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New stereoselective syntheses of *cis*- and *trans*-2-methyl-4-arylpiperidines

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Abstract—A stereoselective approach has been developed for the synthesis of *cis*- and *trans*-2-methyl-4-arylpiperidines from a common intermediate. The Ni-catalyzed hydrogenolysis of *N*-Boc-2-methyl-4-aryl-4-piperidinols, obtained by addition of organometallic reagents on *N*-Boc-2-methyl-4-piperidone, afforded the *trans* derivatives with up to 95% selectivity whereas the corresponding *cis* isomers were obtained in the presence of palladium catalysts.

Diversely substituted chiral non-racemic piperidine derivatives are important pharmacophores found in a wide range of pharmaceuticals.[1] In addition, these derivatives can be found in a number of alkaloid natural products, and as a consequence, the development of efficient and economic syntheses of these compounds is the focus of intense research. In this paper, we will describe a remarkable tunable control in the diastereoselectivity of the reduction of 2,4-disubstituted-4-piperidinols **1** to produce after deprotection both the *trans*-**3** and *cis*-**5** derivatives in a controlled manner (Fig. 1).

In the context of a high priority medicinal chemistry project, we required an efficient stereoselective synthesis of *trans*-2-methyl-4-arylpiperidine derivatives **3**. These compounds can be prepared by α-methylation of the nitrosamine precursor[2] or by addition of methyllithium to the corresponding imine intermediate.[3] However, for a multi-kilogram synthesis, these methods have several disadvantages: linear sequence with subsequent problematic purification of the product from unreacted starting material, need to manipulate highly toxic (nitrosamine) or hazardous (MeLi) reagents, and most importantly, the need to perform a chiral separation in the final step of the synthesis.

In the search for a new approach to these compounds, we developed an efficient synthesis of chiral non-racemic *N*-Boc-2-methyl-4-piperidinone[4] **6** and sought to utilize this optically pure intermediate for the synthesis of **3**. In this context, addition of various arylmetal reagents to the piperidinone **6**, afforded the alcohols **1a–e** with excellent diastereocontrol (>50:1)[5] in good

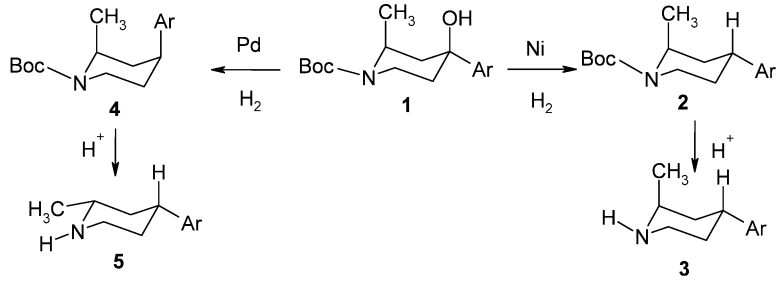

Figure 1.

Keywords: hydrogenolysis; nickel; palladium; piperidines.

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yields after recrystallization from ethyl acetate/*n*-heptane (Table 1). With aryllithium, and to a lesser extent with Grignard reagents, competitive deprotonation of **6** occurred resulting in moderate to low yields. Subsequent separation of the Boc-protected alcohols **1a–e** from the unreacted ketone was tedious. Fortunately, use of the corresponding cerium derivatives solved the problem. Specifically, the Grignard or aryllithium reagent was stirred for 1.5 hours with anhydrous cerium chloride[6] in THF at 20°C before adding ketone **6**.

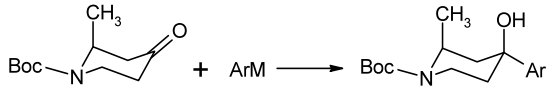
The high diastereoselectivity obtained for the reactions of the organometallic reagents with the ketone **6** is the result of the axial 2-methyl group of the piperidinone, due to a $A^{1,3}$ strain with the Boc protecting group.[7] Hence, only equatorial attack on the ketone takes place consequently giving the *trans* configuration in the resulting alcohols.

Many methods have been reported for the cleavage of tertiary alcohols[8] and a very efficient process has been developed in our laboratories for the synthesis of *cis*-2,4-disubstituted piperidines.[9] We concentrated on a direct metal-catalyzed[10] reduction of the tertiary benzylic alcohols **1a–e**. Indeed, this method was particulary attractive in view of a possible scale-up for several reasons: very short (no need to derivatize the labile tertiary benzylic alcohol), high atom economy (catalytic process) and versatility (access to both *cis* and *trans* compounds).

An extensive parallel screening of heterogeneous hydrogenation catalysts (Ni, Pd, Pt, Rh, Ru, Co, Cu) in various solvents (ethanol, toluene, acetic acid, THF and triglyme) was performed first on the alcohol **1a**[11] for which the *trans* relative configuration of the methyl and naphthyl groups had been proven previously by X-ray diffraction analysis.[12] From that study, we concluded that nickel catalysts were the best for the synthesis of *trans*-2,4-disubstituted piperidine derivative **2a**. DOE[13] was then performed with 3 nickel catalysts (Ni/SiO_2, Ni/Al_2O_3, Raney nickel) and the effect of temperature (80–120°C), pressure (15–50 psi) and solvent (toluene, diglyme, triglyme, 2-pentanol and ethylene glycol) was evaluated. It is worth to note that the qualitative variable 'solvent' was treated as two quantitative variables t1 and t2 (respectively related to the polarity and the polarisability), following a principal component analysis performed on 82 solvents[14] (Fig. 2).

Interestingly, none of the desired product **2a** was formed in the experiments involving Raney nickel, even though a complete reduction of alcohol **1a** was always observed. For that reason, the statistical analysis was run only with Ni/SiO_2 and Ni/Al_2O_3 catalysts to avoid biasing the estimation of the effects by leveling of the

Table 1. Synthesis of *N*-Boc-2-methyl-4-aryl-4-piperidinols



6 **1a-e**

Entry[a]	Ar	M[b]	Product	Yield (%)[c]
1	2-Naphthyl	Li	**1a**	66
		$MgBr/CeCl_3$		70
2	Ph	Li	**1b**	33
		$MgBr/CeCl_3$		80
3	(2-CH_3)-Ph	Li	**1c**	54
		$MgCl/CeCl_3$		78
4	(4-OCH_3)-Ph	Li	**1d**	27
		MgCl		68
		$MgCl/CeCl_3$		78
5	(4-CF_3)-Ph	Li	**1e**	47
		$MgBr/CeCl_3$		50

[a] All reactions were carried out in anhydrous THF under nitrogen at room temperature except for M = Li (−78°C).
[b] We used a 1.25/1.25/1 molar ratio of $CeCl_3$/ArMgX/ketone.
[c] Yields (unoptimized) refer to pure isolated compounds.[5] Purification was achieved by flash chromatography followed by crystallization from *n*-heptane/EtOAc.

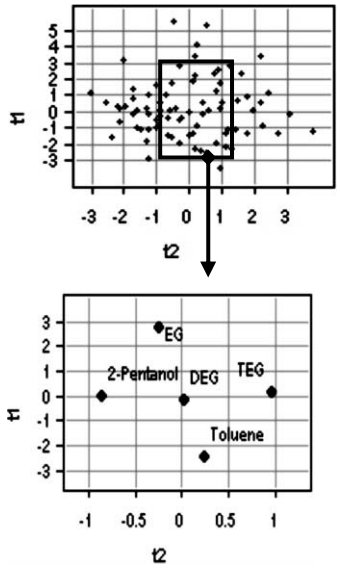


Figure 2. PCA approach for solvent selection.

Table 2. Statistical analysis: parameter estimates

Term	Estimate	Prob>|t|	Significance[a]
Intercept	18	<.0001	***
P (pressure)	−5	0.074	No
T (temperature)	−6	0.041	*
t1 (polarity)	−12	0.006	**
t2 (polarizability)	0	0.897	No
cat[Ni/Al_2O_3]	−10	0.002	**
t1*cat[Ni/Al_2O_3]	13	0.004	**
T*cat[Ni/Al_2O_3]	9	0.005	**
T*P	−6	0.047	*
t1*P	−8	0.049	*

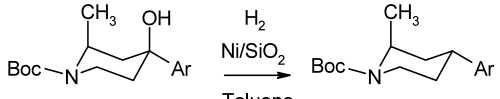
[a] The number of stars reflects importance of the effect (* = minor effect, *** = strong effect). 'No' means that it was not possible to detect any effect.

yields to zero. The statistical analysis (Table 2) showed us that the formation of the *trans* derivative **2a** is favored when the reaction is performed with Ni/SiO_2 as catalyst at 80°C (negative effect of temperature) in an apolar solvent (negative effect of t1). Under these latter conditions, it is optimal to work at 50 psi even though no main effect of pressure is detected (negative interaction terms with T and t1). On the other hand, a very large increase in yield was observed when the reaction was performed in toluene with Ni/SiO_2 as catalyst. This result is due to a strong positive interaction between the parameters 't1' and 'catalyst type'.

We concluded that Ni/SiO_2 in toluene at 80°C under 50 psi H_2 was optimal for the synthesis of **2a** and adjusted then the catalyst loading for that compound (Table 3, entries 1–3).

Under optimal conditions, compound **2a** was obtained in 88% isolated yield with a 91:9 selectivity after 16 h (entry 2). A slightly better selectivity was obtained by decreasing the catalyst loading to 10% by weight but the reaction was then very slow (entry 3). Surprisingly, the monocyclic aromatic compounds **1b–e** reacted much more slowly than the 2-naphthyl analog. In the best case (Ar = Ph), a conversion of about 10% was determined by HPLC after 24 h at 80°C with the highest catalyst loading (entry 4). No improvement was obtained after a brief screening of other apolar solvents;[16] however, some benefit was realized by performing the reactions in toluene at 100°C. The 4-phenyl derivative **2b** was then

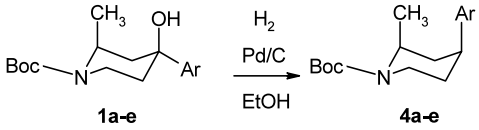
Table 3. Synthesis of *trans*-2-methyl-4-arylpiperidines **2a–e**[15]



Entry[a]	Substrate	T (°C)/time (h)[a]	Product (%)	*trans*/*cis*[f]
1	**1a**	80/16	**2a** (70)[d]	87:13
2	**1a**	80/16[b]	**2a** (88)[d]	91:9
3	**1a**	80/40[c]	**2a** (85)[d]	93:7
4	**1b**	80/24	**2b** (10)[e]	nd[g]
5	**1b**	100/16	**2b** (81)[d]	94:6
6	**1b**	100/16[b]	**2b** (85)[d]	96:4
7	**1c**	100/60	**2c** (22)[d]	90:10
8	**1d**	100/60	**2d** (28)[d]	86:14
9	**1d**	120/6.5	**2d** (75)[e]	83:17
10	**1e**	100/36	**2e** (10)[d]	82:18

[a] Reactions (1–2 mmol scale) were carried out in toluene (~3 ml/mmol) under 50 psi H_2 with 130% by weight of 66% Ni/SiO_2 (Acros) in 10 or 25 ml reactors with magnetic stirring.
[b] 50% by weight of 66% Ni/SiO_2 was used.
[c] 10% by weight of 66% Ni/SiO_2 was used.
[d] Isolated yields (chromatography) of pure product.
[e] In situ yields, determined by quantitative HPLC (external reference).
[f] Determined by capillary electrophoresis and confirmed by ^1H NMR and chiral HPLC.
[g] Not determined.

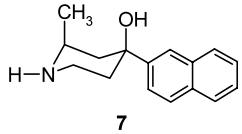
Table 4. Synthesis of *cis*-2-methyl-4-arylpiperidines **4a–e**



Entry[a]	Substrate	Time (h)	Product (%)[b]	*cis*/*trans*[c]
1	**1a**	16	**4a** (70)	68:32
2	**1b**	6	**4b** (52)	82:18
3	**1c**	24	**4c** (24)	83:17
4	**1d**	6	**4d** (54)	76:24
5	**1e**	24	**4e** (0)	nd

[a] All reactions (1–2 mmol scale) were carried out at 80°C in 96% ethanol (~3 ml/mmol) under 50 psi H_2 with 130% by weight of 10% Pd/C (Johnson-Matthey type 331) in 10 or 25 ml reactors with magnetic stirring.
[b] Isolated unoptimized yields (chromatography).
[c] Determined by capillary electrophoresis and confirmed by ^1H NMR and chiral HPLC.

obtained in 81–85% yield with a very high selectivity (entries 5 and 6). The other *trans* derivatives **2c–e** were also obtained with very good selectivities but these reactions were much more slower. The reaction rate was indeed dramatically affected either by increasing the steric hindrance around the reaction center (entry 7) or by the presence of an electron-donating (entry 8) or -withdrawing (entry 10) group. The low yields are due to moderate conversions but also to partial cleavage of the Boc-protective group (from 25 to 50% area of polar products were detected by HPLC). After a further increase of temperature, we obtained the *p*-anisoyl derivative **2d** in 75% yield with a good selectivity (entry 9). Unfortunately, under these conditions the *p*-trifluoromethyl and *o*-tolyl compounds were almost completely transformed into polar products. Obviously, further studies would be necessary to improve the reactivity of these hindered or electron-poor substrates. In this regard, it is worth to mention that the selectivity of the hydrogenolysis of the amino-alcohol **7**[17] was even better (95:5) than that obtained with its Boc-protected precursor **1a**. Even though we did not evaluate the possibility at this stage, it should thus in principle be possible to develop a one-pot process from **1a** till the final compound **3a**.



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The initial screening[11] on alcohol **1a** revealed that the *cis* derivative **4a** was formed with high selectivity in the presence of various palladium catalysts in ethanol. Even though an elegant cationic reduction process (TFA/Et_3SiH) of these tertiary alcohols was developed for the synthesis of *cis*-2-methyl-4-arylpiperidines,[3] we found it relevant to show that these *cis* compounds are also accessible via our metal-catalyzed process (Table 4).

As shown in Table 4, hydrogenolysis of alcohols **1a–d** under palladium catalysis afforded the *cis* isomers **4a–d** with moderate to good selectivities (unoptimized). With the notable exception of the *p*-trifluoromethyl alcohol **1e**, which did not react at all, the reactions carried out with palladium were generally faster than those performed with Ni-catalysts. Yields (unoptimized) are moderate but, as with Ni catalysts, no major by-product was formed except deprotected material.

In conclusion, we have developed a new stereoselective synthesis of *cis*- and *trans*-2-methyl-4-arylpiperidines from a common tertiary alcohol intermediate. We obtained up to 96:4 *trans*/*cis* selectivity with Ni/SiO_2 in toluene whereas the best *cis*/*trans* ratio was 83:17 with Pd/C. In both cases the reaction is very sensitive to electronic as well as steric effects. Further optimization is under way and will be reported in due course for hindered or electron-poor substrates. This highly convergent approach offers however remarkable advantages for the synthesis of the *trans* compounds as compared to the alkylation methods.

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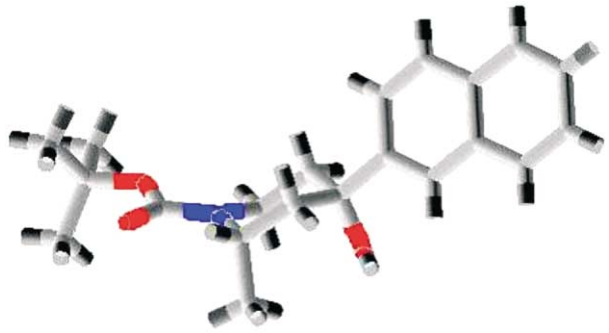
11. The screening was performed at Avantium B.V. (NL).
12. X-Ray diffraction picture of alcohol **1a**:



13. The effects of variables P, T, catalyst, t1 and t2 were evaluated through a triple 2^{4-1}+2 center points design (one design per catalyst type). The statistical analysis was performed using the JMP 4.0.2 software following a stepwise adjustment of a first-order model with interactions.
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15. A 5-reactors parallel hydrogenation manifold was used (see Bradley, D. A.; Schmid, C. R. *Org. Process Res. Dev*. **1997**, *1*, 179–181). Typical experimental procedure: a 10 ml hydrogenation flask is charged with alcohol **1a** (200 mg, 0.6 mmol), Ni/SiO_2 (200 mg, 50% by weight) and toluene (2 ml). The suspension is magnetically stirred at 80°C under 50 psi H_2 during 16 h. The catalyst is filtered through Millipore and washed with EtOH. The filtrate is evaporated to dryness and the residue (200 mg) purified by chromatography on silica gel (AcOEt/*n*-heptane 2:8) to afford pure **2a** (166 mg, 88%). A 87:13 *trans*/*cis* ratio is determined by capillary electrophoresis on a deprotected (TFA/CH_2Cl_2/20°C) sample [Method: Beckman P/ACE system; 30 cm X 50 μm i.d. fused silica capillary column; mobile phase: phosphate buffer+5% (w/v) HS-β-CD aq. soln (pH 2.5); voltage: −10 kV; T: 22°C; λ: 214 nm; injection: 5 s at 0.3 psi; run time: 10 min; t_R *cis* = 3.37 min, t_R *trans* = 3.45 min].
16. The substrate was insoluble in *n*-heptane. Cyclohexane, anisole and α,α,α-trifluorotoluene gave results similar to toluene, no reaction occurred in triethylamine and di-*n*-butyl ether and degradation was observed in trichloroethylene.
17. Cleavage of the Boc protective group was carried out under basic conditions (KOH/*n*-pentanol/150°C) to avoid elimination of the tertiary alcohol.