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Tris(trimethylsilyl)silane: an unprecedented enhancement in the diastereoselectivity of radical cyclisations to give 2,4-disubstituted piperidines

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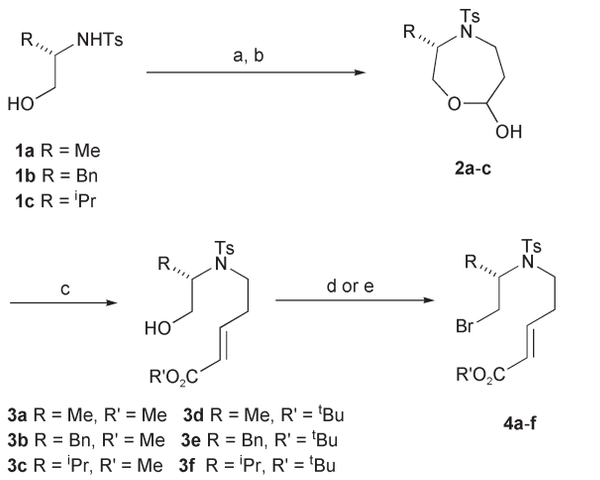
Cyclisation of bromides 4a–f mediated by tributyltin hydride affords predominantly the *trans* piperidines 5a–f with modest diastereomeric ratios, while cyclisation with tris(trimethylsilyl)-silane affords the same products with diastereomeric ratios of up to 99 : 1.

Tris(trimethylsilyl)silane (TTMSS) has emerged as an important hydrogen atom source in radical chemistry.[1] Advantages over the more commonly used tributyltin hydride (TBTH) include lower toxicity and a reduced rate constant for hydrogen atom donation. The latter can be beneficial in radical cyclisation reactions, giving improved selectivity for products of cyclisation rather than direct reduction. We were keen to capitalise on the advantages of TTMSS-mediated radical cyclisations in the synthesis of nitrogen heterocycles, specifically 2,4-disubstituted piperidines, highlighted as an important scaffold for drug discovery,[2] and forming the core of several pharmaceuticals.[3]

Free radical cyclisations are an attractive method for heterocyclic synthesis,[4] and they have formed the basis of a number of piperidine syntheses,[5] although the use of TTMSS has received scant attention.[6] It was envisaged that cyclisation of a primary alkyl radical onto an activated double bond would form the C3–C4 bond of the piperidine, with the substituent adjacent to nitrogen exerting stereocontrol over the forming stereogenic centre at C4. The C2 substituent of the piperidine can be derived from the wide variety of commercially available natural and unnatural amino acids.

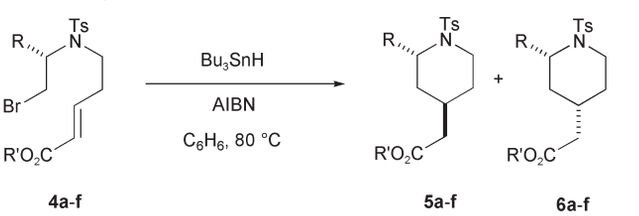
The cyclisation precursors were synthesised in 4 steps, Scheme 1. *N*-Alkylation of the *N*-tosyl amino alcohols[7] **1a–c** with the dimethyl acetal of 3-iodopropanal,[8] followed by acetal hydrolysis resulted in cyclisation to an epimeric mixture of hemiacetals **2a–c**, which were directly subjected to the Wittig reaction to afford the α,β-unsaturated methyl and *tert*-butyl esters **3a–f** in excellent yield. The *E* : *Z* selectivity in the Wittig reactions performed under standard conditions was surprisingly poor (typically 3 : 1 *E* : *Z*), but could be significantly improved by the introduction of benzoic acid under the modified conditions reported by Martin;[9] it was convenient to carry the *E* : *Z* mixture forward and separate at the bromide stage. The methyl esters **3a–c** were converted into the corresponding bromides **4a–c** by treatment with carbon tetrabromide and triphenylphosphine. This procedure proved to be unreliable and low yielding for the *tert*-butyl esters, which were instead converted into the bromides **4d–f** by a two-step procedure involving mesylation of the alcohol followed by displacement with lithium bromide.

We first explored the cyclisation of the bromides using TBTH. Syringe pump addition of TBTH and AIBN to a solution of the substrate in refluxing benzene gave excellent yields of the diastereomeric piperidines **5a–f** and **6a–f**, Table 1. Virtually identical results were obtained on substituting toluene (at 90 °C) for the more toxic benzene. The major diastereomer **5** was identified as the *trans* product from a combination of ^{1}H–^{1}H coupling constants and NOE measurements. This product arises from the preference of the 2-substituent to adopt an axial disposition in the chair-like transition state, thus avoiding the pseudo A^{1,3} strain with the sulfonamide;[10] the radical cyclises onto an equatorial olefin, Fig. 1. The minor isomer was the *cis* piperidine **6**, resulting from a transition state in



Scheme 1 Synthesis of cyclisation precursors. (a) $I(CH_2)_2CH(OCH_3)_2$, NaH, DMF, 70 °C, 59–70%; (b) 2 M HCl, THF, H_2O, 25 °C, 67–80%; (c) $Ph_3P{=}CHCO_2R'$, $C_6H_5CO_2H$, $C_6H_5CH_3$, 90 °C, 78–90%; (d) Ph_3P, CBr_4, CH_2Cl_2, 25 °C, 76–99%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, then LiBr, THF, reflux, 75–95%.

Table 1 Cyclisations of **4a–f** with TBTH[a]



Entry	Bromide[a]	R	R′	**5** : **6**[b]	Yield (%)[c]
1	**4a**	Me	Me	70 : 30	98
2	**4b**	Bn	Me	80 : 20	89
3	**4c**	^{i}Pr	Me	86 : 14	95
4	**4d**	Me	^{t}Bu	75 : 25	99
5	**4e**	Bn	^{t}Bu	83 : 17	85
6	**4f**	^{i}Pr	^{t}Bu	86 : 14	84

[a] Reactions were performed by syringe pump (10 h) addition of benzene solutions of Bu_3SnH and AIBN to a solution of the bromide in refluxing benzene (final concentration 0.015 M). [b] Ratio determined by ^{1}H NMR (**4a**, **4b**, **4d**) or HPLC after chromatography to remove tin residues. [c] Isolated yields following chromatography.

which the 2-substituent adopts an equatorial disposition. Increasing the bulk of the 2-substituent increases the pseudo A^{1,3} strain and favours the *trans* product (entries 1–3), while the bulk of the ester does not appear to have a significant effect on the stereoselectivity (entries 1–3 *versus* entries 4–6).

Moving on to TTMSS, we cyclised the esters **4a–f** in toluene at 90 °C, with addition of TTMSS by syringe pump, Table 2.† Cyclisation yields were a little lower than those obtained with TBTH, but it

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Fig. 1 Proposed pathway to major isomer.

Table 2 Cyclisations with TTMSS[a]

Entry	Bromide[a]	R	R′	**5** : **6**[b]	Yield (%)[c]
1	**4a**	Me	Me	72 : 28	97
2	**4d**	Me	^{t}Bu	77 : 23	86
3	**4b**	Bn	Me	92 : 8	76
4	**4e**	Bn	^{t}Bu	96 : 4	63
5	**4c**	^{i}Pr	Me	97 : 3	73
6	**4f**	^{i}Pr	^{t}Bu	99 : 1	75

[a] Reactions were performed by syringe pump (10 h) addition of toluene solutions of AIBN and TTMSS to a solution of the bromide in toluene at 90 °C (final concentration 0.015 M). [b] Ratio determined by ^{1}H NMR (**4a**, **4b**, **4d**) or HPLC both before and after chromatography. [c] Isolated yields following chromatography.

was in the diastereoselectivities that the difference between the two reagents was most noticeable.

In the examples with the methyl 2-substituent (entries 1 & 2), the diastereoselectivities with TTMSS were similar to those obtained with TBTH, but in all other cases there was a marked improvement on switching from TBTH to TTMSS. Thus benzyl derivative **4b** favoured the *trans* product **5b** with a *dr* of 92 : 8 (entry 3), and this increased to 97 : 3 for the isopropyl derivative **4c** (entry 5). Interestingly, the *tert*-butyl esters of these two derivatives exhibited higher stereoselectivities. For the benzyl compound **4e**, the *dr* was 96 : 4 in favour of *trans* piperidine **5e**, whilst for the isopropyl derivative **4f**, the *dr* rose to 99 : 1 (entries 4 & 6).

Such an enhancement in the stereoselectivity of the cyclisation process on switching from TBTH to TTMSS is remarkable and apparently without precedent. Others have noted increased diastereoselectivity in the reduction of halides on switching from TBTH to TTMSS,[11] an observation attributed to the increased preference for the bulkier TTMSS to approach the intermediate radical from the less hindered face. This explanation cannot account for the enhanced diastereoselectivities observed during the cyclisation of **4a**–**f**.

It is very unlikely that the increased diastereoselectivities are a result of the cyclisation occurring under thermodynamic control. Reversibility in radical cyclisations is very unusual, and most examples are associated with the cyclisation of highly stabilised radicals in conjunction with slow trapping by poor atom donors.[12] Reversibility in this case would be energetically very unfavourable as the radical produced by the cyclisation is much more stable (due to delocalisation with the ester) than the initial primary alkyl radical.

We believe that the reduced rate constant for hydrogen atom donation by TTMSS compared with TBTH could allow the product radicals to undergo side reactions before they are trapped; it is reasonable to assume that these could be different, or could occur at different rates, for the two diastereomers. The slightly lower yields obtained in the TTMSS cyclisations, coupled with the improved diastereoselectivities, suggest that the minor diastereomer may be decomposing by some, as yet unidentified, pathway.

In summary, we have discovered a highly diastereoselective synthesis of *trans* 2,4-disubstituted piperidines from simple acyclic precursors, which should have application to the synthesis of more complex molecules. Experimental and theoretical studies are currently underway in an effort to elucidate the origins of the difference in stereoselectivity between TTMSS and TBTH.

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Notes and references

† TTMSS cyclisation procedure. Preparation of (2*R*,4*R*)-4-(*tert*-butoxycarbonylmethyl)-2-isopropyl-1-(*p*-toluenesulfonyl)-piperidine (**5f**). To a stirred solution of the bromide **4f** (0.222 g, 0.468 mmol) in degassed toluene (10 mL) at 90 °C under Ar were added solutions of AIBN (0.008 g, 0.049 mmol) in toluene (10 mL) and TTMSS (0.26 mL, 0.842 mmol) in toluene (10 mL) by syringe pump at a rate of 0.5 mL h^{-1}. The solution was stirred at 90 °C for a further 12 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (petrol : ethyl acetate, 8 : 1, $R_f = 0.25$) to afford the *title compound* as a colourless oil. (0.13 g, 75%) $[\alpha]_D^{18}$ +34.9 (*c* 0.64 in $CHCl_3$); (Found: C, 63.8; H, 8.5; N, 3.5. $C_{21}H_{33}NO_4S$ requires C, 63.8; H, 8.4; N, 3.5%); ν_{max}(film)/cm^{-1} 2970 (C–H), 2872 (C–H), 1726 (C=O), 1598 (C=C aromatic), 1494 (C=C aromatic), 1454, 1391, 1367, 1337, 1259, 1204, 1152, 1093, 1054; δ_H(300 MHz, $CDCl_3$) 0.71–0.96 (8H, envelope), 1.33–1.48 (10H, envelope), 1.73 (1H, d, *J* 11.4), 1.77–2.13 (4H, envelope), 2.40 (3H, s), 2.91–3.05 (1H, m), 3.53–3.62 (1H, m), 3.74–3.86 (1H, m), 7.25 (2H, d, *J* 8.3), 7.69 (2H, d, *J* 8.3); δ_C(125 MHz, $CDCl_3$) 19.9, 20.2, 21.5, 26.6, 27.4, 28.0, 30.3, 31.5, 40.7, 42.7, 59.5, 80.4, 126.9, 129.5, 139.0, 142.7, 171.4; *m*/*z* (ES$^+$) 418 (34%, $[M + Na]^+$), 362 (100, $[M - CH_2{=}C(CH_3)_2]^+$) [HRMS Found: $(M + Na)^+$ 418.2029. $C_{21}H_{33}NNaO_4S$ requires *M*, 418.2028].

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