Asymmetric Synthesis of 2-Arylpyrrolidines by Cationic Cyclization

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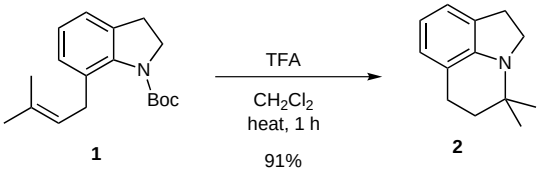
Abstract: Homoallylic amines were prepared by asymmetric deprotonation of benzylamines using *n*-BuLi and (–)-sparteine to give chiral organolithiums to which were added prenyl bromide. Removal of the Boc protecting group gave anilines that were found to undergo Brønsted acid catalyzed or iodine-mediated cyclization to give aryl-substituted pyrrolidine heterocyclic products with high enantioselectivity.

Key words: amines, carbocation, cyclization, enantioselectivity, heterocycles

Recently, we reported that deprotection of the *tert*-butoxycarbonyl (Boc) group from compound **1** by heating with trifluoroacetic acid (TFA) in CH_2Cl_2 resulted in cyclization to give the product **2** (Scheme 1).[1] The mechanism is presumed to involve initial Boc removal then protonation of the alkene and cyclization of the aniline onto the intermediate carbocation. Normally, cationic cyclizations of alkylamines are inefficient due to the preferential protonation of the amine nitrogen atom. However, there are examples of acid-mediated cyclizations of, in particular, sulfonamides.[2,3] After discovering the synthesis of the product **2**, we were interested to explore some of the scope of the cyclization of anilines.[4] Conjugation of the nitrogen atom lone pair with the aromatic ring reduces the propensity for protonation of the nitrogen atom and could allow related cationic cyclizations to give other cyclic amine products.

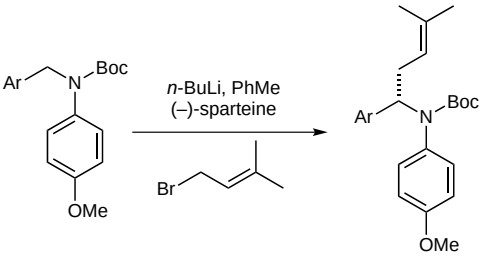


1 2

Scheme 1 Cyclization of an indoline[1]

We chose initially to explore the acid-mediated Boc deprotection and cyclization of compound **4a**. This would result in a novel synthesis of 1,2-diarylpyrrolidines. Aryl-substituted pyrrolidines are present in natural products (such as nicotine), potential pharmaceuticals (such as ABT-418, RP-66803 and SIB-1508Y), and as chiral auxiliaries or catalysts.[5] Compound **4a** has been prepared by Beak and co-workers from the benzylamine **3a**, although it was converted directly into a carboxylic acid (using O_3/CrO_3).[6] Asymmetric deprotonation of the benzylamine **3a** occurs in the presence of *n*-BuLi and (–)-sparteine, and the resulting organolithium species can be reacted with prenyl bromide to give the product **4a**. Isolation of compound **4a** and analysis by chiral stationary phase HPLC showed that the reaction occurred enantioselectively as expected [enantiomeric ratio (er) = 94:6].

Table 1 Asymmetric Deprotonation and Addition of Prenyl Bromide



Entry	Starting material	Ar	Product	Yield (%)	er
1	**3a**	Ph	**4a**	80	94:6
2	**3b**	4-MeC_6H_4	**4b**	65	91:9
3	**3c**	4-FC_6H_4	**4c**	54	91:9
4	**3d**	3,5-$(F_3C)_2C_6H_3$	**4d**	34	98:2
5	**3e**	4-$MeOC_6H_4$	**4e**	64	94:6

In a similar way, the compounds **4b–e** were prepared by asymmetric deprotonation of **3b–e** and addition of prenyl bromide (Table 1). These included the *p*-methyl derivative **4b**, two fluorinated derivatives **4c** and **4d**, and the *p*-methoxy derivative **4e**. The starting materials **3** were prepared from *N*-Boc-*p*-methoxyaniline, sodium hydride, and $ArCH_2Br$.[6]

Several acidic conditions were tested for the Boc deprotection and cationic cyclization of these compounds. The use of triflic acid (in CH_2Cl_2) or neat TFA resulted in decomposition. However, by heating (under reflux) the carbamate **4a** with a solution of TFA in CH_2Cl_2 (0.1 M, 16 h), a mixture of the pyrrolidine **5a** and the secondary amine **6a** was formed in high overall yield (Scheme 2). The ratio of the two products could be changed to favor the pyrrolidine **5a** by increasing the concentration of TFA in CH_2Cl_2 to 1.0 M. After heating for 16 h under these

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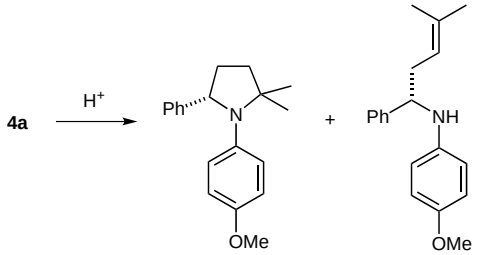
conditions the pyrrolidine **5a** was isolated in 69% yield. Alternatively, by heating with methanesulfonic acid (MsOH) in THF (0.2 M, 1 h), only the amine **6a** was isolated. The er of the product **5a** was determined by chiral stationary phase HPLC (er = 94:6).

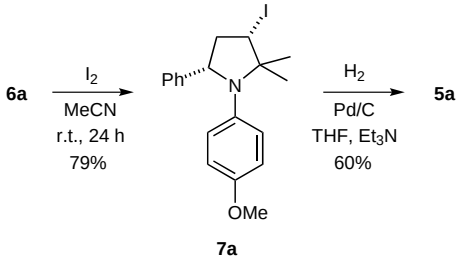
Heating the amine **6a** with TFA (1.0 M) in CH_2Cl_2 gave the expected pyrrolidine product **5a** (56% yield, er = 94:6). Hence the transformation of the carbamate **4a** to the pyrrolidine **5a** proceeds through initial loss of the Boc group to give the amine **6a** followed by acid-mediated cyclization. These steps do not result in any loss of enantiopurity.



	5a	6a
0.1 M TFA CH_2Cl_2	38%	57%
1.0 M TFA CH_2Cl_2	69%	4%
0.2 M MsOH THF	0%	93%

Scheme 2 Acid-catalyzed cyclization of substrate **4a**

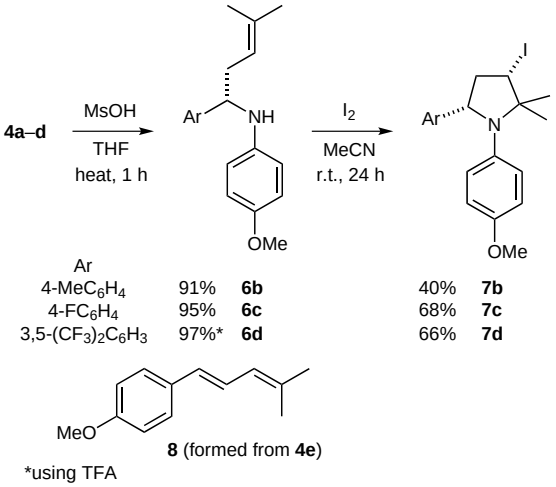
As an alternative to the acid-mediated deprotection–cyclization, we treated the amine **6a** with iodine (Scheme 3).[7] This gave the desired pyrrolidine product **7a** as a single diastereoisomer. The relative stereochemistry was assigned by analogy, as described below. Hydrogenolysis of the product **7a** using a palladium catalyst gave the pyrrolidine **5a** (er = 94:6). Hence, the iodine-mediated cyclization proceeds without racemization.



Scheme 3 Cyclization of aniline **6a** with iodine

We were disappointed to find that acid-catalyzed Boc-deprotection of substituted derivatives **4b–e** using TFA was unsatisfactory, leading to decomposition or the isolation of the amines **6** in variable yields. However, using MsOH led to high yields of the amines **6b**,**c** (**6d** was formed in high yield using TFA) (Scheme 4). Treating compound **4e** with MsOH did not give the same type of product but resulted in the formation of the diene **8**, presumably by an E1-type mechanism due to the enhanced stabilization of the carbocation by the methoxy group.

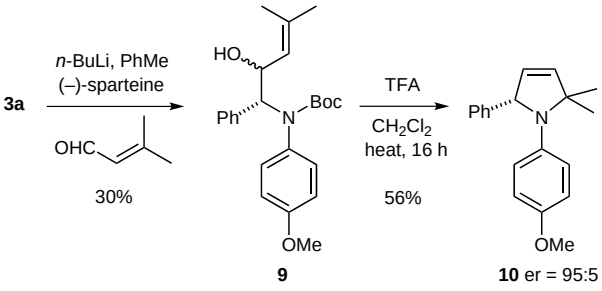
Treatment of the amines **6b–d** with iodine gave the desired pyrrolidine products **7b–d** (Scheme 4). In each case a single diastereoisomer was formed, as shown by NMR spectroscopy. The relative stereochemistry was determined using compound **7d** by ^{1}H NOESY experiments (3% enhancement of CHI on irradiating CHAr and vice versa). No loss of enantioselectivity was assumed, due to the high enantiomeric ratio of the analogues **6a** and **7a**.



Scheme 4 Formation and cyclization of anilines **6b–d**

Asymmetric deprotonation of the benzylamine **3a** and addition of 3-methylcrotonaldehyde gave the product **9** as a mixture of diastereoisomers (dr = 1:1) in low yield (Scheme 5).[8] Subsequent treatment with TFA gave the dihydropyrrole **10**. The enantiomeric ratio of this product was determined by chiral stationary phase HPLC (er = 95:5). Hence, in one pot the Boc and hydroxy groups are removed to give an intermediate allyl cation that undergoes cyclization without racemization.

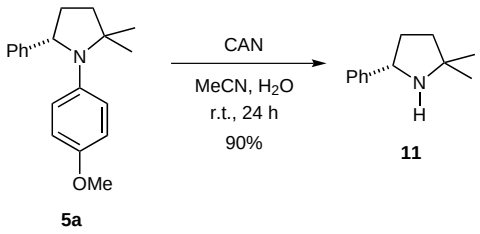
In all the above cases we assume that the absolute configuration of the products is as shown, based on results by Beak and co-workers, who showed that the intermediate chiral organolithium undergoes stereoselective substitution with inversion of configuration.[6]



Scheme 5 Formation and cyclization of carbamate **9**

Finally, we have found that the *p*-methoxyphenyl group can be removed in high yield from the product **5a** using ceric ammonium nitrate (CAN, Scheme 6). The specific rotation of the product **11** {$[\alpha]_D^{20}$ –10 (*c* 1.0, $CHCl_3$)} showed that racemization had not occurred, although the enantiomeric ratio was not determined.

In summary, we have shown that chiral, highly enantiomerically enriched 2-arylpyrrolidines can be prepared by simple asymmetric deprotonation–electrophilic quench followed by cationic cyclization, either with a Brønsted acid or with iodine.[9,10]



5a **11**

Scheme 6 Removal of the PMP group from **5a**

Acknowledgment

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(9) **Procedure for the Acid-Mediated Cyclization**
TFA (0.4 mL, 5.2 mmol) was added to the carbamate **4a** (200 mg, 0.52 mmol) in CH_2Cl_2 (0.5 mL), and the mixture was heated under reflux. After 16 h, the mixture was cooled to r.t., and H_2O (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated. Purification by column chromatography on silica, eluting with PE–EtOAc (9:1), gave the pyrrolidine **5a** (102 mg, 69%) as an oil; $[\alpha]_D^{20}$ +16.3 (*c* 6.5, $CHCl_3$). IR: ν_{max} = 2975, 2930, 1690, 1510 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.23 (5 H, m, Ph), 6.80–6.59 (4 H, m, Ar), 4.26 (1 H, t, *J* = 6.5 Hz, CH), 3.72 (3 H, s, CH_3), 2.06–1.87 (2 H, m, CH_2), 1.77–1.59 (2 H, m, CH_2), 1.52 (3 H, s, CH_3), 1.51 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 128.8, 127.7, 126.9, 115.8, 114.7, 113.9, 112.9, 88.6, 65.7, 55.6, 37.2 (2 × CH_2), 25.5, 25.3. HRMS (ES): *m/z* calcd for $C_{19}H_{24}NO$ [MH^+]: 282.1858; found: 282.1854. Resolution between the enantiomers was achieved using a Beckmann HPLC system fitted with a Daicel Chiralcel OJ column (250 mm × 4.6 mm) as the stationary phase with a mixture of hexane–*i*-PrOH (99:1 v/v) as the mobile phase with a flow rate of 1 mL/min; ambient temperature, detection by UV absorbance at λ = 254 nm. Injection volume 25 μL of the sample prepared in a 2 g/L solution of the eluent. Under these conditions the components were eluted at t_R = 35.5 min (major) and t_R = 48.5 min (minor), er 94:6.
(10) **Procedure for the Iodine-Mediated Cyclization**
Iodine (203 mg, 0.8 mmol) was added to the carbamate **6a** (75 mg, 0.26 mmol) in MeCN (0.9 mL) at r.t. After 24 h, sat. aq Na_2SO_4 (5 mL) was added. After 30 min, the solvent was evaporated, and Et_2O (10 mL) was added. The organic layer was washed with H_2O (5 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography on silica, eluting with PE–EtOAc (9:1), gave the pyrrolidine **7a** (86 mg, 79%) as an oil; $[\alpha]_D^{20}$ +48.0 (*c* 1.0, $CHCl_3$). IR: ν_{max} = 2970, 2920, 1605, 1505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (3 H, m, Ph), 6.92 (2 H, t, *J* = 8.5 Hz, Ph), 6.84 (2 H, d, *J* = 9.0 Hz, Ar), 6.71 (2 H, d, *J* = 9.0 Hz, Ar), 4.81 (1 H, dd, *J* = 9.5, 6.0 Hz, CH), 4.25 (1 H, dd, *J* = 12.0, 6.0 Hz, CH), 3.72 (3 H, s, CH_3), 2.84 (1 H, dt, *J* = 12.0, 6.0 Hz, CH), 2.35 (1 H, td, *J* = 12.0, 9.5 Hz, CH), 1.70 (3 H, s, CH_3), 1.24 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 127.9, 122.3, 120.5, 118.3, 115.4, 115.1, 113.7, 64.2, 63.8, 55.3, 45.9, 36.0, 31.2, 24.5. HRMS (ES): *m/z* calcd for $C_{19}H_{23}INO$ [MH^+]: 408.0819; found: 408.0817.