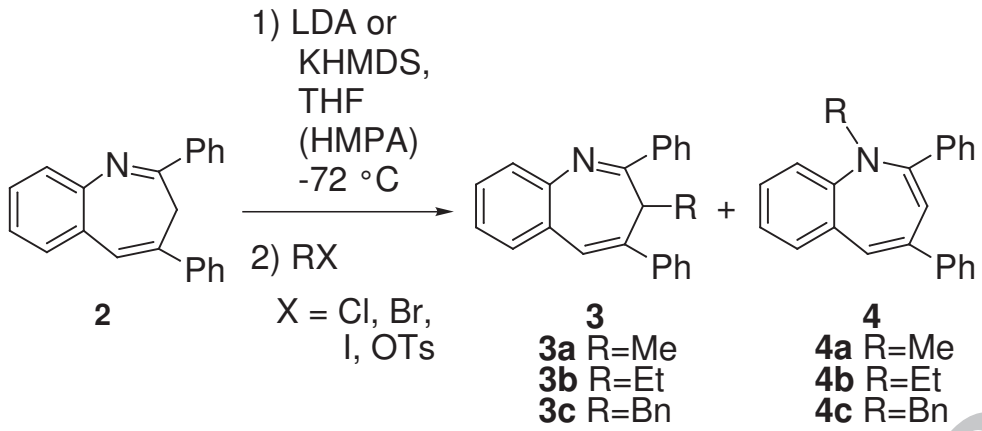






1

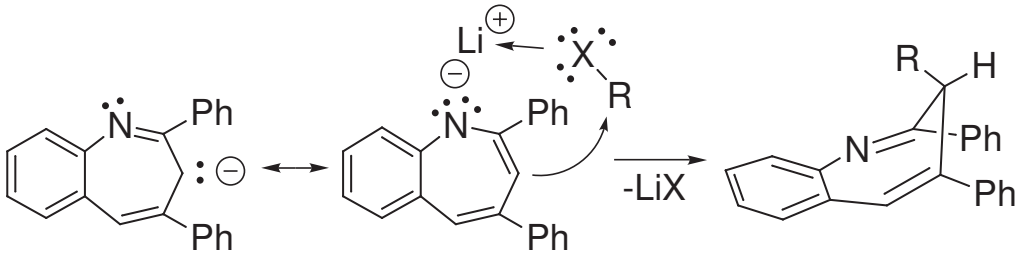
$R^1 \neq$ Me



2

3
3a R=Me
3b R=Et
3c R=Bn

4
4a R=Me
4b R=Et
4c R=Bn



5 **3**

					Isolated yields	
entry	base (eq.)	eq. HMPA	R-X (eq.)	NMR yield (**3**:**4**)	**3**	**4**
1	LDA (2.0)	0	MeI (1)	63 (100:0)	31	0
2	KHMDS (2.4)	0	MeI (1)	0 (-)	0	0
3	KHMDS (2.4)	12	MeI (5)	83 (89:11)	49	8
4	KHMDS (2.4)	12	MeOTs (5)	70 (0:100)	0	49
5	LDA (2.4)	0	EtI (1)	42 (90:10)	n.d.	n.d.
6	KHMDS (2.4)	0	EtI (1)	n.d. (80:20)	n.d.	n.d.
7	KHMDS (2.4)	12	EtI (1)	86 (68:32)	40	21
8	KHMDS (2.4)	12	EtBr (1)	87 (30:70)	22	43
9	LDA (2.0)	0	BnBr (4)	0 (-)	0	0
10	LDA (2.4)	12	BnBr (1)	n.d. (58:42)	n.d.	n.d.
11	KHMDS (2.4)	0	BnBr (1)	83 (67:33)	35	13
12	KHMDS (2.4)	12	BnBr (1)	98 (50:50)	34	33
13	KHMDS (2.4)	12	BnCl (1)	95 (46:54)	32	33

Graphical abstract