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Stereocontrolled synthesis of a prototype library of enantiopure 2,4-disubstituted 4-aryl-6-piperidinones and piperidines

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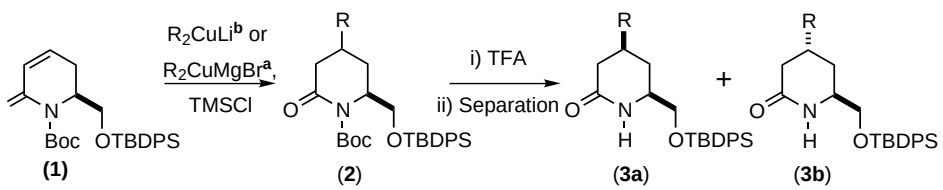
Abstract—Addition of a set of aryl cuprates to *N*-Boc *O*-TBDPS 2-hydroxymethyl 3,4-unsaturated 6-piperidinones affords *syn*-adducts in preference to *anti* when mixed Grignard-cuprates are used. Aryllithio cuprates give more of the *anti*-isomer in some cases. A library of 2-hydroxymethyl carbamates (27 compounds) and 2-hydroxymethyl aryl ethers and thioethers (19 compounds) was generated from a selection of 4-aryl-6-piperidinones, and some were further reduced to the corresponding piperidines (9 compounds).

Substituted piperidines and their piperidinone precursors are considered as versatile molecular frameworks because they allow the deployment of diverse ligands for interactions with receptors and enzymes.[1] One of the largest categories of such structures include an 4-aryl piperidine motif which is found in a number of therapeutically important drugs.[2] Substituted piperidines containing 4-aryl appendages and related analogs are also targets for pharmacological studies.[3] In the preceding paper,[4] we described methods for the stereocontrolled introduction of nitromethyl and related nitroalkyl groups in a 4,5-unsaturated 2-substituted-6-oxo-piperidine nucleus via conjugate additions. Herein we report the synthesis of a group of 2,4-disubstituted 4-aryl-6-piperidinones and piperidines, leading to a prototypical library of 46 enantiopure analogs bearing seven different carbamate, ether and thioether groups for each aryl analog.

Conjugate addition of mixed aryl Grignard cuprates, or diaryl lithiocuprates prepared from the corresponding aryl halide to the 4,5-unsaturated lactam **1**,[5] in the presence of TMSCl followed by treatment with TFA, and chromatographic separation led to the 4-aryl adducts in excellent yields (Scheme 1, Table 1).[6,7] When the cuprate reagent was prepared from the corresponding aryl Grignard, the major products had a *syn* disposition (Table 1, entries 1–4, 6, 8). The phenyl reagent led to a ~1:1 mixture of *syn*- and *anti*-adducts regardless of the nature of the cuprate. Surprisingly, the 4-OTBS phenyl cuprate, prepared from the mixed aryl cuprate and the diaryl lithiocuprate gave opposite selectivities[8] (Table 1, entries 6, 7). The same trend was observed with the dimethyllithio cuprate and the Grignard variant (Table 1, entries 8, 9). Mann, Wermuth and co-workers[9] have found stereochemical differences in related conjugate additions of alkyl and phenyl cuprates in ether. In the latter case, the *anti*-isomers were predominant, contrary to our case. In order to evaluate the influence of an ester and TBDPS ether substituents in the starting α,β-unsaturated lactams, we reacted the Mann/Wermuth methyl ester **4** with the



Scheme 1.

Keywords: piperidine; conjugate cuprate addition.
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Table 1.

Entry	R =	Yield **2** (%) (ratio *syn*/*anti*)[c]	Yield **3a** and **3b** (ratio **3a**/**3b**)[d]
1	4-OMe-Ph[a]	82 (3:1)	99 (4.5:1)
2	4-F-Ph[a]	93 (3.2:1)	66 (5:1)
3	4-Me-Ph[a]	89 (2:1)	64 (1.8:1)
4	Ph[a]	87 (1.4:1)	[e]
5	Ph[b]	87 (1:2)	65 (1:2.1)
6	4-OTBS-Ph[a]	91 (4:1)	[e]
7	4-OTBS-Ph[b]	71 (1:3)	[e]
8	Me[a]	72 (9:1)	81 (11:1)
9	Me[b]	74 (1:5)	80 (1:5)

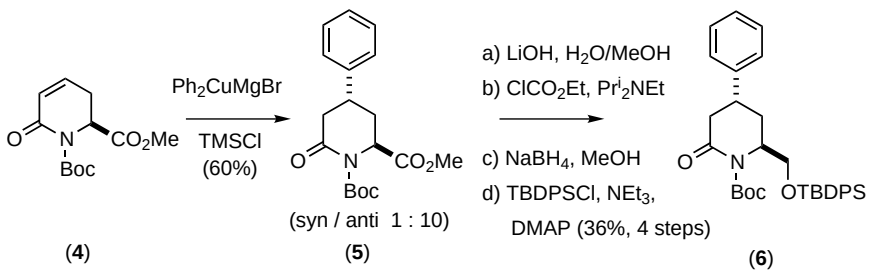
[a] Cuprate prepared from corresponding Grignard reagent.
[b] Cuprate prepared from corresponding lithio reagent.
[c] *syn*/*anti* Ratio determined from NMR spectra.
[d] *syn*/*anti* Ratio determined from isolated yields of **3a** and **3b**.
[e] Reaction not carried out.

mixed diarylmagnesio cuprate in the presence of TMSCl. The resulting major *anti*-product **5** (>10:1) was then converted to the same product **6** (see Table 1, entry 5) obtained from the 6-OTBDPS analog **1** (Scheme 2) using the mixed reagent.

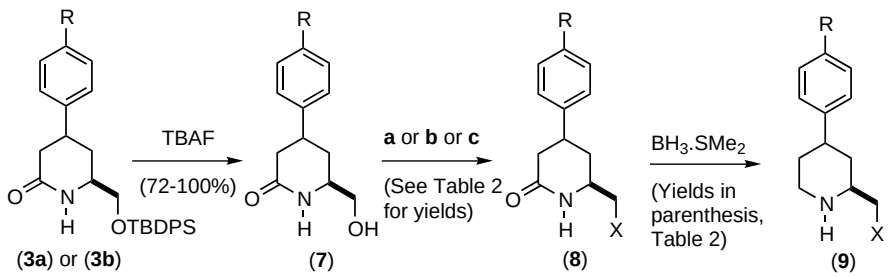
The preponderance of *syn*-isomers **3a** can be rationalized on the basis of $A^{1,3}$ strain[10] in a preferred conformer of **1** in which the bulky OTBDPS group adopts an axial orientation.[3d,9] This was in fact confirmed by decoupling experiments (JH_2,H_3 ax = <1 Hz; JH_2,H_3 eq. ~6.2 Hz). It is possible that the dimethylmagnesio cuprate reagent coordinates in part to the ether oxygen[8,11] and delivers the nucleophile from the same side affording the *syn*-product **3a** as a major isomer. As the reagent gets bulkier the complex is less favored and more *anti*-attack can occur. The substituent effects on the aryl portion may play a subtle role which is more difficult to rationalize.

We then proceeded with the preparation of a representative library of 27 4-aryl 2-*O*-carbamoyl-2-hydroxymethyl 6-piperidinones, and 19 ethers and thioethers (Scheme 3, Table 2). For the former group, we chose a set of commercially available isocyanates to be reacted with some of the *syn*- and *anti*-4-aryl-2-hydroxymethyl 6-piperidinones **7**, depending on their availability and quantity in hand. In general, yields were excellent and the products **8** were isolated as chromatographically homogeneous enantiopure compounds (^{13}C, mass spec., HPLC). The ether and thioether analogs were prepared under the conditions of the Mitsunobu[12] reaction (Table 2). Finally, nine piperidine analogs **9** were prepared from some of the piperidinone compounds **8** by reduction of the lactam group with borane dimethylsulfide[13] (Table 2, % in parentheses).

With the 4-OTBS analog **10** in hand, we explored functionalizations based on the Suzuki[15] and Pd-catalyzed aryl triflate[16] substitution reactions as shown in

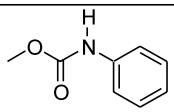
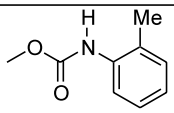
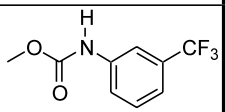
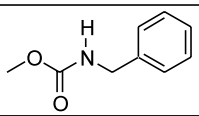
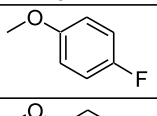
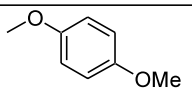
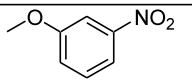
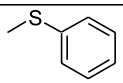


Scheme 2.



Scheme 3.

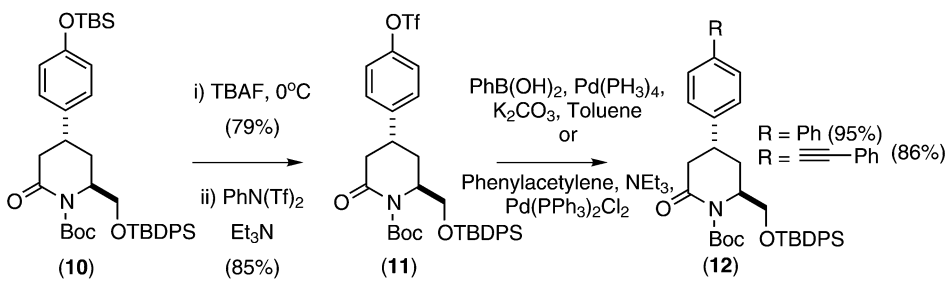
Table 2.

X =	*syn* compounds				*anti* compounds			
	R = H	R = 4-OMe	R = 4-F	R = 4-Me	R = H	R = 4-OMe	R = 4-F	R = 4-Me
	92%	83%	91%	79%	82%	62%	-	94%
	96%	53%	99%	80%	70%	55%	-	77%
	56%	-	91%	87%	68%	-	60%	87%
	70%	59%	55%	75%	76%	-	56%	79%
	-	87% (60%)	63% (88%)	75% (97%)	84% (99%)	-	-	61% (88%)
	-	56%*	50%	61%	73%	-	-	-
	-	76%*	60%	52%	84%	-	-	-
	61% (88%)	55%	96%	99% (99%)	99% (68%)	-	-	73% (88%)

Reaction conditions: (a) ArNCO, pyridine, heat; (b) Ar′OH, DEAD, Ph_2P(Ph-4-NMe_2); (c) Ph_2S_2, nBu_3P; * PPh_3 used instead of $Ph_2P(C_6H_4$-4-$NMe_2)$;[14] - refers to reactions not carried out.

Scheme 4. Thus, treatment of the triflate ester **11** with phenylboronic acid and phenylacetylene individually, in the presence of palladium catalysts afforded the corresponding 4-phenyl **12a** and 4-phenyl acetylenic **12b** derivatives in excellent yields.

In conclusion, we have investigated methods for the stereocontrolled synthesis of 4-aryl piperidines, and the generation a set of 4-aryl-2-substituted 6-piperidinones and piperidines in enantiopure form. A total of 27 4-aryl-2-hydroxymethyl *O*-carbamoyl and 19 ether and thioether analogs were prepared by standard methodology. A selected set of nine original ether and thioether adducts were converted into their piperidine counterparts. The methodology developed in this work should prove useful in the design of larger libraries of substituted enantiopure 4-aryl piperidines.



Scheme 4.

Acknowledgements

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6. *Typical procedure for cuprate addition and diastereomer separation*: To a cooled solution (−40°C) of $CuBr{\cdot}SMe_2$ (5.7 g, 2.8×10^{-2} mol, 5 mol. equiv.) in THF (30 mL), was added tolylmagnesium bromide (56 mL, 5.6×10^{-2} mol, 10 mol. equiv.). The reaction mixture was then stirred, under argon, for 45 min at −40°C. The temperature of the cooling bath was lowered to −78°C and the α,β-unsaturated amide **1** was added by cannula in THF (10 mL) with vigorous stirring of the reaction mixture. TMSCl (10.6 mL, 8.4×10^{-2} mol, 15 mol. equiv.) was added dropwise over 1 min and the reaction mixture was stirred at −78°C for a further 3 h before being allowed to warm up to room temperature over a period of 2 h. Saturated NH_4Cl (200 mL) was added and the mixture was extracted with Et_2O. The combined organic fractions were dried (Na_2SO_4) and removed in vacuo to afford a yellow oil which was purified by silica gel flash chromatography (10% AcOEt/hexane) to give compounds **2** (2.76 g, 89%) as an inseparable mixture of diastereomers. These were then dissolved in CH_2Cl_2 (50 mL) and cooled to 0°C. TFA (5.0 mL, 0.1 volume equiv.) was added and the reaction mixture was stirred under argon for a further 2 h. Excess TFA was removed by evaporation with toluene and careful silica gel flash chromatography (10% MeOH/AcOEt) subsequently afforded compounds **3a** (0.92 g, 41%) and **3b** (0.52 g, 23%) as pale yellow oils (Table 1, R = 4-Me-Ph). Copies of pertinent ^1H and ^{13}C NMR spectra are available upon request.
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