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3-Aminopyrrolidine lithium amide in enantioselective addition of organolithium compounds onto aromatic aldehydes

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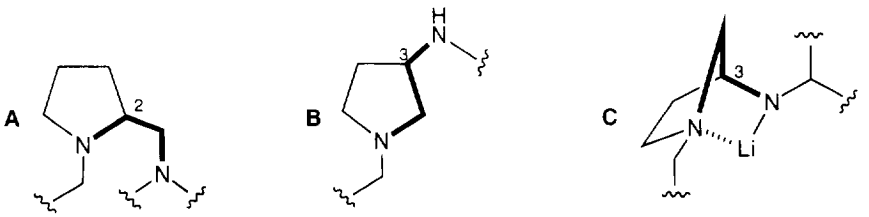
Abstract: New N,N′-disubstituted-3-aminopyrrolidines lithium amides have been used as chiral auxiliaries in the asymmetric condensation of n-butyllithium onto aromatic aldehydes, leading to e.e.s up to 73%. © 1997 Elsevier Science Ltd

The control of the stereochemistry of a newly created asymmetric center through the use of a chiral auxiliary not covalently bonded to a reaction partner remains a widely open frontier in organic chemistry. Hence, the search for a "magic additive"[1] able to turn most condensation reactions into their asymmetric version may appear as a slow moving long-term project. Understandingly, many efforts have been focused on one of the most generic reactions for the C–C bond formation *viz.* the condensation of an organolithium compound onto an aldehyde,[2] and most of these works examine the efficiency of various polydentate amines as chiral inductors. Interestingly enough, chiral lithium amides, a class of reagents first used in asymmetric synthesis in 1980,[3] have comparatively been rarely employed in this reaction.[2c]

We thought that advantage could be taken from a diamino structure which would lead, upon deprotonation, to a relatively rigid lithium amide involving nitrogen atoms not too far apart and linked through a stiffened asymmetric carbon backbone. We infered that the 3-aminosubstituted pyrrolidine structure (3-AP) **B** (Scheme 1) would meet these requirements. The amide derived from such compounds could yield, were the lithium cation chelated by both nitrogen atoms, a bridged and compact conformation of type **C** (Scheme 1).[4]



Scheme 1.

We further reasoned that the chiral amide could form a tight complex either with the aldehyde or with the butyllithium[5] prior to reaction. Such an hypothesis supposes that the transition-state of this enantioselective reaction proceeds, in fact, through a "diastereoselective" pathway.

This prompted us to explore the induction potential of a set of lithium amides derived from these diamines. Surprisingly little attention has been devoted to 3-AP[6] and the few papers mentioning these structures are mainly dedicated to applications in medicinal chemistry. By contrast, their 2-methylamino counterparts **A** (Scheme 1) have been intensively studied in asymmetric synthesis.[7] We have previously described a 6-step synthesis of N,N′-disubstituted 3-aminopyrrolidines from commercial (L)-Z-asparagine.[8] Meanwhile, 3-amino-N-benzylpyrrolidine **1**, a key-intermediate in this

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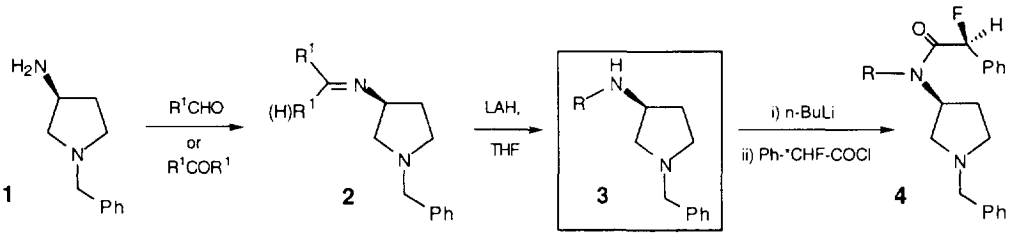
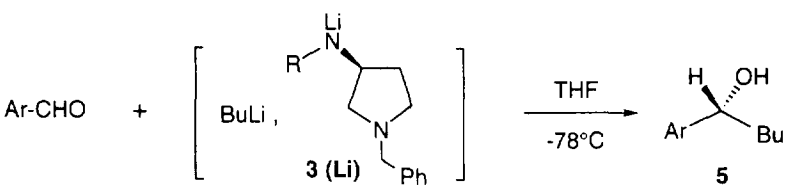
synthesis, has been commercialized under its two enantiomeric forms (Lancaster Synthesis Ltd), shortening this procedure to 2 steps (Equation 1). The condensation of aldehydes (4Å molecular sieves in ether) or ketones (Dean–Stark water trapping in toluene) directly onto **1** indeed provides the imines **2** which are reduced (LAH) to the corresponding N,N′-disubstituted pyrrolidines **3**. This simple approach led us to a set of homochiral amines **3a–d,f,g** (Table 1) in fair to good overall yields 50–90%).



Equation 1

The amide **3e** (R=Bz) was simply prepared by direct treatment of **1** with benzoyl chloride, while amine **3h** required a trans-imination procedure as described by O'Donnell and colleagues.[9] Preservation of the original enantiomeric purity was then checked by derivatization of **3** with α-fluorophenylacetic acid chloride[10] (leading to diastereoisomeric amides **4**[8]).

We then considered the use of these new diamines as chiral auxiliaries in the addition of commercial n-BuLi[11] onto various aromatic aldehydes (Scheme 2), a reaction to be considered amongst the simplest prototypes of the average organolithium condensations used in many C–C bond formation reactions.



Scheme 2.

The first experiments using **3a** (R=CH_2Ph) led us to the observation of a sharp dependence between the yield of the reaction and the Li amide/n-BuLi/PhCHO ratio. Finally, the best results (e.e.* yield) have been obtained for this ratio being 1.5/2.5/1.0. The values presented in the Table 1 have been obtained by first synthesizing the amide **3(Li)** itself (adding, at −20°C, n-BuLi on the chiral amine solution) then cooling the medium to −78°C, before adding the aldehyde.[12] Direct Eu(hfc)$_3$ chiral-shift experiments on the crude organic fractions recovered after acidic aqueous washing proved convenient for the determination of the e.e. of the product alcohols. We have checked in several cases that the e.e. measured directly on these crude mixtures are identical to those obtained after flash-chromatography of **5**. Results are gathered in Table 1.

The influence of the aromatic moiety of the aldehyde on which the condensation is performed is illustrated by entries 1, 6 and 7 of Table 1 which show that an ortho substitution improves the diastereofacial selectivity in this system, a methyl group being more efficient than methoxy.[14] When considering the influence of the amide **3(Li)** structure, entries 1–4 indicate that benzylic and neopentyl R substituents provide comparable induction levels, except if a supplementary heteroatom is introduced: in entry 4, a methoxy benzyl group plummets the selectivity to 3%. Comparably, replacing the 3-amino group by an amido appendage also triggers off a selectivity collapse (entry 5). Finally, a strong influence of amides steric hindrance on chiral induction is clear from entries 7–10. The substitution level of the carbon atom in α of the lateral amino group seems crucial: compounds in

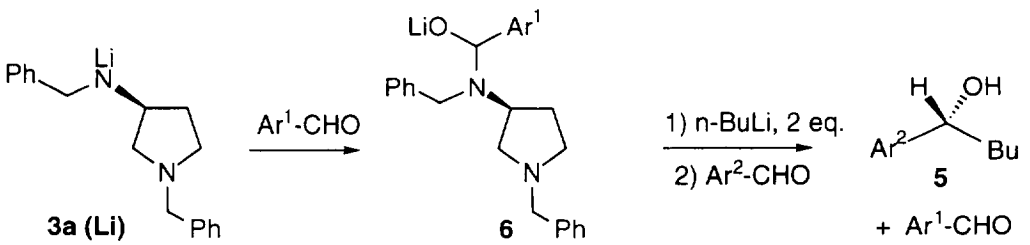
Table 1. Reaction of aromatic aldehydes with n-BuLi in the presence of Li amides derived from amines **3**

Entry	Amine	R	Ar	Yield[a] (%)	ee[b] (%)	Conf.
1	**3a**	$PhCH_2$	Ph	60	20	R[c]
2	**3b**	t-$BuCH_2$	Ph	50	17	R[c]
3	**3c**	α-NaphthylCH_2	Ph	56	18	R[c]
4	**3d**	o-MeO-$C_6H_4CH_2$	Ph	54	3	R[c]
5	**3e**	CO-Ph	o-MeO-C_6H_4	54	4	-[d]
6	**3a**	$PhCH_2$	o-MeO-C_6H_4	61	37	-[d]
7	**3a**	$PhCH_2$	o-Tol	57	49	R[e]
8	**3f**	Cyclohexyl	o-Tol	63	67	R[e]
9	**3g**	Cyclopentyl	o-Tol	63	63	R[e]
10	**3h**	Ph_2CH	o-Tol	70	73[f]	R[e]

(a) Isolated yield; (b) Determined by direct Eu(hfc)$_3$ chiral-shift experiments; (c) Determined by comparison to literature[2a]; (d) To be determined; (e) Determined by chemical correlation from o-methyl mandelic acid[13]; (f) Determined on both crude and purified products.

which this carbon is trisubstituted all behave as better chiral inductors than those with a disubstituted one (**3f–h**, entries 8–10 vs **3a**, entry 7). Given this feature, the inductions due to the cyclohexyl and cyclopentyl moieties are comparable while the diphenylmethyl group further increases the excess (entry 10).

This dramatic sensitivity to the bulkiness of R could be considered in relation to the possible formation of an intermediate hemiaminal-like structure **6** derived from a direct 1,2-addition of the lithium amide onto the carbonyl group (Scheme 3). Comparable observations are indeed reported in literature[15] and trapping of the corresponding intermediate by t-butyl-dimethylchlorosilane has even been achieved.[15c] The cross experiments described on Scheme 3 provide an indirect evidence to support such a mechanism. The first aldehyde (Ph–CHO) added to the preformed amide **3a(Li)** yields the lithiated hemiaminal-like structure **6** (Ar^1=Ph) which remains inert toward the subsequently added BuLi. At this point, addition of a second aromatic aldehyde (o-Tol-CHO) leads, after water quenching, to the formation of the single alcohol **5** derived from this second aldehyde, in absence of any 1-phenyl-1-pentanol. As expected, this latter alcohol is selectively recovered when the order of the addition of the aldehydes is reversed.



Scheme 3.

In both cases, the e.e. of these alcohols is significantly lower than those obtained in conditions of Scheme 2 (8 vs 20% for 1-phenyl-1-pentanol and 20 vs 49% for 1-o-tolyl-1-pentanol). The formation of an hemiaminal probably becomes more difficult with bulky amines **3f–h**: when the reaction of Scheme 3 is performed with amide **3f(Li)**, only alcohol derived from the aldehyde first added (Ar^1=Ph) is recovered.

We tried to strengthen these chemical evidences with spectroscopic data resorting to a multinuclei

high field NMR approach. Amide derived from **3a** has been prepared by deprotonating the amine with Bu^{6}Li (obtained following Fraenkel's procedure[16]) in d_8-THF at -70°C directly in the NMR tube. One equivalent of a tolualdehyde solution in the same solvent has then been slowly added with vigorous stirring, under an ultra-dry argon atmosphere while remaining at the same temperature. The ^{1}H NMR spectrum recorded right after did not exhibit any signal for the aldehyde while five singlets showed up in 6.21–5.85 ppm region. Obtention of these five new signals, for the benzylic proton α to both a nitrogen and an oxygen atoms, possibly stems from the formation of two diastereoisomers during this condensation and from the coexistence of several aggregated forms in THF. On the ^{13}C NMR, we could not observe any carbonyl-corresponding signal but a new peak at 87.5 ppm which would fit an hemiaminal-type carbon. Finally, the ^{6}Li signal at 1.89 ppm[17] originally observed for the amide derived from **3a**[4] was totally replaced by a main singlet at 0.87 ppm, together with smaller peaks at 0.79 and 0.73 ppm. These chemical shifts compare well to those reported in the literature for lithium alcoholates (0.75–0.80 ppm).[18] This whole set of data seems to constitute a fair body of evidence in support to the formation of **6** in the case of amide **3a(Li)**. The procedure[12] followed in Table 1 puts formation of **5** and **6** in competition.

In conclusion, 3-aminopyrrolidines appear to be promising structures for enantioselective transformations. The synthetic access we propose for both enantiomerically pure forms of these new chiral auxiliaries is simple (2 steps from commercially available (R) or (S)-3-aminopyrrolidine to **3a–h**). In the butyllithium condensation onto aromatic aldehydes, their lithium amides can afford alcohols featuring e.e.s as high as 73%, provided the substituent borne by the 3-amino group is bulky enough. Extensions to this work and further applications for these diamines will be reported in due course.

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