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Enantioselective protonation and alkylation of non-covalent mixed aggregates of chiral 3-aminopyrrolidine lithium amides

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Abstract—Non-covalent aggregates of highly polar entities assemble, on a temporary basis, a chiral moiety to a reagent. Attempts to take advantage of this phenomenon with chiral 3-aminopyrrolidine (3-AP) lithium amides are described. The enantioselective protonation of a complex involving these amides and the lithium enolate of 2-methyltetralone by an achiral proton source gives products in which the ee does not exceed 40%. The same class of chiral amides is then applied to the asymmetric nucleophilic alkylation of aldehydes using alkyllithiums and phenyllithium. In this case, a mixed aggregate made up of the lithium amide and the alkyllithium, a structure that has been detailed previously in comparable situations, seems to be directly involved in the reaction. Thus, higher asymmetric inductions are obtained, affording the alkylation products in ee of up to 70%. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Since the pioneering work of Whitesell[1] and Duhamel,[2] chiral lithium amides (CLA) have become versatile tools in asymmetric synthesis. Excellent reviews have detailed their numerous uses,[3] especially as chiral bases in enantioselective deprotonation reactions. Applications of CLAs to natural products synthesis, in particular owing to their capacity to desymmetrize *meso* compounds, have also been described.[4] But CLAs are more than just bases. Davies and colleagues have for instance elegantly taken advantage of the nucleophilic character of these reagents in a diastereoselective version of the hetero-Michael addition of amides to α,β-unsaturated esters.[5] Interestingly, the well-known tendency of these highly polar entities to gather into homogeneous oligomers (ladder type) and to form mixed aggregates with other organolithium compounds has been studied in depth, in particular by Snaith, Mulvey and colleagues,[6] but has received only scarce synthetic interest. We present in this paper two applications (enantioselective protonation (EP) and alkylation reactions) for such chiral non-covalent entities that we have studied recently. We have focused our research on chiral 3-aminopyrrolidine (3-AP) lithium amides that behave as potent auxiliaries in the alkylation reaction.[7] The low-temperature formation of a non-covalent complex involving one lithium amide and one alkyllithium in THF has been established by multinuclear NMR spectroscopy[8] and ab initio calculations,[9] providing a strong molecular basis to this investigation.

Keywords: lithium; amines; enantioselective alkylation; enantioselective protonation; aggregation.

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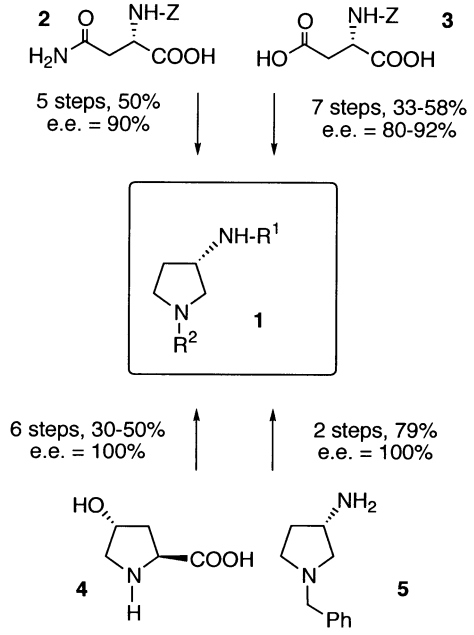
2. Results and discussion

2.1. Synthetic access to chiral 3-aminopyrrolidines

Only a few routes to diamines **1** have been described to date.[10] The four syntheses we have considered are summarized in Scheme 1. Three approaches are based on the transformation of natural amino acids, namely



Scheme 1. Synthetic routes to 3-aminopyrrolidines **1**.

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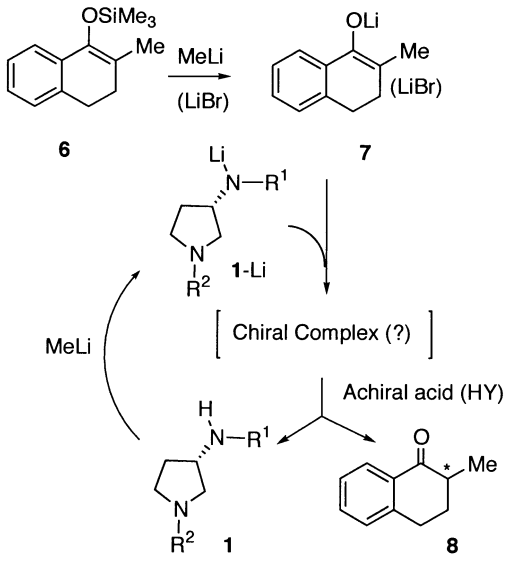
(L)-glutamine **2**, (L)-glutamic acid **3** or 4-hydroxy-(L)-proline **4**. These routes require five to seven steps and provide **1** in 30–60% yield.[11] The ee of the final 3-AP is somewhat eroded when starting from **2** and **3** while **4** can be transformed into enantiomerically pure **1**. The simplest and most efficient access to **1** utilizes 3-amino-*N*-benzylpyrrolidine **5**, commercially available in both enantiomeric forms, the primary amino group being easily transformed in two steps (imination/reduction) into a secondary one. On the other hand, **5** is the only aminopyrrolidine available, limiting this route to R^2=Bn. Actually, this substituent is well suited to most of the applications we have considered to date, as described below.

2.2. Application of 3-AP lithium amides to the enantioselective protonation of lithium enolates

The EP of a prochiral intermediate is a deracemisation method that can offer an efficient access to asymmetric carbonyl compounds.[12] In particular, the EP of ketone and ester enolates has proved efficient in access to complex targets such as (*R*)-α-(+)-damascone and other fragrances, as elegantly demonstrated by Fehr and co-workers.[13] In most cases studied to date, the source of chirality in the key protonation step is also the source of the proton. Thus, tartaric acid derivatives, ephedrine-based aminoalcohols, chiral alcohols, aminoboranes, imides or amine hydrochlorides and a few other sources have been used for an asymmetric delivery of their most acidic proton.[14a] Recent results have shown that a catalytic amount of the chiral proton donor can be sufficient.[13d,e,14b–e] Vedejs has enlarged this classical 'chiral-proton pool' to chiral aniline-Lewis acids couples for which he described the Internal Proton Return (IPR) phenomenon,[15a] particularly efficient for the EP of amide enolates.[15] Another important development has been proposed by Koga who first showed that protonation of 2-methyl-1-tetralone lithium enolate by such simple acids as AcOH can take place in ee of up to 91% provided that the intermediate enolate, generated in the presence of 1 equiv. LiBr, is complexed by a chiral piperidine-derived triamine.[16a,b] Eames has also made a similar observation using a C_2 symmetrical cyclohexyldiamine.[16c] Recently, Tomioka has nicely taken advantage of a comparable enolate–chiral amine complex that undergoes EP using a thiophenol.[16d]

We thought it could be interesting to push forward this concept by aggregating a lithium enolate to a CLA before exposing the chiral complex thus obtained to an achiral proton source (Scheme 2). This would extend the scope of the 3-AP lithium amide aggregates to the large field of lithium enolate chemistry. The formation of heteroaggregates between LDA or tetramethylpiperidine lithium amide and lithium cyclohexenolate in THF has been clearly established by NMR spectroscopy by Collum and colleagues and they have also studied the influence on these complexes of salts or additives such as LiBr or HMPA.[17] Before starting our investigations on the lithiated species, it was necessary to first evaluate the eventual induction potential of the amine itself. This has been achieved through a set of EP experiments involving different lithium enolates (derived from 2-alkylcyclohexanones and 2-methyltetralone) in conditions in which the



Scheme 2.

metal (Li or K) of the enolate, the substituents R^1, R^2 and R^3 of the 3-AP, the presence of lithium salts (LiBr or *t*-BuOLi), the temperature (between −20 and −78°C), the solvent (THF or toluene) and the protonating agent (AcOH or *t*-BuOH) were all varied. These data are not presented here since no significant ee could be measured (by chiral GC on the crude medium) in such conditions. We thus switched to mixtures involving 3-AP lithium amides and ketone lithium enolates (Scheme 2) in the hope that stronger interactions between the partners could lead to higher asymmetric inductions.

The results we are presenting here are limited, for the sake of clarity, to the 2-methyltetralone lithium enolate **7**. The experimental conditions we have retained were inspired from those described by Koga.[16a] The enolate was prepared in toluene or THF by reacting the corresponding trimethylsilyl enol ether **6** with 2.2 equiv. of a commercial MeLi/LiBr (1:1) solution (in ether) at 40°C during 5 min. The medium was then cooled to −78°C before 1.1 equiv. of dissolved 3-AP **1** was added. The resulting mixture was kept at −78°C for 1 h and the proton donor (1 or 2 equiv.) then introduced. The reaction was finally quenched after a further 40 min by an excess of acetic anhydride or of an aqueous solution of citric acid, and the temperature raised to room temperature. The ee were then determined from the pentane extracts of the crude neutralized medium by chiral

Table 1. Protonation of mixtures of 2-methyltetralone lithium enolate **7** and 3-AP lithium amides **1a-Li** (R^1=R^2=Bn) or **1b-Li** (R^1=Bn, R^2=*n*-Pr, Scheme 2)

Entry	Amine	Solvent	LiBr (Equiv.)	HY	Yield (%)	ee (%)
1	**1a**	Tol	0	TFA	95	<3
2	**1a**	Tol	0	HCl	89	<3
3	**1a**	Tol	2	HCl	79	<3
4	**1a**	Tol	2	AcOH	47	<3
5	**1b**	Tol	2	AcOH	91	<3
6	**1a**	THF	0	TFA	81	<3
7	**1a**	THF	0	HCl	93	<3
8	**1a**	THF	2	HCl	93	<3
9	**1a**	THF	2	AcOH	90	<3

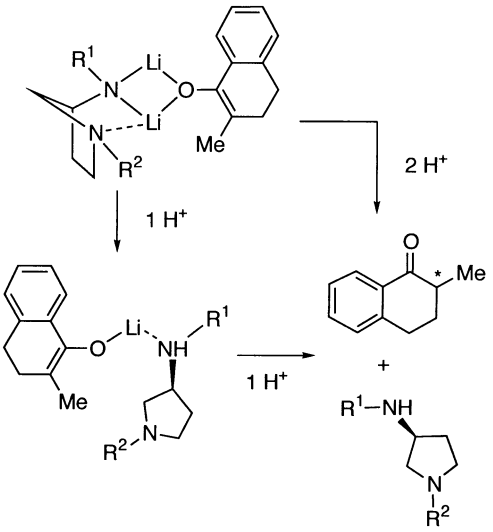
Table 2. Protonation of mixtures of 2-methyltetralone lithium enolate **7** and various 3-AP lithium amides **1-Li** at −78°C in toluene (Scheme 2)

Entry	Amine	R^1	R^2	LiBr (equiv.)	ee (%)
1	**1c**	H	*n*-Pr	2	7 (*S*)
2	**1d**	H	$MeOC_2H_4$	2	6 (*S*)
3	**1e**	H	α-(*S*)-Methylbenzyl	2	<3
4	**1f**	H	α-(*R*)-Methylbenzyl	2	15 (*S*)
5	**1g**	H	CH_2-α-Napht.	2	15 (*S*)
6	**1h**	H	CH_2-β-Napht.	2	15 (*S*)
7	**5**	H	Bn	2	40 (*S*)
8	**5**	H	Bn	0	<3
9	**1i**	Ph	Bn	2	5 (*S*)
10	**1j**	Ph	Ph	2	<3
11	**1k**	$SiPh_2t$-Bu	Ph	2	<3

GC. The data in Table 1 indicate that the induction remains almost null in all cases.

These disappointing results prompted us to turn to a new family of CLAs derived this time from primary amines **1** (R^1=H). To our knowledge, only Muzart, Hénin and colleagues have resorted to a primary amine in an EP experiment.[18] Since no specific protocol has been described for primary lithium amides, we left our procedure unchanged. However, and to keep the experimental exploration of such a large domain within reasonable limits, we chose to first restrict the protonating agent to AcOH (2 equiv.). The structure of the 3-AP was then varied to some extent and the results are gathered in Table 2. The chemical yields have not been measured but the conversions (as determined by GC) are very high (>90%) while the ee, albeit more encouraging than those of Table 1, remained very low. The 'best' result (40% ee) was obtained with amide **5-Li** that bears a benzyl appendage on the ring nitrogen (entry 7). Interestingly, the introduction of a second asymmetric centre on the benzylic position (entries 3 and 4) or enlargement of the aromatic ring (entries 5 and 6) had a significantly negative effect. The central role of LiBr in these aggregation phenomena can be appreciated from entry 8 where the ee dropped to insignificant values when no salt was present in the reaction medium. The importance of the primary character of the 3-AP to preserve the modest induction potential of these compounds is finally confirmed by the results obtained with the anilines **1i** and **1j** (entries 9 and 10) or silylamine **1k** (entry 11).

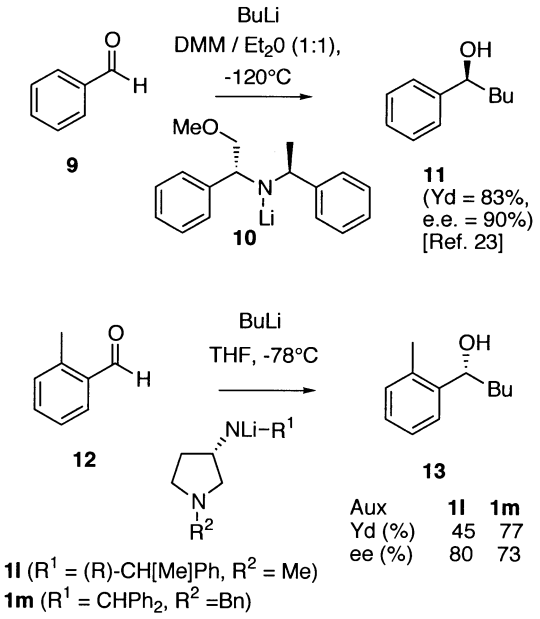
Starting from these data, many variations have been undertaken to improve the efficiency of **1** in the EP reaction. Variations of the experimental parameters have included the temperature (of the synthesis and/or mixing of the enolate or of the protonation), the introduction of ageing phases for the complexes, a lithium/potassium exchange, the addition of various salts or additives (LiF, LiCl, LiI, LiOTf, HMPA or TMEDA), the changes in the proportions of the partners (excess or default of methyllithium), the solvent (THF, Et_2O, DMM or *t*BuOMe), the structure of the enolate (from methyl and phenylcyclohexanones, 2-chlorotetralone or 2,2,6-trimethylcyclohexanone) and the proton donor (water, trifluoro and trichloroacetic acids, malic and maleic acids, phtalimide or BHT). For the sake of brevity, the corresponding results are not shown here, but in none of these cases could the ee be significantly improved for our test reaction.



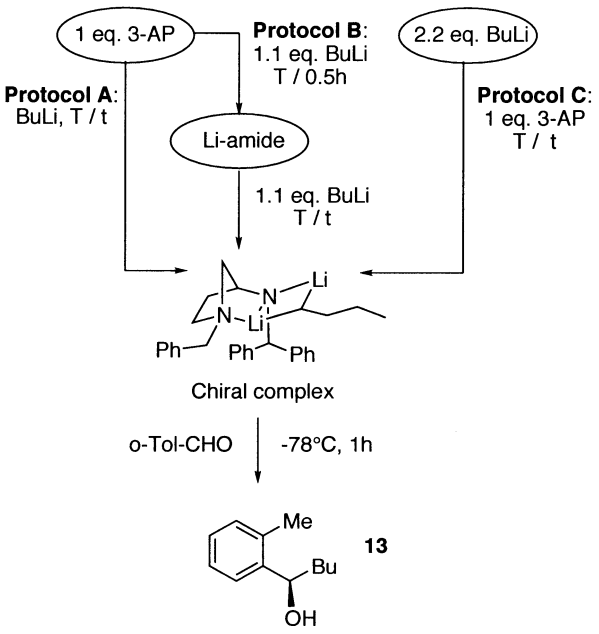
Scheme 3. Stepwise vs. synchronous protonation of a possible 1:1 mixed aggregate between 3-AP lithium amide **1-Li** and 2-methyltetralone enolate **7**.

To our knowledge, the aggregates between CLAs and lithium enolates have not found any application in EP yet,[19] and the study presented here suggests that 3-AP lithium amides will hardly be efficient auxiliaries for this class of reaction. Actually, controlling the stepwise proton transfer towards a 'dianionic' complex raises the crucial issue of the priority order between two competing sites.[15f,20] If the lithium amide is the first to intercept the incoming proton, as expected on simple grounds of thermodynamical basicity, the complex is likely to evolve into an enolate/amine aggregate resembling that studied above (Scheme 3). By contrast, if the enolate is sterically more accessible to the proton, it can become the kinetically most basic site, providing a different chiral environment to the EP key-step. Since our attempts to avoid this possible problem by a double (more or less synchronous) protonation of the putative non-covalent complex by diacids (such as malic or maleic acids) remained unsuccessful (see above), we had to check the induction potential of amine **5** itself. Complexing the usual 2-methyltetralone lithium enolate **7** (prepared this time using only 1.1 equiv. MeLi/LiBr) with 1.1 equiv. **5** according to the procedure described above, followed by the addition of 1.1 equiv. AcOH, finally led to tetralone **8** in quantitative yield and 34% ee. Thus it seems that the simple formation of an enolate–amine complex can almost fully account for the results we obtained and seems to indicate that achieving the selective protonation of an enolate in the presence of a (chiral) lithium amide is difficult to master.

This disappointing observation should not discourage future developments of these non-covalent systems, of which chemistry is already well documented,[21] to other classes of reactions involving enolates. In addition, one should keep in mind that the rational design of the partners will certainly improve thanks to the constant accumulation of data regarding the solution structures of comparable species by spectroscopic techniques such as multinuclear NMR or in situ infrared recordings.



Scheme 4.



Scheme 5. Sketches of the three experimental protocols compared in this work.

2.3. Application of 3-AP lithium amides to the enantioselective alkylation of aldehydes

The second application to non-covalent asymmetric aggregates we have considered is the enantioselective alkylation of aldehydes. If the condensation of chiral complexes of organozinc compounds onto carbonyl groups is currently the object of considerable efforts,[22] the organolithium reagents have been relatively unstudied. They are indeed generally regarded as being too reactive toward aldehydes to be channeled through an asymmetric pathway. However, and as early as 1984, Hogeveen and Eleveld have shown that advantage could be taken of the association between the aminoether-derived CLA **10** and butyllithium in the condensation on benzaldehyde **9**, providing benzylic alcohol **11** in 90% ee (Scheme 4 (top)).[23] Since then very interesting developments have been brought to this original system, following the breakthrough by Davidsson and Hilmersson who have established, from NMR spectroscopic data, that a 1:1 non-covalent complex was formed between **10** and butyllithium.[24] Our own research in this field led us to describe the condensation of the same alkyllithium in the presence of 1.5 equiv. of 3-AP lithium amide **1l**, **m** onto *o*-tolualdehyde **12**, yielding alcohol **13** in 80% ee at −78°C (Scheme 4 (bottom)).[7] Our results have been associated to the NMR[8] and theoretical[9] descriptions of a 1:1 complex between **1m** and butyllithium (represented in Scheme 5).

We decided to investigate in greater detail this last reaction. We were particularly interested in getting a better understanding of the conditions for the formation of such aggregates and in trying to extend the scope of organolithium reagents compatible with these chiral auxiliaries. We thus focused our work on the model reaction of Scheme 4 (bottom), resorting to one of the best chiral inductor we had in hand. The 3-benzhydrylamino-*N*-benzylpyrrolidine **1m** seemed perfectly appropriate since: (i) it gives ee up to 73% in the alkylation with *o*-tolualdehyde;[7] (ii) it is readily prepared from commercial 3-amino-*N*-benzylpyrrolidine **5** in 79% yield and 100% ee; (iii) it is very stable and can be kept over long periods.

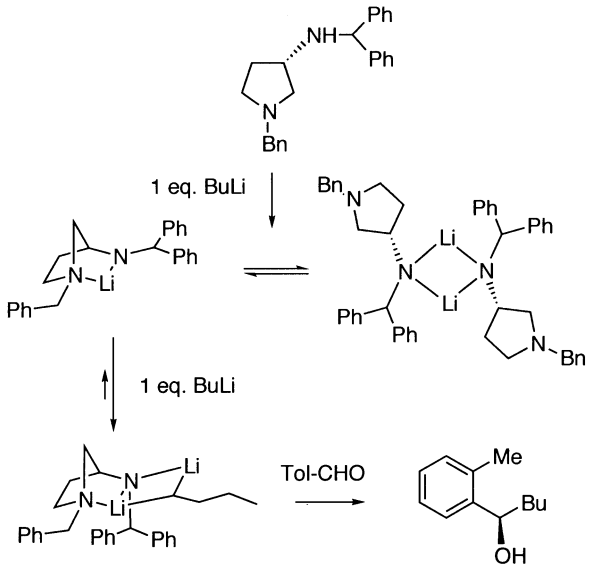
Table 3. Experimental variations of the reaction of Scheme 4 following three different protocols (as sketched on Scheme 5)

Entry	Amine	Protocol	Solvent	BuLi (equiv.)	3-AP (equiv.)	*T* (°C)	*t* (h)	Yield[a] (%)	ee (%)
1	**1m**	A	THF	2.5	1.5	−10	0.5	77	73
2	**1m**	A	THF	5.0	1.0	−10	0.5	97	28
3	**1m**	A	THF	1.2	0.2	−10	1.0	73	23
4	**1m**	A	THF	2.2	1.0	−10	0.5	81	70
5	**1m**	B	THF	2.2	1.0	−20	0.5	97	57
6	**1m**	C	THF	2.2	1.0	−20	1.0	83	66
7	**1m**	A	THF	2.2	1.0	−78	1.5	69	63
8	**1m**	B	THF	2.2	1.0	−78	1.5	72	53
9	**1m**	C	THF	2.2	1.0	−78	1.0	92	58
10	**1m**	A	Et_2O	2.2	1.0	−20	0.5	96	50
11	**1m**	A	Tol	2.2	1.0	−20	0.5	100	21
12	**1m**	A	DME–Et_2O (1:1)	2.2	1.0	−20	0.5	92	3
13	**17**	A	THF	2.2	1.0	−20	0.5	55	37
14	**17**	B	THF	2.2	1.0	−20	0.5	30	15

[a] Based on integrations of NMR spectra.

Our first studies focused on modifications of our 'standard' experimental procedure[7] (Table 3, entry 1) to put into evidence an eventual influence of the aggregation conditions on the selectivity of the reaction in Scheme 4 (bottom). Three different protocols have been designed, as summarized in Scheme 5. In the first one (A), the whole butyllithium was directly added to the 3-AP in solution in THF at temperature (T, −20 or −78°C) and the putative complex let for ageing during time (t). In the second protocol (B), the 3-AP lithium amide was prepared in a first separate step by addition of 1.1 equiv. of butyllithium at the same temperature (T). After 30 min, the second equivalent of butyllithium was added and the mixture aged during time (t) before adding into the reaction. The third protocol (C) was reversed in the sense that the amine in THF was added to 2 equiv. of butyllithium in THF at the same temperature (T), and the mixture left for time (t). In all cases, 1 equiv. of aldehyde also in THF was finally introduced into the medium at −78°C and the reaction quenched after 1 h by aqueous HCl. After the usual work-up, the ee of the alcohols were determined by ^{1}H NMR spectroscopy in $CDCl_3$ in the presence of [Eu(hfc)$_3$].

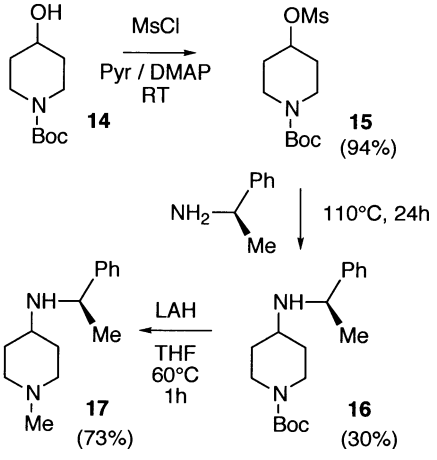
The results are presented in Table 3. The asymmetric inductions we have observed for this system are consistently in favor of alcohol (*R*)-**13**. The first four entries summarize our attempts to use sub-stoichiometric amounts of chiral ligands in the reaction. Entries 2 and 3 clearly indicate that in the presence of a large excess of BuLi or of a sub-stoichiometric (20%) amount of 3-AP, the ee drops, while entry 4 (in which exactly one equivalent of diamine is used) exhibits an ee comparable to the first entry, the reference experiment involving 1.5 equiv. of 3-AP. This observation suggests that if the 1:1 complex we have observed is the reactive entity responsible for the asymmetric induction, it is more efficient than the pure BuLi aggregates (tetramer+dimer) present in THF (see entry 1) but the difference of reactivity between these competing species is not sufficient to warranty a catalytic version of the reaction. In entries 4–9 are compared the results of the three protocols presented above, at two different temperatures (−10/−20 and −78°C) and with 1 equiv. of 3-AP. In the two series, the ee decreases from protocol A to B, the results of C lying in between the two others. It is somewhat risky to draw any conclusion from these very limited variations. However, the relatively good reproducibility of the data suggests that the organization of the reaction medium be consistently altered by the experimental procedure. In particular, we are aware of a possible competition between mixed and homogeneous aggregation processes (Scheme 6). It has indeed been calculated that the stabilization of the lithium dimethylamide–methyllithium complex with respect to the corresponding homogeneous entities [ie $(Me_2NLi)_2$ and $(MeLi)_2$] is extremely small (≈0.2 kcal/mol).[9] The presence of an homogenous CLA dimer on one hand and of an alkyllithium dimer (or higher oligomers) on the other, is expected to result in a drop in the enantioselectivity of the alkylation reaction. Therefore, protocol B (that allows the dimerisation of the lithium amide) should be associated with lower ee than protocol A, as observed experimentally. By contrast, protocol C should favor the mixed aggregation, the lithium amide being generated in the presence of an excess of butyllithium, and thus be associated with higher ee than those obtained following A. Table 3 shows this is not the case, maybe because of the participation of 'higher order' oligomers in which BuLi/3-AP>1.



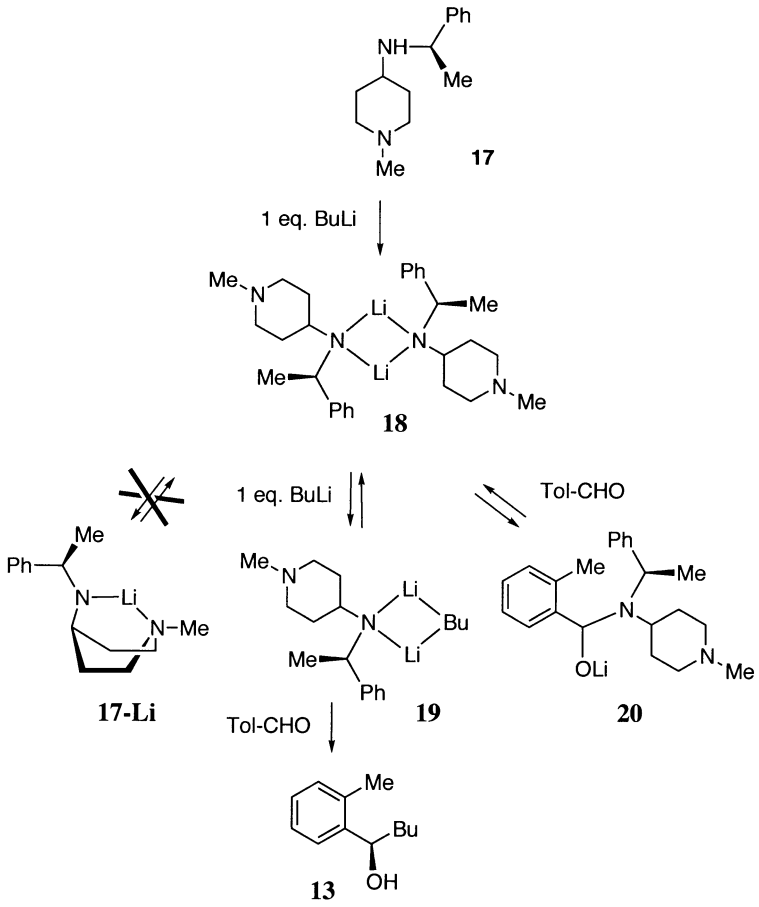
Scheme 6. Possible homo and hetero-aggregation schemes of 3-AP lithium amide **1m-Li**.

As a complement, we examined the influence of typical solvents for this same reaction. Entries 10–12 show that THF is definitely the best solvent for our system since the ee value drops in the three cases we have considered. This is probably to be considered in relation with the strong influence of the medium polarity on these complexes computed recently.[25]

The possible influence of the protocol on the ee has also been evaluated on 4-aminopiperidine **17**. In these diamines, the only asymmetric center is borne by the lateral amino chain. They have been simply prepared following Scheme 7. The starting *N*-Boc-4-hydroxypiperidine **14** is commercially available and can be transformed into the corresponding mesylate **15** (or tosylate) and substituted by α-methylbenzylamine, affording **16** in 30% yield. The final LAH reduction of the carbamate provides diamine **17** in 73% yield.



Scheme 7.



Scheme 8. Possible homo and hetero-aggregation schemes of lithium amide **17-Li**.

The results in Table 3 show that the ee associated with amine **17** are much lower than those derived from **1m**, whatever the experimental conditions. This can be due to the eventual absence of folding of **17-Li** (as suggested by preliminary NMR spectroscopic data)[26] that would favor the dimerization of this species (Scheme 8). The amide dimer **18** would then be in equilibrium with: (i) a mixed aggregate with BuLi (**19**) that can, in turn, react with tolualdehyde to give the expected alcohol **13**; (ii) the α-aminoalcoholate **20** due to the direct alkylation of the amide on the aldehyde.[27] The drop of the yield can thus be explained by the presence of **20** in the medium, that does not react with BuLi and gives back tolualdehyde upon aqueous work up. The low ee can be due to either a weak induction by the mixed aggregate **19** or to the equilibrium between homogeneous and heterogeneous dimers/aggregates **18/19**. In support of this scheme are the results of entry 11, which show that pre-forming the lithium amide (protocol B) decreases both the yield and ee (Scheme 8).

We finally decided to vary the organolithium compounds used in conjunction with the 3-AP **1m**. In Table 4 are gathered the results concerning methyllithium, *n*-butyllithium, *t*-butyllithium and phenyllithium. Entry 1 indicates that switching from butyl to methyllitium decreases the ee (compare entries 1 and 2). It takes an increase in the chiral complex to aldehyde ratio to get back to a comparable induction level (entry 3). By contrast, resorting to the equimolar complex MeLi/LiBr (in ether) reduces the ee to almost zero, indicating that, as in the first section of this work, LiBr has a dramatic effect on these heteroaggregation phenomena, as reported previously by Scolastico et al.[28] A comparable drop in enantioselectivity is observed when using *t*-BuLi (entry 5), probably because this bulky reagent does not aggregate with the 3-AP lithium amide. Finally, we examined the case of phenyllithium (entry 6). Interestingly, this organometallic gives significant ee (58%) and a reversal of the enantioselectivity, the (*S*)-α-tolyl benzylic alcohol being obtained in this case.[29] The origin of this change in the induction is difficult to explain with our model and calls for molecular modeling on the aldehyde docking and rotation steps.

3. Conclusion

Non-covalent mixed aggregates of 3-AP lithium amides can

Table 4. Extension of the reaction of Scheme 4 to four different organolithium compounds

Entry	RLi	**1m**/RLi/TolCHO	Yield (%)	ee (%)
1	MeLi	1:2.2:1	100	58 (*R*)
2	BuLi	1:2.2:1	81	70 (*R*)
3	MeLi	1.5:2.5:1	80	68 (*R*)
4	MeLi+LiBr (1:1)	1:2.2:1	100	5 (*R*)
5	*t*-BuLi	1:2.2:1	77	0
6	PhLi	1:2.2:1	75	58 (*S*)

help to develop enantioselective versions of reactions involving organolithium reagents. The results we present in this paper provide an evaluation of their applicability to two families of reaction, the EP and the asymmetric nucleophilic alkylation of aldehydes. In the first category, the putative 3-AP complexes turned out to behave as relatively modest inductors (ee ≤40%), probably because of the competition between the amide and the enolate for the incoming proton. In the second class, the aggregates seem to react efficiently with the *o*-tolualdehyde and give access to the expected alcohols with ee in ≈70%. The conditions tested led us to the conclusion that the rapid formation of the amide-alkyllithium complex should be favored by direct addition of the whole butyllithium to the amine (protocol A). Further synthetic developments need to be brought to this chemistry of non-covalent aggregates that has already found very promising applications[21] and seems to be extendible to bimetallic systems such as lithium amide/organozinc complexes.[30] Developments to new reagents such as functionalized vinyllithium compounds as well as the theoretical analysis of the ultimate condensation step taking place after the aggregate-aldehyde docking are currently under investigation.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer operating at 300 and 75 MHz, respectively, or on a Bruker Avance DMX 500 spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C). IR spectra were obtained on a Perkin–Elmer 16PC FTIR spectrometer. The mass spectra were recorded on a Jeol AX500 apparatus, under electron impact conditions (EIMS) at 70 eV ionizing potential; isobutane (*t*-BuH) was used for chemical ionization (CIMS). Melting points were taken on a Reichert microscope apparatus. Optical rotations, $[\alpha]_D$, were measured on a Perkin–Elmer polarimeter 341 spectrometer in quartz cells (d=1 dm), using Na and Hg beams.

4.1.1. 3-Aminopyrrolidines 1. Only 3-AP **1b**, **c**, **e**, **f** are new compounds and were prepared following procedures adapted from Ogura[10f] and Moon.[10g] The ee of these diamines have been checked by ^{19}F NMR spectroscopy after derivatisation[11] with chiral α-fluoro-α-phenylacetic acid.[31]

4.1.2. 1-Propyl-3-(*S*)-aminopyrrolidine 1c. This primary amine has been obtained from (*S*)-2-benzyloxycarbonylamino-1,4-dimethanesulfonyloxybutane, prepared from dimethyl *Z*-asparaginate as described in Ref. 10f,g. This dimesylate (3.95 g, 10 mmol) was added to neat *n*-propylamine (5.9 g, 100 mmol), the mixture warmed to 45°C and stirred for 3 h. The excess propylamine was then evaporated under vacuum and the oily residue dissolved in ethyl acetate (100 mL). The solution was washed with water (50 mL), dried ($MgSO_4$) then evaporated. The *N*-propyl-3-benzyloxycarbonylaminopyrrolidine thus obtained was purified by flash chromatography on silica gel (eluting with CH_2Cl_2/MeOH, 90:10) and obtained as a yellow oil (Yd=53%).

The spectroscopic characteristics of this intermediate are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) 0.78 (t, 3H, J=6.1 Hz), 1.58–1.36 (hex, 2H, J=5.7 Hz), 1.70–1.55 (m, 1H), 2.70–1.95 (m, 4H), 2.84–2.72 (m, 1H), 3.11 (m, 2H, J=9.8 Hz), 4.12 (m, 1H), 5.04 (s, 2H), 5.29 (broad d, NH, J=7.5 Hz), 7.28 (s, 5H); ^{13}C NMR: 11.5, 23.2, 23.8, 40.6, 41.7, 45.4, 58.3, 66.9, 126.2, 128.3, 128.9, 137.0, 156.1. CIMS (CH_4) m/z (relative intensity): 291 ($M+C_2H_5^+$; 23); 263 (MH^+; 100%). Anal. calcd for $C_{15}H_{23}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.18; H, 8.48; N, 11.67. $[\alpha]_D^{25}=-4.1$ (c=0.02; dioxane).

The Z-protecting group was removed by hydrogenolysis: palladium hydroxide (20% on carbon, 0.4 g, 2.8 mmol) was stirred in absolute ethanol (70 mL) for 30 min. A solution of the above carbamate (2.0 g, 7.6 mmol in 5 mL ethanol) was then introduced and the stirring continued for 4 h. The catalyst was filtered over a celite pad and the solvent evaporated at 0°C. A chromatography was then performed over silica gel (eluting with CH_2Cl_2/MeOH, 85:15). Aminopyrrolidine **1c** was recovered as a colorless oil (Yd=99.5%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=9.0 Hz, 3H), 1.21 (hex, J=8.0 Hz, 2H), 1.57 (m, 1H), 2.11–2.31 (m, 1H), 2.39 (m, 1H), 2.29–2.48 (m, 1H), 2.66–2.81 (m, 3H), 3.06 (dd, J=9.0, 8.1 Hz, 1H), 3.39–3.48 (m, 1H), 4.60 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 22.1, 35.3, 51.2, 53.6, 58.8, 64.1; EIMS m/z (relative intensity) 128 (M^+, 21), 99 (74), 84 (100), 57 (48); IR (film, NaCl) ν_{max} (cm^{-1}) 3350, 3280, 2968. Anal. calcd for $C_7H_{16}N_2$: C, 65.57; H, 12.58; N, 21.85. Found: C, 65.22; H, 12.61; N, 22.17.

4.1.3. 1-Propyl-3-(*S*)-benzylaminopyrrolidine 1b. To the primary aminopyrrolidine **1c** (1.28 g, 10 mmol) in solution in dry ether (25 mL) was added freshly distilled benzaldehyde (1.38 g, 13 mmol) and the mixture stirred overnight at room temperature over activated 4 Å molecular sieves. The reaction was followed by GC and, upon completion, the solution was filtered and directly added, under argon, over a suspension of $LiAlH_4$ (722 mg, 19 mmol) in THF at 0°C. The reaction was stirred at room temperature for 4 h and then quenched successively with water (0.6 mL), 4 M NaOH (0.6 mL) and finally water (1.9 mL). The solids were filtered over a celite pad that was then washed with CH_2Cl_2 and AcOEt. The solvents were evaporated, and the oily residue redissolved in ether and washed with hydrochloric acid (1 M, 100 mL). This aqueous phase was extracted with AcOEt before being neutralized (NaOH 4N until pH gets basic) and reextracted by AcOEt then CH_2Cl_2. A flash chromatography was then run on silica gel (eluant: petroleum ether/AcOEt/NEt_3, 98.5:1.0:0.5) to provide aminopyrrolidine **1b** as a pale yellow oil (Yd=88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.1 Hz, 3H), 1.49–1.65 (m, 1H), 2.01–2.19 (m, 2H), 2.32–2.68 (m, 7H), 2.73 (dd, J=9.8, 6.2 Hz, 1H), 3.25–3.40 (m, 1H), 3.72 (s, 2H), 7.27–7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 26.0, 32.9, 53.8, 54.8, 57.5, 60.6, 61.3, 126.6–128.6, 141.1; CIMS (*t*-BuH) m/z 219 (MH^+). Anal. calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.82; H, 10.06; N, 13.12.

4.1.4. 1-(*R*)-α-Methyl-benzyl-3-(*S*)-aminopyrrolidine 1e. This primary amine has been obtained from (*S*)-2-benzyloxycarbonylamino-1,4-dimethanesulfonyloxybutane, prepared from dimethyl *Z*-asparaginate as described in Ref. 10f,g. To a sonicated solution of this dimesylate (3.00 g, 7.6 mmol) in dioxane (16 mL) was added neat commercial (*R*)-α-methylbenzylamine (1 g, 1.07 mL, 8.3 mmol). A light precipitate formed that slowly redissolved at room temperature. When the solution cleared off, the temperature was raised to 40°C and the solution stirred for 4 days. The dioxane was then evaporated and the oily residue redissolved in ether (90 mL), dried ($MgSO_4$) and evaporated before being chromatographed over silica gel (eluant CH_2Cl_2/MeOH, 90:10) providing 1-(*R*)-α-methylbenzyl-3-(*S*)-benzyloxycarbonylaminopyrrolidine in 54% yield.

The spectroscopic characteristics of this intermediate are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, 3H, J=6.8 Hz), 1.54–1.45 (m, 1H), 2.26–2.11 (m, 2H), 2.76–2.45 (m, 2H), 3.05 (m, 1H), 3.35 (q, 1H, J=6.7 Hz), 4.33 (m, 1H), 5.19 (s, 2H), 5.63 (broad d, NH, J=8.5 Hz), 7.42–7.14 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 32.5, 50.9, 52.5, 59.7, 65.8, 67.4, 127.1, 127.3, 127.5, 128.5, 128.8, 128.9, 140.4, 145.3, 156.4. CIMS (*t*-BuH) *m*/*z* (relative intensity): 367 ($M+C_3H_7^+$; 5%); 325 (MH^+; 100%). Anal. calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 73.92; H, 7.38; N, 7.54. $[\alpha]_D^{25}$=+6.4 (*c*=0.02; dioxane).

In this case, the presence of the α-methylbenzyl substituent required a selective hydrogenolysis of the Z-protecting group which can be achieved using the Pd/cyclohexadiene method.[32] Thus, the above carbamate (324 mg, 1 mmol) was disolved in absolute ethanol (10 mL) before palladium (10% on carbon, 324 mg), then commercial cyclohexadiene (800 mg, 10 mmol) were added. This mixture was stirred for 1–24 h at room temperature (depending on catalyst batch) under argon and completion of the reaction checked by TLC. Aminopyrrolidine **1e** was finally obtained after a flash chromatography on silica gel (eluant CH_2Cl_2/MeOH, 90:10) as a light-yellow oil (Yd=95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J=6.5 Hz, 3H), 1.51 (m, 1H), 2.04–2.50 (m, 3H), 2.67–2.97 (m, 2H), 3.41 (q, J=6.5 Hz, 1H), 4.04 (m, 3H), 7.21–7.40 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 33.2, 50.9, 51.9, 66.5, 68.1, 128.5, 129.6, 130.0, 157.5; CIMS (*t*-BuH) *m*/*z* (relative intensity) 233 ($M+C_3H_7^+$, 12); 191 (MH^+; 100). Anal. calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.56; H, 9.33; N, 15.12.

4.1.5. 1-(*S*)-α-methyl-benzyl-3-(*S*)-aminopyrrolidine 1f. The same above two-step procedure was followed.

1-(*S*)-α-methylbenzyl-3-(*S*)-benzyloxycarbonylaminopyrrolidine (Yd=53%, yellow solid): ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.35 (m, 4H), 1.95 (m, 1H), 2.65–2.18 (m, 3H), 3.01–2.99 (m, 1H), 4.02 (q, 1H, J=6.3 Hz), 4.34 (m, 1H), 5.11 (broad d, NH, J=8.3 Hz), 5.22 (s, 2H), 7.42–7.14 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 32.7, 50.7, 51.0, 60.0, 66.3, 67.0, 127.1, 127.3, 127.5, 128.5, 128.8, 128.9, 137.9, 146.1, 156.1. CIMS (*t*-BuH) *m*/*z* (relative intensity) 367 ($M+C_3H_7^+$; 7%); 325 (MH^+; 100%). Anal. calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 73.76; H, 7.47; N, 8.86. $[\alpha]_D^{25}$=−6.3 (*c*=0.02; dioxane).

1-(*S*)-α-methyl-benzyl-3-(*S*)-aminopyrrolidine **1f** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J=6.4 Hz, 3H), 1.44 (m, 1H), 2.00–2.16 (m, 2H), 2.49 (m, 3H), 3.00 (q, J=6.4 Hz, 1H), 4.08 (m, 1H), 4.43 (bs, 2H), 7.18 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 32.5, 50.6, 51.3, 65.7, 67.0, 127.5, 128.5, 128.9, 156.4. Anal. calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 74.62; H, 9.51; N, 15.89.

4.1.6. *N*-(*tert*-Butoxycarbonyl)-4-methylsulfonyloxypiperidine 15. To a solution of *N*-(*tert*-butoxycarbonyl)-4-hydroxypiperidine (2.0 g, 9.94 mmol) in dichloromethane (20 mL), pyridine (3.84 mL, 48 mmol, 4.8 equiv.), methanesulfonyl chloride (1.80 g, 15.65 mmol, 1.6 equiv.) and catalytic amount of 4-dimethylaminopyridine were added at 0°C. After being stirred for 86 h at room temperature, the solution was concentrated and ethyl acetate (40 mL) were added. An insoluble salt precipitated and was filtered. The remaining solution was concentrated then purified by chromatography on silica gel (heptane/ether, 50:50) to give **15** as a white solid: (2.57 g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.83 (m, 2H), 1.99 (m, 2H), 3.06 (s, 3H), 3.33 (m, 2H), 3.73 (m, 2H), 4.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 30.6, 37.8, 39.5, 76.6, 79.0, 153.6; IR (film, NaCl) ν_{max} (cm^{-1}) 1700, 1180; EIMS *m*/*z* (relative intensity) 201 (4), 127 (17), 110 (9), 84 (42).

4.1.7. *N*-(*tert*-Butoxycarbonyl)-4-(1′-(*R*)-phenylethyl)-aminopiperidine 16. A mixture of *N*-(*tert*-butoxycarbonyl)-4-methylsulfonyloxypiperidine **15** (1.58 g, 5.63 mmol) and (*S*)-α-methylbenzylamine (5 mL, 38.8 mmol, 6.9 equiv.) was heated at 115°C for 24 h. After cooling to room temperature, ethyl acetate (60 mL) and 4 M NaOH (10 mL) were added and stirred vigorously. The aqueous phase was extracted with ethyl acetate (2×30 mL) and the organic phases were combined and washed with water. The concentrated residue was diluted with methanol (5 mL) and a solution of L-(+)-tartaric acid (0.95 g, 6.27 mmol) in methanol (25 mL) was added. The solution was kept at room temperature for one day and filtrated. The filtrate was concentrated and ether (10 mL) and 1N HCl (10 mL) were added and stirred vigorously for 15 min. The organic phase was extracted with water (15 mL) and the aqueous phases were combined and washed with ethyl acetate (3×5 mL). Sodium hydrogen carbonate was slowly introduced followed by a few drops of 4N aqueous sodium hydroxide. The aqueous solution was extracted with dichloromethane (3×10 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated to give **16** as a pale yellow oil (0.52 g, 30%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (d, J=6.6 Hz, 3H), 1.41 (s, 9H), 1.64 (m, 2H), 1.89 (m, 2H), 2.42 (m, 1H), 2.63 (m, 2H), 3.94 (q, J=6.6 Hz, 1H), 3.95 (m, 2H), 7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 27.4, 30.9, 32.1, 41.7, 51.1, 53.6, 78.3, 125.5, 126.0, 127.5, 153.7; IR (film, NaCl) ν_{max} (cm^{-1}) 3317, 1694; EIMS *m*/*z* (relative intensity) 247 (19), 143 (18), 105 (100).

4.1.8. *N*-Methyl-4-(1′-(*R*)-phenylethyl)aminopiperidine 17. A solution of *N*-(*tert*-butoxycarbonyl)-4-(1′-(*R*)-phenyl-

ethyl)aminopiperidine **16** (0.62 g, 2.04 mmol) in dry THF (30 mL) was added over 20 min to a suspension of lithium aluminum hydride (0.39 g, 10.18 mmol, 5 equiv.) in freshly distilled THF (20 mL), placed under nitrogen atmosphere at 0°C. The solution was stirred at room temperature for 4 h then heated at 60°C for 1 h. After cooling at 0°C, the excess of LAH was hydrolyzed by successive addition of cold water (0.8 mL), 4N aqueous sodium hydroxide (0.8 mL) and cold water (1.0 mL). The white precipitate was filtered on celite and washed with dichloromethane (10 mL). The filtrate was concentrated and the residue was dissolved in ether (10 mL). 1N aqueous hydrochloric acid (10 mL) was added and the solution was stirred at room temperature for 15 min. The acidic aqueous layer was extracted and sodium hydrogen carbonate was slowly added until pH 9. The medium was then extracted with dichloromethane (3×10 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated to give **17** as a colorless oil (0.33 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, J=6.6 Hz, 3H), 1.37–1.44 (m, 2H), 1.70 (m, 1H), 1.88 (m, 2H), 1.94 (m, 1H), 2.22 (s, 3H), 2.30 (m, 1H), 2.77 (m, 2H), 3.96 (q, J=6.6 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 27.4, 30.9, 32.1, 41.7, 51.0, 53.0, 78.3, 125.5, 126.0, 127.5, 153.7; IR (film, NaCl) ν_{max} (cm^{-1}) 3317; EIMS m/z (relative intensity) 218 (M^+, 20), 91 (100).

4.2. General procedure for the enantioselective protonation of 2-methyltetralone lithium enolate by acetic acid

A typical run was as follows. The 2-methyltetralone trimethylsilylenolether **6** was prepared from commercial rac-2-methyltetralone **8** following the methodology described by Duboudin et al.[33] in 85% yield. All spectral data were in agreement with those in literature.[16a] To 185 mg (0.8 mmol) of **6** in THF or toluene (2 mL) was added, at room temperature and under argon, 0.55 mL of a 1:1 commercial solution of MeLi/LiBr (1.60N in ether, 0.9 mmol, 1.1 equiv.) and the mixture stirred for 30 min at room temperature before being warmed up to 40°C for 5 min. The medium was then brought to −78°C before 1.1 equiv. of chiral 3-AP **1** in 2 mL of the corresponding solvent was added. The mixture was then maintained at this temperature for 1 h before 1 equiv. (or 2 equiv. depending on the experiment) of the proton donor (in solution in 2 mL of the solvent) was added rapidly. After 30 more min, 3 mL of a 10% aqueous solution of citric acid were added before letting the medium warming up to room temperature. The organic solution was washed with 1N HCl (2×10 mL) then by water (10 mL). The organic layer was then dried ($MgSO_4$), and evaporated to provide crude 2-methyltetralone **8** that can be flash chromatographied on silica gel when needed. Yields were in general in the 90% range. The ee of **8** was determined by GC on a Chiralcell B-TA, 20 m×0.3 mm or Chiralcell G-TA, 15 m×0.3 mm columns. All spectral characteristics for **8** were identical to those published in literature.[34] The 3-AP **1** can be recycled from the aqueous acidic phase in relatively good yields and without racemisation.

4.3. General procedure for the enantioselective addition of organolithium reagents to *o*-tolualdehyde

A typical run was as follows. After the 3-AP lithium amide/butyllithium complex (0.2 mmol in 3 mL solution) was prepared following one of the three protocols A, B or C described in the results and discussion section, freshly distilled *o*-tolualdehyde in 0.5 mL dry THF solution was added slowly at −78°C. After stirring 1 h at the same temperature the reaction was quenched by 1N HCl and extracted with Et_2O (3×10 mL). The extracts were dried and concentrated under reduced pressure. Flash chromatography (heptane/Et_2O, 80:20) of the residue on silica gel gave pure sec-alcohol. The benzylic alcohols obtained are all described in the literature.[7b,35] Their enantiomeric excesses were determined by Eu(hfc)$_3$ chiral-shift NMR experiments and configurations were determined by comparing the optical rotation with the literature data.

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