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STEREOSELECTIVE CONDENSATIONS OF α'-LITHIO PYRROLIDINE AMIDINES

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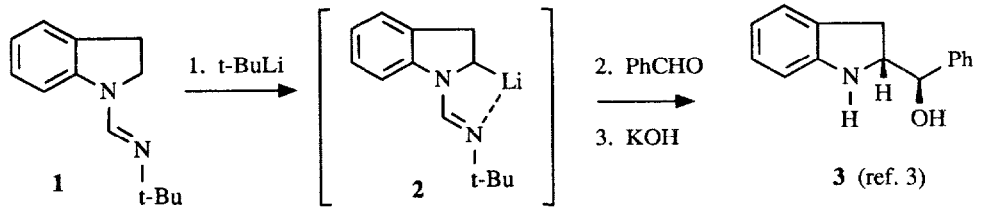
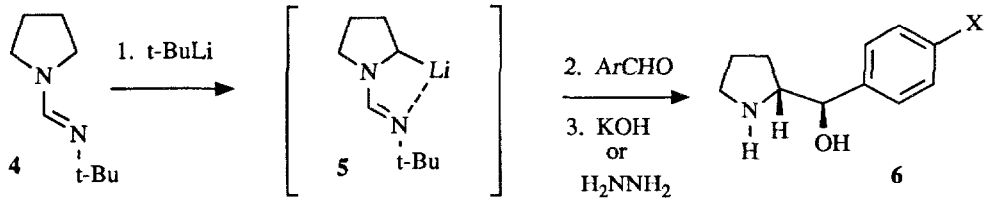
Abstract: *The condensation of α'-lithio pyrrolidine amidine **5** with aromatic aldehydes gives hydroxymethyl pyrrolidines **6** with high* threo-erythro *selectivity (ca. 95:5). In contrast, the analogous reaction with lithio-piperidine amidine **9** is stereorandom.*

The discovery that α-amino carbanions are stabilized by an adjacent formamidine functionality has led to the development of these reagents as extremely useful synthetic intermediates.[1] However, very little information is available concerning the potential diastereoselectivity of achiral formamidine reagents such as **1** and **4**.[2] For example, Meyers has reported that metalation of dihydroindole formamidine **1** followed by condensation with benzaldehyde and hydrolysis gives alcohol **3** with a preference for the *threo* diastereomer in a ratio of 97:3 (Equation 1).[3] On the other hand, the simpler pyrrolidine amidine **4**, has been reported,in an isolated example, to give only moderate *threo* selectivity in its condensation with benzaldehyde (1:1 to 3:1, Equation 2).[4] On closer scrutiny of this reaction, we found that *formamidine **4** gives pyrrolidine **6a** (X=H) with high diasetereoselectivity (threo:erythro = 95:5)*. Other aromatic aldehydes give similar results, further demonstrating the high *threo*

Equation 1.



Equation 2.



selectivity of formamidine **4** (Table 1). The assignment of *threo* configuration to the major product from this reaction is consistent with ^{1}H NMR spectral data reported for analogs prepared by other methods[5,6], and was confirmed by single crystal X-ray analysis of **6d** dibenzoate.[7]

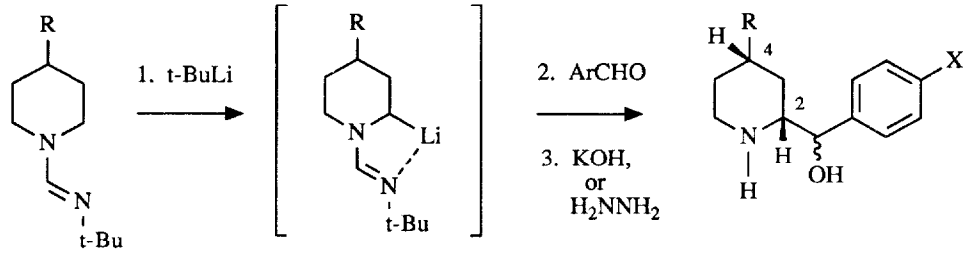
Table 1. Stereoselective Preparation of Pyrrolidinemethanols 6 (Equation 2).

Product (6)	X	Solvent	Threo:Erythro[a]	Yield[b]
a	H	80:20 Et_2O:THF	95:5	84%
	H	THF	95:5	81
b	F	80:20 Et_2O:THF	95:5	83
	F	THF	95:5	87
c	Cl	THF	93:7	90
d	Br	THF	94:6	76
e	OMe	THF	>98:2	93
f	Me	THF	95:5	87

a: Determined by integration of benzylic doublets in the ^{1}H NMR spectrum at 200 MHz. *Threo:erythro* ratios were unchanged by Kugelrohr distillation. *b:* Isolated yields.

In contrast to **4**, the homologous piperidine amidine **7** displays essentially no diastereoselectivity in its reaction with benzaldehyde, and instead produces piperidinemethanols **11** and **12** with *threo:erythro* ratios of 55:45 (Equation 3 and Table 2).[8,9] However, condensation of 4-t-butyl piperidine amidine **8** gives benzaldehyde adduct **14** with somewhat higher *threo* selectivity (85:15).

Equation 3.



7 (R=H) **9** (R=H) **11,12,13** (R=H)
8 (R=t-Bu) **10** (R=t-Bu) **14** (R=t-Bu)

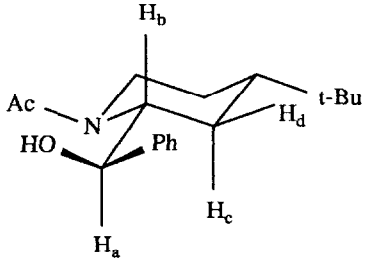
The assignment of configurations for the pair of 4-t-butyl products **14** as 2,4-*cis* rather than 2,4-*trans* is based on literature precedent and ^{1}H NMR decoupling experiments. First, both Meyers[4] and Beak[10] have shown that 4-substituted piperidines such as **8** form dipole stabilized anions in which lithium occupies an equatorial position, and that the configuration of the equatorial organolithium species is retained during its reaction with

Table 2. Preparation of Piperidinemethanols (Equation 3).

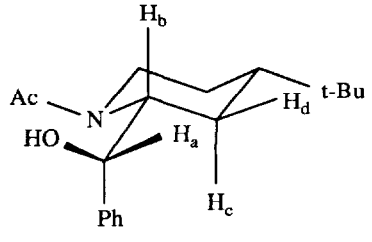
Product	R	X	Solvent	Threo:erythro[a]	Yield[b]
11	H	H	80:20 Et_2O-THF	55:45	86%
11	H	H	THF	54:46	37[c]
12	H	F	80:20 Et_2O-THF	55:45	90
12	H	F	THF	53:47	36[c]
13	H	OMe	80:20 Et_2O-THF	73:27	87
14	t-Bu	H	80:20 Et_2O-THF	85:15	60

a: Determined by integration of benzylic doublets in the ^1H NMR spectrum at 200 MHz. *b:* Isolated yields. *c:* Low yield may be due to slow deprotonation of **7** and **8** in THF (ref. 9).

electrophiles. Second, the mixture of diastereomers **14** was converted into a mixture of acetamides **15** (Ac_2O, pyridine) which were separated by MPLC (EtOAc-hexane on SiO_2). Decoupling experiments clearly indicate that H_b is axial in both isomers (**15**,*threo* (major): J_{ab}=9.1, J_{bc}=11, J_{bd}=5; **15**,*erythro* (minor): J_{ab}=1, J_{bc}=9, J_{bd}=4). Taken in conjunction with Meyers' and Beak's results, these data led us to the assign the relative 2,4-configuration of *both* **15** isomers as *cis*. The assignment of *threo* configuration to the major and *erythro* to the minor product, respectively, was made by analogy to the pyrrolidines **6** and by correlation with spectral data reported for other 2-piperidinemethanols (chemical shifts of H_a: **15**,*threo*, δ=4.42 ppm; **15**,*erythro*, δ=4.52 ppm).[6]



15, *threo* (major)



15, *erythro* (minor)

The dramatic difference in stereoselectivity displayed by pyrrolidine amidine **4** and piperidine amidine **7** may be the result of differences in the conformational flexibility of the respective α'-lithio intermediates. Whereas intermediate **5** is locked into a single conformation, the homologous piperidine intermediate **9** is capable of cyclohexane-like ring flipping in which lithium alternates between pseudoaxial and pseudoequatorial positions (Figure 1). In fact, this equilibrium between conformations was suggested by Meyers to explain the formation of products derived from single electron transfer reactions during alkylation of this reagent.[4] The conformational mobility of **9** apparently also causes the lack of diastereoselectivity in its reaction with aldehydes. Under the conditions used in this study, an equilibrium mixture of **9eq** and **9ax** (R=H) is presumably established, and subsequent condensation with benzaldehyde is stereorandom (Table 2, compounds **11** and **12**; *threo:erythro* =

55:45). When R=t-Bu, though, **10eq** is the dominant intermediate and the result is improved stereoselectivity (Table 2, compound **14**; *threo:erythro* = 85:15). However, the fact that 4-t-butyl amidine **8** does not lead to even greater *threo* selectivity is probably an indication that the proposed **9eq** ⇌ **9ax** equilibrium alone is insufficient to adequately explain the absence of selectivity by **7** (R=H).

Figure 1.

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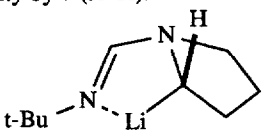

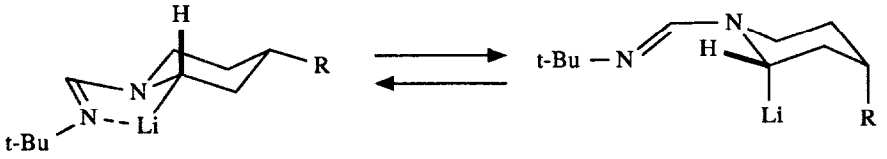

9eq (R=H) **9ax** (R=H)

10eq (R=t-Bu) **10** (R=t-Bu)

In summary, pyrrolidine formamidine **4** is highly *threo* selective in its condensation reactions with aromatic aldehydes, while the closely related piperidine formamidine **7**, on the other hand, is almost completely devoid of diastereodifferentiating ability. The piperidine amidine may be "coaxed" into stereoselective reactions, however, by restricting its conformational mobility with a pendant t-butyl group.

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