Synthesis of 6-Substituted 7-Bomoazabicyclo[2.2.1]heptanes *via* Nucleophilic Addition to 3-Bromo-1-azoniatricyclo[2.2.1.0]-heptane Bromide

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Abstract: We describe herein an efficient method for the preparation of a functionalised bicyclic framework (6-substituted 7-bromo-aza-bicyclo[2.2.1]heptane) through the selective opening of the aziridium **2** with organocuprates in up to 90% yield. These interesting chiral building blocks were then utilised as novel ligands in the rearrangement of epoxides to afford chiral allylic alcohols.

Keywords: asymmetric catalysis; aziridinium opening; diamine ligand; enantiopure; organocuprates

Introduction

Small, easily accessible enantiopure chiral molecules are of great interest in both the development of new efficient asymmetric catalysts and as building blocks in the synthesis of larger chiral molecules. In recent years our group has developed a number of low molecular weight bicyclic compounds; with applications as chiral ligand for the transfer hydrogenation of ketones[1,2] (e.g., **1a**) and the rearrangement of epoxides into allylic alcohols[3] (e.g., **1b**).

A limitation of these ligands is the difficulty in introducing diversity during the synthesis and the lack of a possible anchoring point on which to attach a solid support material, allowing a simpler purification and the catalyst to be easily recycled. We consequently investigated the development of versatile methods to prepare such functionalised chiral building blocks.

Our attention was drawn to the work of Shapiro[4] and Pombo-Villar[5] on the ring opening of enantiomerically pure aziridinium bromide **3a** with stabilised nucleophiles. Complete inversion of configuration of the ring system occurs due to the fact that only the less sterically hindered bond of the aziridinium bromide is available for S_N2 nucleophilic attack (Scheme 1). A later patent[6] describes the ring opening of the racemic aziridinium bromide **3b** with hydride as the nucleophile, leading to an unsubstituted bicyclic structure. In each case they employed this strategy to synthesise analogues of the muscarinic agonists arecoline and epibatidine.

We decided to extend this methodology by investigating the reactivity of the aziridinium ion **2** towards hard nucleophiles derived from organolithium- or Grignard-type reagents. This would allow a convenient route to a large number of enantiopure bicyclic molecules, bearing various substituents at the 6-position and a bromine atom on the bridgehead position, allowing for further functionalisation and introduction of more diversity to these molecules (Scheme 1).

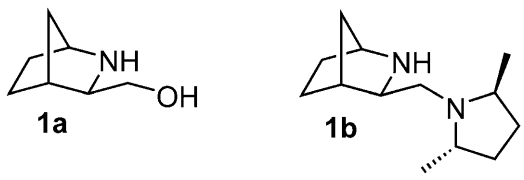
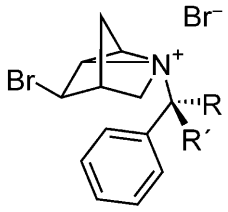


Figure 1. Low molecular weight bicyclic compounds **1a** and **1b**.



2 R = H, R´ = Me
3a R = Me, R´ = H
3b R = H, R´ = H

Figure 2. Aziridinium bromides **3a**–**c**.

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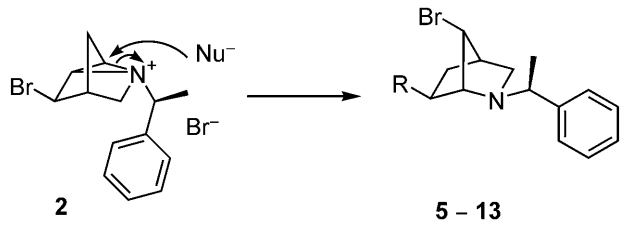


Scheme 1.

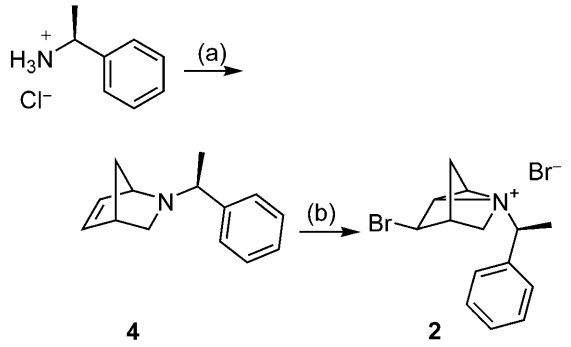
Results and Discussion

Following an analogous procedure[7] the Diels–Alder adduct **4** was form by the *in situ* reaction of (*S*)-phenylethylamine hydrochloride with aqueous formaldehyde and cyclopentadiene (Scheme 2). Compound **4** was then converted to the aziridinium salt **2** by treatment with bromine[8].

Initially we chose to use organocopper reagents known for their high reactivity and chemoselectivity as nucleophiles to open the aziridinium bromide **2**. Our primary studies investigated the use of lower-order cuprates as possible nucleophiles. Thus cuprates of the general formula R_2CuLi were prepared by combining two equivalents of an organolithium with one of copper(I) iodide.

The first homocuprate addition was achieved with MeLi as the organolithium species, leading to compound **5** as a single product in 57% yield (Table 1, entry 1). After this initial result we wanted to determine the scope of the reaction by testing other commercially available organolithium reagents. The use of *n*-butyllithium resulted in a reduction in yield to 39% under the same conditions (Table 1, entry 2). Furthermore, the use of more bulky butyl organolithium did not produce any open product; with the corresponding *sec*-butyl and *tert*-butyl organocopper reagents reacting with the aziridinium (Table 1, entries 3 and 4). Surprisingly however, the use of phenyllithium produced the open product **9** in good yield (60%) (Table 1, entry 5).

Due to the fact that bulky alkyllithium groups did not successfully open **2** using the above conditions, we decided to use higher-order cyanocuprates as nucleophiles.



Scheme 2. (a) Cyclopentadiene, CH_2O, H_2O, r.t., 16 h; (b) CH_2Cl_2, Br_2, 0 °C, 10 h, 75%.

When CuCN is exposed to two equivalents of an alkyllithium, a diionic species of the general formula $R_2Cu(CN)Li_2$ is produced. Such cuprates are far more reactive and stable than the corresponding lower-order cuprates.

The use of these more reactive organocopper reagents as nucleophiles allows the opening of **2** with bulkier alkyl groups. Compound **6** having an *n*-butyl group in the 6-position can now be obtained in over 90% yield (Table 2, entry 2), while compound **7** bearing the bulky *sec*-butyl group can now be prepared in 57% yield (Table 2, entry 3). We observed little change in the reactivity of the PhLi cuprate (Table 2 entry 5). However, the reactivity of the MeLi cyanocuprate decreased compared to its lower-order equivalent, the yield of **5** dropping from 57% to 46% (Table 2, entry 1). This result emphasises the unpredictable nature of organocopper reagents. Unfortunately, attempts to introduce the very bulky *tert*-butyl group were again unsuccessful.

Since the number of readily available organolithium reagents is limited, we decided to investigate the possible use of Grignard species to form organocopper reagents suitable to open the aziridinium bromide **2**. Initially we tried to use only a catalytic amount of copper salt (Table 3, entry 1), but no open product was observable under these conditions. Subsequently, we tried to use a stoichiometric amount of copper source compared to the Grignard reagent (Table 3, entry 2) forming a lower-order organocopper of the general formula $RCu \cdot MgX_2$, but again no reaction occurred. This is probably due to the low reactivity of these organocopper species.

We then tested the more reactive magnesio-cuprates of the type R_2CuMgX and $R_2Cu(CN)MgX$, formed by

Table 1. Addition of lower order cuprate to aziridinium bromide **2**.

Entry	R	Copper reagent	Yield [%][a]	Compound
1	Me	Me_2CuLi	57	**5**
2	*n*-Bu	*n*-Bu_2CuLi	39	**6**
3	*s*-Bu	*s*-Bu_2CuLi	0	**7**
4	*t*-Bu	*t*-Bu_2CuLi	0	**8**
5	Ph	Ph_2CuLi	60	**9**

[a] Yield of isolated product.

Table 2. Addition of higher-order cyanocuprate to aziridinium bromide **2**.

Entry	R	Copper reagent	Yield [%][a]	Compound
1	Me	$Me_2Cu(CN)Li_2$	46	**5**
2	*n*-Bu	*n*-$Bu_2Cu(CN)Li_2$	91	**6**
3	*s*-Bu	*s*-$Bu_2Cu(CN)Li_2$	57	**7**
4	*t*-Bu	*t*-$Bu_2Cu(CN)Li_2$	0	**8**
5	Ph	$Ph_2Cu(CN)Li_2$	64	**9**

[a] Yield of isolated product.

Table 3. Addition of organocuprates derived from Grignard reagents to **2**.

Entry	Cu(I) source	Equivs.	Grignard reagent	Equivs.	Yield [%][a]	Product
1	CuCN	0.1	EtMgBr	1.1	0	**10**
2	CuCN	1.1	EtMgBr	1.1	0	**10**
3	CuCN	1.1	EtMgBr	2.2	86	**10**
4	CuI	1.1	EtMgBr	2.2	65	**10**
5	$CuBr \cdot SMe_2$	1.1	EtMgBr	2.2	62	**10**
6	CuCN	1.1	EtMgI	2.2	52	**10**
7	CuCN	1.1	MeMgBr	2.2	82	**5**
8	CuCN	1.1	VinylMgBr	2.2	0	**11**
9	$CuBr \cdot SMe_2$	1.1	VinylMgBr	2.2	0	**11**
10	CuCN	1.1	*n*-PrMgBr	2.2	0	**12**
11	$CuBr \cdot SMe_2$	1.1	*n*-PrMgBr	2.2	49	**12**
12	CuCN	1.1	*n*-BuMgBr	2.2	45	**6**
13	CuCN	1.1	*i*-PrMgBr	2.2	60	**13**
14	$CuBr \cdot SMe_2$	1.1	*i*-PrMgBr	2.2	0	**13**

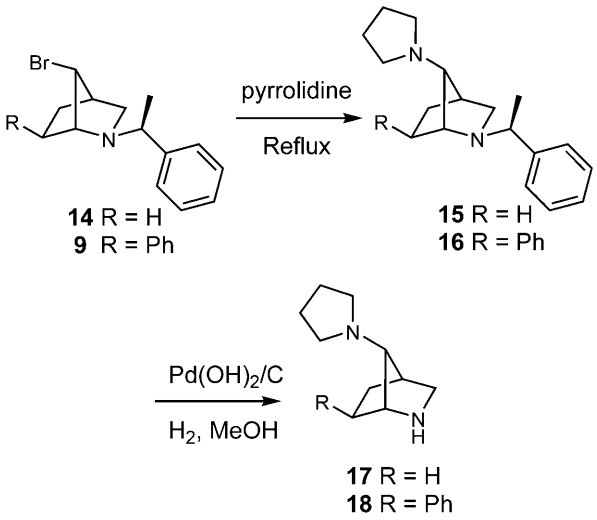
[a] Yield of isolated product.

the addition of two equivalents of Grignard reagent to one equivalent of copper(I) salt. The resulting organocuprates are very reactive and thermally unstable, effective stirring and cooling are essential for both reagent formation and subsequent introduction to the aziridinium bromide. We initially used CuCN as the copper source and EtMgBr (Table 3, entry 3), which lead to the formation of **10** in excellent yield (86%). Variation of the copper source resulted in a lower activity with CuI and $CuBr \cdot SMe_2$ forming **10** in 65 and 62% yield respectively (Table 3, entry 5 and 6). Changing the Grignard reagent from the bromide to the iodide (Table 3, entry 6) did not improve the reactivity of the corresponding magnesio cuprate, with **10** formed in 52% yield.

After the encouraging result obtained using EtMgBr we investigated the scope of the reaction by using a variety of Grignard reagents. MeMgBr in combination with CuCN afforded **5** in 83% yield (Table 3, entry 7). Surprisingly the use of vinylmagnesium bromide with either CuCN or $CuBr \cdot SMe_2$ as copper source (Table 3, entry 8 and 9, respectively) could not open **2** to form the desired product. When using larger Grignard reagents yields decreased but stayed within an acceptable range, compound **6** having a butyl group in the 6-position was produced in 45% yield using CuCN as copper source (Table 3, entry 12). While under the same conditions compound **2** did not react with the corresponding propyl-cuprate. However, it was found that the use of $CuBr \cdot SMe_2$ enabled the addition of *n*-propyl with **12** produced in 49% yield (Table 3, entry 11). Addition product **13**, bearing the bulky isopropyl substituent can be formed in 60% yield when CuCN is employed as the copper source. Interestingly, unlike with *n*-propyl the use of $CuBr \cdot SMe_2$ yielded no product (Table 3, entry 13 and 14, respectively). These results highlight the difficulty in predicting which copper salt provides the best yield for a particular Grignard reagent. CuCN seems to be the first choice but if it is unsuccessful other cupper sources must always be tested prior to discounting the use of a particular Grignard reagent.

After developing successful methods for the synthesis of a variety of enantiopure 6-substituted 7-bromo-azabicyclo[2.2.1]heptanes we wanted to investigate the potential use of these new bicyclic intermediates for chiral ligand synthesis.

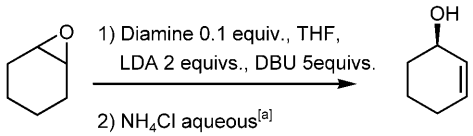
We decided to apply these building blocks to the synthesis of chiral diamines which could be used as ligands for the rearrangement of an epoxide into a chiral allylic alcohol. In order to determine the effect of substitution on the 6-position, diamines featuring either a hydrogen or a phenyl were prepared. The aziridinium ion **2** was ring opened using Red-Al® as hydride donor to produce the unsubstituted bicycle **14** in 84% yield (Scheme 3).



Scheme 3. Synthesis of the diamines **17** and **18**.

Nucleophilic substitution of the bromide in the 7-position of compound **14** and **9** by pyrrolidine produced the protected diamines **15** and **16** in excellent yield. Removal of the benzylic protecting group by hydrogenation at atmospheric pressure led to both the non-substituted diamine **17** and the 6-phenyl substituted diamine **18** in quantitative yield.

The two diamines were tested as a catalytic chiral base in the rearrangement of cyclohexene oxide using LDA as stoichiometric base (Scheme 4). The corresponding allylic alcohol was obtained in 60% ee after 12 hours using the non-substituted diamine **17** and 61% ee after 14 hours using the 6-phenyl substituted diamine. This result is very promising since only very few catalytic systems exist for this reaction.[3,9] Substitution at the 6-position does not affect the selectivity or the activity of the catalyst offering us an ideal anchoring point for a polymer or other solid support.



diamine	R	conversion[b] [%]	time [h]	ee[c] [%]
17	H	100	12	60
18	Ph	100	14	61

[a] Reaction were performed as previously reported by our group.[3]
[b] Conversion was determined by GC analysis with dodecane as an internal standard.
[c] Enantiomeric excess was determined using chiral GC, the major enantiomer was identified as the (*R*) form.

Scheme 4.

Conclusion

We have developed successful methods to prepare a variety of enantiopure 6-substituted 7-bromoazabicyclo[2.2.1]heptane, using organocopper reagents as nucleophiles for the regioselective opening of the tricyclic aziridinium bromide **2**. The usefulness of these 6-substituted 7-bromoazabicyclo[2.2.1]heptane compounds as intermediate in the preparation of successful chiral ligands for catalytic asymmetric synthesis has been highlighted.

Experimental Section

General Remarks

Flash chromatography was performed on silica gel (Matrex 60A, 37–70 μm). Analytical TLC was carried out on precoated plates SIL G-60 UV254, purchased from Macherey-Nagel. Polarimetry was performed using a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR were obtained on a Varian Unity 400 using the residual peak from $CDCl_3$ $\delta = 7.26$ for ^{1}H or $CDCl_3$ $\delta = 77.0$ for ^{13}C as reference. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF was distilled from a sodium-benzophenone solution.

(1*R*,4*S*)2-[(*S*)1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene (4)

Formaldehyde (37%, 15.5 mL, 190 mmol) was added to a solution of (−)-(*S*)-1-phenylethylamine hydrochloride (21 g, 133 mmol) in water (60 mL) and the solution was stirred at 0 °C for 15 min then freshly distilled cyclopentadiene (25 mL, 380 mmol) was added. The mixture was vigorously stirred at 0 °C for 4 hours before being diluted with water (250 mL) and washed (hexane/Et_2O, 1:1, 3 × 100 mL). The aqueous layer was made alkaline by addition of KOH pellets and extracted with Et_2O (3 × 100 mL). The organic phases were dried ($MgSO_4$) and evaporated. The crude product was subjected to purification by column chromatography (EtOAc/pentane, 70:30) to offer pure **4**; yield: 51%. All spectroscopic and physical data were in accordance with those published.[7]

(1*R*,2*R*,3*R*,4*R*,6*R*)-3-Bromo-1-[(*S*)-1-phenylethyl]-1-azoniatricyclo[2.2.1.0]heptane Bromide (2)

A solution of **4** (15 g, 75 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 1 hour to a cooled solution of Br_2 (3.6 mL, 67 mmol) in CH_2Cl_2 (50 mL) and the solution was kept at 0 °C overnight. The yellow crystals that formed were filtered and recrystallised from CH_2Cl_2/Et_2O to afford **2** as colourless crystals; yield: 19 g (72%). All spectroscopic and physical data were in accordance with those published.[8]

General Procedure for Nucleophilic Addition of Lower-Order Cuprates (R_2CuLi) to 2

A solution of organolithium (1.54 mmol) was added dropwise at −30 °C to a slurry of cuprous iodide (145 mg, 0.77 mmol) in THF (2 mL) under an argon atmosphere. The solution was stirred for 30 min at 0 °C. The reaction mixture was cooled again to −30 °C, and aziridinium bromide **2** was added portionwise. After 2 hours the reaction was allowed to slowly reach room temperature (over several hours). The black/brown reaction was poured into a solution of saturated NH_4Cl (5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers dried over $MgSO_4$. The solvent was evaporated and the resulting oil subjected to a short column chromatography of silica gel (pentane/diethyl ether, 90:10).

General Procedure for Nucleophilic Addition of Higher-Order Cuprates [$R_2Cu(CN)Li$] to 2

A solution of organolithium (1.54 mmol) was added dropwise at −30 °C to a slurry of CuCN (145 mg, 0.77 mmol) in THF (2 mL) under an argon atmosphere. The solution was stirred

for 30 min at 0 °C. The reaction mixture was cooled again to −30 °C, followed by the portionwise addition of aziridinium bromide **2**. After 2 hours the reaction mixture was allowed to slowly reach room temperature. The black/brown reaction was poured into a solution of saturated NH_4Cl (5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers dried over $MgSO_4$. The solvent was evaporated and the resulting oil subjected to a short column chromatography of silica gel (pentane/diethyl ether, 90:10).

General Procedure for Nucleophilic Addition of Organocopper-Derived Species from Grignard Reagents to 2

A solution of Grignard reagent was added dropwise at −50 °C to a slurry of copper salt in THF (2 mL) under argon atmosphere. The solution was stirred for 30 min at −20 °C, then the reaction mixture was cooled again to −50 °C, and aziridinium bromide **2** was added portionwise. After 2 hours the reaction mixture was allowed to slowly reach room temperature. The black/brown reaction was poured into a solution of saturated NH_4Cl (5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers dried over $MgSO_4$. The solvent was evaporated and the resulting oil subjected to a short column chromatography of silica gel (pentane/diethyl ether, 90:10).

Characterization data for products **5**, **6**, **7**, **9**, **10**, **12**, **13**, **14**, **15**, **16**, **17**, and **18** are available in the Supporting Information.

(1*R*,4*R*,7*R*)-2-[(*S*)1-Phenylethyl]-7-bromo 2-azabicyclo[2.2.1] heptane (14)

Red-Al® (65 wt %, 8.5 mL, 28.9 mmol) was added to a solution of **2** (10.3 g, 28.9 mmol) in tetrahydrofuran (250 mL) cooled to −10 °C. After stirring for 2 hours, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution (125 mL) followed by brine (125 mL), and then extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over magnesium sulfate and then concentrated on a rotary evaporator to afford **14** as a colourless oil; yield: 7.6 g (27.5 mmol).

(1*R*,4*S*,7*R*)-2-[(*S*)-1-Phenylethyl]-7-pyrrolidino-2-azabicyclo[2.2.1]heptane (15)

Compound **14** (0.5 g, 1.8 mmol) was dissolved in pyrrolidine (5 mL), and heated under reflux for 18 hours. Volatiles were removed under vacuum and the resulting oil washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL) and dried over $MgSO_4$. Removal of the solvent in vacuum afforded **15** as a colourless oil; yield: 430 mg (90%).

(1*R*,4*R*,6*S*,7*S*)-2-[(*S*)-1-Phenylethyl]-7-pyrrolidino-6-phenyl-2-azabicyclo[2.2.1]heptane (16)

Following the procedure described for compound **15** using 9 (250 mg, 0.7 mmol), compound **16** was obtained in 88% yield (213 mg).

(1*R*,4*R*,7*R*)-7-Pyrrolidino-2-azabicyclo[2.2.1]heptane (17)

$Pd(OH)_2$ on carbon (80 mg, 20 wt %) was dried under vacuum for 4 hours, and then added to a solution of the benzyl-protected amine **15** (400 mg, 1.48 mmol) in MeOH (15 mL). The reaction mixture was stirred overnight at room temperature under a hydrogen atmosphere. The solution was filtered over celite and the solvent removed under vacuum to afford **17** as a yellow oil in quantitative yield.

(1*R*,4*R*,6*S*,7*S*)-7-Pyrrolidino-6-phenyl-2-azabicyclo[2.2.1]heptane (18)

Following the procedure described for compound **17** using **6** (150 mg, 0.43 mmol), compound **18** was obtained as a yellow oil in quantitative yield.

Acknowledgements

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