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Expedient Synthesis of Homochiral 1-Aryl-Substituted 4,5-Dihydro-1*H*-imidazoles and Their Modification to N-Heterocyclic Carbene Precursors

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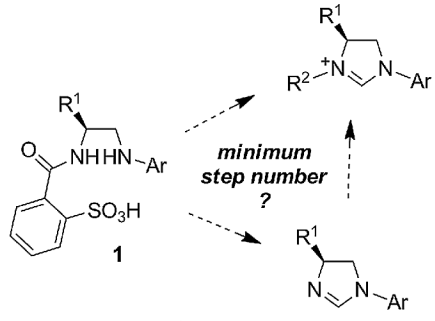
The amidoamines (*S*)-$Ar^1CONHCHRCH_2NHAr^2$ [Ar^1 = *o*-$C_6H_4SO_3H$, R = Bn, *i*Bu, *i*Pr; Ar^2 = 2,6-*i*$Pr_2C_6H_4$, 2,6-$Et_2C_6H_4$, 2,4,6-$Me_3C_6H_2$] cyclise to (*S*) 1-aryl-substituted 4,5-dihydro-1*H*-imidazolinium species with $HC(OEt)_3$ in moderate-to-excellent yields on heating to 150–175 °C (nine examples, four isolated yields of 48 to >97 %). They are attained as their *o*-$C_6H_4(SO_3^-)(CO_2Et)$ salts. The latter are readily deprotonated to afford analytically pure (*S*) 1-aryl-substituted 4,5-dihydro-1*H*-imidazoles (imidazolines). The purification of the intermediate sulfonate salts is not always necessary, and analytically pure imidazolines are isolated by simple kugelrohr distillation (nine examples, 45–95 %) after basification. Imidazoline alkylation provides a library of (*S*)-*N*-alkylimidazolinium salts (23 examples, 74–97 %). As the initially required amidoamines are available in simple one-pot reactions, the overall approach constitutes a rather efficient approach to this useful family of chiral N-heterocyclic carbene (NHC) ligand precursors (effectively three steps from commercial *N*-Boc-α-amino alcohols; BOC = *tert*-butyloxycarbonyl).

Introduction

In 2012, we introduced a cascade method for the efficient conversion of *tert*-butyloxycarbonyl-protected (Boc-protected) α-amino alcohols to the chiral amidoamines **1** using 2-sulfobenzoic anhydride.[1] As these intermediates were very easy to prepare, we wondered if they could be used to attain imidazolinium salt libraries either directly or by the initial formation of the 4,5-dihydro-1*H*-imidazoles (imidazolines) followed by their subsequent alkylation (Scheme 1). Such an approach is desirable owing to its relative step efficiency. Literature procedures to such N-heterocyclic carbene (NHC) ligand precursors[2] are characterised by: (1) the closure of natural-pool α-amido alcohols by conversion of the OH group to a suitable leaving group;[3] (2) the reduction of amides, derived from protected α-amino acids, and subsequent closure of the resultant diamine;[4] (3) the derivatisation of chiral aziridines;[5] or (4) alternative routes to suitable diamine cyclisation precursors, typically Buchwald–Hartwig-type couplings.[6] Approaches (1)–(4) are all rather step intensive, and the attainment of a library of imidazolines and then their NHC precursors through *N*-alkylation can become a rather drawn out process, which limits the range of chiral ligands that can be prepared in a timely manner. Although alternative concise approaches to chiral imidazolinium salts have been reported,[7] the use of **1** offers a potential alternative general route to chiral-pool imidazolines and their alkylation products, although some of the required processes might require forcing conditions (compare ref.[1] vs. ref.[2]).



1	R^1	Ar
aa	Bn	2,6-*i*$Pr_2C_6H_3$
ab	Bn	2,6-$Et_2C_6H_3$
ac	Bn	2,4,6-$Me_3C_6H_2$
ba	*i*Bu	2,6-*i*$Pr_2C_6H_3$
bb	*i*Bu	2,6-$Et_2C_6H_3$
bc	*i*Bu	2,4,6-$Me_3C_6H_2$
ca	*i*Pr	2,6-*i*$Pr_2C_6H_3$
cb	*i*Bu	2,6-$Et_2C_6H_3$
cc	*i*Pr	2,4,6-$Me_3C_6H_2$

Scheme 1. Consideration of **1** as a potential imidazoline and NHC salt precursor. Compounds **1aa**, **1ca** and **1cc** are known; the others were prepared in a similar manner (ref.[1] and Supporting Information).

Results and Discussion

The amidoamine **1aa**, prepared by our previously reported one-pot method,[1] was used as a test bed for the

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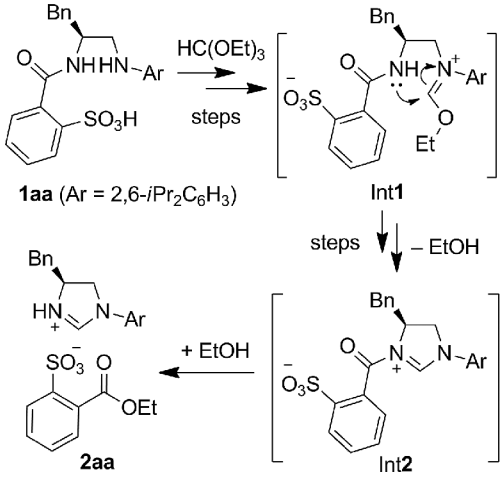
proposed new chemistry. The condensation of the amine with triethyl orthoformate is expected to lead to the iminium intermediate (Int**1**), which, if it cyclises and eliminates ethanol, would provide the NHC precursor salt (Int**2**) directly and efficiently (Scheme 2). In practice, the conversion of **1aa** was very sluggish under simple reflux in ethanol and did not reach completion. However, the heating of the reaction mixture in a commercial microwave reactor at 150 °C (250 psi) caused the high consumption of **1aa** within 1 h. Similar reactivity could be attained in an autoclave, but longer reaction times (up to 16 h) and higher external temperatures (175 °C) were needed to secure complete conversion. The significant darkening of the reaction mixture that occasionally occurred under these conditions could be somewhat avoided by the use of HCO_2H as a coadditive. The coelution of **1aa** and the new product formed in these reactions necessitates the completion of the transformation. In general, the use of the autoclave procedure was preferred as this allowed significant quantities of **1aa** to be used (2 to >10 g per run).



Scheme 2. Proposed mechanism of the cyclisation of amidoamine **1aa** under treatment with $HC(OEt)_3$ in ethanol.

Initially, it seemed that Int**2** could be isolated from a discoloured band under polar chromatography conditions (dichloromethane/MeOH 5% v/v). The spectroscopic data (^1H and ^{13}C NMR) and elemental analysis data were in good accord with the presence of an (Int**2**)·EtOH adduct. However, attempts to remove the "EtOH" from the sample were unsuccessful, and a molecular ion for Int**2** could not be detected in its nominal mass spectra (regardless of the ionisation mode). To shed light on this conundrum, a range of additional derivatives was prepared by both microwave and autoclave heating methods (Table 1). Fortunately, one of these derivatives (**2ca**) was crystalline and allowed us to identify that the in situ ethanolysis of Int**2** leads to the formation of the imidazolinium sulfonates **2**. The molecular connectivity of **2ca** is shown in Figure 1. We could not find an exact precedent for the transformation of **1** to **2**, but some related conversions are known. For example, $ArNH(CH_2)_2NHCHO$ units cyclise in the presence of strong acids.[8]

Table 1. Preparation of imidazolinium sulfates (**2**) by microwave or autoclave heating.[a]

	R^1	Ar	Method	Yield [%]
2aa	Bn	2,6-$iPr_2C_6H_3$	A	>80[b]
2aa	Bn	2,6-$iPr_2C_6H_3$	B	48
2ab	Bn	2,6-$Et_2C_6H_3$	A	67
2ab	Bn	2,6-$Et_2C_6H_3$	B	82
2bc	*i*Bu	2,4,6-$Me_3C_6H_2$	B	92
2ca	*i*Pr	2,6-$iPr_2C_6H_3$	A	60

[a] Conditions for cyclisation: method A: microwave heating, 150 °C (250 psi), 1 h; method B: heating in autoclave at 175 °C (300 psi), 5–16 h; isolated yields after chromatography unless otherwise indicated. [b] Conversion determined by NMR spectroscopy after 1 h.

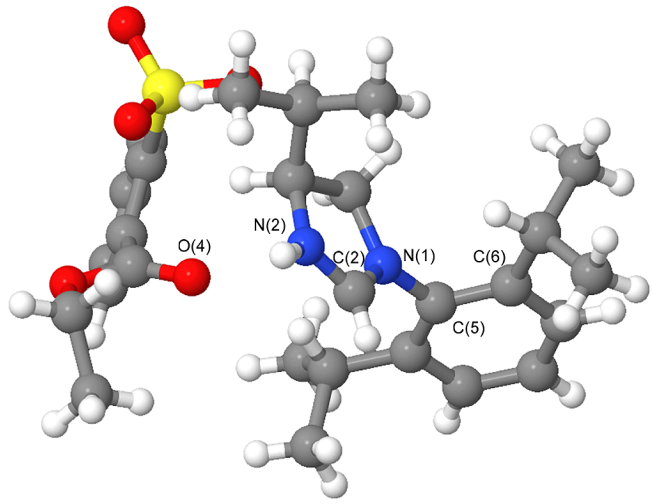


Figure 1. X-ray crystal structure of imidazolinium sulfate **2ca**. Selected angles [°] and nonbonding distances [Å]: N(1)–C(2)–N(2) 113.1, C(2)–N(1)–C(5)–C(6) 97.0, N(2)···O(4) 3.22.

Selected results from runs that led to isolable crystalline or tractable samples of **2** are shown in Table 1. The only common pattern in the reactivity is that the most-hindered systems, that is, those containing the 2,6-$iPr_2C_6H_3$ unit, are the slowest to react (requiring 16 h in the autoclave but significantly less under microwave heating). Provided temperatures in the region 150–175 °C are used, high conversions (often quantitative) are finally attained. Small amounts of dark polar residues are always formed even when **1** is completely converted; this is especially the case in reactions with initial concentrations of more than 1 M or those that have been heated for a long period (>12 h). The yields shown in Table 1 more accurately reflect the difficulties in the isolation of **2** rather than the reaction efficiency. These highly polar species commonly occlude solvent; must be chromatographed in polar solvent mixtures that commonly lead to coelution of the starting material, product and byproducts; and provide samples that are attained as intractable dark oils.

Because of the issues above, we experimented with basic workups of such oils to isolate the (*S*)-1-aryl-substituted 4,5-dihydro-1*H*-imidazoles **3** directly from the mixtures. Compounds **2aa** and **2ca** were selected for the optimisation,

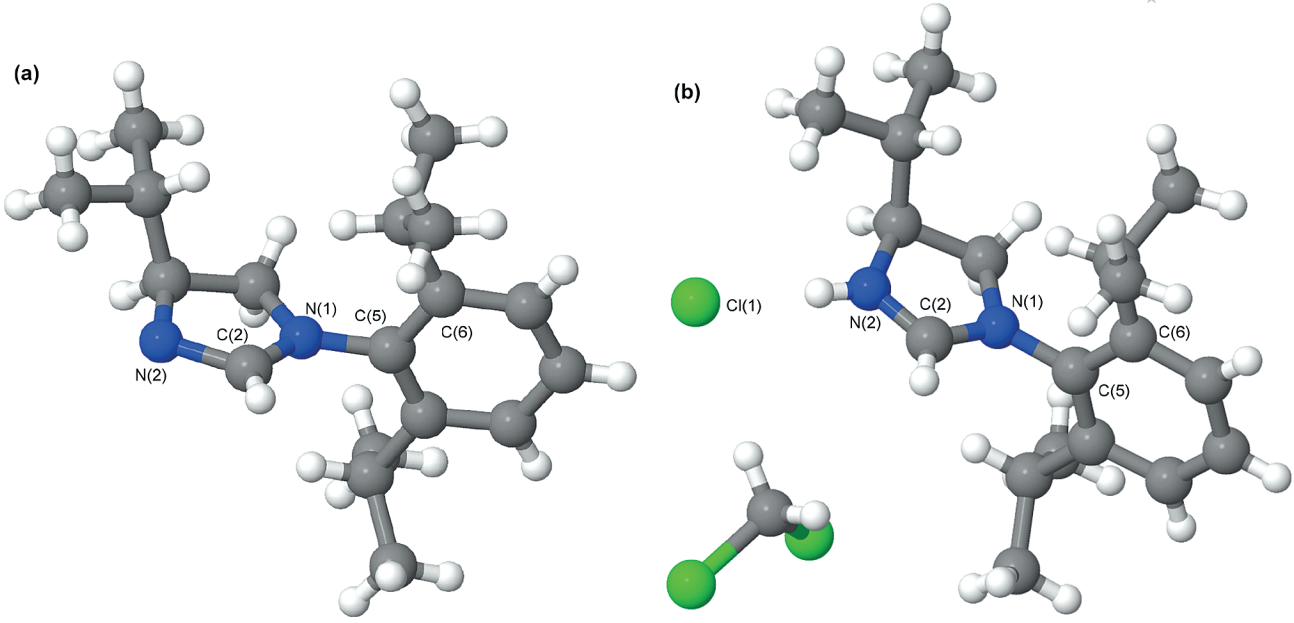
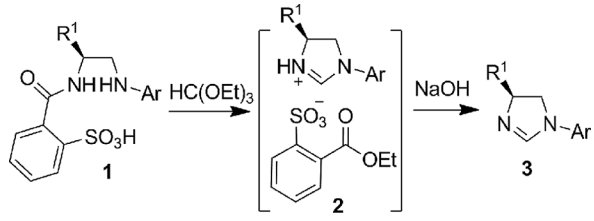


Figure 2. (a) Imidazoline **3ca**; selected angles [°]: N(1)–C(2)–N(2) 117.8, C(2)–N(1)–C(5)–C(6) 111.5. (b) Imidazoline hydrochloride salt **3ca**·HCl (dichloromethane solvate); selected angles [°] and nonbonding distances [Å]: N(1)–C(2)–N(2) 112.9, C(2)–N(1)–C(5)–C(6) 88.7, N(2)···Cl(1) 3.14.

as they were the product obtained in the lowest yield (48%, Table 1) and the most crystalline example, respectively. When these samples of **2** were partitioned with dichloromethane and aqueous sodium hydroxide (2 M), we isolated brown oils, which later solidified. Analysis of these crude materials by ^{1}H NMR spectroscopy confirmed that deprotonation had taken place and that the conversion to **3** was essentially complete in both cases with only traces of impurities present. The ^{1}H NMR chemical shift of the NCHN imidazoline proton is diagnostic of imidazolinium salts **2** ($\delta \approx 8$ ppm), and the equivalent chemical shifts of imidazolines **3** ($\delta \approx 7$ ppm) are in line with the sharp drop in the electron-withdrawing ability of the nitrogen atom on removal of the positive charge. The crystallisation of **3ca** from pentane confirmed the success of the deprotonation strategy (Figure 2, a), whereas an attempted slow recrystallisation from CH_2Cl_2/pentane led only to HCl abstraction from the solvent and the formation of **3ca**·HCl (Figure 2, b).

Considerable experimentation revealed four critical issues for the efficient isolation of free imidazolines **3**: (1) They are rather susceptible to protonation; Et_2O and anhydrous Na_2CO_3 should be used as the extraction solvent and drying agent, respectively, rather than CH_2Cl_2 and Na_2SO_4. (2) They have a degree of solubility in 2 M NaOH unless this is "salted out" with saturated NaCl (brine); if more concentrated NaOH solutions are used, some degradation of **3** occurs. (3) The direct isolation of **3** from crude **2** is possible, but this is facilitated by prior filtration chromatography of **2** (if it is not the major component of the crude material). (4) Owing to their propensity to protonation, the chromatographic purification of **3** in CH_2Cl_2/MeOH can be compromised (trace uncharacterised yellow impurities with R_f = 0.4–0.5 are formed). The optimal chromatographic conditions were 1% w/w Na_2CO_3 in SiO_2 and CH_2Cl_2/MeOH 19:1, which had been filtered through solid Na_2CO_3. Alternatively, crude **3** could be purified to colourless oils through kugelrohr distillation (Table 2). This provides analytically pure colourless oils that often solidify on cooling. The overall synthesis of **3** from *N*-Boc-α-amino alcohols by such "telescoped" procedures (direct use of **2**)

Table 2. Direct preparation of imidazolines **3** by combined cyclisation and deprotonation followed by distillation.[a]

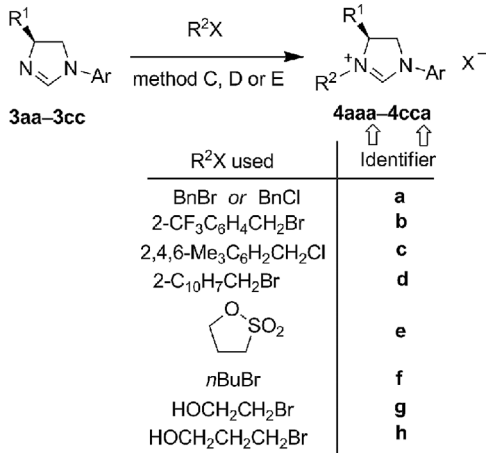


	R^1	Ar	B.p. [°C]/*P* [Torr]	Yield [%]	Ref. (steps)[b]
3aa	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	213/0.18	95	[9] (5)
3ab	Bn	2,6-Et$_2$C$_6$H$_3$	210/0.17	71	this paper (3)
3ac	Bn	2,4,6-Me$_3$C$_6$H$_2$	143/0.11	49	this paper (3)
3ba	*i*Bu	2,6-*i*Pr$_2$C$_6$H$_3$	164/0.23	94	this paper (3)
3bb	*i*Bu	2,6-Et$_2$C$_6$H$_3$	161/0.18	80	this paper (3)
3bc	*i*Bu	2,4,6-Me$_3$C$_6$H$_2$	117/0.09	65	this paper (3)
3ca	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	143/0.11	83	this paper (3)
3cb	*i*Pr	2,6-Et$_2$C$_6$H$_3$	163/0.07	89	this paper (3)
3cc	*i*Pr	2,4,6-Me$_3$C$_6$H$_2$	163/0.42	90	[4a] (4)

[a] Conditions: cyclisation: autoclave, 175 °C (300 psi), ca. 5 h; deprotonation: 2 M NaOH saturated with NaCl; drying: anhydrous Na_2CO_3 followed by distillation under the conditions given. The isolated yields of **3** relative to **1** are given. [b] The number of steps that require the isolation of an intermediate, as presented in the cited reference.

compares well with existing literature routes to these compounds. Although it is necessary to start from the amino alcohols, these are commercially available, and this route avoids the problematic reductions of α-amino acid derived amide intermediates, which are common to some of the other routes to **3**. Regardless of the comparisons made, the distillation approach via crude **2** that is outlined here is convenient and suitable for use on larger scales without the need for chromatography.

To demonstrate the utility of this route to provide ready access to a range of **3**, the imidazolines of Table 2 were alkylated with a range of electrophiles (Scheme 3). Acetone is recognised as the most general solvent for the alkylation of imidazole-based heterocycles, but such reactions can be sluggish and often require overnight reflux. The heating of such reaction mixtures in commercial microwave reactors typically results in complete conversion in under an hour. Such conditions are particularly useful for alkylations with propanesultone [which lead to imidazolinium compounds with pendant $(CH_2)_3SO_3^-$ groups; Method D]. For reactive benzylic halides, rapid conversions could also be attained under simple heating in toluene (100 °C). Such reactions gave complete conversions and good-to-excellent yields in all primary cases tried; secondary Ph_2CHBr did not react. The most problematic electrophiles were simple *n*BuBr and the closely related $HO(CH_2)_nBr$ (n = 2, 3). In these cases, only sealed-tube reactions in MeCN led to high yields after extended reaction times (16–22 h). For reasons that are unclear, the use of pressurised systems is mandatory; reflux in MeCN alone at atmospheric pressure gave inferior yields. The improvements offered to challenging alkylations under these conditions can be seen in the yield of **4aag** versus that of **4aah** (Table 2). The purification of these imidazolinium salts **4** was normally achieved by simple recrystallisation from CH_2Cl_2/pentane. When this approach failed, column chromatography (CH_2Cl_2/methanol 5%) was used to



Scheme 3. Alkylation of imidazolines **3** to provide imidazolinium salts **4**. Method C: R^2X (1.2 equiv.), toluene, 100 °C, 60 min; method D: R^2X (1.2 equiv.), acetone, microwave heating, 150 °C (250 psi), 40 min; method E: R^2X (1.2 equiv.), MeCN, sealed tube, 120 °C, 22 h. Not all potential combinations of substituents have been prepared.

achieve the separation of **4** from any unreacted starting materials before recrystallisation. To confirm the validity of our approaches, we conducted a representative crystallographic study of **4caa** (Figure 3). The application of methods C–E allowed the rapid preparation of a wide range of salts **4** in good-to-excellent yields, and the results are summarised in Table 3.

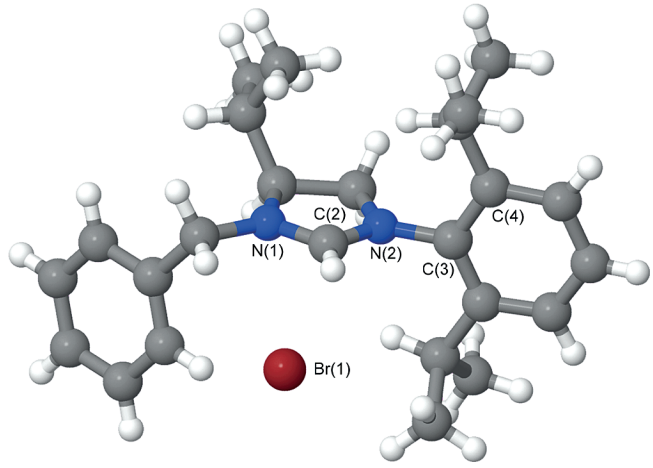


Figure 3. X-ray crystal structure of imidazolinium salt **4caa**. Selected angles [°] and nonbonded distances [Å]: N (1)–C(2)–N(2) 113.2, C(2)–N(2)–C(3)–C(4) 89.6; C(2)···Br(1) 3.45.

Table 3. Preparation of imidazolinium salts **4**.[a]

	R^1	Ar	R^2	X	Method	Yield [%]
4aaa	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	Bn	Br	C	83
4aab	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	2-CF$_3$C$_6$H$_4$CH$_2$	Br	C	84
4aac	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	2,4,6-Me$_3$C$_6$H$_2$CH$_2$	Cl	C	98
4aae	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	$^-$O$_3$S(CH$_2$)$_3$	–	D	83
4aag	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	HO(CH$_2$)$_2$	Br	C	50
4aah	Bn	2,6-*i*Pr$_2$C$_6$H$_3$	HO(CH$_2$)$_3$	Br	E	83
4aba	Bn	2,6-Et$_2$C$_6$H$_3$	Bn	Br	C	74
4abe	Bn	2,6-Et$_2$C$_6$H$_3$	$^-$O$_3$S(CH$_2$)$_3$	–	D	77
4aca	Bn	2,4,6-Me$_3$C$_6$H$_2$	Bn	Br	C	85
4baa	*i*Bu	2,6-*i*Pr$_2$C$_6$H$_3$	Bn	Br	C	79
4bae	*i*Bu	2,6-*i*Pr$_2$C$_6$H$_3$	$^-$O$_3$S(CH$_2$)$_3$	–	D	85
4bba	*i*Bu	2,6-Et$_2$C$_6$H$_3$	Bn	Br	C	78
4bbe	*i*Bu	2,6-Et$_2$C$_6$H$_3$	$^-$O$_3$S(CH$_2$)$_3$	–	D	81
4bca	*i*Bu	2,4,6-Me$_3$C$_6$H$_2$	Bn	Br	C	94
4bce	*i*Bu	2,4,6-Me$_3$C$_6$H$_2$	$^-$O$_3$S(CH$_2$)$_3$	–	D	85
4caa	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	Bn	Br	C	99
4caa	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	Bn	Cl	C	76
4cab	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	2-CF$_3$C$_6$H$_4$CH$_2$	Br	C	92
4cad	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	2-C$_{10}$H$_7$CH$_2$	Br	C	92
4caf	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	*n*Bu	Br	E	91
4cag	*i*Pr	2,6-*i*Pr$_2$C$_6$H$_3$	HO(CH$_2$)$_2$	Br	C	41
4cba	*i*Pr	2,6-Et$_2$C$_6$H$_3$	Bn	Br	C	82
4cca	*i*Pr	2,4,6-Me$_3$C$_6$H$_2$	Bn	Br	C	99

[a] Reaction conditions: 1.2 equiv. of alkylating agent, method C–E. Method C: ArCH$_2$X (1.2 equiv.), toluene, 100 °C, 60 min; method D: sultone **e** (1.2 equiv.), acetone, microwave heating, 150 °C (250 psi), 40 min; method E: *n*BuBr or $HO(CH_2)_nBr$ (n = 2 or 3; 1.2 equiv.), MeCN, sealed tube, 120 °C, 22 h.

Conclusions

Overall, the synthetic sequence Boc-α-amino alcohol to **1** and then **2**–**4** offers some attractive features. The amido-

amines **1** can be prepared on large scales in one-pot reactions that require no transition metal catalysis to form the C–NHAr bonds. Similarly, as the present route starts at the correct (alcohol) oxidation level, no hydride reducing agents are required (although high temperatures are needed). This is important as alternative routes that require the reduction of CONHAr units can become capricious as the steric demand of the Ar group becomes larger. In the approach described here, the ability to prepare and use **2** directly without purification on larger scales allows rapid access to a range of imidazolines **3**, especially if distillative approaches are used (Table 2). Finally, the conditions for handling and alkylating **3** have been optimised. The applications of **3** and **4** in asymmetric catalysis are under investigation and will be reported in due course.

Experimental Section

General: The general experimental equipment has been described previously.[10] The preparations of **3** and **4** are representative, and full experimental details and data are given in the Supporting Information.

(*S*)-4-Benzyl-1-(2,6-diisopropylphenyl)-4,5-dihydro-1*H*-imidazole (3aa):[4a] General method B (see Supporting Information) with amidoaminesulfonic acid **1a** (4.34 g, 8.78 mmol), ethanol (47 mL), triethyl orthoformate (10 mL) and formic acid (1 mL) for 4 h at 175 °C gave crude **2aa** as a green solid (4.68 g) after evaporation of the solvents. The crude solid was dissolved in dichloromethane (45 mL), followed by diethyl ether (45 mL), and the mixture was stirred. Once the solution became homogeneous, sodium hydroxide solution (25 mL) was added cautiously (exothermic). Once the mixture had cooled (ca. 10 min), solid sodium chloride (5 g) was added. The reaction mixture was then transferred to a separating funnel, and the aqueous layer was extracted with dichloromethane (2 × 100 mL) and diethyl ether (2 × 100 mL). The organic layers were combined, dried with anhydrous sodium carbonate and filtered, and the solvents were evaporated. Purification by chromatography (2–5% methanol in dichloromethane as the eluent, silica) gave **3aa** as a crystalline solid (2.67 g, 95%). The compound could also be purified by kugelrohr distillation (213 °C at 0.18 Torr) to give a highly crystalline colourless solid, which could also be recrystallised from pentane by evaporation to afford small cuboid crystals. The data in the Supporting Information are consistent with those reported previously.[4a]

(*S*)-3,4-Dibenzyl-1-(2,6-diisopropylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium Bromide (4aaa):[4a] General method C (see Supporting Information) with imidazoline **3aa** (0.24 g, 0.75 mmol), benzyl bromide (100 μL) and toluene (2.0 mL) for 60 min (100 °C) gave a white crystalline solid (0.29 g, 83%). The data in the Supporting Information are consistent with those in the literature.[4a]

CCDC-1037080 (for **2ca**), -1037081 (for **3ca**), -1037082 (for **3ca**·HCl) and -1037083 (for **4caa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Full experimental data for the preparation of all compounds and their spectra.

Acknowledgments

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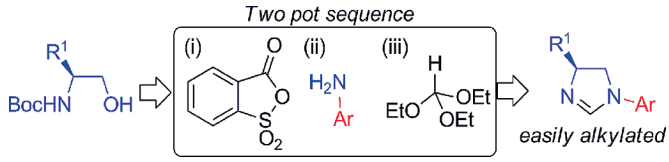
Nitrogen Heterocycles



2-Sulfobenzoic anhydride acts as a temporary protecting group and allows the prompt synthesis of chiral imidazolines on multigram scale without the need for Buchwald–Hartwig couplings or reducing agents.

Keywords: Synthetic methods / Asymmetric synthesis / Nitrogen heterocycles / Amino alcohols / NHC ligand precursors

