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Synthesis and kinetic resolution of *N*-Boc-2-arylpiperidines†

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The chiral base *n*-BuLi/(–)-sparteine or *n*-BuLi/(+)-sparteine surrogate promotes kinetic resolution of *N*-Boc-2-arylpiperidines by asymmetric deprotonation. The enantioenriched starting material was recovered with yields 39–48% and *ers* up to 97 : 3. On lithiation then electrophilic quench, 2,2-disubstituted piperidines were obtained with excellent yields and enantioselectivities.

Piperidines substituted in the 2-position with at least one aryl group are a class of molecules often possessing high biological activities and are therefore of interest to synthetic organic, medicinal and process chemists.¹ For example, piperidine **1** is a poly ADP ribose polymerase inhibitor (Fig. 1).² Piperidine **2** is a lead compound for orally active NK₁ antagonists.³ Piperidine **2** was synthesised by Xiao and co-workers as a mixture of diastereomers *via* the THF-mediated lithiation-substitution of (±)-*N*-Boc-2-phenylpiperidine.^{3a} The need for a stereoselective synthesis is exemplified by the ~50-fold difference in activity between the HCl salt of the (*R,R*) and the (*R,S*) diastereomers (IC₅₀ 0.3 nM and > 15 nM, respectively).⁴

A general approach to the asymmetric synthesis of 2,2-disubstituted piperidines continues to pose a problem for synthetic chemists. Building on their expertise of lithiated nitrogen-containing heterocycles, Coldham and O'Brien and co-workers reported that the Boc group in *N*-Boc-2-phenylpiperidine rotates rapidly, even at –78 °C, to allow high yields of lithiation at the benzylic position and that the organolithium is configurationally stable at low temperature.⁵ This led to the synthesis of enantiomerically enriched 2-alkyl-2-phenylpiperidines, such as piperidine **4a**, using enantiomerically enriched *N*-Boc-2-phenylpiperidine **3a** (Scheme 1).

The enantioenriched *N*-Boc-2-phenylpiperidine (*S*)-**3a** was obtained by an asymmetric reduction of the corresponding cyclic imine.^{5a} An alternative approach is by Negishi reaction using the chiral organozinc species formed either from the

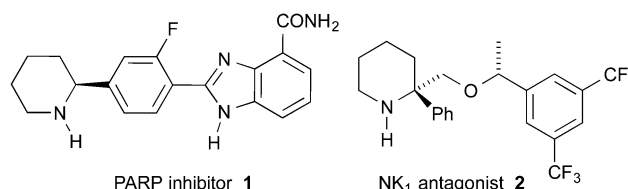
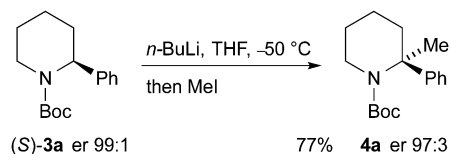


Fig. 1 Some biologically active 2-arylpiperidines.



Scheme 1 Lithiation-substitution of piperidine **3a**.

2-tributylstannane, itself formed by dynamic resolution of 2-lithiated *N*-Boc-piperidine,⁶ or directly by 'catalytic dynamic resolution',⁷ although the latter method was unsuccessful in our hands. We therefore sought a simpler method and wondered if racemic *N*-Boc-2-arylpiperidines were amenable to kinetic resolution. There is growing interest in the kinetic resolution of amines, mostly by *N*-acylation.⁸ In contrast, the kinetic resolution of amines by deprotonation has received very little study.⁹ The closest example is that from Beak and co-workers, who showed that the chiral base *n*-BuLi/(–)-sparteine can effect a kinetic resolution of an acyclic *N*-Boc- α -methylbenzylamine, albeit with fairly low selectivity (*er* up to 81 : 19 for 12% yield of recovered starting material).^{9a} In this paper, we report that *N*-Boc-2-arylpiperidines are excellent substrates for highly selective kinetic resolution by asymmetric deprotonation.

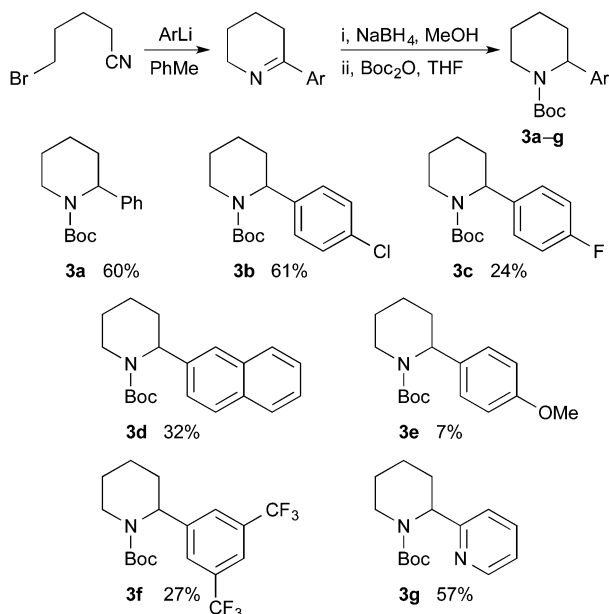
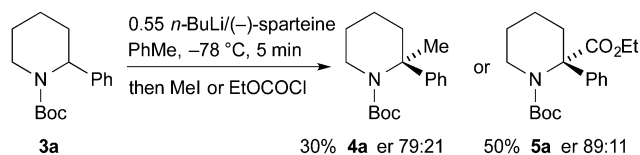
Racemic *N*-Boc-2-phenylpiperidine and related 2-aryl or 2-heteroaryl derivatives can be prepared by several different methods.¹⁰ We selected to extend the method used for racemic **3a**,^{5a} for the preparation of a variety of *N*-Boc-2-arylpiperidines (Scheme 2). Addition of the aryllithium, obtained by bromine–lithium exchange, to 5-bromovaleronitrile, followed by reduction of the intermediate cyclic imine with sodium borohydride and addition of Boc₂O gave

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Scheme 2 Synthesis of (±)-*N*-Boc-2-arylpiperidines **3a–g**.Scheme 3 Initial study of the kinetic resolution with pre-mixed *n*-BuLi/(-)-sparteine.

the desired racemic piperidines **3a–g**. Reasonable yields for the three-step procedure were obtained, except with *p*-MeOC₆H₄Li which gave significant amounts of methoxybenzene, perhaps due to its propensity to abstract a proton alpha to the nitrile. The corresponding organomagnesium reagent was no more successful.

For the kinetic resolution of these substrates, we initially focused on developing conditions using the substrate **3a**. A mixture of 0.55 equiv. of *n*-BuLi and (-)-sparteine (pre-mixed for 5 min) in PhMe was used for the lithiation of *N*-Boc-2-phenylpiperidine **3a** (Scheme 3). After 5 min, addition of iodomethane gave the product **4a** in 30% yield with a promising er (79:21). With the electrophile ethyl chloroformate, both the yield of the product **5a** and the er were improved. By changing the solvent to Et₂O, a similar er (87:13) of **5a** was obtained but in reduced yield (see ESI† for yield and er of recovered **3a**). The er was determined by chiral stationary phase (CSP) HPLC and the optical rotation of **4a** (see ESI†) matched that reported for the (*S*) enantiomer.^{5a} These data predict, as expected based on the lithiation of *N*-Boc-piperidine,¹¹ that the enantiomer (*S*)-**3a** is preferentially lithiated by *n*-BuLi/(-)-sparteine.

As an alternative, we investigated a different method of addition, whereby *n*-BuLi and (-)-sparteine were not premixed. *n*-BuLi was added to a solution containing the piperidine **3a** and (-)-sparteine in PhMe. After different time periods the electrophile EtOCOCl was added (Table 1). A marked improvement in the er of the product **5a** was obtained, and this was associated with a

Table 1 Kinetic resolution to give **5a** with *n*-BuLi and (-)-sparteine^a

Entry	Time (min)	Yield ^b 5a (%)	er ^c 5a
1	10	16	95:5
2	30	27	95:5
3	60	33	93:7
4	120	36	93:7
5	180	42	92:8

^a For yield and er of recovered **3a**, see ESI. ^b Yield of isolated product. ^c Determined by CSP HPLC.

significant decrease in yield. By increasing the reaction time to 3 h, it was possible to obtain the product **5** with er 92:8 and a yield of 42% (entry 5).

To investigate the differences in reaction times for these methods, we performed *in situ* IR spectroscopy to monitor the stretching frequency of the carbonyl group (Fig. 2). When using pre-mixed *n*-BuLi/(-)-sparteine (Fig. 2a), partial lithiation occurs over about 15 min, as judged by the steady but partial loss of $\nu_{\text{C=O}}$ 1691 cm⁻¹ (C=O stretch for **3a**) and formation of a new peak at 1640 cm⁻¹ (assigned to $\nu_{\text{C=O}}$ in the lithiated intermediate). However, without pre-mixing, the lithiation required several hours (Fig. 2b). The method chosen clearly impacts on the selectivity, with the slower lithiation allowing a

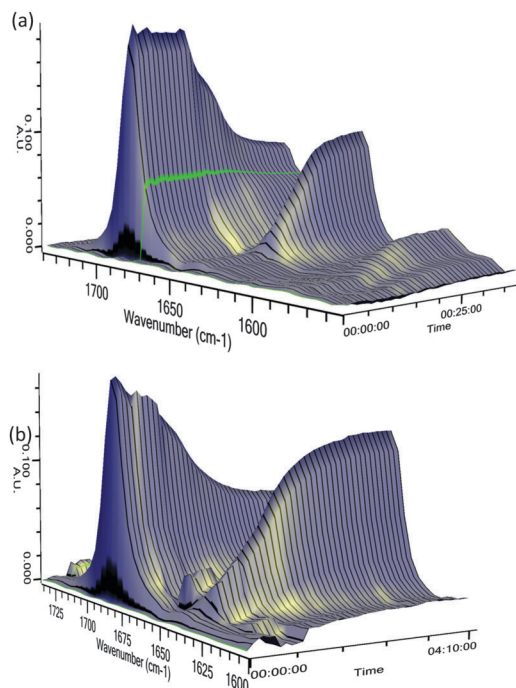


Fig. 2 *In situ* IR plots of the lithiation of **3a** with *n*-BuLi/(-)-sparteine at -78 °C in PhMe with time in h:min:s. (a) $\nu_{\text{C=O}}$ **3a** (1691 cm⁻¹), pre-mixed *n*-BuLi/(-)-sparteine added at time 16 min, $\nu_{\text{C=O}}$ lithiated **3a** (1640 cm⁻¹); (b) $\nu_{\text{C=O}}$ **3a** (1691 cm⁻¹) and (-)-sparteine then *n*-BuLi added at time 16 min, $\nu_{\text{C=O}}$ lithiated **3a** (1640 cm⁻¹).



Table 2 Kinetic resolution of **3a** with *n*-BuLi and (–)-sparteine

Entry	Equiv. <i>n</i> -BuLi and (–)-sp	Yield ^a (%) and er ^b 3a (%)	Yield (%) and er ^b 5a (%)
1	0.55	50 (77:23)	42 (92:8)
2	0.7	45 (96:4)	51 (86:14)
3	0.8	31 (92:8)	56 (77:23)
4	1.0	13 (98:2)	74 (57:43)

^a Yield of isolated starting material. ^b Determined by CSP HPLC.

more selective reaction. The faster reaction occurs with the premixed *n*-BuLi/(–)-sparteine complex that will have a higher concentration of the dimeric aggregation state.¹²

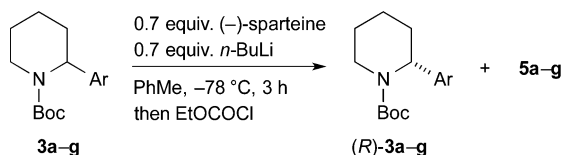
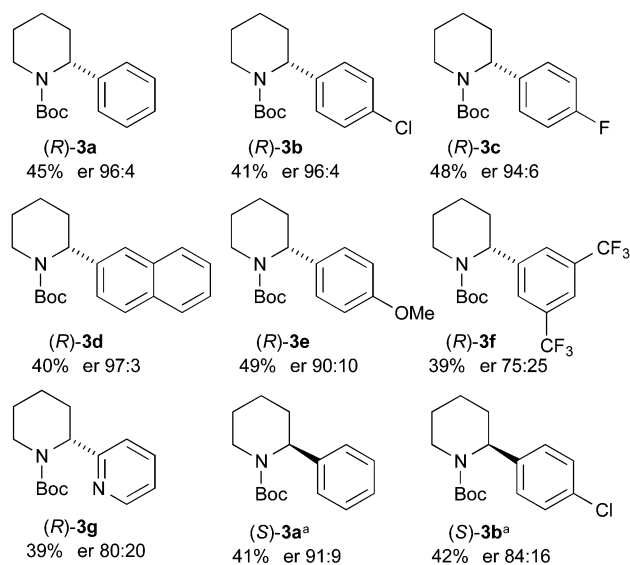
With optimised conditions in-hand, we studied the use of other electrophiles but these gave lower yields and ers (37% yield, er 82:18 using allyl bromide; 24% yield, er 74:26 using MeI). The lower selectivities may be due to partial racemisation of the lithiated intermediate prior to slower electrophilic quench.

Due to the variation in er dependent on the choice of electrophile, we decided to focus on obtaining a good yield and er for the recovered starting material. This was investigated by varying the number of equivalents of the chiral base (Table 2). The best conditions that we found used 0.7 equiv. of *n*-BuLi and (–)-sparteine and gave an excellent yield and er of recovered **3a** (entry 2). A yield of 45% with er 96:4 (*R*:*S*) corresponds to a relative rate of reaction for the two enantiomers $k_{rel} \sim 22$.¹³

The kinetic resolution was then tested with the different 2-arylpiperidines that were prepared as shown in Scheme 2. We were pleased to find that high levels of selectivity could be achieved with many of these compounds (Scheme 4). The yields and er values of the recovered starting materials are given in Scheme 4 for the different aromatic derivatives and it was found that both electron-poor (*p*-chloro **3b**, *p*-fluoro **3c**) and electron-rich (*p*-methoxy **3e**) substituents are tolerated in the kinetic resolution. However, some loss in selectivity occurs with the 3,5-bis-trifluoromethyl **3f** and 2-pyridyl **3g** derivatives. This may be due to a faster and therefore less selective lithiation with these more acidic substrates.

In addition, we have demonstrated that the other enantiomer of the 2-arylpiperidine can be formed by changing the chiral ligand to O'Brien's (+)-sparteine surrogate.¹⁴ This resulted in the formation of (*S*)-**3a** (41% yield, er 91:9) and (*S*)-**3b** (42% yield, er 84:16).

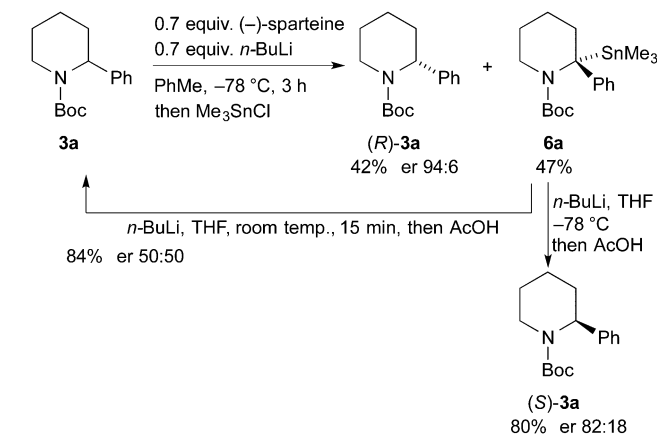
This methodology is reliant on using ethyl chloroformate as a sacrificial electrophile, consuming the undesired enantiomer. The kinetic resolution was tested with Me₃SnCl as the electrophile

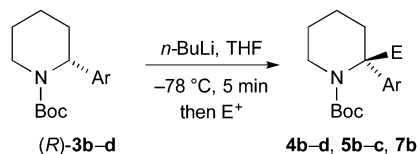
Scheme 4 Kinetic resolution of various *N*-Boc-2-arylpiperidines.

^a(+)-sparteine surrogate used in place of (–)-sparteine

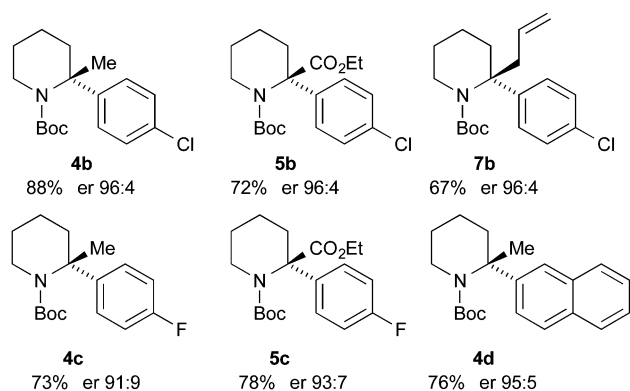
(Scheme 5). This could enable a subsequent tin–lithium exchange to recover the starting material after proton quench. The kinetic resolution performed well using this electrophile to give the recovered piperidine **3a** in 42% yield and er 94:6. The er of the stannane **6a** was not determined but this product was treated with *n*-BuLi in THF followed by addition of acetic acid. When this reaction was conducted at –78 °C, the piperidine (*S*)-**3a** was isolated with er 82:18, suggesting that tin–lithium exchange and protonation occurs with retention of configuration. However, when the exchange and protonation was conducted at room temperature, racemic **3a** was recovered in high yield. Therefore this approach allows recycling of the undesired product to allow a further kinetic resolution.

Finally, we have performed THF-mediated lithiation then substitution on the enantioenriched recovered starting materials to show that these are amenable to the formation of 2,2-disubstituted piperidines without loss of enantioselectivity.^{5,15} Treatment of the piperidine (*R*)-**3b** (er 96:4) with *n*-BuLi followed by MeI, EtOCOCl or allyl bromide gave the products **4b**, **5b**, and **7b** with good yields

Scheme 5 Kinetic resolution of *N*-Boc-2-phenylpiperidine with Me₃SnCl quench.

Scheme 6 Lithiation-substitution of various *N*-Boc-2-arylpiperidines.

and with no loss of enantioselectivity (Scheme 6). Similarly, piperidines (*R*)-3c (er 94 : 6) and (*R*)-3d (er 97 : 3) gave the products 4c, 5c, and 4d with good yields and very little reduction in er. Based on related chemistry using piperidine 3a,⁵ we assume that the absolute configuration of these products is as shown, in which lithiation and electrophilic quench occur with retention of configuration.



The chiral base *n*-BuLi with (–)-sparteine or the (+)-sparteine surrogate is effective for the kinetic resolution of racemic *N*-Boc-2-arylpiperidines in PhMe. The recovered starting material can be isolated with high enantiomer ratios, especially if *n*-BuLi and the chiral ligand are not pre-mixed. Use of *in situ* IR spectroscopy helped to optimise the conditions for the kinetic resolution. By using a trialkyltin halide electrophile, the quenched product can be recycled by tin–lithium exchange and protonation. After kinetic resolution, the recovered enantioenriched *N*-Boc-2-arylpiperidines can be deprotonated with *n*-BuLi in THF at -78°C and quenched with electrophiles without loss of enantiopurity to provide highly enantioselective syntheses of 2,2-disubstituted piperidine products.

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